Battle Casualties in Korea

Studies of the Surgical Research Team

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Volume IV. Post-traumatic Renal Insufficiency

Army Medical Service Graduate School

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Chapter 1

Introduction

Major William H. Meroney, MC, USA

This volume contains selected reports of members of the Surgical Research Team, Army Medical Service Graduate School, who concerned themselves primarily with study and treatment of battle casualties with renal failure. Many of the reports are published or are in press in current civilian journals, but they are collected here to provide a one-volume reference and to give perspective to evolving concepts. Space did not permit inclusion of all reports nor all information in the original versions of those selected. Some reports have been deferred pending confirmation of clinical observations by repetition or by animal experimentation. However, a reference volume containing complete data—raw, uninterpreted—will soon be filed with the Army Medical Service Graduate School to provide final detail when needed.

Most of the observations reported were completed at the Renal Insufficiency Center (Fig. 1) in Wonju, Korea, at a time when the main line of resistance was about 75 miles northward. Some studies, by their very nature, involved the more forward installations; others required analyses so complex that the specimens were sent to Japan or the U. S. The personnel of the Research Team were few, but they were joined or supported by a huge team of Eighth Army officers and men deployed through all echelons. Not only Medical Service personnel, but engineers, pilots and others contributed by transporting patients, supplies and specimens and providing or maintaining equipment. Few of these individuals were familiar, initially, with the mission of the Surgical Research Team, and their cooperation did not come about automatically. Considerable effort by men of vision and energy produced the rather remarkable phenomenon of the safe delivery of a patient to Wonju immediately following cessation of his urine flow. No less remarkable was the facility which received this patient. Within minutes of the time the helicopter touched the ground by the door of the admitting office, the patient had been examined, an electrocardiogram had given a close estimate of the concentration of plasma potassium, blood had been drawn for chemical analyses, and a decision had been made whether immediate artificial kidney dialysis was indicated. There was no precedent for the existence in the battlefield of such instruments as the artificial kidney and the supporting laboratory and paraphernalia (Figs. 2 and 3).

Numerous individuals contributed to this venture and their names are recorded elsewhere. It seems proper, however, to repeat here a few primarily responsible. Dr. F. A. Simeone, at the behest of Colonel William S. Stone, MC, conducted the original survey which revealed the problem of renal failure in battle casualties in Korea. Captain Lloyd H. Smith, MC, demonstrated the need for an artificial kidney and first established it in the combat zone. Captain Roy Mundy, MSC, established the laboratory without which the artificial kidney would have been inoperable. The parent unit to which the Renal Center was attached was the 11th Evacuation Hospital, commanded by Colonel Harold W. Glascock, MC, later by Colonel Fred W. Seymour, MC, both of whom deserve special mention for their support and kindness. The Renal Center functioned as a unit of the Surgical Research Team, which was commanded by Captain John M. Howard, MC, supervised by Colonel Richard P. Mason, MC, and directed by Colonel William S. Stone, MC.

At the advisory level, several civilian consultants visited Wonju and helped to steer the effort on a course productive of practical results. Dr. A. C. Corcoran and Dr. William A. Altemeier, in particular, will long be remembered for their sage observations and agreeable endurance.

Some reports in this volume present experiences of several individuals observing the same patients from different points of view; others present experiences with a different group of patients at a different time. The conclusions of the investigators, therefore, do not agree in every detail. It will be noted, however, that certain themes recur in one report after another. The agreement among independent investigators adds to the validity of the observations, but it uncovers one of the major shortcomings of the series of studies. The experiences of each participant were not adequately transmitted to his successors, and sometimes painful repetition could have been avoided. Even so, a new arrival in the theater gained considerable information from the incumbent and was able to continue some projects and expand some ideas already established. It is to prevent unnecessary repetition by future workers that this volume is presented at this time. Further seasoning might allow preparation of a more polished version, but during the delay world events might require that some version be available.

The reports are based upon studies of approximately 150 patients with acute oliguria and approximately 50 patients with conditions simulating renal insufficiency or with renal insufficiency without oliguria. The studies establish several points which have been debated or little appreciated in the literature. There is no question now of the efficacy of artificial kidney dialysis in saving the lives of

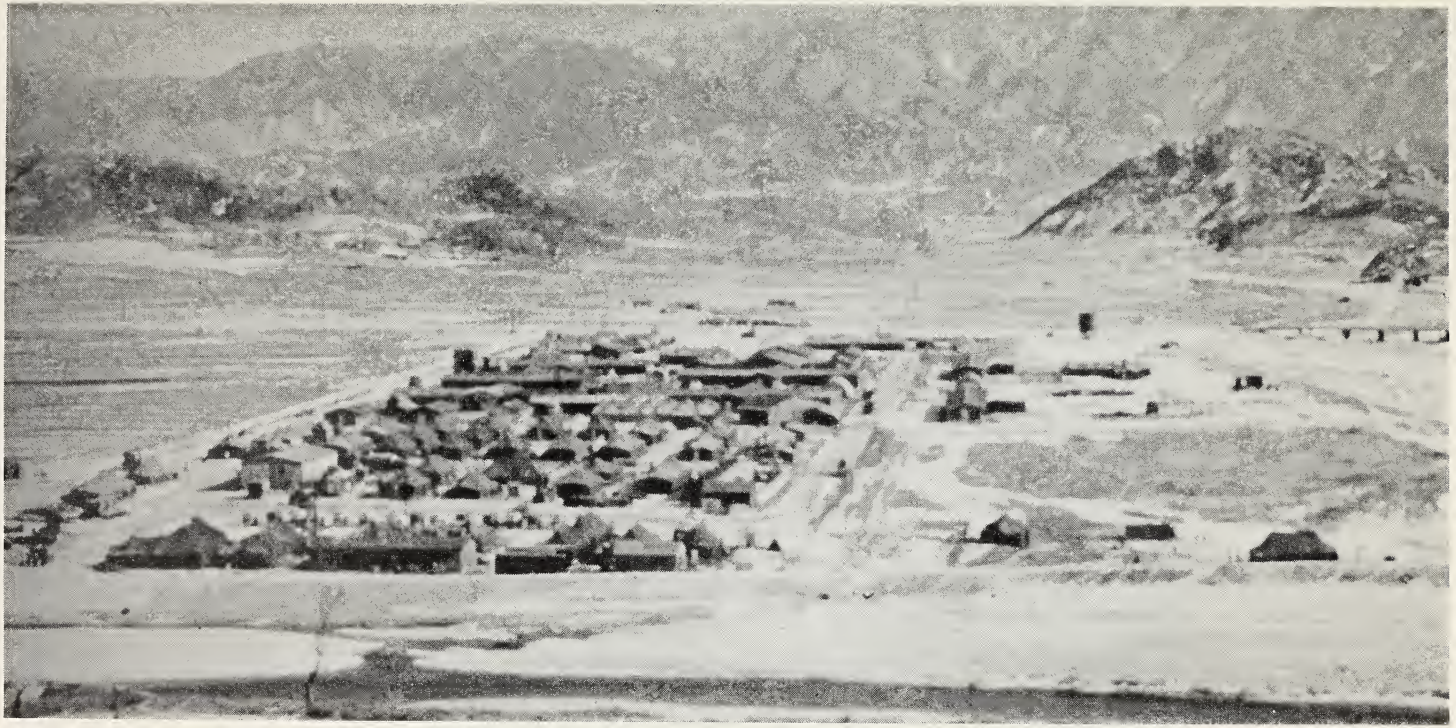

FIGURE 1. 11th Evacuation Hospital (semi-mobile) to which the Renal Insufficiency Center was attached.

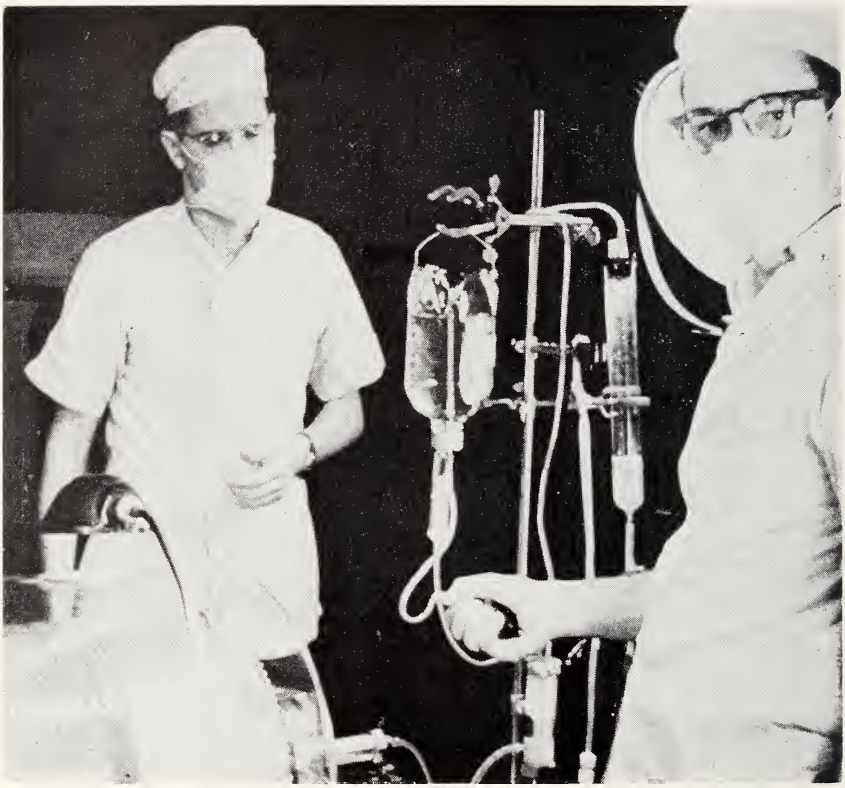

FIGURE 2. Artificial kidney (Kolff type) in operation at the Renal Insufficiency Center.

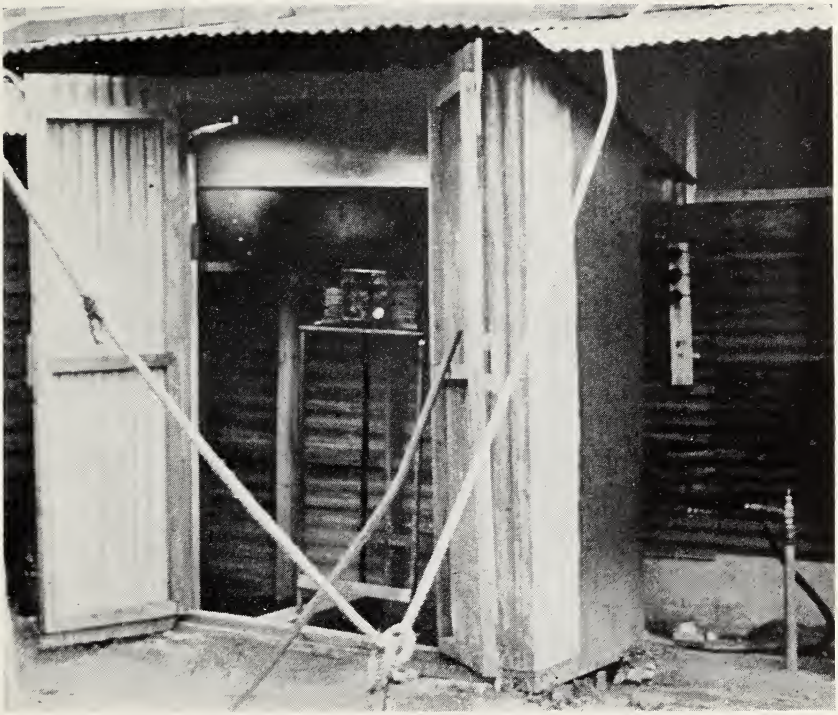

FIGURE 3. Water for artificial kidney being heated in an airplane wing tank by gasoline field stove.

certain patients who would have died without it. Many died anyway, but in them dialysis was effective in controlling uremia and served to separate, for the first time, the manifestations of uremia from those of sepsis. When a seriously injured man is noted to be oliguric, there is a great temptation to attribute all features of his condition to uremia. Correction of the chemical abnormalities by dialysis is followed by striking, if temporary, amelioration of all signs and symptoms if uremia alone is responsible; those features which persist after effective dialysis are the result of some other disorder. This technic served to clarify some manifestations of generalized sepsis and aseptic necrosis. Patients with oliguria who have little devitalization of non-renal tissue, particularly muscle, experience no symptoms until the retention of urinary chemicals produces marked aberration of concentration of plasma chemicals, and several days pass before this occurs. Patients with nausea and vomiting, tremulousness, disorientation and convulsions during the first few days of oliguria do have azotemia, but correction of the azotemia by dialysis causes little if any clinical improvement. These patients have hypotension, or sepsis, or muscle necrosis, or central nervous system damage unrelated to uremia. Amputation, débridement or supportive measures correct the clinical features with correcting the chemical abnormalities. The chemical abnormalities progress at an astonishing rate, however, if the devitalized tissue is not removed. This requires that surgery be prompt and radical, and if it is incomplete, dialysis must be done early and frequently. This difference in degree of tissue destruction in war wounds and civilian injuries probably accounts for the difference in opinions regarding the necessity for dialysis.

Much has been written about the clinical syndrome of potassium intoxication. In Korea it was noted that plasma potassium could rise to 10 mEq./L. and produce no symptoms whatever. Symptoms and signs usually ascribed to excess potassium—tingling of extremities, reflex changes, respiratory distress, circumoral paresthesias and central nervous system signs—were associated with hypocalcemia and usually could be obliterated instantly by infusion of calcium. However, when hyperkalemia progressed to the degree that the electrocardiogram showed prolongation of the QRS complex, in the presence of a normal calcium concentration, the symptoms and signs returned. These observations are consonant with Ringer's classic descriptions of the behavior of potassium and calcium on isolated amphibian hearts. The mutual antagonism of these ions, which has received insufficient attention in this century, provides a life-saving tool for the treatment of potassium intoxication.

The water requirements during anuria received considerable attention in these patients. Although tools for definitive studies were not

available, many careful clinical observations indicated that the usual rules of thumb are not reliable in this type of patient. Endogenous water production and insensible water loss have been studied carefully in normal persons, but the estimates so derived do not apply during excessive catabolism secondary to tissue damage with infection, hyperpnea secondary to acidosis, or dependence upon intravenous glucose for nutrition. These patients appeared to require little more than half of the 40 cc./hour usually suggested. This fact and some prevailing misconceptions of renal physiology allowed overhydration in some patients. Missionary efforts were reasonably successful in restraining those differently oriented from overhydrating patients to "flush out the kidneys" or "to rule out dehydration."

Most of the patients in this series had undergone long periods of hypotension, which presumably was the cause of the oliguria. Patients with comparable wounds and hypotension failed to develop oliguria, but defects of renal function were demonstrated in many of them. A few transfusion reactions were documented, but not all produced renal failure. There is a growing suspicion that pigments do not cause tubular necrosis, although the shock with which they may be associated can cause the lesion. Hemorrhagic fever and chemical agents accounted for a few cases in the series. Dehydration was not observed as a cause for oliguria. On the basis of the available data, shock remains the major cause of renal insufficiency in this series of cases.

The mechanism of renal function during oliguria was considered from several points of view, but no definite conclusions were reached. It was apparent, however, that published theories of function were incompatible with some of the observations. Data suggested that the kidney with tubular necrosis functioned as if it were qualitatively normal but quantitatively insufficient. The studies of wound healing and resistance to infection are difficult to assess. The predisposition of the uremic patient to complications is well recognized, but the particular defense systems studied do not appear abnormal. Also, some patients have been observed to heal one wound and not another. Relative starvation, vitamin imbalance, wasting of specific tissues, and associated infections are interwoven in such a way that their individual effects have not been distinguished. From the purely clinical point of view, failure of wound healing was associated with local infection, and weight loss beyond that expected from the caloric intake was associated with systemic infection. There were not enough control studies to establish whether renal insufficiency, per se, contributed significantly. Also, the dangers inherent in artificial kidney dialysis under field conditions were not fully assessed, but the dangers

in withholding dialysis were well enough established to justify the procedure.

The net results of this experience are that a Renal Center in support of a field army in combat can be expected to save lives, to influence favorably the standards of medical and surgical care in other units, and to provide information from study of abnormalities in extreme degree which can be applied in the recognition and treatment of abnormalities of lesser degree. The optimal location of such a center will be governed by numerous factors in geography, tactics, weather and logistics which can be resolved into a single factor: evacuation time. The center may be located in any area otherwise suitable which can be reached by the casualty within 3 days, provided the recommended measures in medical management are employed. The mobility of a Renal Center is not yet established, but the practicality of a mobile, self-contained unit is under consideration.

Chapter 2

Post-traumatic Renal Insufficiency in Military Casualties I. Clinical Characteristics*

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I. Introduction

Post-traumatic renal insufficiency is a major problem in military medicine. In World War II, 40 per cent of one group of severely wounded patients developed acute post-traumatic renal insufficiency with a case fatality rate of 90 per cent among the severely oliguric.[1] Renal lesions were found in 18.6 per cent of 427 unselected battle casualties who died in Army hospitals.[2] Among 165 autopsied Korean battle casualties pathological evidence of renal damage occurred in 39 per cent and clinical uremia was severe enough to account for death in 14 per cent of the cases.[3]

The renal lesion in acute renal failure of traumatic and other origin has been studied by several investigators,[2, 4-6] and the underlying similarity in the lesions has been emphasized by Lucke.[4] The definitive description and concept of pathogenesis has been further clarified by the work of Oliver.[7] A unified concept of acute renal failure as a clinical and biochemical sequel of several diseases has been documented by Swan and Merrill.[8]

The type of injury to the kidney and the subsequent clinical and biochemical changes in the renal insufficiency of military casualties are not qualitatively different from those seen in civilian medicine; but special consideration of the former seems warranted because—(1) development of clinical uremia and potassium intoxication is accelerated in this group of patients, with a resulting excessively high case

*Previously published in *American Journal of Medicine 18:* 172, 1955.

fatality rate; (2) this rapid course presents special therapeutic problems in which use of the artificial kidney requires evaluations; (3) occasional civilian patients injured in accidents, or after extensive surgery, develop renal failure with these characteristics;[9] (4) there is a clear possibility, in the event of war, of widespread civilian casualties who may be expected to follow a similar course and to present similar problems.

The experience presented here includes all patients, 51 in number, who developed post-traumatic renal insufficiency and were admitted to a Renal Insufficiency Center* in Korea during 1952. This represents most of the combat casualties who developed oliguria, as defined below, and who survived the first 48 hours of resuscitation and surgery; patients who developed overt transfusion reactions were excluded from this group. The Center was equipped with a trained staff, an adequate supporting laboratory and a Brigham-Kolff-type artificial kidney. Ten additional patients were treated in a detailed, preliminary survey by members of the staff before the artificial kidney was available or a permanent location for the Center established. This experience presented here constituted a unique opportunity to evaluate the usefulness of a center for the treatment of this group of patients in the forward chain of casualty evacuation.

II. Definitions and Methods

By *post-traumatic renal insufficiency* is meant impairment in renal function secondary to diffuse parenchymal renal damage[7] following trauma to the patient. Manifestations of post-traumatic renal insufficiency include the characteristic urinary, chemical and clinical findings in patients with acute renal failure of any origin. These findings are superimposed upon the expected sequelae of the antecedent wound. from which they cannot always be clearly differentiated.

Oliguria is arbitrarily defined as a urine output of less than 500 ml. in 24 hours. This is based on the demonstration that 500 ml. approximates the lowest sufficient volume of urine to clear the plasma of a normal metabolite load at normal maximal renal concentrating ability.[10] Of course, with impairment of concentrating ability high levels of azotemia may occur at much higher rates of urine formation.

Diuresis is defined as beginning when a 24-hour urine volume equals or exceeds 1 liter after a preceding period of oliguria. During the

*Operated jointly by the Surgical Research Team, AMSGS, Washington, D. C., and personnel of the Eighth Army, Korea.

recovery phase the level of azotemia is seldom lowered by a urine volume of less than 1 liter.*

The 24-hour urine collections were taken by constant drainage from an inlying Foley catheter. Blood for chemical determinations was drawn with minimal stasis into previously heparinized syringes, centrifuged promptly and the plasma analyzed (by the following methods) for nonprotein nitrogen,[11] carbon dioxide combining power [12] and chloride.[13] Sodium and potassium were measured in diluted, heparinized plasma by means of a Baird-Associates flame photometer using an internal lithium standard.

Electrocardiograms were taken with a direct-writing Sanborn electrocardiograph using standard and unipolar limb leads and precordial leads V1 through V6.

III. Diagnosis and Incidence

The incidence of post-traumatic renal insufficiency as defined above could be determined only by the routine use of sensitive diagnostic renal function tests on a large random sample of wounded men. Unfortunately, such a study has not been carried out. The diagnostic criterion used at the forward hospitals as a basis for referring patients to the Renal Insufficiency Center was that of oliguria (less than 500 ml./24 hours) without hypotension on the second or third postwound day. The presence of uncomplicated dehydration as a cause of oliguria was excluded by a urinary specific gravity of less than 1.030 (it was usually below 1.020). Diagnosis was occasionally substantiated by lack of a diuresis in response to a water-load test, such as the infusion of 1,000 ml. of 5 per cent dextrose in water intravenously in 1 hour. These simple criteria indicated the patients' need for specialized therapy and doubtless excluded many cases of milder renal damage.† Because potassium intoxication and clinical uremia developed rapidly in the oliguric patients, they were evacuated to the Center as soon as the diagnosis was made.

During the last 6 months of 1952 there is reason to believe that almost all combat casualties who developed oliguria and who survived 48 hours after surgery were referred to the Renal Insufficiency Cen-

*In contrast to the finding of Swan and Merrill,[8] 24-hour urine volumes in these patients did not usually increase at noticeably different rates below and above a 400 ml. daily output level; however, typical diuresis uniformly followed daily urinary outputs of 750 to 1,000 ml.

†As will be emphasized below, it is possible that renal insufficiency without oliguria might represent more of a therapeutic problem in an older casualty population, but this was rarely the case in these military casualties whose average age was 22.7 years.

ter. During this period 42 patients were referred to the Center from among approximately 8,000 wounded or injured-in-action patients admitted to medical treatment facilities.[14] This represents an incidence of about 0.5 per cent or 1 oliguric patient per 200 surviving casualties. In a group of 4,000 consecutive acutely wounded patients treated at one forward hospital (1952–53), 19 patients developed oliguria, an incidence also approximating 0.5 per cent.

Post-traumatic renal insufficiency therefore is a statistically minor complication of wounding. This is not a cogent indication of its importance in military medicine, however. Approximately 20 per cent of soldiers hit in action in Korea were killed instantly or died before they reached forward hospitals.[14] Of the casualties who reached the forward hospitals alive, approximately 97 to 98 per cent survived their wounds. Most of these had relatively minor wounds with uncomplicated convalescence. It is in the smaller number of severely wounded that renal failure constitutes an important cause of death during the postoperative period. In Italy during World War II at least 40 per cent of a group of very severely wounded casualties* studied at one forward hospital developed acute renal failure. Uremia was thought to be the major cause of death, accounting for 54 per cent of all fatalities in this group and resulting in an over-all mortality among severely wounded of 19 per cent.[1]

In Korea prompt evacuation made possible the early treatment of casualties with massive injuries. Forty-three such casualties who lived 3 days or longer after receiving 15 or more pints of blood on the day of injury were studied by the Surgical Research Team. Twenty-one per cent of this group developed oliguria and an additional 14 per cent developed azotemia and clinically evident uremia while maintaining a daily urinary output of more than 500 ml.[15] It is this range of incidence which indicates the real importance of post-traumatic renal insufficiency as a military medical problem.

It may be anticipated that the incidence of post-traumatic renal insufficiency will vary in different military situations, depending on the availability of blood and the rapidity with which casualties are evacuated. Hence the data from Korea may represent a minimum

*Non-transportable injured. In the subsequent discussion it is recognized that there is no completely satisfactory, objective definition of the term *severely wounded* as employed here. Because of improved technics of evacuation and medical care in the forward areas more extensive wounds became compatible with survival. In general, the "severely wounded" were those patients whose immediate survival, in the judgment of physicians in the forward areas, *depended* on prompt evacuation, resuscitation and surgery. In such patients, large volumes of injured tissue were regularly found and hypotension responded only to massive transfusions.

incidence with present methods of evacuation, resuscitation and surgery.

IV. Etiology

Extensive studies on the effects of shock [1, 16-21] and of hemoglobin [22-27] on renal function in man, and attempts to produce acute renal failure in experimental animals [28-31] have not completely elucidated the relative roles of renal ischemia and of blood or tissue pigments in the pathogenesis of the renal tubular damage Although it was realized that little could be added to the basic information about pathogenesis in such an uncontrolled, clinical study, an attempt was made to evaluate some of the antecedent and possibly etiological factors in this group of patients. It was hoped that a pattern might emerge by which the occurrence of post-traumatic renal insufficiency in an individual patient could be predicted.

1. Evacuation Time

As a general rule the acutely wounded patient is carried by litter from the point of wounding to the aid station supporting his battalion. Preliminary first aid treatment is given. Severely wounded patients are then evacuated to a forward surgical hospital by helicopter during the day and by ambulance at night. Less severely wounded patients travel by litter-jeep or ambulance through regimental collecting and division clearing stations and for definitive surgery if necessary at the forward surgical hospital. Albumin, dextran and whole blood are given as indicated along the route of casualty evacuation, and entries are made on the field medical record. Subsequent data have been obtained from these entries.

The time required for this evacuation sequence from time of wounding to forward hospital admission averaged 4.6 hours (range, 1 to 11 hours) in 51 patients whose records permitted this calculation. Approximately half of the patients reached a forward hospital within 3 hours of the time of wounding. The average time of evacuation in a control group of 41 severely wounded patients who did not develop renal insufficiency was 3.5 hours. It can be concluded that the delay in resuscitation necessitated by evacuation per se did not lead to the development of post-traumatic renal insufficiency.

2. Duration and Severity of Hypotension

(Systolic arterial blood pressure of less than 100 mm. Hg.)

In 50 patients from whose records estimates could be made, the duration of hypotension averaged 7.3 hours (range, 2 to 26 hours). Over half of the patients were hypotensive for 6 hours or less, but

no patient in this group was hypotensive for less than 2 hours. The mean duration of hypotension is considerably longer than the average evacuation time. This reflects the fact that persistent hypotension frequently prolonged preoperative resuscitative efforts, or recurred during or following operation.

Serial blood pressure readings were not available on any patient (and single readings only on 6) prior to admission to the forward surgical hospital, so that any estimate of the total duration of arterial hypotension is necessarily crude. These estimates include the evacuation time when the patient was hypotensive on hospital entry, unless normal blood pressures were previously recorded.

The estimated duration of hypotension in a control group of 41 severely wounded patients who did not develop oliguria was approximately 6 hours. It can be concluded that hypotension alone cannot be incriminated as a cause of renal failure. The amount of volume replacement therapy administered at the forward surgical hospital and during the prior evacuation period constitutes a further general measure of the degree of hypotension.

All 61 patients* received whole blood (and occasionally albumin, plasma or dextran) during the immediate post-wound period. Total volume therapy averaged 5.9 liters per patient (range, 0.5 to 15.5 liters). Whole blood accounted for 95.3 per cent of the total volume therapy given with the remainder divided among plasma 2.4 per cent, albumin 1.8 per cent and dextran 0.5 per cent. This approximated the relative use of these various oncotic agents in all the wounded at the time of this study. The resuscitative use of volume therapy was distributed in time as follows:

During evacuation to hospital	11%
Before surgery at hospital	30%
During surgery at hospital	40%
Postoperative period	12%
Unable to assign	6%

This distribution of volume replacement gives only a fair index of the presence and severity of hypotension, however, because (a) during evacuation blood was not always readily available and was difficult to administer, and (b) many of the most severely wounded patients were operated upon before their blood pressures were restored to normal.

In the group of 41 severely wounded patients who did not develop post-traumatic renal insufficiency, each received an average of 12 liters of volume therapy, largely as whole blood, during the total period of resuscitation (first 24 hours after wounding). It is possible

*See Introduction, p. 8.

that the more liberal use of whole blood may have protected these patients against more severe renal damage.

3. Hemolysis and Plasma Hemoglobin

Type O whole blood was used exclusively in these patients. No overt transfusion reactions occurred. If increased, but subclinical, hemolysis of the recipients' erythrocytes by the hemagglutinins of the transfused blood contributed to the pathogenesis of the renal damage, it would be anticipated that fewer patients with type O blood would be found in this series than the relative incidence of type O in the population as a whole. Table 1 lists the blood types in the present series and a random sample of Occidental individuals; the differences are not statistically significant. This agrees with a similar study carried out by the Board for the Study of the Severely Wounded in World War II.[1]

Table 1. Incidence of Blood Types in Patients With Acute Post-traumatic Renal Insufficiency

Agglutinogen	No. of Patients	Per Cent	Per Cent of Normal Population*
O	23	55	41. 8
A	12	29	37. 7
B	5	12	13. 9
AB	2	5	6. 6

*From Sunderman and Boerner: Normal Values in Clinical Medicine, p. 74, W. B. Saunders Company, 1949.

Because of the long supply route from the United States, whole blood was used in the forward areas in Korea 7 to 28 days (average of about 2 weeks) after its withdrawal from the donor. Figure 1 illustrates the relationship between the age of blood and its plasma hemoglobin level.[32, 33] Thus a patient receiving 6 liters of 2-week-old blood receives an infusion of about 2 gm. of hemoglobin at a time when there is probably marked renal vasoconstriction. In a study of renal function in casualties in Korea, however, Ladd could find no correlation between the plasma hemoglobin concentration and the degree of impairment of inulin and PAH clearances.[16] He also found similar reduction in clearance in two patients resuscitated with dextran alone and in one patient resuscitated with fresh type-specific, compatible whole blood. The plasma hemoglobin concentrations and

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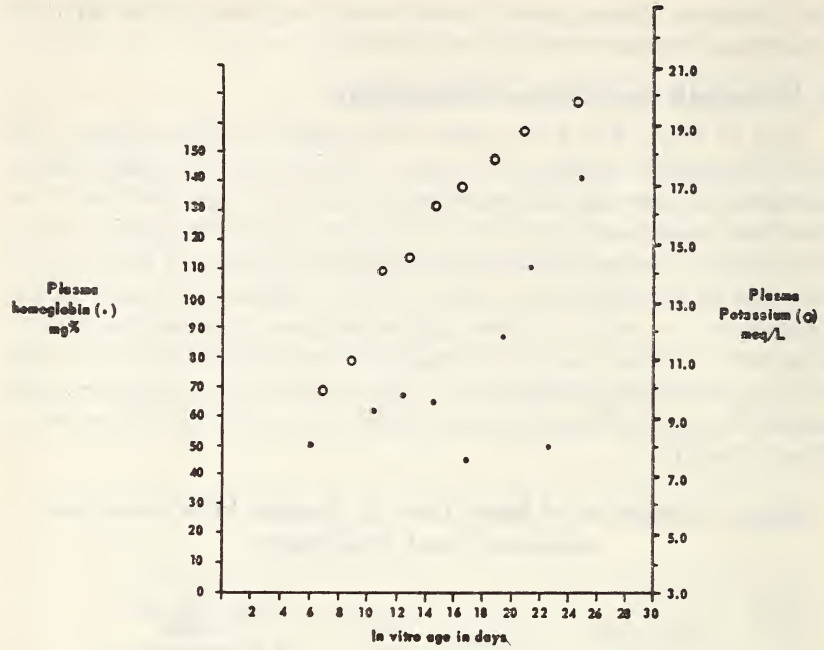

FIGURE 1. Plasma hemoglobin (•) and potassium (0) of stored blood in relation to age. Values are means of at least 10 samples except for those on day 7 (5 samples) and day 9 (2 samples). Plasma was obtained from bottles later used for resuscitation at a forward surgical hospital.

total amount infused are low in comparison with amounts producing renal vasoconstriction in man.[24 25] Myoglobin may have been implicated in patients with massive tissue destruction or with severe, prolonged shock.[1]

4. Severity and Location of Wound

Post-traumatic renal insufficiency tended to occur as a complication in the most severely wounded, as might be anticipated from what is known of the pathogenesis of the condition and from the amount of volume replacement (5.9 liters per patient) needed for resuscitation. Ladd found that the renal blood flow and filtration rate were in general depressed in direct relation to the severity of the wound, as graded by an arbitrary point system for estimating the extent of the physiological impact including volume replacement required and amount of tissue damage.[16]

Table 2 lists the location of wounds encountered in the present series of patients compared with similar data obtained during World War

II [1] and in previous combat experience.[14, 34] Both perforating and penetrating wounds occurred in all groups.

Table 2. Number of Wounds of Selected Sites per 100 Casualties With Wounds of Any Site: General Casualty Population Compared With Patients With Post-traumatic Renal Insufficiency

Site of Wound	Korean Conflict [1]		Patients with Renal Failure	
	All Wounded in Action Admissions [2]	Patients Dying of Wounds [2]	Present Series 61 Patients	World War II 78 Patients [3]
Head, face, neck, extremities, with and without fracture	145	98	50	50
Abdomen [4]	13	33	59	35
Chest	13	17		22
Thoraco-abdominal	1	6	26	14
Liver	1	4	21	19
Kidney	1	3	23	17
Spinal cord and vertebrae	2	4	2	1
Crush	[5] NA	[5] NA	5	6

[1] Based on preliminary unpublished data compiled from tabulations of individual medical records on all battle wound and battle injury admissions to medical treatment facilities in 1950–1952. Data obtained from Medical Statistics Division, Office of The Surgeon General, Department of the Army.

[2] Data for wounded in action admissions (WIA) include data for patients dying of wounds (DOW).

[3] Studied by Board for the Study of the Severely Wounded.[1]

[4] Includes pelvis and excludes liver and kidney.

[5] Not applicable (NA) to data for all WIA and DOW, all of which have been tabulated according to anatomical site, including those whose diagnosis was "crushing."

The higher incidence of thoraco-abdominal and abdominal wounds in patients developing renal failure compared with the general casualty population or with the group dying after initial hospital care is striking. Duration of hypotension and volume of whole blood given were also generally greater in patients with wounds of the trunk. Of interest also is the high incidence of wounds of the kidney usually resulting in nephrectomy. None of the patients sustained bilateral renal trauma, however.

In summary, prolonged periods of hypotension, infusion of necessarily large volumes of relatively old whole blood, and the severity

of the initiating wounds are possible factors in the etiology of post-traumatic renal insufficiency, implicated by their uniform occurrence in the oliguric patients referred to the Renal Insufficiency Center. There were a number of casualties, however, who failed to develop oliguria despite apparently identical histories and similarly severe wounds and prolonged periods of hypotension.

Likewise the occurrence of acute post-traumatic renal insufficiency could not be *predicted* on the basis of the foregoing data. However, such prediction with an accuracy of about 33 per cent [15] was possible by observing the response of low postoperative blood pressures to whole blood transfusion. Many of the patients might well have died in shock without energetic and sustained resuscitative care in the postoperative interval. Patients who did not develop oliguria usually experienced a prompt blood pressure response to small transfusions. This experience indicated that acute renal failure impended in the postoperative period when an excessively large volume of blood was required to correct hypotension in the absence of continuing hemorrhage.

V. Renal Insufficiency Without Oliguria

Table 3 presents eight patients studied at the Renal Insufficiency Center who had marked impairment of renal function but who were never, or only transiently, oliguric. Renal insufficiency without oliguria probably occurred much more frequently than indicated here, but with absent or undiscovered oliguria and without obvious clinical uremia, such patients passed through the regular chain of evacuation. Potassium intoxication was usually not a serious problem in this group of patients.*

Clearance studies of renal function indicate that there is probably some measurable damage to the kidneys in almost all casualties who are severely wounded and undergo a period of hypotension.[1, 16] It is not clear whether such patients develop the same type or severity of morphologic renal lesion as that seen in the oliguric patients. The smooth frequency distribution of the duration of oliguria in surviving patients suggests that at least the functional renal lesion in oliguric patients differs only in degree of severity rather than qualitatively from that in non-oliguric patients (Fig. 2). The characteristic peak

*Patient 17 had severe hyponatremia (serum Na, 117 mEq./L.) on admission to the Renal Insufficiency Center. A concurrent potassium level of 7.3 mEq./L. was associated with marked ECG findings of potassium intoxication. Dialysis was performed at once. Further inquiry revealed renal disease in the past in which his physician recommended his taking added salt. Persistent hyponatremia required such therapy during the diuretic phase.

Table 3. Patients With Evidence of Renal Failure Without Oliguria

Pt. No.†	Type of Wound	Evacuation Time	Duration of Hypotension	Volume of Colloid Therapy	Maximum NPN (BUN) Concentration		Minimum Urine Volume		PWD of Diuresis
		hrs.	hrs.	liters	mg. % on PWD*		ml. on PWD		
17	Bilateral blast amputation of legs with extensive infection; superficial wounds; laceration of femoral vein	3. 0	5. 0	14. 3	219	8	1050	2	
24	Lacerations, inf. vena cava; 2 perforations of duodenum	3. 5	4. 0	12. 0	235**	6	915	3	
31	Perforations, hepatic and splenic flexures of colon; laceration of inf. vena cava; bruise of duodenum	2. 5	3. 0	8. 7	109***	2	500	1	2
52	Perforations, rt. and lt. lobes of liver, ascending colon, duodenum and stomach	?	?	3. 5	321	6	1000	1	
A	Bilateral traumatic amputation of legs at mid-calf, with many metal and bone fragments	2	8	9. 5	(130)	5	1100	1	
B	Perforated colon	8	8	1. 0	100	4	800	4	
C	Extensive lacerations of scalp, face, arms, left leg and back; multiple perforations of small bowel; fractures of both humeri	3	4	13. 3	85	4	1200	1	
D	Perforations of kidney, spleen, lumbar spinal canal with lower-extremity diplegia	4	?	4. 3	210	5	750	1	

†Patients 17, 24, 31, 52 from the series reported here. Patients A–D selected from experience at a forward surgical hospital.[15]
*Post-wound day.
**On PWD 3: CIn 2 mil./min.; CPAH 10 ml./min. On PWD 7: urine volume was 3600 ml., CIn 22 ml./min.; CPAH 131 ml./min.; TmPAH 27.6 mg./min.
***On PWD 3: urine volume was 1540 ml., CIn 41; CPAH 208 ml./min.; TmPAH 30 mg./min.

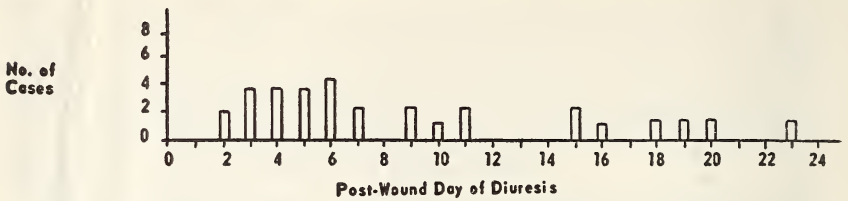

FIGURE 2. Post-wound day on which urine volume exceeded 1,000 ml./24 hours in 29 surviving patients with post-traumatic renal insufficiency.

expected on days 9 to 11 is not seen although it might have been found had a larger number of patients survived long enough for diuresis to begin.

The occurrence of (1) renal damage demonstrated by relatively sensitive clearance technics, (2) marked azotemia and occasionally clinical uremia without oliguria or with very transient oliguria, and (3) overt oliguria of varying duration among severely wounded casualties who have sustained a period of hypotension suggests that there is a regular gradation of renal damage following wounding. Attention has been largely directed toward the most marked degree of renal damage manifested by oliguria because it alone appears to require specialized treatment.

VI. Potassium Intoxication

The frequency and rapidity of potassium intoxication constitute the most important difference between the post-traumatic renal insufficiency of combat casualties and the acute renal failure usually seen in civilian practice.

Myocardial potassium intoxication occurs in the presence of hyperkalemia but its severity is not strictly correlated with the plasma potassium concentration. Potentiated by concurrent hyponatremia, hypocalcemia, and possibly other factors, its actual myocardial effect and the imminence or remoteness of fatal cardiac arrest are accurately reflected in the electrocardiogram.[35–41]

Figure 3 compares the first recorded plasma potassium concentration, corresponding to the day of admission to the Renal Insufficiency Center, with the theoretically expected value in the non-traumatized "normal" as calculated by Strauss.[42] Nine plasma potassium values fell within normal or expected limits; the low value in one of these patients may be explained by severe metabolic alkalosis due to unreplaced gastrointestinal fluid losses. Elevated initial plasma potassium concentrations were recorded in all but 6 of 51 oliguric patients and in 6 of 8 "non-oliguric" patients. In one patient a plasma potassium value of 7.5 mEq./L. was noted on the *first* post-wound day, and

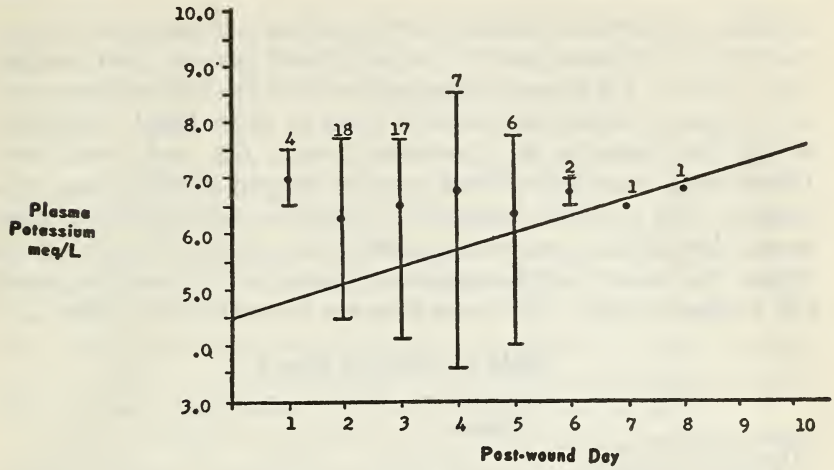

FIGURE 3. Plasma potassium concentrations on admission to Renal Insufficiency Center. Average and range of values given for the number of patients indicated in each group. Diagonal represents theoretical accumulation of 0.3 mEq./L./24 hours.[42]

concentrations exceeding 7.0 mEq./L. occurred in one-third of the patients within the first 4 days of wounding. Death from cardiac arrest secondary to potassium intoxication occurred not infrequently as early as the fourth day after injury prior to the use of the artificial kidney. All patients demonstrated electrocardiographic evidence of myocardial intoxication sometime during the course of oliguria persisting longer than 5 days.

In 20 patients with adequate records, the mean increment of plasma potassium concentration *following the initial value* (obtained on admission) was 0.7 mEq./L. per 24 hours, over twice the theoretical rate.[42] The average patient may therefore accumulate lethal concentrations of plasma potassium (9.0 mEq./L. or above) within 6 days of wounding, well before significant diuresis may be expected. Because of frequent hemodialyses, supervening diuresis, use of cation exchange resins for potassium removal and gastrointestinal losses of potassium, increments in plasma potassium concentrations following the initial values rarely reflect the true rate of catabolic potassium liberation, but rather afford a *minimum* estimate of it.

Case 1 was studied before the artificial kidney was available in Korea and illustrates the practical clinical problem:

A 20-year-old infantryman received multiple shell fragment wounds of his left arm with a severed brachial artery and damage to his median and ulnar nerves. Débridement and direct anastomosis of the brachial artery were performed 4.5 hours later at a forward surgical

hospital. Although admission blood pressure at the surgical hospital was 140/80 and pulse was 104, systolic blood pressure soon dropped below 100 mm. Hg where it remained for 12 hours before, during and after surgery despite infusion of 8 liters of whole blood. Postoperatively the patient's skin remained warm, dry and vasodilated. Thirty-seven hours later, blood pressure reached 110/70 where it remained. The left arm appeared non-viable. On the fourth post-wound day, clinical uremia appeared with stertorous breathing and stupor, the patient bled from nose and gums, mild cyanosis appeared and he died quietly. Pertinent data are summarized in Table 4.

Table 4. Data in Case 1

Post-wound Day and Time		Urine Volume	Plasma		ECG	Treatment
			NPN	K		
	hrs.	ml.	mg.%	mEq./L.		
1	0600	68	73. 8	4. 3		1000 ml. 5% D/W
2	0600	79	158	7. 5	Moderate K intoxication	1500 ml. 5% D/W
3	0600	100	220	8. 0		40 gm. cation exchange resin;* 1000 ml. 5% D/W
4	0100	179	232	8. 6		
	0800		272	8. 7	Severe K intoxication	40 gm. cation exchange resin
	1920		277	11. 2		Oxygen

*All resin used was the carboxylic exchanger SKF No. 648, furnished by Smith, Kline and French Laboratories.

Death on the fourth post-wound day in cardiorespiratory failure is felt to have been due to potassium intoxication.

There are three general reasons why potassium intoxication may occur so frequently and progress so rapidly in this group of patients:

(1) *The Breakdown of Infused Erythrocytes.* Erythrocytes contain approximately 100 mEq. of potassium per liter of cells. Figure 1 illustrates the rise of potassium concentrations in the plasma of stored blood prior to infusion into casualties in Korea.[32] The average patient in this series receiving 5.9 liters of 15-day-old blood during resuscitation received 50 mEq. of potassium in the infused plasma. Following transfusion about 10 per cent of infused red cells disappear from the circulation within the first few hours, with consequent liberation of about 30 mEq. of potassium. Destruction of infused red

cells is accelerated in the severely wounded for several days following wounding as evidenced by falling hematocrits, slight elevations of serum bilirubin and studies of red cell survival.[33]

However, an infusion of 80 to 100 mEq. of potassium may not be expected to raise plasma levels significantly since it is distributed in an exchangeable body pool of about 3,300 mEq. in a normal 70 kg. subject.[43] The potassium of infused plasma and that derived from erythrocytes of diminished viability do not produce significant hyperkalemia. This is demonstrated by eight patients who received between 6.5 and 24 liters of whole blood during resuscitation.[44] The mean plasma potassium on admission to a forward surgical hospital was 4.4 mEq./L. (range, 3.5 to 5.4); following resuscitation and surgery the mean level was 4.8 mEq./L. (range, 3.0 to 6.2).

(2) *The Breakdown of Tissue Cells.* Potassium is contained primarily in muscle cells in a concentration of nearly 160 mEq./L. of cell water. Potassium is released from this reservoir in the wounded man by destruction of tissue at the site of initial injury, in the course of secondary infection, and because of ischemia and necrosis secondary to injury of nutrient blood vessels. Tissue catabolism is accelerated by the stress of wounding and surgery, fever, starvation and the immobility imposed by bed rest, casts and painful wounds. The rate of potassium release apparently varies widely according to the nature of the wound and the amount of ischemia and infection. In a number of cases, progression of hyperkalemia seemed to be blunted by removal of a gangrenous extremity or a second débridement of a dirty wound.[45]

(3) *Electrolyte Shifts.* Especially in the presence of acidosis, movement of potassium ions from the intracellular to the extracellular fluid may further contribute to the rising plasma potassium concentration.[8, 37]

Despite the large excretory load of potassium in patients with varying degrees of post-traumatic renal insufficiency, usually only those patients who were actually oliguric developed dangerous hyperkalemia (see footnote, sec. V). This reflects the remarkable ability of the kidney to excrete potassium even when diseased.[46]

VII. Clinical Manifestations

The progressive clinical, biochemical and electrocardiographic abnormalities following acute urinary suppression and their prompt resolution with diuresis are now well recognized and will not be recounted here.[8, 37, 42] In acute renal failure following wounding this basic pattern is altered in the following important respects: (1) rates of clinical and chemical change, (2) prominent malnutrition,

loss of body weight, rapid edema accumulation, (3) severe infection, (4) impaired wound healing, (5) bleeding tendency and anemia, and (6) the incidence of hypertension.

(1) Rates of Clinical and Chemical Change

(a) *Clinical Uremia.* Anorexia, nausea, vomiting, lethargy and drowsiness attributable to uremia appeared in two-thirds of these patients by the fifth post-wound day and, as evidenced by clinical improvement following hemodialysis, as early as the second day. In several patients without intervening dialysis or diuresis, lethargy soon progressed to disorientation and coma, and death usually occurred approximately 6 days following wounding.[47]

Many manifestations of clinical uremia could often be attributed rather to the expected effects of severe sepsis, extensive wounds, reparative surgery of the chest or gastrointestinal tract, and persistent or recurrent hypotension. However, uremic symptoms usually developed in patients without such severe intercurrent processes when NPN concentrations exceeded 200 to 250 mg. per 100 cc. in the absence of diuresis.* Since these levels usually occurred by the fifth post-wound day (see below) uremia was thought also to contribute to the clinical picture in most instances, in addition to the other factors.

The clinical behavior of these patients contrasts sharply with that in cases of acute renal failure of non-traumatic origin in which uremic symptoms may appear by the sixth or seventh day and remain mild throughout the entire course.[8]

(b) *Azotemia.* Figure 4 compares the first recorded plasma NPN concentrations, corresponding to the day of admission to the Renal Insufficiency Center, on each of 52 patients with the theoretically expected value.[42] Initial values are uniformly higher than the theoretical figure. *Following the initial value*, the mean rate of plasma NPN accumulation in the entire series is 50 mg. per 100 cc. per 24 hours, four times the rate calculated by Strauss.[42] This may occur despite the therapeutic regimen described in the companion paper.[47]

The accelerated accumulation of NPN is a measure of the accelerated catabolism which characterizes these patients and corresponds to rates of clinical progression and of developing hyperkalemia and potassium intoxication (see section VI).

(c) *Hyperkalemia* has been discussed in section VI.

*Onset of diuresis was usually associated with marked clinical improvement although NPN levels continued to rise. One patient was clinically well with a massive diuresis (5 to 8 liters of urine per day) for six consecutive days during which NPN exceeded 300 mg. per 100 cc.

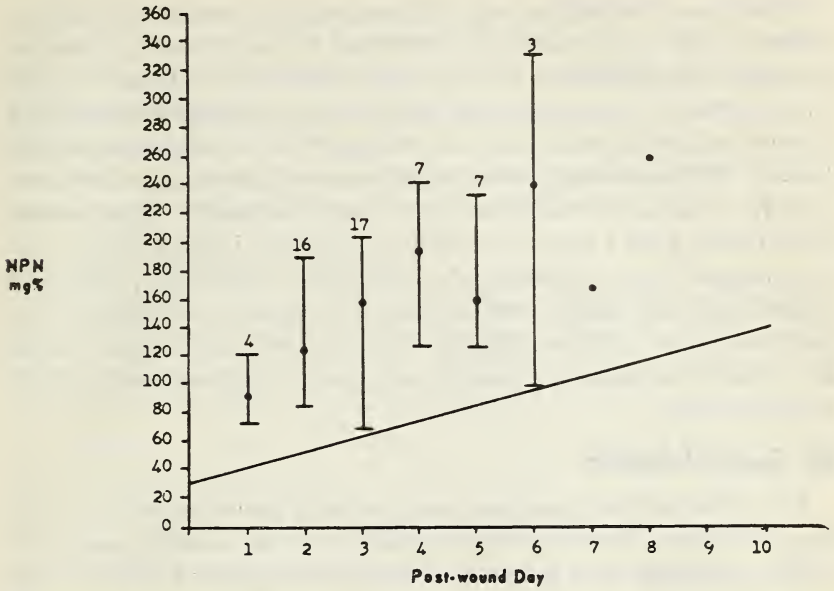

FIGURE 4. Plasma NPN concentrations on admission to Renal Insufficiency Center. Average and range of values given for the number of patients indicated in each group. Diagonal represents theoretical accumulation of 12 mg./100 cc./24 hours.[42]

(2) Malnutrition, Loss of Body Weight, Rapid Edema Accumulation

Marked wasting of both muscle and subcutaneous fat was noted in patients surviving longer than 7 to 10 days. Adequate body weight measurements not affected by changes of casts, interval amputations and large débridements are available in 16 patients. The mean body weight loss was 1 kg. per day (range, 0.5 to 1.6), clinical degree of hydration remaining approximately constant. Patients lost between 10 and 30 per cent of their admission weights during an average course of 11 days (range, 4 to 33 days). Marked fluid restriction had been enforced in these patients, and weight loss was not usually more rapid during diuresis.

Parenteral caloric intake varied between 100 and 1,000 calories per 24 hours. Oral or intragastric intake was only rarely possible but permitted 1,000 to 2,500 calories per 24 hours during the oliguric phase. All caloric intake was sharply curtailed by necessary volume restriction, ileus or direct injury to the gastrointestinal tract. Caloric intake was thought to be insufficient in all instances despite vigorous efforts to increase it.

Accelerated catabolism was demonstrated in several striking instances when peripheral edema developed in the presence of positive non-colloid fluid balances not exceeding 400 ml./day. It was thought that, relative to tissue mass, the body water pool gained volume at a rate exceeding the combined rates of insensible, sweat and other fluid losses. With restricted intake, such increments in volume could arise only from the preformed water and water of oxidation of the catabolized tissue, with a small contribution from the infused glucose. It is concluded that conventional replacement allowances (measured water losses plus 750 to 1,000 ml./day) are excessive for patients with post-traumatic renal insufficiency. In any event, fluid balance should be adjusted on clinical grounds, not made to approximate a fixed, empiric value.

(3) Severe Infection

Penicillin and streptomycin were routinely given beginning on the day of injury. Broad-spectrum antibiotics were usually substituted within 5 days in most patients. Despite liberal use of antibiotics in patients whose renal antibiotic excretion was undoubtedly impaired, fever, leukocytosis, pulmonary and/or wound infection regularly occurred as is shown in Table 5. Whether the blood or tissue antibiotic concentrations achieved exerted any harmful effects could not be evaluated in this group of patients.

Table 5. Incidence of Infection on Patients With Post-traumatic Renal Insufficiency

Data	No. Patients with Adequate Records	No. Patients Affected	Per Cent Patients Affected
1. Site of infection			
a. *Wound*, including peritonitis or empyema in missile tract	45	38	84
b. *Pulmonary*, including purulent tracheal secretions; lung and pleura not in missile tract	39	30	77
2. Fever	39	37	95
3. Leukocytosis*	38		
a. 10—20 thousand/cu. mm.	15		
b. 20—30 " "	16		
c. Over 30 " "	7		

*Highest recorded value during course.

Peritonitis and/or empyema (localized or generalized) were found in 16 or roughly one-third of patients with adequate records. An additional 10 patients had extensive infection of buttock or extremity wounds necessitating either reamputation or repeated débridement. Evidence of massive infection was the prominent finding at autopsy and was thought to be the main cause of death in the majority of fatal cases after the artificial kidney became available.[47]

(4) Impaired Wound Healing

Granulation tissue appeared in some open wounds between the fifth and tenth post-wound days, but never in areas of infection and necrosis. Failure to slough necrotic tissue and establish a clean, granulating surface by the tenth post-wound day was taken to indicate impairment in the reparative process. Dehiscence of incisions and of vascular and even intestinal anastomoses provided another index. Dehiscences were thought to be rare in the general casualty population.[48]

In this group of patients, absence of granulation and of healing of open wounds was noted beyond 10 days in 16 of 24 records with specific data. Dehiscence of one or another type occurred in 9 instances or 16 per cent of 55 adequate records. In the absence of histological studies, the true incidence of delayed capillary and fibroblastic proliferation in the healing wound sites cannot be stated, nor can the relation of these to infection, anemia, azotemia, electrolyte imbalance, edema and nutrition be established.

(5) Bleeding Tendency and Anemia

Bleeding from the gastrointestinal tract, ecchymoses in skin, mucous and serous membrances, or epistaxis *unrelated* to trauma or unhealed surgical lesions was recorded in 15 or 27 per cent of 55 patients. In two patients with serious bleeding, bleeding time, clotting time and platelet counts were normal; in two additional patients the prothrombin time was prolonged in one, normal in the other. The use of heparin during hemodialysis accelerated bleeding in only two instances. Bleeding occurred on days prior to hemodialysis and in patients not subjected to the procedure.

Low and falling hematocrits irrespective of bleeding occurred in all patients surviving for 7 days or longer. In four patients hematocrits failed to rise significantly after whole blood transfusions even in the absence of, or with minimal amounts of blood loss. Frequent blood transfusions in an attempt to support blood pressure, wound healing and nutrition rendered pertinent studies impractical.

(6) The Incidence of Hypertension

Blood pressures of 140/90 mm. Hg or above were recorded in 85 per cent of 42 patients with adequate records during the course of acute renal failure. In 70 per cent, hypertensive blood pressure levels were recorded within the first four post-wound days. Most of the remaining patients who did not develop hypertension harbored severe wound infections, empyema or peritonitis. The average maximum blood pressure on the sixth post-wound day was 160/99, although readings of 180–200/100–110 were not infrequent. The clinical course was not apparently affected by the occurrence or degree of hypertension. These findings confirm observations in World War II[1, 4] in which hypertension was uniformly noted in patients with acute renal failure. Elevated levels of blood pressure were also recorded in two-thirds of the patients studied by Swan and Merrill.[8]

Case 2 illustrates several of the foregoing features. Daily urine output, NPN, potassium and hematocrit values are presented in Figure 5.

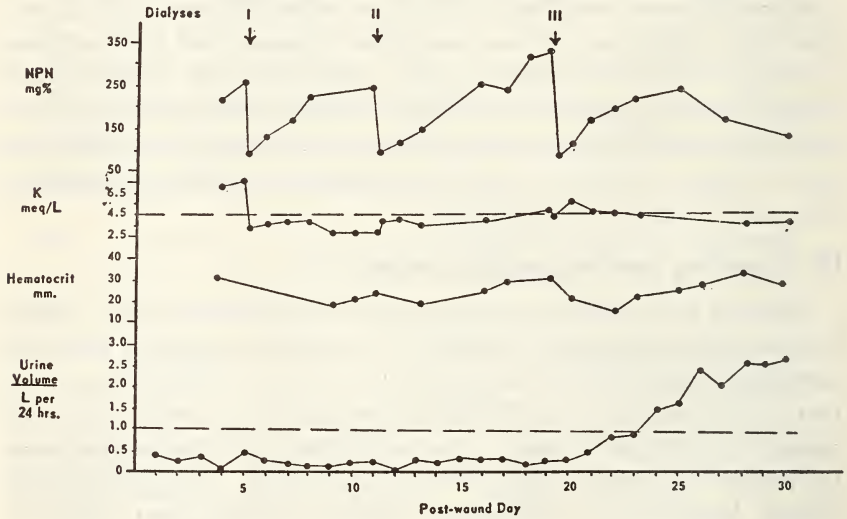

FIGURE 5. Data in Case 2.

A 27-year-old infantryman sustained traumatic amputation of his right leg at the knee with multiple penetrating wounds of both buttocks and right arm in a land mine explosion. Evacuation required 5 hours during which 100 ml. albumin was given. Blood pressure was unobtainable by auscultation on admission to the forward surgical hospital. At surgery, severed vessels were ligated, a traumatic rectovesical fistula was discovered and repaired, and a diverting colos-

tomy established. Hypotension persisted for 16 hours and 3.6 liters of whole blood was used. Oliguria persisted on the third post-wound day and evacuation to the Renal Insufficiency Center was accomplished on the fourth.

Diuresis occurred on the twenty-third post-wound day, the most prolonged oliguria of any surviving patient. Although potassium intoxication occurred only prior to dialysis I, it is doubtful whether this patient could have survived the recurrent clinical uremia without repeated hemodialyses. Response of appetite, mental awareness and ability to cough was dramatic after dialyses I and II, less so after dialysis III. Infection was evident: A persistent cough productive of purulent sputum and a deeply-lying abscess in the right popliteal fossa were noted on the fourth post-wound day. Both infection and impaired wound healing were apparent on the twentieth post-wound day when the left leg wound was found to have necrotic skin flaps; some granulation tissue was noted in uninfected areas. On the twenty-fourth day urine appeared in the buttock wound indicating probable dehiscence of the retrovesical repair site. Wounds seemed improved on the twenty-eighth day and were granulating well by the thirty-third day. Epistaxis on the tenth post-wound day and melena between the twentieth and twenty-fourth days suggested a bleeding tendency since the patient sustained no facial or gastrointestinal wounds proximal to the colostomy. The hematocrit remained low in spite of 8 liters of transfused whole blood between the ninth and thirty-first post-wound days. All transfusions were well tolerated. A weight loss of 17 kg. or 32 per cent of admission body weight occurred in 34 days, despite oral food intakes after dialyses and parenteral allowances exceeding 400 calories daily. Generalized peripheral edema is recorded on the nineteenth day; preceding average positive measured fluid balance did not exceed 500 ml. per day.

VIII. Summary

Post-traumatic renal insufficiency is important as a cause of illness and death in initially surviving combat casualties and may be seen in civilian medical practice after accidents or extensive surgery. Hypotension appears to be a primary etiological factor although delay in therapy, inadequate blood replacement, increase in plasma hemoglobin and other pigments, and the severity of the wound may contribute to the extent of renal damage and to the hypotension itself. Impairment of renal function following trauma may be reflected in different patients by sensitive clearance tests only, by azotemia and decreased urinary concentrating ability, by transient oliguria, or by marked oliguria of varying duration. This suggests a wide variabil-

ity in the extent of functional and parenchymal renal injury. With few exceptions, only the oliguric patients develop sufficient electrolyte abnormality or clinical uremia to require special care. In the latter instances rapidly progressive potassium intoxication necessitates prompt evacuation to a treatment center and, in the patients reported here, was the major cause of death prior to the use of hemodialysis. In addition to potassium intoxication, evidence that accelerated tissue catabolism characterizes post-traumatic renal insufficiency is found in (1) rapidly developing clinical uremia with corresponding rates of NPN accumulation, (2) early signs and marked degree of weight loss and emaciation, and (3) edema formation on less than conventional fluid intake allowances. The contrast with acute renal failure of non-traumatic origin has been repeatedly emphasized. Frequently occurring extensive and progressive infection, impaired wound healing and a marked bleeding tendency in some patients complicate the clinical course and intensify the therapeutic challenge.

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In addition to those mentioned in the Introduction to this volume, the authors wish to acknowledge the vital contributions made to this study and the operation of the Renal Insufficiency Center by the Surgeons, USAFFE and Eighth Army, Korea; the Center laboratory staff, especially Cpl. Burton F. Pease and Pfc. John T. Mackemull; the nurses and medical technicians of the 11th Evacuation Hospital under Capt. Mary Wilborne, ANC, Capt. Alice Service, ANC, and Lt. Anna Smyth, ANC; the Hospital laboratory staff under Lt. Robert P. Gibb, MC; and by the many officers and men of the chain of casualty evacuation to whom the patients who survived also owe their lives.

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Chapter 3

Post-traumatic Renal Insufficiency in Military Casualties II. Management, Use of an Artificial Kidney, Prognosis*

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During the past few years there has been widespread interest in the treatment of acute renal failure of diverse origins by medical management alone,[1, 2] or by the added use of some means for reversing the chemical changes of uremia, such as the artificial kidney,[3] peritoneal lavage,[4] and gastric or intestinal lavage.[5] The majority of uncomplicated cases of acute renal failure can be successfully maintained until the onset of diuresis by carefully avoiding overhydration and providing sufficient calories to minimize protein catabolism. The artificial kidney has found its chief use in civilian medicine as an adjunct to medical management, occasionally life-saving in cases of spontaneous potassium intoxication or severe uremic intoxication.[5]

Patients with renal insufficiency following trauma present special problems in management because clinical uremia, high levels of azotemia and kalemia, and myocardial potassium intoxication develop rapidly.[6] Conventional methods of therapy are frequently insufficient to limit the rapid progression of uremia either in civilian practice [7] of in battle casualties. A mortality rate of approximately 80 to 90 per cent was found in casualties with post-traumatic renal insufficiency in World War II [8] and in the Korean War (see below). Because of this excessive mortality rate a Renal Insufficiency Center was established in Korea in an attempt to improve the therapeutic results. An evaluation of the Brigham-Kolff artificial kidney in post-traumatic renal insufficiency was carried out at this center.

Organization of Renal Insufficiency Center

Through the cooperation of the Eighth Army a Renal Insufficiency Center was established at a large evacuation hospital in central Korea

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about 70 miles from the front. The importance of such a location is the accessibility within helicopter range of the forward hospitals, where most of the cases of post-traumatic renal insufficiency occur. The average period of time between wounding and arrival at the center was 3.2 days in the 51 patients admitted during 1952.

Patients who survived remained at the Renal Insufficiency Center until diuresis and sufficient recovery made it possible for them to reenter the regular chain of evacuation safely. A laboratory capable of carrying out all of the usual clinical chemistries was established. The chemical methods used have been listed in the accompanying paper.[6] A Brigham-Kolff type of artificial kidney was utilized, consisting of a partially submerged rotating drum with a continuous helically wound cellophane tube of approximately 20,000 sq. cm. surface area. The technic of operating this type of artificial kidney has been described in detail.[9] The usual dialysis was carried out for 6 hours at a blood flow rate of 250 to 350 cc./minute. Occasionally when hyperkalemia was the only indication, dialysis was limited to 3 or 4 hours.

Medical Treatment

The principles of the medical management of acute renal failure have been well described elsewhere.[1, 2] Within the limitations imposed by the severity of the wounds in this group of patients, these principles were followed as outlined below:

1. Oliguric Phase

(a) *Fluid Restriction.* Fluid intake was initially restricted to a maximum of 600 to 800 cc. per 24 hours (a rough estimate of insensible loss) plus the estimated loss of urine, drainage from wounds, and gastric or intestinal suction. The presence of fever, sweating and an unknown amount of endogenous water production from catabolism limited the accuracy of the fluid balance. Careful daily weights taken on a stretcher-type bedside balance were of great value as a check on fluid requirements. An attempt was made to maintain a steady decrease in body weight throughout the oliguric period. A marked loss of body mass occurs during the catabolic phase of acute renal failure, which is often masked by fluid retention until after diuresis.[10] A program to produce a gradual decline in weight rather than maintenance of the initial weight during the oliguric phase of acute renal insufficiency prevents a "relative overhydration." During their care at the Renal Insufficiency Center almost all of the patients required repeated transfusions or underwent such surgical procedures as ampu-

tations or débridements. This placed restrictions on the over-all reliability of daily weights as an index of fluid balance.

(b) *Caloric Intake.* The end-products of carbohydrate and fat catabolism are CO_2 and H_2O, both of which can be eliminated by way of the lungs. Protein catabolism imposes the main excretory burden on the kidneys. With the loss of protein there is also loss of other intracellular components, especially potassium. Although the uremic syndrome cannot at present be related to a specific chemical change, the severity of uremic symptoms appeared to vary approximately with plasma NPN concentrations during oliguria. Suppression of protein catabolism by supplying carbohydrate and fat to the metabolic pool should therefore be attempted. Gamble demonstrated that 100 gm. of glucose would prevent ketosis and reduce the negative N balance by 50 per cent in normal fasting men.[11] An increase of carbohydrate intake to 200 gm. did not produce a further significant reduction in protein catabolism. An attempt was therefore made to supply at least 100 gm. of glucose per day, giving the daily basal fluid requirement as 15 per cent glucose in a peripheral vein. Repeated observations of profound tissue wasting led to increased use of 50 percent dextrose infused into cannulated major veins. Seventy-one per cent of the patients treated at the Renal Insufficiency Center had abdominal wounds, which restricted attempts to force orally high caloric regimens. Oral feeding was instituted as soon as possible in all cases.

(c) *Treatment of Acidosis, Hyponatremia and Hypochloremia.* Hyponatremia and hypochloremia were already in evidence in the majority of the 51 patients at time of admission to the Renal Insufficiency Center, an average of 3.2 days after wounding. The average admission plasma values were sodium 133 mEq./L. (range of 113 to 164), chloride 87 mEq./L (62 to 108), and carbon dioxide 24.2 mEq./L (14.8 to 43.4). The subsequent values of sodium, chloride and carbon dioxide varied markedly depending on the treatment. Despite rigid fluid restriction, there was a general tendency toward further decreases in plasma sodium and chloride during the oliguric period suggesting intracellular shifts or progressive hydration from endogenous water production. The plasma values were usually returned to normal during dialysis with the artificial kidney, as will be discussed below. Because of the danger of producing pulmonary edema, hypertonic saline was given only as necessary to reduce the toxicity of a concurrent hyperkalemia and to raise plasma sodium levels which had fallen below 115 to 120 mEq./L. There was usually a gradually increasing metabolic acidosis during the oliguric period, reflecting the retention of fixed acids. Here also treatment with sodium lactate or

sodium bicarbonate was usually given only if acidosis was severe (CO_2 combining power below 12 to 15 mEq./L.). Occasionally metabolic alkalosis secondary to gastric suction was found on admission and in one patient required ammonium chloride therapy. Treatment with the artificial kidney invariably returned the acid-base balance toward normal, although this reversal was seldom complete.

(d) *Treatment of Anemia.* A progressive anemia is a frequent finding in acute renal failure of any origin. Although the mechanism is not entirely understood, it seems probable that both decreased blood formation and increased blood destruction occur during uremia.[10] The picture is complicated in the present series of patients by the large amounts (average of 6 liters) of relatively old (2 weeks) type O blood which they had received during resuscitation. A study of the limited survival time of this blood is presented in another paper from the Surgical Research Team.[12] In addition, recurrent bleeding from various sites in these patients required large amounts of blood for replacement purposes.[6] Despite the fact that their admission hematocrits averaged 40 per cent, the 51 patients in this series required an average of 4,950 cc. (range 0 to 13,000 cc.) of fresh, type-specific blood during an average period at the Renal Insufficiency Center of 12.9 days (3 hours to 33 days). In the first patients transfusions were rarely given electively for a moderate reduction in hematocrit because of the danger of pulmonary edema. When wound healing was a problem, however, packed red cell transfusions were given with increasing frequency to maintain the hematocrit in excess of 35 per cent. These were well tolerated. It was noted on several occasions that patients could tolerate large amounts of blood during and immediately following hemodialysis, despite having previously developed pulmonary edema during the infusion of much smaller volumes of blood.

(e) *Treatment of Hyperkalemia.* The frequency of hyperkalemia and the rapidity with which it developed in this group of patients have been presented in the accompanying paper (ch. 2).[6] Plasma potassium values were measured daily or oftener if they seemed to be rising rapidly. Electrocardiographic tracings were usually obtained at the time of potassium analysis on all patients with significant elevations of plasma potassium, and were relied upon to estimate the seriousness of the medical emergency.

The physiological antagonism between extracellular potassium and sodium or ionized calcium was employed in the emergency treatment of acute potassium intoxication. Hypertonic saline (200 to 400 cc. of a 3 to 5 per cent solution) was given if the plasma Na was below normal. The use of calcium in the treatment of hyperkalemia received a much more thorough evaluation at the Renal Insufficiency Center during

the 6 months following the period covered in the present report, and will be presented in a separate communication.[13] Also in the treatment of acute hyperkalemia large amounts of 50 per cent glucose and insulin (1 unit per 2 to 3 gm. glucose) were given intravenously, to reduce extracellular potassium by inducing its intracellular deposition with glycogen.[14] These measures were temporarily effective at best and were usually followed within a few hours by emergency dialysis on the artificial kidney.

An ammonium carboxylic cation exchange resin* was used both in the treatment of acute potassium intoxication and in an attempt to maintain normal potassium levels after hemodialysis. A dose of 25 gm. of resin as a 10 per cent suspension in water was usually given once or twice daily by retention enema or in divided doses over several hours orally. The high incidence of abdominal wounds (71 per cent) served as a serious limitation on the usefulness of the resins in the group of patients who were the most severely wounded. The use of the resin in the treatment of acute potassium intoxication was disappointing. The plasma potassium levels usually remained elevated or even rose despite the use of the resin in the early phase of the clinical course. In the absence of severe abdominal wounds, when the resin could be regularly employed, it seemed of considerable value in preventing a secondary rise in plasma potassium after normal values had been established by hemodialysis.[15]

The use of the artificial kidney in the treatment of hyperkalemia will be discussed in the following section.

2. Diuretic Phase

The beginning of diuresis (600 cc. of urine per 24 hours) by no means marks the ends of the therapeutic problems. In the present series one-third of the deaths (9 out of 27) occurred after the onset of diuresis. Several days of diuresis were usually required to bring about significant chemical and clinical improvement. Because of this delayed response, 7 of the 72 dialyses with the artificial kidney were carried out after the onset of diuresis. Fluids were given in proportion to the degree of diuresis, but no effort was made to maintain a constant weight. Most patients lost weight at the time of diuresis, indicating a previous overhydration despite rigid fluid restriction. Urinary sodium was measured and was partially but not quantitatively replaced. As emphasized by Swan and Merrill,[10] quantitative replacement of the sodium loss during the early diuretic phase is not necessary and may prolong diuresis. No patient developed clinical or chemical sodium

*SKF #648. This was kindly supplied to us by the Smith, Kline, and French Laboratories.

depletion during this phase. The hypernatremia-hyperchloremia syndrome described by Luetscher and Blackman [17] was not observed in this series. Most of the deaths during the diuretic phase were attributable to complications of wounding, as will be discussed below.

The Use of the Artificial Kidney

1. Number of Dialyses and Indications

Dialyses with the artificial kidney were carried out 72 times in 31 of the 51 patients treated at the Renal Insufficiency Center. The artificial kidney was not used in 20 patients for a variety of reasons, such as relative mildness of the uremia, or early death from the complications of the attending wounds. This will be considered later under the discussion of prognosis. The number of treatments received by the individual patients varied from one to six: 1 dialysis, 9 patients; 2 dialyses, 10 patients; 3 dialyses, 9 patients; 4 dialyses, 1 patient; 6 dialyses, 2 patients.

Figure 1 presents the time distribution of the dialyses following wounding. Also shown are the primary indications for the individual dialyses—hyperkalemia, 29 dialyses; marked uremia without significant hyperkalemia, 22 dialyses; or marked uremia accompanied by hyperkalemia, 21 dialyses. This classification of the indications is somewhat arbitrary, but demonstrates the trend toward early devel-

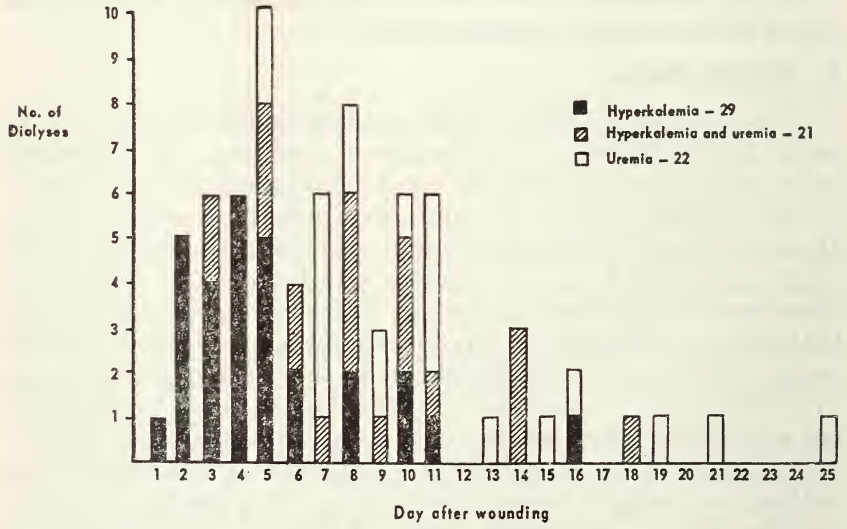

FIGURE 1. Time distribution and primary indications for 72 dialyses with the artificial kidney in the treatment of 31 patients.

opment of potassium intoxication. One patient required dialyses for hyperkalemia on the first day after being wounded.

The indications for use of the artificial kidney at the Renal Insufficiency Center were not rigidly defined, but depended on clinical judgment in each case. In general, dialysis was carried out if ECG evidence of myocardial intoxication was marked. Dialysis was almost always carried out if the plasma potassium value was greater than 7.5 mEq./L., since definite ECG changes of myocardial potassium intoxication were then invariably present. The average plasma potassium values at the time of dialysis in both the groups termed "hyperkalemia" and "uremia plus hyperkalemia" were 7.1 mEq./L. It is realized that plasma potassium values of less than 9.0 mEq./L. are seldom fatal. The decision to carry out dialysis in the plasma potassium range of 6.5 to 7.5 mEq./L., even with ECG changes limited to the T wave alone, was based on the observed rapidity with which plasma potassium rose in this series of patients and the usual concomitant presence of hyponatremia and hypocalcemia. Early in this experience, before the establishment of the Renal Insufficiency Center, plasma potassium rose from 8.0 mEq./L. to a fatal level of 11.2 mEq./L. within a day in one patient, despite the use of cation exchange resins. Another patient died in cardiac arrest after his plasma potassium rose from 6.1 mEq./L. to 9.1 mEq./L. within a single day. It was thought advisable, therefore, to carry out dialysis electively at relatively low levels of hyperkalemia to diminish the risk of acute elevations in extracellular potassium concentration and consequent myocardial intoxication.

Twenty-two of the dialyses were carried out for uremia without significant hyperkalemia and 21 dialyses for uremia accompanied by hyperkalemia. At the time of treatment the average NPN values in these two groups were 275 mg. per 100 cc. and 308 mg. per 100 cc. respectively. A decision for the use of the artificial kidney was not based on the level of azotemia, which in one patient was allowed to rise to 504 mg. per 100 cc., but on the severity of the clinical signs and symptoms of uremia, especially clouding of consciousness with inability to clear tracheal secretions by coughing, marked nausea and vomiting with restriction of caloric intake, signs of neuromuscular irritability, and dyspnea. On several occasions dialyses were carried out with milder degrees of uremia or hyperkalemia to prepare an oliguric patient for a major surgical procedure, such as an amputation or extensive débridement.

2. Results of Treatment With the Artificial Kidney

The chemical results of an uncomplicated, 6-hour dialysis in the treatment of uremia can be predicted with reasonable accuracy. The plasma sodium, potassium and chloride concentrations return to nor-

mal levels, if there is an initial abnormality. The CO_2 combining power, as an index of acidosis, returns toward but does not usually attain a normal value. The NPN level is usually reduced to 75 mg. per 100 cc. to 125 mg. per 100 cc., depending on its initial value and the flow rate of blood maintained through the artificial kidney. The average changes in blood chemistries for the 72 dialyses are shown in Table 1.

Table 1. Average Chemical Results of Dialysis With the Artificial Kidney (Average duration of the 72 dialyses—5.3 hours)

	NPN mg. %	K mEq./ L.	Na mEq./ L.	Cl mEq./ L.	CO_2 mEq./ L.
1. Total dialyses—72					
Before	246	6. 5	135	92	17. 2
After	108	4. 3	138	105	21. 4
2. "Hyperkalemia dialyses"—29					
Before	191	7. 1	132		
After	93	4. 3	139		
3. "Hyperkalemia plus uremia dialyses"—21					
Before	308	7. 1	138		
After	123	4. 4	141		
4. "Uremia dialyses"—22					
Before	275	5. 0	143		
After	120	4. 1	141		

The clinical results of treatment with the artificial kidney are not as easy to appraise. Occasionally there was clinical improvement during the course of the dialysis as shown by an objective clearing of consciousness or decrease in dyspnea, or a spontaneous statement from the patient that he felt much improved. Maximal clinical improvement was usually noted in 12 to 24 hours after treatment, and was particularly evident in loss of nausea and vomiting, a return of appetite, a clearing of consciousness and a decrease in dyspnea. The subjective improvement was sometimes of such a degree that several patients requested another dialysis after the return of uremic symptoms during continued oliguria. Noted previously was the fact that patients were often able to receive transfusions of whole blood during and soon after dialysis without respiratory distress, although smaller amounts of blood given prior to treatment with the artificial kidney led to dyspnea and early pulmonary edema. Not all of the patients treated with the artificial kidney demonstrated noticeable clinical improve-

ment despite the usual chemical changes. This clinical refractoriness was found only in patients with unusually severe wounds or complications of wounds.

The results of treatment with the artificial kidney in terms of survival value will be discussed under prognosis.

3. Complications of Dialysis

The use of the artificial kidney is not without risk, especially in such a group of desperately ill patients. Operational difficulties in the dialyses, such as the development of a leak in the dialyzing membrane, or clotting of blood in the return reservoir, were rare and did not seriously affect the completion of dialysis. The complications observed in the patients were:

(a) *Hypertension.* A progressive hypertension has been previously described as occurring in 10 to 15 per cent of dialyses.[3] The hypertension does not invariably occur and cannot be predicted in the individual case. Its cause remains obscure. Excluding dialyses complicated by excessive bleeding and transfusions, in 14 of 49 dialyses without initial hypertension (BP less than 150/90) there was a significant rise of blood pressure from a mean initial value of 135/74 to a mean maximal value of 215/109. In one patient the blood pressure rose from an initial level of 180/100 to 270/130 mm. Hg. The elevation of blood pressure usually occurred progressively, beginning after 1 or 2 hours of treatment with the artificial kidney. Occasionally Apresoline (℞) was used to lower or prevent further elevations of blood pressure. No clinical complications could be attributed to this hypertensive effect of dialysis in the present series of patients. In several patients with hypotension at the start despite repeated transfusions, blood pressures rose and became stabilized during dialysis.

(b) *Periods of Hypotension.* Blood pressures less than 100/60 were recorded in 12 of 72 dialyses, excluding those patients who were hypotensive before entering the operating room. The fall in blood pressure usually occurred during cannulation of the artery and vein under local Procaine (℞) anesthesia, or during the early period of dialysis when flow through the artificial kidney was being established. Response to transfusion was rapid in most cases with a return to normal blood pressure. Hypotension occurring during dialysis was usually related to bleeding from the patients' wounds, and responded to transfusion.

(c) *Bleeding.* Many of the patients who received treatment with the artificial kidney had been severely wounded within 72 hours prior to dialysis, followed by extensive, reparative surgical procedures.

Furthermore, during their treatment at the Renal Insufficiency Center approximately one of every four patients had bleeding episodes unrelated to previous trauma, such as cutaneous ecchymoses, epistaxes and bleeding from the gastrointestinal tract. During dialysis, intravenous heparin, 50 to 120 mg., was given to prevent the blood from clotting during its circulation through the artificial kidney and return reservoir, a period of approximately 2 minutes. The occurrence of hypertension during dialysis has been described above. With this combination of predisposing factors it was anticipated that hemorrhage would be the major complication of dialysis in such a series of recently wounded soldiers. It is therefore surprising that only two patients exhibited bleeding of sufficient degree to cause hypotension and necessitate stopping the dialysis. Brisk bleeding from a wound involving the rectum and urethra in one patient was controlled by packing and the use of protamine sulfate intravenously. The second patient had extensive wounds of the liver, right kidney, diaphragm and jejunum. Three days before dialysis, on the thirteenth day after wounding, an emergency laparotomy had to be performed to control bleeding from the hepatic wounds. During the night prior to dialysis 5 pints of whole blood where required to maintain blood pressure because of bleeding from the abdominal wound and liver. Because of severe uremia and potassium intoxication dialysis was carried out on the sixteenth day after wounding. There was exacerbation of bleeding during the procedure requiring repeated transfusion. The patient died in shock 16 hours after dialysis. Some oozing of blood was frequently seen from open débrided wounds, amputation stumps, and the cutdown sites for cannulation of the artery and the vein. This was easily controlled, however, without interfering with completion of dialysis. Sites from which bleeding could be anticipated were usually packed before beginning the procedure.

(d) *Fever.* In 55 per cent of the dialyses the oral or axillary temperature rose above 100° F from a previously normal value, and rarely (5 times) the temperature reached 103 to 104°. During six dialyses shaking chills were observed, with no evidence of hemolysis. The fever was probably related to pyrogenic contamination of the water supply obtained under field conditions. This represents a much higher rate of febrile reactions than that observed under more ideal operating conditions.

Surgical Management

A detailed description of the surgical management of these patients cannot be presented here. In practice, however, the limiting factor in survival for most patients was the severity of the initial wound and its subsequent complications (see below), rather than renal damage

per se. Radical débridement of wounds, early amputation of areas of gangrene, and continued careful search for localized infection subject to drainage were of the utmost importance in patients with reduced renal function. On a number of occasions the rapid progression of uremia was blunted by the discovery and drainage of an abscess or amputation of a mangled extremity. Also of great practical importance was the frequency of pulmonary complications. In these patients with malnutrition, weakness, clouding of consciousness and nausea over periods of 1 to 3 weeks, atelectasis and bronchopneumonia were constant hazards. Tracheal suction, the use of a Stryker frame, and even tracheotomy were sometimes necessary to maintain adequate pulmonary function.

Prognosis

1. Control Mortality (prior to the arrival of the artificial kidney)

Military casualties with post-traumatic renal insufficiency represent a special problem in therapy. The prognosis is much less favorable in general than in the less complicated civilian patients with acute renal failure. In World War II a mortality rate of 91 per cent was found in casualties who developed oliguria of less than 100 cc. per day.[8] On arrival in Korea a survey of the forward hospital units was carried out by the Surgical Research Team to determine the incidence and mortality rate of post-traumatic renal insufficiency among the military casualties. It was found that during the preceding 3 months approximately 50 oliguric patients were treated at these hospitals with a mortality rate of 80 to 90 per cent. During the same period of time Moots reported the death of 8 in 9 patients with post-traumatic renal insufficiency at a single forward hospital.[16] Before the artificial kidney was available and the Renal Insufficiency Center was established in Korea, 10 casualties with acute renal failure were treated under the supervision of the Surgical Research Team using the medical regimen discussed above. Eight of these ten patients died, with an average survival time of 6.8 days after wounding. Although these "control" groups are not as large or as strictly comparable as might be wished, it seems likely that the mortality rate of post-traumatic renal insufficiency with oliguria in military casualties approximates 80 to 90 per cent even in patients receiving an intensive medical program. Many of the deaths, however, are not due to uremia per se, but to the severity of the attending wounds, as will be discussed below.

2. Mortality Rate at Renal Insufficiency Center

During the last 8½ months of 1952 fifty-one patients with post-traumatic renal insufficiency were treated at the Renal Insufficiency Center. Thirty-one of the patients (61 per cent) received one or more dialyses with the artificial kidney, with an average of 2.3 dialyses per patient. Twenty-one of these 31 patients (68 per cent) died, with death occurring at an average time interval of 12.4 days after wounding. Of the 20 patients who were treated without the use of the artificial kidney, 6 died, a mortality rate of 30 per cent. It is to be emphasized that this group of patients in no way represents a control for those treated by dialyses. Only those with the least severe cases of acute renal failure, without marked uremia or dangerous hyperkalemia, were treated by medical management alone. The six patients who died in this medically treated group were found clinically and at autopsy to have either overwhelming infection or hemorrhage, rather than uremia, as the cause of death. The combined mortality rate for the 51 patients was 53 per cent. This is the figure of greatest significance in evaluating the over-all effectiveness of the Renal Insufficiency Center. Table 2 summarizes these mortality figures and includes a summary of the other available figures for comparison.

3. Cause of Death

Approximately two-thirds of the patients with post-traumatic renal insufficiency who were treated with the artificial kidney died. Despite the efficacy of dialysis in returning the chemical abnormalities toward normal and usually in improving the signs and symptoms of uremia, these patients died within a time interval varying from 5 to 28 days after wounding. In almost every case death was attributable to some complication of the initial wound, such as infection or secondary hemorrhage. Six illustrative cases have been listed in Table 3.

Table 2. Summary of the Mortality Rates and Survival Times of Military Patients With Post-traumatic Renal Insufficiency in This and Other Series

Patients	Lived	Died	Mortality Rate	Av. Survival Time after Wounding of Patients Who Died
(1) Renal Insufficiency Center				
Treated with Art. Kidney	10	21	68%	12.4 days
Treated without Art. Kidney	14	6	30%	10.3 days
Total Group	24	27	53%	12.0 days
(2) "Control Cases"	2	8	80%	6.8 days
(3) Cases of Moots [16]	1	8	89%	?
(4) Survey Cases of the Surgical Research Team	approx. 50–60 cases		ca. 80–90%	?
(5) World War II [8] *	3	30	91%	43% within 5 days 91% within 10 days

*These figures are for those patients with "anuria," i. e., less than 100 cc. urine on at least one day and in general the severest cases of post-traumatic renal insufficiency. Their over-all mortality rate for "oliguria" (65%) cannot be used here because the group contained all patients with less than 600 cc. of urine for a single day. At least 35% of these transiently oliguric patients did not develop NPN's greater than 65 mg. per 100 cc. and would not have been included in the other comparative series.

Table 3. Causes of Death in Six Patients Who Died Despite Treatment With the Artificial Kidney (An autopsy was performed in each case)

Case	Initial Wound	No. of Dialyses	Day of Death	Cause of Death
4	Abdominal injury by penetrating missile with surgical removal of spleen and left kidney, repair of the stomach, gallbladder and jejunum, and colostomy for perforation of the transverse colon.	3	15	Peritonitis, gangrene of a segment of jejunum. Shock following extensive bleeding from the wound of exit and from the infarcted bowel.
5	Concussion and contusion of abdomen in a truck accident with rupture of spleen and right kidney, tear of duodenum and avulsion of common bile duct from it, tear of portal vein. Spleen and right kidney were removed at operation and duodenum and portal vein repaired.	3	16	Portal vein thrombosis with ascites and hemorrhagic colitis and ileitis. Peritonitis and a small subhepatic abscess.
8	Shrapnel wounds with extensive laceration and destruction of the liver, fracture of two ribs and a compound fracture of the right arm. Multiple small wounds of both legs.	3	9	Patient died in irreversible shock with hemorrhage into and necrosis of the right lobe of the liver and a bile peritonitis.
18	Shrapnel wound penetrating sacrum with laceration of rectum and retroperitoneal hematoma. Multiple wounds of legs, later requiring amputation of the right leg below the knee. At the initial operation, the rectum was repaired and a colostomy performed.	2	5	Patient developed irreversible shock despite vigorous transfusion with fresh cross-matched blood. It was felt that the extensive grossly infected wound involving the left buttock and sacrum and extending into the pelvic cavity contributed largely to his shock.

Table 3—Continued

Case	Initial Wound	No. of Dialyses	Day of Death	Cause of Death
24	Shell fragments caused laceration of the right diaphragm, liver and shattering of the right kidney. A nephrectomy was done and repair of the diaphragm and liver carried out.	4	25	Death seemed attributable to infection—with empyema, bronchopneumonia, atelectasis, and a pneumothorax. Progressive diuresis never occurred during this long course, although the urine volume reached 1,200 cc. on one day.
27	Penetrating wound of right lower chest with lacerations of the liver, gallbladder, duodenum, and pancreas. Gallbladder was removed and the other lacerations repaired.	1	14	Patient had only 1 dialysis for hyperkalemia (8.4 mEq./L.). Diuresis occurred on the 7th day and was going well when there was death from abdominal hemorrhage secondary to separation of the duodenal laceration and from a penetrating ulcer of the stomach.

Illustrative Cases

The following two case histories are presented to illustrate (1) the successful use of the artificial kidney, and (2) a failure of dialysis to prevent a fatal outcome despite temporary biochemical improvement.

Case 28. This 25-year-old infantryman was wounded by mortar fire, receiving multiple wounds of both legs and his left arm. Compound fractures of both tibias and fibulas were present as well as numerous soft tissue wounds. Despite a 2,500 cc. transfusion of whole blood prior to and during his operation, the patient's blood pressure remained at 75 to 100/50 to 70 throughout the 2½-hour procedure at which the fractures were reduced and the wounds débrided. During the next few days, marked oliguria was noted. Five days after injury he reached the Renal Insufficiency Center—nauseated, drowsy, and complaining of numbness of his extremities and a feeling of generalized weakness. On physical examination he appeared pale, drowsy and acutely ill. Pulse was 110 and blood pressure 140/80. His hand grip was weak, but reflexes were active. Both legs and his left hand were in casts. An ECG revealed elevation and peaking of the T waves and broadening of the QRS complex, indicative of potassium intoxication. The plasma K was 8.6 mEq./L. Hypertonic glucose and insulin were given as an emergency measure, with reduction of the plasma K to 7.4 mEq./L. Dialysis with the artificial kidney was carried out for 6 hours with the following results:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	268	7. 4	137	90	19. 8
Post-dialysis	76	4. 2	140	104	25. 3

During the dialysis the patient showed considerable clinical improvement, with disappearance of his nausea and the feeling of numbness and weakness. He stated that he felt much better. The following day under general anesthesia the patient's left lower leg was amputated because of early gangrene and his other wounds débrided. He tolerated the anesthesia and surgery without difficulty. Severe oliguria continued and over the next 5 days the patient again became weaker and nauseated. Despite the use of 60 gm. of cationic exchange resin by retention enema each day, the plasma K rose to 7.1 mEq./L. with a return of the T wave peaking in the ECG. Another 6-hour dialysis was therefore performed on the tenth day of oliguria, with the following chemical results:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	256	7. 1	135	95	14. 0
Post-dialysis	106	3. 7	141	102	20. 0

Again there was symptomatic improvement during and immediately following the dialysis. The patient was able to take food by mouth. Four days after this dialysis the urine volume had reached 615 cc. per 24 hours, but there had been a return of nausea, drowsiness and weakness. Again the ECG demonstrated peaking of the T waves and slight broadening of the QRS complex. A third 6-hour dialysis was therefore carried out on this 14th day of oliguria, with the following chemical results:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	322	7. 5	131	90	14. 2
Post-dialysis	191	4. 7	140	102	23. 8

During this dialysis urea was placed in the bath at a nitrogen concentration of 120 mg. per 100 cc. to maintain an osmotic load on the recovering kidneys during this beginning diuresis. This explains the failure of the NPN to drop as much as usual. The patient described "clearing of his head" and loss of nausea within a few hours after dialysis. The gradual diuresis continued, reaching 1,130 cc. on the sixteenth day but the NPN and plasma K did not begin to fall until the nineteenth day when the urine output reached 3,000 cc. per day. Convalescence thereafter was uneventful.

Comment. This patient had an extended period of oliguria. His renal function was insufficient to lower plasma potassium and NPN until the nineteenth day. During this period hyperkalemia with ECG changes of potassium intoxication occurred three times, despite the use of exchange resins. Each time it was effectively reversed by dialysis. From the experience at the Renal Insufficiency Center it is unlikely that this patient would have survived with medical management alone.

Case 26. This 21-year-old soldier was wounded by grenade fragments, with a penetrating wound of the right flank and right abdomen. At the forward hospital 2,000 cc. of blood was given to combat deep shock. A laparotomy revealed a retroperitoneal hematoma, laceration of the right kidney, a small laceration of the duodenum, and three lacerations of the inferior vena cava, two above the right renal vein and one at the entrance of the left renal vein. The right kidney was removed and the duodenum was repaired. Attempts at repairing the inferior vena cava were unsuccessful, so that clamps were left in place partially

occluding the vena cava and the left renal vein and protruding from the anterior abdominal wall. Severe blood loss during the procedure necessitated 8,500 cc. of whole blood to maintain his blood pressure. Because of persistent oliguria the patient was transferred to the Renal Insufficiency Center 3 days after wounding. On entry, the patient was alert and cooperative. Blood pressure was 140/90, and the general physical examination was normal except for the abdominal wounds. The plasma potassium was 7.2 mEq./L., but there were minimal T wave changes in the ECG. Sixty grams of the cation exchange resin was given by retention enema, as well as hypertonic glucose with insulin. The following day there was a definite increase in the amplitude of the T waves and some widening of the QRS complex. A 4-hour dialysis was performed:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	296	6. 9	134	78	15. 3
Post-dialysis	174	3. 9	144	99	23. 1

During the following 4 days the patient did well clinically, and the daily urine volume gradually rose to 1,000 cc. He received a total of 120 gm. of resin by enema and was maintained on gastric suction in an attempt to prevent the recurrence of hyperkalemia. Despite this therapy the serum K rose again and the ECG revealed signs of potassium intoxication. The patient was drowsy, nauseated and dyspneic. Another 4-hour dialysis was therefore carried out on the eighth day after wounding:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	304	7. 5	134	80	10. 9
Post-dialysis	148	4. 3	139	93	19. 3

Following this dialysis the urine volume rose steadily, and the patient was much improved. The NPN and the plasma K rose for two more days, and then gradually fell with the continuing diuresis. Thirteen days after wounding, when plasma K was 3.7 mEq./L. and the NPN 204 mg. per 100 cc., the clamps were removed from the inferior vena cava under general anesthesia. There was transient hypotension, responding to 500 cc. of whole blood. Two days later he complained of generalized abdominal pain and went into shock. A laparotomy was performed and revealed brisk bleeding from the inferior vena cava. Because the vein wall was friable, ligation was performed just below the renal veins. The patient died in irreversible shock several hours later, despite a total of 7,500 cc. of whole blood before, during and after the operation. Autopsy revealed a massive hemoperitoneum with the bleeding originating from a laceration at the junction of the left renal vein with the inferior vena cava.

Comment. This patient seemed to be recovering from acute renal failure when his death was brought about by hemorrhage from his original wound. Until this occurred the artificial kidney seemed to contribute to his survival, especially in the decisive control of potassium intoxication.

Discussion

The therapeutic problems presented by military casualties with post-traumatic renal insufficiency differ only in degree from those that arise during the treatment of acute renal failure in civilian practice. This is an important difference, however, and is reflected in the excessive mortality rate in this group of patients—80 to 90

per cent before the establishment of the Renal Insufficiency Center. After the center was organized and the artificial kidney put into operation the mortality rate was still 53 per cent, with the majority of deaths probably attributable to complications of the original wounds. Figures for the mortality rate of acute renal failure in civilian practice vary widely. In a series of 85 cases of acute renal failure at the Peter Bent Brigham Hospital the over-all mortality rate was 48 per cent.[10] It is to be emphasized that many of these patients were problem cases, sometimes referred *in extremis* from other hospitals. In the only other large civilian series reported there was an over-all mortality rate of 31 per cent in 64 cases.[18] It is not valid, however, to compare these figures closely with those obtained in the treatment of such a special group of patients as the military casualties presented in this report. The striking feature of these patients with post-traumatic renal insufficiency was the rapidity with which chemical and clinical uremia and potassium intoxication developed, reflecting the marked catabolic response to injury, infection, and the presence of ischemic or devitalized tissue. This accelerated accumulation of nitrogenous waste products and extracellular potassium, documented in the accompanying paper (p. 7), occurred despite an intensive medical regimen, the use of exchange resins, attempts to control infections with antibiotics and surgery, and the early removal of devitalized tissue by débridement or amputation.

Before the establishment of the Renal Insufficiency Center the average survival time after wounding of patients who died with acute renal failure was only 6.8 days. The artificial kidney was effective in bringing about both chemical and clinical improvements, but had to be used repeatedly in many patients because of the catabolic load. The average survival time of fatal cases was almost doubled (12.4 days) in those patients treated with the artificial kidney and extended to a period usually sufficient for diuresis to begin, except in the patients with severest renal damage.

The metabolic characteristics of these patients are not peculiar to battle casualties, but are found in severely traumatized patients in any setting, civilian or military. Experience with the relatively benign nature of acute renal failure in uninjured and uninfected patients should not be misapplied to those who have developed renal insufficiency in the course of extensive surgical or accidental trauma.

Regarding future military operations, two questions should be raised: (1) Is a specialty center for the treatment of fluid and electrolyte problems feasible and valuable in a military theater? (2) Should such a center include the use of an artificial kidney? Specialty centers for the treatment of acute neurosurgical problems and

the treatment of epidemic hemorrhagic fever were of considerable value in the Korean military theater. Problems in electrolyte and fluid balance arise frequently in military casualties, not only in cases of acute renal failure but in the treatment of patients with burns or abdominal wounds. A specialty center for the treatment of these problems has its main advantage in the associated laboratory capable of carrying out accurate determinations of plasma electrolytes. In the experience presented here such a laboratory was established and operated effectively under field conditions. This work was carried out during the time of a military stalemate. Under mobile combat conditions, however, such a laboratory could be quickly transported in a single truck and re-established during the movement of the parent hospital.

The value of such a center is difficult to establish in statistical terms. Following the establishment of the Renal Insufficiency Center and with the use of the artificial kidney there was a fall in the over-all mortality rate from post-traumatic renal insufficiency of about 30 to 35 per cent (from 80 per cent to 53 per cent). Statistically this is not a very impressive reduction, and the observer is reduced to counting the individual patients who seemed to survive because of the special treatment, such as the use of the artificial kidney. With the use of an artificial kidney the limiting factor in survival in the present series of patients seemed to be the severity of the attending wounds. Because of this it is felt that the mortality rate accompanying acute renal failure in military casualties will be lowered below 50 per cent only with great difficulty and primarily through advances in the surgical care of the wounded.

Summary

(1) The management of 51 patients with post-traumatic renal insufficiency included fluid restriction, attempts to maintain caloric intake, use of cation exchange resins, the treatment of anemia and electrolyte disturbances and the use of a Brigham-Kolff artificial kidney.

(2) Interval surgical care of these patients was of great importance not only because of the severity of their wounds, but particularly because of the necessity for removing necrotic and infected tissue in patients with renal failure.

(3) The mortality rate accompanying acute renal failure in military casualties in Korea was approximately 80 to 90 per cent and a similar mortality rate was found during World War II. After the establishment of a Renal Insufficiency Center and with the use of a Brigham-Kolff-type artificial kidney, the over-all mortality rate in the 51 patients was 53 per cent.

(4) Dialysis with the artificial kidney was carried out 72 times in 31 patients of this series. It was effective in restoring clinical and chemical abnormalities toward normal, and seemed to contribute to the reduction in mortality in this group of patients.

(5) The limiting factor in survival for most military patients with acute renal failure is the extent of the underlying wounds with attending infection and impaired wound healing.

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Chapter 4

The Management of Acute Renal Insufficiency*

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General Considerations

Renal insufficiency has been described in association with numerous pathologic conditions which do not involve the kidneys primarily. Insults to non-renal systems of the body may provoke compensatory responses which protect the organism as a whole but damage the kidneys secondarily. The prime example of this phenomenon is shock, in which blood is shunted away from organs whose functions are not immediately necessary for survival. By the time critical functions are restored, organs with low priority for blood, such as the kidneys, may have undergone ischemic changes of severe degree. Insults to non-renal systems may release to the plasma pigment or other intracellular materials which are concentrated in the kidneys and produce obstruction or cellular degeneration. There are numerous other ways in which kidneys may be damaged, but these two are considered to be of greatest importance in war or traumatic disaster.

Once renal damage has occurred, it may assume greater importance than the original condition as a factor in prognosis unless specialized treatment is instituted. Comprehensive studies by the Board for the Study of the Severely Wounded in World War II [1] revealed that the degree of oliguria was correlated with the mortality rate. In a group of 186 severely wounded men with an over-all mortality rate of 35 per cent, those with a urinary output of 100 to 600 cc. per 24 hours had a mortality rate of 47 per cent, and those with a urinary output of less than 100 cc. per 24 hours had a mortality rate of 91 per cent. The researches conducted by these and many other investigators provided a greater understanding of renal failure which allowed development of newer methods of treatment which lower the mortality rate.

In the Korean War renal failure as a complication in the severely wounded was comparable with that seen following shock in World War II. Pigment nephropathies were not recognized as significant

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causes of renal failure in this study, a fact which is a tribute to the excellence of the blood replacement program and which probably also stems from the infrequent occurrence of crushing injuries. Members of the Surgical Research Team observed that oliguria occurred most frequently in the individuals who were most severely wounded and whose resuscitation was most difficult. Of the first 10 such patients observed, 9 died of potassium intoxication.

In April 1952, an artificial kidney was put into operation by the Surgical Research team at the Renal Insufficiency Center at Wonju, about 75 miles behind the main line of resistance. This unit was attached to the 11th Evacuation Hospital and was operated as a joint effort of the Army Medical Service Graduate School in Washington, the 406th Medical General Laboratory in the Far East Command, and the 8th Army Medical Service in Korea. During the 16 months of its operation this unit received approximately 160 patients who had, or initially were suspected of having, renal insufficiency. The greatest number of patients cared for at any one time was 11, and the average number was about 4. However, the intensive care and study given these patients required that three to five internists, one surgeon, four to six nurses, six to nine corpsmen, and two to four laboratory technicians work full time on this effort. In addition, all of the personnel of the hospital, particularly the anesthesiologist, pathologist, laboratory technicians, supply officer and utilities officer, contributed significantly to this effort. The operation of the unit centered around the artificial kidney and the laboratory, but all of the personnel and facilities utilized in the care of any seriously ill patients were even more concerned for these patients.

The immediate net result of this investment was a reduction in overall mortality rate from about 90 per cent to about 55 per cent. When the biochemical abnormalities resulting from renal failure were controlled, the degree of renal failure no longer paralleled the mortality rate. A less tangible but probably more important result of the control of renal failure was the dissociation of the effects of uremia from the effects of other clinical disorders. Upon the completion of 6 hours of treatment with the artificial kidney, a patient is momentarily relieved of uremic symptomatology, and the remaining symptoms can be traced to their proper source.

If the source of such symptoms can be located and corrected, the symptoms resulting from uremia alone can then be assessed as they reappear in ensuing days of oliguria. The importance of such maneuvers lies in the difficulty of assessing symptoms and assigning priority to therapeutic procedures in a man with multiple abnormalities in addition to oliguria. If one is not to be confounded by the complexities of such a patient, the clinical patterns to be expected from each

disorder alone must be established. It was not uncommon in Korea for a moribund patient to be rushed as an emergency to the Renal Center when, in fact, none of his symptoms were the result of uremia. The surgical care which may have represented the patient's only chance for survival was not given by those best qualified and in the best situation to give it. Other patients whose threats to life were primarily of renal origin could have been treated more satisfactorily if the information gained at the Renal Center had then been available in the forward area. It is the purpose of this report to outline the concepts and methods employed at the Renal Center which appear to have the greatest practical application, with specific reference to 48 renal and 11 non-renal patients observed by the authors. The system presented is subject to revision, as analyses now pending are completed, as further information becomes available from other workers, and as any divergent opinions are resolved. A more detailed account of individual cases and raw data is recorded elsewhere.[2]

Recognition and Transfer

The diagnosis of renal insufficiency should be suspected if the urine output falls below 500 cc. per 24 hours, about 20 cc. per hour. The patient and his records should then be re-examined with the following possibilities in mind:

Reflex Oliguria. This term is used to designate the transient oliguria which occurs following surgery or other trauma. The condition may not be reflex in origin, but it appears to be a normal response to this type of stress and lasts only a few hours.

Hypotension. The blood pressure in the renal artery is an essential component of renal filtration pressure. When hypotension is observed in the arm, renal filtration can be expected to be diminished. The resulting oliguria causes an increase in plasma NPN which can be misleading, because a patient with persistent hypotension may have central nervous system signs which resemble those of uremia at a later stage. It is important to distinguish the conditions because the treatment is quite different. The most practical approach to the differential diagnosis is to defer a diagnosis of renal failure until normal blood pressure is restored. The condition which produced the hypotension should receive first attention, because it likely will kill or be cured before renal failure, if it be present, requires any treatment.

Dehydration. A severe degree of dehydration is required to produce oliguria of 20 cc. per hour, and either history or physical examination should confirm this unusual diagnosis. If any question remains, the

high specific gravity of urine excreted by normal kidneys during dehydration should settle the point, because the urine of acute post-traumatic renal failure characteristically has a low specific gravity. The practice of administering a fluid load as a test for dehydration is dangerous and should not be necessary.

Obstruction. In the post-traumatic state urinary tract obstruction is suspected when there is flank pain with genital radiation, when the scanty urine contains crystals of drugs or heme casts, or when there is total anuria. Even the most severe cases of rental insufficiency usually are painless and the patients excrete 30 to 40 cc. of urine per day. If there is no urine whatever, first attention should be given the urethral catheter, for obstruction by mucus is not uncommon. Daily irrigation of the catheter with a bland fluid which is measured when instilled and recovered should prevent this complication. If obstruction is still suspected, cystoscopy and catheterization of the ureters are indicated.

Acute Tubular Nephrosis. If a patient with the usual state of hydration excretes less than 20 cc. of urine per hour after 5 to 10 hours of normal blood pressure, and there is no evidence of obstruction, the diagnosis of acute renal failure is justified. Pathologically, this lesion was first described as epithelial necrosis in the lower segment of the tubule, but subsequent studies indicate that the necrosis occurs throughout the length of the tubule.[3] Functionally, there is serious impairment of the capacity of the kidneys to excrete or conserve selectively the substance in excess or in scarce supply. During the acute stage the problem is excretory. All of the plasma substances which normally appear in the urine accumulate in the plasma, where some of them are toxic. The renal lesion is potentially reversible, and if the patient can be maintained for the few days or few weeks required for regeneration of the tubular epithelium, spontaneous diuresis will occur. During the diuretic phase, the problem is lack of conservation. Scarce and essential substances are washed out in the copious urine flow, and serious chemical deficits can occur.

Once the diagnosis of renal failure has been made, it is essential that the symptomatology be re-appraised to establish which components are uremic in origin. When one is faced with a deteriorating clinical status in a patient with serious wounds and oliguria, there is a strong tendency to blame uremia for all of the symptoms and to neglect other disorders. With two exceptions, the symptoms of uremia do not appear, in our experience, until the fifth to eighth day of anuria when the NPN is 250 to 300 mg. per 100 cc. The first exception is overhydration, which is not really a symptom of the pa-

tient's disease but of the doctor's error. The second exception is severe potassium intoxication, which only occurs as a sequel of incomplete care of other features of the patient's condition. If neither overhydration nor potassium intoxication is present, anuria must persist for many days before it provokes symptoms.

It follows that other pathologic processes should be sought in a patient who is symptomatic during the first few days of anuria. Symptoms which resemble those of uremia are observed in patients with wound infection, generalized sepsis, or shock, but the offending agents cannot be dialyzed from the patient's plasma. There is no gain but potentially total loss in transferring such a patient to a renal center. If the basic condition cannot be corrected, there is even less chance of success after the delay and trauma of evacuation. If such a patient is to survive, resuscitation and débridement must be completed before transfer, and he must be able to maintain a blood pressure of more than 100 mm. Hg throughout the journey without stimulants or infusions. Once these conditions are fulfilled, the oliguric patient can be transferred for definitive care of uremia with good prospects for success.

The methods for management of acute renal failure and allied conditions which were developed from the Korean experience have general application and are reviewed below. The problems in management are considered in order requiring first action by the physician.

Fluid Balance

First and continuing consideration should be given to the prevention of overhydration. The evils of water intoxication are well known, yet this preventable complication is common. The total fluid intake per 24 hours should be in the range of 500 to 600 cc. plus the measured output, increasing to about 700 to 800 cc. plus the measured output if the weather is hot or the patient is feverish. The measured output usually is the total of urine and gastric suction, although diarrhea, not present in our cases, might increase the output significantly. This average intake allowed a daily weight loss of ½ to 1 lb. (0.23 to 0.5 kg.) without producing clinical evidence of edema or dehydration.

The best route for administration of the fluids is oral, if the patient is able to tolerate them. In our patients, however, fluids administered orally, even by duodenal tube, provoked vomiting. This compounded the problems of fluid and electrolyte balance and also added the risk of aspiration pneumonia; thus the intravenous route was used almost exclusively. Restriction of orally administered fluids can be quite difficult. Patients so restricted often suffer a cruel thirst, yet their thirst is not an accurate gauge of their needs. If allowed to drink freely,

they will literally drown themselves. When denied fluids, they develop great craftiness in prevailing on compassionate neighbors and attendants for small sips of any fluid or for pieces of ice, a bountiful and easily overlooked source of water. When unobserved, they will quaff heartily from flower vases, emesis basins, or urinals with great stealth and cunning. It is the physician's responsibility to prescribe the proper amount of water and to insure that no violation of his order occurs. Careful oral hygiene and unlimited quantities of chewing gum, together with an explanation of the reasons that compel the apparent cruelty, are usually adequate to control thirst. The amount of water prescribed must contain all the solids to be administered during the 24 hours, these will be discussed later.

Potassium Intoxication

The only chemical abnormality that is likely to cause death in the first week of uremia is potassium intoxication. Normally, potassium exists in high concentration inside cells but does not exceed a level of 5.5 mEq. per liter in the plasma. Normal daily catabolism of cells provides the plasma with a small quantity of potassium that is readily excreted. This amount of potassium can be handled by an anuric patient for many days, even several weeks, without accumulation of significant quantities in the plasma.[4] However, the basic condition that originally produced the renal insufficiency is often characterized by excessive loss of potassium from cells. This was especially evident in these patients, many of whom had suffered extensive tissue damage from trauma or infection and in whom the plasma potassium rose to high levels as early as the second day of oliguria. Devitalized tissue, whether permanently destroyed or temporarily embarrassed by trauma, infection, chemical or physical agents, or hypoxia, gives up potassium to the plasma.[5] In the plasma excess potassium is exceedingly toxic, and the first and most important evidence of toxicity is cardiac.

The toxic effect of potassium on the heart is recorded on the electrocardiogram long before any other signs or symptoms appear. The degree of electrocardiographic abnormality produced by a given excess of plasma potassium will vary widely, however, depending on the activity of other factors. Under experimental conditions, such as the infusion of potassium into the plasma of normal dogs, it has been shown that the electrocardiographic effects of progressive increments of plasma potassium are mostly consistent[6]; in clinical situations, however, the electrocardiogram has not previously been shown to be a

reliable gauge of the plasma potassium level. The function of the heart with respect to potassium is the result not only of the absolute level of plasma potassium but also of factors that influence the effects of potassium. The electrocardiogram is, in fact, an accurate gauge of the plasma level of potassium in man when there is no abnormality except hyperpotassemia.[7] The discrepancies stem from the rarity with which pure hyperpotassemia occurs. In the oliguric patient, substances that normally would be excreted in the urine are retained within the body, and some of these substances affect the behavior of potassium.

Calcium. The retention of inorganic phosphate, though not itself harmful, is associated with a fall in the level of plasma calcium during oliguria. Figure 1 demonstrates the consistency with which a given excess of plasma phosphate is associated with a predictable deficit of plasma calcium. A deficit of plasma calcium is of cardinal importance during oliguria because calcium is a specific antagonist of potassium and hyperpotassemia and hypocalcemia occur at the same time.

As the plasma potassium level rises, the degree of toxicity recorded by the electrocardiogram is consistent with it only if the plasma cal-

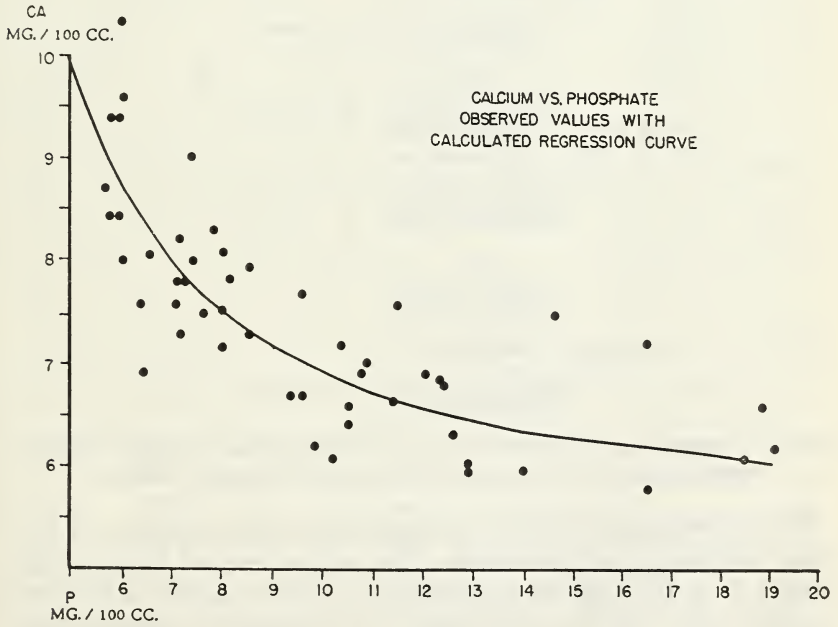

FIGURE 1. Graph of random pairs of phosphate and calcium determinations in oliguric patients.

cium level is maintained; otherwise, the electrocardiographic abnormality and the threat to the patient's life are greatly increased. Since in oliguria the plasma calcium level regularly is depressed by a rise in the plasma phosphate level at the same time that the plasma potassium level rises, the electrocardiogram of the untreated patient bears little relationship to the plasma level of potassium. Replacement of the calcium deficit produces a striking improvement in the electrocardiogram, which then is reverted to that degree of abnormality characteristic of the plasma potassium level (Fig. 2).

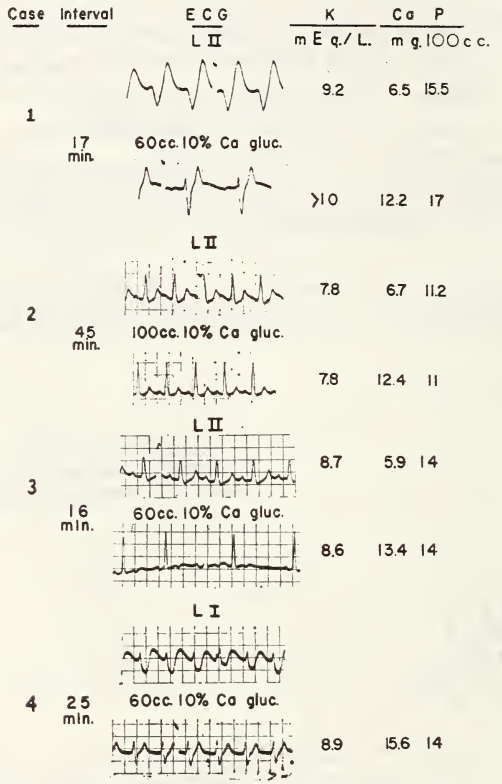

Figure 2. Effects on the electrocardiograms of four uremic patients with advanced potassium intoxication of intravenous infusion of calcium.

The improvement following a single intravenous injection of calcium, however, is very transient. The plasma level of calcium falls quickly from the high level immediately after injection to the preinjection level, which is governed by the phosphate concentration. Although a rise in the plasma phosphate level reduces the plasma calcium level, the converse is not true; phosphate, unlike calcium, cannot be driven into the body repositories by such a maneuver. Intravenous

dextrose infusion will cause a slight reduction in the plasma phosphate level, but not enough to allow a rise in the plasma calcium level sufficient to antagonize potassium. Short of hemodialysis, the only effective way to maintain a normal level of calcium in plasma that is high in phosphate is by continuous intravenous infusion of calcium.

The effect of calcium on potassium toxicity is purely one of antagonism. The measurable level of potassium, as well as phosphate, is unaffected by raising the plasma calcium level. Once the calcium deficit is replaced, the electrocardiogram reflects the plasma level of potassium rather accurately, although still other factors less apparent in these patients have been shown to be influential.[8] Digitalis, which was rarely indicated in our patients, antagonizes potassium [9] in a manner similar to calcium. Digitalis and calcium appear to be additive in this respect, and great care should be used if both agents are administered to the same patient. There is particular danger if the excess potassium is suddenly removed by hemodialysis,[10] allowing digitalis, enhanced by a high calcium concentration, to exert its toxicity without the opposing action of potassium.

Small excesses of potassium produce no electrocardiographic abnormality except elevation and peaking of the T waves, best seen in the precordial leads (Fig. 3). As the plasma potassium level increases further, the T wave abnormalities progress in the precordial leads and become obvious in the limb leads, but they have no quantitative significance in severe hyperpotassemia. Progressive changes in the QRS complex, best seen in the limb leads, are much more ominous. In the limb leads, the angle between the S wave and the ST segment widens and encroaches on the horizontal component of the ST segment until it is obliterated. P waves disappear; the T waves diminish in height and become rounded at the top; and finally, the R–S angle increases, and the smooth biphasic curves resemble a sine wave.

When mild intoxication, indicated by T wave abnormality only, suddenly progresses to the severe intoxication indicated by QRS widening, it usually is the result of a fall in the plasma calcium level. Infusion of calcium should cause instant reversion of the tracing to its former degree of abnormality. If calcium does not produce an immediate effect, this indicates that the plasma potassium level has increased. Sudden rises in the plasma potassium level occur during oliguria when tissue cells are subjected to stress. Hemolysis infection or trauma may allow the release of all the potassium contained in the affected cells. Smaller amounts of potassium may temporarily leave hypoxic cells, only to be recovered by the cells when normalcy is restored. Hypoxia from hypotension, convulsions, certain types of

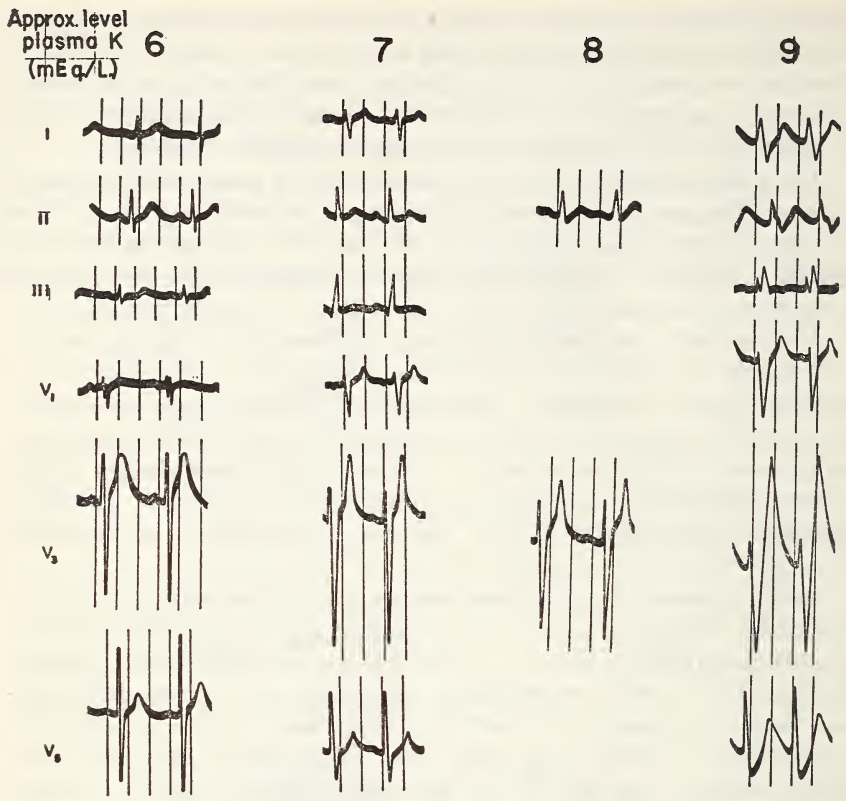

FIGURE 3. Electrocardiograms of patients with relatively pure potassium excess. Peaked T waves are seen throughout the series; when the plasma potassium level reaches 7 mEq. per liter, wide QRS complex and wide S-ST angle appear; these abnormalities increase at the level of 8 mEq. per liter, with a wide R-S angle; the final electrocardiogram shows marked deterioration and may show nodal rhythm.

anesthesia, pulmonary edema and simple breath-holding has been observed to cause such a reversible shift of potassium.[11] In our experience, a rapid increase in the electrocardiographic evidence of potassium intoxication that was not responsive to calcium invariably was associated with a rapid increase of the plasma potassium level associated with one of the above conditions.

Progressive potassium intoxication caused no symptoms in these patients until it had reached the stage at which the electrocardiogram showed severe deterioration similar to that of the fourth tracing in Figure 3. Patients who had symptoms with a less abnormal electrocardiogram were found to have other causes for their symptoms.

Many of the disorders associated with hyperpotassemia, such as those noted above, produce severe symptoms. Correction of the basic condition relieved the symptoms in our patients, although in many instances the plasma potassium was still greater than 8 mEq. per liter and the electrocardiogram was appropriately abnormal. At the time of the tracings shown for case 1 in Figure 2, the patient had neither signs nor symptoms. If one attempts to follow the course of the intoxication in patients with this condition by changes in tendon reflexes, respiratory symptoms, or any other known means except electrocardiography or blood chemistry, the patient will probably be dead before corrective action can be taken.

Sodium. Another ion that should be used in the practical management of potassium intoxication is sodium. Sodium and potassium are inversely related in the plasma of the oliguric patient; raising the plasma sodium concentration causes a fall in plasma potassium concentration and modifies the electrocardiographic effects of potassium intoxication (Fig. 4). Potassium concentration is depressed with a rise in sodium concentration independently of the other ions involved, indicating that the agent responsible for the change is sodium and not the anion. An alkaline salt of sodium is preferred, however, because the retention of organic acids regularly produces acidosis in these patients. The changes in the concentration of potassium and the other substances are not attributable to dilution. Although tissue analyses were not performed, it is presumed that raising the plasma sodium concentration forces potassium back into cells.

The improvement in the electrocardiogram that followed a rise in the plasma sodium level and a fall in the plasma potassium level was sometimes greater than would be expected from the lower level of potassium. This suggests that sodium, in addition to depressing the plasma concentration of potassium, may also have some antagonistic effect similar to that of calcium. Figure 5 shows the beneficial effect of raising the plasma calcium level followed by still further improvement from administration of sodium chloride. The last tracing in this series is almost normal, although the potassium concentration still is 7.2 mEq. per liter. Obviously, all of the factors influencing the response of the electrocardiogram to a given potassium concentration have not been considered. Infusions of hypertonic solutions of sodium salts, do, however, provide an effective and practical means for modifying potassium intoxication. Again it is emphasized that all of the patients in this series were young men without known previous cardiovascular disease, a fact that undoubtedly influenced their responses and that should be considered if these methods are applied to dissimilar patients.

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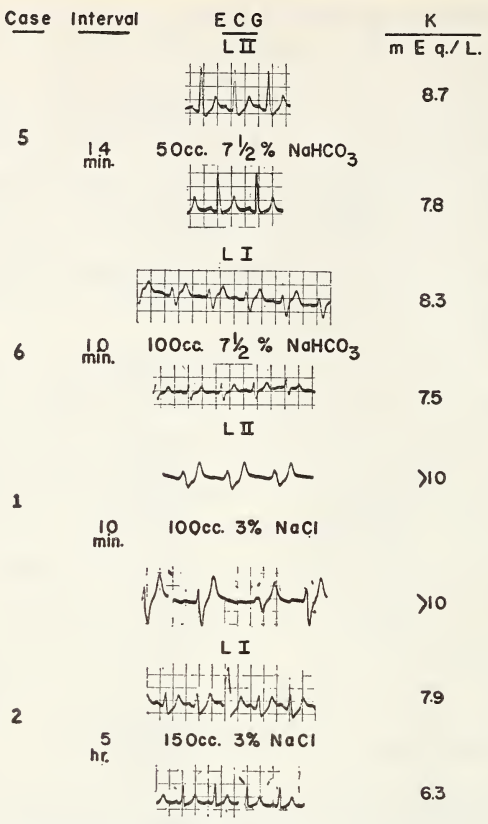

FIGURE 4. Electrocardiographic effects of the administration of sodium bicarbonate and sodium chloride to patients with potassium intoxication.

Dextrose. The plasma potassium level may also be reduced by the infusion of a hypertonic dextrose solution.[12] Its metabolism, which can be hastened with exogenous insulin, removes potassium and phosphate from the plasma. While calcium antagonizes the effects of potassium without changing the quantity present in the plasma and sodium forces potassium into cells by some physicochemical means, glucose carries potassium into cells by a more active process. As glycogen is formed, potassium, as well as phosphate, is incorporated into the carbohydrate complex; this is an effective, though slow, method of controlling potassium intoxication. Results similar to those of a dextrose-insulin combination could be expected from the use of fructose, which does not require insulin for its early metabolism, but this compound was not used.

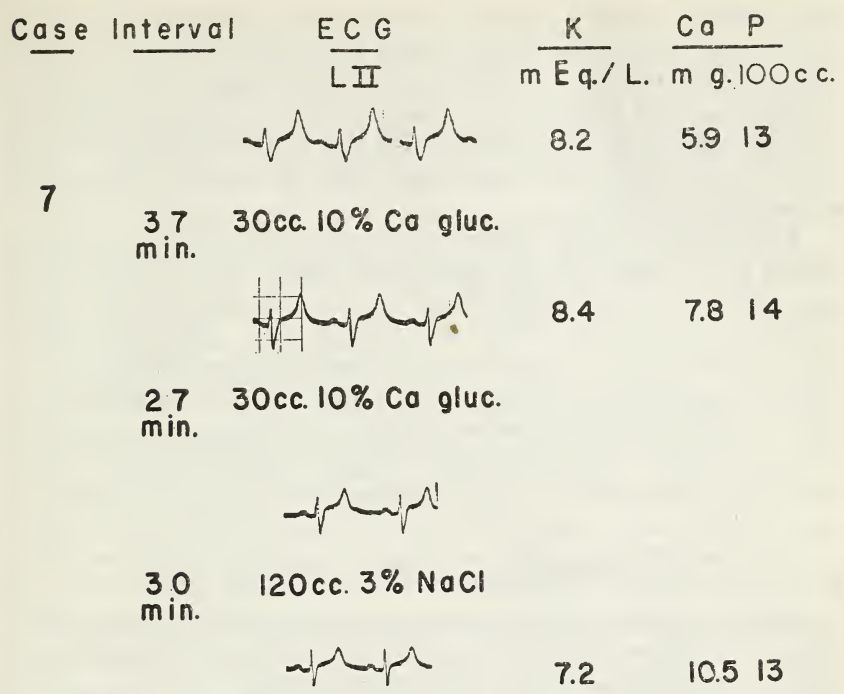

FIGURE 5. Electrocardiograms of a patient with potassium intoxication showing improvement following two elevations of the plasma calcium level and further improvement from subsequent administration of sodium chloride.

If dextrose is to be used effectively by the intravenous route, it should be given continuously. Intermittent intravenous injection of dextrose causes a sharp spike in blood sugar level followed by hypoglycemia. The hypoglycemic period has the double disadvantage of failure to remove potassium during that period, and provocation of glycolysis with further release of potassium to the plasma. Also, if nutrition is limited to intermittent intravenous feedings of dextrose, the period between infusions is one of relative starvation, which is characterized by cell destruction and release of potassium.

On the basis of the above observations, the following standard solution was devised and was found to be effective in controlling potassium intoxication for many days.

Calcium gluconate 10%	100 cc.
Sodium bicarbonate 7.5%	50 cc.
Dextrose 25% in H_2O	400 cc.
(Containing 25 units of regular insulin)	
Isotonic sodium chloride solution or $\frac{1}{6}$ M sodium lactate	Volume of output

This solution should be given intravenously, preferably through a catheter, in a large vein at a constant rate of about 25 cc. an hour. Water-soluble vitamins should be added to this basic solution. Our patients received daily 2 gm. of ascorbic acid, 50 mg. of thiamine chloride, and 20 mg. of vitamin K, but this vitamin prescription was chosen in the interests of a concurrent study of wound healing and is not necessarily optimal.

If the laboratory can provide frequent determinations of plasma sodium levels, the sodium content of the fluid should be varied to maintain a plasma level of about 150 mEq. per liter. If not, the amount suggested can be given empirically without fear. The only complication arising from administration of more than the desired concentration is aggravation of thirst. This is uncomfortable for the patient, and if he is allowed excess water pulmonary edema may be provoked. None of the dire effects attributed to sodium administration [13] were observed in these patients, and it would appear that it is not the sodium alone but the excess water that may accompany it that is dangerous. In older patients or in those who have cardiovascular disease, additional hazards may be associated with a high plasma sodium level. It is unlikely, however, that the dosage recommended would have adverse effects. A likelier source of harm is overhydration; the necessity for water restriction must be kept constantly in mind.

If frequent determinations of the plasma potassium level show that it is not elevated, it would not be necessary to use calcium in the infusion, as its purpose is to antagonize an elevated plasma potassium level. The only other reason for giving calcium would be to prevent tetany if the plasma calcium level were depressed. However, in patients with this condition the plasma calcium level is not depressed unless the potassium level is elevated because hypocalcemia is caused by an elevation of the plasma phosphate level, and phosphate rises at the same time as potassium; therefore, calcium should be given only if the plasma potassium level is elevated. If frequent determinations of potassium cannot be done, the electrocardiographic changes noted are sufficiently specific to guide logical therapy.

The constituents of the basic solution should be tailored for the individual patient when possible. If an item is omitted, its volume should be replaced by an isotonic solution or distilled water.

Ion-Exchange Resins. Ion-exchange resins are effective agents for the withdrawal of potassium from the plasma into the intestine under certain circumstances.[14] In this series of patients, however, those whose potassium levels were highest were unable to take anything by mouth. Rectal instillation of resins was attempted repeatedly, but

such intractable concretions were formed that the amount of water necessary to remove them caused water absorption and overhydration. An attempt was made to contain resins in a silk tube that could be inserted and extracted from the rectum mechanically, but the procedure was very painful for the patient; effective exchange occurred only at the surface of the resin bolus, even when a silk tube of only 5 mm. diameter was used; and only 7 mEq. of potassium was extracted by 30 gm. of resin left in the rectum for 24 hours. It was intended to utilize a colostomy for this method but a suitable patient was not found. The impression was gained that resins would not be more effective than the intravenous therapy described.

Dialysis. Artificial-kidney dialysis is the most effective treatment known for removing potassium, but dialysis for hyperpotassemia alone is, in our experience, rarely indicated. The use of this technic is discussed below under the heading, Clinical Uremia. We have had no experience with other methods of dialysis.

Less Urgent Problems in Management

Nutrition. Principally fat and carbohydrate are recommended during the oliguric phase of acute uremia, because of the potential toxicity of protein.[15] Maximal caloric intake is desirable to prevent the patient from burning his own tissues to supply his caloric needs, but the exact quantity of fat or carbohydrate necessary is unknown. Various high-calorie mixtures, such as olive oil and glucose, frozen butter balls, and commercial fat emulsion preparations, were given by mouth and by gastric and duodenal tube. Unfortunately, the patients who needed it most were nauseated by any of the forms of oral feeding. Intravenous administration of fat was not done in these patients because a satisfactory preparation was not available.[16] Caloric intake, in the main, was limited to intravenous administration of dextrose, which was given as outlined above. This is far from ideal but will sustain the patient. Current studies with newer antiemetic drugs offer hope for successful oral or tube feeding.

Clinical Uremia. After a few days of oliguria (in this series 5 to 8 days), the syndrome of clinical uremia develops. The patient gradually becomes lethargic and shows evidence of mental torpor, yet his extremities are tremulous and hyperreflexic. The nausea that may have been present for days now become active vomiting and retching. Intractable hiccups are usual. These clinical manifestations first appeared in our patients when the plasma nonprotein nitrogen level was about 250 mg. per 100 cc. The consistency with which this figure was

associated with the clinical findings was remarkable, and it came to be useful in allowing one to predict from a nonprotein nitrogen value of about 200 mg. per 100 cc. that that patient would show the symptoms of uremia on the following day.

At this juncture artificial-kidney dialysis is strongly indicated. Six hours of dialysis will produce dramatic relief of symptoms as well as restoration of electrolyte balance. It does nothing for renal function, of course, but it clears the plasma of the substances that normally would have been excreted in the urine. The patient is then ready to start anew on his course of uremia; if diuresis does not occur within several days, dialysis should be repeated each time the symptoms recur until renal function is recovered. Dialysis was performed one or more times in 27 of our 46 patients; 14 underwent dialysis once, 6 twice, and 7 three times.

It is important to recognize the syndrome of clinical uremia and to know when to expect it, because similar signs and symptoms can be produced by hypotension or sepsis. In our patients with renal insufficiency the nonprotein nitrogen rose gradually to the critical level of 250 mg. per 100 cc. over a period of about a week. This level or symptoms of uremia did not occur before the fifth day of oliguria, and the average was later. When symptoms appeared dialysis usually was performed, eliminating the symptoms. If dialysis was not performed the symptoms progressed gradually, and 2 or 3 days elapsed before such threatening clinical manifestations as coma, convulsions, and pericarditis appeared. In patients with prerenal azotemia secondary to shock or sepsis, symptoms appeared at any time, usually within 1 or 2 days, and were totally unrelated to the nonprotein nitrogen level. The onset often was abrupt and the progression rapid. Dialysis was quite successful in restoring chemical balance but did not improve the clinical manifestations. The rate at which plasma potassium and phosphate levels rose after dialysis also was quite different from that seen in patients with renal insufficiency. Within a day, or even a few hours, of a normal post-dialysis level, great increments of potassium and phosphate were again found in the plasma. The condition that had produced the symptoms was still present, and it was associated with devitalization of tissue, which gave up its intracellular materials to the plasma. Dialysis, therefore, was virtually useless, and time was lost in this procedure that should have been spent in treating the basic condition of the patient.

The measures outlined for the treatment of potassium intoxication were effective, in patients without necrotic tissue, for the period prior to the appearance of clinical uremia. In some instances dialysis was avoided because diuresis occurred before clinical uremia appeared, and, in others, the use of these measures made fewer dialyses neces-

sary. In the presence of clinical uremia no attempt was made to control potassium further by medical means, because the dialysis that was otherwise indicated was superbly effective in removing potassium.

When an artificial kidney is not available, medical management of potassium intoxication may save the patient's life for the moment but should be used with a view to providing time for transport to a renal center. Where an artificial kidney is available, this method will allow dialyses to be performed on a reasonable schedule for clinical uremia only and should obviate emergency dialyses for potassium intoxication.

Anemia and Hemorrhage. Of the various causes of anemia in posttraumatic renal insufficiency, the only one studied in this series of patients was severe purpura similar to that seen in chronic uremia. Bleeding into the skin, nasopharynx, and intestine appeared after 12 to 15 days and was related only to the duration, not the severity, of the uremia. Unlike the other manifestations of uremia, the hemorrhagic tendency was entirely unaffected by artificial kidney dialysis or by diuresis; to the contrary, the severest bleeding occurred several days after the onset of diuresis. The only positive temporal relationship was the cessation of bleeding with the resumption of normal diet; however, the absence of hemorrhagic diathesis during pure starvation discourages speculation on this point.

A search for the cause of the bleeding revealed no intrinsic clotting defect, only capillary fragility. The condition was unrelated to abnormality of plasma electrolytes and was unaffected by vitamins C or K or fresh blood transfusions. The replacement of the blood lost was considered desirable, yet transfusions were feared because a minor reaction might have exaggerated significance in patients so seriously ill. Nevertheless, small transfusions, 200 to 300 cc. daily, were given regularly without apparent harmful effect.

Bleeding was originally considered a contraindication to artificial kidney dialysis, because of the necessity for heparinization before and during the procedure. On several occasions, however, dialysis was performed as a lifesaving procedure on patients who were bleeding. During the procedure large quantities of blood were available for immediate use if bleeding should be aggravated, and after the neutralization of heparin with protamine at the end of the procedure, packed erythrocytes were given. No alarming bleeding occurred, and so it became the practice to perform dialysis whenever indicated, regardless of hemorrhagic tendencies. The risk of dialysis in the presence of hemorrhage was considered to be less than the risk of the complications of uremia if dialysis were withheld, and subsequent experience supported this view.

Infection and Antibiotics. The specific infections encountered in battle wounds in these patients will not be reviewed here. In general, their successful management depended mainly on thorough and frequent dressings. An amount of devitalized tissue and infection that may be acceptable in a patient with normal renal function may be lethal in the oliguric patient. Small amounts of tissue, particularly muscle, contain sufficient potassium to kill if it is released into plasma that is not being cleared by the kidney. Removal of such tissue must be prompt and thorough, and the approach must be much more radical than is customary with good surgeons. If the point at which devitalized tissue merges with normal tissue is not apparent to the surgeon, he should débride farther. Excessive débridement may cost the patient precious tissue, but inadequate débridement may cost his life.

Remnants of devitalized tissue usually can be suspected if the plasma potassium and phosphate levels are inordinately high with respect to nonprotein nitrogen. The measures outlined above will control the potassium level; the phosphate level, however, is little affected by such measures, and it is a useful index of the presence of necrosis. A plasma phosphate level reaching 10 mg. per 100 cc. before the nonprotein nitrogen level reached 150 mg. per 100 cc. indicated severe tissue destruction in these patients, and on several occasions deep necrosis underlying a wound with a clean surface was first suspected from this relationship.

Antibiotics cannot be relied upon to control infection in devitalized tissue. Also, the proper methods for administration of antibiotics have not been clarified. The principal route for excretion of antibiotics is through the urine, and during oliguria tremendous concentrations accumulate in the blood if usual doses are given. The importance of this fact was not investigated in these patients, but recent reports of serious intoxications from certain antibiotics require that great caution be observed.[17]

The systemic infection oftenest seen in patients with this condition is pneumonia. This complication is particularly likely to occur if the syndrome of clinical uremia is present and is not interrupted by hemodialysis. The hazard of pneumonia was combated in these patients by deep breathing exercises, voluntary coughing, frequent turning, and good general nursing care. Patients whose cooperation was doubtful because of associated wounds or illnesses were placed on Stryker frames so that turning and drainage could be assured.

The diagnosis of oliguria carries with it a poor prognosis, although the renal lesion itself is usually reversible. The onset of infection may well be enough additional insult to cause a death that would not other-

wise have occurred. The seriousness and the potential reversibility of the illness demand that no effort be spared in preventing or treating the complication of infection.

Salt Wasting During Diuresis. The onset of diuresis was arbitrarily defined in these patients as the day on which urine volume exceeded 1 liter. Once this volume was reached, the output increased rapidly, often 100 per cent or more on successive days, until a peak volume of 3 to 6 liters was attained. As the urine volume increased, the urinary concentration of nonprotein nitrogen, sodium, potassium, and phosphate increased similarly, and the total output of salts reached high values within 1 or 2 days. At this stage the kidneys excrete salts wantonly, without regard for the body's needs. Fortunately, appetite and food tolerance have returned at this stage, and salt depletion is partially offset by the food intake. Daily supplements of sodium and potassium, however, must be added to prevent serious depletion. Sodium chloride, 4 to 6 gm., and potassium chloride, 1 to 2 gm., added to a regular diet daily for about a week were found to be adequate. Fluids were administered freely without noticeable aberrations of fluid balance.

Summary

In a study of acute renal insufficiency in war casualties, it was found that total fluid intake per 24 hours should vary between 500 and 800 cc. plus the output. Potassium intoxication, the only chemical abnormality that threatens the patient's life during the first week of oliguria, produces no clinical signs or symptoms in patients with this condition until death is imminent. The electrocardiogram shows early and continuing evidence of the intoxication, and if other plasma chemicals are at normal levels the electrocardiogram is a rather accurate gauge of the plasma potassium concentration. Plasma calcium is depressed, however, when potassium is elevated, because of the associated retention of inorganic phosphate. As calcium is a specific antagonist of potassium, its administration causes striking modification of the electrocardiographic effects of potassium intoxication. Administration of sodium or of dextrose with insulin lowers the plasma potassium level. Continuous infusion of a standard mixture of calcium, sodium, and dextrose will protect the patient from potassium intoxication for many days, allowing transportation of the patient to a center where hemodialysis can be performed if necessary.

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Chapter 5

Observations on the Surgical Care of Patients With Post-traumatic Renal Insufficiency*

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Acute renal failure following battle injury was noted in Germany in World War I,[1] following air raids in England in World War II,[2] and was also investigated in the Italian Theater of operations at that time.[3] Lucké [4] has stated that lower nephron nephrosis is the most frequent form of fatal kidney disorder encountered among military personnel during war. The Second Auxiliary Surgical Group [5] reported anuria to be the principal or contributing cause of death in 4.6 per cent of a large series of fatal abdominal cases in World War II. The latter were thought to represent patients in whom early fatality had only just been averted, but nevertheless fatal physiologic or structural changes in the kidney had not been avoided. Renal failure following battle injury is most likely to occur with severe or multiple injury which has been associated with prolonged shock.[5]

The mechanism of renal damage is not entirely understood. Some of the proposed theories have been reviewed elsewhere [4, 6, 7] and need not be repeated here. Prolonged selective renal vasoconstriction is probably of prime importance resulting in the development of widespread areas of renal tubular degeneration.[8]

Post-traumatic renal failure is associated with a high mortality rate. Beecher and his associates [3] reported an over-all fatality rate of 65 per cent in 78 patients with acute renal failure; this may be separated into a fatality rate of 47 per cent for patients with oliguria and 91 per cent for those with anuria.** Uremia was the primary cause of death in 67 per cent of the fatalities. Ninety-four per cent of all deaths occurred within the first 10 days. Lucké [4] reported that 74 percent of the patients in a series of 100 fatal cases of post-traumatic renal failure reviewed at the Armed Forces Institute of Pathology died within 8 days. Overhydration, potassium intoxication, or unknown toxins as-

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**Oliguria=urinary output of 100 to 600 ml. in 24 hours.
Anuria=urinary output of less than 100 ml. in 24 hours.

sociated with the syndrome of uremia have been considered to be the most common causes of death.

Since World War II, there have been advances in the therapy of acute renal failure. These have been directed primarily toward the prevention of overhydration and the control of undue tissue catabolism. The latter minimizes the release of potassium into the circulation. In addition, ion exchange resins and artificial hemodialysis are used to lower dangerously elevated serum potassium levels and possibly to eliminate unknown toxins associated with uremia.

A center for the treatment of acute renal failure was established in Korea under the direction of the Army Medical Service Graduate School, Walter Reed Army Medical Center, and operated in collaboration with Eighth United States Army. The treatment of renal failure at the center has been discussed in another paper [9] and will be mentioned only briefly here. It is the purpose of this paper to draw attention to some of the surgical problems encountered in the management of these patients.

Clinical Material and Methods

Observations reported in this study were made on 37 casualties admitted to the Post-traumatic Renal Insufficiency Center, Korea, during the months of April, May, June and July, 1953. Two of these patients were injured in vehicle accidents, 1 was severely burned, and the remaining 34 were wounded by small arms fire or by missiles from exploding mortar shells, hand grenades, or land mines. Resuscitation and initial surgery were carried out at several surgical hospitals. The diagnosis of post-traumatic renal insufficiency was suspected when urinary output was less than 20 ml. per hour provided the systolic blood pressure was above 90 mm. Hg. Plasma potassium determinations carried out on specimens of blood obtained from a few patients at forward surgical hospitals aided in the diagnosis when they were elevated. Patients were transported by air to the Renal Center, a distance of about 75 miles. They were admitted directly to the ward where blood pressure, pulse rate, temperature and electrocardiogram were recorded immediately. A catheter was inserted in the bladder if not already present and irrigated to eliminate the possibility of mechanical block. Blood for plasma chemical determinations was drawn and the following analyses were done at once: sodium, potassium, chloride, carbon dioxide capacity, nonprotein nitrogen, calcium and phosphate. The hematocrit and white blood counts were also

measured. Thereafter all of the above laboratory procedures were determined daily or more frequently. The analytical methods used have been described previously.[10]

The clinical management of the patients was the joint responsibility of the medical and surgical staff of the Renal Center. The diagnosis of acute renal insufficiency was made at the center when a patient excreted less than 500 ml. urine per 24 hours in the presence of a stable blood pressure and a reasonable state of hydration. The development of azotemia supported the diagnosis. An autopsy was performed on almost all patients who died. The characteristic kidney lesion [4, 7] of post-traumatic renal failure was found in all the autopsied patients grouped under that diagnosis in the present series.

The medical management, which has been discussed elsewhere,[9] can be summarized under four headings:

1. *Fluid Balance.* Total fluid intake per 24 hours usually was restricted to 500 to 800 cc. plus the volume of the obvious fluid output. Whole blood was not counted as fluid intake.

2. *Electrolyte Balance.* The principal abnormalities noted were increased concentration of plasma potassium, phosphorus and organic acids and decreased concentration of plasma sodium, calcium and bicarbonate. The first group are primarily intracellular substances which accumulate in uremic plasma when cells are devitalized or destroyed. The removal of such cells by thorough débridement diminishes the rate of accumulation of the substances in the plasma. Conversely, a rapid accumulation of these substances in the plasma suggests that devitalized tissue is still present and should be sought for.[11] The only electrolyte abnormality which is known to be lethal during oliguria is potassium intoxication, and greatest efforts were directed toward its control.

Replacement of the deficit of sodium caused the potassium concentration to fall. When the salt used was sodium bicarbonate, acidosis was modified at the same time. Replacement of the calcium deficit caused amelioration of the toxic effects of potassium without changing the concentration of potassium in the plasma. Infusions of hypertonic glucose with insulin also lowered potassium concentration and digitalis also antagonized potassium toxicity. If the effectiveness of these measures was exhausted, artificial kidney dialysis was employed.

3. *Clinical Uremia.* As the plasma NPN concentration rose above approximately 250 mg. per 100 cc., there was a gradual progression of anorexia, nausea, vomiting, hiccups, somnolence and tremulousness. If oliguria had continued untreated, these manifestations would have progressed to death. However, artificial kidney dialysis usually was

employed, and the clinical and chemical abnormalities were corrected. When dialysis corrected the chemical abnormalities but not the clinical manifestations, it was found that some other disorder, such as sepsis, and not uremia, was responsible for the symptoms and signs.

4. *Supportive Treatment.* Maximal caloric intake of carbohydrate and fat (no potassium or protein) is desirable, but nutrition was usually limited to intravenous glucose (100 to 200 gm.) with vitamin supplements. Whole blood transfusions were given freely for anemia.

Twenty-four patients from the present series had post-traumatic renal insufficiency. The diagnosis could not be made in 13 patients admitted to the center, who were, however, treated there. Because the latter patients were seriously wounded, they serve as a control group. Although these patients were not oliguric on the basis of the somewhat arbitrary definition used, they may have sustained renal damage, which may occur in severely wounded battle casualties.[3]

Results

Table 1 records the distribution of wounds in the two groups of patients. Wounds confined to the extremities formed the largest single category in the oliguric group. This did not obtain in the non-oliguric group. But the combined incidence of patients who sustained extremity wounds, either alone or in combination with injury elsewhere, was not very different in the two groups. All the extremity wounds resulted in muscle damage and presumably the opportunity for ab-

Table 1. Distribution of Wounds in Severely Wounded Patients

	Oliguric		Non-oliguric	
	Number Patients	Per Cent	Number Patients	Per Cent
Extremity	11	45. 8	3	23. 1
Abdominal	5	20. 8	3	23. 1
Extremity and abdominal	4	16. 6	4	30. 7
Thoraco-abdominal and extremity	1	4. 2	1	7. 7
Thorax and extremity	1	4. 2	1	7. 7
Thorax and spinal cord	1	4. 2	----------	----------
Head injury	1	4. 2	----------	----------
Burn (60%)	----------	----------	1	7. 7
Total	24	100. 0	13	100. 0

sorption of myoglobin into the circulation. For this reason, the relatively high number of patients in the oliguric group whose injuries were confined to the extremities is of interest. However, it is possible that this finding is only a manifestation of the high incidence of extremity wounds in general. Beecher and his associates [3] also found extremity wounds to be the most frequent in their combined anuric-oliguric series. Multiple injuries were nearly always present in both oliguric and non-oliguric patients from the present series, which is to be expected in any group of severely wounded battle casualties.

Table 2 records the major complications encountered in the patients under study at the Renal Center. Significant infection was present in 83 per cent of the oliguric patients. These included myositis, peritonitis, septicemia, lung abscess and wound infection. Sixty-three per cent of the non-oliguric patients who survived a sufficient length of time also developed complicating infection. These included myositis, peritonitis (including a patient with overlooked stomach perforation) and a patient with an infected burn.

The most frequent complication found in the oliguric group was myositis, which in this series was found only in the extremities.

Table 2. Significant Complications in Patients at Renal Insufficiency Center

Complication*	Oliguric 24 Patients		Non-oliguric 13 Patients	
	Number Patients with Complication	Per Cent	Number Patients with Complication	Per Cent
Myositis	15	62. 5	3	23. 1
Peritonitis	2	8. 3	3	23. 1
Lung abscess	1	4. 2		
Septicemia	3	12. 5		
Wound infection	1	4. 2		
Burn infection			1	7. 7
Postoperative shock	4	16. 7	5	38. 5
Uncontrolled hemorrhage	2	8. 3	1	7. 7
Excessive bleeding after secondary débridement	6	25	1	7. 7
Failure arterial repair	6	25		
Overlooked stomach perforation			1	7. 7
Evisceration	1	4. 2		

*More than one complication was found in some patients.

Necrosis and infection of the muscle appeared to be the result of inadequate initial débridement in most instances. The involved muscles were edematous, discolored, friable and foul-smelling. The lesions were usually localized and often confined to one or more muscle compartments, although systemic manifestations were sometimes severe. However, in several instances muscle involvement was extensive and one case of extensive crepitant myositis of the thigh is included in the series, from which *Cl. perfringens* was isolated. Temperatures of most of the patients with myositis were between 101 and 104° F., and the pulses were rapid. Leukocytosis with an increase in the per cent of neutrophils was a prominent but not a consistent feature.

The patients did not complain commonly of wound pain, except with manipulation. The apparent absence of pain in some patients may have been because many of them were confused and disoriented. The latter condition appeared to be related to the presence of hypotension, a possible bacterial toxemia and also at times to uremia. The temperatures and pulses were normal in two patients at a time when wound examination revealed extensive muscle necrosis and infection. Bacteriological studies [12] from wounds were not always complete but the findings showed a polybacterial flora which included saccharolytic and proteolytic varieties of Clostridia, Streptococci (beta hemolytic, gamma and micro-aerophilic) and a variety of gram-negative bacilli. The available data do not permit a correlation between the clinical appearance of the involved muscle and the microorganisms isolated, except in the patient with crepitant myositis from which *Cl. perfringens* was isolated.

Clostridial-like myositis was found in amputation stumps to which skin traction had been applied at a forward hospital in four of six patients admitted with such traction. There was no positive evidence that skin traction and possible compression of the distal stump actually promoted the development of muscle necrosis and infection. It is possible that initial débridement was inadequate, but it was probably unwise to apply skin traction to a stump after initial débridement if there was any question as to the viability of the muscle. This would be particularly true if the onset of acute renal failure was suspected because the chemical effects of myositis were more difficult to control when renal failure was present.[9]

The principles employed in the treatment of muscle necrosis and infection were surgical excision of the involved muscle and the administration of large doses of antibiotics. The latter were usually given empirically as follows: Penicillin was used both intravenously

and intramuscularly in the crystalline form in doses varying from 300,000 units to 12 million units per day in different patients. In addition, streptomycin or one of the tetracycline compounds was administered; usually 1.0 gm. of the former intramuscularly and 1.5 gm. of the latter was given intravenously or by mouth daily.

Myositis appeared to have been controlled in 9 of the 15 affected oliguric patients. The available data do not permit an accurate evaluation of the effect of the above antibiotics on the myositis in the patients who survived. Six patients died despite aggressive surgery and antibiotic therapy.

The finding of such a high incidence of myositis in the oliguric patients is of interest because of a possible etiological relationship. But acute renal failure was also found in patients with clostridial-like myositis, and conversely, patients were seen with clostridial-like myositis, without oliguria. Unfortunately, the data are insufficient to compare the bacterial flora in the pathological muscle from patients with and without oliguria.

The other types of infection recorded in Table 2 do not require much comment. They represented types of infection likely to complicate severe injury. The three cases of septicemia were apparently due in each instance to a single species of microorganism, a hemolytic Staphylococcus, a proteus bacillus, and a paracolon bacillus; only the latter patient died.

The patients with arterial injury and attempted repair who developed oliguria are of interest. The group included three femoral, two posterior tibial, and one brachial artery injury. The systemic effect and pathological sequence following a major arterial injury may be similar in some respects to that encountered in the "crush syndrome."[2] It is possible, therefore, that there may have been a direct etiological relationship between the muscle ischemia resulting from arterial injury and subsequent renal failure. But gangrene may occur in an extremity distal to the site of arterial repair without the occurrence of oliguria.[13] A review of the records suggests that the poor results obtained following arterial surgery in the six patients under discussion were probably the result of errors in judgment. Primary amputation might have been the wiser choice because of extensive associated injury.

Uncontrolled gastrointestinal tract hemorrhage was a late complication in two patients and may have been due to uremia. Another patient had uncontrolled retroperitoneal bleeding which appeared at autopsy to have originated from lumbar veins or from an overlooked tear in the inferior vena cava. This patient died on the operating

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table while undergoing a laparotomy in an attempt to control oozing. He had received 25 liters of bank blood.

Excessive bleeding following secondary débridement of muscle was noted in seven patients. Uremia did not seem to be the cause of the bleeding as the complication was encountered soon after injury when the nonprotein nitrogen was relatively low. All the patients had received low-titer group O blood and there was no clinical evidence that they had sustained a transfusion reaction; moreover, blood specimens drawn during the episodes did not reveal hemolysed plasma. Only one of these patients did not have oliguria but other wounded patients without oliguria (not reported in this paper) were seen at a Mobile Army Surgical Hospital with this complication. The oozing was so profuse that serious blood loss occurred. The only effective method of controlling hemorrhage was either the application of tight compression dressings or extensive cauterization. Hemostats were not very effective except when applied to obvious blood vessels. Otherwise, their use promoted further hemorrhage. Freshly drawn ACD-blood was given to two of these patients but we are not certain of its effect in controlling the oozing. The use of the cautery or of compression in wounds is often not desirable and this was particularly true in the type of wounds under discussion. They were already heavily contaminated with aerobic and anaerobic microorganisms so that any procedure which caused interference with local circulation or promoted tissue necrosis was undesired.

Nine patients in the present series were admitted to the Renal Center in shock or with an unstable blood pressure which could only be maintained at about 100 mm. Hg by the administration of norepinephrine continuously. They had been transported by air from forward hospitals because of oliguria, with the expectation that they could be managed more adequately at the Renal Center. All of them had received initial surgery. Data on their diagnosis and course are presented in Table 3.

Hypotension was associated with infection in four or these patients, and with uncontrolled retroperitoneal bleeding in another. Oliguria persisted in three of the nine hypotensive patients following restoration of the blood pressure by the administration of transfusions and/or norepinephrine. Oliguria did not persist in four others and could not be determined in two patients because of our inability to resuscitate them. The general policy in the Korean theater of operations was to avoid transporting patients with postoperative hypotension. The above patients represented an exception to this rule for the reason given and also because the potential of the Renal Center was being continuously evaluated. These data demonstrate the apparent futility of transporting patients with postoperative hypotension to a renal

Table 3. Diagnosis and Result of Patients Admitted to Renal Center With Postoperative Shock

Patient Number	Diagnosis	Result*	Oliguria**
100	Overlooked stomach perforation Peritonitis	Survived	Absent
107	Extensive head injury	Died (1.5)	Present
109	Multiple abdominal visceral injury ? Peritonitis	Died (2)	Absent
122	Multiple extremity wounds	Died (1)	
128	Uncontrolled retroperitoneal bleeding	Died (1)	Present
129	Bilateral traumatic amputation thighs Myositis	Died (7)	Present
130	Multiple abdominal and extremity injuries	Survived	Absent
131	Multiple abdominal visceral injury Fulminating peritonitis	Died (1)	Absent
139	Multiple abdominal and thoracic injury	Died (2 hrs.)	

*Number in parenthesis indicates survival time in days at Renal Center.

**The output of less than 500 ml. urine in 24 hours at the Renal Center in the presence of a stable blood pressure and adequate fluid intake.

failure center, if facilities for resuscitation are available at the forward level. Not only may movement be detrimental to the patient but it is impossible to predict whether or not a hypotensive oliguric patient will develop persistent oliguria.

Comparison of Complications in Patients From Oliguric and Non-oliguric Series

The significance of the differences in incidence of the various complications encountered in the oliguric and non-oliguric patients in this study is somewhat difficult to evaluate. Probably the only important difference was the higher incidence of myositis in the oliguric group. It may be because of this that the incidence of post-débridement bleeding was higher in the oliguric group also.

Fatality Rate and Survival Time

Table 4 records the fatality rate and also the mean survival time of the fatalities in the oliguric and non-oliguric groups. Mortality was high regardless of urinary output although it was somewhat higher in the oliguric series. Thirteen of the oliguric patients excreted less than 100 ml. urine per 24 hours and the fatality rate was 77 per cent. Eleven of the oliguric patients excreted between 100 ml. and 500 ml.

Table 4. Fatality Rate and Survival Time at Renal Insufficiency Center

	All Patients	Oliguric	Non-oliguric
Admitted	37	24	13
Died	26	18	8
Fatality rate	70%	75%	62%
Average time from injury to death (days)	7.7	8.1±1.32*	6.5±1.0*

*Standard error of the mean.

urine per 24 hours; the fatality rate was 73 per cent in that group. The mean survival time from injury to death in fatal cases was not significantly different in the two groups. Two patients in the non-oliguric group who failed to survive postoperative hypotension were excluded from these calculations.

Causes of Death

It is difficult to establish absolute causes of death in a complex disease, and the separation of these causes from the effects of renal disease is somewhat arbitrary. Table 5 lists what were considered to be the principal causes of death in patients from both series. The incidence of death from infection was similar in the two groups although death from myositis was more common in the oliguric group. Renal failure was the immediate cause of death in only one of the oliguric patients.

Table 5. Principal Causes of Death in Patients at Renal Insufficiency Center

Cause of Death	Oliguric 24 Patients	Non-oliguric 13 Patients
	Number of Patients	
Myositis	6	1
Peritonitis		2
Hemorrhage	2	1
Shock		2
Septicemia	1	
Head wound	1	
Infected 60% burn		1
Cerebral embolus	1	
Fat embolus	1	
Multiple injury		1
Hyperkalemia	1	
Undetermined	5	

A relatively rapid rise in plasma potassium developed without symptoms and was first recognized from an electrocardiogram which was taken routinely. The patient died before artificial hemodialysis could be commenced. Death in this patient occurred on the eleventh post-wound day; he had undergone hemodialysis on two previous occasions because of high plasma potassium. The cause of death could not be determined in five other oliguric patients. Deaths in the latter patients did not appear to be due to chemical imbalance, and no lesions were found at autopsy which were considered incompatible with life.

Transportation of Poor-risk Patients to the Renal Center Because of High Plasma Potassium

Operation of the Renal Center on a mobile basis seemed to be impracticable. Therefore, it was necessary to transport patients with acute renal failure to the Center. The plasma potassium level may reach 7 or 8 mEq. per liter within 24 hours of injury in patients with post-traumatic renal insufficiency. Transportation of such patients is usually hazardous because other contraindications to movement are often present also. For example, hypotension, continued bleeding, progressive infection or unstabilized head or chest injury may be present. Nevertheless, because of the fear of early death from potassium intoxication, a number of patients were sent to the Renal Center for possible hemodialysis who would not have been moved otherwise. Upon arrival at the Renal Center aggressive medical and surgical therapy was commenced and hemodialysis carried out if necessary. During the period of this study, 16 such patients were admitted to the Renal Center with a plasma potassium above 6.0 mEq. per liter.

Table 6 records data on the subsequent course of these patients. Only 2 of the patients survived although 12 of the others lived 2 days or longer at the Center. None of the deaths were the result of pulmonary edema, hyperkalemia or uremia *per se*. Hemodialysis was carried out on 11 of these patients, usually more than once; but in only 3 of the patients of whom 2 subsequently died was this done within 24 hours of admission. All of these patients received intensive medical therapy to combat the effect of acute renal failure so that hemodialysis was not considered necessary in every patient. Transportation to the Renal Center was of value to only 2 of these 16 patients if end result alone is considered. Probably all 16 patients would have died if a renal center had not been available to them. However, the data in Table 6 also suggest that the elimination of the renal component as a cause of death may lead to an improved mortality rate if other causes of death can also be controlled.

Table 6. Clinical Course of Patients Admitted to Renal Center With Plasma Potassium Above 6.0 mEq./L.

Patient No.	Admission K mEq./L.	Dialyzed	Day of First Dialysis after Admission to Renal Center	Final Result	Day of Death after Admission to Renal Center	Apparent Cause of Death
89	6. 2	Yes	4	Died	21	Peritonitis, GI hemorrhage.
91	7. 1	Yes	6	Died	8	Myositis
92	7. 5	Yes	4	Died	5	Multiple lung abscesses
97	6. 0	No		Died	6	Myositis
99	7. 0	No		Died	4	Undetermined, no autopsy
102	6. 7	Yes	3	Recovered		
104	8. 2	Yes	1	Recovered		
107	7. 8	No		Died	1	Massive head injury
108	7. 3	Yes	4	Died	8	Myositis
125	6. 9	Yes	2	Died	3	Undetermined
128	8. 0	Yes	1	Died	1	Uncontrolled retroperitoneal bleeding
129	7. 0	Yes	2	Died	8	Myositis
132	6. 6	No		Died	3	Cerebral edema
133	7. 0	Yes	3	Died	6	Septicemia
135	7. 5	No		Died	2	Undetermined
137	7. 3	Yes	1	Died	2	Undetermined

Hemodialysis and Survival

Eighteen of the twenty-four oliguric patients presented in this study were dialyzed, usually more than once; six of these dialyzed patients survived. It is believed that the latter would have died if facilities for hemodialysis had not been available to them. But, as discussed above, specific treatment for acute renal failure including hemodialysis will not necessarily save patients with the post-traumatic variety of acute renal failure if there are other surgical complications. The following two case examples are presented to demonstrate that fact in more detail and also to indicate the type of surgical problem encountered.

Patient No. 110. A 22-year-old Negro male sustained traumatic amputation of both legs following a land mine explosion on 8 June 1953. Tourniquets were applied, and the patient was treated at a battalion aid station 1¾ hours after injury by the administration of 1 liter of dextran, 0.25 grain morphine sulfate, and 0.5 ml. tetanus toxoid. The patient was transferred to a collecting station

where he arrived with a blood pressure of 95/60 and a pulse rate of 100. He was subsequently transferred to a clearing station, arriving 4 hours after injury with a blood pressure of 90/?. Fifteen hundred cc. of blood was given, the tourniquets being left in place. Transfer was effected to a Mobile Army Surgical Hospital where the patient was admitted approximately 5 hours after injury. Débridement of a left above-knee stump and right below-knee stump was carried out 7½ hours after injury. Twenty-five hundred cc. of blood was given during the procedure which was accompanied by a fall in blood pressure to shock levels for a short period of time. The blood pressure stabilized after operation and the urinary output was 1,100 cc. during the following 24 hours. A second débridement of both amputation stumps was done on 10 June (2 days later). Except for an initial drop at the beginning of the procedure, the patient's blood pressure remained satisfactory throughout the operation. The 24-hour urinary output was 250 cc. on that day.

The patient was transferred to the Renal Center by air on 11 June because of persistent diminished urinary output and a reported plasma potassium of 6.1 mEq./L. He arrived at the Center with a blood pressure of 118/74, a pulse rate of 100 and a temperature of 100° F. He was alert, hiccuping, and complained of nausea. Fluid intake was restricted to about 800 ml. per day, 600,000 units of crystalline penicillin b.i.d., and 0.5 cm. streptomycin b.i.d. were continued, and other general measures for the management of acute renal failure were instituted. The patient vomited at intervals so that for several days the only caloric intake was that received by vein in the form of 25 per cent glucose. Areas of necrotic muscle were found in both amputation stumps on 13 June, requiring re-amputation on both sides. This procedure was tolerated poorly; the blood pressure dropped to 60/20, and 2,500 ml. of blood containing norepinephrine was required. The blood pressure rose to 100 systolic, but again dropped following the return of the patient to his bed; he was given another 1,000 cc. of blood. The shock position was maintained during the night, and the systolic blood pressure remained around 90 mm. Hg. There was considerable bloody drainage from both stumps due to excessive oozing following the re-amputations, which was difficult to control and required tight compression dressings. Subsequently the patient improved but by 16 June he was somewhat stuporous. At that time the nonprotein nitrogen was 255 mg. per 100 cc., and the plasma potassium 8.2 mEq./L. Hemodialysis was carried out but discontinued after 2½ hours because blood clots formed in the tubing. The patient was somewhat improved following dialysis; but 2 days later a 6-hour hemodialysis was carried out because of increasing somnolence and a rising NPN and plasma potassium. The response to dialysis was excellent and during the succeeding 4 days urinary output gradually increased. Daily dressings showed progressive granulation of the amputation stumps. On the fifteenth day after injury the 24-hour urinary output was 710 ml., NPN 233 mg. per 100 cc., and plasma potassium 7 mEq./L. The patient was again drowsy so hemodialysis was done once more with a good result. Subsequently, urinary output continued to rise and reached a peak of 6,080 cc. on 2 July. Coincident with the increased urinary output, the patient's clinical state improved, manifested by increased appetite and alertness. He was subsequently evacuated to Japan for further wound care.

Data regarding fluid balance and laboratory findings are given in Figures 1, 2, and 3. Figure 1 reveals that the patient was febrile throughout his stay at the Renal Center. The hematocrit was subnormal during that time, although a 500 ml. blood transfusion was given almost every day. Fluid balance was reasonably well managed with diuresis commencing on the fourteenth day.

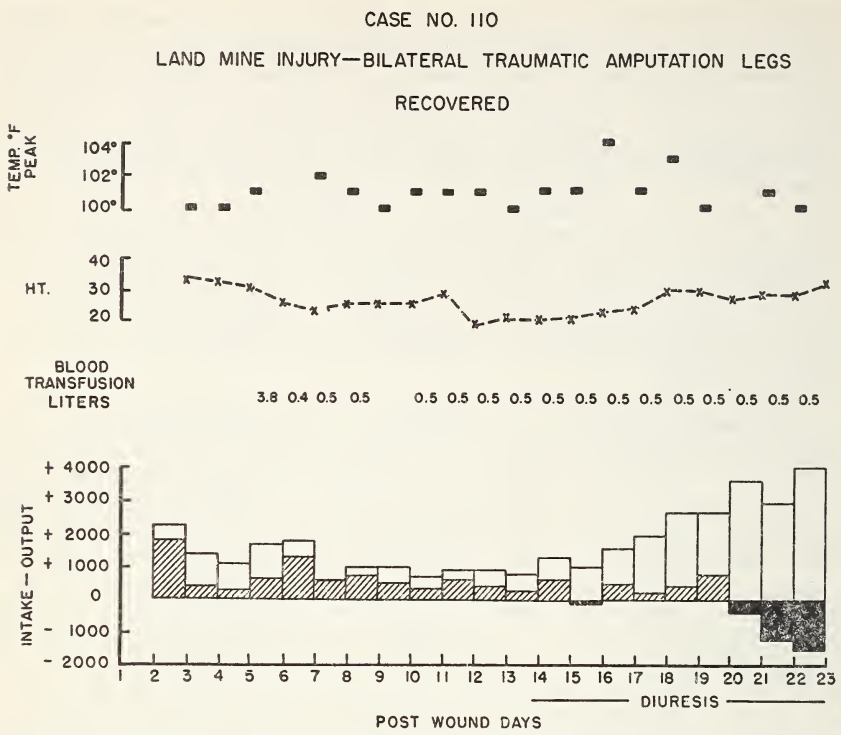


Figure 1. Patient No. 110. Daily record of fluid balance, not corrected for insensible water loss. Charting follows method described by Moore and his associates.[14] The daily temperature peak, hematocrit and the volume of blood administered are also recorded.

Caloric intake was low for most of the hospital stay. Figures 2 and 3 present the chemical data from the patient and show the effect of artificial hemodialysis on these. The levels of potassium, phosphate and nonprotein nitrogen in the plasma increased during the oliguric phase with return towards normal with hemodialysis. Carbon dioxide capacity fell as oliguria persisted and rose with hemodialysis. The fluctuations in the plasma levels of sodium, chloride and total calcium were not so consistent because of the intermittent therapeutic administration of these agents. It is our opinion that hemodialysis was one of the life-saving procedures used in this patient.

Patient No. 129. A 23-year-old Negro male who sustained traumatic amputation of both legs and a laceration of the left forearm due to a land mine explosion on 8 July 1953. Tourniquets were applied to the legs and the patient was admitted to a forward surgical hospital 1½ hours after injury. He was in severe shock and was given 3,000 ml. of blood. Bilateral, guillotine amputations of the thighs and débridement of the forearm wound were commenced 7 hours after injury. A further 3,000 ml. of blood was given during the operative procedure, which lasted 2 hours. The postoperative blood pressure remained at about 110/70 for the first 6 hours but then became non-perceptible.

The diagnosis of impending acute renal failure was suspected because no urine could be obtained by catheterization so the patient was transferred by air to

the Renal Insufficiency Center. He was admitted to the Center approximately 20 hours after injury with a temperature of 103° F., a pulse rate of 150 per minute, and a respiratory rate of 32 per minute. The blood pressure was not perceptible, but the patient's skin was warm and dry and he was restless and responded slowly to questions. Following the rapid transfusion of 1,000 ml. of blood the pressure returned to 100/80. This then stabilized at about 130/80 approximately 26 hours after injury. The potassium level in the plasma was 7.0 mEq./L. on admission to the Center. Examination of the wounds on the morning after initial surgery revealed a severe myositis involving the entire abductor group of the left thigh stump including the sartorius and vastus medialis muscles. The affected muscles were pulpy, avascular and purple-blue in color. A brownish exudate with a characteristic foul smell was present but crepitation was absent. Other muscle groups in the same thigh appeared uninvolved. The right amputation stump also appeared in satisfactory condition. An extensive débridement was done on the left side, removing the major portion of the medial muscle groups up to the pubic bone. A large metal fragment was found among the necrotic muscle groups in the region of the inguinal ligament, appar-

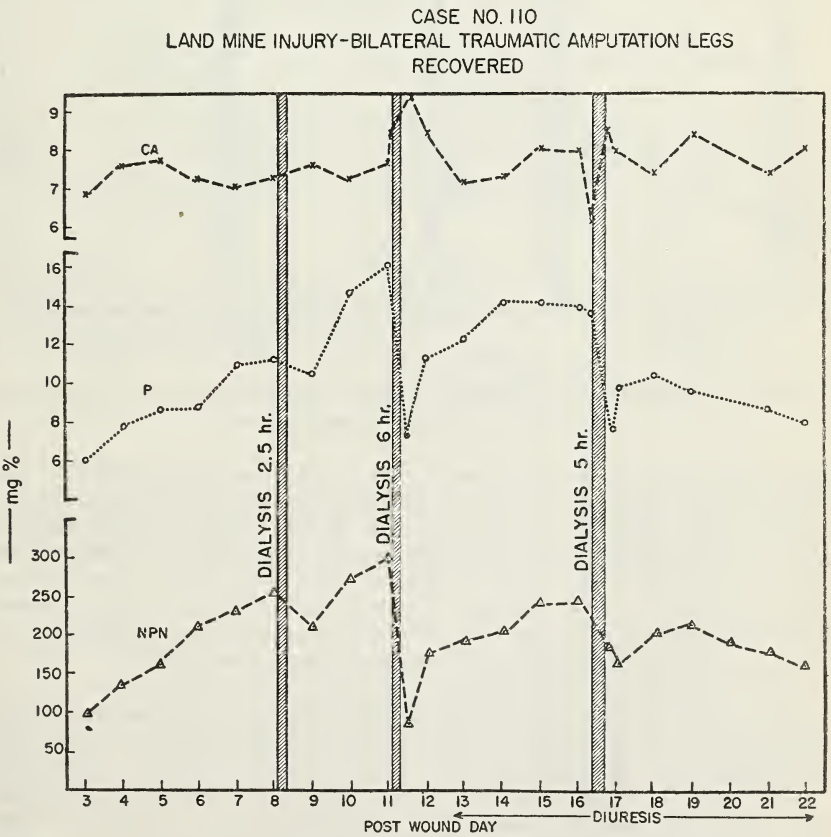


Figure 2. Patient No. 110. Plasma calcium, phosphorus and nonprotein nitrogen. Effect of hemodialysis.

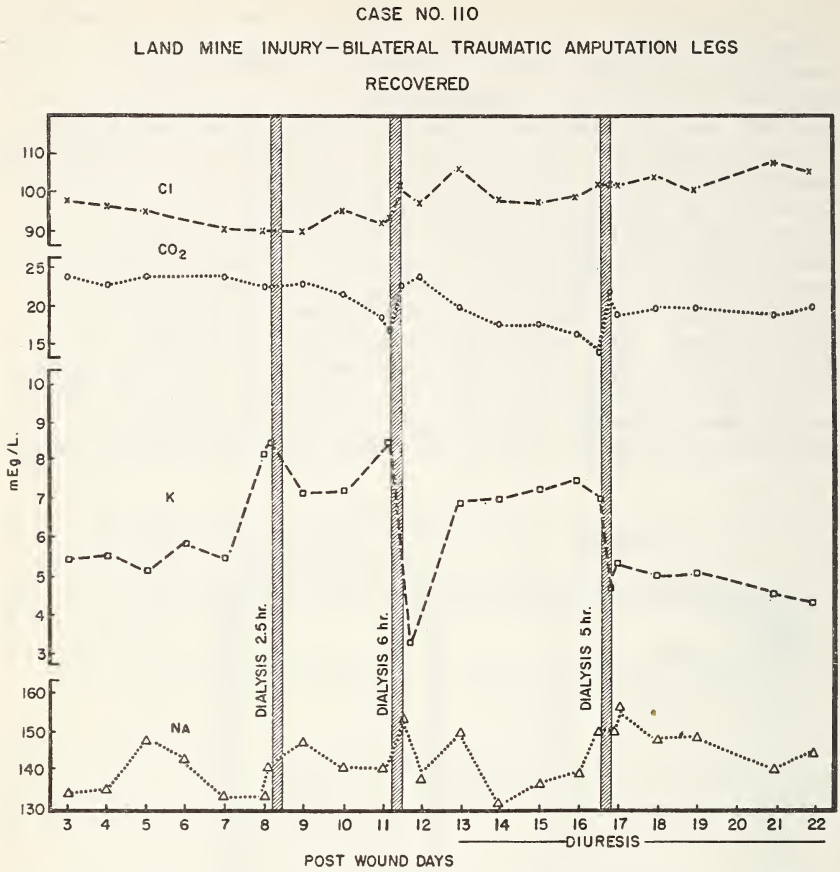


FIGURE 3. Patient No. 110. Plasma chloride, carbon dioxide content, potassium and sodium. Effect of hemodialysis.

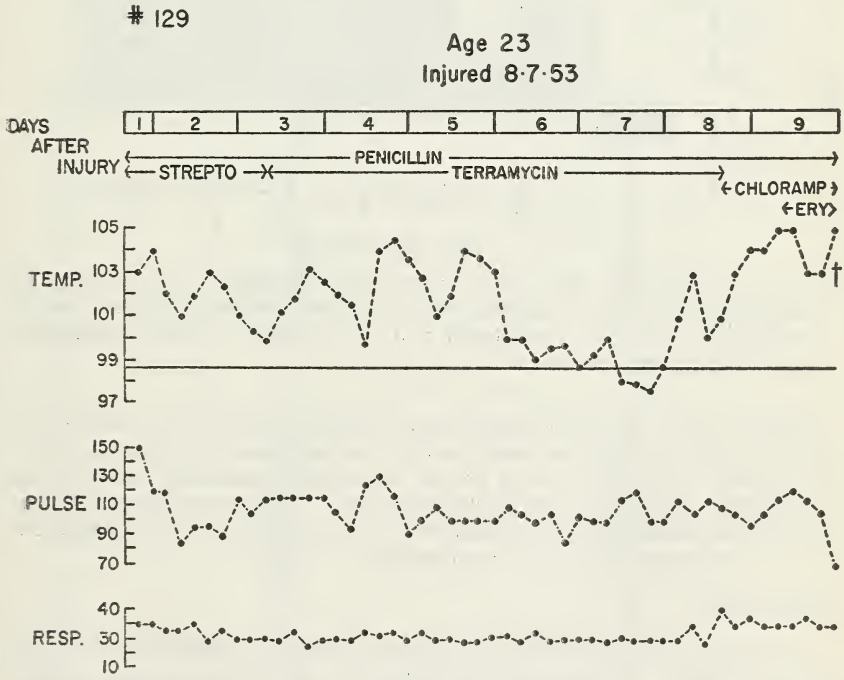
ently having traveled up along fascial planes. The blood pressure was unstable during the operative procedure and required continuous supporting blood transfusion. The wound was dressed daily and on each occasion further débridement of progressively involved necrotic muscle was necessary. The first of these procedures was done under anesthesia which precipitated a sustained fall in blood pressure. The subsequent débridements were done without general anesthesia, but the blood pressure fell with each operative procedure even though manipulation was gentle and only dead tissue was excised.

It was obvious early in the patient's course that a hip disarticulation was required to get above all devitalized infected muscle. However, we were not of the opinion that the patient could tolerate such major surgery. Artificial hemodialysis was performed on two occasions for apparent clinical uremia but the persistence of symptoms after chemical balance was restored was interpreted as evidence that myositis provoked the toxic manifestations. The patient's blood pressure persisted at hypotensive levels during the final 2 days of life. He remained drowsy and confused and hiccuped constantly. A precordial friction

rub developed and was thought to be due to mediastinal emphysema. Death occurred on the ninth post-wound day. Examination of the left stump at autopsy revealed residual areas of infected necrotic muscle confined to the posteromedial aspect. Other muscle groups showed areas of discoloration similar to the fish-flesh appearance described in the crush syndrome. The right amputation stump did not appear to be infected. The only other finding of significance was the presence of mediastinal emphysema. The primary cause of death was probably necrotizing myositis with complicating acute renal insufficiency.

Figure 4 shows some of the clinical data from this patient. The course was febrile except for a relatively short period. The pulse and respiratory rates were rapid. The white blood count was persistently elevated and the per cent of neutrophils above normal. The dosages of chemotherapeutic agents were as follows: penicillin, 1 million units every 4 hours intravenously; oxytetracycline, 0.5 gm. intravenously every 6 hours; chloramphenicol, 0.5 gm. orally every 6 hours; and during the last day of illness, erythromycin, 0.4 gm. orally.

Figure 5 records data on daily fluid balance, hematocrit and blood transfusions. The hematocrit fell progressively even though blood transfusions were administered. The patient's fluid balance was controlled reasonably well.



WBC X 1000	12.3	13.4	11.8	11.2	12.1	14.3	13.3	16.2
PHAG. INDEX	88%	86%	82%	90%	80	80%	—	82%
COMP. TITER	0	1:16	1:16	1:32	1:32	1:32	0	1:16
TET. AT. UNITS/ML.	0.6				0.3		0.4	

FIGURE 4. Patient No. 129. Daily temperature, pulse and respiration related to total white blood count, phagocytic index, complement titer and synthesis of tetanus antitoxin.

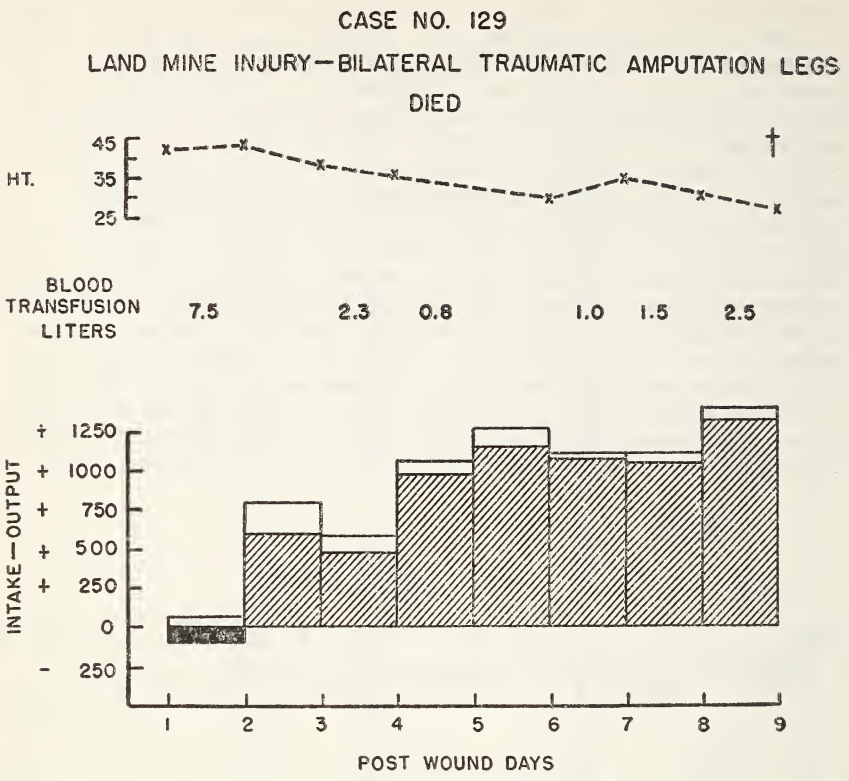


FIGURE 5. Patient No. 129. Daily record of fluid balance, not corrected for insensible water loss. Charting follows method described by Moore and his associates.[14] The daily rematocrit and the volumes of blood administered to the patient are also recorded.

Figures 6 and 7 record the chemical data from the patient. The levels of non-protein nitrogen, phosphorus and potassium in the plasma increased as oliguria progressed with return towards normal following hemodialysis. Acidosis was progressive until the seventh post-wound day. The observations on calcium, chloride and sodium were influenced in part by the intermittent administration of these substances and also by hemodialysis.

Comment

The above two patients had sustained similar injuries and both became oliguric. A comparison of the chemical data reveals similar findings with the exception that the abnormal changes progressed more rapidly in patient No. 129. It is believed that this was related to the degree of the pathological changes in the muscle of the left amputation stump. Hemodialysis was first required on the third post-wound day with patient No. 129, whereas it was not needed until the eighth post-wound day with the other patient. But with both patients

hemodialysis restored the chemical deviations toward normal. Likewise, the other data from each patient which are presented in figures 1, 4, and 5 are quite similar. These observations appear to show that the specific measurable effects of acute renal failure were being controlled in both patients. But patient No. 129 died because of our inability to overcome the progressive necrotizing infection confined to a portion of the left amputation stump.

Discussion

The patients reported in the present study constituted a small selected group of the most severely founded casualties. Many of them were alive only because of extraordinary efforts made by medical personnel at forward levels. Uncontrollable circumstances often prevented the immediate application of all the desired appropriate thera-

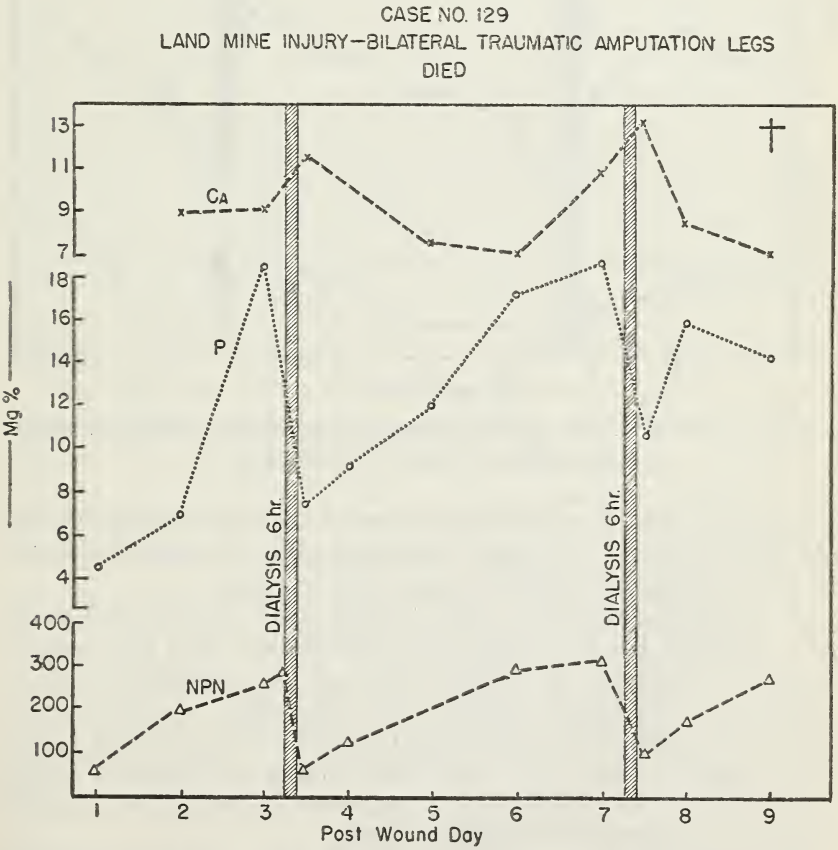


Figure 6. Patient No. 129. Plasma calcium, phosphorus and nonprotein nitrogen. Effect of hemodialysis.

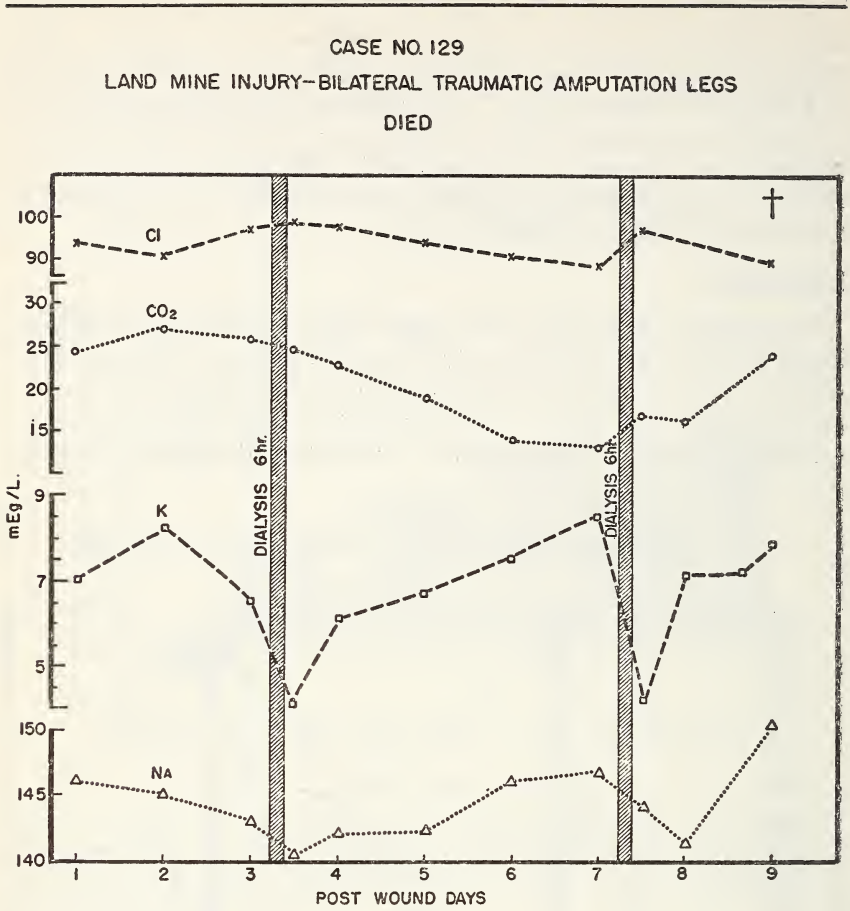


FIGURE 7. Patient No. 129. Plasma chloride, carbon dioxide content, potassium and sodium. Effect of hemodialysis.

peutic measures. For this reason some of the observations and conclusions reported in this paper are not necessarily applicable to the management of patients with less severe battle injury.

If the onset of oliguria is a direct reflection of the magnitude or degree of tissue damage, it may be impossible to obtain valid control patients in studying the clinical course of post-traumatic renal insufficiency. The control subjects used in this study were severely injured and had been sent to the Renal Center because acute renal failure was suspected. Some of them had elevated nonprotein nitrogen plasma levels, but the degree of change manifested by the chemical data was much greater in the oliguric group.

The data from this study do not reveal any new factors of possible etiological significance in acute renal failure. Severe shock had been

present in 23 of the oliguric patients and was probably present in the other patient also. An inadequate history prevents a positive statement about the presence or absence of shock in the latter patient. All but three of the non-oliguric patients also had histories of severe shock and again the histories were inadequate where shock was not recorded. Therefore, the presence of severe shock following battle injury is not necessarily followed by persistent oliguria after resuscitation. This confirms the observations of the Second Auxiliary Surgical Group in World War II.[5] They reported a 7.1 per cent incidence of oliguria (including anuria) in 140 patients admitted to forward hospitals with a systolic blood pressure under 41 mm. Hg. The incidence was 2.5 per cent in patients admitted with a systolic pressure between 41 and 70 mm. Hg.

Wounds confined to the extremities were more common in oliguric patients from the present study; because extremity wounds were not present in all of the oliguric patients, their significance as an etiological factor is hard to evaluate. Specific analyses for myoglobin were not performed. For the same reason the possible etiological significance of the high incidence of clostridial-like myositis is in doubt. A transfusion reaction in shocked patients was thought to be etiologically significant in two of the oliguric patients. Three others sustained direct injury to one kidney and these, too, may have ben coincidental rather than truly significant in the etiology of the renal syndrome. It is possible that renal damage was the result of the cumulative effects of several insults which individually were insufficient to produce the lesion.

The high incidence of surgical complications in both the oliguric and non-oliguric patients was not surprising considering the circumstances. Of particular interest was the high incidence of infection found in both the oliguric and non-oliguric patients reported in this study. This was thought to be the primary cause of death in approximately 45 per cent of the fatalities. The effect of severe injury and of acute renal failure on resistance to infection in battle casualties has been the subject of a separate study by one of us (H. H. B.) ; these results have been reported in detail in another communication.[10] No evidence has been found that such patients were more prone to infection because of a deficiency in the natural or acquired antibacterial defense mechanisms. It was difficult to obtain reliable data in Korea on the incidence of serious infection in patients with severe battle injury who were not admitted to the Renal Center. And, as discussed above, the problem of securing valid control subjects with comparable injury but no renal disease may be insurmountable. However, the

incidence of infection was of the same order in the two small groups reported in this paper.

Complicating infection renders the control of the specific effects of acute renal failure much more difficult even if artificial hemodialysis is used.[9] Therefore, it is of the utmost importance to recognize infection early and to institute vigorous treatment without further delay. We found it important to examine all wounds at once in patients newly admitted to the Center, regardless of the accompanying history. Immediate secondary débridement was necessary in 14 of the 37 patients from the present study. Subsequently the wounds should be examined at least once a day to be certain that devitalized tissue or progressive infection are not present. Secondary débridements should be done as soon as the need is recognized and should be thorough and radical if oliguria is present. Likewise, it may be wiser to amputate an extremity without delay if there is any doubt about its viability rather than temporize in the interest of conserving a limb. Patients with post-traumatic renal insufficiency present such a poor prognosis that an error in judgment on the conservative side in wound management may precipitate a fatality. Nor may there be sufficient time to correct such an error because of the rapid deterioration of the clinical state. However, it was not always possible to undertake the desired radical surgery in some patients because of their extremely poor tolerance of any manipulation. In other patients, in whom excessive bleeding had followed secondary débridement, the subsequent débridements were sometimes curtailed because of the fear of serious hemorrhage. The above recommendations do not necessarily apply to other less severely wounded non-oliguric patients where the therapy of acute renal failure is not a factor. In the latter type of casualty the policy of minimal disturbance of wounds during the period between initial débridement and secondary closure was usually satisfactory.

The data presented on the transportation of patients with high plasma potassium levels to the Renal Center for possible hemodialysis are not encouraging. Only two patients survived and only one of these required dialysis within 24 hours of admission; but none of the deaths were due to hyperkalemia.

The arrival of patients at the Renal Center with high plasma potassium levels who were also in shock and whose wounds required débridement because of myositis presented a particularly difficult problem. Resuscitation was first attempted and then a decision had to be made on whether to dialyze the patient's blood or débride the wounds. If the latter was done first, there was the risk of sudden death on the operating table, possibly due to a further increase in the level

of potassium in association with anesthesia, hypotension, or wound manipulation. Furthermore, the heparinization required during the subsequent hemodialysis might promote bleeding from the freshly débrided wounds. If hemodialysis was done first, then myositis might progress during the 6 to 8 hours required for hemodialysis. When such a decision was required in patients reported in this study, hemodialysis was done first; but because most of the patients died eventually, there is little evidence that the decision was the correct one.

There appears to be little advantage in transporting other oliguric patients in whom the immediate danger from hyperkalemia is not great to a renal center if any of the well-established contraindications for moving patients are present. The anti-potassium fluids and electrolyte therapy advocated by Meroney and Herndon may be life-saving in such a situation.[9]

The fatality rate and survival time of the small series of oliguric patients reported in this study were somewhat different from those reported by Beecher and his associates.[3] The fatality rate for anuric patients was 14 per cent better and for oliguric patients 26 per cent worse than those reported in the World War II study. The latter difference is hard to understand and may be due to the smallness of the present series. But a significant finding in the present study is that the primary cause of death was thought to be the result of renal failure *per se* in only one patient. In the World War II study, uremia was the primary cause of death in 67 per cent of the fatalities. From this it seems apparent that careful medical management supplemented by artificial hemodialysis may control the abnormalities resulting from acute renal failure. Because such abnormalities may be lethal, their control is essential. It is equally clear that such management is only one facet in the therapy of patients with post-traumatic renal insufficiency. Other derangements, either apparent or unknown, which are responsible for the high fatality rate associated with this syndrome must also be sought for and treated.

Summary

1. The surgical care of 24 patients with post-traumatic renal failure (lower nephron nephrosis) and of 13 seriously wounded but non-oliguric casualties has been discussed. The effects of acute renal failure were controlled by careful medical management and also by artificial hemodialysis.

2. Significant infection was the most frequent complication encountered in both groups; the incidence was 83 per cent in the oliguric patients and 63 per cent in the non-oliguric patients.

3. Myositis, usually of a localized type and probably secondary to traumatic devascularization of muscle, was the most frequent complication found in the oliguric group. This could not be adequately controlled in 6 of 15 affected patients.

4. Other serious complications occurring in both groups of patients were postoperative shock and excessive wound bleeding after secondary débridement.

5. The fatality rate was high in both groups and the mean survival time of fatal cases from each group was not significantly different.

6. Renal failure was the immediate cause of death in only one of the oliguric patients. The principal causes of death in all of the fatal cases have been listed. Complicating infection was responsible for approximately 45 per cent of fatalities in each group.

7. Artificial hemodialysis was considered to be a life-saving procedure in one-third of the patients from the present series so treated. The data appear to show that the renal component can be eliminated as a cause of death in patients with post-traumatic renal insufficiency. If the fatality rate is to be further improved, then other causes of death must also be eliminated.

8. Severe trauma and shock were the only etiological factors consistently present in patients developing oliguria. Reaction to blood transfusion was not a prominent factor in the etiology of lower nephron nephrosis in patients from the present series.

9. If serious progressive surgical complications are present, a patient with lower nephron nephrosis probably should not be transported to a specific renal treatment center for possible artificial hemodialysis.

10. Complications of injury, especially infection, must be recognized early and treated aggressively to facilitate the control of the effects of renal failure.

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Chapter 6

The Role of Surgery in the Treatment of Post-traumatic, Acute Renal Failure*

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In the past decade many publications have dealt with acute renal failure,** describing its clinical manifestations, plasma electrolyte changes, complications and therapy.[12, 14, 29, 30, 32] Recently much stress has been laid on the occurrence of hyperkalemia in this syndrome.[6, 7, 8, 13, 15, 18] It is recognized that potassium intoxication is in some cases the major cause of death.[15, 18, 32] A number of methods were devised to reduce the serum potassium in patients so threatened.[4, 11, 20, 33] One of these methods which has met with considerable success in hemodialysis by means of the artificial kidney,[1, 16, 28] The artificial kidney is also used to reduce the level of diffusible catabolites which have accumulated in the extracellular fluids and can modify the symptoms of uremia.[14, 17, 18]

The following studies were carried out at a specialized treatment center in Korea where casualties who developed post-traumatic renal insufficiency were referred. An artificial kidney was employed as an adjunct in controlling uremia. Frequently, extensive areas of nonviable tissue were not or could not be removed in the initial surgery of these patients at forward surgical hospitals. It is our purpose to describe the clinical and laboratory course of some of these patients and to show that certain serum electrolyte disturbances were more rapid in onset and perhaps greater in magnitude than serum electrolyte deviations seen in patients who develop renal insufficiency of nontraumatic etiology, and to illustrate how these differences in clinical and chemical tempo lead to a somewhat changed approach in the medical and especially in the surgical management.

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*In press: *Surgery, Gynecology and Obstetrics.*

**This term is used in the sense defined by Oliver, *et al.*,[21] to include lesions previously called lower nephron nephrosis, crush syndrome, hemoglobinuric nephrosis, traumatic anuria and necrotizing nephrosis.

Methods

Serum potassium and sodium were determined by the flame photometer using an internal lithium standard,[2] serum chloride by the method of Schales and Schales,[27] serum CO_2 combining power by the manometric method of Van Slyke,[22] plasma nonprotein nitrogen and nonprotein nitrogen of the artificial kidney bath by selenium-sulfuric acid digestion and Nesslerization of the protein-free filtrate. Hematocrits were measured by the method of Wintrobe.[34]

The term *oliguria* is used to indicate a urinary output of less than 500 cc. per day. *Diuresis* indicates a rise in the urinary output above 1,000 cc. per day following a period of oliguria. All patients with oliguria were treated according to a basic medical regimen which included fluid intake restriction, intake of at least 400 calories per day, ambulation within the limits of tolerance, digitalis as indicated, testosterone propionate in an attempt to reduce the rate of protein catabolism,[17, 19] antibiotics, electrocardiograms daily or oftener, and daily plasma nonprotein nitrogen and electrolyte determinations.

To aid in the control of hyperkalemia S. K. F. Special Resin No. 648,* a cross-linked, polyacrylic, ammonium carboxylate, cation exchange resin was employed, whenever possible, orally or by retention enema. When hyperkalemia could not be controlled by resin therapy, when ECG changes progressed in spite of medical measures, or when the symptoms of uremia became severe an artificial kidney was used. The artificial kidney employed was the modification of Kolff's model [14] described by Merrill, Thorn, *et al.*[16] Intravenous glucose solutions, insulin and hypertonic sodium chloride were often used as an emergency therapy of potassium intoxication.[18]

The following case reports are presented in three groups: *Group I:* Moderately wounded patients, free of any great amount of tissue damage or infection who have developed acute renal failure as the result of transfusion reactions. This is considered a control group. *Group II:* Patients with acute renal failure complicated by the presence of massive tissue necrosis and infection in whom the necrosis or infection could not be removed. *Group III:* Patients with acute renal failure associated with severe necrosis of tissue or infection in whom the infection or necrosis could be removed.

For the sake of conciseness vital signs and laboratory studies obtained on admission are listed together in Table 1.

*This material was provided by Smith, Kline and French Laboratories, Philadelphia.

Table 1. Admission Data, Renal Insufficiency Center

	Vital Signs					Laboratory Studies					
	Age in yrs.	B.P. mm./Hg.	Pulse	Resp.	Temp. °F.	Na mEq./L.	K mEq./L.	Cl mEq./L.	CO_2 mEq./L.	NPN mg. per 100 cc.	Hemat. mm.
Group I											
A	20	120/70	74	18	99. 6	128	3. 8	91. 2	23. 5	88. 6	29
B	22	106/70	100		97. 0	128	6. 1	89. 6		203	14
Group II											
A	20	84/60	120	52	100. 8	137	6. 6	92. 5	21. 6	87	
B	21	120/70	88		99. 6	125	6. 1	88	27	88. 2	40
C	21	150/90	125	28	99. 6	129	7. 5	88	28	191	42
D	21	120/70	110	20		128	7. 3	79. 5		174	27
Group III											
A	22	120/90	110	32	101. 5	113	6. 2	82	21	144	30
B	23	170/105	90	16		116	6. 6	88	21. 9	163	30

Case Histories

Group I. Patients with acute renal failure unaccompanied by marked infection or gross amounts of devitalized tissue.

Case A. An exploding land mine inflicted a traumatic amputation of the right foot and penetrating wounds of the right wrist, left thigh and left knee to this patient. At a Mobile Army Surgical Hospital (MASH) 2 hours after injury, admission blood pressure was 120/80. Guillotine amputation of the right lower leg, arthrotomy of the left knee joint and débridement of the other wounds were performed, during which 2,500 cc. of dextran and 1,000 cc. of whole blood were given. The patient did well on the first three postoperative days but was repeatedly transfused because of a low hematocrit. On the fourth postoperative day a hemolytic transfusion reaction developed. In the following 12 hours the urinary output was only 100 cc. A water load test of 1,000 cc. of 5 per cent dextrose in water produced no increase in urinary output after rapid infusion. Because of his oliguria the patient was evacuated to the Renal Insufficiency Center (RIC) where he arrived 24 hours after the reaction.

Physical Examination. The only abnormality found on examination was the postoperative state described above.

Hospital Course. The 24-hour urinary output, which was 100 cc. on the first day, gradually increased, exceeding 1 liter on the eighth post-reaction day. Serum potassium never rose above 5.0 mEq./L. Nonprotein nitrogen rose gradually, reaching a maximum of 273 on the ninth post-reaction day. Following the onset of diuresis, the NPN gradually dropped, returning to normal on the sixteenth post-reaction day. The patient's wounds remained clean, and granulations began to appear as the NPN returned to normal. He was evacuated on the eighteenth post-reaction day.

Case B. This Turkish soldier received shell fragment wounds to both thighs. At operation 7½ hours after injury, a severed right femoral artery was repaired by end-to-end anastomosis. The patient's other wounds were débrided. Hypotension did not occur either before or during the procedure. Postoperatively he made excellent progress. His right foot remained pink with a good dorsalis pedis pulse. On the seventh postoperative day during a secondary closure of his wounds, the patient received a pint of mismatched blood which resulted in a hemolytic reaction associated with hypotension, cyanosis and a hemorrhagic diathesis. Despite transfusions the patient remained hypotensive during most of the first 24 hours following the reaction. His urine was noted to be scant and dark. Because of the hypotension and oliguria the patient was evacuated to the RIC on the second post-reaction day.

Physical Examination. The patient was alert; sclerae were icteric; heart and lungs were normal. Examination of his legs revealed the secondarily closed thigh wounds, moderate edema of the right leg and bilaterally palpable dorsalis pedis pulses. The ECG showed evidence of early potassium intoxication.

Hospital Course. Because of his very low hematocrit the patient was given 1,000 cc. of fresh whole blood on admission. On the fourth post-reaction day he became lethargic, confused and vomited frequently. Serum potassium rose to 6.3 mEq./L. and the ECG indicated increasing potassium intoxication. For these reasons dialysis by means of the artificial kidney was performed during which serum potassium fell to 3.6 mEq./L. and the NPN fell to 83 mg. per 100 cc. On the fifth post-reaction day he was alert and cooperative and vomiting had ceased. Ion-exchange resins were started by mouth. During 12 days of oliguria the NPN rose in small increments to 284 mg. per 100 cc. and potassium remained normal.

Management of the diuretic phase was complicated by urine volumes between 6,000 and 8,000 cc. for 8 days accompanied by vomiting, but he was evacuated in good condition on the thirtieth post-reaction day. This patient's wounds remained clean but showed no signs of healing during the period of oliguria; with the onset of diuresis granulations formed rapidly and the wounds healed.

Group II. Cases with acute renal failure complicated by massive wounds or infections in which the infection could not be controlled or the devitalized tissue thoroughly removed.

Case A. This patient sustained a rifle bullet wound in the epigastrium with much loss of tissue from the abdominal wall, transection of the transverse colon and a large laceration in the right lobe of the liver. Blood pressure on admission to a hospital 24 hours after wounding was 90/68. At surgery the liver was sutured and the colon was exteriorized through the wound of entry since this defect could not be closed in any other way. During the first 24 hours postoperatively the systolic pressure remained below 90 despite transfusions of 5,500 cc. of blood, 850 cc. of plasma and 200 cc. of albumin. Urine output on the first post-wound day was 200 cc. A water load test produced a minimal response. Because of his oliguria the patient was transferred to the RIC 36 hours after operation.

Physical Examination. The patient appeared critically ill with a flushed face, mental confusion, and shallow, rapid respirations. Heart and lungs were normal. A portion of the exteriorized colon was black and necrotic. The abdomen was silent. The ECG showed moderate peaking of the T waves and shortening of the S–T segment without QRS prolongation.

Hospital Course. On admission the colostomy was opened and the necrotic bowel débrided. Because plasma potassium had reached a level of 6.6 mEq./L. with ECG changes only 36 hours after operation, dialysis was undertaken for 3 hours against a bath in which the potassium had been omitted. Plasma potassium was reduced to 3.8 mEq./L. and NPN fell to 61.4 mg. per 100 cc. Blood pressure rose to 128/74 by the end of dialysis, and the patient appeared clinically improved. Immediately after the dialysis 60 gm. of cation-exchange resin was given by rectum.

As indicated in Figure 1, plasma NPN rose precipitously. Paralleling this change the patient deteriorated clinically with development of disorientation and a uremic frost. Dialyses on the sixth and ninth post-wound days were followed by brief clinical improvement and abrupt relapse. Following the third diaylsis plasma potassium rose 2.7 mEq./L. and the NPN rose 117 mg. per 100 cc. in less than 24 hours. Daily urine output gradually increased to a maximum of 425 cc. on the ninth post-injury day. Evidence of peritonitis with a distended silent abdomen and rectal temperatures of 100° to 103° were present throughout the patient's course despite appropriate therapy. On the tenth post-wound day the patient's blood pressure became unobtainable and he died. Serum potassium taken 8 hours before death was 8.6 mEq./L.

Gross Autopsy Findings. Extensive generalized peritonitis was found with 100 cc. of purulent exudate lying free in the pelvis. No perforation of the bowel was found except in the exteriorized segment. There was a 6 cm. laceration of the right lobe of the liver surrounded by some fibrin. Not more than 2 per cent of the liver was involved. The kidneys weighed 250 gm. each and showed a dark purple medulla with some thickening of the cortex.

Case B. This patient was injured by a land mine, and when he reached a MASH 3 hours after injury blood pressure was unobtainable. The patient was resusciated with 5,000 cc. of whole blood. At surgery a left supracondlylar

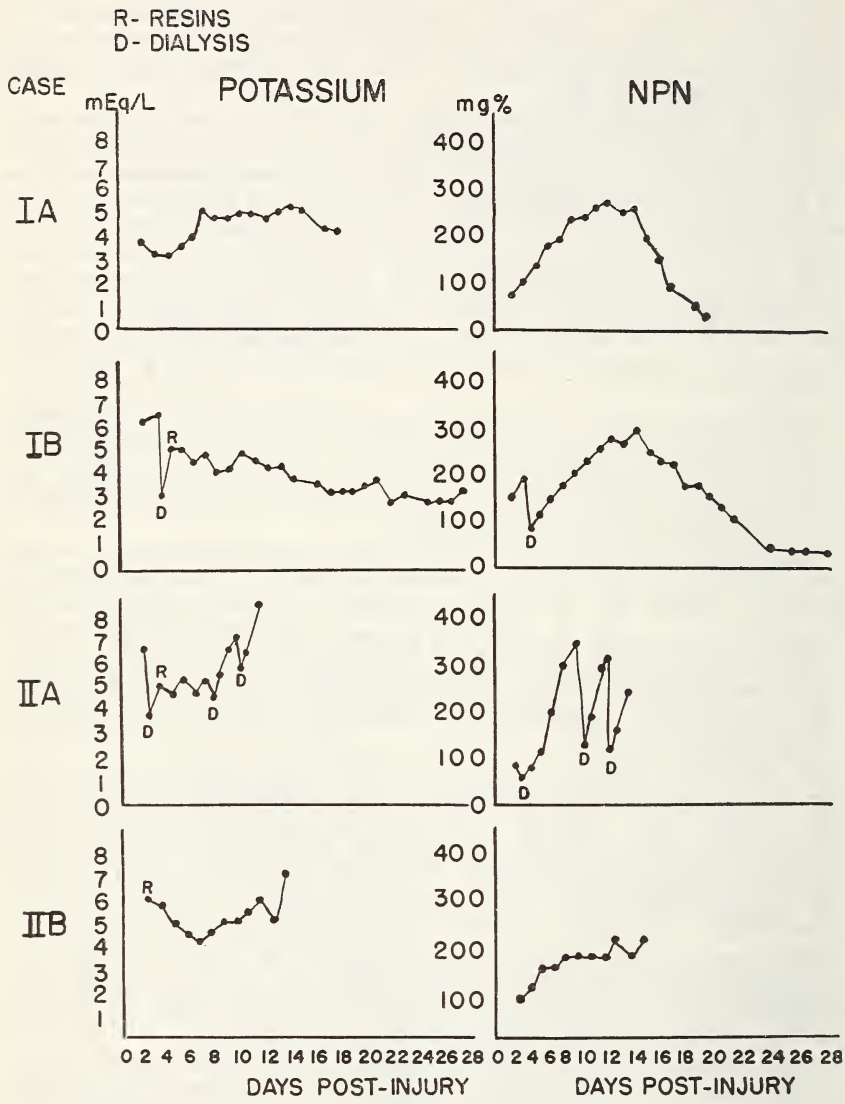
R- RESINS
D- DIALYSIS
CASE
mEq/L
POTASSIUM
mg%
NPN
IA
IB
IIA
IIB
R
D
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
DAYS POST-INJURY

FIGURE 1.

amputation, right orchidectomy and extensive débridement of a large avulsed area of skin and muscle over the right anterior thigh were carried out; wounds of the right buttock and right arm were débrided. A posterior splint was applied to the right arm for a compound, comminuted fracture of the right radius. Surgery was well tolerated without hypotension. However, on the first post-injury day urine output was only 200 cc. Early on the second post-wound day a water load test produced no diuresis and the patient was transferred to the RIC for treatment.

Physical Examination. The patient's wounds were as described above. The avulsion over the right thigh was massive with the loss of skin and some muscle over an area of 18 by 18 cm. The right forearm was quite edematous over the fracture site and crepitation of the bone fragments was felt. The lungs were clear and the heart was normal. Active peristaltic sounds were present. Two Penrose drains had been left in the deep wound of the right buttock. Rectal examination was negative. The ECG was essentially normal.

Hospital Course. Because of the lowered sodium and elevated potassium on admission, 300 cc. of 3 per cent saline was given intravenously and 60 gm. of cation-exchange resin was administered by rectum. Plasma potassium dropped to 5.1 mEq./L. on the day following admission. Diuresis began on the sixth post-injury day and the patient continued to do well until the tenth post-wound day, when a rectal temperature of 102.8°, leukocytosis of 22,500 cells per cu. mm., and increasing lethargy were noted. All dressings were changed and the wounds were found to be relatively clean although draining profusely. A long arm cast was applied to the right arm replacing the posterior splint. There was no abdominal distention and the patient continued to take fluids well by mouth. On the eleventh and twelfth days he deteriorated clinically and became disorienated. Despite an output of 4,000 cc. of urine on the eleventh day his serum potassium increased slowly to 6.0 mEq./L. and his NPN reached 205 mg. per 100 cc. On the thirteenth day some foul drainage appeared on the long arm cast. The cast was removed revealing a large abscess in an inadequately débrided wound track which extended from the right wrist to the elbow. This abscess was opened widely and 300 cc. of foul pus was removed; cultures grew *Aerobacter aerogenes* and *Staphylococcus aureus.* The patient showed little improvement following the procedure, and in the afternoon of the thirteenth day he suddenly and rather unexpectedly died. Plasma potassium that morning was 7.1 mEq./L. None of his wounds showed evidence of granulations or other signs of healing.

Gross Autopsy Findings. One of the perforating wounds of the buttock communicated with a compound fracture of the tip of the sacrum and a perirectal abscess which extended to the peritoneal floor of the pelvis. The bowel was intact. Muscles of the right forearm were soft, friable and purple red. The brachial artery was thrombosed at the level of the mid-humerus. There was marked cerebral edema. Renal congestion was noted.

Case C. This patient was wounded by mortar fire sustaining comminuted fractures of the right tibia, fibula and femur and multiple large penetrating soft tissue wounds of both legs, and left buttock and the right flank with extensive muscle damage. On admission to MASH 2 hours after injury, blood pressure was 100/40 and the urine was grossly bloody. In the course of débridement under anesthesia the patient's blood pressure became unobtainable and surgery was discontinued. A total of 14,000 cc. of blood, 50 cc. of plasma and 200 cc. of albumin were given on the day of injury, followed by 2,500 cc. of blood on the second post-injury day. Hypotension persisted, however, and the average uri-

nary output was 100 cc. per day. The patient was, therefore, transferred to the RIC.

Physical Examination. The patient was acutely ill but oriented. Massive destruction of the musculature of both legs and the left buttock was noted. The right lower leg and foot were cold. Heart, lungs and abdomen were normal. The ECG showed characteristic evidence of potassium intoxication.

Hospital Course. Dialysis by means of the artificial kidney was begun within 4 hours after admission. During this 6-hour treatment plasma potassium fell from 7.6 to 5.3 mEq./L. and NPN fell from 191 to 52 mg. per 100 cc.; the patient seemed much improved. Six hours after dialysis a right below-knee amputation with extensive débridement of both legs anteriorly and posteriorly was done. The wound of the right flank was explored and the right kidney was found to be lacerated. It was left in place and the renal bed was drained. The patient tolerated the procedure well and returned to the ward in good condition. In spite of oral resin therapy plasma potassium rose within 48 hours after the first dialysis to 7.1 mEq./L.; NPN rose to 163 mg. per 100 cc. A second dialysis reduced the potassium to 4.1 mEq./L. and the NPN to 67 mg. per 100 cc. Thirty-six hours later, on the eighth post-injury day, potassium intoxication had recurred and the patient developed a silent, tender, distended abdomen and jaundice. Bile peritonitis was suspected and exploratory laparotomy seemed necessary. A third dialysis was undertaken in preparation for surgery but was interrupted by the development of cardiac arrest. The chest was opened and cardiac massage was carried out. Cardiac function resumed after 15 minutes of massage. Blood pressure rose to 180/70 during the next hour as dialysis was continued and serial ECG's showed disappearance of potassium intoxication. Although regular heart action continued, the patient's blood pressure began to fall after the first hour. Repeated small transfusions were of temporary benefit only. Dialysis was continued for 6 hours. The patient was returned to the ward in poor condition and died early on the ninth post-injury day.

Gross Autopsy Findings. A major portion of the posterior muscle groups of both thighs and the left calf were absent. Despite the extensive débridement much necrotic muscle remained. No evidence of wound healing was present. Both kidneys were enlarged with a combined weight of more than 500 gm. The right kidney contained a laceration 6 cm. long and was surrounded by a large hematoma.

Case D. This patient was wounded by mortar fire sustaining a traumatic amputation of the left upper thigh at the hip, multiple penetrating wounds of both buttocks and of the lumbar region and avulsion of most of the skin and much muscle tissue over the left buttock. He arrived at a MASH 9 hours post-injury with a blood pressure of 80/40. At operation a compound, comminuted fracture of the lower sacrum was found with multiple perforations of the rectum and a large amount of feces in the wound. A large hematoma was found in the pelvis surrounding the bladder and rectum. The bladder was intact. A double-barreled sigmoid colostomy was performed, and the wounds were débrided. During the operation the patient's blood pressure was unobtainable for 45 minutes. It finally rose to 86/40. In the first 6 hours postoperatively the blood pressure varied between 90/60 and 70/40. The patient received a total of 8,000 cc. of whole blood on the day of operation. On the first post-injury day urinary output was only 200 cc.; the patient was transferred to the RIC on the second post-wound day.

Physical Examination. The patient was alert, well hydrated and there was no edema. Wounds were as described above, and in addition there was a com-

pound, comminuted fracture of the right fibula. The wounds of the buttock contained much foul-smelling necrotic tissue. Heart and lungs were normal. Reflexes were equal and active. ECG findings of widened QRS complexes and high peaked T waves indicated marked potassium intoxication.

Hospital Course. Prior to dialysis the patient received hypertonic sodium chloride and glucose-insulin infusions; plasma potassium fell to 6.8 mEq./L. During a 5-hour dialyis, plasma potassium fell to 5.1 mEq./L. and the NPN to 97.8 mg. per 100 cc. Sixty grams of cation-exchange resin was then given orally. At this time bowel sounds were present and active. He took oral feedings well and continued to do so throughout his course. During the next 12 hours (third post-injury day) the plasma potassium rose 2.5 mEq./L. to a level of 7.6 mEq./L. again with marked, characteristic ECG changes. A second dialysis for 4 hours reduced the serum potassium to 4.0 mEq./L. Soon after dialysis, débridement of the large avulsed area of the left buttock was begun. The entire left gluteus maximus, most of the gluteus medius and minimus and the remaining hamstring muscles were black and necrotic. There was no evidence of gas in the tissue planes and it was felt that this extensive gangrene of muscle was due to blast effect. All of the involved muscle groups were resected as thoroughly as possible, exposing portions of the ileum and the posterior portion of the capsule of the hip joint. The lower third of the sacrum was found to be partially avulsed exposing the retrorectal space. This area was drained. A large wound of the right buttock was also débrided. The patient withstood the procedure fairly well and was returned to the ward in fair condition. Another 60 gm. of cation exchange resin was given orally.

As indicated in Figure 2, the plasma concentrations of potassium and NPN continued to be remarkably labile. Despite a second and third débridement on the fifth and twelfth post-injury days, all of the necrotic tissue could not be removed. Dialysis was repeated on the sixth, eleventh and fourteenth post-wound days with relief in each instance of disorientation, stupor and nausea but with a subsequent relapse in 24 to 72 hours. During the fourteenth post-wound day the plasma potassium rose from 4.7 to 7.8 mEq./L. or 3.1 mEq./L. in a 24-hour period; in the same interval the NPN rose 144 mg. per 100 cc. The patient became semi-comatose and his blood pressure became unstable. Emergency treatment with hypertonic saline, glucose and insulin lowered the plasma potassium to 7.4 mEq./L. Following this sixth dialysis the plasma potassium was 5.1 mEq./L. and the NPN 131 mg. per 100 cc. However, despite digitalization, nasal oxygen, small amounts of whole blood, 20 cc. of adrenal cortical extract and nor-adrenalin, the patient's blood pressure was labile and at times unobtainable during and after the dialysis. After dialysis the blood pressure continued at very low levels despite all supportive measures and the patient died, 6 hours after dialysis, on his sixteenth post-wound day. The maximal daily urine volume never exceeded 400 cc.

Gross Autopsy Findings. The muscle tissue of the left hip and in the area over both buttocks had undergone extensive destruction. It was estimated that two-thirds of the skin over the left buttock and one-third of the skin over the right buttock was missing. The remaining muscle was soft, hemorrhagic and necrotic in many places. The muscles and retroperitoneal tissue of the pelvic floor showed extensive destruction and necrosis. A rubber drain was noted extending into the retropubic space where a well localized, well drained abscess cavity was present. Sinus tracts communicated through the shattered sacrum and coccyx with the perirectal space. Little or no granulation tissue was present. The right kidney weighed 165 gm.; the left, 190 gm. Both kidneys showed congestion of the renal medullae.

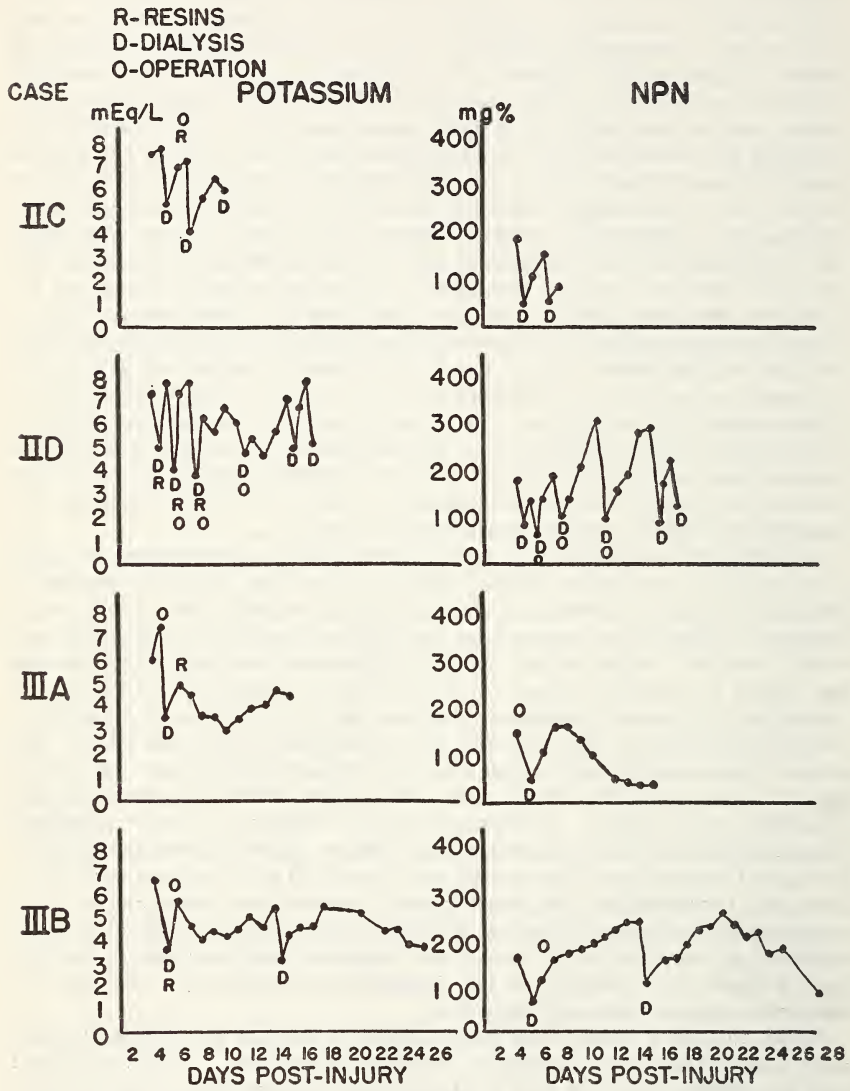
R-RESINS
D-DIALYSIS
O-OPERATION
CASE
POTASSIUM
NPN
mEq/L
mg%
IIC
IID
IIIA
IIIB
DAYS POST-INJURY
DAYS POST-INJURY

FIGURE 2.

Group III. Patients with acute renal failure complicated by the presence of infection or large amounts of necrotic tissue in which the infection could be controlled or the devitalized tissue removed.

Case A. This patient was injured by a land mine, sustaining extensive, macerating wounds of both legs with compound, comminuted fractures of both tibiae and fibulae. He arrived at a MASH 1½ hours after injury at which time he was thought to be moribund. Blood pressure and pulse were unobtainable. In the first 24 hours after wounding the patient received 6,500 cc. of blood but his blood pressure remained unstable and at hypotensive levels for 12 hours. At operation his wounds were débrided and long leg casts were applied bilaterally. During the first post-injury day the patient's urinary output was 980 cc., but renal clearance studies done by a research unit attached to the MASH showed a marked reduction of renal clearance. On the second post-injury day the patient became delirious and violent. His temperature rose to 103° rectally. Renal clearances were further reduced and total urine output for the day was only 320 cc. Because of the progressive depression of renal function the patient was transferred to the RIC. At the time of evacuation it was noted that the left foot was cold, and it was thought that amputation might be necessary.

Physical Examination. The patient was semi-comatose. Reflexes were hypoactive but present symmetrically. Heart, lungs and abdomen were normal. Long leg casts were present on both legs and were soaked by foul-smelling drainage. On removal of the casts, both legs to the knees were seen to be severely mangled and markedly necrotic, with subcutaneous emphysema. Cultures were taken which later showed *Clostridium welchii.* The ECG showed changes indicative of moderate potassium intoxication.

Hospital Course. In the presence of advanced bilateral gas gangrene it was felt that immediate operation was indicated. Because of the patient's elevated plasma potassium and lowered plasma sodium, emergency therapy in the form of intravenous hypertonic saline, glucose and insulin was given. However, an ECG obtained following this therapy showed an increase in potassium effect with widening of the QRS complex and increased peaking of the T waves. Another hemodialysis was in progress at this time and there seemed no alternative but to proceed with the operation. The patient underwent bilateral above-knee amputation done by two teams working simultaneously. The patient was hypotensive throughout the procedure with a blood pressure of 90/60 despite transfusion. He returned to the ward in very poor condition. Immediately postoperatively his temperature rose to 107.5° rectally and remained between 105° and 107° despite iced alcohol baths and rectal aspirin. He was completely comatose and areflexic. The pupils were dilated and did not respond to light. Respirations were Cheyne-Stokes and gasping in character. At one point the patient was apneic for 1 minute but after artificial respiration spontaneous respirations resumed. Repeat ECG showed marked progression of potassium intoxication. The patient's pulse reached 150 per minute and arrythmias on the basis of ectopic auricular foci developed. Another infusion of saline, glucose and insulin was given. Serum analysis following this showed that the sodium had risen to 132 mEq./L. but the potassium had also risen to 7.4 mEq./L., an increase of 1.2 mEq./L. in 8 hours despite vigorous emergency therapy.

Dialysis was started as soon as the artificial kidney was available for use. At this time the patient was still comatose. His pulse was weak and at times unobtainable. Blood pressure was 96/62. After 2 hours of dialysis during which small amounts of blood were given the blood pressure was 116/70 and the patient responded weakly to vocal stimuli. At the end of the 6-hour dialysis blood pres-

sure was 160/80, the patient was fully conscious and talking although still somewhat disoriented. The NPN had fallen from 144 to 53.4 mg. per 100 cc. with the removal of 86 gm. Plasma potassium had dropped from 7.4 to 3.6 mEq./L. with the removal of 300 mEq./L. Temperature was 102° rectally and respirations were 24 and regular. The patient was returned to the ward in good condition and given 60 gm. of cation-exchange resin by rectum. The remainder of the patient's course was uneventful. Diuresis started on the seventh post-injury day. NPN rose to a peak of 168 mg. per 100 cc. on the eighth post-injury day and fell rapidly thereafter. The plasma potassium remained under good control, never rising above normal limits after the dialysis. The amputation stumps remained clean and granulation tissue began to appear on the tenth post-injury day. The patient was evacuated on the sixteenth post-injury day.

Case B. This patient, wounded by mortar fire, was admitted to a MASH 3 hours after injury with penetrating wounds of both knees and thighs, most extensive on the left with transection of the left superficial femoral and left popliteal arteries. Blood pressure was 90/50. At operation his wounds were débrided and re-anastomosis of the injured femoral and popliteal arteries was performed. Before and during operation the patient received 4,500 cc. of blood. After operaton the left foot was cold and mottled and its survival was considered unlikely. On the first post-injury day the urine output was 480 cc.; the patient was nauseated, restless and apprehensive. On the second post-injury day he vomited all oral intake. The 24-hour urine volume was only 150 cc. Because of the persistent oliguria the patient was evacuated to the RIC.

Physical Examination. The patient was fairly well oriented but was hiccuping and gagging. His wounds were as described above. The left foot and lower leg to the level of the mid-calf were cold and mottled; the left dorsalis pedis and popliteal pulses were absent. Heart and lungs were not remarkable. Good peristaltic sounds were heard. The ECG showed changes indicative of early potassium intoxication.

Hospital Course. Although the patient's chemical state did not constitute an emergency, a dialysis was decided upon as the quickest method of returning his high potassium and lowered sodium to normal, stopping his vomiting and rendering his course more manageable. Dialysis was carried out for 5 hours on the third post-wound day. Serum sodium rose to 141 mEq./L., potassium fell to 3.9 mEq./L and NPN to 71 mg. per 100 cc. On the fourth post-injury day the patient was much improved and no longer nauseated. Thirty grams of cation-exchange resin was given by mouth. On the fifth post-injury day, only 24 hours after dialysis, the serum potassium was found to have risen 1.9 mEq./L. to a level of 5.8 mEq./L. despite resin therapy. NPN had risen to 124 mg. per 100 cc. The left lower leg remained cold and mottled to the mid-calf although no definite line of demarcation was in evidence. Because of the rapidly rising potassium and NPN, immediate amputation was deemed advisable without waiting for further demarcation. At operation a below-the-knee approach was first attempted, but it was found that all muscles of the posterior compartment of the leg were necrotic and supracondylar amputation was done. The patient withstood the procedure well. By the following day the serum potassium had fallen to 4.8 mEq./L. Thereafter the potassium and NPN rose only in small increments. By the thirteenth post-injury day the NPN was 253 mg. per 100 cc. and the serum potassium, 5.6 mEq./L. The patient was drowsy, confused and vomiting frequently. In order to control these symptoms another dialysis was performed. Potassium was reduced to 3.2 mEq./L. and NPN to 120 mg. per 100 cc. The

patient's clinical condition became much improved. Diuresis began on the eighteenth post-injury day after which plasma NPN gradually fell to normal levels. The amputation stump and other wounds remained clean but there were few signs of healing until about the eighteenth or nineteenth day when granulation tissue appeared and began rapidly to fill in the wounds. The patient was evacuated in good condition.

Discussion

Since the potassium concentration of intracellular fluid is normally about 150 mEq./L. compared to the 4.0 mEq./L. found in extracellular fluids, potassium intoxication is avoided only by unknown mechanisms at the cell membrane which maintain the physiological concentration gradient. The maintenance of this gradient requires work and it is likely that an injured cell will be less able and a dead cell unable to prevent free diffusion of this ion.

Recent clinical and experimental evidence appears to support this hypothesis: Bywaters [3] emphasized the rapid development of marked uremia and hyperkalemia in war casualties who have acute renal failure. He found that patients suffering from crushing wounds of the extremities complicated by oliguria frequently died in the first week after injury, most often on the sixth day. Death occurred very suddenly and was frequently preceded by cardiac irregularities. The electrocardiogram showed changes indicative of potassium intoxication and the serum potassium level was often twice normal. Blood urea levels rose as high as 400 to 500 mg. per 100 cc. in a relatively brief period. Mortality exceeded 80 per cent. It was Bywaters' impression that these changes were due to the release of large amounts of potassium and nonprotein nitrogen from necrotic muscle in the absence of a renal excretion route. Samples of necrotic muscle taken from the patients at autopsy showed a loss of 66 per cent of potassium and 70 per cent of creatinine compared to samples of undamaged muscle from the same body.

In patients who have had the circulation to a limb occluded by a tourniquet for 30 minutes to 1 hour, Rewell [24, 25] noted an increase in serum potassium following the release of the tourniquet. He concluded that the anoxic cells release potassium or an agent which produced potassium release from cells elsewhere in the body.

In the experimental animal, muscle injury and necrosis from heat, cold or trauma results in major shifts of fluid and electrolytes.[9, 23, 26] Injured muscles lose potassium and gain sodium while uninjured cells throughout the body gain potassium and lose sodium. The loss of potassium from injured cells is progressive and parallels the disinte-

gration of the cells. Pirozynski and Webster [23] showed that the severity of the injury was directly related to the electrolyte change.

The characteristic differences between the three groups of patients presented here suggest that undébrided, dead or injured tissue in the presence of renal insufficiency is associated with increased rates of potassium and nonprotein nitrogen accumulation in the extracellular fluid. In Group I acute renal failure occurred as the result of transfusion reactions which took place some time after the patients were wounded. Little injured tissue or infection complicated the picture of renal insufficiency. It should be emphasized that although oliguria persisted for 8 days in one case and 12 days in the other the nonprotein nitrogen rose only in small increments over this period and the level of serum potassium was easily controlled. In case IB the patient had a moderate hyperkalemia on admission secondary perhaps to potassium liberation during the hemolytic episode. After one dialysis no further hyperkalemia occurred.

The patients in Group I may be contrasted with those in Group II in whom undébrided necrotic tissue remained. Patients in Group II rapidly accumulated plasma potassium and nonprotein nitrogen in three instances despite repeated dialyses and the administration of ion-exchange resins in all (Figs. 1 and 2). This was most marked in case IID where the plasma potassium rose as much as 3.1 mEq./L. and the NPN 144 mg. per 100 cc. in 24 hours.

In case IIA the patient had little apparent direct tissue damage but suffered from advanced infection. In case IIC large amounts of crushed and injured tissue were not sufficiently débrided while infection played an ostensibly minor role. Patient IID had massive tissue injuries associated with very rapid accumulation of potassium and nonprotein nitrogen. Following vigorous débridement of the dead tissues the plasma potassium concentration seemed better controlled for several days. Another period of rapidly increasing uremia and hyperkalemia followed, probably due to uncontrolled infection and progressive necrosis of tissue in the pelvic floor. Case IIB is of special interest: a progressive rise of plasma potassium up to 7.1 mEq./L. occurred despite a diuresis of 4,000 cc. of urine per day containing up to 42 mEq./L. of potassium. This is in sharp contrast with most previous experience among patients with renal failure, namely, that hyperkalemia is rare if the urinary output exceeds 500 cc. per day.[17]

If we accept the concept that the presence of infected and necrotic tissue is associated with a rapid and dangerous development of potassium intoxication and clinical uremia in the oliguric patient, then early surgical removal of this tissue would seem a logical step in treat-

ment. The third group of patients presented demonstrate the use of surgical measures to aid recovery. In patients IIIA and IIIB hyperkalemia and uremia were much more easily controlled after large areas of non-viable and infected tissue were removed. In patient IIIB, serum potassium and nonprotein nitrogen rose rapidly after dialysis, but following amputation of the avascular extremity, nonprotein nitrogen rose only in small increments and potassium was easily controlled by ion-exchange resins throughout 18 days of oliguria. It should be noted that in both these cases the entire portion of non-viable tissue was contained in the extremities and could be removed *in toto* at a single operation.

The proper treatment of patients with post-traumatic renal insufficiency requires a well coordinated team of internists and surgeons skilled in the use of fluid and electrolyte therapy. Because of the traumatic nature of their lesions such patients will usually be seen and treated first by surgeons, who must be alert to the possibilities of a complicating acute renal failure. Whereas *hypo*kalemia is a frequently emphasized and well recognized postoperative complication,[19] renal failure with a rapidly developing dangerous *hyper*kalemia following trauma has received little emphasis; that it can be considered as an indication for operation is a new concept. Needless to say, post-surgical potassium therapy is emphatically contraindicated under these circumstances.

Basic surgical principles are modified only in that they are even more vigorously and energetically applied in the presence of acute renal failure. When an area of infected or injured tissue is suspected by the appearance of the earliest suggestive symptoms or signs, drainage or débridement should promptly be performed. Application of this principle would dictate removal of all doubtful tissue in the course of débridement rather than following a "wait and see" policy despite the temptation to be less radical in a patient who is critically ill. This applies also to patients who have lost the blood supply to a limb and in whom a line of demarcation is sought prior to amputation. With normal kidney function the products of decomposition of ischemic tissue are excreted readily without clinical signs of change in the plasma electrolyte; waiting for demarcation is justifiable. In the oliguric patient under the same circumstances the products of tissue breakdown cannot be excreted and the dangers of fulminating uremia and hyperkalemia may render any delay extremely hazardous.

In the reverse situation a sudden increase in the rate of accumulation of plasma nonprotein nitrogen or potassium concentrations in the oliguric patient may indicate occult infection or necrosis. A careful

examination of the patient may show an early subphrenic abscess, a pelvic abscess, or an area of infection hidden by a cast (as in case IIB).

A striking feature in patients with acute renal failure was the delayed appearance of granulation tissue and wound healing. This was true in all the groups presented. Frequently the onset of diuresis and a fall in the serum nonprotein nitrogen seemed to coincide with a sudden increase of granulation tissue and accelerated wound healing. Whether this finding may be explained by the accumulation of metabolic end-products which inhibit the healing process or by the state of "excessive response" described by Moore [19] is not known. In any case, the expectation of delayed healing must be kept in mind when the wounds of these patients are being treated or operation is contemplated. Dehiscence occurs frequently. When suture material is selected it should be of the type that will retain its strength and can be left in place until kidney function returns and uremia abates.

Delayed wound healing may result in a vicious cycle: Deficient tissue repair and poor localization of infection contribute to further infection with increased tissue injury and necrosis; this tissue injury in turn contributes to a greater degree of uremia, thus wound healing is further delayed and the opportunity for further infection and necrosis is enhanced.

Surgery is of course of the greatest help in those patients with necrosis and infection confined to the extremities. Here the entire area affected can be removed, leaving the smallest possible surface exposed to reinfection. Such patients should have the best prognosis and it has already been noted that both patients in our third group were of this type.

Post-traumatic renal insufficiency is seen only occasionally in civilian practice: Renal failure following accidental crush injuries, traffic accidents with massive trauma or shock, and occasionally renal failure superimposed on radical surgery are examples. However, in event of a civil catastrophe or war such problems can become commonplace. A full understanding of the problems of therapy will help to reduce mortality in these circumstances.

Summary and Conclusions

1. The case histories of eight patients with acute renal failure have been presented. In two of these cases renal insufficiency followed transfusion reactions. In six cases the renal insufficiency occurred after trauma.

2. Accumulation of potassium and nonprotein nitrogen in the serum of patients with renal insufficiency is accelerated in the presence of

large amounts of necrotic tissue or infection. Fatal myocardial potassium intoxication may develop rapidly and is a recurrent hazard.

3. Control of the hyperkalemia and uremia in these patients is accomplished only through frequent use of the artificial kidney, and the patient's clinical condition often rapidly deteriorates unless the necrotic tissue is removed or the infection brought under control. Amputation, débridement and drainage, therefore, must be undertaken at the earliest evidence of abscess or necrosis even though the patient may be critically ill.

4. Wound healing is delayed in these patients. This should not deter surgery but should be considered as a factor in the type of approach and materials used.

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Chapter 7

The Phosphorus: Nonprotein Nitrogen (P:NPN) Ratio in Plasma as an Index of Muscle Devitalization During Post-traumatic Oliguria*

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During the course of management of war casualties with oliguria, it was noted that inorganic phosphorus concentration in plasma rose to higher levels earlier in those patients with necrotic muscle wounds. It was expected that nonprotein nitrogen concentration in plasma also would rise at a greater rate when necrotic tissue was present, but it was not observed to do so. The rise in concentration of phosphorus out of proportion to nonprotein nitrogen appeared to be associated consistently with muscle necrosis. On several occasions the presence of muscle necrosis deep in a wound which appeared healthy on the surface was first suspected from a rise in the ratio of phosphorus to nonprotein nitrogen (P : NPN) in the plasma.

In order to test the validity of this clinical observation, the records of all the oliguric patients admitted to the Renal Insufficiency Center in Korea were reviewed. The purpose of this report is to relate these chemical and clinical findings in 28 selected patients and to propose the P : NPN ratio in plasma as a useful aid in the recognition of devitalized muscle during post-traumatic oliguria.

Clinical Material and Methods

Twenty-eight patients were selected from a larger series on the basis of the following criteria :

(a) Renal insufficiency following trauma in young men who were presumably normal prior to injury.
(b) Urine flow less than 500 cc./24 hours.
(c) No other significant loss of fluid or non-volatile solutes.
(d) Plasma NPN greater than 100 mg./100 cc.
(e) Not yet subjected to hemodialysis by the artificial kidney.
(f) No visible discoloration of plasma.
(g) NPN and P determined on the same specimen of plasma.
(h) Clinical evaluation by someone other than the author: one not aware of the chemical relationships to be considered.

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On the basis of clinical evaluation alone, all of the patients who fulfilled the above requirements were divided into four groups:

Group I. Massive necrotizing myositis which could not be excised completely or remained unrecognized ante mortem. All of these patients followed a characteristic clinical course of progressive mental torpor, disorientation, and hypotension culminating in death (cases ♯91, 93, 97, 108, 115, 121, 129, 132, 133, 137).

Group II. Necrotizing myositis which was completely excised or amputated (cases ♯92, 104, 110, 130, 135).

Group III. Superficial infection of large muscle wounds, controlled with conservative measures (cases ♯87, 95, 96, 102, 125, 127).

Group IV. No apparent involvement of muscle but may have had severe, even fatal, infection or trauma of other tissues (cases ♯98, 107, 113, 114, 119, 128, 136).

Chemical methods: Nonprotein nitrogen by the method of Folin and Wu.[1] Potassium by the flame photometric method of Hald.[2] Inorganic phosphate by the method of Fiske and Subbarow.[3] Other phosphorus fractions were not measured.

Chemical Findings and Discussion

The plasma values for nonprotein nitrogen, potassium and inorganic phosphates are listed in Table 1. The time scale is based upon the number of days after wounding, since the exact time of onset of oliguria was not always known. When a patient underwent hemodialysis, the relationships of the plasma chemicals were altered and the subsequent values are not included in the table.

The average of the daily NPN concentrations for all of the patients progresses by a rather regular increment each day. The daily average for each group similarly increases stepwise, and when these values are plotted against time they fall on a relatively straight line (Fig. 1). There is little difference among the daily averages of the four groups, and there is no significant difference between the average of the patients with and without myositis.

On a particular day the NPN concentrations vary considerably from one patient to another regardless of group; yet the successive daily values for many patients progress more or less regularly. For instance, patient #110 (see Table 1) has a concentration of 106 mg./100 cc. on day 3 as compared with a group average of 140 and an over-all average of 158; yet this patient's concentration of NPN increases by

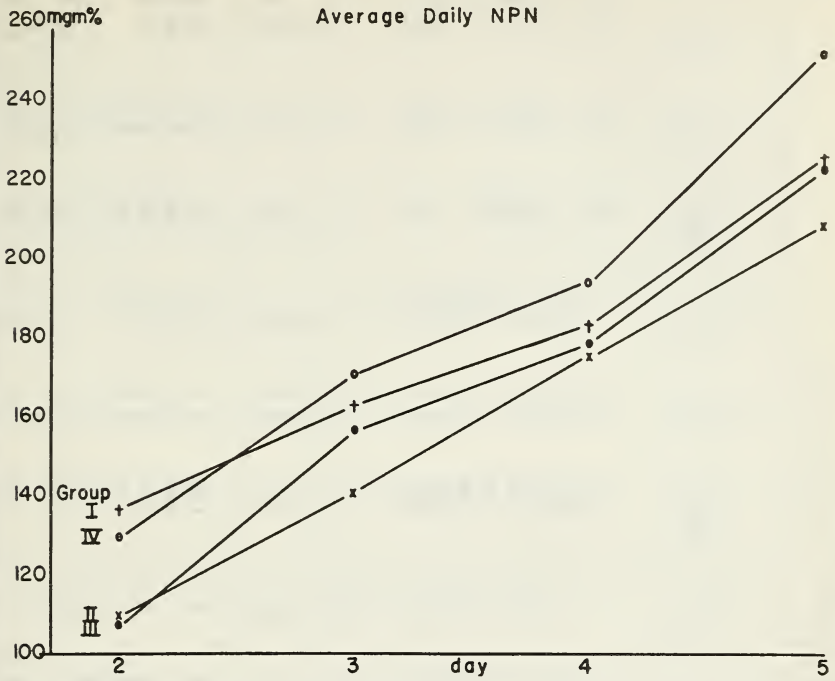

FIGURE 1. The average NPN concentration for each clinical group, plotted against time in days following wounding.

increments which are regular and which parallel the average increments for the group on subsequent days. It would appear that such a patient is displaced forward on the time scale and that day 3 actually is day 1 or 2. It is likely that such errors occurred, because the chart is constructed as if oliguria dated from injury. The regularity of the daily increase in NPN concentration in all the patients, as illustrated by the linearity of the curves in Figure 1, suggests that the rise in NPN concentration per day is related to the duration of oliguria but not to the presence or degree of tissue necrosis.

The potassium which accumulates in the plasma during oliguria, when no potassium is administered, represents loss of potassium from the tissues. The food intolerance usually accompanying acute uremia results in a caloric deficit, and tissues are catabolized to supply nutritional requirements. The accumulation of potassium in the plasma can be minimized when carbohydrate feedings or infusions are provided.[4-7] When additional cells are devitalized by trauma, infection, or other physical or chemical agents, the additional potassium released to the plasma may exceed the capacity of the body to remove

Table 1. Plasma Chemical Data

(NPN and P are expressed in mg./100 cc., K in mEq./L.)

Post-wound Day	2			3			4			5		
Case No.	NPN	K	P	NPN	K	P	NPN	K	P	NPN	K	P
Group I												
91	124	7. 2	6. 7	176	7. 1		211	5. 6		249	7. 2	11. 9
93				102	7. 9		150	7. 8	12. 3			
97				167	6. 0	7. 8	191	5. 9		250	6. 4	11. 5
108							105	6. 5	9. 5	182	7. 3	9. 8
115	106	6. 5	5. 0	119	5. 9	6. 0	136	6. 3	7. 3	180	7. 6	11. 7
121				139	5. 0	4. 3	188	4. 7	12. 9			
132	134	6. 5	8. 5	178	6. 6	12. 3	255	7. 5	16. 3		7. 1	16. 5
133	130	7. 0	5. 3	152	7. 3	11. 3	220	8. 7	14. 4	257	8. 8	16. 8
137	129	8. 6	11. 4									
129	196	8. 3	7. 0	261	6. 5	18. 7						
Total	819	44. 1	43. 9	1294	52. 3	60. 4	1456	53. 0	72. 7	1118	44. 4	78. 2
No.	6	6	6	8	8	6	8	8	6	5	6	6
Aver.	136	7. 4	7. 5	162	6. 5	10. 1	182	6. 6	12. 1	224	7. 4	13. 0
Group II												
92				171	8. 3	8. 8	190	8. 1	10. 4	231	7. 9	12. 6
104							206	8. 4	14. 6	235	7. 6	14. 0
110				106	6. 1	6. 0	138	5. 6	7. 9	166	5. 2	8. 6
120	104	4. 5		131	4. 8	5. 1	166	5. 3	6. 8	197	6. 4	
135	114	8. 1	6. 0	151	8. 0	10. 9						
Total	218	12. 6	6. 0	559	27. 2	30. 8	700	27. 4	39. 7	829	27. 1	35. 2
No.	2	2	1	4	4	4	4	4	4	4	4	3
Aver.	109	6. 3	6. 0	140	6. 8	7. 7	175	6. 9	9. 9	207	6. 8	11. 7

Group III												
87							151	7.0		182	7.1	11.3
95	102	5.2	5.8	173	5.3		192	6.0		239	6.8	7.0
96	112	5.0	5.0	120	5.4			4.6		200	5.1	
102				163	7.4	8.5	189	6.7	9.3	267	8.3	12.6
125				167	6.9	5.7	213	5.7	8.2	266	6.8	9.7
127							147	7.4	6.4	177	6.9	7.2
Total	214	10.2	10.8	623	25.0	14.2	892	37.4	23.9	1331	41.0	47.8
No.	2	2	2	4	4	2	5	6	3	6	6	5
Aver.	107	5.1	5.3	156	6.3	7.1	178	6.2	8.0	222	6.8	9.6
Group IV												
98				177	5.5	5.8	209	7.1	9.1	245	7.0	9.9
107				177	7.4	7.3	231	7.9	8.3			
113				170	3.2		196	3.5	7.2	214	5.4	6.1
114							131	4.6	4.8		4.3	7.4
119	145	6.9	3.6	176	6.5	3.9	220	5.2	3.5	295	8.3	3.2
128	113	8.2	5.5									
136				151	5.2	6.2	173	5.1	6.5	247	5.4	7.5
Total	258	15.1	9.1	851	27.8	23.2	1160	33.4	39.4	1001	30.4	34.1
No.	2	2	2	5	5	4	6	6	6	4	5	5
Aver.	129	7.6	4.6	170	5.6	5.8	193	5.6	6.6	250	6.1	6.8
Over-all												
Total	1509	82.0	69.8	3327	132.3	128.6	4208	151.2	175.7	4279	142.9	195.3
No.	12	12	11	21	21	16	23	24	19	19	21	19
Aver.	126	6.8	6.3	158	6.3	8.0	184	6.3	9.2	225	6.8	10.3

it.[8] Muscle cells are rich in potassium, and the degree of devitalization of muscle might be expected to correlate well with the concentration of plasma potassium. Indeed, the patients in Group I did tend to have higher values initially, but the concentration did not continue to rise progressively. Because of the lethal properties of potassium, maximal efforts were directed toward its control, and the over-all average plasma level was no higher on day 5 than on day 2 (Fig. 2). If measures for the control of hypergalemia[9,10] are employed, the concentration found after treatment will be of little value in the estimation of cell destruction.

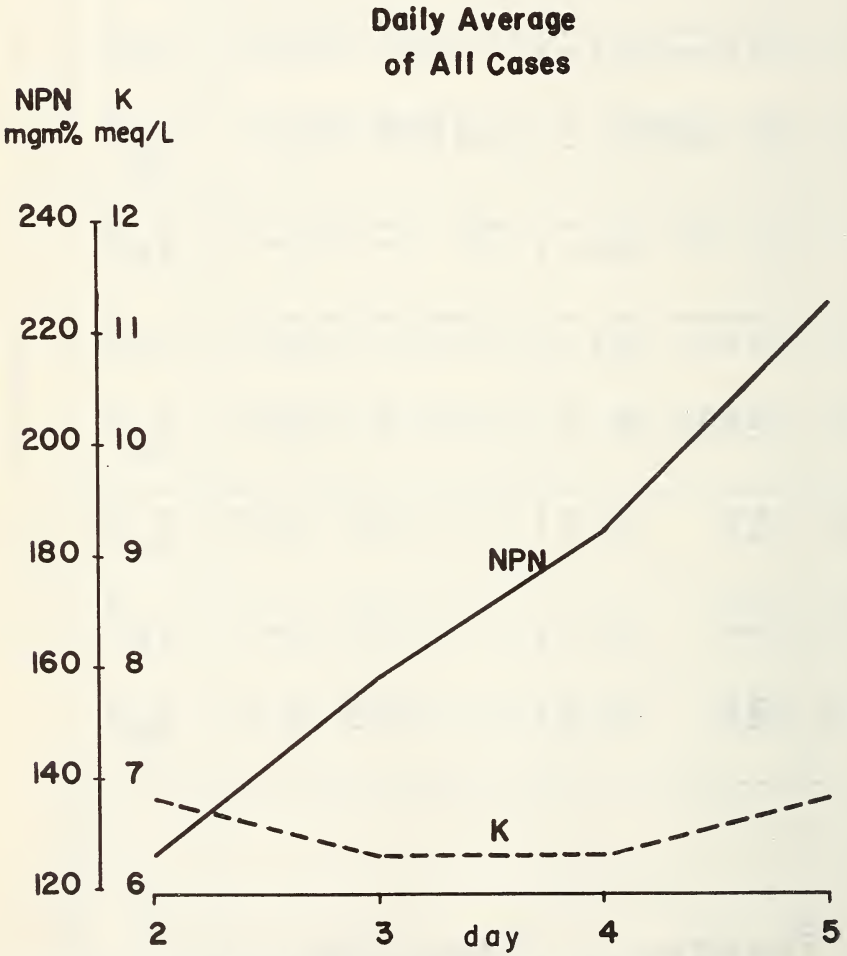

Figure 2. Average daily potassium concentration compared with NPN on successive days.

Plasma phosphate, like NPN, is little affected by the non-dialyzing measures which are directed toward the control of potassium. Phosphorus is largely an intracellular substance, and when it is delivered to the plasma, effective means to cause it to be re-incorporated into tissue have not been demonstrated. Except for the small amounts of phosphorus which are removed from the plasma under the influence of carbohydrate feedings or infusions,[11] that which is in plasma remains there until renal function is recovered or hemodialysis is instituted. The plasma level of phosphate should then be a gauge of the extent of devitalization of tissue which is rich in phosphate. Such a tissue is muscle, and Figure 3 demonstrates the average plasma phosphate concentration for each of the four groups representing clinical estimates of degrees of muscle damage. Group I, which is constituted of patients with massive muscle necrosis which was fatal, shows the highest average value; Group II, which is constituted of patients with massive muscle necrosis which was extirpated before it progressed to a lethal degree, shows the next highest value; Group III, which is constituted of patients with superficial muscle infection which was controlled by conservative treatment, shows the next highest value; and Group IV, representing varying degrees and types of trauma and infection but no gross muscle damage, shows the lowest value.

As time passed, myositis appeared and progressed, and the plasma phosphate concentrations for patients with and without myositis diverged. As shown in Table 2, the difference between the mean phosphate values of the patients with and without myositis is not signifi-

Table 2. Plasma Phosphorus (mg./100 cc.) in Patients With Myositis (Groups I and II) Compared With Patients With No Myositis (Groups III and IV)

Post-trauma Day	2	3	4	5
Myositis				
No.	7	10	10	9
Mean	7. 1	9. 1	11. 2	12. 6
SD	2. 2	4. 5	3. 3	2. 8
No Myositis				
No.	4	6	9	10
Mean	5. 0	6. 2	7. 0	8. 2
SD	0. 98	1. 6	2. 0	2. 7
Difference between Means	2. 1	2. 9	4. 2	4. 4
Standard Error of Difference	1. 0	1. 6	1. 2	1. 3
P	$>.05$	$>.05$	$<.01$	$<.01$

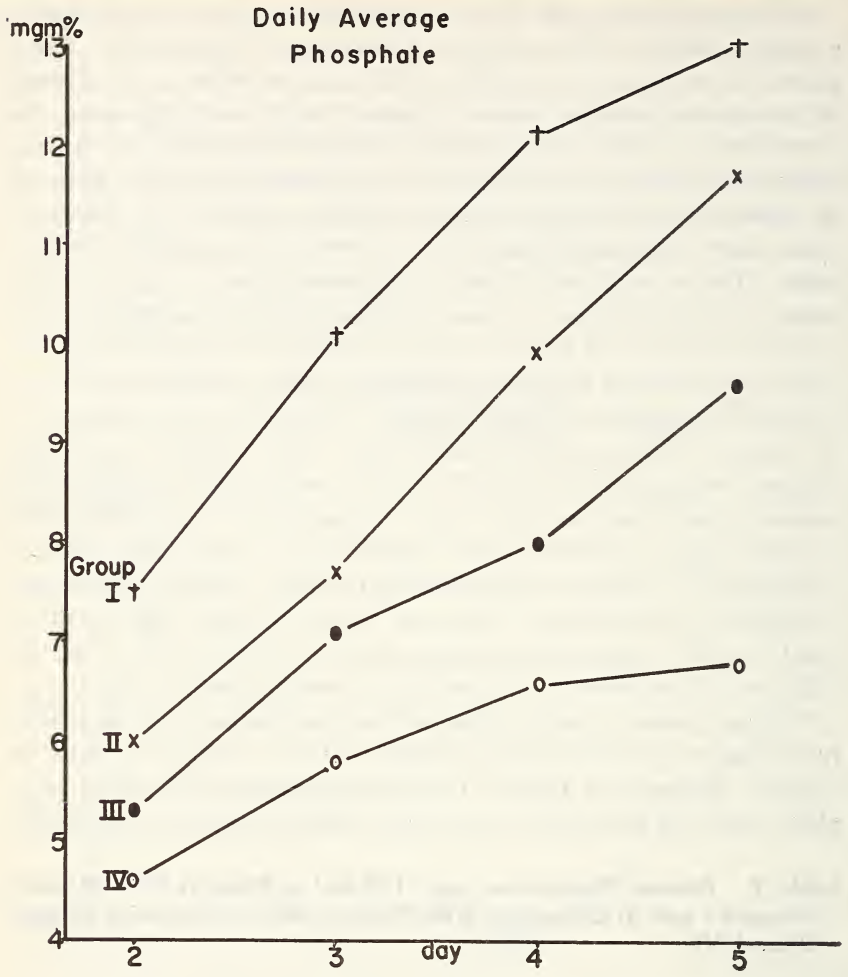

FIGURE 3. The daily average inorganic phosphate concentration for each clinical group, plotted against time in days following wounding.

cant on days 2 and 3 but is significant on days 4 and 5. The difference might have been more striking if five patients with high values had not been dropped from the myositis groups because of death or hemodialysis.

It is noted in Figure 3 that all of the groups show progressive daily increases in concentration, and the average value for each group is higher on day 3 than the average value for the group next higher on the graph on day 2. A value which would be acceptable in Group IV on day 4 would fall into the Group I range if it occurred on day 2. Therefore, in order to assess a particular value, the factor of time must

be considered. As previously noted, the duration of oliguria is not always known. Inaccuracies of immediate recognition and recording of the onset of oliguria are not uncommon in civilian as well as military situations. Under these conditions, if the NPN is used as a unit of time, the rise in phosphate concentration may be related to NPN concentration. Both NPN and phosphate concentrations rise progressively, and the average values rise together (Table 1). In these patients the rise in NPN is related to time, not muscle damage; the rise in phosphate is related to muscle damage and also to time. The degree of muscle damage should then be reflected by the degree of phosphate rise per unit NPN. Figure 4 demonstrates that the relation

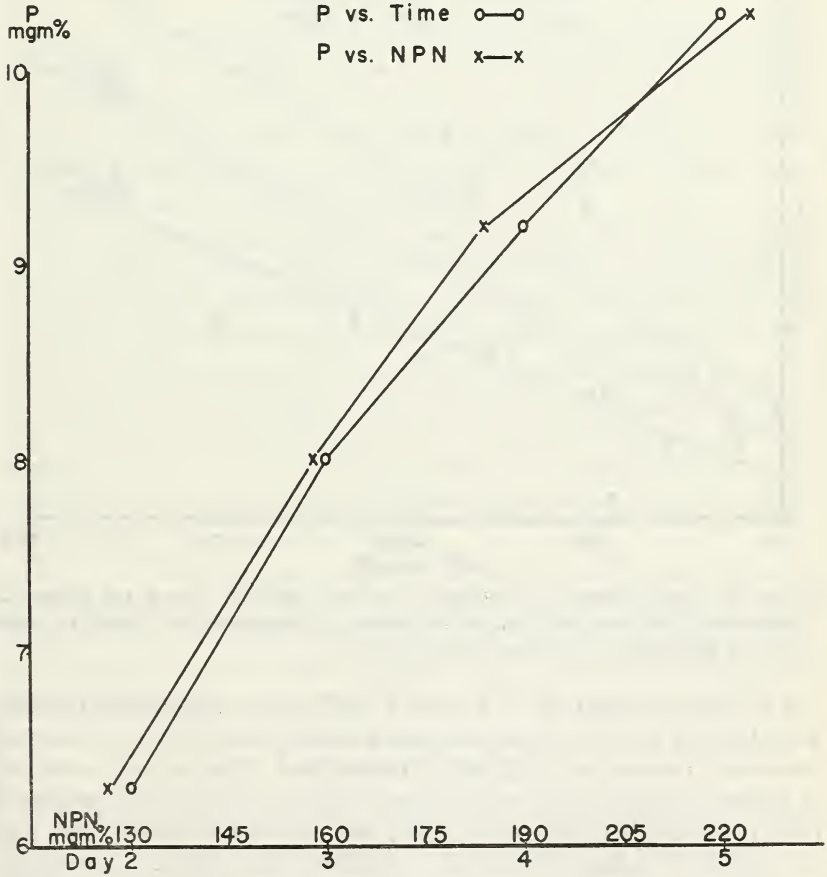

Figure 4. The daily average inorganic phosphate concentration for all patients plotted against time and against NPN, indicating that NPN can be used as a unit of time.

of phosphate concentration to time is practically identical with its relation to NPN concentration.

The highest P : NPN ratio for each patient is plotted in Figure 5. The highest ratios occur in Group I (mean 0.071), the lowest in Group IV (mean 0.039) and the intermediate in Groups II and III. All the patients with myositis, Groups I and II, were compared with all the patients with no myositis, Groups III and IV. Thirteen of the fifteen patients with myositis have ratios above 0.05; 10 of the 13 patients with no myositis have ratios below 0.05 ($P<.01$).

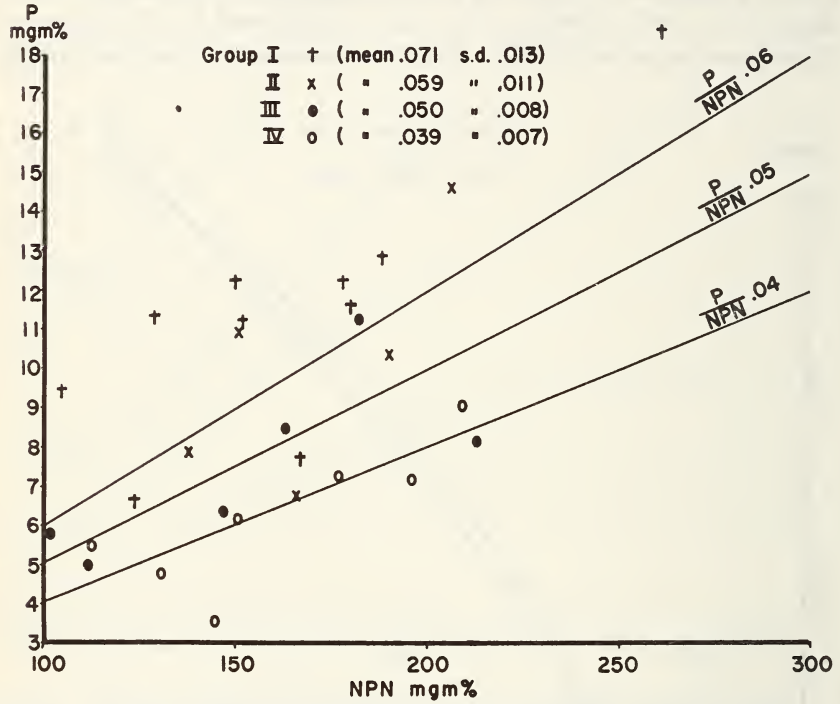

Figure 5. The highest P : NPN ratio for each patient. Lines are drawn at ratios 0.04, 0.05 and 0.06 to show the degree of phosphate rise allowed to maintain the same ratio at different levels of NPN.

After this association of a high P :NPN ratio and muscle necrosis was observed in several patients, and a much lower ratio was observed in several patients with massive trauma and fulminating infections of abdomen and thorax, the presence of muscle necrosis was predicted from the P :NPN ratio alone. Each such attempt was successful, and the chemical changes sometimes antedated the clinical changes by several days. Surgeons who are confronted with the problem of distinguishing viable from non-viable muscle may find the P : NPN ratio a helpful guide in oliguric patients.

This relationship should not obtain unless severe oliguria is present; otherwise the phosphate which is released from muscle would be excreted in the urine. Also, a patient with a generalized disease of which renal insufficiency is but one component may show a great rise in plasma P:NPN ratio without muscle necrosis. In such a patient the increased release of phosphate from tissues is a reflection of catabolism in many areas. In oliguria secondary to trauma and shock, however, there appears to be less generalized catabolic response which causes a release of phosphate from tissues, and an increase in the P:NPN ratio should prompt the surgeon to re-examine all wounds of muscle.

Summary and Conclusions

The relationships between the rates of accumulation of plasma NPN, potassium and inorganic phosphate were examined in 28 severely wounded patients with post-traumatic renal insufficiency. The patients were divided into four groups on the basis of the presence or degree of devitalization of muscle, and the clinical evaluations were compared with the chemical findings.

NPN in plasma was found to rise at a fairly regular rate regardless of the type or amount of tissue destroyed. Plasma potassium concentration was reduced by vigorous treatment, and the post-treatment value bore little relationship to muscle damage or the other chemicals. Plasma phosphate rose more rapidly and to higher levels in patients with greater muscle damage. Since there are no standards of reference for the levels to which phosphate would rise in the absence of muscle damage in a given time, and the duration of oliguria in a particular patient may be unknown, the NPN can be used as a unit of time to which the phosphate can be related.

The P:NPN ratio can be used as an index of the degree of muscle destruction. A ratio above 0.05 indicates muscle damage, and a ratio rising above 0.06 should direct suspicion toward a large and potentially lethal area of muscle necrosis which may not be apparent on the wound surface.

Acknowledgments

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Chapter 8

Wound Healing in Patients With Battle Wounds and Severe Renal Dysfunction

Stanley M. Levenson, M. D.

In January 1953, it was generally considered that delays in wound healing were infrequent among patients with battle injuries except among those patients who also had acute renal failure. This view was held by most of the Chiefs of Surgery at the American hospitals in Korea and Japan and by the Surgical Consultants to the Eighth Army in Korea and to the Far East Command. The occasional delay observed in the patients without renal dysfunction was considered a consequence of—

(1) local infection (often associated with inadequate initial débridement);
(2) local ischemia (tight sutures; rarely progressive vascular occlusion);
(3) peculiarities of the site of injury (e. g., lower leg wounds are notoriously slow in healing).

Systemic factors were not considered important.

It should be stressed that there were clinical "impressions." No systematic tabulation of wound healing had been made, nor was there specific knowledge about the quality of wound healing.

In contrast, it was generally felt that serious wound infections and delays in wound healing were common in patients with serious renal dysfunction. In particular, the physicians at the Renal Center were of the firm opinion that wound healing was impaired in these latter patients and that wound complications contributed significantly to their high mortality (50 to 60 per cent). To obtain some specific data in this regard, all the clinical and autopsy records of the 70 patients admitted to the Renal Center from its opening in the spring of 1952 through the middle of February 1953 were reviewed by the author with Captain Teschan who had been in charge of the renal ward during most of this period.

The records of the first 16 patients were inadequate; of the remaining 54 patients, 12 were discarded either because of inadequate records (5) or because of short survival times (7). Forty-two records, then, were deemed adequate for analysis. However, it should be mentioned that the progress notes were written by internists, that the records were not specifically directed towards problems of wound healing, that bac-

teriologic studies were inadequate and that only casual attention was paid to the wounds at autopsy. No histologic studies of the wounds were done.

Among the 42 patients whose records were analyzed, gross impairment of wound healing was noted in 31. The term "impairment" is used in a broad sense and is not meant to imply a specific defect in wound healing. Mortality among the patients with impaired wound healing was high; wound complications were among the more frequent and important causes of death (Tables 1, 2, 3, 4 and 5).

Two general types of wounds were present in these patients—wounds closed primarily, such as laparotomy incisions, and wounds left open after débridement. Among the 42 patients whose records were analyzed, there were 28 who had *laparotomies* (Table 6). Six of these were in the group with unimpaired wound healing and, as indicated by group classification, none of these wounds ruptured. Among the 31 patients with impaired wound healing, 22 had laparotomies. There were five abdominal wound *dehiscences* in this group. This incidence of wound rupture was apparently higher than occurred in patients with serious battle wounds but without renal dysfunction. However, this cannot be stated with certainty, since no over-all systematic tabulation of wound healing among the battle casualties of the Korean conflict has been made. In this regard there has been considerable difference of opinion among the Surgical Chiefs and Consultants as to the incidence of postoperative hernias in laparotomized patients; opinions have varied from "very few" to "very many."

Table 1. Wound Healing in Patients With Battle Injuries and Renal Dysfunction

1. Group with Apparent Unimpaired Wound Healing

Patient Number	Initial Injury and Initial Operative Treatment
26	Bullet—left flank penetration (through and through); laceration of inferior vena cava below renal vein; 2 perforations of duodenum Rx: Laparotomy Repair of perforations of duodenum Ligation of inferior vena cava
30	Land mine—traumatic amputation right leg, pen. wds. right wrist, left thigh, left knee Rx: Guillotine amputation right lower leg, arthrotomy 1 knee joint, débridement of wounds Transfusion reaction—4th pwd. day

Table 1. Wound Healing in Patients With Battle Injuries and Renal Dysfunction—Continued

1. Group with Apparent Unimpaired Wound Healing

Patient Number	Initial injury and Initial Operative Treatment
34	Small arms fire—pen. abd. left to right, with perforations splenic flexure of colon (2), laceration of inferior vena cava; fracture body L_2, bruised duodenum, perforations (2) of hepatic flexure Rx: Laparotomy; ligation inferior vena cava; exteriorization of splenic and hepatic flexures
48	Burp gun—4 perforations small bowel Rx: Laparotomy; closure of perforations of small bowel
55	Mortar shell—penetrating wd. of abdomen, avulsion right colon, fecal contamination peritoneal cavity; penetrating wound left knee (into joint). Rx: Laparotomy, right colostomy; ileo-transverse colostomy; Débridement left knee wound
58	Grenade Fx. 1, tibia, right lateral malleolus, 5 perforations of ileum, perforations rectosigmoid; penetrating wounds right buttock and penis Rx: Laparotomy, resection of ileum with end-to-end anastomosis; suture of rectosigmoid diverting sigmoid colostomy; débridement of peripheral and buttock wounds with casting of extremities.
59	Shrapnel—lacerations cheek and forehead; avulsive type wound over left mid-humerus; lacerations left hand, lacerations both thighs, compound comminuted fracture left lower leg; laceration of penis; laceration right anterior chest (superficial) Rx: Débridement, casting
60	Bullet—through-and-through wound of pharynx with fractured jaw Rx: Wiring of jaw; débridement neck wounds with closure of pharyngeal perforation on left.
63	Gunshot wound—penetrating wounds, right and left chest, with lacerations left lower lobe, left lung, spleen, diaphragm, Fx. 5th and 6th ribs, left. Rx: Formal thoracotomy, repair lacerations of lung; splenectomy, débridement of wounds.
64	Jeep accident—Transection prostatic urethra, lacerations of diaphragm, esophagus. Fractured pelvis with separation of symphysis Rx: Laparotomy 1—cystotomy Laparotomy 2—Same day, repair diaphragm and repair of esophagus.
65	105 mm. artillery gun exploded—penetrating missile wounds right forearm, right shoulder, right thigh, left hand, with separation right acromioclavicular joint, fracture right humerus, right forearm, left hand, traumatic amputation left thigh, MFB right thigh. Rx: Débridements; ligation right brachial vein, amputation left thumb.

Table 2. Wound Healing in Patients With Battle Injuries and Renal Dysfunction

I. Group with Apparent Unimpaired Wound Healing

Patient Number	Oliguria* (No. of Days)	Day of Diuresis	Max. Plasma NPN	No. of Dialyses	Lived or Died**	Lap.	Dehiscence	Comments
			(mg./100 ml.)					
26	0	3	235	0	L	+	0	
30***	0	8	273	0	L	0	—	30 lb. wt. loss in 14 days, then rapid wt. gain
34	0	2	109	0	L	+	0	Minor renal dysfunction, 30 lb. wt. loss, duodenal fistula—healed
48	0	3	228	0	L	+	0	23 lb. wt. loss
55	0	6	360	0	L	+	0	
58	—	13	202	0	L	+	0	20 lb. wt. loss
59	2	4	225	0	L	0	—	
60***	1	22	296	3	L	0	—	
63	0	5	306	0	L	0	—	
64	1	4	195	0	L	+	0	
65	1	3	247	0	L	0	—	33 lb. wt. loss

*Urine volume less than 500 cc./24 hrs.
**Urine volume greater than 1,000 cc./24 hrs.
***Transfusion Reaction.

Table 3. Wound Healing in Patients With Battle Injuries and Renal Dysfunction

II. Group With Apparent Impaired Wound Healing

Patient Number	Initial Injury and Initial Operative Treatment
17	Truck Accident—blunt injury to abdomen, ruptured spleen, injured right kidney, avulsion of CBD, tear of portal vein, laceration of duodenum Rx—Laparotomy, right nephrectomy, splenectomy, cholecystostomy, choledochoduodenostomy, repair of duodenum and repair of portal vein
18	Land mine—Bilateral thigh and lower leg wounds FCC right femur, superficial wounds left thigh, left arm; right femoral vein severed near inguinal ligament Rx—Débridement; right femoral vein ligated; amputation above knee, right
19	Pen. missile, shrapnel; penetrating wounds both thighs with laceration right femoral artery and vein below profunda Rx—Anastomosis femoral artery; femoral vein ligated; débridements
20	Mortar—wounds both knees and thighs Rx—Débridement—repair of left popliteal and femoral artery; ligation of vein
21	Shrapnel—Penetrating wound of abdomen with laceration of distal ileum, cecum, ascending colon, hepatic flexure, right kidney; penetrating wound left chest with hemopneumothorax Rx—Laparotomy, resection of involved bowel; ileo-transverse colostomy, kidney packed and right lateral gutter drained; thoracentesis
22	Rifle—perforating wounds left groin, ileum, jejunum, sigmoid colon, dome of bladder Rx—Laparotomy Anastomosis of small bowel Exteriorization of colon, repair of bladder Suprapubic cystostomy
23	Bullet 45—Perforation abdominal wall; perforation left arm; perforation small bowel and sigmoid; laceration of mesentery with hemoperitoneum Rx—Laparotomy; end-to-end anastomosis of small bowel closure of lacerations; transverse colostomy
28	Land mine—Extensive FCC Tibia, bilateral avulsion of skin of legs and thighs and upper arm; FCC third digit, left hand Rx—Débridement of wounds—long leg cast
29	Burp gun—Abdominal perforation, macerated left kidney, perforation splenic flexure of colon, multiple perforations of jejunum, laceration of posterior prostate and prostatic urethra, perforation anterior wall of rectum Rx—Laparotomy; débridements; resection and suture of small bowel injuries; colostomy; left nephrectomy

Table 3. Wound Healing in Patients With Battle Injuries and Renal Dysfunction—Continued

II. Group With Apparent Impaired Wound Healing

Patient Number	Initial Injury and Initial Operative Treatment
31	Mortar fragment—Penetrating wound chest; penetrating wound of heart; laceration right lung with right hemopneumothorax, embolization of MFB to left hypogastric artery Rx—Laparotomy; embolectomy; cardiac arrest, which responded to massage; thoracentesis
32	Land mine—traumatic amputation left leg below knee; extensive avulsion skin of right thigh; FCC 4th finger. Rx—Débridement of right wrist and forearm Supracondylar amputation of left leg Amputation proximal portion 4th finger and portion of thumb Right orchidectomy
33	Mortar shell—left hemothorax; FCC ribs 5–8, hemopericardium with cardiac tamponade, lacerations diaphragm, perforations of stomach, jejunum, and splenic flexure of colon, lacerations of spleen and left kidney; FCC left humerus, tibia, fibula and carpal bones Rx—Laparotomy; aspiration of pericardial space; repair of gastrointestinal perforations, with exteriorization of colon (left), splenectomy, repair of right kidney, thoracotomy
36	Gunshot wound—4″ lacerations right lobe of liver; perforation right colon and its mesentery Rx—Laparotomy—Suture of laceration with drainage; repair of colon with exteriorization
38	Mortar—Traumatic amputation of left leg; perforating wounds both buttocks, FCC of sacrum; perforation of rectosigmoid, perivesical hematoma. Penetrating wounds right foot and avulsion of right calf; FCC right fibula and right 5th metatarsal bone Rx—Laparotomy; colostomy, high right amputation; left leg with débridement of buttocks wounds and right leg wounds
40	Grenade—Large wound medial aspect left thigh with avulsion skin, adductor and some extensor muscles. Superficial laceration left temporal and frontal area of head, multiple deep lacerations of right thigh Rx—Débridement
42	Bullet wound—pen. abdomen—2 wds. bladder, perf. rectum, shattered sacrum Rx—Laparotomy—suprapubic cystostomy; closure of rectal wd.; diverting colostomy drain presacral area; débride sacrum and wounds
43	Shell fragment—pen. wd. right sacrum; laceration of rectum; retroperitoneal hematoma; small lac. extremities; FCC right tibia Rx—Laparotomy, sigmoid colostomy; drainage of hematoma; débridements of wds., casting of right leg

Table 3. Wound Healing in Patients With Battle Injuries and Renal Dysfunction—Continued

II. Group With Apparent Impaired Wound Healing

Patient Number	Initial Injury and Initial Operative Treatment
45	Land mine—superficial laceration right foot, 10 x 8 cm. rent in liver; shattered right kidney; small jejunal perforation, rent in diaphragm; left thoracotomy tube Rx—Laparotomy; débrided missile tract; rent diaphragm repaired; thoracotomy tube; right chest; right nephrectomy; suture jejunum and liver
47	Shell fragment—hemoperitoneum laceration of pancreas, colon, gastrohepatic omentum; superficial wound left wrist Rx—Laparotomy; repair of omentum; exteriorization of right colon with loop colostomy
49	Shell fragment—large perforating wound right lateral chest wall external to pleura; contusion right kidney, superficial wounds right thigh, large pen. wd. right popliteal fossa with peroneal n. paralysis Rx—Laparotomy; repair of kidney; débridement chest and extremity wounds
52	Shell fragment—right lower chest and flank—laceration right diaphragm, liver, shattered right kidney Rx—Laparotomy; repair of diaphragm and suture of liver; right nephrectomy; right thoracotomy
53	Gunshot—right buttock and abdomen; comminuted fracture right acetabulum; laceration of rectum; perivesical hematoma, laceration several branches of hypogastric a. with hemoperitoneum laceration sciatic nerve and lower sacral plexus Rx—Laparotomy—ligation of vessels; colostomy and presacral and perivesical drains; débridement
56	Perforating wounds of right and left lobes of liver, thru-and-thru perforation of gallbladder; 2 perforations ascending colon; 2 perforations duodenum; 1 perforation anterior stomach Rx—Laparotomy; suture of liver; repair of perforations of duodenum; ascending colostomy; suprahepatic drains and drain foramen of Winslow; cholecystectomy
57	Shell fragment—penetrating wound right lower lateral chest, abdomen, right buttock, with laceration right lobe liver, perforation gallbladder and duodenum, pancreas, gastroduodenal artery Rx—Laparotomy; suture of liver; cholecystectomy; exploration of CBD, suture of duodenum and pancreas; drainage of liver and pancreas
61	Mortar fragments—FCC of both tibiae and fibulae; fracture left cuboid, navicular, right med. malleolus; FCC 1st metacarpal left hand; many MFB and soft tissue wounds—legs and left arm Rx—Left femoral artery explored-intact; ligated bilateral post-tibial artery; débridement; open reduction of fracture

Table 3. Wound Healing in Patients With Battle Injuries and Renal Dysfunction—Continued

II. Group With Apparent Impaired Wound Healing

Patient Number	Initial Injury and Initial Operative Treatment
62	Land mine—traumatic amputation right leg; penetrating wound left leg; post-popliteal area; penetrating wound of buttock with laceration of prostate, urethra, bladder, and rectum, right hand, fracture 4th and 5th metacarpal Rx—Laparotomy; débrided; right AK amputation; ligation post-tibial vein; colostomy; repair bladder; suprapubic cystostomy
66	Shrapnel fragment—laceration spleen; left kidney; colon; stomach; small bowel Rx—Laparotomy; splenectomy; left nephrectomy; gastrojejunostomy; colostomy
67	Grenade—large gaping thigh wound (left); FCC left upper femur Rx—splinted left leg; débrided; Kirschner pin through femoral condyles
68	Shell fragments—penetrating wounds right lower anterior chest wall, abdomen; penetrating wound right forearm; penetrating wound right buttock; penetrating wound right heel with fracture of os calcis; 2° and 3° burns of right forearm, hand, and thigh Rx—Laparotomy; evacuation and drainage of large retroperitoneal hematoma; débridement external wounds (inadequate débridement buttock wound)
69	Exploding parachute flare; penetrating wounds of right buttock and peroneal areas; massive blast concussion wound of the right buttock; lateral to rectum and perineum, with widespread devitalization of the perineal and ischiorectal tissue, including right bulbocavernosus and reaching up the right perineum with marked anterior and posterior hematoma. Severance of membranous urethra, with destruction of the apical portion of the prostate. Comminuted fracture of right posterior pubic ischium Rx—Laparotomy; no intraperitoneal injury; bladder opened and closed; re-establishment of urethral continuity over a #24 Foley catheter; diverting sigmoid colostomy; drainage of perivesical space; pack placed in the right pelvis and buttock wound from above
70	Bullet (30 caliber)—Penetrating wounds left buttock, abdomen, chest; fractured left pelvis; perforations descending colon (3); perforations jejunum (3); laceration spleen, left kidney; perforation of diaphragm (left) laceration left lung Rx—Laparotomy; nephrectomy; splenectomy; resection jejunum with end-to-end anastomosis; resection of sigmoid with double-barreled colostomy; repair diaphragm; débridement buttock wounds. Thoracotomy later for hemopneumothorax

Table 4. Wound Healing in Patients With Battle Injuries and Renal Dysfunction

II. Group with Apparent Impaired Wound Healing

Patient Number	Oliguria* (No. of Days)	Day of Diuresis**	Max. Plasma NPN (mg./100 ml.)	No. of Dialyses	Lived or Died	Lap.	Dehiscence (Postop. Day)	Cause of Death	Comments
17	0		321	3 D,	16 day	+	+(14)	Portal vein thrombosis, subhepatic abscess, stricture of common bile duct, uremic colitis.	Peritonitis, ascites.
18	1(?)	3	219	1	L	0	—		Malnutrition, infection in stump, decubitus ulcers.
19***	1	12	284	1	L	0	—		Wound infection.
20	1	18	263	2	L	0	—		Wound infection.
21	4	9	254	0	L	+	0		Infection of peripheral wounds.
22	0	14	265	0	L	+	0		Edema, dehydration, bleeding tendency.
23	0	6	394	0 D,	26 day	+	+(16)	Pulmonary infarcts with abscess formation, bronchopneumonia and atelectasis.	Edema, dehydration cachexia, peripheral wound infection.

*Urine volume less than 500 ml./24 hrs.
**Uurine volume greater than 1,000 ml./24 hrs.
***Transfusion reaction.

Table 4. Wound Healing in Patients With Battle Injuries and Renal Dysfunction—Continued

Patient Number	Oliguria (No. of Days)	Day of Diuresis	Max. Plasma NPN (mg./100 ml.)	No. of Dialyses	Lived or Died	Lap.	Dehiscence (Postop. Day)	Cause of Death	Comments
28	2	6	168	1	L	0	—		One stump wound clean, other stump wound infected.
29	1	10	268	2	L	+	0		Cachexia, osteomyelitis.
31	4	9	260	0	L	+	+(11)		No obvious reason for dehiscence (No stay sut.), cardiac arrest, shock, emaciation perit., intes. obst., sec. to dehiscence.
32	0	4	205	0 D,	13 day	0	—	Spreading infection of right arm, cerebral edema, marked bronchopneumonia	Retained foreign body
33	0	6	360	3 D,	29 day	+	0(?)	Massive peritonitis, pelvic abscess, bilateral renal abscess, bilateral adrenal infarcts	Cachexia, wound infection; no gross dehiscence but held only by sutures
36	0		344	3 D,	10 day	+	0	Massive peritonitis, perihepatic abscess	Edema; infection of laparotomy wound, peritonitis

38	0		305	6	D,	16 day	+	0	Extensive necrosis of leg stump with infiltration of fascial plane; extensive necrosis of buttocks with infection	Retained foreign body
40	0	15	379	2		L	0			Retained foreign body
42	1		316	6	D,	17 day	+	0	Large subdiaphragmatic abscess; peritonitis	Bleeding, wound infection
43	0		183	2	D,	5 day	+	0	Massive necrosis of buttock wound and perirectal area, bronchopneumonia	Wound infection
45	0		336	2	D,	19 day	+	0	Left empyema, marked bilateral hydrothorax	Wound infection
47	0		367	1	D,	11 day	+	+ (10)	Peritonitis, subdiaphragmatic abscess	Peritonitis, infection lap. wound
49	0		228	0		L	+	0		Bleeding; wound infection
52	0	19	324	4	D,	25 day	+	0	Bronchopleural fistula with empyema	Malnutrition
53	0	11	345	2		L	+	0		Wound infection
56	0		321	0	D,	10 day	+	0	Severe gastrointestinal bleeding with aspiration of bloody vomitus	Cachexia, bleeding, breakdown of sutured diaphragm
57	1	7	316	1	D,	13 day	+	0	Breakdown of duodenal suture line with adjacent abscess resulting in massive intra-abd. bleeding	Wound infection
61	0	16	322	3		L	0			Wounds apparently healed except wound infection right foot

Table 4. Wound Healing in Patients With Battle Injuries and Renal Dysfunction—Continued

Patient Number	Oliguria (No. of Days)	Day of Diuresis	Max. Plasma NPN (mg./100 ml.)	No. of Dialyses	Lived or Died	Lap.	Dehiscence (Postop. Day)	Cause of Death	Comments
62	1	23	316	3	L	+	0		Sutures too tight (?)
66	0		328	1 D,	8 day	+	0	Peritonitis, gastrointestinal fistula, septicemia (? clostridia)	Peritonitis
67	0	17	328	3	L	0			Malnutrition
68	14		325	2 D,	14 day	0		Spreading infection of buttock wound	Wound infection (inadequate initial débridement ?)
69	?	10	309	1	L	+	+(9)		Old hematoma leading to dehiscence
70	0		300	1 D,	8 day	+	0	Severe bronchopneumonia and atelectasis	At postmortem, lap. wound had minimal tensile strength

Table 5. Wound Healing in Patients With Renal Dysfunction

Group	Number of Patients	Number of Deaths	Average Day of Death
Patients with unimpaired wound healing	11	0	
Patients with impaired wound healing	31	16	15

Table 6. Wound Healing in Patients With Renal Dysfunction

Group	Patients	Laparotomies	Dehiscences
Patients with unimpaired wound healing	11	6	0
Patients with impaired wound healing	31	22	5

The actual incidence of impaired healing of laparotomy wounds among the patients with renal dysfunction may well be higher than indicated by the figures of wound ruptures. Once it appeared that these patients might be having difficulty in wound healing, sutures were left in for many weeks. Under this circumstance, the wounds of some patients were described as held together only by the retention sutures, with no apparent healing having occurred. Further, a number of patients whose laparotomy wounds looked good and appeared to be healing normally, died 7 or more days after injury; no special examination of the abdominal incision was made routinely, but in an occasional instance, when the sutures were removed at autopsy, or an attempt was made to excise a portion of the wound for histologic study, the wound fell apart.

Among the five patients with actual wound rupture, a possible local reason for the dehiscence was apparent in three (Table 7). In one,

Table 7. Wound Healing in Patients With Renal Dysfunction

Dehiscences of Laparotomy Wounds	
Number of patients with laparotomies	28
Number of dehiscences	5
Apparent "local cause" for dehiscence	3
Peritonitis with ascites	1; 14th day
Hematoma	1; 9th day
Wound infection	1; 10th day
No apparent "local cause" for dehiscence	2; 11th and 16th days

dehiscence occurred on the ninth postoperative day and examination revealed an extensive hematoma in the wound (Pt. No. 69). In another, Pt. No. 47, dehiscence occurred on the tenth postoperative day—peritonitis and an infected abdominal wound were present; in the third, Pt. No. 17, dehiscence occurred on the fourteenth day—severe peritonitis with ascites was present. No specific local reason for dehiscence was noted in the other two patients. In one of these two, dehiscence occurred on the eleventh day (Pt. No. 31); in the other, (Pt. No. 23) on the sixteenth day. Disruption this late postoperatively is unusual and would suggest a definite delay in the healing process. At the time of the dehiscence, this last patient was emaciated. The abdominal wound was resutured and he lived for 9 more days. At autopsy, the resutured wound was described as follows: "There is a longitudinal midline abdominal surgical incision measuring approximately 12 cm. in length around which radiate multiple superficial draining sinuses measuring 2 cm. in length. Granulation tissue lines the upper half of the surgical incision which presents an opening measuring 5 x 1 cm. The base of this sinus tract is lined by dense yellow-red granulation tissue. Wire sutures support the incision." Two more of the patients whose ruptured laparotomy wounds were resutured died, but the wounds were not specifically examined at autopsy.

Two of the five patients with dehiscences lived (Table 8). The resutured wound apparently healed uneventfully in the patient whose dehiscence had been presumably secondary to the hematoma. The other patient who survived was the patient whose wound had ruptured 11 days postoperatively with no local cause for dehiscence being apparent. After resuturing, he developed peritonitis and intestinal obstruction. These complications were considered by those caring for the patient as subsequent to the dehiscence, rather than present before, and perhaps etiologically important for, the first dehiscence. A third laparotomy was performed on this patient through another incision

Table 8. Wound Healing in Patients With Renal Dysfunction

Healing of Resutured Dehisced Laparotomy Wounds	
Number of secondary sutures of dehisced laparotomy wounds	5
Number of patients surviving	2
"Normal" healing of resutured wound	1
"Abnormal" healing of resutured wound	1
Number of patients dying	3
"Abnormal" healing of resutured wound	1
Quality of wound healing unknown	2

19 days after the resuturing of the first laparotomy wound. Localized intraperitoneal abscesses and obstructing adhesions were found. One week later, purulent material drained from the first and second abdominal incisions. Shortly thereafter, a fecal fistula appeared in the other abdominal incision. The patient had lost a considerable amount of weight (over 30 pounds) and was transferred to a general hospital in Japan for further therapy.

Among the 31 patients with gross impairment of wound healing, the open wounds were often described as indolent, with granulation tissue either absent, or when present, soggy and edematous. In a number of these patients, progressive necrosis and suppuration of the wounds was described. This was noted particularly in some of the patients with buttock wounds. ("The temperature was up to 104° and the buttock wound now contained a soupy sanguinopurulent exudate, with increasing extent of necrosis"—Pt. No. 68.)

It should be pointed out that the time of secondary closure of the open wounds was delayed in patients with renal failure. In patients without renal dysfunction, such wounds were usually closed 5 to 10 days after injury. Patients with renal dysfunction were often sickest during this time and secondary closure was rarely carried out during this period. Consequently, the wounds of patients with renal dysfunction remained open for significantly longer periods of time than in patients without renal dysfunction. Similarly, these patients were among the most seriously injured and usually were in severe shock in the early period after injury. Thus, it is possible that, under these circumstances, débridement might have been inadequate in certain of these patients. This will be discussed more fully in the section on *infection.* There is also some question as to the quality of the later surgical care of these patients.

A comparison between the two groups of patients (those patients with unimpaired wound healing vs. those with impaired wound healing) was made to determine some of the factors which might have had some bearing on the observed differences in wound healing. It appears that those patients with impaired wound healing were, in general, the more seriously injured, sicker, more uremic, required more dialyses, had greater changes in water and electrolyte metabolism with associated edema and/or dehydration, lost more weight, had more severe infections, and showed a higher incidence of abnormal bleeding. The severity of anemia could not be adequately estimated. No conclusive evaluation of the factors responsible for the delays in wound healing can be made from the available data, but it would appear that in the majority of patients multiple factors were operative and pre-

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sumably interrelated. *Serious uremia*, *serious infection*, and *serious malnutrition* were the most frequent factors. The following two case reports are indicative of the complexity of the problem:

Patient No. 33. This 21-year-old white male was injured at 1800 hours, 25 August 1952, by a mortar shell. When he reached the Clearing Company at 2100 hours, he was in shock and was given whole blood. He reached the 8209 MASH at 2300 hours in deep shock; blood pressure, 80/60. The heart sounds were almost inaudible; a cardiac tamponade was suspected and was confirmed by aspiration. Immediate transfusion raised the blood pressure promptly to 130/90 within 15 minutes; he received a total of 300 cc. blood preoperatively and was operated on at 1400 hours. At operation, he was found to have a hemopericardium, left hemothorax with fractures of ribs 5 to 8, contusion of the lower lobe of the left lung, laceration of the left diaphragm, multiple perforations of the stomach, jejunum, and splenic flexure of colon, laceration of the spleen and left kidney, compound, comminuted fracture of left humerus, left carpal bones, and left tibia and fibula. The following operative procedures were done: resection of the anterior thirds of the left sixth and seventh ribs with insertion of two thoracotomy tubes; repair and débridement of the left side of the diaphragm; closure of perforations of stomach and jejunum; exteriorization of splenic flexure of colon; splenectomy; removal of foreign body from cortex of left kidney; drainage tubes, left flank; débridement of left side of chest; irrigation and splinting of left wrist, humerus, and tibia and fibula. During the operation, he received an additional 3,000 cc. blood. After operation he required 1,500 cc. more blood before his blood was stabilized above shock levels, 7 hours postoperatively.

On 26 and 27 August (the first and second post-injury days) his urinary output was below 300 cc. daily. He was transferred to the 11th Evacuation Hospital the next day. On admission, he was in good general condition. Blood pressure, 130/80; pulse, 118, temperature, 100°; respirations, 26. The exteriorized loop of colon was opened to form a double-barreled colostomy. The extremity wounds were infected, and maggots were present in the wound in the left wrist. The thoractomy tubes were removed when a chest x-ray showed only slight atelectasis at the left base. Laboratory data on admission were as follows: K, 6.2 mEq./L. plasma; Na, 116 mEq./L. plasma; NPN, 154 mg. per 100 ml. plasma; hematocrit, 48 per cent; WBC, 9,450 cu. mm.; urine showed 1.014 specific gravity, 1+ protein, 15 to 20 RBC's per high-power field. Because of the hyperkalemia, an immediate hemodialysis was performed; the K fell to 3.8 mEq./L. plasma and the NPN to 92 mg. per 100 ml. plasma. An EKG was normal. On the next day he was given 60 gm. ion-exchange resins by rectum in an attempt to control hyperkalemia; no further difficulty with hyperkalemia was encountered.

Oliguria continued until the sixth post-injury day. By the twelfth post-injury day a peak was reached of 3,000 cc. urinary output. During this time the plasma NPN climbed to 360 mg. per 100 ml. on the tenth day. At this time he became lethargic and complained of marked lassitude. Tarry stools passed through the colostomy. He would not take fluids or food orally. A repeat dialysis was done with the following biochemical changes resulting:

	Plasma				
	NPN	K	CL	CO_2	NA
	mg./100 ml.	mEq./L.	mEq./L.	mEq./L.	mEq./L.
Pre-dialysis	360	4. 7	105	15. 4	142
Post-dialysis	54	4. 3	112	20. 5	135

During the next day the tarry stools from the colostomy continued and 1,000 cc. of blood was required to maintain his blood pressure. He began to run a fever, up to 103° rectally, and WBC rose to 28,000 with a shift to the left. Physical examination was unchanged at that time; a chest x-ray was negative save for minimal atelectasis at the left base. Antibiotic therapy was changed from terramycin to penicillin and streptomycin. Despite this, the fever continued to rise and on 9 September (the fifteenth post-injury day) he was found to have a large pelvic abscess by rectal examination. The extremity wound remained in poor condition, with no healing and much purulent drainage. He became weaker but was able to eat well. During this time, his urinary output continued to be around 1,500 cc. daily, with a specific gravity of 1.010–1.012, 1+ protein. The plasma NPN had fallen to 110 mg. per 100 ml. by this time but began to rise again despite a urinary volume of over a liter per 24 hours.

With the onset of the pelvic abscess and the high fever (reaching peaks of 105° daily) he began to deteriorate clinically, becoming weaker and less responsive. Weight loss was marked and he took on a cachetic appearance. On the eighteenth post-injury day, a large abscess appeared in the left anterior lower leg, at the site of a previous cut-down. He became intermittently delirious. The penicillin-streptomycin therapy was discontinued and terramycin reinstituted. A frequent cough productive of purulent sputum appeared, but physical examination and x-rays of the chest were negative. By the twenty-fourth post-injury day, the pelvic abscess seemed smaller and more fluctuant by rectal examination; temperature was 103° and WBC, 19,500. At this time he was weak and disoriented. Feedings through a gastric tube were begun. The plasma NPN was up to 196 mg. per 100 ml. with a plasma (mEq./L.) K 4.1, Na 158, Cl 120 and CO_2 21.5. The wounds, including the areas around the wire sutures of the laparotomy incision, were in extremely poor shape, with poor healing and several superficial sinuses.

On the twenty-sixth day, the plasma NPN was 240 mg. per 100 ml. and his clinical condition was rapidly deteriorating. It was felt by the clinical staff that the continued uremia might be accentuated by the necrotic tissue in the wounds and the massive infection in his peritoneal cavity. Another dialysis was done with the following chemical results:

		Plasma			
	NPN	Na	K	Cl	CO_2
	mg./100 ml.	mEq./L.	mEq./L.	mEq./L.	mEq./L.
Pre-dialysis	240	160	4. 2	118	14. 0
Post-dialysis	99	138		114	20. 2

During the dialysis, his blood pressure fell to below 60 systolic and remained there for an hour despite the use of 2,500 cc. blood. Following dialysis, the blood pressure came up to 100 systolic; the patient seemed more alert and oriented for about 24 hours. Two days later, his blood pressure fell to 80 to 60 systolic; he became much weaker and became almost nonresponsive. The plasma NPN was up to 203 mg. per 100 ml. The urinary volume, which had dropped abruptly to 200 cc. on the twenty-sixth day, rose to 1,300 cc. per day. His temperature was 102° and WBC, 26,000. On the twenty-ninth day, the blood pressure gradually fell and was unobtainable. His respirations became gasping and no cardiac sounds could be heard after a shift in his position on the Stryker frame. Intracardiac adrenalin gave a prompt and vigorous return of cardiac action. He was then given norepinephrine intravenously by slow drip. With this, the blood

pressure and pulse were maintained at satisfactory levels, but the patient remained comatose and non-responsive. He remained in this state for some 16 hours. Nine hours prior to death he was given 500 mg. cortisone through the gastric tube; no appreciable effect was evident. He died on the thirtieth day after injury.

At autopsy, the body was described as that of a well developed, thin, white male. There was a large defect in the skin over the left lateral chest measuring 7 x 5 cm. This defect extended down to the ribs. A double-barreled colostomy was present in the right upper quadrant of the abdomen. The skin around the colostomy was retracted, revealing slightly purulent granulation tissue, over an area 8 x 5 cm. Multiple small satellite skin ulcers, 0.5 to 2.0 cm. in diameter, surrounded the colostomy. There was a compound, comminuted fracture of the neck of the humerus easily visible through a large defect in the skin of the axilla. The brachial plexus and axilliary vessels were plainly visible through this defect. Multiple small bone fragments protruded through a through-and-through wound of the left hand. A moderate amount of green-yellow pus exuded from both sides of this wound and probing of the wound revealed a large abscess pocket surrounded by necrotic bone and muscle. Granulation tissue covered a defect in the skin over the anterior of the left leg. This defect measured approximately 12 x 4 cm.

Pathologic diagnosis were—

(1) Acute pyelonephritis with miliary abscesses.
(2) Cystitis.
(3) Peritonitis; abscesses of cul-de-sac, subhepatic region and upper left quadrant of abdominal cavity.
(4) Massive necrosis of adrenals with abscesses.
(5) Petechiae of cerebral cortex.
(6) Acute tracheitis, bronchopneumonia.
(7) Infected wounds of extremities.

Patient No. 67. This 20-year-old white Marine corporal was hit in the left thigh by an enemy grenade at 0430 hours on 22 December 1952. Arrived at C Company, 1st Medical Battalion at 0715 hours; blood pressure was 102/48; pulse, 90; a large gaping wound high on the left thigh with a large hematoma was noted, and an obvious compound fracture of the left upper femur. The peripheral pulses were good and no neurologic damage was detected. The wound was dressed, and the patient's leg was placed in a Thomas splint; 500 cc. whole blood was given.

The patient was then evacuated to a hospital ship by helicopter, where he arrived at 0900 hours 22 December. Said to be "shocky" on arrival. X-ray showed compound, comminuted fracture of left femur with overriding. Wound débrided under cyclopropane-ether anesthesia. No damage to major arteries or nerves noted. A Kirschner pin was inserted through femoral condyles for traction. Because of a fast, weak pulse (BP not stated) he was given 650 cc. whole blood during the operative procedure; it was stopped because of a reaction (tachycardia and fever). Macrodex was then started, and 1,000 cc. given. After operation he received another 1,000 cc. whole blood, at the end of which he became "ill" and 1,500 cc. more Macrodex was given. His urine became almost black.

The next day he vomited several times, and his total urine output was 400 cc.; postoperative intake, 1,330 cc. By the second post-injury day he had soreness in both kidney regions. Catheterization at this time produced only 100 cc. of dark

urine. A BUN was 94 mg. per 100 cc. hemoglobin, 55 per cent. Because of his oliguria he was transferred to the 11th Evacuation Hospital, the Renal Center.

On admission, temperature was 98.4°; blood pressure, 160/100; pulse, 84. He appeared quite well, except for profound anemia, occasional vomiting and moderate dehydration.

Adm. Lab.

Hct.—18%
Na—145 mEq./L. plasma
K—7.1 mEq./L. plasma
NPN—193 mg./100 ml. plasma
Cl—92 mEq./L. plasma
CO_2—21.6 mEq./L. plasma
EKG—Moderately tall and peaked precordial T waves. No QRS prolongation.

On admission to the Renal Center, he was started on gastric drainage, K-exchange resins and intravenous hypertonic glucose and insulin. On 28 December, the sixth post-injury day, rapidly progressive EKG changes of K intoxication necessitated his first hemodialysis on the artificial kidney. There was little clinical change following dialysis except for a rise in blood pressure to hypertensive levels. His blood pressure remained high throughout both his oliguric and diuretic phases, ranging from 150 to 210 systolic and 70 to 110 diastolic. On the fifth post-injury day, he had been put in a 1½ leg spica cast.

On 31 December, the ninth post-injury day, he developed a right parotitis. He had a low-grade spiking fever. That evening, he developed pulmonary edema with a loud gallop rhythm and mushy heart sounds. He was digitalized intravenously with considerable, but not complete, clearing of his heart failure. For the next several days, he continued to show recurrent pulmonary edema with marked respiratory distress. This occurred in the face of a markedly negative fluid balance, with a weight loss averaging over 1 kg. daily and with evidence of peripheral dehydration. This was considered evidence of intrinsic myocardial damage. The pulmonary edema was treated with the usual measures; extremity tourniquets seemed to be the most effective measure. On 6 January, the fifteenth post-injury day, he was dialyzed for the third time because of a rapid rise in the serum K to 9.5 mEq./L. Following this, he showed considerable improvement.

The next day he put out 550 cc. urine and 1,400 cc. on the following day. This urinary output then rapidly increased, and a massive diuresis began, reaching a peak of 6,350 cc. on the twenty-third post-injury day. With this diuresis, he showed further rapid weight loss. No further clinical pulmonary edema occurred.

His uremia, with drowsiness, nausea, vomiting and high plasma NPN, continued for about 1 week after the onset of his diuresis. Since he tolerated nothing by mouth, he required large volumes of parenteral fluids, including potassium. He was given cortisone from the twenty-second to twenty-sixth days post-injury in an effort to improve his anorexia and nausea. (No mention of efficacy made.) On the twenty-sixth day he underwent another débridement. The wound contained much necrotic tissue and showed no evidence of granulations or healing. Repeated cultures grew out *A. aerogenes*, *Proteus*, *Staphylococcus albus*, and *B. pyocyaneus*. In vitro, these showed greatest suspectibility to chloramphenicol but the patient received intravenous aureomycin, since no parenteral chloramphenicol was available.

The patient presented a great nutritional problem, having virtually starved for about 4 weeks, with a 45-pound weight loss. In addition, his fracture was in a very poor alignment, and his wound was unhealed. His previous marked anemia (with hematocrit as low as 15 per cent) was corrected by a total of 3,200 cc. of blood given during his diuresis. His diuresis was subsiding, but he still could not take all of his required fluids by mouth at the time of his transfer to Japan on the thirtieth post-injury day.

As mentioned, among the factors which appear important in the pathogenesis of the impaired wound healing in these patients are *serious uremia*, *serious malnutrition* and *serious infection*.

Severity of the Renal Dysfunction: Dialysis

Renal dysfunction was greater in the group with impaired wound healing. The average time of diuresis among the patients with improved wound healing was 12 days after injury, as opposed to the average time of 5 days of 10 of the 11 patients with unimpaired wound healing (Table 9). In addition, 11 patients with impaired wound healing died 5 to 19 days after injury without ever diuresing. Similarly, whereas only 3 of the 11 patients with unimpaired wound healing had maximum levels of plasma nonprotein nitrogen over 275 mg. per 100 ml., two-thirds of the group with impaired healing had such high levels.

Among the patients with apparently unimpaired wound healing, there was only one who required dialysis (Table 9). This was a Korean soldier with wounds of the face and neck who developed a severe hemolytic reaction to a transfusion of 1,000 cc. of blood during his initial operative treatment. Following this, he developed oliguria and was transferred to the 11th Evacuation Hospital on the third post-injury day. During a prolonged period of oliguria (19 days), uremia, three dialyses on the artificial kidney, anemia (hematocrit 20 to 30 per cent, decreased plasma protein concentration (total plasma

Table 9. Wound Healing in Patients With Renal Dysfunction

Group	Number of Patients	Day of Diuresis	No. Patients with Maximum Blood NPN over 275 mg./100 ml.	Number of Patients Dialyzed	Number of Dialyses
Patients with unimpaired wound healing	10	5	2	0	0
	1	22	1	1	3
Patients with impaired wound healing	31	*12	21	24	56

*Includes 11 patients who died 5 to 19 days after injury without ever diuresing.

protein 4.4 to 6.0 gm./100 ml. plasma), and low dietary intake, the neck and face wounds, as well as the cut-down wounds, showed apparently "normal and entirely satisfactory healing." These wounds were in well vascularized areas in which healing is usually favorable.

Among the 31 patients with apparently impaired wound healing, there were 24 who required dialyses. The average number of dialyses in these patients was about 2.3. At the moment, there is no specific evidence to implicate the dialysis procedure *per se* as an important factor in the pathogenesis of the impaired wound healing—e. g., there were a number of patients with impaired wound healing who did not have dialyses. The fact that many more patients in the impaired healing group were dialyzed than in the group with unimpaired healing may be simply indicative of the severity of the hyperkalemia and uremia of the former group. On the other hand, one cannot definitely rule out the dialysis procedure itself as an important factor—e. g., what is the wash-out of the water-soluble vitamins (specifically ascorbic acid) during dialysis?

Malnutrition

Weight loss is a constant feature of the patient with serious injuries and renal dysfunction. The average weight loss was greater among those patients with impaired wound healing. Weight losses of 20 to 25 pounds were common among the group with unimpaired healing, while among the group with impaired healing 30 to 40 pound weight loss was not uncommon. What the weight loss specifically represents in terms of body tissue, water, fat, etc., is not known. The first weights recorded are those on admission of the patient to the 11th Evacuation Hospital. At this time, many of the patients were presumably waterlogged. Insensible water loss must be an important fact in the weight loss of these patients, since prolonged hyperpnea is a common feature. However, examination of metabolic data available in a few patients reveals a large nitrogen loss (i. e., NPN accumulation in the body water, NPN lost by dialysis, and NPN excreted in the urine). In one patient, this amounted to about 45 gm. N per day, which represents the daily breakdown of about 2.5 pounds of body tissue (excluding fat). It is not possible at present to compare this figure with the nitrogen loss by patients with serious injury without associated renal dysfunction—the data are not available. Urinary nitrogen losses of 45 gm. of nitrogen per day (or greater) are not uncommon among young adult males with serious injuries without associated renal dysfunction, but these latter patients have not been on nutrient intakes as low as the patients studied at the 11th Evacuation Hospital. We know that the level of dietary intake makes a considerable difference in the amount of nitrogen excretion and net nitrogen loss after injury.

Providing an adequate nutrient intake was a very difficult problem in these patients. Many were unable to take food orally over long periods of time. Parenteral alimentation was limited by the policy of rigid fluid restriction during the period of oliguria (which in some cases has persisted for 2 to 3 weeks). The problem was further complicated by the policy of no protein administration during this same period. (One wonders whether in the face of a very low caloric intake the nitrogen load is any less in those patients not receiving protein than in those receiving some protein.) Consequently, the nutrient intake of these patients was very low and grossly inadequate. The average daily caloric intake when the patient had been on only parenteral fluids was 500 to 1,000 calories per day—supplied as glucose. No data are available as to the utilization of carbohydrates by these patients (cf. the "intolerance" to carbohydrates by individuals with extensive injuries) but the rate of infusion has been generally slow. When fluid intake was restricted, the glucose was usually given as a 25 or 50 per cent solution by continuous drip through a polyethylene cannula inserted into the iliac vein via the femoral vein. No instance of pulmonary infarction was noted, but at autopsy in one patient a large thrombus with one end unattached was found in the iliac vein at the site of the infusion.

The only parenteral vitamin preparations which were available were vitamin C (in 500 mg. ampules), thiamine chloride (50 mg./cc.), and various vitamin K preparations. This resulted in a markedly imbalanced vitamin intake.

It was not possible to determine the oral dietary intake of these patients from the available records, but it would appear that the oral food intake was low until long in the convalescent period. A high-carbohydrate, high-fat liquid feeding supplying about 2,500 calories had been tried as a tube feeding (continuous drip) in one or two patients for short periods of time. Oral vitamin intake had usually been three of the standard Army multivitamin capsules per day.

Infection

Infection was one of the major complications among the severely injured patients with renal dysfunction. Among the 31 patients with impaired wound healing, wound infection was almost universally present. Infection, either in the wound or elsewhere, is listed among the causes of death in all but 1 of the 16 patients in this group who died. Intra-abdominal abscesses are listed six times; peritonitis is listed four times; spreading infection of peripheral wounds, four times; severe bronchopneumonia, four times; septic infarcts (lung, kidney, etc.), twice; and empyema, twice. Inadequate bacteriologic data are available.

In view of certain observations of an increased migration of bacteria across the intestinal wall in uremic dogs, the autopsy records were examined to see whether there had been any instances of peritonitis in the absence of intra-abdominal injury. No instance of peritonitis in the absence of a previous laparotomy was found. There were one or two instances of mild peritoneal infection in patients with a "negative" laparotomy, but the possibility of undiscovered intra-abdominal injury cannot be ruled out.

As mentioned, an important difference between the handling of wounds of the patients with renal dysfunction as compared with those without renal dysfunction was the time of secondary closure of open wounds. In patients without renal dysfunction, wounds were usually closed 5 to 10 days after injury. Patients with renal dysfunction were usually very sick during this time and secondary closure was rarely carried out during this period. Consequently, the wounds of patients with renal dysfunction remained open for significantly longer periods of time than in patients without renal dysfunction.

Adequacy of débridement is one of the important factors in wound infection. The question may be raised whether inadequate débridement may not have been more frequent among these patients than indicated by the finding of retained non-metallic foreign bodies noted in a few patients (Table 4). Many of these patients were very severely injured and were in profound shock before and during the initial operative treatment. It is possible that inadequate débridement or hasty closure of an abdominal wound, due to efforts to salvage life, might have been carried out.

At the time the Renal Center was first set up, it was not realized that a surgeon was needed whose only responsibility was the care of these patients. The surgical care of these patients was in the hands of the general surgical staff of the hospital. These surgeons had other duties and responsibilities and they were not able to give undivided attention to these patients. Under these circumstances, it is likely that the surgical care was not optimal in some instances.

Cross-infection was one of the factors possibly important in the high incidence of wound infection among this group of patients. These patients were kept on a single ward and it was not possible to carry out, either on the ward or in the dressing or operating rooms, many procedures which have been advocated for the prevention of cross-infections. There were no bacteriologic data available, however, to support or negate this opinion.

Bleeding Tendency

A number of the patients with renal dysfunction showed an abnormal bleeding tendency. During the second week in February 1953,

two of the four patients in the ward at the time had clotting times greater than 2 hours. This persisted over a period of days with associated excessive blood loss. This was an unusual proportion of "bleeders" but the problem was seen often enough to make its incidence significant.

A study of the basic defect (or defects) in the clotting mechanism is reported elsewhere.[1]

Wound healing is probably delayed in the presence of excessive bleeding into the wound, and perhaps indirectly by excessive bleeding elsewhere than in the wound.

Proposed Observations of Wound Healing

It is evident from reviewing the records of these patients that wound healing was a very important complication among the patients with renal dysfunction. It would appear that in the majority of the patients multiple factors were operative and presumably interrelated. However, it is apparent that with the available data, no specific conclusion as to the relative importance, or interrelationship, of the various factors can be made. Studies to define the problem specifically and thereby lead to improved prophylaxis and therapy are indicated.

Some of the problems which need solution are as follows:

1. *What is the course of normal wound healing* (*open wounds, sutured wounds, etc.*) *in man?*

There is a paucity of detailed correlated (clinical, histologic, bacteriologic, etc.) information regarding wound healing in man. There are very few controlled clinical studies and none specifically applicable to the problems at hand. Most of the specific data regarding wound healing have been obtained in animals. The differences in wound healing among various species make it imperative that caution be used in directly relating the results of animal experiments to man.

2. *What is the effect of magnitude of injury on wound healing, and if an effect is present, to what factors may it be attributed? What is the significance of the "catabolic" reaction to injury?*

Very few objective data of the physiological and clinical sequelae indirectly attributable to the early "catabolic" reaction to injury are available. There are conflicting opinions as to the harm resulting from this period, and depending on the viewpoint taken attempts are or are not made to reverse the process. Much of the conflict is due to the *lack of objective indices* of the benefits, or lack of benefits, of mitigating the early metabolic disturbances.

The injured man must heal his wounds for successful recovery; systematic observations of the healing of wounds, traumatic, operative

and experimental, would provide objective evidence in one important area as to the significance of the "catabolic" period. For example, the seriously injured individual acts biochemically like a scorbutic for some time after injury; does he also act like a scorbutic in regard to the healing of his wounds? Further, the intensity of the urinary nitrogen loss following injury may be decreased by the injection of testosterone propionate. Since the anabolic effects of testoterone are different for different tissues, what does the decrease in urinary nitrogen excretion mean in terms of wound healing?

It has been postulated by some that no attempt be made to reverse the "catabolic" reaction because it is a "defense mechanism" to supply metabolites to the injured area. There is no concrete evidence to support this. There is no reason, at the moment, to assume that the injured area is necessarily more proficient than other tissues in "utilizing" the circulating metabolites. We have recently studied the healing of experimental laparotomy wounds in normal and severely burned rats.[2] Observations of the gross appearance, tensile strengths and histologic features of the incisions were made. The healing of laparotomy wounds in the burned rats was significantly different from that in the unburned controls. Epithelization was not affected, but there was a definite delay in the formation of granulation tissue in the incisional wounds of the burned animals with a lag in the appearance and maturation of the fibroblasts and the ground substance. The eventual number and amount of these two elements, however, did not appear to be affected, and abundant granulation formed in the wounds of the burned rats in time. In some of the burned rats the wound area appeared somewhat more edematous than that of the controls. The incidence of wound infection was also somewhat higher among the burned animals.

3. *Is there a specific effect (direct or indirect) of renal dysfunction on wound healing? Or are the delays due to associated abnormalities in nutrition, water balance, ability to resist infection, etc.?*

4. *What is the basis for the apparent high incidence of wound infection in the patients with renal dysfunction?*

Various degrees of renal dysfunction should be produced experimentally in a number of different ways. Emphasis should be directed towards simulating the clinical problem of "lower-nephron nephrosis." The course of wound healing in animals with renal dysfunction, untreated and treated in a variety of ways, including dialysis, should be studied. Observations on local and systemic infection and various immune responses should be made. These data may be correlated with various nutritional and metabolic measurements.

It is well recognized that *infection*, when present, is a detriment to wound healing. A careful study of wound infection is important, not only in the early post-injury period, but throughout the healing period. Why is wound infection so frequent, and so serious, in the severely wounded patient with renal dysfunction? Does the malnutrition predispose to wound infection, or does the wound infection accelerate the development of malnutrition? What is the ability of the seriously injured man in regard to antibacterial defense? Following simple starvation, lymphoid tissue is markedly depleted; chronically protein-depleted rats are unable to synthesize certain antibodies as well as normally nourished animals. What is the ability of the seriously wounded man who is on a totally inadequate diet to form antibodies? What is the efficiency of phagocytosis, etc., in such an individual? (A preliminary study on some aspects of these latter two problems is reported elsewhere by Balch.[3]) What is the effect of extracorporeal dialysis on resistance to infection? For example, in vitamin C deficiency, susceptibility to infection is increased; it is possible that there is a considerable "washout" of ascorbic acid during dialysis. Further, most of these patients may be on various antibiotics, certain of which, when given orally, may lead to nutritional disturbances under certain circumstances.

5. *What are the effects of plasma substitutes and/or anemia on wound healing?*

It would appear that in many instances a combination of whole blood and dextran (or some other plasma substitute) may be satisfactory for early replacement therapy of shock. Under this circumstance, a certain degree of *anemia* will be present at the time the patient is evacuated further to the rear. Ordinarily, surgeons feel that anemia *per se* is detrimental to wound healing and will be inclined to transfuse such patients prior to secondary closure, etc. Is this a necessary, or wise, procedure (considering possible shortage of blood, transfusion reactions, etc.)? Is there a direct effect of anemia on wound healing or is there, perhaps, an indirect effect? Is hemoglobin a very high priority protein in the severely injured patient during the catabolic period and, if so, will protein be diverted from the healing wound to form hemoglobin if anemia is present? No conclusive data on the influence of anemia on wound healing in man are available; the data in animals are controversial.

What is the effect of plasma expanders *per se* on wound healing? Data in this regard are meager. Rhoads and his co-workers observed that whereas there was a delay in the healing of abdominal wounds in hypoproteinemic edematous dogs, there was no delay in hypopro-

teinemic dogs given acacia intravenously in amounts sufficient to eliminate the edema, but which, at the same time, accentuated the decrease in plasma protein concentration.[4] Thorsen has reported no delay in the healing of incisional wounds in rabbits given dextran.[5] We have observed no gross abnormalities in the healing of burns in patients who have received large amounts of dextran, but no special studies of the wounds were made.

6. *What are the optimal prophylactic and therapeutic nutritional (dietary, hormonal, etc.) regimens for the wounded patient with or without renal dysfunction?*

If the period of metabolic derangement persists, progressive nutritional deterioration with its consequent well-known ill effects occurs. What is the optional nutritional (dietary, hormonal, etc.) care of these individuals?

What Is Needed

A study of the individual and his wounds directed toward a comprehensive correlation and evaluation of systemic and local phenomena is indicated. Such a study will entail the use of a variety of technics, clinical, metabolic, bacteriologic and pathologic. The clinical studies should be supplemented by animal studies in a variety of species.

Some Factors in Wound Healing Requiring Control:

A. *Systemic Factors*
   1. Extent and sites of wounds.
   2. Associated injuries (and/or illnesses).
   3. Circulatory system (shock, sludging, etc.).
   4. Metabolic and nutritional state (including anemia, antibiotics, all nutrients, etc.).
   5. Plasma substitutes (primary and secondary effects).
   6. Infection (including "resistance" of individual, etc.).
   7. Blood clotting mechanism.

B. *Type of Wounds*
   1. Contaminated wounds, débrided and secondary sutured (including time of secondary suture).
   2. Contaminated wounds débrided and primarily closed.
   3. Clean, incised wounds closed primarily (including type of closure, etc.).

C. *Local Factors*
   1. Extent and sites of wounds (including surrounding and supporting tissues; proximity to joints; direction of wound relative to lines of stress, etc.).

2. Blood supply (arterial and venous).
3. Infection (including antibiotics, etc.).
4. Wound edema or dehydration (local or systemic basis).

D. *Medical and Surgical Care*

The quality and types of medical and surgical care are, of course, of paramount importance, but will not be discussed in this paper.

Conclusion. This analysis of wound healing among patients with serious battle injuries and renal failure confirmed the impressions of various physicians, that wound complications were frequent and important in these patients. Further, the analysis has indicated the complexity of the problem, some possible interrelationships among various factors and the need for concrete objective study, clinical and experimental.

Summary

1. The clinical and autopsy records of the 70 patients admitted to the Renal Center from its opening in the spring of 1952 through the middle of February 1953 were reviewed. Forty-two records were deemed adequate for analysis. However, the progress notes were written by internists, the records were not specifically directed towards problems of wound healing, bacteriologic studies were inadequate and only casual attention was paid to the wounds at autopsy. No histologic studies of the wounds were done.

2. Among the 42 patients whose records were analyzed, gross impairment of wound healing was noted in 31. The term "impairment" is used in a broad sense and is not meant to imply a specific defect in wound healing. Mortality among the patients with impaired wound healing was high; wound complications were among the more frequent and important causes of death.

3. It would appear that "impairment" of wound healing among these patients was greater than occurred in patients with serious battle wounds but without renal dysfunction. However, this cannot be stated with certainty, since no over-all systematic tabulation of wound healing among the battle casualties of the Korean conflict was made.

4. Among the patients with battle wounds and renal dysfunction, a comparison was made between those patients with unimpaired wound healing and those with impaired wound healing to determine some of the factors which might have had some bearing on the observed differences in wound healing. It appears that those patients with impaired wound healing were, in general, the more seriously injured, sicker, more uremic, required more dialyses, had greater changes in water and electrolyte metabolism, lost more weight, had more severe infections, and showed a higher incidence of abnormal

bleeding. The severity of the anemia could not be adequately estimated.

5. It would appear that in the majority of these patients multiple factors were leading to wound healing difficulties. These factors were presumably interrelated in the apparent *serious uremia*, *serious infection* and *serious malnutrition*. Some aspects of the pathogenesis and significance of these factors are discussed.

6. With the data at hand, no specific conclusion can be made covering the relative importance, or interrelationship, of the various factors. Studies are needed to define the problem specifically and thereby lead to improved prophylaxis and therapy. Such studies will require various clinical, metabolic, bacteriologic and pathologic technics. Some of the problems which need solution are as follows:

a. *What is the course of normal wound healing (open wounds, sutured wounds, etc.) in man?*

b. *What is the effect of magnitude of injury on wound healing, and if an effect is present, to what factors may it be attributed? What is the significance of the "catabolic" reaction to injury?*

c. *Is there a specific effect (direct or indirect) of renal dysfunction on wound healing? Or are the delays due to associated abnormalities in nutrition, water balance, ability to resist infection, etc.? What is the basis for the apparent high incidence of wound infection in the patients with renal dysfunction?*

d. *What are the effects of plasma substitutes and/or anemia on wound healing?*

e. *What are the optimal prophylactic and therapeutic surgical and nutritional (dietary, hormonal, etc.) regimens for the wounded patient with or without renal dysfunction?*

7. Some factors requiring control in wound healing studies are discussed.

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Chapter 9

Bacterial Flora of War Wounds of Patients with Renal Failure*

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A study of the flora of war wounds in patients who developed anuria during the first 4 days following injury was conducted during 1953 at the 11th Evacuation Hospital. There has been extensive speculation on the possibility that toxins from Clostridia in wounds contribute significantly to the renal shut-down syndrome. If this were the case, it was felt that such patients would show an anaerobic flora at variance with that observed in wounded men not suffering renal complications. Data on this latter category of patients were concurrently collected.

Materials and Methods

Wounds were observed for appearance, location and nature of injury. Cultures were made from biopsy specimens and from swabs, and blood cultures were obtained. Biopsy specimens were planted in chopped meat medium at the time of operation, and shipped to the 406th Medical General Laboratory for anaerobic culture. Swabs were cultured locally in thioglycollate broth and on aerobic blood agar plates. Blood cultures were made in evacuated rubber-stoppered bottles with trypticase soy broth under reduced oxygen tension. Antibiotic sensitivities of anaerobes were determined by a tube dilution technic using thioglycollate broth. Aerobes were tested by use of antibiotic-impregnated absorbent disks containing graded doses of antibiotic.

Observations

A total of 31 patients were studied. Of these, 25 provided only biopsy and swab cultures. Blood cultures were obtained on 8 cases. Seven patients were cultured at autopsy.

The Clostridia recovered from wound specimens in 25 anuric cases are shown in Table 1. Eighty-five strains of sixteen species, and one unidentified Clostridum, were recovered. The proportion of patients

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Table 1. Clostridia Recovered From Wounds and Tissue Specimens in 25 Anuric Patients

Species	Total No. of Strains Recovered	Per Cent of Total	No. of Patients Positive	Per Cent of Patients
*Cl. perfringens**	18	21. 0	7	28
Cl. sporogenes	25	29. 3	9	36
*Cl. novyi**	10	11. 7	4	16
Cl. bifermentans	5	5. 9	3	12
Cl. multifermentans	5	5. 9	3	12
Cl. parabotulinum	1	1. 1	1	4
Cl. lentoputrescens	3	3. 5	2	8
Cl. tertium	2	2. 3	1	4
*Cl. tetani**	3	3. 5	3	12
Cl. aerofoetidum	2	2. 3	1	4
Cl. tetanomorphum	1	1. 1	1	4
*Cl. carnis**	2	2. 3	2	8
Cl. butyricum	3	3. 5	2	8
Cl. paraputrificum	2	2. 3	2	8
*Cl. histolyticum**	1	1. 1	1	4
Cl. sphenoides	1	1. 1	2	8
Cl. unclassified	1	1. 1	1	4
	85			

*Species pathogenic for laboratory animals.

positive for each species is shown. This detailed listing permitted a comparison with findings on patients not in renal failure. Predominant species included *Cl. sporogenes* (29 per cent), *Cl. perfringens* (21 per cent) and *Cl. novyi* (11.7 per cent) of the total strains. It will be noted that 34, or 40 per cent, of the total strains recovered were of species usually termed pathogenic. Thirty-six per cent of patients were positive for *Cl. sporogenes*, 28 per cent for *Cl. perfringens*, 16 per cent for *Cl. novyi* and 12 per cent for *Cl. multifermentans*. Seventeen of the twenty-five had wounds which harbored Clostridia. Of 81 tissue specimens cultured, only 40 were positive for Clostridia. These proportionate values are summarized in Table 2.

It will be seen that 68 per cent of the patients, and 49.7 per cent of the specimens, were positive for Clostridia. In terms of those cases positive for Clostridia, an average of five strains of Clostridia were recovered per patient. From the 40 positive tissue specimens, an average of 2.12 strains per specimen were obtained.

When the proportion of specimens to strains of pathogenic Clostridia was considered, it appeared that 41.9 per cent of specimens yielded

Table 2. Clostridia Recovered From 81 Specimens Collected From 25 Anuric Patients

	Number	Per Cent
Patients studied	25	100
Number of patients harboring Clostridia	17	68. 0
Total specimens	81	100
Total specimens positive for Clostridia	40	49. 7
Total strains of Clostridia recovered	85	
Average number of strains per positive patient	5	
Average number of strains per positive specimen	2. 12	

toxigenic Clostridia. Of all patients cultured, 44 per cent harbored toxigenic Clostridia. One anaerobe, *Cl. difficile*, was recovered from the 10 blood cultures run. Among 7 autopsied cases, 25 specimens yielded 5 strains of Clostridia. These included *Cl. sporogenes*, *Cl. bifermentans*, *Cl. capitovale* and two strains of *Cl. multifermentans*. No toxigenic strains were recovered from autopsies.

The aerobic flora in war wounds is numerically predominant, and undoubtedly plays a prominent role in the course of recovery. Three hundred fifty-seven aerobic strains were recovered from the 81 tissue specimens cultured as described above. Results are summarized in Table 3. Prominent major groups were Streptococci (49.1 per cent of total), *Proteus* species (10 per cent) *Bacillus* species (14 per cent) and Staphylococci (9.6 per cent of strains). The totals of Streptococci were similar for clinical cases and autopsies. On the other hand, *beta*-hemolytic Streptococci were more numerous from autopsies than from clinical material (23.6 per cent contrasted with 16.2 per cent). The Streptococcus strains included 7.3 per cent of anaerobic or microaerophilic forms.

Among autopsy specimens, 76 strains were recovered. An increase in proportion of Proteus strains, and a slight decrease in Staphylococci, were the principal differences apparent between tissue specimens and autopsy samples.

The flora of the blood stream included that observed in numerous instances during artificial kidney dialysis of patients. The bacterial content of the dialysis bath was very high, and it is possible that the blood stream flora originated there. Streptococci were the most frequently encountered form, representing 34.4 per cent of total strains recovered from blood. *Proteus* species and *Aerobacter aerogenes* were next common in frequency.

Table 3. Aerobic Flora of Wounds and Blood and From Autopsies of 25 Anuric Patients

Species	Sources						Total
	Tissues and Wounds		Autopsies		Blood		
	No. of Strains	Per Cent of Strains	No. of Strains	Per Cent of Strains	No. of Strains	Per Cent of Strains	
Staphylococcus, hemolytic	13	3. 7	2	2. 7	1	4. 4	16
Staphylococcus, nonhemolytic	21	5. 9	2	2. 7	1	4. 4	24
Streptococcus, beta-hemolytic	58	16. 2	18	23. 6	3	13. 0	79
Streptococcus, alpha-hemolytic	23	6. 5	1	1. 3	1	4. 4	25
Streptococcus, nonhemolytic	68	19. 1	17	22. 4	3	13. 0	88
Streptococcus, anaerobic, beta-hemolytic	16	4. 5	1	1. 3	1	4. 0	18
Streptococcus, anaerobic, alpha-hemolytic	6	1. 7	1	1. 3	0	0	7
Streptococcus, anaerobic, nonhemolytic	4	1. 1	0	0	0	0	4
Bacillus species	50	14. 0	10	13. 2	2	8. 7	62
Corynebacterium species	12	3. 3	0	0	0	0	12
Pseudomonas species	10	2. 8	0	0	1	4. 4	11
Proteus species	36	10. 0	18	23. 6	5	21. 7	59
Aerobacter aerogenes	6	1. 7	1	1. 3	3	13. 0	10
Escherichia coli	12	3. 3	0	0	0	0	12
Paracolobactrum species	6	1. 7	2	2. 7	2	8. 6	10
Paracolobactrum aerogenes	0	0	1	1. 3	0	0	1
Alcaligenes species	10	2. 8	1	1. 3	0	0	11
Serratia marcescens	1	0. 3	0	0	0	0	1
Gram-negative rods, unclassified	5	1. 4	1	1. 3	0	0	6
	357		76		23		456

A short summary of the total aerobic flora is presented to clarify the relative distribution of bacterial forms in Table 4. The striking predominance of Streptococci is conspicuous. Representative samples of strains of Streptococci were typed; over 90 per cent were Group D, with some group H and K noted.

Table 4. Combined Aerobic Flora of Wounds and Blood and From Autopsies of 31 Anuric Patients

Organism		No. of Strains	Per Cent of Total
Staphylococcus	40		8. 8
Hemolytic		16	
Nonhemolytic		24	
Streptococcus	221		48. 4
Alpha-hemolytic		25	
Beta-hemolytic		79	
Nonhemolytic		88	
Anaerobic, alpha-hemolytic		7	
Anaerobic, beta-hemolytic		18	
Anaerobic, nonhemolytic		4	
Bacillus species	62		13. 6
Pseudomonas species	11		2. 4
Proteus species	59		13. 0
Corynebacterium species	12		2. 6
Coliform	50		11. 0
Aerobacter aerogenes		10	
Escherichia coli		12	
Paracolon sp.		10	
Alcaligenes sp.		11	
Paracolobactrum aerogenes		1	
Gram-negative rods, unclass.		6	
Serratia marcescens	1		0. 2
Total	456		

Antibiotic Sensitivity of Flora of Wounds in Anuric Patients

The clostridial flora of the wounds studied was sampled for antibiotic sensitivity to penicillin, aureomycin, terramycin and chloramphenicol. Antibiotic concentrations inhibiting over 80 per cent of each predominant species tested were determined; a small number of strains in each species were resistant to higher levels of antibiotic. In the case of chloramphenicol, this resistance was extremely high; the proportion of resistant strains was lower in the case of penicillin, aureomycin and terramycin.

The sensitivity values observed are summarized in Table 5. The inhibitory levels of three principal species of Clostridia from these

Table 5. Antibiotic Sensitivity of Principal Clostridial Species in Wounds of Anuric Patients

Clostridium Species	No. of Strains Tested	Amount of Antibiotic Inhibiting over 80 Per Cent of Strains Tested			
		Penicillin	Terramycin	Aureomycin	Chloromycetin
		units/ml.	*mcg./ml.*	*mcg./ml.*	*mcg./ml.*
Cl. perfringens	12	0. 7	1. 0	0. 5	12. 5
Cl. sporogenes	15	0. 6	0. 7	0. 5	10. 0
Cl. novyi	10	0. 4	0. 25	0. 4	10. 0
Cl. bifermentans	4	0. 35	0. 35	0. 3	7. 5
Cl. multifermentans	4	0. 25	0. 45	0. 3	7. 5

Table 6. Antibiotic-resistant Clostridia From Wounds of Anuric Patients

Species	Antibiotic	No. Tested	No. Resistant	Maximum Level Tolerated
Cl. perfringens	Penicillin	12	2	5 u./ml.
	Aureomycin	12	1	1 mcg./ml.
	Terramycin	12	1	5 mcg./ml.
	Chloramphenicol	12	2	20 mcg./ml.
Cl. sporogenes	Penicillin	15	3	5 u./ml.
	Aureomycin	15	3	1 mcg./ml.
	Terramycin	15	2	5 mcg./ml.
	Chloramphenicol	15	1	20 mcg./ml.
Cl. novyi	Penicillin	10	1	5 u./ml.
	Aureomycin	10	1	1 mcg./ml.
	Terramycin	10	1	5 mcg./ml.
	Chloramphenicol	10	2	20 mcg./ml.

wounds were comparable with those seen in other extensive series of wound Clostridia studied; no essential increase in resistance was noted. The antibiotic-resistant strains observed included two *Cl. perfringens*, three *Cl. Sporogenes* and two *Cl. novyi*. These grew in concentrations of 5 units/ml. for penicillin, 1 mcg./ml. for aureomycin, 5 mcg./ml. for terramycin and 20 mcg./ml. for chloramphenicol. The reactions of these resistant strains are shown in Table 6.

Sensitivity of aerobic flora was set up with antibiotic-impregnated disks on blood agar plates. The levels of antibiotic indicated are the amounts present in the disks. Streptomycin was included in this series. Table 7 shows the results of these tests. The predominance of

Table 7. Sensitivity of Aerobic Microbial Flora From 25 Anuric Patients to 5 Antibiotics

Organisms	No. of Strains Tested	Penicillin (Unit) 1 unit		Aureomycin (2.5 mcg.)		Terramycin (2.5 mcg.)		Streptomycin (12.5 mcg.)		Chloromycetin (12.5 mcg.)	
		S*	R*	S	R	S	R	S	R	S	R
Staphylococcus, hemolytic	12	2	10	9	3	7	3	1	11	7	1
Staphylococcus, nonhemolytic	12	5	7	11	1	11	1	6	7	4	
Streptococcus, nonhemolytic	14	4	10	7	7	6	8	5	9	1	1
Streptococcus, beta-hemolytic	12	4	7	2	10	2	10	1	11	2	1
Streptococcus, alpha-hemolytic	10	2	8	1	9	2	8	1	8		1
Aerobacter aerogenes	5		5	3	2	1	4	1	4	2	2
Proteus species	24	1	23	3	20	2	21	1	21		13
Paracolon species	13	1	12	3	11	2	12	3	10		1
Escherichia coli	5		5	2	3	2	3	4	1		
Alcaligenes species	4		4	2	2	2	2		4		
Pseudomonas aeruginosa	4	1	3	2	2	3	1	1	3		
Totals	115	20	94	45	70	40	73	24	89	16	20

*S = Sensitive.
R = Resistant.

penicillin-resistant forms is a conspicuous feature of this series, although other flora also show a markedly resistant trend.

Discussion

The bacterial flora of the wounds of patients with anuria showed no significant departures from that which might have been observed in another series of seriously wounded men. The totals for Clostridia are somewhat higher in terms of number of patients involved than were those of a series of patients not classified as anuric, but if a selection had been made of severe wounds only, the flora would have been similar in distribution.

Antibiotic-resistant forms of Clostridia were slightly more numerous than were those observed in a series of strains selected at random from recently wounded men. This increase in proportion of antibiotic-resistant strains is a not surprising result of the exposure of wound flora to antibiotic. There was not a large preponderance of resistant strains.

The aerobic flora was similar to that observed in recent wounds of patients not suffering with anuria. The predominant flora were cocci, with Streptococci the major part of the whole. The *beta*-hemolytic strains were chiefly D (enterococci). *Proteus* strains were relatively common.

The blood stream aerobic flora was profuse, but this must be interpreted in light of the fact that many of these cultures were drawn on men undergoing dialysis. Invasion through the dialyzing membrane could have accounted for the apparent transient bacteremia these men experienced. Some selectivity was shown in the preponderance of *Proteus* strains surviving in the blood; the antibiotic employed may have reduced the number of cocci found.

Summary

A series of 31 anuric patients were studied by means of wound and blood cultures. A profuse anaerobic and aerobic flora was found, but there was no indication that a specific alteration of the nature of wound flora occurred. Antibiotic-resistant strains were found in increased numbers over those recovered from more recent wounds, and an extensive antibiotic-resistant aerobic flora was present. There was no specific indication of an infection pattern typical of the anuric patient.

Chapter 10

The Effect of Severe Battle Injury and of Post-traumatic Renal Failure on Resistance to Infection*

Major Henry H. Balch, MC, USAR

Introduction

Acute infection remains one of the serious complications of severely wounded soldiers. A statistical analysis has been reported of 1,273 battle casualties who died in forward surgical hospitals near the end of World War II.[1] Fourteen per cent of these died of complicating surgical infection. In the Korean War, 5 of 20 deaths occurring in 138 severely wounded soldiers at a forward level were the result of complicating infection.[2] Wounds are usually contaminated with many aerobic and anaerobic pathogenic microorganisms.[3] Furthermore, devitalized tissue in wounds presents a suitable environment for bacterial multiplication, spread, or toxin production. Wound infection can usually be prevented by early and adequate surgical débridement which removes most of the non-viable tissue and perhaps the majority of contaminating bacteria; such adequately débrided wounds can often be closed on the fifth post-wound day regardless of their bacterial flora at that time provided the classical signs of infection are absent.[4]

Infection has been reported to be more common in patients with renal failure.[5] Sixty-nine per cent of a small series of fatal cases of post-traumatic renal insufficiency in World War II had severe complicating infection.[2] Likewise, a high incidence of infection was noted in similar cases under study in Korea.[6]

Several physiologic and biochemical changes have been described following severe injury.[7,8] The subsequent development of post-traumatic renal insufficiency causes further variations.[7,9] Therefore, it is possible that body defense mechanisms may also be altered in these conditions and so contribute to the development of infection.

There are several mechanisms of body defense following bacterial invasion. The microorganisms may be trapped and eliminated by lymph nodes draining the area. Cells of the reticuloendothelial system and wandering phagocytes may ingest and destroy pathogens, a process which is much more effective if specific antibody is present. In addition, natural and specific antibody (globulins) participates in

*In press: *Annals of Surgery.*

the lysis of some bacterial species and also neutralizes the toxic products of others. The term complement designates a group of proteins found in normal serum which possess several properties of importance in antibacterial defense. These include a capacity to render microorganisms more susceptible to phagocytosis and also to kill bacteria coated with antibody. Therefore, if a defect in globulin synthesis or a depression of reticuloendothelial cell function or leukocyte activity follows severe injury, the defense effort might be seriously impeded.

The purpose of the present investigation was to study antibacterial defense systems in a group of severely wounded casualties with and without post-traumatic renal insufficiency. This was accomplished by measuring (a) the phagocytic activity of circulating leukocytes, (b) the body's capacity to synthesize specific antibody, and (c) the plasma complement level in patients. The findings were then related to other clinical data and an attempt was made to assess their significance in the development of infection.

The study was undertaken during the months of June, July and August, 1953, as one facet of the Army Medical Service Graduate School's research activities in Korea. Patients were studied at the 46th Mobile Army Surgical Hospital and at the 11th Evacuation Hospital.

Methods

Measurement of Phagocytosis. The method used has been described in detail in the previous communication.[10] The capacity of neutrophilic polymorphonuclear leukocytes (neutrophils) to ingest coagulase-positive Staphylococci (strain I) was measured. One-tenth of a milliliter of a standardized suspension of microorganisms was added to 1.0 ml. of heparinized blood. The mixtures were placed in glass tubes 12 x 0.8 cm. in size, which were then stoppered and rotated in a 37° C incubator at 11 r. p. m. for 60 minutes. Blood smears were then prepared and ingestion was recorded as the percentage of neutrophils containing Staphylococci.[11] Blood samples were taken from patients one or more times each day. Fourteen seriously wounded patients without oliguria and twelve seriously wounded casualties with post-traumatic renal insufficiency were studied. Twelve slightly wounded soldiers served as control subjects. All casualties had received chemotherapeutic drugs.

Complement Titrations. The level of complement was measured by determining the highest dilution of plasma which would lyse 0.5 ml. of a standardized suspension of sensitized sheep red cells. All dilutions were made with Kolmer's saline (0.85 per cent NaCl+0.01 per

cent $MgSO_4$), the double-dilution technic being used. Sensitized sheep red cells preserved not longer than 21 days in dextran-gelatin-veronal solution[12] were used. The mixtures of plasma and cells were incubated in a water bath at 37° C for 30 minutes and the end point was read as the highest dilution of plasma causing 100 per cent hemolysis. Blood samples were taken from patients daily or more often. Plasma was separated immediately and the titrations were done without delay. Fourteen seriously wounded patients without oliguria and twelve seriously wounded casualties with post-traumatic renal insufficiency were studied. Seventeen lightly wounded soldiers served as control subjects.

Antibody Synthesis. The capacity to synthesize specific antibody was determined by measuring at intervals the level of circulating tetanus antitoxin following the subcutaneous administration of 0.5 ml. alum-precipitated formalized tetanus toxoid to previously immunized casualties. The toxoid was injected within a few hours of wounding. Blood was drawn for antitoxin titration at various intervals depending in part on the patient's survival or his evacuation from the combat zone. Plasma was separated from cells and frozen. At a later date the samples were carried to the United States for antitoxin assay. The antitoxin level was titrated in mice using a tetanus toxin of known potency obtained from the National Institutes of Health. In general, the method of assay was that used by Pillemer.[13] All dilutions of plasma or toxin were made with a solution of 0.9 per cent sodium chloride which contained 1 per cent peptone. Three mice were used with each dilution. Each titration was controlled by a parallel titration using standard tetanus antitoxin. Data from 7 casualties are reported in this study.

Chemical data* reported in this study were determined as follows: Nonprotein nitrogen by the method of Folin and Wu;[14] sodium potassium by the flame photometric method of Hald;[15] inorganic phosphate by the method of Fiske and Subbarow;[16] chloride by the method of Schales and Schales;[17] carbon dioxide capacity by the method of Van Slyke and Cullen;[18] and calcium by Clarke and Collip's[19] modification of Kramer and Tisdall's method.

Clinical Record. Patients included in this study were carefully followed either at a forward surgical hospital or at a special center for the treatment of post-traumatic renal insufficiency. Prolonged observation was not always possible because of evacuation or death of the patient.

*I am indebted to Major Wm. H. Meroney, MC, Chief, Renal Insufficiency Center, Korea, for permission to publish the chemical findings from patients studied at that center.

Patients were considered severely wounded if they had sustained multiple injuries, were in severe shock, and required a large volume of blood for resuscitation.

Post-traumatic renal insufficiency was diagnosed clinically when a wounded soldier excreted less than 500 ml. urine per 24 hours in the presence of an adequate blood pressure and a reasonable state of hydration. The diagnosis was confirmed by chemical data and, in the patients who died, by the autopsy findings.

Results

Phagocytosis by Neutrophils Following Injury

Table 1 records phagocytosis of coagulase-positive Staphylococci by neutrophils from different groups of subjects. In the present experi-

Table 1. Phagocytosis Related to Injury

Post-wound Day	No. Subjects	Per Cent Neutrophils Showing Ingestion	Standard Error of Means
Non-wounded			
0–1	6	94. 4	±2. 18
Slightly Wounded			
0–1	12	88. 2	±2. 5
Severely Wounded without Clinical Post-traumatic Renal Insufficiency			
0–1	6	68. 4	±5. 5
1–2	5	61. 2	±12. 1
2–3	4	81	±4. 2
3–4	5	82	±5. 4
Severely Wounded with Post-traumatic Renal Insufficiency			
1–2	5	83. 6	±3. 7
2–3	8	82	±1. 7
3–4	6	83	±2. 1

ments the bacterial suspensions used were always adjusted to the same turbidity and the neutrophil count per cubic millimeter was determined for each blood preparation. The over-all ratio averaged 1 neutrophil to approximately 30 bacteria. Since bacteria were always present in considerable excess, the differences in ratio of bacteria to neutrophils in different experiments are probably not an important factor. In any event, under the conditions of our experiments, the degree of phagocytosis appeared to be independent of the neutrophil count.

The differences shown between the non-wounded and lightly wounded subjects could have been due to chance. The latter group

were all ambulatory patients and were studied within 12 hours of injury. So, any general stress effect which might have resulted from exposure to enemy action did not interfere with staphylococcal ingestion under the experimental conditions of the study.

Phagocytosis by neutrophils from severly wounded subjects without post-traumatic renal insufficiency was significantly diminished within the first 24 hours of injury. The reduction was still present on the second post-wound day, but the findings were not so definite. On subsequent days, the findings were within the range of those found in the lightly wounded control group. The differences in mean phagocytosis by neutrophils from patients with post-traumatic renal insufficiency and those from the slightly wounded control group could have been due to chance.

Therefore, the only group of patients showing significantly diminished phagocytosis were the severely wounded who were studied on the day of injury. In all these instances, blood for study was drawn at the end of resuscitation from shock.

Table 2 relates the white blood count per cubic millimeter and neutrophil activity to the volume of blood and dextran used in the resuscitation of individual casualties. In six of the cases the data were ob-

Table 2. Complement Titer Leukocyte Count and Mean Ingestion of Staphylococci by Neutrophils Immediately Following Large Blood Transfusions

Patient Number	Post-wound Day	Volume Blood Used in Resuci-tation	Volume Dextran Used in Resuscii-tation	WBC per cu. mm.	Per Cent Neu-trophils	Per Cent Neu-trophils Contain-ing Sta-phylococci	Comple-ment** Titer
		L	L				
3	1–2	5	1. 9	15, 400	73	56	16
4	1–2	5		14, 000	81	18	32
15	0–1	7	0. 5	13, 250	72	66	16
16	0–1	7. 5		14, 650	70	56	8
21	0–1	8. 5	1. 0	16, 800	79	62	16
26	0–1	5. 5*	1. 0	15, 800	76	56	4
	0–1	10		13, 400	66	62	4
	0–1	12		16, 600	72	74	8
	0–1	13		15, 300	74	70	8
27	0–1	12*		9, 850	80	88	16
	0–1	23		11, 850	77	90	16
28	0–1	26		5, 500	70	82	16

*Volumes of blood are reported on a cumulative basis.

**Reciprocal of highest dilution giving 100% hemolysis.

Table 3. Relationship of Daily Plasma Calcium to Phagocytosis

Patient No. 126		Patient No. 129	
Calcium mg./100 cc.	Per Cent Neutrophils Containing Staphylococci	Calcium mg./100 cc.	Per Cent Neutrophils Containing Staphylococci
5. 8	78	7. 0	82
6. 4	84	7. 1	80
7. 1	86	7. 9	90
7. 5	88	9. 0	88
7. 8	80	9. 1	86
8. 0	72	11. 0	80
8. 0	88	11. 5	84
8. 1	92	13. 2	78
8. 4	82		
11. 6	84		

tained within 24 hours of injury and immediately following the administration of the volume of bank blood recorded in the table. The elevated white blood counts were probably not the result of hemoconcentration, since in the majority of such wounded soldiers hematocrits were normal or low. These findings show that even after the administration of three or four times a normal blood volume of bank blood, optimal numbers of leukocytes were present in the circulation. Furthermore, the percentage of neutrophils was higher than normal. But, as already reported, in several instances the percentage of active neutrophils was diminished. The findings did not appear to be related to the magnitude of injury as judged by the volume of blood required for resuscitation nor to the amount of bank blood used. All the patients who received dextran showed a depression of phagocytosis, but so did others not receiving this colloid. White blood cells found in a patient's blood immediately following large transfusions were probably autogenous and not contributed by the transfusions. The latter were all of bank blood flown from the United States. Most of the bottles of blood were more than 10 days old but all less than 21 days. Examination of several such samples invariably revealed very low white blood counts, neutrophils being absent.

These data do not show why phagocytosis is depressed. The return toward normal by the second post-wound day could have been due to the output of new neutrophils by the bone marrow although there is no evidence to prove this. The initial depression in phagocytosis could

also have been due to humoral factors, with restoration towards normal by the second day. Citrate has been reported to interfere with phagocytosis,[11] but it probably was not a factor in these patients because patients numbers 27 and 28 showed no significant depression in phagocytosis; yet they received the largest quantities of citrate blood.

Calcium ions are reported to be essential for optimal phagocytosis.[11, 20, 21] Table 3 shows the realtionship between daily total plasma calcium and the ability of neutrophils to ingest Staphylococci. These data, taken from two patients with acute renal failure, show no consistent pattern. Therefore, under these experimental conditions, variations of plasma calcium within a wide physiologic range did not affect ingestion. Furthermore, other observations showed that the administration of sufficient calcium gluconate to elevate the blood pressure temporarily in hypotensive patients did not alter phagocytosis.

Post-traumatic Renal Insufficiency and Phagocytosis

Post-traumatic renal failure leads to reasonably predictable changes in the level of many of the blood constituents. The hematocrit and the sodium, chloride, carbon dioxide and calcium levels in plasma are often depressed. But potassium, phosphorus and nonprotein nitrogen are usually elevated. Successful dialysis of a patient's blood through an artificial kidney for 6 hours restores all of these except the hematocrit towards normal. Table 4 records such data from patients with acute renal failure. The determinations were obtained at the beginning of hemodialysis and at its completion 6 hours later. The criteria employed for the use of artificial hemodialysis were either potassium intoxication or severe clinical uremia. Phagocytic activity did not appear to be related to any of the changes in plasma chemistry, and was not depressed even in the blood of patients with severe clinical uremia.

Phagocytosis and Development of Infection

Because multiple factors probably are concerned in the development of infection following injury, it may be unwise to attempt to relate phagocytosis and the development of infection in individual cases. With this reservation, a listing has been made in Table 5 showing whether or not infection developed in five cases with early postwound depression of neutrophil activity. In no instance can it be stated that the onset of infection was aided by the lowered neutrophil activity. For example:

Patient number 4 was first admitted to a Mobile Army Surgical Hospital 1½ hours after injury. Preliminary resuscitation was ac-

Table 4. Blood Chemistry, Phagocytic Index, and Complement Titer Before and After Hemodialysis

Patient No.	Hemat.	Na	K	Cl	CO_2	NPN	Ca	P	WBC	Per Cent Neutrophils	Per Cent Neut. Containing Staphylococci	Complement Titer****
		mEq./L.	mEq./L.	mEq./L.	mEq./L.	mg./100 cc.	mg./100 cc.	mg./100 cc.	per cu. mm.			
125												
0 hours	31	151	6. 0	104. 5	21. 2	255	8. 8	9. 7	17, 200	91	88	8
6 hours	29	138	3. 5	99	25. 8	91. 4	9. 0	5. 1	18, 000	91	84	8
126*												
0 hours		125	6. 8	81	27. 5		5. 8	15. 7	11, 050	54	78	16
6 hours		150	2. 8	92. 7	24. 3		8. 1	6. 9	10, 500	59	92	16
127												
0 hours	26. 5	133	6. 4	91. 7	20	170*	8. 1	8. 6	11, 430	77	82	8
6 hours	27	140	4. 6	95. 8	24. 3	105		5. 6	14, 600	74	90	<1
128												
0 hours	45	146	8. 2	95	22. 5	113		5. 5	12, 300	92	84	<1
4 hours	44	145	5. 4	96	26		10	3. 6	13, 200	90	92	<1
129**												
0 hours	38	143	6. 5	97. 6	26	261	9. 1	18. 7	13, 400	74	86	16
6 hours	36	140	4. 1	99. 6	25. 3	65	11. 5	7. 6	14, 200	80	84	32
129***												
0 hours	29. 5	147	8. 5	89	13. 3	320	11	20	14, 300	68	80	32
6 hours	35	144	4. 1	97. 4	17. 1	100	13. 2	10. 8	17, 200	76	78	16
133												
0 hours	21	133	8. 5	91. 8	12. 6	224			17, 100	81	80	32
6 hours	36	145	4. 9	96. 6	18. 5	95			15, 300	74	78	16

*Patient with acute hemorrhagic fever.
**Third post-wound day.
***Sixth post-wound day.
****Reciprocal of highest dilution yielding 100% hemolysis.

Table 5. Relation of Early Post-wound Phagocytosis to Development of Infection

Patient Number	Per Cent Neutrophils Showing Ingestion on 1st or 2nd Post-wound Day	Infection		
		Serious	Moderate	Minor
3	56		+	
4	18	+		
15	66			+
26	56		+	
27	88			

complished, and then because of a heavy patient load he was transferred by air to another surgical hospital. Here the patient load was also heavy and further transfusion was required while awaiting operating room space, which became available 15 hours after injury. The patient's injuries included a large penetrating flank wound with transection of the sigmoid colon, a compound fracture of the left tibia involving the knee joint, large perforating wounds of the thighs, traumatic amputation of the right hand and compound fracture of the left humerus. At operation no definite peritonitis was noted and the colon was exteriorized; the extremity wounds were thoroughly débrided. At that time 18 per cent of the test neutrophils ingested Staphylococci. The patient's postoperative course was marked by extreme lethargy and failure to cough or ventilate adequately. Atelectasis developed which was not controlled by bronchoscopy or tracheotomy and frequent intratracheal aspiration. The abdomen remained soft and the extremity wounds were not clinically infected. The patient died on the fourth post-wound day at which time approximately 62 per cent of circulating neutrophils were active. From the time of initial surgery until death the temperature persisted at 102 to 103° F, the pulse at 120 to 130 per minute, and the respirations fluctuated between 30 and 50 per minute. Urine output was greater than 1,000 ml. per day. The patient was given penicillin, streptomycin and oxytetracycline. The outstanding finding at autopsy was bilateral lung atelectasis with multiple small abscesses.

Because the wounds remained clean and significant peritonitis was absent, it seems unlikely that a general depression in neutrophil activity was of primary importance in the development of lung abscesses. It is more probable that some local factor such as unrecognized aspiration of foreign material into the lung during anesthesia was the precipitating factor.

357521—55——12

Figure 1 shows mean neutrophil activity determined from daily estimations in seriously wounded patients with and without acute renal failure. They are further grouped into those who died of uncontrolled infection (myositis, peritonitis or septicemia) and those not clinically infected or in whom infection was controlled. Except for patients numbers 3 and 4, the differences shown between individuals in each group did not seem of importance. Furthermore, there was no significant difference between the groups. These data appear to show that neutrophil activity was well maintained during the course of serious illness following severe battle trauma. The development of acute renal failure did not depress the ability of neutrophils to ingest Staphylococci. The pressure of normal numbers of active neutrophils did not prevent death from uncontrolled infection.

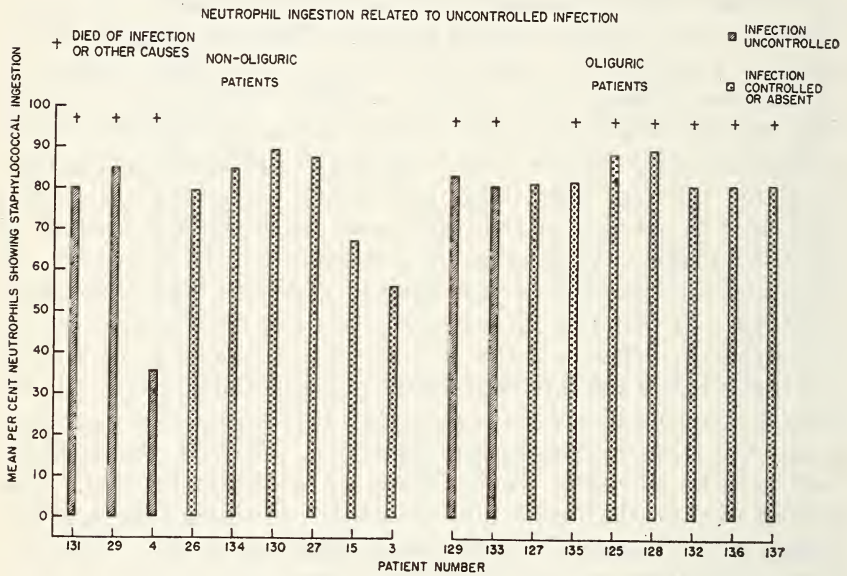


Figure 1. Capacity of neutrophils to ingest Staphylococci related to the presence of uncontrolled infection.

Complement Titer Following Injury

Complement titers were determined in three categories of patients: a series with minor injuries which includes the patients used as controls in the phagocytosis studies, another series of severely wounded soldiers without clinical renal insufficiency, and a third group of severely wounded with acute renal failure. Freshly drawn plasma was used in these titrations because preliminary tests showed that the amount of heparin used to prevent coagulation did not alter the titer

under the experimental conditions used. The original concept in this part of the study was to undertake preliminary experiments to evaluate whole complement activity following severe injury. If any significant change was found, the plan was to attempt a more comprehensive study of the effect of injury of the several fractions of complement. For this reason, and because the studies were done under field conditions, plasma was titrated by the double-dilution method, reading 100 per cent hemolysis as the end point. Because of the large blood volume shifts and *also* the hemodilution which accompanies hemorrhagic or traumatic shock, it seemed probable that the significance of any small variation in complement detected by more refined technics would be difficult to interpret.

Table 6 records the dilution of plasma from different subjects required to hemolyze completely 0.5 ml. sensitized sheep red cells. The findings for the slightly wounded patients are comparable with those found by others in normal individuals.[22, 23, 24] The table also shows complement titers obtained from severely wounded patients without clinical evidence of acute renal failure. Because of the wide range in plasma dilution, the possible error between observations of successive tubes is at least 100 per cent. For this reason the range of levels of complement activity shown by some severely wounded patients cannot be considered significant. However, the table shows that most of the specimens examined were within the control range.

Table 6. Complement Activity in Plasma of Battle Casualties
End Point = 100% Hemolysis

Slightly Wounded	Seriously Wounded without Oliguria					
17 Patients	14 Patients					
	Post-wound Day					
Complement* Titer	0–1	0	1	2	3	4	5
	No. Patients	No. Patients					
64					1		
32	12	1	2		2	1	1
16	5	5	4		2	1	
8		1	2	3	1		1
4		1					

*Reciprocal of highest dilution yielding 100% hemolysis.

Table 2 also records complement titers in the plasma of a group of patients immediately following large transfusions of bank blood. Complement levels were in the normal range even after the administration of bank blood in an amount equivalent to 3 or 4 times a normal blood volume. These patients had been in severe shock, which in patients numbers 26 and 27 was continuing as the successive estimations of complement were made. In the former case there appeared to be some depression in complement titer until 12 liters of blood had been given, but the complement then changed towards normal. The administration of such large quantities of blood to Korean War casualties has been discussed by others.[25] The evidence suggests that, despite such large transfusions, residual blood volumes were usually subnormal. In other words, continuing hemorrhage was probably occurring and some of these patients may have received the equivalent of a complete exchange transfusion. It is possible that the complement found in these patients was contributed by the bank blood. Titration of complement activity in the plasma from several samples of bank blood (10 to 21 days old) showed titers of 1:32 to 1:16. The presence of magnesium in the diluent probably replaced the citrate-bound magnesium in the bank plasma and probably explains the finding of normal levels of complement in the bank blood samples. The observations reported in this study do not include complement titers in severely injured casualties before resuscitation was commenced. If complement was depressed, it apparently returned to normal in the majority of cases following resuscitation.

Table 7 records complement titers in patients with post-traumatic renal insufficiency. The results were similar to those found in the non-oliguric group, and most of the findings were within our normal range. Possibly there was some decreased activity in individual titrations of plasma from different patients, but the observations cannot be considered significant. Complement was apparently absent in single samples of plasma taken from four patients. One of these (patient number 128) was suffering from hemorrhagic shock and had received 21 liters of blood before the specimen was drawn for assay. Twelve hours later the titer was 1:8. There was no apparent explanation for the failure to detect complement activity in these samples of plasma, and in each instance complement was present on the next day. Table 4 records the complement activity of plasma from several patients with acute clinical uremia (125, 126, 127, 129, 133). These were within the control range and the complement determinations before and after hemodialysis (with the exception of patient number 127) were not significantly different in spite of considerable

Table 7. Complement Activity in Plasma of Battle Casualties End Point=100% Hemolysis

Seriously Wounded with Oliguria
12 Patients
Post-wound Day

Complement Titer*	1	2	3	4	5	6	7
	No. Patients						
32		1	1	1	2	1	
16	1	1	3	3		1	
8	1	1	1		2		1
4							
<1	2						2

*Reciprocal of highest dilution yielding 100% hemolysis.

changes in the blood levels of nonprotein nitrogen, potassium or phosphorus following hemodialysis. Complement was also normal where plasma calcium was low and in patients with relatively severe acidosis.

Complement Activity and Phagocytosis

A reduction in complement activity may be accompanied by a depression in phagocytosis of microorganisms if the complement fractions which have been identified with the normal opsonins of the plasma are absent.[26] In Tables 2 and 4, data on phagocytosis and complement activity from the same specimen of blood may be compared. There was no consistent relation between complement and phagocytosis under the experimental conditions studied. This finding is not necessarily significant because we have no data on the distribution of the separate fractions of complement. For example, if C′3 was lowered out of proportion to the other components, the plasma might fail to hemolyze sensitized cells but still opsonize microorganisms.[26]

The suggestion has been made that a low complement titer might predispose a patient to terminal infection,[27] but others have failed to find complement titers to be of any general prognostic value.[24] In Table 8 are listed the complement titers found in the plasma of several patients on the day of death. All were severely wounded, and patients numbers 115, 120, 129, 132, 133, 135, 136 and 137 had complicating acute renal failure. The values were all within our normal

range. It is difficult to establish absolute cause of death in a complex disease, but the table also lists what was considered to be the most prominent cause of death in each case. The observed complement titers were not of any prognostic value and were not significantly lower in patients dying of infection or of secondary irreversible traumatic shock.

Table 8. Complement Titer in Wounded Casualties on Day of Death

Patient Number	Complement Titer*	Most Prominent Cause of Death
Patients without Post-traumatic Renal Insufficiency		
4	64	Multiple lung abscess
16	8	Traumatic shock
21	16	Extensive head injury
28	16	Traumatic shock and hemorrhage
29	8	Clostridial myositis
Patients with Post-traumatic Renal Insufficiency		
115	16	Clostridial myositis
120	32	Hyperkalemia
129	16	Clostridial myositis
132	32	Undetermined
133	8	Para-colon septicemia
135	8	Fat embolus
136	32	Undetermined
137	16	Undetermined

*Reciprocal of highest dilution yielding 100% hemolysis.

Antibody Synthesis

Figure 2 shows the tetanus antitoxin response of two severely wounded patients who did not develop clinical evidence of post-traumatic renal insufficiency. They were given a booster dose (0.5 ml.) of alum-precipitated tetanus toxoid within a few hours of injury. Similar data are recorded in Figure 3 from five severely wounded patients with complicating acute renal failure. All of the patients had received a previous booster injection of tetanus toxoid within 6 months of injury, and all the samples of plasma contained at least 0.1 unit of tetanus antitoxin per ml. within 1 to 4 days after injury. These antitoxin levels were probably present at the time of injury, because the response to the booster injections in normal individuals

does not usually appear before 4 days.[28, 29] Two of the patients studied failed to show any response during the period of observation. One of these was oliguric and died on the eighth post-wound day from clostridial myositis. The other did not have renal failure but was evacuated from the combat zone, and so observation after the seventh day was not feasible. Antitoxin titers in all of the other patients showed a progressive rise. In one of these patients the rise did not

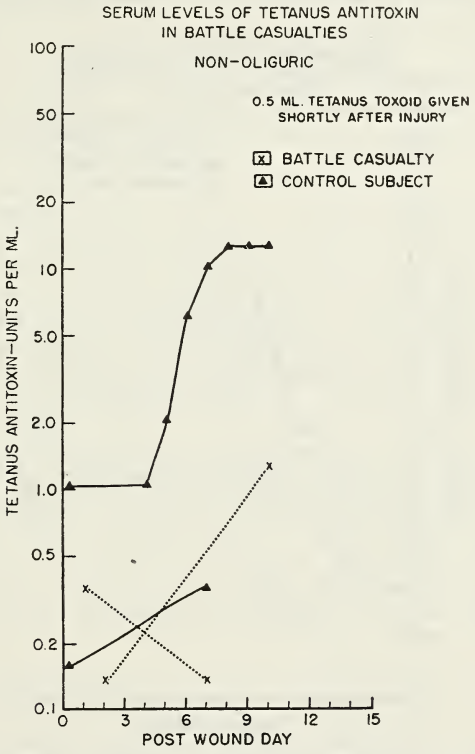


Figure 2. Synthesis of tetanus antitoxin by severely injured battle casualties without complicating acute renal failure. Controls are from published observations of others.[29, 30]

appear until the eighth post-wound day. Normal subjects show considerable variation in antitoxin response following the administration of a booster dose of tetanus toxoid.[29, 30] Furthermore, an increase in the circulating antitoxin may not appear until at least the sixth day after immunization and perhaps longer.[31]

The findings reported in this study fell within previously observed variations in the response of normal subjects to a booster injection of

tetanus toxoid. Therefore, the data showed no evidence of any defect in the capacity of seriously wounded soldiers with or without acute renal failure to synthesize tetanus antitoxin. There might possibly have been some delay in the appearance of circulating antitoxin in this category of patient. This, however, does not necessarily reflect a defect in the capacity to synthesize antitoxin but might have been due to a delay in the absorption of antigen following prolonged shock after injury. Both of the patients who appeared not to have syn-

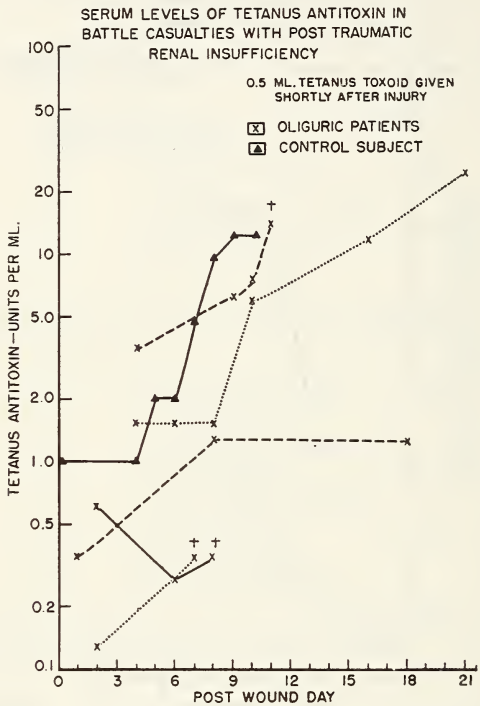


FIGURE 3. Synthesis of tetanus antitoxin by severely injured battle casualties with complicating acute renal failure. Control is from published observations of Mueller and his associates.[30]

thesized antitoxin by the seventh and eighth post-wound days suffered severe shock; as did one patient in whom we had daily determinations and in whom the titer failed to rise until the eighth post-wound day. On the other hand, antitoxin titers in two of the oliguric patients were rising despite clinical deterioration until death of the patients. This confirms previous observations [32] that the capacity to synthesize antitoxin may be retained by patients in spite of a progressively deteriorating illness.

Clinical Examples

The following clinical examples are included to demonstrate the type and degree of injury studied. Daily observations of leukocyte and complement activity are recorded and also tetanus antitoxin levels when determined. An attempt has been made to relate the laboratory data to the clinical course.

Severely Injured Without Post-traumatic Renal Insufficiency

Patient Number 29. A 20-year-old white soldier injured at approximately 1700 hours on 19 July 1953. He was admitted to a Mobile Army Surgical Hospital at 0100 hours, 20 July 1953. Injuries included a penetrating wound of the abdomen; a large avulsion-type wound of the posterior aspects of the left thigh and leg with extensive muscle destruction; soft tissue wounds of the left shoulder, left forearm, right foot and hand.

The patient received 1,000 ml. blood before admission to hospital and was given another 2,000 ml. before operation. A further 3,500 ml. blood was given during surgery. No intra-abdominal lesion was found at exploratory laparotomy. An extensive débridement of wounds of the left leg was done where the popliteal vein was found to be severed and the sciatic nerve severely damaged. The main arterial supply to the leg appeared intact. All other soft tissue wounds were débrided. A padded by-valved long-leg cast was applied to the leg. The following chemotherapeutic agents were administered: crystalline penicillin, 600,000 units b. i. d.; streptomycin 0.5 gm. b. i. d.; and terramycin (oxytetracycline), 0. 5 gm. b. i. d.

Sixteen hours after completion of the operation, the patient's temperature was 103.4° F, pulse 120 per minute, and blood pressure 105/70. The left leg was cold and moist, and the surgeon stated that he could not feel the dorsalis pedis pulse; the patient was given 500 ml. of blood. During the following 24 hours his condition was recorded as improved, the leg and foot were warmer, and the temperature subsided to 99° F. The pulse persisted between 120 and 140 per minute and the respirations between 24 and 32 per minute. The blood pressure continued at about 100/70 and urinary output was 600 ml. during the first 24 hours after surgery.

The patient was evacuated approximately 48 hours after operation because of the heavy patient load. He was held at a clearing station for 24 hours where he complained of pain in the left leg but the wound was not examined.

On admission to an evacuation hospital 4 days after injury the left foot and lower leg were gangrenous. There was also extensive infection and necrosis of the posterior thigh muscles which were covered with maggots. An amputation was done below the knee joint and extensive secondary débridement was done in the thigh. Two and one-half liters of blood and also noradrenalin were required during the operation because of hypotension. The thigh wounds continued to bleed following this procedure, and the patient was returned to the operating room for a further attempt to control oozing. This could not be accomplished with hemostats so that a very tight padded compression dressing was applied. The patient's subsequent postoperative course was one of continuing hypotension requiring blood and noradrenalin. Pulmonary edema developed but did not respond to treatment. An attempt to decrease metabolic activity in the infected left thigh by local hypothermia and the application of a tourniquet was unsuccessful. The patient died 5 days and 8 hours after injury. During the

entire period at the evacuation hospital urinary output was between 50 and 100 ml. per hour so long as the systolic blood pressure was maintained by transfusion and/or vaso-pressor drugs.

Plasma chemistries on the day of death were: sodium 145 mEq./L., chloride 97.8 mEq./L., potassium 3.3 mEq./L., carbon dioxide capacity 25.2 mEq./L., non-protein nitrogen 54 mg./100 cc., and inorganic phosphate 2.8 mg./100 cc. On the day before death the white blood count was 17,300 per cu. mm. of which 81 per cent were neutrophils. Eighty-four per cent of these neutrophils were active by our test of phagocytic function. The complement titer was 1 : 8.

The positive autopsy findings were severe pulmonary edema and extensive superficial necrosis and infection of muscle bundles in the posterior thigh.

Comment. Data reported prior to the patient's arrival at the evacuation hospital were taken from the records so that speculation about early treatment must be guarded. It is probable that an initial error in judgment was made in not amputating the extremity at that time. Furthermore, developing myositis was not recognized at the time of evacuation, yet the rapid pulse and respirations suggested its presence. The subsequent loss in continuity of care owing to patient evacuation during a time of heavy casualties allowed necrosis and infection to progress unobserved until the cast was removed at the evacuation hospital. In retrospect, only a hip disarticulation might have saved this patient at that time, but the surgeon thought the patient would not tolerate the procedure. There are no data on the state of the patient's natural antibacterial defense shortly after injury, but at the evacuation hospital no abnormality was apparent in complement level or phagocytosis. It seems more probable that the fatal infection was primarily the result of errors in surgical management.

Patient Number 134. A 24-year-old white soldier wounded by land mine at 0530 hours 15 July 1953. The patient was admitted to a forward surgical hospital shortly after injury having been given 1,250 ml. of albumin for shock. The wounds included extensive destruction of the right anterior thigh and knee joint, a compound fracture of left tibia and fibula, and a supracondylar fracture of the right humerus.

At operation the following procedures were done: a below-knee amputation of the left leg, radical débridement of the right anterior thigh and knee joint with ligation of the femoral vein, and débridement of the right arm. Eight liters of blood was given before and during surgery. The operation lasted 2 hours and the postoperative condition was reported as good. During the subsequent 24 hours the patient's condition was reported to be poor with profuse sweating, hiccuping and vomiting. The systolic blood pressure fluctuated between 90 and 100, the pulse was about 130 per minute, and urinary output was diminished. Twenty-four hours after injury an attempt was made to transport the patient to the Renal Insufficiency Center by air, but owing to fog the helicopter was unable to reach its destination. The patient was returned to the forward hospital where his blood pressure fluctuated between 85/60 and 104/70 for several hours. This subsequently stabilized and transfer was effected to the Renal Center about 60 hours after injury. At that time the blood pressure was 110/80, pulse 120 per minute, and temperature 100.4° F. The urinary output was good. Examination of the wounds revealed extensive necrosis of muscles in the left lower leg amputation stump together with necrosis of muscle groups in the right thigh. Bilateral supracondylar amputations were done and also secondary débridement of the right arm. Urinary output remained satisfactory and the subsequent clinical course was uneventful. The patient was transferred to Japan 10 days after injury, where the wounds were successfully closed.

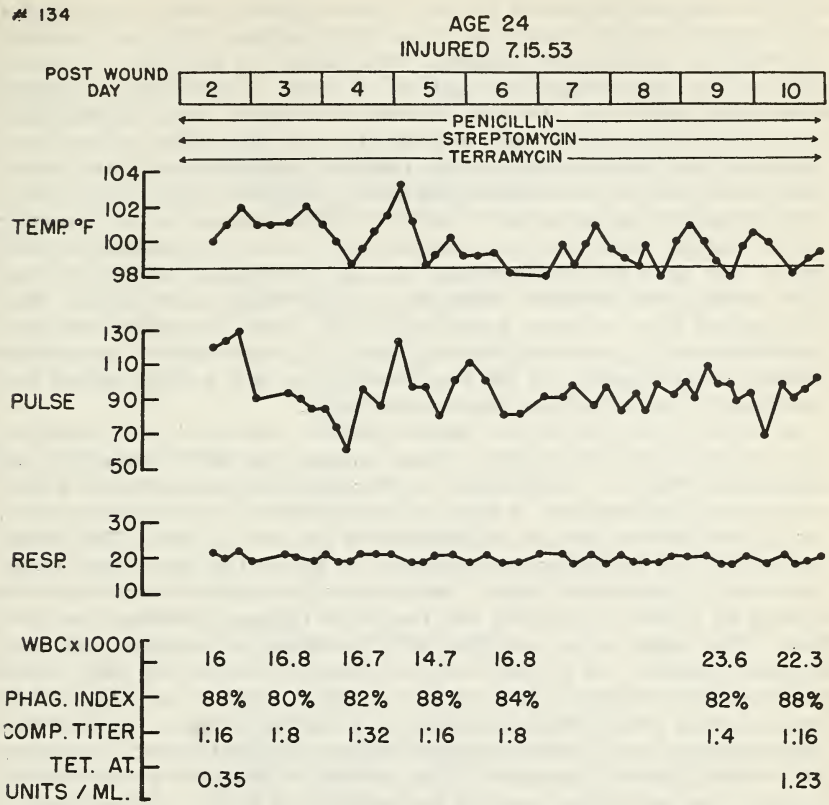


FIGURE 4. Phagocytosis, complement titer and synthesis of tetanus antitoxin related to other clinical data from patient number 134.

Chemotherapy at the Renal Center consisted of 300,000 units of crystalline penicillin every 3 hours and 2 gm. of oxytetracycline daily.

Figure 4 summarizes some of the clinical and laboratory observations. The daily white blood counts showed considerable elevation which was also associated with an increase in the percentage of neutrophils. Phagocytic activity was within the normal range as were the complement titers except for the observation on the ninth post-wound day. During the period of observation the level of circulating tetanus antitoxin per milliliter increased 251 per cent.

Comment. It is often difficult to decide whether all devitalized muscle has been excised at initial débridement with land mine injury of the extremities. It seems likely that inadequate débridement was the primary factor in the development of muscle necrosis in this patient. There was never any evidence of invasive infection, and following secondary débridement the problem was controlled. The data showed no defect in the defense mechanisms studied.

Severely Injured With Post-traumatic Renal Insufficiency

Patient Number 135. A 21-year-old white soldier wounded by mortar fire at approximately 0400 hours 18 July 1953. The injuries were as follows: com-

minuted compound fracture of the right femur, tibia and fibula with extensive soft tissue destruction; penetrating wound of left anterior thigh; and penetrating wounds of the right arm and hand. This patient was given 500 ml. dextran shortly after injury followed by 1,500 ml. of blood. A tourniquet was placed around the right thigh. He was admitted to a Mobile Army Surgical Hospital at 0850 hours with a blood pressure of 80/50. Three liters of blood was given and also 1,200,000 units procaine penicillin intramuscularly. The tourniquet was released at 1100 hours. The patient was then transferred by air to another surgical hospital owing to the heavy patient load and lack of operating space. Further transfusion was required and operation commenced at 1500 hours. The right leg was amputated through the femoral fracture site and other wounds were débrided. Skin traction was applied to the stump. Two and one-half liters of blood was given at that time. Crystalline penicillin, 600,000 units b. i. d., and streptomycin 0.5 gm. b. i. d., were ordered. Diminished urinary output appeared on the first postoperative day, and the patient was transferred by air to the Renal Insufficiency Center.

On arrival at the Center, the patient appeared acutely ill, was perspiring, pale, but alert and well oriented. Blood pressure was 126/70, pulse 110, and temperature 100.8° F. Examination of the right thigh stump revealed a foul-smelling crepitant myositis. A right hip disarticulation was done immediately, and it was believed that all involved muscle had been excised. This second amputation was undertaken approximately 30 hours after the original amputation and 41 hours after injury. The patient's postoperative course was complicated by a high temperature and fast pulse rate and persistent oozing of blood. This could not be controlled with hemostats and required tight compression dressings. On the day after hip disarticulation the left thigh wound was secondarily débrided. The patient remained euphoric and obviously ill although there was no further evidence of clostridial myositis. He died suddenly approximately 28 hours after admission to the Renal Center. At autopsy the wounds appeared clean without any evidence of myositis or of obvious infection. The pathologists reported fat embolism to be the primary cause of death.

Figure 5 records some of the data in connection with this patient. There was a leukocytosis of which 79 per cent were neutrophils. Of these, 82 per cent showed phagocytic activity. The complement titer was within normal limits. The plasma chemistries shortly before death were as follows: sodium 162 mEq./L., potassium 8.0 mEq./L., chloride 83 mEq./L. carbon dioxide capacity 23 mEq./L., nonprotein nitrogen 151 mg./100 cc., calcium 20.8 mg./100 cc., and inorganic phosphate 10.9 mg./100 cc. The following microorganisms were reported from culture of the necrotic muscle: *Clostridium perfringens*, *Proteus vulgaris*, beta hemolytic Streptococcus, non-hemolytic Streptococcus and *E. coli.*

Comment. This case represented an example of *Clostridium perfringens* myositis following compound comminuted fracture of the femur. Important factors in assessing therapy were a time lag of 11 hours between injury and initial débridement, and the presence of a tourniquet around the right thigh for about 7 hours. Other important factors were that the surgery was carried out by a surgeon who was not experienced in the handling of this type of traumatic injury. Furthermore, skin traction was applied to a stump which was probably inadequately débrided and the wound was not inspected for 30 hours. Nevertheless, by radical amputation at the Renal Center, all of the affected muscle was excised. There was no evidence of any defect in body defense systems predisposing this patient to gas gangrene. On the other hand, on the

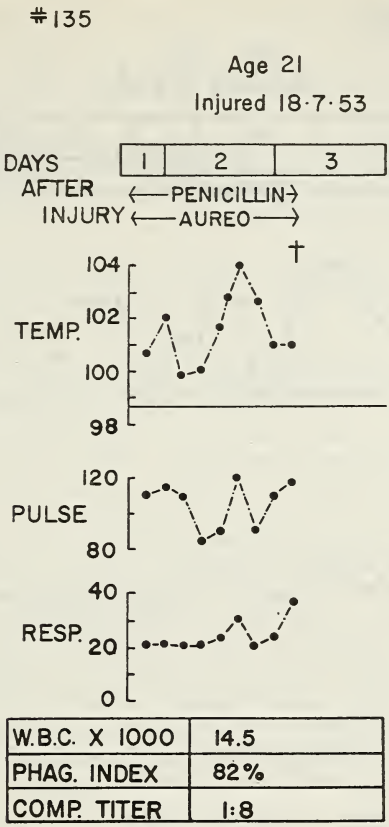
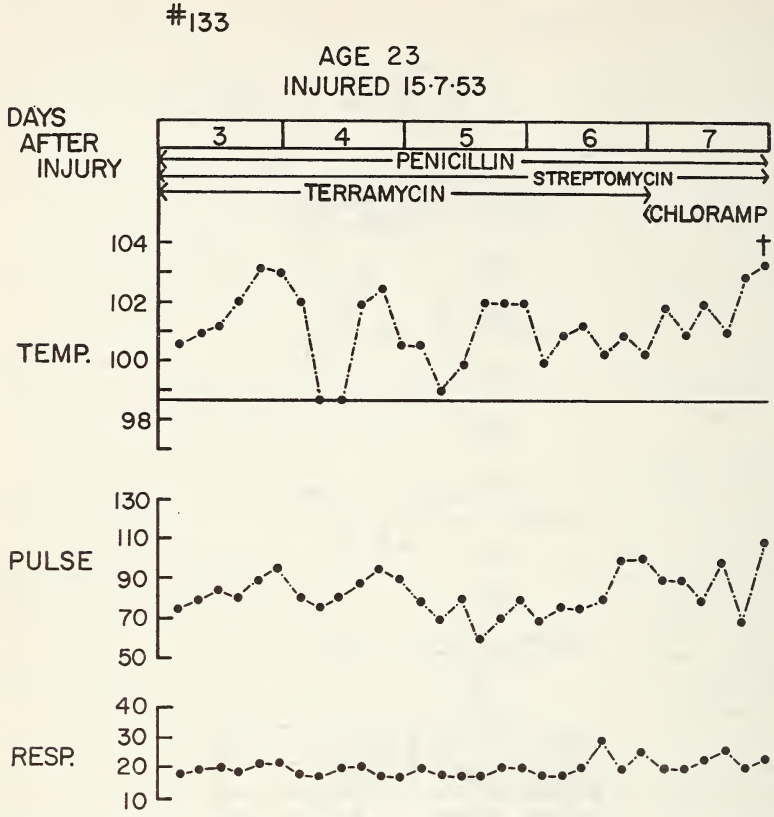


Figure 5. Phagocytosis and complement titer related to other clinical data from patient number 135.

basis of the autopsy findings it is probable that serious infection had been overcome by a combination of surgery and chemotherapy.

Patient No. 133. A 23-year-old Negro male wounded by mortar fire at approximately 1145 hours on 15 July 1953. The injuries were as follows: a penetrating wound of the left buttock, penetrating wounds of the left thigh and both legs, comminuted fracture of the left ischium and left pubic ramus. Resuscitation was commenced at 1230 hours and the patient arrived at a Mobile Army Surgical Hospital at 1730 hours. He was reported to have been in severe shock and had been given albumin but the quantity was not recorded. At the MASH his initial blood pressure was 80/0, and 2,500 ml. of blood was given. At operation the following procedures were reportedly done: a left sigmoid colostomy because of a laceration of the lower sigmoid colon, a suprapubic cystotomy because of complete destruction of the prostatic urethra, and débridement of all other wounds. The patient was placed on 600,000 units of procaine penicillin b. i. d., oxytetracycline 2 gm. daily, and streptomycin 0.5 gm. b. i. d. The patient was transferred to the Renal Insufficiency Center on 17 July, because of diminished urinary output, where he arrived approximately 50 hours after injury. At that time he



W.B.C. X 1000	16.2	16.6	15.4	17.1	19.1	18.8
PHAG. INDEX	86%	78%	78%	80%	78%	78%
COMP. TITER	1:16	1:8	1:16	1:32	1:16	1.8
TET. AT. UNITS/ML.	0.13					0.35
BLOOD CULTURE	NEG.	NEG.	POS.	POS.	POS.	

FIGURE 6. Phagocytosis, complement titer and synthesis of tetanus antitoxin related to other clinical data from patient number 133.

appeared acutely ill but alert and well oriented. Examination of the wounds revealed obviously inadequately débrided gluteal muscles; the muscles of the left lower leg were foul-smelling, prolapsed and nonviable; the left foot was cold and without detectable arterial pulsation. An extensive re-débridement was done of the entire left buttock, removing the gluteus maximus and medius muscles, the piriformis muscle, and part of the obturator internus muscle. The rectum, prostate and inferior portion of the bladder were thus exposed in the wound. The left leg was amputated above the knee. During this time the blood pressure was unstable, requiring the support of blood plus noradrenalin. The patient's subsequent course was one of severe illness with episodes of unstable blood pressure and continuing renal insufficiency. Artificial hemodialysis

was carried out on three occasions with the result that deviations in the normal levels of plasma electrolytes were corrected for relatively short periods of time. On the fifth day after injury a paracolon septicemia developed. The wounds were examined and re-débrided on several occasions without any further evidence of progressive wound sepsis. The patient died on the seventh post-wound day.

The ultimate cause of death was considered to be septicemia, possibly secondary to septic thrombophlebitis of pelvic veins. At autopsy no focus of infection was found other than that which had been observed clinically on the surface of the extensive buttock wound. An unexpected finding was a large contusion of the opposite buttock muscle which, however, was not infected.

Figure 6 records some of the data pertinent to this patient. The white blood count was elevated with an accompanying increase in the percentage of neutrophils. The majority of these neutrophils appeared active and complement levels were within the normal range. Circulating tetanus antitoxin was rising in response to the booster dose during this deteriorating illness. The patient had received penicillin, streptomycin and oxytetracycline. Chloramphenicol was finally used in an attempt to control the septicemia because the microorganisms were sensitive to this agent *in vitro*. Wound culture revealed the presence of an unclassified Clostridium, *Aerobacter aerogenes*, *Proteus mirabilis*, beta hemolytic Streptococcus, gamma Streptococcus, and a micro-aerophilic Streptococcus.

Comment. The data do not indicate a decrease in resistance to infection in this patient. It was quite apparent that the left buttock wound had not been properly débrided, not only because of the appearance of the muscle when first examined at the Renal Center but also because during secondary débridement portions of the patient's identification card were removed from the wound. Furthermore, our finding of a cold lower leg with a wound showing prolapsed nonviable muscle indicates that this lesion had been present for many hours and should have been treated before the patient was evacuated by air. Although sepsis was an outstanding complication in this patient, it is probable that inadequate initial surgery and postoperative care were predominant factors in its development.

Discussion

The observations reported in this study are from a small but carefully studied series of patients with battle injury. A significant depression in neutrophil polymorphonuclear leukocyte activity within the first 24 hours or so of severe wounding in several patients was the only abnormality noted in the antibacterial defense mechanisms studied. This observation was found shortly after the administration of relatively large volumes of stored blood and may be directly related to that fact. Unfortunately, there are no data on neutrophil activity from severely injured patients before resuscitation was commenced. But it is interesting that with two patients neutrophil activity improved despite the continuing administration of bank blood. The depression in neutrophil activity shortly after severe trauma might have been a manifestation of adrenal cortical hyperactivity although no observations were made in this study on endocrine function. Others have reported finding *in vitro* a depression in the phagocytosis of opsonized type I pneumococci by leukocytes from nine patients re-

ceiving ACTH or cortisone therapy.[33] We did not find any significant fall in staphylococcal phagocytosis in a few patients receiving ACTH therapy.[34] Phagocytosis of *Streptococcus viridans* by the reticuloendothelial system of rats treated with cortisone has also been reported normal although the evidence suggested a possible delay in the subsequent destruction of the microorganisms.[35] Also, macrophage activity in tissue culture exposed to Kendall's Compounds E and A has been reported normal.[36]

Another interesting observation from the present study is the finding of elevated total white blood counts in patients who have received the equivalent of two or three total exchange transfusions within a few hours of injury. Therefore, it must be concluded that either these cells were not lost during hemorrhage or more likely that their replacement from the bone marrow or elsewhere was rapid and continuous.

The finding of normal complement activity in most cases following acute hemorrhage in this study agrees with observations of others on the effect of hemorrhage in animals on complement levels. The removal of 50 to 83 per cent of circulating complement in dogs by repeated plasmaphoresis was usually followed by a return to normal serum titers within 24 hours.[37] In guinea pigs restoration of complement occurred within 4 to 6 hours after its removal by severe hemorrhage.[38] It is probable, therefore, that complement continually enters the intravascular compartment by diffusion from tissues or by the lymphatics.[39] Isolated observations of depressed complement activity such as were found in this study must be interpreted with caution because of unpredictable fluctuations in complement in a variety of diseases and even in the same disease.[24]

The finding of normal antibody synthesis reported in this paper is not surprising. The advantages in the use of the anamestic response as a measure of the capacity to synthesize antibody have been discussed in a previous communication; quantitative studies showed that seriously ill moribund patients retained a normal capacity to synthesize specific antitoxic globulin.[32] Furthermore, observations on guinea pigs showed that the secondary immune response to the administration of diphtheria toxoid occurred after protracted exposure to cold, or after the production of severe *Clostridium welchii* myositis, or after reticuloendothelial blockage with large amounts of India ink.[40] The absence of a detectable increase of circulating antitoxin until the seventh post-wound day in three of the patients studied is of interest. There has been considerable discussion about the desirability of administering prophylactic tetanus antitoxin to previously immunized casualties instead of toxoid at the time of injury. This was the practice of the

British Army in World War II because of the possibility that the response to a booster dose of tetanus toxoid might not be sufficiently rapid to protect in cases of tetanus with a short incubation period. Miller and Ryan [31] have recently advised the injection in opposite extremities of both prophylactic antitoxin and toxoid in previously immunized patients who sustain shock or have massively contaminated wounds. The data recorded in the present study lend support to this proposal.

No evidence has been found that patients with post-traumatic renal insufficiency are more susceptible to bacterial infection. Evidence is presented showing that such patients may synthesize antibody as well as normal control subjects. Furthermore, complement activity, white blood count and the capacity of neutrophils to ingest Staphylococci may be within the normal range.

The occurrence of infection following severe trauma may be the result of many factors. The case examples presented show the importance of delay in treatment or of inadequate surgical débridement in initiating this complication. A deficient caloric intake has been said to predispose to infection. Many of the patients with renal failure had low caloric intakes, but the present studies failed to show that antibacterial defense was affected. This confirms previous observations of the effect of malnutrition on antibacterial defense in humans.[32, 41] Miles and Niven [42] have suggested, on the basis of observations in the guinea pig skin, that local tissue ischemia resulting from shock may promote the initiation of bacterial infection. This seems reasonable, but should not be an important factor if initial wound surgery is adequate.

The present studies do not prove conclusively that severely traumatized patients possess normally functioning antibacterial defense mechanisms. However, it seems likely that other factors, such as the degree of tissue damage, the length of time between injury and initial surgery, or the adequacy of débridement, are the most important factors in the initiation of infection.

Summary

1. The capacity of the body to resist bacterial infection after severe battle injury has been studied. Phagocytosis, the level of circulating complement and the body's capacity to synthesize tetanus antitoxin have been measured. The findings have been compared in casualties with and without complicating acute renal failure. The above data have been related to the clinical course of the patients with particular emphasis on the development of infection.

2. A significant depression in neutrophil polymorphonuclear leukocyte activity was found within the first 24 hours or so of wounding in several patients. This was the only abnormality noted in the antibacterial defense mechanisms studied. Phagocytosis returned towards normal within 48 hours.

3. No evidence was found that battle casualties with or without complicating acute renal failure are more prone to develop infection because of a possible deficiency in the antibacterial defense mechanisms studied.

4. Factors such as the degree of tissue damage, the amount and nature of bacterial contamination, the length of time between injury and initial surgery, and the adequacy of wound débridement and of postoperative care are probably of prime importance in the initiation and development of infection after injury.

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Chapter 11

Renal Sequelae of War Wounds in Man

Functional Patterns of Shock and Convalescence

First Lieutenant Michael Ladd, MC, USAR

Introduction

Acute renal failure, secondary to systemic pathological conditions, presents a bizarre challenge to all branches of clinical medicine. That following physical violence is frequently progressive and unrelenting,[1] showing the most accelerated course with a mortality rate of close to 80 per cent.[2] This form may be expected to increase in incidence and severity, both in civilian life and in the military theater, with increasingly successful methods of resuscitation from traumatic shock. Because of its unpredictable incidence and capricious nature, post-traumatic renal failure (PTRF) is a most frustrating postoperative complication.

The enigmas associated with this clinical syndrome seem largely due to a prevailing ignorance of its pathogenesis.[3, 4] Obviously, much of the apparent mystery should resolve upon clarification of etiological mechanisms. The present investigation was planned to elucidate which primary derangement in renal function was ultimately responsible for the subsequent occurrence of PTRF. Accordingly, the early response to systemic injury was traced through convalescence in battle casualties in the forward Korean military theater. The observed sequence of discrete renal functional events, linking wound shock to subclinical states of post-traumatic renal insufficiency (PTRI) or manifest PTRF, is summarized below.

Clinical Methods

Data were collected from United Nations casualties evacuated through the 8209th Mobile Army Surgical Hospital between April and September, 1952, while this unit was situated in the Yangu Valley on the Eastern Korean front.

The subjects were of varied nationality, aged 18 to 27 years, and had been wounded in combat approximately 3 hours prior to admission. Emergency first aid administered at a collecting station before helicopter (or rarely ambulance) evacuation has been described else-

where.[5] Except for urethral catheterization and intermittent blood sampling, study patients were treated routinely by attending medical personnel. Resuscitation from traumatic shock was preceded by a delay period between wounding and medical attention, that (except for three instances of 6, 7, and 12 hours respectively) ranged between 1 and 5 hours, averaging 3 hours. As pointed out by Howard,[5] this differed significantly from the situation on the Western Korean front, as well as that described for World War II.[6] Admission to the hospital was followed by massive transfusion, roentgenography and intestinal intubation in preparation for surgery. During surgical anesthesia, blood transfusion was continued as indicated by changes in blood pressure and pulse. Seven to ten liters of whole blood was often administered intravenously or intra-arterially within the preoperative period (average duration 2 hours). The total amount received during the entire period of resuscitation (average duration was 6 hours to completion of surgery) exceeded 10 liters in 9 of the 40 cases studied. The properties and various components of this banked blood, which was almost exclusively 10 to 20 days old, were concurrently under study by Olney[7] and have been reviewed elsewhere.[8] An occasional casualty could only be transiently resuscitated by continuous transfusions, amounting to as much as 20 liters of whole blood. This represents the only situation where a parallel may be drawn to the irreversible shock state[37] seen in animals.

Renal function was studied at intervals during resuscitation and surgery and during the first postoperative week. The clearance of inulin (C_{IN}) was used to measure glomerular filtration and that of $\overline{PAH}$ (C_{PAH}) as an index of effective renal plasma flow. The clearance of endogenous creatinine (C_{CREAT}) has been proposed as a more convenient measure of glomerular filtration.[9] However, in 68 simultaneous clearance comparisons during convalescence, the ratio C_{CREAT}/C_{IN} averaged 0.8 (range 0.7 to 1.3 in nine patients) when C_{IN} fell below 90 cc./min. It averaged 1.0 (range 0.9 to 1.2 in five subjects) when C_{IN} exceeded 100 cc./min. During resuscitation of one subject, C_{CREAT}/C_{IN} increased progressively from 0.6 to 1.2. Evidence of altered tubular permeability as well as the tendency for analytical artifact[18] to become exaggerated by metabolic sequelae of wounding, make the endogenous creatinine clearance highly unreliable under such circumstances. Proximal tubular function was measured by the maximal excretory capacity for PAH (Tm_{PAH})[4] and distal tubular function by the facultative ability to concentrate and dilute the glomerular filtrate.

Conventional clinical and analytical technics were necessarily modified because of the primitive environmental conditions. For instance, a constant plasma level of test substances was maintained by vigilantly regulating their infusion rate with an ordinary tunnel clamp. Forty minutes were always allowed to elapse between the injection of priming solutions and subsequent clearance periods; but during resuscitation, rapid adjustments in cardiovascular dynamics precluded any compensation for errors due to urinary dead space [10] or for delays in equilibrium between plasma and interstitial fluid.[11] Urine was obtained through an inlying Foley catheter, each urine collection period being terminated by washing the bladder three or four times with 50 cc. aliquots of sterile saline followed by air insufflation. Since many patients suffered from abdominal wounds, it was infrequently possible to express the bladder manually. To reduce errors from this source, the duration of collection periods usually exceeded 30 minutes, and data from three or more consecutive periods were averaged for final compilation. Heparinized blood samples were drawn from the most accessible vein or artery at convenient intervals. Plasma concentrations were plotted against time semilogarithmically so that mean values could be interpolated 3 minutes before the midpoint of each urine collection period.

Analytical Methods

PAH and inulin were measured in unyeasted cadmium sulfate filtrates of plasma and diluted urine, the former by the method of Smith *et al.*,[12] and the latter according to Schreiner's modification [13] of Roe's resorcinol method. For calculations of Tm_{PAH}, the F. W. factor was corrected for plasma protein (determined by the method of Phillips *et al.*[14] and plasma PAH concentration using Taggart's nomogram,[15] and assuming an A/G ratio of 2.5. Subsequently it was found [16] that one lot of ampuled inulin (U. S. Std. Products # 2341A) contained significant quantities of fermentable chromogen. Experiments in which this material was used have been deleted, and the present data were obtained with preparations containing less than 5 per cent fermentable chromogen (William Warner lot # 019101 and 023090 and U. S. Std. Products # 237A1). Plasma inulin concentrations were always greater than 30 times the concentration of blank reducing substances, and were raised to levels ranging between 200 and 300 mg. per 100 cc. whenever low urine flows necessitated excessive dilution with bladder washout fluid. Repeated plasma and urine recoveries showed less than 3 per cent of chemical analyses to have an error exceeding $\pm$ 5 per cent.

Osmolarity of plasma and urine samples was calculated from their freezing point depression as recommended by Wesson,[19] using a Leeds and Northrup Wheatstone bridge with a Western Electric Thermistor No. 14B mounted on a leucite stirring rod. All clearance data were converted to 1.73 square meters surface area.

Results

Renal Function During Resuscitation From Wound Shock

Clearance Measurements during Resuscitation. The renal clearance of inulin (C_{IN}) and PAH (C_{PAH}) was measured throughout resuscitation in six variably wounded casualties. In general, the results were similar to those previously reported by Lauson,[17] supporting an identity between the immediate renal response to traumatic shock in civilian and military casualties.

Figure 1 compares renal clearance patterns in two casualties during the period from admission to recovery from anesthesia. Patient Number 17 (Fig. 1a) was a Turkish soldier who stepped upon a land mine 6 hours before admission. He sustained a traumatic amputation of the forearm, compound fractures of both tibiae and fibulae and extensive soft tissue destruction about the arms and legs. His course typifies that of mildly wounded men, developing little post-traumatic renal insufficiency. Moderate "shock" (classified according to the criteria presented by Beecher *et al.*[6] was present on admission. He responded well to 2.5 liters of whole blood transfused during 2 hours of preoperative preparation. With induction of anesthesia, clearance values dropped abruptly from high preoperative levels, returning slowly thereafter. The ratio C_{IN}/C_{PAH} (filtration fraction, hereafter referred to as FF) remained above normal throughout in all such lightly wounded men. Of considerable interest is the elevation in urine flow seen in such cases during reaction from anesthesia, a phenomenon to be discussed subsequently.

Patient Number 36 (Fig. 1b) exemplifies the response to more profound injury. This American soldier sustained major shell fragment wounds of the chest, abdomen and extremities 7 hours before admission. He was given both plasma and blood at a battalion aid station within 30 minutes of wounding and presented only moderate shock on admission to the hospital. His condition proved to be less stable than that of Patient Number 17 and 25 points of blood were required during resuscitation. Although pulse and blood pressure were well controlled before surgery was undertaken, neither urine flow nor clearance levels responded as quickly. During an extensive thoraco-abdominal exploration, very little urine appeared and no recovery diuresis was manifest during reaction from anesthesia. Clearance levels never rose following induction of anesthesia, renal failure becoming evident

Data from a lightly wounded casualty (Case No. 17) are shown in Figure 1a. The course of a more severely wounded soldier (Case No. 36) is shown for comparison in Figure 1b. Clearance ordinates are plotted logarithmically. Filtration Fraction (C_{IN}/C_{PAH}) is expressed in per cent; arterial blood pressure in mm. of mercury. Normal averages are used as baselines. Arrows each represent 500 cc. whole blood transfusions. Vertical dotted lines enclose the period of anesthesia. Each patient presented moderate peripheral circulatory insufficiency on admission, but recovered a stable blood pressure and pulse rate preoperatively. Clearance values and urine flow rose progressively during resuscitation, more so in Case No. 17 (Fig. 1a). However, the preoperative time interval was insufficient to allow complete recovery of renal function in either case. Induction of anesthesia depressed clearances and urine flow abruptly. This cessation of renal function proved reversible in Case No. 17 (Fig. 1a), but was irreversible for Case No. 36 (Fig. 1b). During reaction from anesthesia, no recovery diuresis was manifest by the latter.

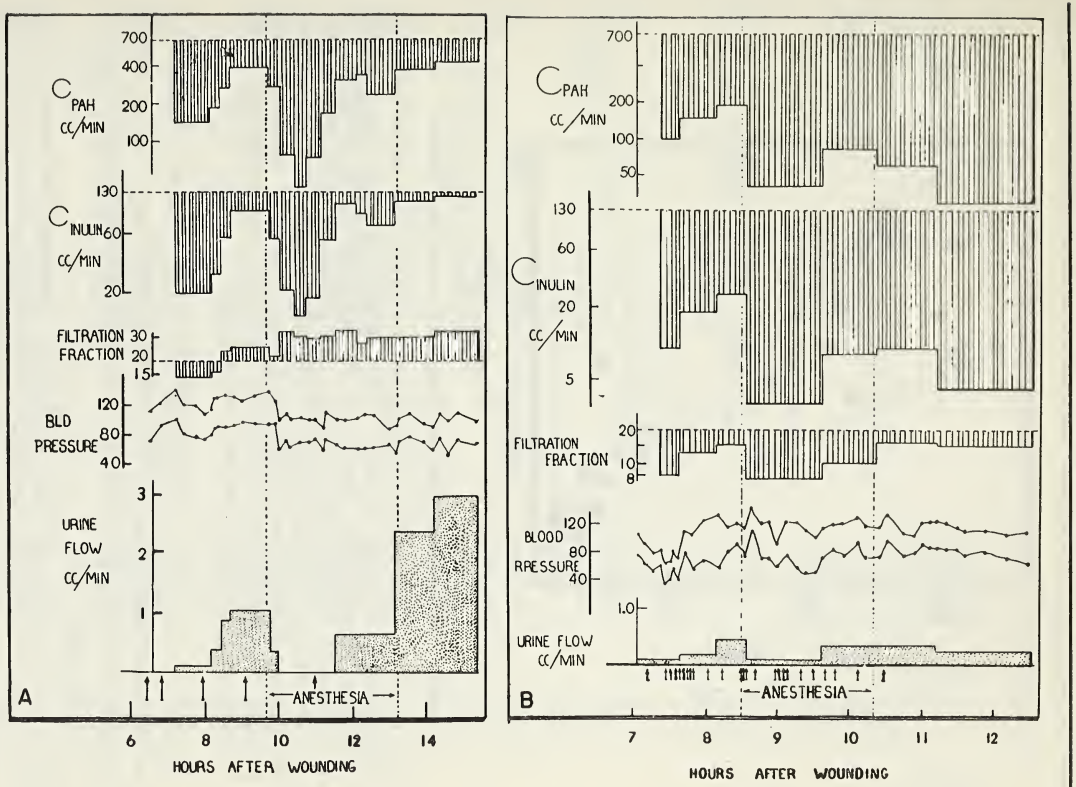

FIGURE 1. Renal Function during Resuscitation of Two Casualties.

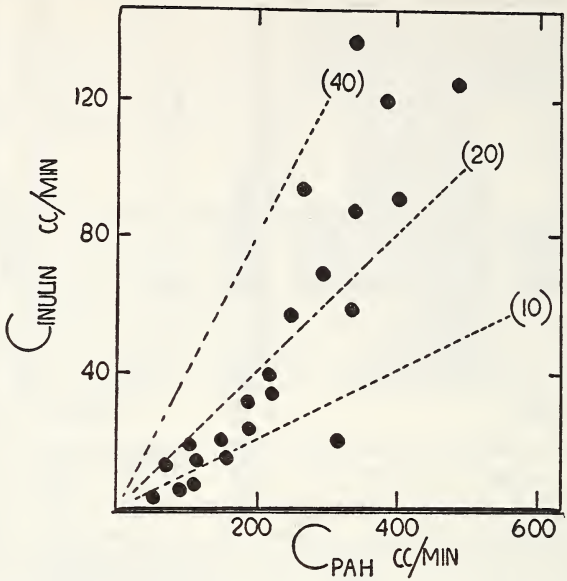

FIGURE 2. Relationship Between C_{IN} and C_{PAH} during "Shock."

Filtration rate (C_{IN} in cc./min.) is plotted on the vertical scale against effective renal plasma flow (C_{PAH} in cc./min.). Each point represents one collection period obtained preoperatively, during the resuscitation of six casualties. In this and succeeding charts, clearance values are plotted on arithmetical scales. Diagonal dotted lines repersent filtration fractions of 40, 20 and 10, respectively. FF was depressed at low values for C_{PAH}, and rose as clearance values increased. This suggests re-establishment of glomerular filtration, under conditions of relative renal ischemia by efferent arteriolar constriction.

(as oliguria) in the early postoperative period. Shortly afterward the patient was transferred to the Renal Insufficiency Center, where following several courses of artificial dialysis, he succumbed to peritonitis 1 month later.

Figure 2 relates C_{IN} to C_{PAH} during the preoperative resuscitation of all six patents. FF was depressed at low clearance levels and became elevated during recovery from shock. This indicates re-establishment of glomerular filtration under conditions of relative renal ischemia by efferent arteriolar constriction.

It is noteworthy that preoperative transfusions of whole blood usually obliterated clinical signs of shock without restoring C_{IN} or C_{PAH} to normal. Both C_{IN} and C_{PAH} rose progressively with each collection period, but in five of six cases, insufficient time to effect full recovery was allowed prior to anesthesia. Table 1 compares the glomerular function of six casualties during actual surgical anesthesia with that of two healthy controls undergoing circumcision with "simulated major surgical anethesia." Pentothal, nitrous oxide, oxygen and ether

Table 1. Renal Hemodynamics During Surgical Anesthesia

Case Number Operative Procedure	Period	Blood Pressure mm. Mercury	C_{PAH} cc./min.	C_{IN}/C_{PAH}
2	Immed. preoperatively	120/70	680	22
(Circumcision)	Induction	80/50	500	16
	Surgery	140/82	540	20
	Immed. postoperatively	130/80	700	30
3	Immed. preoperatively	120/74	800	18
(Circumcision)	Induction	100/60	440	25
	Surgery	130/70	500	25
	Immed. postoperatively	120/80	710	24
4	Immed. preoperatively	120/65	410	41
(Débridement of buttocks)	Induction	150/70	88	14
	Surgery	90/50	400	20
	Immed. postoperatively	120/90	700	38
21	Immed. preoperatively	135/80	700	30
(Laparotomy, closed reduction of femur)	Induction	80/50	170	8
	Surgery	120/75	800	20
	Immed. postoperatively	140/80	380	30
17	Immed. preoperatively	120/80	380	24
(Débridement of legs, open reduction tibia)	Induction	100/70	42	30
	Surgery	100/65	320	34
	Immed. postoperatively	110/66	410	30
23	Immed. preoperatively	145/90	400	31
(Débridement of buttocks, legs, ligat. vena cava)	Induction	60/40	80	11
	Surgery	115/60	300	20
	Immed. postoperatively	110/60	450	19
18	Immed. preoperatively	110/65	250	22
(Débridement and casting legs and buttocks)	Induction	80/40	80	12
	Surgery	70/40	100	18
	Immed. postoperatively	100/50	300	20
36	Immed. preoperatively	115/80	180	14
(Extensive thoracoabdominal exploration)	Induction	90/60	40	8
	Surgery	100/60	80	10
	Immed. postoperatively	120/60	60	15

were administered in each case by either of two anesthetists using comparable technics. Induction of anesthesia invariably depressed renal function abruptly, the percentage change being inversely related to the preoperative clearance level. Since glomerular filtration and renal plasma flow recovered more sluggishly than the general circulatory status would suggest, there is some question as to the urgency with which the depressant effect of surgical anesthesia should be superimposed. Although immediate surgery is generally [41] considered an inte-

gral part of resuscitation, it apparently constitutes additional trauma; hence, the premature induction of surgical anesthesia may irreversibly compromise the renal circulation.

Urine Flow during Shock and Resuscitation. Data are available from 52 casualties for hourly urine flow during resuscitation. Table 2 compares the mean values and standard deviations for hourly urine excretion with the degree of injury (estimated by a point scoring system described below). Between admission and operation mildly, moderately and severely injured casualties excreted essentially equal amounts of urine. However, during and after surgery, the more

Table 2. Hourly Urine Flow During Resuscitation (as cc. Per Hour)

Grade of Injury	Preoperative	During Surgery	Postoperative		
			2d Hour	4th Hour	6th Hour
Mild, 0–30 points (25 cases)	20±9	120±50	130±8	108±9	70±10
Moderate, 30–40 points (15 cases)	65±18	40±8	110±12	29±11	90±3
Severe, > 40 points (12 cases)	21±12	19±3	71±7	22±5	23±3

severely wounded showed a significant depression in urine flow as compared with lightly wounded men. Figure 3 shows oliguria, at this stage, to reflect a general depression in glomerular filtration. The direct relationship between C_{IN} and urine flow (correlation coefficient for 47 observations in 6 casualties was 0.74) indicates a relative increase in tubular water reabsorption at low filtration rates, as would normally be expected according to current concepts of glomerulo-tubular balance.[4]

A phenomenon noted in three minor casualties was the excretion of 300 to 500 cc./hour for 1 to 2 hours after admission for no apparent cause. Low U/P ratios for endogenous creatinine (<15) indicated decreased tubular reabsorption, rather than increased glomerular filtration. Presumably some hormonal or neurogenic component of the wound sequence initiated this phenomenon, since it was not dependent upon either oral or intravenous fluid administration.

Recovery Diuresis after Anesthesia. A "recovery diuresis," consistently manifest during reaction from anesthesia, was roughly proportional to the severity of the injury and gave a crude measure of the prevailing clearance level. Minor casualties excreted an average of 2 cc./min. during the first two postoperative hours, although their urine flow could be increased to the range of 10 to 20 cc./min. by concomitant infusions of glucose or saline. Conversely, severely wounded men

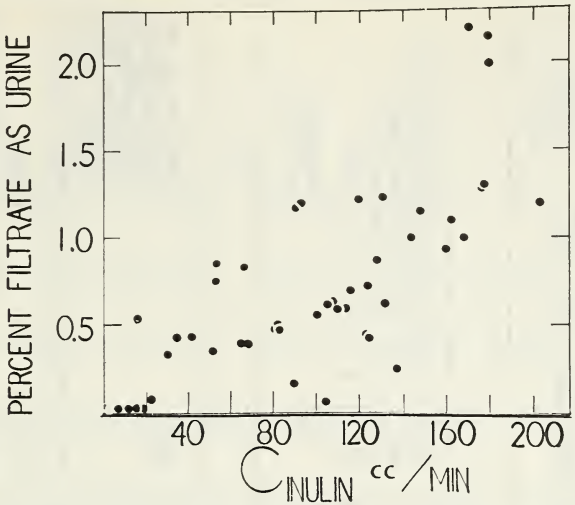

FIGURE 3. Urine Flow and Filtration Rate during Resuscitation.

Urine flow (vertical scale), expressed as per cent of the filtration rate, is related to the filtration rate itself (C_{IN} in cc./min.). Each point represents one collection period, from one of six casualties examined during the interval between admission and reaction from anesthesia. During this phase, urine flow varied directly with glomerular filtration, a relative increase in tubular reabsorption occurring at low values for C_{IN}.

excreted less than 2 cc./min. even in the presence of saline or glucose infusions. This blunting of recovery diuresis reflected a persistent postoperative depression of glomerular filtration, despite maintained arterial blood pressure and regardless of supportive postoperative transfusions. No recovery diuresis was manifest by any patient (e. g., Cases Number 36, 44 and 45) who subsequently developed fulminating PTRF. These observations give prognostic importance to the hourly bedside record of urine flow. Impending severe renal failure probably may be predicted within 8 hours of wounding by the absence of a recovery diuresis (in the presence of normal arterial pressures). Anuria at this time justifies top priority in the evacuation chain.

The Wound Shock Sequence and Postoperative Renal Hemodynamics

C_{IN} and C_{PAH} were variably depressed after recovery from anesthesia, more so in the more severely wounded. Mean values for 376 clearance periods from 78 separate experiments upon 40 convalescent casualties are summarized in Table 3. These observations are further supported and qualified by additional information that is included in this table, but discussed in subsequent pages.

Table 3.

(a) Subject	(b) Injury	(c) Adm. BP	(d) Duration BP<100/60	(e) Pints Trans. Blood	(f) Point Units of Trauma	(g) Hrs. Post-op.	(h) Urine output on day of test cc./24 hrs.	(i) C_{IN} cc./min.	(j) C_{PAH} cc./min.	(k) C_{IN}/C_{PAH} %	(l) Tm_{PAH} mg./min.	(m) C_{IN} Tm %	(n) C_{PAH} Tm %	(o) Outcome
						Controls								
1	Circumcision.	130/66				Control	4200	155.0	620	25.0	61.0	2.54	10.20	Ret. to duty.
2	Circumcision.	140/82				Control	1800	160.0	770	20.8	71.5	2.24	10.75	Ret. to duty.
2	Circumcision.	125/70				Control	1280	140.0	850	16.0	51.0	2.75	16.70	Ret. to duty.
4	Two subcutaneous shell fragments.	120/67				Control (?)	5000	162.0	420	39.0	98.0	1.65	4.39	Evac.
5	Back sprain.					Control		140.0						Ret. to duty.
6	Back sprain.					Control		135.0						Ret. to duty.
						Peripheral Injuries								
7	Soft tissue damage to legs.	0/0	1 hr.	0	2	14 62	2400 1000	143.0 145.0	340.0 966.0	42.4 15.0				Rec'd. 1000 cc. dist. H_2O intravenously during anesthesia. No ill effects. Evac. 3rd day.
8	Neg. laparotomy soft tissue dam. to thigh.	80/20	<30 min.	2	8	20	?	147.0	435.0	33.8	135.0	1.09	3.22	Evac.
9	Soft tissue dam. to legs. Bilat. frac. os calcis.	120/80	<30 min.	*2	9.5	15	700	150.5	475.0	31.7				Evac.
10	Fr. humerus, ribs, dam. to tissue of chest wall & arms.	100/70	30 min.	5	10	57	550	173.0	760.0	24.0				Accidentally given 1000 cc. distilled water intravenously at battalion aid station-no ill effects. Evac.

11	Soft tissue & lac. femoral artery. Massive hemorrhage.	0/0	2 hrs.	13	11	10 84 200	1400 1500 40	131.0 146.2 1.1	302.0 501.0 12.0	43.0 29.2 9.1				Postop. transf. reaction at 196 hrs. Trans. to Kidney Center on 9th day. Evac. Japan 38th day. Recovered.
12	Frac. tibia and fibula. Traumatic amp. of foot.	120/80	30 min.	2	12	29	?	139.0	485.0	28.8				Evac.
13	Traumatic amp. soft tissue dam. to legs.	120/76	1 hr.	*0	12	24 96	1850 120	86.5 2.8	289.0 18.8	29.9 14.7	103.0	0.84	2.81	Transf. reaction followed by oliguria on 4th day. Uneventful recovery after dialysis. Evac. to Japan in 1 month.
14	Amp. leg, soft tissue dam., frac. opposite tibia.	0/0	4–5 hrs.	8	17	90	1000	135.0	550.0	24.5				Evac.
15	Traumatic amp. of foot. Frac. tibia, soft tissue dam. to opposite leg.	110/60	4 hrs.	13	16	14 62	930 1250	126.0 132.0	575.0 690.0	21.9 19.1				Evac.
16	Fracture humerus. Soft tissue dam. to shoulder.	118/70	30 min.	2	17	36 64	? ?	120.0 159.0	384.0 860.0	31.0 19.0	68.0	1.77	5.65	Evac.
17	Frac. tibia, traumatic amp., soft tissue dam. to arm.	110/70	2 hrs.	5	18	36	1190	220.0	675.0	33.1				?
18	Bilat. frac. femur and pelvis.	82/40	4 hrs.	18	30	1 8 26 96 8 days	450 7750 3550 1800 1200	54.4 25.5 81.1 118.0 139.0	188.0 95.4 366.0 620.0	28.9 26.8 22.1 19.0	90.0 90.0 90.4 78.8	0.61 0.28 0.90 1.76	2.09 1.06 4.06	Evac. to Japan on 10th postop. day.
19	Bilat. frac. tibia & femur, massive soft tissue injury, delayed amp.	110/40	1½ hrs.	13	40	13 55 120 14 days	630 570 1300 3600	23.5 17.0 10.0 118.0	162.5 71 530	14.5 14.1 22.3	22.0 30.0	1.07 0.57	7.38	Transf. to the Kidney Center after 72 hrs. Artificial dialysis 5th day. Evac. 3 wks. Recovered.

*Received Dextran as blood substitute.

Table 3—Continued

(a) Subject	(b) Injury	(c) Adm. BP	(d) Duration BP<100/60	(e) Pints Trans. Blood	(f) Point Units of Trauma	(g) Hrs. Post-op.	(h) Urine output on day of test cc./24 hrs.	(i) C_{IN} cc./min.	(j) C_{PAH} cc./min.	(k) C_{IN}/C_{PAH} %	(l) Tm_{PAH} mg./min.	(m) C_{IN} Tm %	(n) C_{PAH} Tm %	(o) Outcome
	Peripheral, with Associated Abdominal Injuries													
20	Soft tissue dam. to buttocks tr. amp. hand. Pref. small bowel.	80/40	4 hrs.	4	8	19	?	159.0	552	29.0	69.0	2.30	8.00	Evac.
21	Frac. femur, lac. in stomach and small bowel.	60/40	<30 min.	15	25	45	2550	197.0	506.0	39.0				Evac.
22	Lac. of sm. b. & colon. Extensive soft tissue dam. to head and neck.	70/50	<30 min.	13	29	17	2700	120.0	446.0	27.0				Evac.
						45	1250	188.0	563.0	33.0				
						61	?	146.0	462.0	31.4				
23	Ext. dam. to soft tissue of thigh. Lac. vena cava, frac. pelvis, head injury.	80/60	1 hr.	18	41	3	675	63.4	386.0	16.4				Died on 2nd day.
						18	600	7.4	59.0	12.5	19.6	0.38	3.02	Subdural hematoma.
24	Frac. femur, both tibia, perf. in small bowel, colon vena cava.	0/0	3 hrs.	20	37	13	250	29.2	172.5	16.9	52.0	0.56	3.32	Evac. to Japan on 15th day.
						33	560	47.0	112.2	41.7	50.8	0.92	2.21	
						85	550	39.0	132.0	29.5	60.8	0.64	2.18	
						190	1300	115.0	432.0	26.7	49.5	2.32	8.72	
						270	1350	124.0	659.0	18.9	49.1	2.52	13.40	
25	Ext. dam. to soft tissue of abd. wall, back & legs, head, neck & arms. Bilat. frac. humerus, multiple perf. sn. b. & stomach. Lac. liver.	50/0	<30 min.	24	44	8	250	22.0	180.0	12.2	48.0	0.46	3.75	Evac. on 5th day.
						41	1250	59.5	371.0	16.1				"Eviscerated," died
						72	2000	88.0	400.0	22.0	52.0	1.70	7.70	"uremia" 2nd week.
26	Hemothorax. Lac. of lung, spleen, liver, kidney, sm. b., colon. Frac. femur, soft tissue to thigh.	80/60	4 hrs.	28	48	14	Nil	1.4	16.0	8.8				Died 18 hrs.

Thoracic Injuries

27	Perf. sternum and pericardium.	118/70	?	2	7	68 89	?	166.0 159.0	772.0 900.0	22.0 18.0	101.0 77.0	1.65 2.07	7.65 11.70	Evac.
28	Lac. liver, hemothorax.	?	<30 min.	4	11	28	?	156.0	678.0	23.0				Evac.
29	Hemothorax, frac. rib, neg. laparotomy.	90/50	2 hrs.	15	17	38	980	126.0	533.0	23.7				Evac.
30	Massive hemorrhage from axillary artery, hemothorax. Lac. of lung.	0/0	3½ hrs.	25	25	6 48	800 1000	147.0 160.0	331.0 430.0	44.3 37.3				Evac.
31	Massive hemorrhage from axillary artery, hemothorax. Lac. of lung. Frac. humerus.	0/0	2 hrs.	15	28	38	1300	135.0	556.0	24.3	97.0	1.40	5.72	Evac.

Thoraco-abdominal Injuries

32	Hemothorax, small lac. liver and spleen.	110/71	?	8	18	11 38 82	600 650 800	180.0 176.0 136.0	461.0 576.0 428.0	39.1 31.0 32.0	135.0 110.0 143.0	1.33 1.60 0.95	3.42 5.24 3.00	Evac.
33	Hemothorax. Ext. lac. lung, liver, spleen, stomach, pancreas.	0/0	2 hrs.	28	41	6	Nil	2.4	34.3	7.0				Died 16 hrs.
34	Ext. lac. lungs. Bilat. hemothorax, shattered dome, liver, frac. humerus.	100/60	1 hr.	10	31	3 52 122	1575 2500 1575	45.0 98.9 137.0	187.0 352.0 444.0	24.0 28.1 30.9	92.7 95 0 101.0	0.49 1.04 1.36	2.02 3.71 4.40	Evac.
35	Hemothorax, lac. lung, stomach, spleen, sm. b., liver.	0/0	1 hr.	13	36	41	680	67.0	339.0	20.0				Evac.
36	Lac. stomach, sm. b., liver, spleen, colon, cardiac tamponade, lac. lung, frac. ribs, humerus, tibia, fibula, soft tissue dam. to leg and arm.	80/60	4 hrs.	25	45	4	378	4.2	28.5	14.3	34.0	0.12	0.84	Trans. to Kidney Center 2nd day. Died 1 mo. later of peritonitis.

Table 3—Continued

(a) Subject	(b) Injury	(c) Adm. BP	(d) Duration BP<100/60	(e) Pints Trans. Blood	(f) Point Units of Trauma	(g) Hrs. Post-op.	(h) Urine output on day of test cc./24 hrs.	(i) C_{IN} cc./min.	(j) C_{PAH} cc./min.	(k) C_{IN}/C_{PAH} %	(l) Tm_{PAH} mg./min.	(m) C_{IN} Tm %	(n) C_{PAH} Tm %	(o) Outcome
						Abdominal Injuries								
37	Perforations of liver and gallbladder.	140/90	<30 min.	5	10	34		148.0	500.0	29.7				Accidentally given 800 cc. distilled water-intravenously between 24 & 30 hrs. postop. No ill effects. Evac.
38	Multiple perf. sm. b., massive intra-abdominal hemorrhage.	80/60	8	25	14.5	13	1000	120.0	353.0	34.0	76.0	1.58	4.65	Intestinal obst. 5th day.
						200	150	16.0	59.0	26.3	37.0	0.44	1.60	Died, pneumonia 12th day.
39	Perf. of sm. b., colon, bladder.	100/70	<30 min.	9	33	9	800	74.0	246.0	30.0	82.0	0.90	3.00	Rec'd. by error, 5000 cc. 0.9% Nall. In 24 hrs. showed oliguria and pulmonary edema. Trans. to Kidney Cen. on 3rd day. Evac. in 3 wks.
						50	Nil	2.0	11.6	17.0				
40	Lac. sm. b., colon, spleen, bladder. Ext. retroperitoneal trauma.	70/40	1 hr.	13	37	11	650	61.1	219.0	27.9				
						29	1950	118.5	633.0	18.8				
						60	1200	120.5	442.0	27.3				
41	Hemothorax, lac. of lung, stomach, sm. b., kidney, spleen, femoral vein. Ext. soft tissue dam. to thigh and abd. wall.	80/40	1 hr.	25	43	35	1200	25.0	251.0	20.0				Evac.
						19 days	2300	132.0	521.0	25.3				

42	Ext. retroperitoneal soft tissue dam. Lac. vena cava. Perf. in sm. b., stomach, colon. Ext. destruction of thigh & buttock.	130/70	3 hrs.	21	42	14 62 150 360	255 925 1360 2000	5.2 17.7 18.6 144.0	26.4 105.0 108.0 667.0	19.8 16.9 17.5 26.8.	23.9 20.0 22.7 66.0	2.17 0.89 0.82 2.18	1.11 5.25 4.76 10.12	Trans. to Kidney Cen. 9th day. Evac. to Japan 1 mo. Recovered.
43	Liver, sm. b., pancreas, spleen (crush injury).	138/90	<30 min.	22	43	36	300	4.5	21.0	21.5				Trans. to Kidney Cen. 3rd day. Died in 3 wks. Portal vein thrombosis.
44	Ext. lac. of sm. b., liver, colon.	100/80	1 rh.	15	43	46	57	0.9	4.5	19.0				Trans. to Kidney Cen. 3rd day. Died from peritonitis, 2 wks.
45	Lg. lac. liver, sm. b., kidney, spleen, colon, stomach.	100/70	<30 min.	14	45	17	48	1.4	14.3	9.7	21.0	0.07	0.68	Died 2nd day.

Table 4. Quantitative Estimation of Trauma

Section 1: Physiological loss incurred through damage to organ

Location of Wound	Organ Injured	Point Score
Subcutaneous Tissue:	Devitalized volume equivalent to one closed fist.[21]	0. 5
Chest:	Hemothorax necessitating simple tap.	1. 0
	Thorocotomy	3. 0
Abdomen:	Stomach, or small bowel,	
	2 perforations	3. 0
	>2 perforations	3. 0–7. 0
	Negative laparotomy	1. 0
	Colon	1. 5
	Rectum	2. 0
	Bladder	1. 5
	Liver, small laceration	1. 0–3. 0
	mod. laceration	3. 0–5. 0
	large laceration	5. 0–7. 0
	Spleen	2. 0
	Pancreas	3. 0
	Vena cava, primary closure	3. 0
	ligation	7. 0
Extremities:	Wrist	1. 0
(Traumatic	Foot	2. 0
amputations:)	Arm	2. 0
	Below knee	5. 0
	Knee	6. 0
	Thigh	7. 0
Fractures:	Humerus	1. 0
	Tibia	1. 3
	Tibia and fibula	1. 5
	Pelvis (simple)	1. 0–3. 0
	(moderate)	3. 0–7. 0
	(severe)	7. 0–10. 0
	Femur	3. 0

Section 2: Magnification of wound damage by delay in therapy

Multiply total score for tissue injury by factor computed as follows:

$$1.0+\frac{\text{Hours of Delay}}{10}=\text{F.}$$

Section 3: Transferred blood volume. A measure of individual variation in response, and the degree of "shock"

Volume of Blood	Point Score
5 bottles (2.5 liters)	1. 0
10 bottles (5 liters)	3. 0
15 bottles (7.5 liters)	5. 0
20 bottles (10 liters)	7. 0
25 bottles (12.5 liters)	10. 0

Churchill [20] has defined the magnitude of a battle wound as "the vector sum of its many components acting in the direction of deterioration." Table 4 gives a point-scoring system constructed to quantitate the potential influence of three "vector components" upon postoperative renal function. These are, in order of priority, the systemic insult incurred through damage to a given organ, the length of delay before treatment, and individual sensitivity to injury (degree of "shock"). Section 1 gives a point score arbitrarily allocated to the more commonly injured organs. It is based upon the relative physiological priority of their continued undamaged state. For example, destruction of abdominal organs should merit higher point scores than the loss of an equivalent volume of subcutaneous tissue.

The distribution of wound site among the various grades of PTRI (measured by the depression of C_{IN}) is given in Table 5. As noted by others,[5, 6, 22, 23] severe renal insufficiency most characteristically followed abdominal injuries, being more frequently irreversible after damage to more than three solid organs. This type of injury can also be seen to give rise to the highest point scores. Most of the patients in the lowermost ranks of Table 5 would, no doubt, have died had no facilities for rapid evacuation, resuscitation and surgery been immediately available. It should be noted that high, or supernormal, filtration rates probably occurred more frequently than indicated in Table 5, since this series of patients was selected according to the probability of their developing PTRI. However, the apparent scarcity of PTRF following thoracic and peripheral wounds seems valid since few, if any, cases escaped notice. Absorption of blood and necrotic debris should theoretically promote pyrogenic renal hyperemia.[4] This may, in some measure, have reduced the severity of renal ischemia after thoracic and peripheral injuries.

The passage of time intensifies noxious aspects of trauma, mild hemorrhage culminating in irreversible shock because of delayed replacement.[40] To compensate for this, wound severity was corrected for delay time between injury and medical attention by multiplying tissue damage score by $\frac{\text{hours of delay}}{10} + 1.0$, as in section 2 of Table 4.

During resuscitation, it was the custom of attending surgeons either to speed up or slow down the rate of blood transfusion depending upon conventional indices [6] of cardiovascular stability. Because identical wounds frequently effected a variable clinical picture in different soldiers, (different degrees of clinical shock) comparable casualties rarely needed the same volume of blood. Presumably this variation depended upon unequal volumes of hemorrhage plus individual differ-

Table 5. Number of Cases in Each Grade of Functional Impairment

% of Normal Function (estimated by C_{IN})	Peripheral Injuries	Peripheral w/Abdominal Injuries	Thoracic Injuries	Thoraco-abdominal Injuries	Abdominal Injuries		
					1 Organ	2 Organs	3 Organs
Higher than normal	2	1	1	1	0	0	0
Normal	8	3	4	0	3	0	0
50–80% of normal	1	1	0	2	1	0	0
25–50% of normal	1	1	0	0	0	0	0
5–25% of normal	1	1	0	0	1	1	0
<5% of normal	0	0	0	2	1	0	2
Total	13	7	5	5	6	1	2

ences in sensitivity to a given wound. Accordingly, the required transfusion volume may be considered a rough index of these two inseparable components of the total wound insult. Their contribution was measured by arbitrarily adding one point to the total trauma score for each 2.5 liters of transfused blood (see sec. 3 of Table 4).

In Figure 4 mean values for C_{IN} are plotted against the postoperative time interval. Casualties exposed to more drastic violence (closed

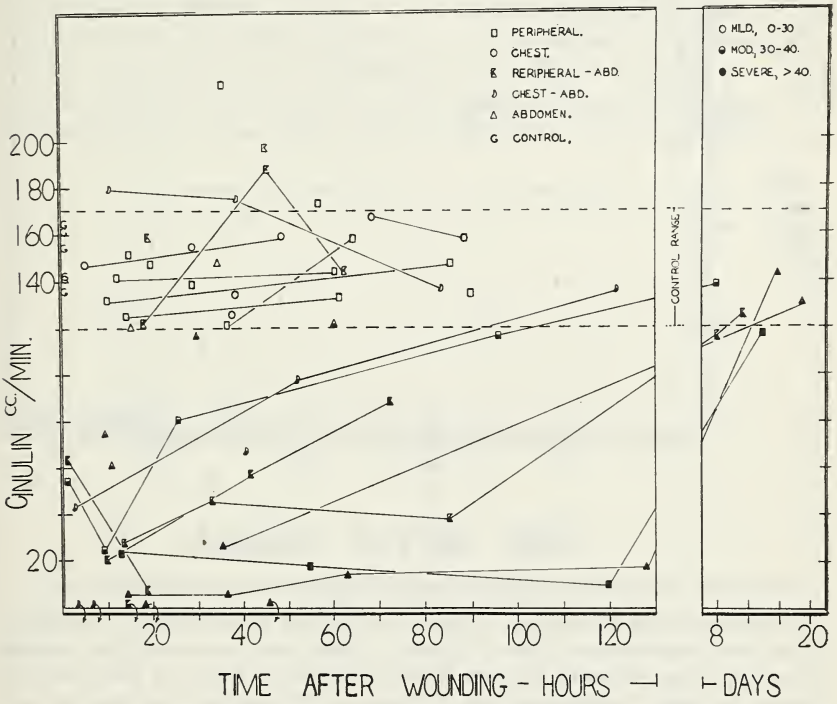

Figure 4. Glomerular Filtration during Convalescence.

Filtration rate (C_{IN} in cc./min.) is related to the postoperative time interval in hours. In this and succeeding charts, unless otherwise stated, each point represents the average of several urine collection periods. Lines join consecutive observations from the same subjects. Horizontal dotted lines delineate the control range for C_{IN} (from six non-injured soldiers). The same symbols are used in subsequent charts, although the key for the symbols appears in this figure only. Squares represent peripheral wounds; circles, thoracic wounds; the heavy letter K, periphero-abdominal wounds; half-moons, thoraco-abdominal wounds; triangles, abdominal wounds; and the capital letter G, control subjects. The magnitude of injury (see Table 4) is given by open symbols for less than 30 units of trauma (mild injury), half-filled symbols for 30 to 40 units of trauma (moderate injury), and closed symbols for more than 40 units of trauma (major injury). Patients who subsequently died in uremia are indicated by arrows curving over the baseline. All cases are described in detail in Table 3.

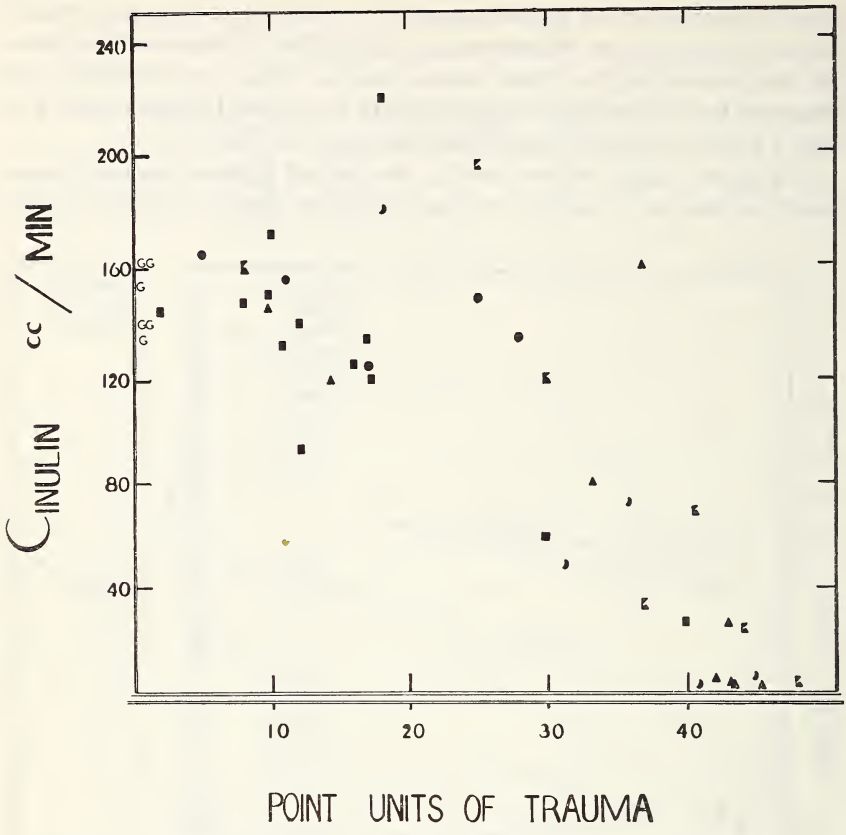

FIGURE 5. The Effect of Total Wound Insult upon Glomerular Filtration.

Filtration rate (C_{IN} in cc./min.) is related to the total wound insult, as computed by the point trauma score given in Table 4. Each point represents the average of several urine collection periods obtained within 48 hours of resuscitation. Symbols for wound site are as given in Figure 4. Glomerular filtration was not significantly depressed by less than 30 units of trauma. The greatest degree of PTRI followed abdominal or combined abdominal wounds, where the degree of trauma exceeded 40 point units.

symbols) suffered more profound and prolonged postoperative depression in glomerular filtration. Conversely normal or supernormal values for C_{IN} followed minor wounds (open symbols); moderate injury was followed by intermediate clearance levels. Most patients recovered normal function within 3 weeks, but more severe grades of renal failure were associated with such extensive injuries that death usually ensued from secondary causes [2] (e. g., peritonitis) before full recovery of renal function occurred. Such cases are identified in Figure 4 by arrows curving over the baseline.

In Figure 5 values for C_{IN}, observed within 48 hours of injury, are related to the point score computed from the total trauma scale shown in Table 4. The data clearly show that postoperatively glomerular filtration was inversely related to the total wound insult. In Figure 6 the same data for C_{IN} are plotted against the volume of transfused blood required to effect resuscitation. There is some indication that at this time C_{IN} may be roughly related to the previous extent of shock, but the data show considerable scatter. No single component of the wound insult showed as good a correlation with postoperative renal function as did the total point score. Filtration was frequently reduced ($C_{IN}<70$ cc./min.) following abdominal or peripheral wounds producing little shock and requiring relatively few transfusions. On the other hand, more profound or prolonged states of peripheral col-

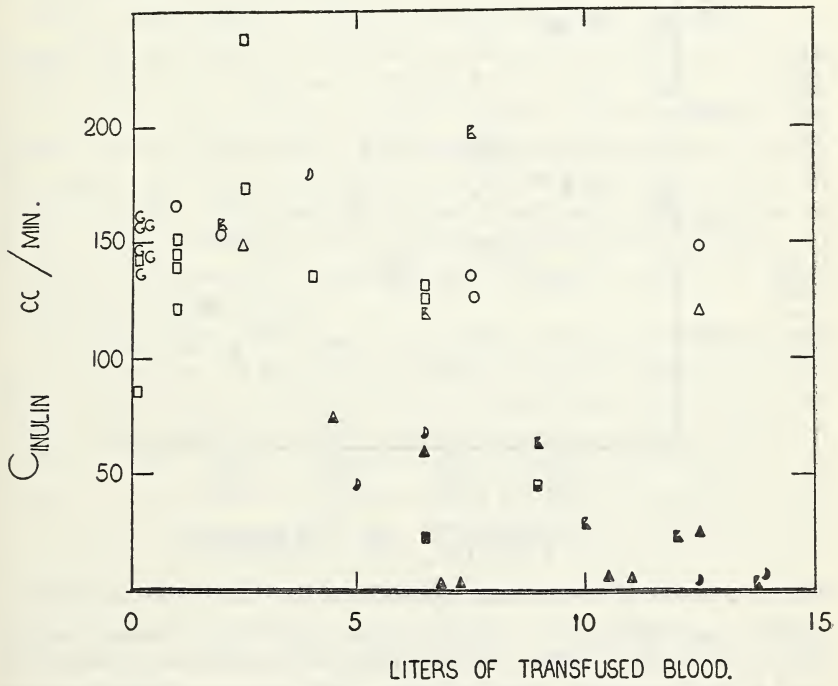

FIGURE 6. The Effect of "Shock" upon Glomerular Filtration.

The degree of "shock," measured by liters of blood needed for resuscitation, is related to the level of glomerular filtration (C_{IN} in cc./min.) observed afterwards. Each point represents the average of several urine collections obtained within 48 hours of resuscitation. Symbols for wound sites are as given in Figure 4. Mild injuries (open symbols) failed to depress filtration, yet frequently required blood replacement exceeding the normal blood volume. Conversely, filtration was depressed by moderate (half-closed symbols) or severe (closed symbols) injury, whether transfusion volume was excessive (more than 10 liters), or not.

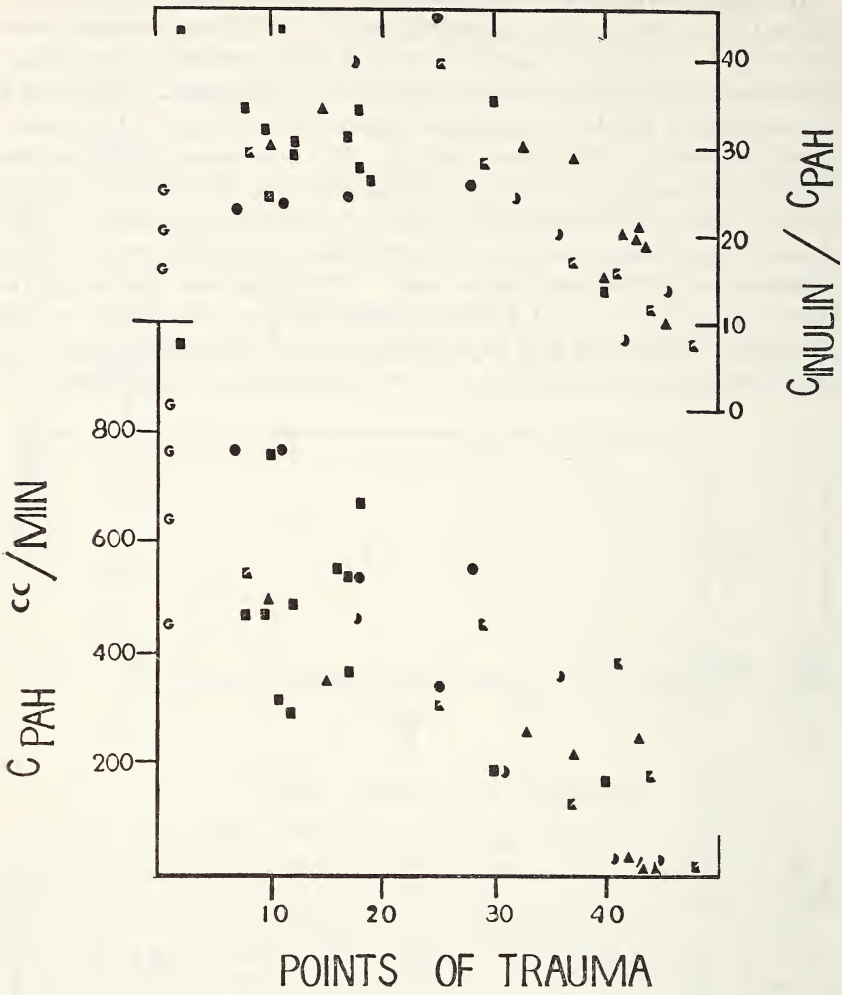

FIGURE 7. Effect of Wound Insult upon Plasma Flow and Filtration Fraction.

Effective renal plasma flow (C_{PAH} in cc./min.) below, and filtration fraction C_{IN}/C_{PAH} in per cent) above, are plotted against the total wound insult computed by the trauma scale given in Table 4. Each point represents the average of three to five urine collection periods from one experiment within 48 hours of wounding. Symbols represent different wound sites given in the key for Figure 4. These data suggest that following mild to moderate trauma, glomerular filtration was maintained by efferent arteriolar constriction. After more than 35 point units of trauma this compensatory mechanism apparently failed to prevent greater decrements in filtration than plasma flow. Thus, the filtration fraction declined to about half the normal value following drastic wounds.

lapse accompanied major arterial hemorrhage. These commonly followed thoracic wounds, required massive transfusions, yet rarely preceded PTRI. Such critical emergencies were encountered more frequently than the data would indicate, but after it was realized that renal sequelae were unlikely to follow, they were seldom documented by laborious clearance measurements.

As shown by the data given in Table 3, the duration of preoperative hypotension was unrelated to the clearance level after surgery. Similarly postoperative hypotension was prolonged to the same extent in patients with and without reduced renal function. These observations detract from the significance of "shock" per se as an etiological factor in the genesis of PTRI. Similarly, Mallory [23] found "patients with mild or no shock and patients with severe shock to have an equal incidence of fatal nephropathy."

With minor grades of injury, FF was inversely related to C_{PAH}, suggesting maintenance of glomerular filtration by efferent arteriolar construction; but, as shown in Figure 7, after more than 35 units of trauma, FF progressively declined. Figure 8 indicates that for any given level of plasma flow, increasingly greater amounts of trauma decreased the relative magnitude of efferent arteriolar constriction, depressing FF. The most extreme renal response to trauma appeared to be a reduced filtration fraction at low clearance levels. Conversely, when FF progressively increased with time at low clearance levels, recovery seemed imminent.

Two theoretical mechanisms conceivably causing erroneous depression in clearance are tubular back diffusion and decreased extraction by secretory tissues. Although both mechanisms are suspect in pathological states, the observed low ratios for C_{IN}/C_{PAH} can be attributed to neither. Back diffusion should most reasonably be expected to depress C_{PAH} more than C_{IN} because PAH possesses a smaller molecule and a greater diffusion coefficient. Reduced tubular extraction should also elevate the ratio C_{IN}/C_{PAH}, because only PAH depends on tubular secretion.[4] A possible explanation for the low ratios may be a proximal shift in the locus of vasoconstriction from efferent to afferent glomerular arteriole, with progressively greater degrees of total wound trauma.

The Effect of Hexamethonium and High Spinal Anesthesia During Convalescence

During hexamethonium infusion (8 subjects) and spinal anesthesia to T5 (2 subjects), mean arterial pressure (taken as the diastolic pressure plus one-third of the pulse pressure [24]) fell more than C_{PAH}, sug-

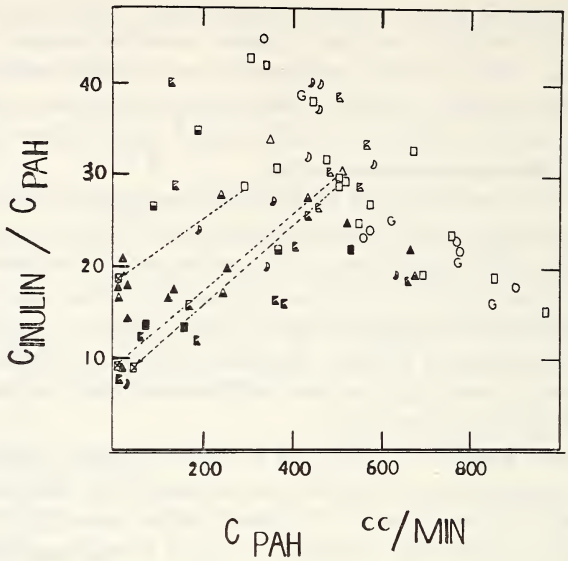

FIGURE 8. Effect of Trauma on the Relation Between FF and Plasma Flow.

Filtration fraction is shown to vary inversely with C_{PAH} in the more lightly wounded (open figures). At comparable levels of plasma flow, FF was depressed by moderate (half-closed symbols) or severe (closed symbols) injury. Each point represents the average of several collection periods from one postoperative test. Consecutive observations from casualties in whom renal failure was precipitated by some postoperative complication are joined by dotted lines. These three patients, initially suffering from mild PTRI, each showed high values for FF before the postoperative complications. Subsequently FF declined with the onset of severe renal failure (false PTRI). As C_{PAH} recovered during the convalescence of severely wounded patients, FF progressively rose, but as C_{PAH} recovered during the convalescence of patients with minor wounds, FF progressively fell. The key to symbols for wound sites appears in Figure 4. All cases are described in detail in Table 3.

gesting decreased renal vascular resistance. Concomitantly, FF rose in lightly wounded patients, remained unchanged in moderately injured patients, and fell in severely wounded patients. This also suggests that the locus of renal vascular reactivity varies with the degree of trauma.

Renal Clearance Pattern and Postoperative Blood Volumes

Plasma volume (T_{1824}) was measured in 14 casualties on the day of clearance determinations as described elsewhere.[7] After mild to moderate trauma (<40 units), estimated blood volume (but not red cell mass) correlated roughly with C_{IN}, C_{PAH}, and ERBF (effective renal

blood flow, calculated from C_{PAH} and the hematocrit as follows: $ERBF = C_{PAH} \div 1 - Hct.$).

In contrast to the pattern seen during chronic anemia in dogs [74] and man,[75] FF varied inversely with blood volume (but not red cell mass). Figure 9 shows that during convalescence from lesser wounds (10 cases), progressive improvements in blood volume were associated with corresponding elevations in renal blood flow. This would suggest that efferent arteriolar constriction may simply represent a com-

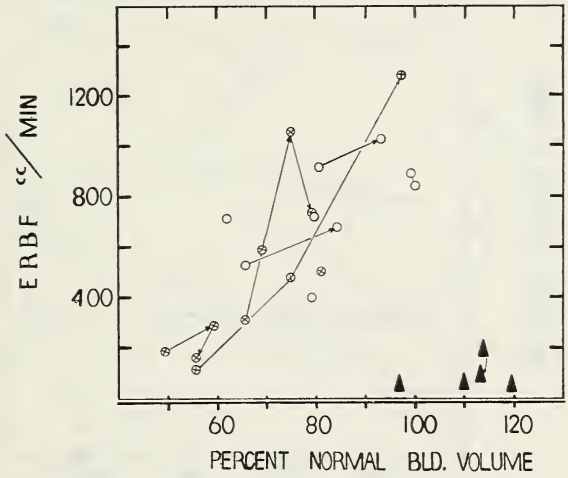

FIGURE 9. Renal Blood Flow and Blood Volume during Convalescence.

Effective renal blood flow (ERBF in cc./min.) is plotted on the vertical scale against blood volume (as per cent of the normal expected value). Each point is the average of several clearance periods on the day of blood volume determination. Solid lines join consecutive observations upon single individuals made on successive postoperative days. After minor (open circles) or moderate (crossed circles) trauma, ERBF was directly related to blood volume. However, the severe renal insufficiency caused by major trauma (>40 point units) was associated with early hypervolemia (solid triangles). The data suggest that the lesser grades of PTRI may be aggravated by *hypo*volemia but that *hyper*volemia develops soon after the onset of extreme renal insufficiency.

pensatory adjustment to hypovolemia, long known to follow major surgery.[7, 21] However, the four cases of massive trauma (>40 point units) did not fit this pattern. Although C_{IN}, C_{PAH}, FF and ERBF remained severely reduced following resuscitation, blood volume appeared to be normal or supernormal. At this stage, the presence of hypervolemia may distinguish fulminating [1] renal failure (solid triangles) from reversible PTRI (open and crossed circles).

Tubular Function During Convalescence

In 35 experiments upon 17 casualties, functioning, proximal tubular mass [4] was estimated by the maximal limit to PAH secretion (Tm_{PAH}). The results are summarized in Table 3. The virtual volume of plasma cleared per unit functioning tubular tissue was expressed by relating C_{PAH} to Tm_{PAH} as shown in Figure 10. Similarly glomerular function per unit functioning tubular tissue is given in Figure 11 by relating C_{IN} to Tm_{PAH}. Ratios falling below the normal range (inclosed by

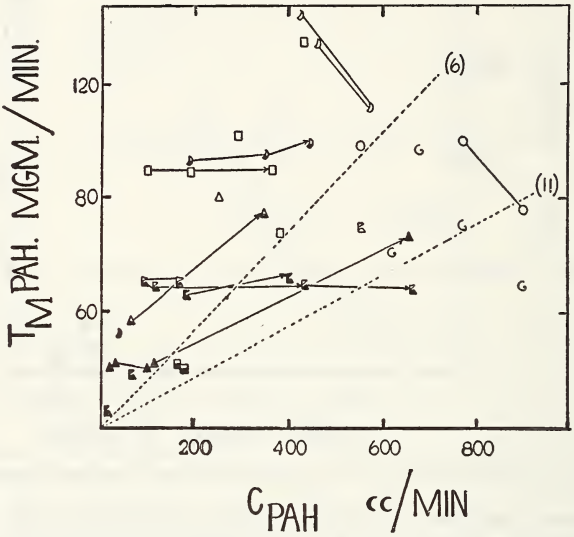

FIGURE 10. Renal Plasma Flow and Tubular Mass during Convalescence.

The functioning tubular mass (Tm_{PAH} in mg./min.) is plotted on the vertical scale, in relation to the effective renal plasma flow (C_{PAH} in cc./min.). Each point represents the average of several urine collection periods during one post-operative test. Symbols for wound sites are the same as in preceding figures. Dotted horizontal lines enclose the normal range for the ratio C_{PAH}/Tm_{PAH} (normal range 6 to 11). Solid lines connecting successive observations on single subjects show that ratios, initially low after wounding, returned toward normal during convalescence. Some lightly wounded casualties demonstrated super-normal values for Tm_{PAH} despite significant reduction in renal plasma flow.

diagonal dotted lines) indicate a greater impairment in glomerular than tubular function. Actually, Tm_{PAH} may have been even greater than observed because relatively low tubular loads (due to ischemia) could hardly saturate all functioning nephrons at low clearance rates. Low values for Tm_{PAH} may thus reflect virtual exclusion of normal functioning nephrons by reduced blood flow. It is unlikely that

hyperactive residual tubules could cause Tm's of the observed magnitude by "vicariously" clearing blood delivered from inert nephrons. Clearly, low ratios for C_{IN}/Tm_{PAH} show relative ischemia of functioning nephrons.

Maintenance of Tm_{PAH} precludes reduced tubular extraction and supports the validity of C_{PAH} as an indication of renal ischemia. In the absence of hypotension, this must reflect locally increased renal

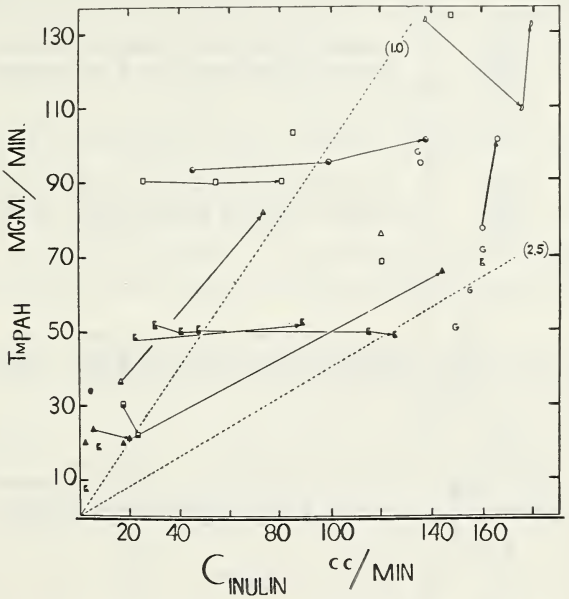

FIGURE 11. Glomerular Filtration and Tubular Mass during Convalescence.

The abcissa is the same as in the preceding figure, glomerular filtration (C_{IN} in cc./min.) being plotted on the horizontal scale. As in Figure 10, ratios falling to the left of the dotted diagonal lines (representing the normal range for the ratio C_{IN}/Tm_{PAH} of 1 to 5) indicate a greater impairment in glomerular than in tubular function.

vascular resistance. Apparently trauma gives rise to some systemic trace effect, operating to diminish renal vascular caliber in rough proportion to the degree of systemic insult. High values for Tm_{PAH} noted in lesser grades of PTRI are incompatible with the presence of acute tubular necrosis suggesting that this morphological feature is only secondary to a continued functional disturbance in renal vascular tone. According to this view, azotemia stems from reduced filtration and tubular necrosis is only a secondary sequela of extreme and protracted post-traumatic renal ischemia.

Table 6. Hypertonic Parameter in Convalescent Casualties

Case No.	C_{IN} cc./min.	V cc./min.	Cosm / C_{IN} per cent	V / C_{IN} per cent	Cosm cc./min.	T_cH_2O cc./min.	T_cH_2O/C_{IN} per cent
43	5	0. 4	11. 7	8. 9	0. 5	0. 1	2. 8
2	84	10. 5	16. 9	12. 6	14. 1	3. 6	4. 3
41	47	5. 6	18. 0	11. 9	8. 5	2. 9	6. 1
38	16	3. 2	24. 8	19. 8	4. 0	0. 8	5. 0
10	166	8. 5	10. 8	5. 1	17. 9	9. 5	5. 7
35	76	12. 5	21. 0	16. 4	16. 0	3. 5	4. 6
17	230	39. 6	19. 5	17. 2	44. 7	5. 3	2. 3
25	61	9. 6	25. 5	15. 9	15. 4	5. 8	9. 6
21	194	33. 3	19. 9	17. 2	38. 6	5. 3	2. 9
29	122	7. 3	10. 8	6. 0	13. 2	5. 9	4. 8
5	106	26. 0	28. 9	24. 7	30. 7	4. 5	4. 2
6	146	19. 0	15. 8	13. 0	23. 1	4. 1	2. 8
31	104	9. 8	14. 4	9. 3	15. 0	5. 3	5. 1
18	36	6. 3	22. 0	17. 5	7. 9	1. 3	4. 5
45	4	0. 9	26. 4	22. 3	1. 0	0. 2	4. 1
42	24	3. 3	17. 7	13. 9	9. 3	0. 9	3. 8

Just as Tm_{PAH} measures proximal tubular integrity, the activity of the distal system is reflected by the facultative parameters [25-27] to water reabsorption. Quantitative limitations to the concentrating mechanism (T_cH_2O) [27] observed during infusions of pitressin and mannitol, at variably depressed clearance levels, are summarized in Table 6. At load/T_c ratios >2, the urine appeared dilute by crude urinometry, although cryoscopic analysis demonstrated significant hypertonicity. When C_{IN} exceeded 70 cc./min., the absolute volume of solute-free filtrate abstracted to effect urinary concentration averaged 5.2 cc./min. This is almost identical with that found by Zac, Brun, and Smith (5.1 ± 1.5 cc./min.) in uninjured man.[26] At lower values for C_{IN}, the magnitude of T_cH_2O bore a constant functional relationship to the filtration rate, a pattern previously demonstrated during experimentally reduced filtration in the uninjured dog and seal.[28, 29] Thus, the normal degree of urinary concentration was achieved (in all 16 casualties) by abstracting approximately 4 per cent of the filtrate at all clearance levels, regardless of the degree of PTRI.

Table 7. Hypotonic Parameters During Convalescence

Case No.	Days Post-operative	C_{IN} cc./min.	Cosm cc./min.	V cc./min.	C_{H_2O} (V-Cosm) cc./min.	C_{H_2O}/C_{IN} Per Cent
7	2	148	0. 8	12. 8	12. 0	8
18	2	80	4. 4	11. 2	6. 8	9
13	2	94	3. 1	15. 3	12. 2	13
19	2	25	8. 4	11. 2	2. 8	11
15	3	130	1. 4	15. 3	13. 9	11
5	5	140	2. 0	18. 0	16. 0	9
						10

Table 7 gives the maximal volume of osmotically unbound water [25, 30] excreted during water diuresis by three casualties showing low values for C_{IN}. Comparable data are included for three other subjects with high clearance levels. When factored upon the filtration rate, maximal urinary hypotonicity, measured by the free water clearance (C_{H_2O}) was independent of the filtered, or execreted, urinary solute load. C_{H_2O} consistently approximated 10 per cent of the filtrate, regardless of the level of glomerular function. This would indicate that the relative magnitude of distal sodium reabsorption (TdNa)[27] was

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comparable to that of normal uninjured man,[30] constituting further evidence for preservation of tubular integrity.

It is noteworthy that within 48 hours of >35 units of battle trauma, the osmolar clearance (Cosm)[25-30] increased, the osmotic U/P ratio declined asymptotically toward 1.0, and plasma NPN exceeded 100 mg. per 100 cc. in all of six cases where this was measured. Comparable patterns of falling urinary specific gravity accompanied by parallel elevation in urine flow and plasma NPN have been illustrated in reports of extrarenal azotemia following transfusion reactions,[31] uterine rupture with shock,[32] gastrointestinal hemorrhage [33] and other acci-

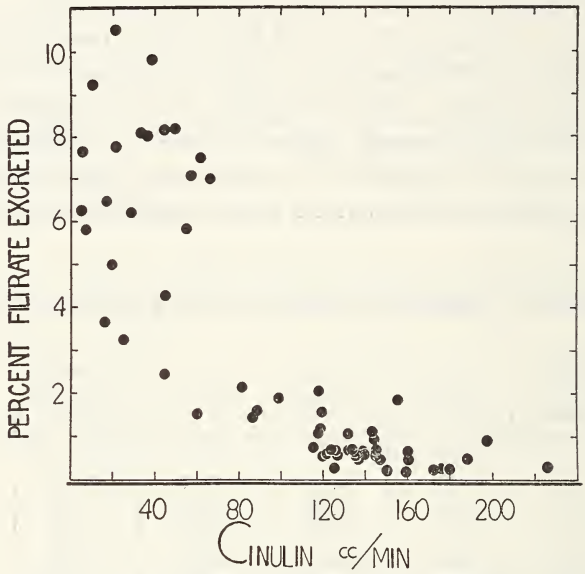

FIGURE 12. Urine Flow and Filtration Rate during Convalescence.

Daily urine output is expressed on the vertical scale as per cent of the prevailing filtration rate (C_{IN} in cc./min.). Unlike the pattern seen early after injury, tubular water reabsorption was depressed in casualties showing low filtration rates. Azotemia, consequent to increased catabolism, or decreased filtration, or both, presumably accounts for the osmotic diuresis approaching 10 per cent of the filtration rate in severe PTRI.

dents. Figure 12 shows that during convalescence (as opposed to the pattern seen early after trauma in Fig. 1) the daily urine output approximated 10 per cent of the filtrate in moderate to severe grades of PTRI. Similarly, Howard [5] has observed that 14 per cent of massively wounded casualties maintained daily urine outputs over 500 cc. despite clinical evidence of acute renal failure and uremia.

Data in table 6 constitute a strong argument against structural damage to the concentrating mechanism as a basis for isosthenuria. Actually the pattern shown in Figure 12 typifies any osmotic diuresis,[4, 34-39] the solute load in this case comprising urea, creatinine, sulfates and phosphates. Teschan [2] notes that these osmotically active tissue metabolites accumulate four times as fast in PTRF as in uremia of non-traumatic origin. Osmotic loads impeding the proximal reabsorption of more than 4 per cent of the filtrate would necessarily obliterate urinary concentration because of this quantitative limitation to T_cH_2O. At high values for $Cosm/C_{IN}$, the effect of T_cH_2O would be almost imperceptible, except by freezing point determinations. Evidently, in battle casualties the accelerated accumulation of osmotically active tissue metabolites caused an osmotic diuresis preventing the occurrence of oliguria and masking all but the most extreme grades of renal failure.

Heme Pigment Metabolism and Renal Function

Gross hematuria has frequently been noted after traumatic injuries in man [1, 31, 42, 43] and animals [44-46] and has been attributed to glomerular damage [46] from ischemic muscle metabolites,[47-49] as has proteinuria.[3, 44-46] The present group of casualties invariably exhibited dense proteinuria and hematuria. Theoretically, these abnormal urinary constituents alone would provide ample source for the precipitation [3, 23] of heme pigment. But, in addition, the urinary supernatant was not uncommonly deeply colored, particularly after massive transfusion. Olney [7] found the greatest concentration of free plasma hemoglobin in patients receiving the largest amounts of the oldest blood, but it disappeared from the plasma within 6 hours and could not explain persistent postoperative pigmenturia. Free urinary pigment was never noted in the absence of extensive muscle injury. On the other hand, many casualties with severe peripheral injuries and extensive muscle damage produced perfectly clear urine. No correlation was evident between the maximal plasma hemoglobin observed during or after transfusion (25 patients in Olney's series) and subsequent renal function. Neither the absolute amount of pigment excreted nor the per cent of circulating pigment excreted bore a consistent relationship to prevailing or subsequently determined clearance levels. The most massive intravascular hemolysis probably took place in three patients accidentally given distilled water intravenously. Patient Number 7 received 1,000 cc. during débridement of shell fragment wounds of the legs and buttocks. Patient Number 10 received approximately 1 liter of distilled water at a battalion aid station prior to

admission and Patient Number 37 received 800 cc. on the first post-operative day. No renal functional impairment was subsequently manifest in either case.

Large, coarse, reddish brown granules were frequently present in the urinary sediment of the more severely injured man. They were clearly visible to the naked eye and experimental mannitol diuresis usually flushed out a shower of these bodies, which disappeared from subsequent urine collections. Oliver [3] points out that since these casts originate in, and by inference, obstruct straight collecting tubules, many proximal nephron units must be rendered impotent by their presence. It has frequently been suggested [23, 50–52] that such bodies might cause renal failure either by obstruction or irritation. But, in five casualties, the formation of such casts was precluded by instituting a mannitol diuresis (500–2,000 gm. of mannitol intravenously) during and after resuscitation. Centrifuged urine from these five patients never revealed large casts, yet the prevention of urinary stasis and precipitation did not measurably improve renal function. Two of the five patients never recovered from PTRF and the three others showed clearance patterns comparable to untreated casualties with equivalent trauma point scores. In view of the above findings, as well as abundant experimental evidence reviewed elsewhere,[3, 4] the role of heme pigment must be relegated to a position of secondary importance insofar as the genesis of post-traumatic renal insufficiency is concerned.

Clinical Statistics

Table 8 gives pertinent data bearing upon the relative incidence of renal failure during early convalescence from wounding in 1,000 consecutive major surgical patients evacuated through the 8209th Surgical Hospital between April and September, 1952. Only cases of severe renal dysfunction are included, since it was impossible to document all cases of minor or subclinical renal insufficiency (less than 30 point units of trauma). The latter occurred much more frequently than the present data would indicate. However, it is highly unlikely that severe renal failure had a higher incidence than given in Table 8, because hospital personnel were alert to its possible occurrence and no casualties manifested oliguria or anuria without prompt recognition. Since definitive medical care is, to a large extent, dependent upon terrain and logistics of any military theater, these figures may be considered applicable only to this particular sector. Furthermore, it must be admitted that the intensified general interest in potential

Table 8. Distribution of Severe Renal Insufficiency Among Major Surgical Cases

First Indication	Total Cases	Case Numbers
Blunted Recovery Diuresis		
Lived more than 48 hours	4	(36, 42, 43, 44)
Died within 48 hours	8*	(26, 33, 45)
Oliguria Following Postop. Complication		
Transfusion reaction	2	(11, 13)
Intest. obst. and pneumonia	1	(38)
Overhydration, pulmonary edema	1	(39)
Total (excluding early deaths)	8	
Oliguria, Persistently Depressed C_{IN}, Hypertension		
Not dialyzed	4	(18, 24, 25, 42)
Persistently Depressed C_{IN}, Hypertension, No Oliguria		
Received artificial dialysis	1	(19)
Received no dialysis	3	(35, 40, 41)
Total	8	
Grand Total (excluding early deaths)	16 (1.6 percent of 1,000 consecutive cases)	

*Includes 5 unnumbered cases, recorded, but not documented by clearance studies.

candidates for renal failure may have precluded some factors normally contributing to its genesis.

It is noteworthy that acute renal failure of non-traumatic origin was frequently precipitated by a postoperative complication soon after wounding. Table 9 summarizes pertinent data obtained from all postoperative patients showing oliguria (<300 cc. urine/24 hours) who survived more than 48 hours beyond resuscitation. The figures show an equal incidence for both true PTRF and renal failure of non-traumatic origin (false PTRF). Seven of these oliguric patients were subsequently transferred to the Renal Insufficiency Center because of uremia. The five most severely injured (>40 point units of trauma) showed marked renal functional impairment immediately after resuscitation, as anticipated from their trauma scores. Here, oliguria unquestionably originated from wound trauma.

Two of the four other patients exhibited fairly high initial postoperative clearance values since they had suffered relatively little injury. One (Case Number 39) showed a moderate postoperative depression in clearance values because he had been badly injured (33 trauma points). Since the hematocrit in the fourth patient was only

Table 9. Distribution of Patients With Severe Oliguria

(Urine output less than 300 cc./24 hours)

Oliguria First Noted After Resuscitation

(True PTRF)

First Test					Complication		Subsequent Test			Outcome
Case No.	Point Units of Trauma	Hours after Surgery	C_{IN} cc./min.	C_{PAH} cc./min.	Type	Day	Hours Postop.	C_{IN} cc./min.	C_{PAH} cc./min.	
44	43	46	1	5						Died 3 weeks**
36	45	4	4	29						Died 3 weeks**
43	43	36	5	21						Died 2 weeks**
42	42	14	5	26			360	144	667	Recovered 4 weeks**
25	44	8	22	180			72	88	400	Evac. on 5th day, eviscerated, died uremia, 2d week.

Oliguria First Noted After Complication

(False PTRF)

First Test					Complication		Subsequent Test			Outcome
Case No.	Point Units of Trauma	Hours after Surgery	C_{IN} cc./min.	C_{PAH} cc./min.	Type	Day	Hours Postop.	C_{IN} cc./min.	C_{PAH} cc./min.	
13*	*12	*24	*87	*289	Transf. React.	4	96	3	19	Recovered 5 weeks**
11	11	84	146	501	Transf. React.	8	200	1	12	Recovered 4 weeks**
39	33	9	74	246	Overhydration	2	50	2	11	Recovered 3 weeks**
38	15	13	120	353	Intestinal obstruction	4–5	200	16	59	Died 12 days

*Resuscitated with dextran wholly in place of blood.

**Transferred to the Artificial Kidney Center because of uremia.

15 at the time of study, clearances were presumably depressed [73] by severe anemia. This patient received dextran wholly in substitute for blood. The transfusion reaction occurred while manifest anemia was being rectified, after completion of preliminary clearance studies. Shortly after the initial postoperative studies, each of the latter group met with unforeseen accidents. These were recognized too late, in each case, to forestall the onset of acute oliguria. It is not unlikely that during great military activity similar accidents might never have been recognized at all, since with heavy casualty loads, meticulous postoperative attention becomes impractical. Under such conditions acute renal failure (of nontraumatic origin) might easily be attributed to the wound shock sequence and incorrectly be considered true PTRF. Theoretically, any circumstance favoring the occurrence of such postoperative complications would increase the apparent incidence of true PTRF in the field. This may explain, in part, the apparenty higher incidence noted in World War II [6, 23] as well as the recognized lack of correlation between wound shock and the subsequent renal outcome.[2, 6, 23]

Discussion

During World War II, "hemoglobinuric nephrosis" [23] was found in 19 per cent of 427 battle casualties autopsied in Italy. An even higher incidence (36 per cent) of "lower nephron nephrosis" [54] was observed among 315 battle casualties autopsied at the 406th General Medical Laboratory [22] in Tokyo between 1951 and 1952. These figures are at variance with the clinical incidence of PTRF shown in Table 8 as well as with Teschan's [2] observation that renal failure was clinically manifest (including transfusion reactions, hemorrhagic fever, etc.) by less than 1 per cent of the 8,000 casualties incurred during the 1952 Korean campaign. Clearly, estimates based upon pathological material seem to exaggerate the actual incidence, and by implication, the importance of this complication in military medicine.

There are at least two possible explanations for this apparent paradox between morphological and clinical statistics. The first thing is that renal insufficiency frequently occurs in subclinical form. Newburgh [53] showed that renal function may be reduced to one-tenth of normal without overt clinical manifestations, as is also apparent in the present study. Clinically imperceptible PTRI may predispose towards renal failure of nontraumatic origin (false PTRF). Secondly, among battle casualties at least, many deaths may be attributable to other causes and yet bear conventional pathological stigmata of "lower nephron nephrosis," [22, 54] "shock kidney," [55] "hemoglobinuric nephrosis," [23] etc.

Casualties dying within 48 hours of injury (for instance Cases Number 26, 33 and 45, included in Table 8) are an obvious source of such confusion. They are typically anuric and azotemic,[2, 42, 56] differing from survivors of true PTRF chiefly by their rapid exodus. Serial determinations of plasma NPN in Case Number 26 showed values of 73 mg. per 100 cc. at 6 hours and 105 mg. per 100 cc. by the twelfth postoperative hour. It is well known that marked structural alterations occur within the kidney of such individuals if they survive for 18 hours.[23, 54, 55, 65] These patients do not fit the ambiguous clinical criteria[2, 6] of PTRF; but the histories of anuria and azotemia, together with the morphological findings,[22, 23, 54] force pathologists to classify these cases with other varieties of post-traumatic tubular necrosis. Hence, necropsy material is bound to suggest a higher incidence of renal sequelae.

Current speculation regarding the pathogenesis of PTRF is, in large part, derived from autopsies of battle [23, 54] and air raid [42, 62] casualties dying in uremia during World War II. The clinical syndrome of PTRI is generally presumed to reflect tubular damage incurred during shock by renal ischemia [57–60] because the most striking morphological findings are limited to the renal tubules. It is inferred that glomerular filtration is restored upon resustication from shock. Uremia is thus attributed to back diffusion [57–60] through damaged tubular walls, as observed by Richards [61] in the poisoned frog kidney.

Since the extent of tubular necrosis was believed to be proportional to the severity or duration of hypovolemic shock,[17, 42, 56–60, 62–65] prompt transfusion was recommended to prevent its occurrence.[66] This prophylactic program of immediate blood replacement proved entirely feasible in the Korean Theater and was enthusiastically applied. Because of the liberal supply and free use of huge (up to 20 liters per patient) quantities of whole blood, hypovolemia was quickly and easily reversed. Thus Howard [5] notes that "irreversible shock" [40] was never encountered by the Surgical Research Team. Under such conditions, hypovolemia became the most easily controlled component of wounding, but this did not prevent the subsequent development of PTRI.

The present observations fail to support the conventional concept that PTRI reflects the degree of tubular damage incurred during "shock." [57–60] In battle casualties, plasma flow and filtration were reduced during traumatic shock, but these indices remained persistently depressed after resuscitation without comparable reduction in proximal or distal tubular function. Although infrequently recognized, experimental traumatic shock in animals is followed by a similar per-

sistent renal ischemia.[64, 67-69] This strongly suggests that systemic injury exerts its long-lasting effect primarily upon the renal vasculature rather than the renal tubule. If tubular necrosis occurs, it would not appear to reflect direct injury received during shock, but is more likely to result secondarily from a continued interference with renal blood flow during convalescence. The present low ratios for C_{PAH}/Tm_{PAH} and the increased renal arterial-venous oxygen saturation difference found by Breed [70] and Bull [31] in man argue against the presence of an intrarenal shunt.[71] Since PTRI is not apparently accompanied by decreased cardiac output [72] nor concomitant hypotension, the only explanation for the persistence of renal ischemia after resuscitation is increased renal vascular resistance.

Normally the kidney maintains an almost constant renal blood flow despite reduced perfusion pressure [4] by changes in renal vascular tone proximal to the glomerulus. Experimental evidence [73] would indicate that following severe trauma this autonomy of the renal circulation may be obliterated or severely impaired. The renal response to minor war wounds must have entailed chiefly vasoconstriction distal to the glomerulus because C_{IN} was maintained or even elevated, despite low values for C_{PAH}. This pattern seemed influenced by postoperative plasma volume. Also, it was exaggerated by decrements in peripheral blood flow following ganglionic blockage or spinal anesthesia. Hence, the observed efferent arteriolar constriction may conceivably represent part of a prolonged systemic circulatory reaction to trauma. Conversely, C_{IN} was depressed by severe injury to a greater extent than C_{PAH}. Since low ratios for C_{IN}/C_{PAH} cannot be explained either by back diffusion or reduced tubular extraction, they are attributed to a relative increase in vascular resistance proximal to the glomerulus. Evidence of afferent arteriolar spasm has been observed by Sheehan and Moore [52] and by Bell [65] and is compatible with decreased glomerular reactivity postulated by deWardener [73] to follow serious injury.

Summary

The renal function of military casualties was examined on over 100 separate occasions, during resuscitation from traumatic shock (6 cases), or during the interval between resuscitation and convalescence (40 cases).

The following discrete indices were measured intermittently: urine flow, C_{IN}, C_{CREAT}, C_{PAH}, Tm_{PAH} and the hypotonic and hypertonic parameters of urine excretion conventionally designated C_{H2O} and T_cH_2O respectively. The following components of wounding were examined for a relationship to postoperative renal function: degree and

duration of hypotension, transfusion volume, extent of intravascular hemolysis, postoperative blood loss (estimated by T1824 dilution) and the total wound insult computed by a point scoring system.

The conclusions drawn are that PTRI is primarily due to functional changes within the renal vascular bed, to which tubular disease may be a late secondary sequela, which are roughly proportional to the sum of all components of wounding but are independent of any single component, such as "shock." The predominant, measurable, renal abnormality is intractable ischemia, due to persistently increased renal vascular resistance following resuscitation from wounding. In its mild form, PTRI is characterized by relative efferent arteriolar resistance, but with progressive stages of wound severity, proportionately greater renal ischemia may reflect an increase in both efferent and afferent resistance and may secondarily result in loss of secretory activity. Excessive urinary solute loads accompanying azotemia, consequent to increased catabolism, or decreased filtration, or both, probably account for relative polyuria and isosthenuria, because no impairment in the urinary concentrating mechanism (T_cH_2O) was demonstrable for at least 3 days after manifest renal insufficiency.

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Chapter 12

Renal Changes in Patients Dying of War Wounds: Korea, 1950–1952

A Preliminary Report

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Shortly after the onset of war in Korea there was concern lest the use of group "O" blood for all transfusions in the combat zone should cause serious reactions and a high incidence of acute renal failure.* When, after the first 6 months of combat, it became apparent that this fear was exaggerated, study of autopsy material was continued in an effort to learn more about the relation between fatal battle wounds and renal complications. The results of these studies were published in the annual reports of the 406th Medical General Laboratory [1, 2, 3] and played a part in indicating the need for and justifying the establishment in 1952 of a renal failure center in Korea. Subsequently, publication of the study of the physiologic effects of wounds in the Mediterranean Theater in World War II [4] showed that the experience in Korea was a confirmation of previous experience. It is probable that acute renal failure had always been an important complication of severe battle trauma, but had received little notice masked as it was by the direct effects of trauma and the attendant shock and infection. Of 324 autopsies performed on men who died after receiving wounds in battle in Korea, 111 showed the histologic changes of acute renal failure.

Materials and Methods

During the period 1 July 1950 to 1 January 1953, the protocols and tissues of autopsies on 324 battle casualties who died in military medical installations in the Far East were studied by the Pathology Department of the 406th Medical General Laboratory in Tokyo. Autopsies on patients who died of battle wounds were irregularly performed in the surgical hospitals in Korea and generally in 1950 and 1951 only

*In this report acute renal failure, acute renal insufficiency, lower nephron nephrosis, hemoglobinuric nephrosis and acute tubular necrosis are considered synonymous in that they refer to a similar pathologic process.

when death was unexpected or unexplained. Autopsies were regularly performed on battle casualties who died in evacuation hospitals in Korea and in the hospitals in Japan. There was a considerable increase in the percentage of autopsies performed on men who died of wounds in hospitals in Korea as the battle situation became stabilized. In 1950 the ratio of autopsies to deaths from wounds was unknown but quite low; in 1951 it was approximately 3 per cent and in 1952 it was approximately 25 per cent. In 1950 and the first few months of 1951, a policy of rapid evacuation of patients to hospitals in Japan was in effect and much of the information obtained during this time came from these hospitals.

As the percentage of autopsies increased in the hospitals in Korea, protocols and clinical histories were given in greater detail and probably with greater accuracy. In part, this reflected the static battle situation which permitted more thorough study of patients and, in part, also reflected the influence of the various research teams in Korea which stimulated investigation along many lines.

Table 1. Regional Distribution of War Wounds in 324 Autopsies

Region	1950	1951	1952	Total
Head, neck, or spine	44	22	9	75
Thorax	4	6	11	21
Abdomen	19	10	13	42
Abdomen and thorax	12	8	11	31
Extremities	18	17	19	54
Abdomen and extremities	9	9	17	35
Multiple	19	18	*29	66
Total	125	90	109	324

*Including 6 with severe burns.

An attempt to determine whether the regional distribution of wounds (Table 1) was similar to that reported for other wars [5] failed because the present autopsies, yielding more accurate information, frequently implicated multiple regions of injury while previous surveys, based on simple inspection and information giving only the presumed major wound of entrance, reported only a single region of injury.

Autopsy material from men who died of battle wounds was received from the 1st Medical Field Laboratory in Korea and from all hospitals in Korea and Japan. A special search was made in all cases for evidence of renal changes using paraffin sections stained with

hematoxylin and eosin. Selected cases were further studied using the following stains: fat, Schiff periodic acid, Feulgen, Heidenhain, LaPelhne, Dunn-Okajima, and Wilder reticulum. The protocols of the 111 autopsies with histologic evidence of renal failure were studied to determine what part blood transfusion, shock, severity of injury, site of injury, and infection played in the pathogenesis of the renal lesions.

Clinical Course

The relation between severe trauma and acute renal failure was obscure and required cautious interpretation of clinical findings. The severely injured patient frequently showed clinical evidence of renal failure which was transient and disappeared with recovery from shock. Persistence of clinical findings was therefore required to establish the clinical diagnosis of acute renal failure. Consequently, diagnosis became difficult in patients so severely injured that death occurred within a few days after injury. Often in such patients there was little, if any, clinical evidence that death was hastened or made inevitable by superimposed renal failure although recognizable renal changes were found at autopsy. Further, evidence of nephropathy was found so frequently in patients who died of war wounds that, in some cases, it could be considered, like pulmonary edema and septic splenitis, a system or organ failure associated with the delayed death peculiar to trauma and the battle environment.

In the study on the physiologic effects of wounds in World War II [4] it was concluded "that the clinical syndrome of renal insufficiency which follows shock is remarkable chiefly for the scarcity and mildness of its symptoms" and that "the symptom complex of oliguria, pigment excretion, azotemia and hypertension established the diagnosis." Search for such evidence is not always practical under battle conditions, and therefore, the pathologist's report of a renal complication sometimes surprised the clinician. Review of the protocols showed in retrospect that especially in 1950 the diagnosis might have been made more frequently (Tables 2 and 3) but not in all cases. Some of the patients died of their wounds before clinical evidence of renal failure developed, while in others the renal changes were probably a terminal event.

The severity of the azotemia varied considerably, and frequently was not sufficient of itself to establish a diagnosis of renal failure. Since rapid tissue breakdown and destruction could also produce azotemia, an ante-mortem diagnosis of acute renal failure usually was not made without other evidence. Similarly, oliguria was usually present

Table 2. Recorded Ante-mortem Evidence of Renal Failure in 111 Patients With Renal Changes at Autopsy

Ante-mortem Findings	1950	1951	1952	Total
Azotemia	0	2	1	3
Oliguria	4	6	6	16
Oliguria and azotemia	12	9	21	42
Oliguria and hypertension	1	0	0	1
Uremia	12	3	2	17
Oliguria, azotemia and hypertension	1	2	3	6
Total with ante-mortem findings	30	22	33	85
Total with renal changes at autopsy	43	35	33	111

Table 3. Clinical Diagnoses of Renal Failure in 111 Patients with Renal Changes at Autopsy

Clinical Diagnosis	1950	1951	1952	Total
Lower nephron nephrosis	12	15	27	54
Possible lower nephron nephrosis	1	2	0	3
Uremia	3	3	2	8
Total with diagnoses of renal failure	16	20	29	65
Total with renal changes at autopsy	43	35	33	111

during shock and in patients living only a few days this was not of great aid in establishing a diagnosis of acute renal failure.

A clinical diagnosis of acute renal failure was made more frequently in 1952. Many of these patients were treated at the Renal Failure Center but there was also a greater awareness among medical officers in other hospitals of the possibility of renal complications and a greater effort was made to treat this complication.[6]

Possible Etiologic Factors

Blood Transfusion. During the period of this report, more than 200,000 bottles of group "O" blood were sent to Korea, most of which was used for the treatment of the battle wounded. Blood labeled "Low Titer" could be given to all patients and blood labeled "High Titer"

was intended for group "O" patients only. It was neither practical nor possible to cross-match patients in forward hospitals or to determine the Rh type of the recipients. Very few reports were received of transfusion reactions. In only 4 of the 324 autopsy procotols was such a reaction reported and in only 2 of these was the reaction considered of sufficient severity to warrant naming transfusion reaction as a contributory cause of death. However, all four patients showed typical renal changes at autopsy.

Progressively larger amounts of blood were used in the treatment of battle casualties as the war continued. This was true also for the amount of blood given to the battle casualties who were found to have renal changes at autopsy (Table 4). These patients received more blood than the average of approximately 4.3 bottles of blood given to all battle casualties who were transfused,[7] indicating that these patients were among the more seriously injured. The studies of the Surgical Research Team indicated that serious transfusion reactions due to the use of group "O" blood were rare.[8]

Table 4. Blood Transfusions to Patients Who Died of War Wounds and Had Histologic Evidence of Renal Changes—87 Autopsies

	1950	1951	1952	Total
Number of patients	35	22	30	87
Total bottles of blood	203	198	360	761
Average—bottles per patient	5. 8	9	12	8. 7
Extremes—bottles per patient	1–52	2–28	2–40	

Battle Trauma. Although it was desirable and perhaps theoretically possible to distinguish the renal effects of traumatic shock, tissue damage and infection, this could not be accomplished. Many variables influenced and determined the response to therapy and the occurrence of acute renal failure. These included the degree and duration of shock, the interval between injury and treatment, the site and severity of injury, the presence of infection, the climate and weather, the battle situation, the number of casualties requiring treatment at the same time, etc. Information concerning many of these factors was either fragmentary or unavailable.

Shock. Because of the large amount of blood given to the patients who died and showed renal changes at autopsy, it was assumed that most had suffered shock of a significant degree and duration. The protocols of 19 patients who died in 1952 stated that traumatic shock

had been present in all, with a duration of 1½ to 20 hours and an average duration of slightly over 3 hours. The average interval between injury and surgery was 7 hours. For the other cases, only an estimate of the severity of shock could be made. This was based on the blood pressure when recorded, the pulse rate, the hematocrit, the type and severity of injury, the interval between injury and treatment, and the amount of blood transfused. Using such estimates, of 75 patients who could be evaluated, 58 had suffered severe shock probably for a considerable duration and 17 had suffered moderate shock.

Severity of Injury. The autopsy protocols of the 111 men showed renal changes were reviewed to determine the severity of their wounds. Twenty-five were judged to have wounds of moderate severity and 86 were classified as severely wounded. Those with wounds considered to be moderate would ordinarily have been expected to respond to modern forms of treatment if some other factor or combination of factors, such as prolonged shock, infection, gangrene, renal failure, secondary hemorrhage, had not complicated the course of recovery. Those judged to have severe battle wounds had a guarded or poor prognosis because of the amount and type of tissue damaged by the missile or because the wounds involved vital organs. A similar estimate of the patients who did not have renal changes at autopsy is not available.

Site of Injury. Study of the protocols of the 324 patients who died after receiving wounds in battle indicated that there was a relation between the site of injury and the ocurrence of renal failure (Table 5). Two groups were compared in an attempt to explain this. The first group consisted of all patients who died of wounds of the head,

Table 5. Regional Distribution of Fatal Wounds and Incidence of Autopsy Evidence of Acute Renal Failure

Region Wounded	Number Wounded	Number with Renal Changes	Per Cent with Renal Changes			
			1950	1951	1952	Average
Head, neck or spine	75	4	5	9	0	5
Thorax	21	0	0	0	0	0
Abdomen	42	26	63	50	69	62
Abdomen and thorax	31	12	57	25	27	39
Extremities	54	28	61	65	32	52
Abdomen and extremities	35	13	44	56	24	37
Multiple	66	28	37	56	38	42
Total	324	111	34	39	30	34

neck, spine or thorax. Few of these patients had histologic changes of acute renal failure at autopsy although many were exposed to the various factors accepted as possible causes of acute renal failure. Patients with head wounds usually suffered little shock and often did not receive blood transfusions but patients with thoracic wounds did suffer shock and were transfused. Infection occurred in all types of wounds. The second group consisted of all patients who died of wounds of the abdomen or extremities. This group had a high incidence of acute renal failure. Abdominal wounds generally had a relatively high mortality rate while extremity wounds, as a group, had a low mortality rate. Both severe extremity wounds and abdominal wounds were associated with shock, large blood transfusions and infections. It was not apparent why a majority of patients who died after receiving wounds of the abdomen or extremities showed autopsy evidence of acute renal failure while such evidence could not be found in any patient who had a fatal wound involving the thorax alone.

Infection. Infection present at the time of autopsy was difficult to evaluate as a factor in the pathogenesis of the renal changes. It appeared that infection frequently progressed because of lowered resistance in part due to renal failure but one could not be certain that infection had played a role in causing the renal failure or in making the renal changes more severe. A common clinical observation at the Renal Failure Center [6] was that the blood nonprotein nitrogen level frequently rose more rapidly after dialysis than would be anticipated and that often this unexpected rise was an indication of the presence of unrecognized infection. Study of 24 patients who were treated at the Center and who had renal changes at autopsy (Table 6) indicated that patients with infections tended to have a high blood nonprotein nitrogen level.

Table 6. Relation Between Azotemia and Infection

	Highest Recorded Blood Nonprotein Nitrogen Level				
Finding at autopsy	35–100	100–200	200–300	300–400	400–500
Infection present	2	4	3	9	1
Infection absent	0	3	1	0	1

Severe infection was frequently present and often involved more than one region (Table 7). Peritonitis and cellulitis were the most frequent findings. The incidence and severity of infections found at autopsy of patients who did not have renal lesions are not available.

Table 7.—Presence of Infection at Autopsy

	1950	1951	1952	Total
No. of patients with renal lesions	43	35	33	111
No. of patients with infections	?	27	23	?
Peritonitis	28	14	15	56
Cellulitis	12	8	10	30
Pleuritis	11	2	5	18
Pericarditis	2	0	0	2
Brain abscess	0	2	0	2
Meningitis	0	1	0	1
Pyelonephritis	0	0	4	4

Pathology

Although certain features of interest were observed in the study of these cases, little was added to our knowledge of the pathogenesis of or the actual site of injury in this condition variously known as lower nephron nephrosis,[9] hemoglobinuric nephrosis,[10] acute tubular necrosis,[11] acute renal failure,[12] etc. All of the cases met the requirements for histologic diagnosis although there was considerable variation in the severity of the lesions.

Weight of Kidneys. In most instances the kidneys were heavier than normal and in the few patients who had one kidney removed surgically, the remaining kidney showed hypertrophy. The weight of both kidneys, and of single remaining kidneys, after nephrectomy ranged from 200 to 725 grams with a median weight of 450 grams. The kidneys of patients who lived more than 13 days after wounding usually weighed more than 600 grams and those of patients who lived less than 10 days after wounding usually weighed less than 400 grams.

Histologic Observations. Necrosis of the epithelial cells of the tubules was a constant finding but no consistent relation could be recognized between the amount of tubular necrosis and the severity of injury, duration of life after injury, severity of renal failure, number of pigmented casts, or number and size of foci of inflammation.

Pigmented casts were also frequently present but no relation could be found between the number of casts in the cortex or the medulla and the duration of life after wounding in 31 of the patients who died in 1952. Casts were found in larger number in the medulla than in the cortex.

Foci of interstitial inflammation in the kidney were absent to minimal in patients who died within 5 days after injury, were numerous

and extensive in patients who lived from 6 days to 2 weeks after being wounded and tended to be fewer but larger in patients living more than 2 weeks after injury (Table 8). The infiltrates were found predominantly in the region of the cortico-medullary junction but when renal failure was severe and of long duration they were also found in the cortex about necrotic distal convoluted tubules. Because of the epithelial degeneration and the cellular reaction, involvement of the proximal portion of the nephron could not be recognized with certainty.

Table 8. Severity of Interstitial Infiltration and Interval Between Injury and Death

Interval Between Injury and Death (days)	Number of Patients	Severity of Interstitial Infiltration			
		Minimal	Mild	Moderate	Severe
3–5	10	8	1	1	0
6–10	8	3	2	2	1
11–15	8	1	2	2	3
16–19	5	1	2	1	1

Mallory [4] reported significant fat droplet alterations in the epithelial cells of renal tubules in men dying 18 to 96 hours after injury and traumatic shock. He interpreted these changes as being morphologic evidence of parenchymatous injury and functional impairment. A search was made for similar changes in the kidneys of 23 of the patients who died in 1952 and showed renal changes at autopsy. Only one of these men died in the critical 18- to 96-hour interval after injury. Fat droplets measuring one to several micra in diameter were observed in many of the kidneys. They were found most frequently in the ascending tubules and less frequently in distal convoluted and collecting tubules. They were most prominent in sections from three patients who lived less than 6 days after injury but on the other hand were minimal in sections from three other patients who lived less than 6 days after injury. Control sections from patients who died a few hours after injury contained more fat droplets than this last group of three patients.

Tissues from the 23 patients studied for fat droplet changes were also studied for the presence of iron in the tubules. Controls for this study were provided by producing athrocytosis in rats [13] by the injection of human hemoglobin. Within 2 days after such injections, gran-

ules appeared in the epithelial cells of the proximal portion of the nephron which had the same affinity as erythrocytes for the LaPehne and Dunn-Okajima stains. In none of the 23 human patients was there similar evidence of demonstrable iron or hemoglobin in the epithelial cells of the tubules. However, in sections from patients who had a short interval between injury and death, the pigmented casts in the proximal portion of the nephron showed some affinity for the stain. Similar casts in the distal portion of the nephron took the stain less intensely and those in the collecting tubules generally did not react at all. The pigment in the casts was not unequivocally identified as hemoglobin.

Discussion

It has been shown that the changes of acute renal failure are frequently found at autopsy in patients dying after being wounded in battle and that this is related, at least in part, to the degree and duration of shock, the region wounded and the severity of the wound. In addition to saving many lives, modern treatment of battle wounds delayed the death of the severely wounded and permitted the development and recognition of complications such as acute renal failure. In a certain number the renal changes were probably an indication of the failure of one system during the process of slow death after trauma. It was difficult to evaluate the effect of the renal changes in some of these cases because death occurred before clinical signs and symptoms could be recognized, and because in others the process was probably so mild that recovery from renal failure could have occurred were it not for the injuries and infection. However, the majority of patients did succumb to the combination of trauma, infection and acute renal failure. This combination occurs more frequently under military situations than in civilian life because the factors associated with the development of renal failure occur more frequently under battle conditions.

The diagnosis of acute renal failure was not always evident but when clinicians became aware of the frequency of occurrence of this complication they were much more successful in recognizing its presence. In 1950, 37 per cent of the cases were diagnosed and in 1952, 88 per cent were recognized. With increasing accuracy of diagnosis, more patients were treated more vigorously for renal failure with a saving of some lives. In war the severely wounded will continue to develop acute renal failure and it is likely that successful methods of prevention and treatment offer an opportunity for further reduction in the mortality rate from war wounds.

Conclusions

1. Approximately a third of men dying from war wounds in medical installations show histologic evidence of the changes associated with acute renal failure.

2. Predisposing factors for the development of these changes include site and severity of injured and duration and severity of shock.

3. The use of group "O" blood for all transfusions did not appear to be an important factor in causing acute renal failure.

4. Wounds of the abdomen and extremities were associated with a high incidence of renal changes and wounds of the head, neck, spine or thorax with a low incidence of renal changes.

5. Progressive and severe infection was frequently present in patients who showed renal changes at autopsy.

6. Diagnosis of acute renal failure required a high index of clinical suspicion.

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Chapter 13

Metabolic Effects of Injury; Studies of the Plasma Nonprotein Nitrogen Components in Patients With Severe Battle Wounds*

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There have been many studies attesting to the importance of nutrition in surgical patients. Derangements of protein metabolism in the acutely or chronically ill have been particularly emphasized. Impaired wound healing, increased susceptibility to anesthesia, shock and infection, and malfunction of the liver and intestinal tract are some of the complications observed in protein-deficient patients. Under these circumstances, operative deaths are more frequent, convalescence is prolonged, and mortality increased.

The possibility was suggested a number of years ago that disturbance in the metabolism of the essential amino acids is one of the important factors in the pathogenesis of the malnutrition following injury.[6] However, there are no conclusive data regarding this viewpoint.[5, 13, 22, 30] That amino acids are fundamental to protein synthesis and many energy processes in all animals is well known; yet, the quantitative study of these compounds in man is in its comparative infancy. Lack of appropriate methodology accounts in part for the scarcity of information in this important field.

A practical method for the quantitative fractionation of plasma amino acids was introduced in 1951, when Stein and Moore [23] perfected the method of ion exchange chromatography. Until that time, the little information available concerning individual amino acids of plasma had been obtained by the use of a microbiologic technic, a method based on the extent of growth of mutant bacterial strains on a medium containing the plasma sample. This method is open to the objection that these organisms are somewhat nondiscriminating in their choice of nutrient, and metabolize certain amino conjugates as well as single amino acids. The microbiologic method, then can be expected, in general, to give false high values for some plasma amino acids. By

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the ion exchange chromatographic technic on the other hand, differentiation of the free amino acids from amino conjugates is possible. Accordingly, we have used this technic.

The present study was undertaken with the end in view of determining whether any trends could be found in the plasma levels of the free amino acids of severely wounded soldiers from whom serial specimens were obtained beginning early after injury. These subjects were chosen because it is precisely this type of patient who demonstrates the greatest metabolic derangements after injury—that is, the seriously injured, but previously healthy and well nourished, young adult male.

These young men were wounded during the Korean hostilities in 1952–53. They were cared for by the Army Medical Service Graduate School Surgical Research Team and the Eighth Army Medical Corps.

Methods

Virtually all the samples analyzed were obtained as plasma in 2.5 per cent sodium citrate (1 ml. citrate to 5 ml. blood). The plasma samples were frozen immediately after separation of the cells and kept frozen thereafter. Deproteinization was accomplished by ultrafiltration in a Monel metal apparatus, previously described.[26] This method yields a filtrate with an approximate maximum molecular weight species of about 15,000 to 20,000.

The individual amino acids were separated by the ion exchange chromatographic technic devised by Stein and Moore,[23] and the analyses were accomplished by the photometric ninhydrin method of the same workers.[31] About 4 ml. of the plasma filtrates was required for the analysis. Of the common amino acids, tryptophane and arginine were not determined; the former is destroyed on the column, the latter requires additional hours for its separation.

An acid labile amino component (amino acid conjugate) was isolated in many samples. The fraction containing this component was evaporated in each case by a stream of air to about 2 ml. It was then hydrolyzed with 6N HCl in a sealed tube at 110° for 20 hours. The resultant hydrolysate was evaporated of its hydrochloric acid as above, made up to 4 ml. with water and re-chromatographed in the usual manner.

Other small molecular weight, plasma nitrogenous compounds were also determined. These are urea, creatine and creatinine, uric acid, purines, and total nonprotein nitrogen. Uric acid was estimated from measurements of absorption at 293 mμ, and 305 mμ. The validity of this determination on plasma ultrafiltrates, even in the presence of

large quantities of aromatic amino acids has been demonstrated by us.[27] Purines were grossly estimated from the absorption at 260 mμ.

Urea and NPN were analyzed at first by the micro method of Seligson and Seligson,[29] and later by a titrimetric modification. From 0.005 to 0.02 ml. of the ultrafiltrate was required for each of these analyses.

Creatine and creatinine were determined by application of the Jaffe reaction [11] to about 0.05 ml. of the plasma filtrate.

Our results are presented either as μM of nitrogen per 100 ml. ultrafiltrate (amino acids), or as mg. of nitrogen per 100 ml. ultrafiltrate (NPN, urea, creatine and creatinine, uric acid and purines). We have chosen to express the amino acids, in micromoles (μM), a unit possibly not as familiar as milligrams, but more logical. Since the ratio of nitrogen to total weight of one amino acid is different from that of any other, the expression of levels in terms of mg. of amino acid or mg. of nitrogen leads to a distorted impression of the relative quantitative importance of the various amino acids. By the use of the micromole unit, the amino acids are compared, in effect, molecule for molecule, regardless of size or weight.

Absorption spectra were obtained on ultrafiltrates, diluted 20 times with water, with the Beckman Du spectrophotometer in 1 cm. quartz cells. We have found that ultraviolet absorption spectra of plasma ultrafiltrates are useful in estimating certain plasma constituents, viz., uric acid and other purines, and the aromatic amino acids, phenylalanine, tyrosine and tryptophane. The ultrafiltrates are ideally suited for this procedure, since they have no absorbent material added to them in vitro, and they are naturally buffered near pH 7.

Results

Plasma Nonprotein Nitrogen Components (NPN, Urea, Creatine Plus Creatinine, Uric Acid, Other Purine Nitrogen, and Amino Acids)

We studied variations in the plasma amino acid levels and the other NPN components, in five critically wounded young soldiers. Four of those men died. Shock and renal failure were present in all in varying degrees. In four, the renal failure was persistent. Although the plasma urea concentrations rose as much as 30 times normal, the total free plasma amino nitrogen concentration remained near normal.

Extracorporeal dialysis by a Kolff-type artificial kidney was performed on three patients. Temporary biochemical and/or clinical improvement followed the dialyses, but eventually, all died. The

total free amino nitrogen concentration was little affected by the dialysis procedures. The plasma levels of certain individual amino acids were often near normal in spite of the serious injury, shock, severe renal failure, near starvation, infection and extracorporeal dialysis. In contrast, the levels of some other amino acids changed markedly. It is likely that any wide fluctuations of the individual amino acids indicate a basic upset in the body economy.

In the following section, the observations in each individual patient will be described.

Patient No. 1, T. M. L. This 25-year-old Korean was wounded by an M–1 30-caliber armor-piercing bullet. Resuscitation (including infusion of 1 liter of blood) was begun within an hour of injury and he was never in severe shock preoperatively. Operation, performed under pentothal, nitrous oxide and other anesthesia, was begun 2½ hours after injury. Five liters of blood was infused during the operation, which lasted 5 hours. The missile had penetrated the right lung and pleural cavity, traversing the thickness of the liver, lacerating the vena cava (4 mm.), and tangentially wounding the superior pole of the left kidney. A left nephrectomy was done; the vena cava laceration was repaired; gelfoam was packed into the missile tract in the liver; an intercostal Foley catheter was inserted into the right pleural space. There was no uncontrollable hemorrhage or hypotension during surgery. Penicillin and streptomycin were given.

Throughout his course, he did not move his legs, and had absent reflexes and sensation in his lower extremities. A collapsed vertebra at D–12 was demonstrated, presumably due to damage from the missile, and it was assumed that his spinal cord had been damaged at about this point. Postoperatively, he was oliguric and was transferred on the second post-injury day to the Renal Insufficiency Center.

During the next 2 weeks, he ran a stormy course. Severe pneumonia, high fever, weight loss, persistent renal dysfunction, nitrogen retention, acidosis and hyperkalemia were important complications. He received aureomycin and, later, chloramphenicol. Extracorporeal dialysis on an artificial kidney of the Kolff type was carried out on the fourth post-injury day because of potassium toxicity. The resultant reductions in plasma K and NPN concentrations were only transient, however, and repeat dialyses were performed on the eighth and twelfth day after injury.

Our first analyses were done on a plasma sample obtained on the latter day, just prior to dialysis. The plasma K was 7.7 mEq./L., Na, 152 mEq./L.; Cl, 104 mEq./L.; CO_2, 12 mEq./L.; NPN and urea were 392 and 336 mg. per 100 cc. respectively. Purine, uric acid, creatine and creatinine N were moderately elevated, while the *total amino acids were slightly low.* Aspartic acid, methionine, phenylalanine, and histidine were somewhat elevated, while the other amino acids were all lower than normal (Table 5). The effect of the dialysis on the nonprotein nitrogen components will be discussed later in a special section devoted to this matter (Effect of Extracorporeal Dialysis on the Plasma Nonprotein Nitrogen Components).

Following this dialysis, he continued to deteriorate, with increasing respiratory tract infection, spreading wound infections, high fever, uremia, hyperkalemia and melena. A fourth dialysis, with again only temporary improvement, was done on the sixteenth day.

Tracheotomy was done to enable suction of tracheobronchial secretions. Because of a spiking fever, right upper quadrant pain and fixation of the diaphragm on the right, extraperitoneal exploration of the right subdiaphragmatic space was carried out on the eighteenth day. No abscess was found. The next day, he suddenly died of respiratory failure following aspiration.

The postmortem diagnoses were surgically repaired vena cava, liver and diaphragm, surgical absence, left kidney; atelectasis, right lower lobe and right middle lobe of lung; emphysema, left side of chest; abscess, left lower lobe of lung; pneumothorax, left; edema, right upper lobe of lung, bronchopneumonia (?); hematoma, liver and diaphragm; hypertrophy, right kidney and congestion of renal medulla; abscess, retroduodenal region; splenomegaly; malaria (?); trichuriasis; decubiti, left buttock and sacrum.

Patient No. 2, F. H. This 23-year-old American soldier was burned and wounded when a trip flare exploded. His legs and lower trunk were burned and a flaming missile penetrated his abdomen. He was hypotensive for only a brief time preoperatively; during this time he received 1,500 cc. of blood and 750 cc. of plasma. Penicillin was given.

Operation was begun 7 hours after injury and lasted 5 hours. The lower abdominal wall was severely burned, and most of the small intestine was charred and necrotic. The anterior abdominal wall was débrided with excision of the external oblique muscle, rectus muscle and fascia, scrotum and testes. His penis was severely burned. All of the ileum and most of the jejunum were resected, and an end-to-side jejuno-transverse colostomy was done. A small portion of proximal jejunum were resected and an end-to-end jejuno-jejunostomy was done. The terminal ileum was closed and exteriorized with the cecum. The total, circumferential deep burns of both legs were then débrided with removal of all skin to subcutaneous tissue. Pressure dressings were applied. He remained moderately hypotensive (about 90/60) throughout the operation and received 5,500 cc. of blood.

Between the first and seventh post-wound days, he did relatively well, with stable blood pressure, daily urine outputs between 2,000 and 3,000 cc. and urine specific gravity up to 1.028. He ran a low-grade fever of about 100° with occasional spikes over 102°. He received a daily total of 1,000 to 2,000 cc. of blood plus plasma, as well as 3,000 to 5,000 cc. of about half and half glucose in saline and glucose in water. The BUN never rose above 45 mg. per 100 cc. during this time. On the sixth day he developed icterus, which gradually increased.

On the seventh post-injury day, a homologous split-thickness skin graft (from a cadaver) was applied to his left thigh and leg, under brief (10-minute) N_2O anesthesia. Following operation, his urine output dropped abruptly to less than 10 cc. per hour. His general condition deteriorated, and he became lethargic and began vomiting. Because of continuing oliguria, he was transferred by helicopter to the Renal Insufficiency Center on the ninth day.

On admission, he was jaundiced and his temperature was 101°. The lower abdominal wall was almost all gone, except for a thin layer of peritoneum and transversalis fascia. There was a profuse, dirty watery and possible fecal discharge between the tissue layers at the edge of the burned area. There were large masses of necrotic tissue in the groin area. The deep burn of the buttocks was crusted. His penis was black and necrotic. Penicillin and streptomycin were given.

Admission plasma chemistries: Na, 160 mEq./L.; K, 5.8 mEq./L.; Cl, 110 mEq./L.; CO_2, 23.4 mEq./L. The hematocrit was 31 percent. The plasma nonprotein nitrogen fractions were measured for the first time on this day (Table 1).

This plasma NPN and urea nitrogen were very high, 336 and 269 mg. per 100 cc. respectively. The uric acid, other purines, and creatine plus creatinine fractions were also elevated—2 to 3 times normal. In contrast, the total of the 19 free amino acids was normal. However, the distribution of the individual amino acids was abnormal. Glutamic acid, aspartic acid, phenylalanine and methionine were 2 to 2½ times normal; isoleucine, tyrosine and histidine 1½ times normal; proline, glycine, lysine and the glutamine-serine-asparagine complex were about half normal; threonine, alanine, valine, leucine and cystine were normal.

Table 1. Ultrafilterable Nitrogen Components of Plasma

(Patient F. H.)

Day Post-Injury	9	10	Normal
mg. N/100 ml. Plasma Ultrafiltrate			
NPN	336. 0	400. 0	26. 0
Urea N	269. 0	364. 0	15. 4
Creatine+Creatinine N	7. 2	9. 8	2. 5
Uric Acid N	5. 2	9. 1	1. 5
Purine N	2. 1	6. 4	1. 0
Amino Conjugate N		5. 4	0. 2
Amino N	3. 6	4. 3	3. 5
μM./100 ml. Plasma Ultrafiltrate			
Aspartic Acid	5. 5	4. 1	2. 4±1
Threonine	11. 7	11. 7	13. 1±2
Glutamic Acid	31. 4	10. 0	13. 8±8
Proline	9. 1	19. 0	23. 0±4
Glycine	19. 0	19. 8	24. 0±2
Alanine	31. 0	34. 0	31. 9±4
Valine	28. 0	31. 6	23. 0±0. 5
Methionine	4. 3	4. 5	2. 2±0. 5
Isoleucine	11. 2	12. 6	7. 5±0. 5
Leucine	12. 6	17. 6	11. 6±0. 5
Tyrosine	10. 0	13. 4	6. 0±0. 5
Phenylalanine	17. 9	28. 2	7. 1±0. 5
Histidine	21. 4	30. 6	14. 1±2
Lysine	7. 2	22. 6	16. 1±2
Taurine	5. 0	4. 5	4. 8±1
Glutamine+Serine+Asparagine	28. 6	44. 6	49. 8±3

He continued virtually anuric and late on the tenth post-wound day, he suddenly began having respiratory difficulty and became unresponsive rather abruptly. He was flaccid, with weak deep tendon reflexes and appeared to have respiratory paralysis. He was immediately given 3.75 gm. $NaHCO_3$ intravenously, followed by 80 cc. of 3 per cent saline, with prompt improvement of respiration and revival of consciousness. A blood sample drawn just before this emergency treatment showed that the serum potassium was 8.3mEq./L. (Earlier that day, plasma Na was 156 mEq./L.; K, 7.5 mEq./L.; Cl, 113 mEq./L.; CO_2, 22 mEq./L.) At the same time, NPN, purine N, uric acid N, and creatine and creatinine N had also risen (table 1). Despite the extremely high NPN, amino acid N was only slightly elevated (4.3 mg. per 100 cc.). Most of the amino acids

remained at their previous levels, or rose. Threonine, proline, alanine and taurine were normal at this time. Glutamic acid, in contrast to the other amino acids, fell sharply. There was a corresponding rise in that function containing glutamine.

In the next few hours, he became progressively more hypotensive despite administration of hypertonic saline bicarbonate, glucose and insulin, and noradrenalin, and died before dialysis could be performed.

Postmortem diagnoses were second and third degree burns of abdominal wall, buttocks, perineum, penis, scrotum and legs; diffuse phlegmonous inflammation and necrosis, anterior abdominal wall; ileocolic anastomosis, and cecostomy; skin grafts, left leg; bilateral castration and surgical absence of scrotum; hepatitis, acute, toxic, renal hypertrophy, bilateral, with clinical renal insufficiency; acute hemorrhagic esophagitis with massive bleeding; focal fat necrosis, head of pancreas, minimal; pulmonary edema, moderate; cerebral edema, moderate; arachnoid cyst, right temporal lobe of brain; icterus.

Patient No. 3, K. D. This 22-year-old American soldier was wounded by shell fragments. The wounds included multiple perforations of the small bowel, multiple perforations of the sigmoid, two holes in the urinary bladder, severe comminuted, compound fractures of the left femur and left tibia and multiple soft tissue wounds of the buttocks and abdominal wall.

Prior to operation, he was given 4,000 cc. of blood. His blood pressure was normal.

Operation, lasting 7 hours, was begun 6 hours after injury. Operation consisted of repair of the eight holes in the small bowel, three bowel resections, colostomy, cystostomy and débridement of the many wounds. With the onset of pentothal induction (later nitrous oxide-oxygen-ether anesthesia) his blood pressure fell from 106/84 to 66/42, and his pulse rose from 100 to 116. Four milligrams norepinephrine dripped in with 500 cc. of blood immediately raised his pressure from 90/50 to 100/60. Later in the operation, his blood pressure was maintained with difficulty despite the administration of considerable blood with added norepinephrine. At operation, peritoneal contamination was massive. He was given 3,500 cc. of blood during operation while the measured operative blood loss was 1,670 cc.

A hemoclastic reaction was strongly suggested by a drop in his white blood cell count 1 hour after operation to 1,850 and abnormal clot formation. His platelet count at this time was 710,000; hematocrit, 55 per cent. His plasma volume (Evans Blue) was 2,220 cc. and calculated blood volume 4,720 cc. His blood pressure was about 90 to 100 systolic and 50 to 60 diastolic; pulse rate, around 120 per minute. One thousand cc. of dextran was then given over a period of 4 hours. No changes in blood pressure or pulse occurred. His hematocrit was then 42.5 per cent; plasma volume, 3,070 cc. and blood volume, 5,200 cc.

Throughout the first postoperative night, his blood pressure ranged about 80/50; pulse, 130; respirations, 40. Fifteen hundred cc. of blood and the same amount of dextran were then given over a period of 7 hours, with a rise in his blood pressure to 112/80 and a drop in his pulse rate to 104. His plasma volume had risen to 3,750 cc. and his blood volume to 5,980 cc. This was 24 hours postoperatively. Five hundred cc. more blood was given.

At this time, his plasma urea concentration was 74 mg. per 100 cc. Plasma uric acid concentration was slightly elevated as were creatine and creatinine; the purine fraction and total amino acids were essentially normal. Methionine, glutamic acid, tyrosine, aspartic acid and proline were normal; histidine, taurine, alanine and phenylalanine were somewhat elevated; leucine, isoleucine, lysine, valine, threonine and glycine were somewhat low (Table 2).

Table 2. Ultrafilterable Nitrogen Components of Plasma (Patient K. D.)

Day Post-Injury	1½	2½	3½	5	6	7	8	11	12	Normal
	mg. N/100 ml. Plasma Ultrafiltrate									
Urea N	74. 2	107. 0	98. 5	84. 0	104. 0	116. 0	122. 0	42. 4	46. 4	15. 4
Creatine + Creatinine N	4. 2	7. 0	3. 7	2. 4	3. 3	3. 1	3. 2	2. 7	2. 6	2. 5
Uric Acid N	2. 4	3. 0	2. 4	3. 2	2. 9	2. 8	2. 4	2. 0	1. 7	1. 5
Purine N	1. 1	2. 2	0. 9	1. 7	0. 5	0. 5	0. 5	1. 2	1. 4	1. 0
Amino Conjugate N				1. 48			1. 42	1. 2		0. 2
Amino N	3. 1	4. 4	3. 5	3. 0	4. 8	4. 0	4. 6	2. 8	2. 8	3. 5
	μM./100 ml. Plasma Ultrafiltrate									
Aspartic Acid	3. 0	6. 9	6. 6	7. 0	9. 2	6. 9	8. 2	5. 2	4. 1	2. 4±1
Threonine	10. 1	20. 0	14. 3	12. 5	17. 3	16. 8	21. 1	9. 0	7. 8	13. 1±2
Glutamic Acid	11. 0	14. 8	8. 5	12. 5	11. 8	10. 9	10. 4	20. 1	26. 1	13. 8±8
Proline	20. 0	30. 6	11. 8	11. 7	27. 7	17. 6	28. 0	3. 0	1. 9	23. 0±4
Glycine	16. 2	22. 9	13. 5	16. 4	24. 6	22. 6	31. 2	17. 3	16. 0	24. 0±2
Alanine	38. 0	66. 0	28. 6	33. 0	55. 0	47. 2	60. 1	19. 2	18. 6	31. 9±4
Valine	17. 2	21. 3	25. 7	36. 8	42. 1	44. 1	22. 0	26. 4	19. 2	23. 0±0. 5
Methionine	1. 7	3. 1	6. 4	2. 4	8. 1	4. 3	5. 9	2. 8	trace	2. 2±0. 5
Isoleucine	1. 2	5. 7	7. 9	5. 6	13. 0	8. 8	8. 5	4. 8	6. 1	7. 5±0. 5
Leucine	8. 2	16. 1	17. 3	14. 6	25. 7	22. 5	18. 3	13. 8	19. 9	11. 6±0. 5
Tyrosine	6. 7	7. 7	7. 2	7. 0		10. 0	11. 7	7. 2	5. 6	6. 0±0. 5
Phenylalanine	9. 1	12. 2	12. 7	14. 8		12. 8	12. 7	21. 5	25. 8	7. 1±0. 5
Histidine	25. 5	11. 7	30. 7	5. 1	20. 4	2. 0	16. 5	8. 6	5. 5	14. 1±2
Lysine	12. 8	32. 5	18. 3	6. 6	26. 9	13. 5	28. 9	14. 8	22. 2	16. 1±2
Taurine	7. 6	4. 6	4. 6	trace	trace	trace	3. 6	8. 9	16. 2	4. 8±1
Glutamine + Serine + Asparagine	30. 0	39. 8	32. 6	25. 7	38. 4	38. 0	42. 1	15. 9	14. 9	49. 8±3

During the second postoperative night his blood pressure again fell to 94/64, and his pulse rose to 140 per minute. No bleeding was evident. Five hundred cc. of dextran was given with no obvious improvement.

Fifty-five hours after injury, forty-eight hours after operation, infusion of noradrenalin in glucose in water intravenously was begun. His blood pressure gradually rose to 120/70, but his pulse continued at a rapid rate (140 per minute). Oxygen, per nasal catheter, had changed the appearance of his skin from a cyanotic to a reddish flush. Throughout the day his blood pressure was maintained at 115–125/65–80 and his pulse rate gradually fell to 115 per minute. The infusion of noradrenalin was gradually slowed and stopped the next day. His blood pressure was maintained thereafter at normal levels.

Sixty-six hours after injury and fifty-nine hours after operation, the NPN components had all risen. The amino nitrogen was now 4.4 mg. per 100 cc., while urea nitrogen was 107 mg. per 100 cc. Of those amino acids previously normal, all but glutamic acid had risen; alanine and phenylalanine continued to rise, while taurine and histidine fell; the previously low amino acids all rose, some above normal.

Ninety-one hours after injury, his plasma volume was 3,600 cc. and blood volume, 6,100 cc. His blood pressure had been normal for about 36 hours. The plasma total free amino nitrogen concentration was normal, while plasma urea was still elevated (99 mg. per 100 cc. uric acid nitrogen was 2.4 mg.; purine nitrogen, 0.9 mg.; creatine plus creatinine nitrogen, 3.7 mg.) Methionine, aspartic acid and histidine were greatly elevated; leucine, tyrosine and phenylalanine were elevated slightly; isoleucine, lysine, valine, alanine, threonine, taurine and glutamic acid were normal; proline and glycine were low.

After the third postoperative day, his course was uneventful. Plasma urea continued elevated through the eighth post-injury day. Creatine plus creatinine and purine nitrogen remained near normal, uric acid gradually fell to normal, while the total amino nitrogen fluctuated slightly around normal. Aspartic acid continued to rise through the sixth postoperative day, and then fell steadily to the eleventh day. Methionine fell transiently through the fourth post-injury day, only to rise to its peak (3 times normal) on day 6 post injury. Thereafter, it too fell. Valine, tryosine, alanine, threonine, glycine, leucine and isoleucine reached their highest values (about twice normal) between days 6 and 8 post injury, and then fell. In contrast, phenylalanine, glutamic acid and taurine, which were respectively high, normal and low during the first week, rose thereafter, and all were high on the last day of study. Histidine and lysine fluctuated widely from day to day from above to below normal.

Patient No. 4, A. K. This 22-year-old American soldier received a perforating abdominal wound by an M–1 rifle bullet. His blood pressure, which was 115/85 when first recorded at 2 hours after injury, fell to 90/60 1 hour later. Five hundred cc. of blood was started and he was sent to a Mobile Army Surgical Hospital by ambulance. Four and three-quarters hours after injury he had received a total of 1,000 cc. of blood and his blood pressure was 120/80. He had been given penicillin and tetanus toxoid.

Laparotomy was begun 7 hours after injury after the patient had received an additional 1,500 cc. of blood. Anesthesia consisted of pentothal and nitrous oxide-oxygen-ether. The wound was a through-and-through perforation of the abdomen with resulting perforating wounds of the liver, kidney and colon. About 1,500 cc. of blood was aspirated from the abdomen during surgery. A colostomy and drainage of the liver and kidney wounds were performed.

During operation, his blood pressure became imperceptible for about 30 minutes, but was elevated to 60 or 80 systolic as noradrenalin was added to the blood. He was given 7,500 cc. of blood during the operative procedure which lasted 5 hours. Operative blood loss was measured at 2,420 cc.

Our first analysis was performed on blood taken 12 hours after injury, immediately after operation. His hematocrit was high, about 70 per cent. Plasma urea concentration was moderately elevated (36 mg. per 100 cc.) while all the other nonprotein nitrogen components were normal. Methionine, alanine, lysine, leucine, taurine, phenylalanine and glutamic acid were elevated; tyrosine, aspartic acid, proline, threonine, glycine and isoleucine were low; valine and histidine were normal (Table 3).

During the next 24 hours, he received 2,500 cc. of gelatin, 500 cc. of dextran, and 3,000 cc. of 5 per cent glucose in water, some of which contained terramycin. His urine output was low, blood pressure was normal, but pulse and respirations were rapid. Plasma urea nitrogen had risen, as had all the other NPN components. Total amino nitrogen was definitely elevated (5.8 mg. per 100 cc.). Valine stayed normal, and lysine, glutamic acid and taurine fell. All the other amino acids rose. During the next day, he continued oliguric; blood pressure was normal. Aureomycin was begun. His plasma urea rose, as did the NPN components except the total amino nitrogen, which fell slightly below normal. All the amino acids fell, except for isoleucine, which stayed normal, methionine, which remained high, and taurine, which rose. Plasma Na was 125 mEq./L.; K, 5.7 mEq./L.

Because of persistent oliguria, he was transferred to the Renal Center on the second post-injury day. On arrival, he was feverish and toxic with signs of left lower lobe pneumonia. His sputum was positive for Staphylococcus and Proteus, the latter sensitive only to chloromycetin. The response to chloromycetin, however, was poor. The patient became clinically jaundiced, presumably secondary to the liver injury, the serum bilirubin reaching a peak of 14.5 direct and 25.3 total 5 days after injury.

He was on constant Wagensteen suction and lost 600 to 2,200 cc. of dark fluid daily. Oral feeding was not possible. Varying quantities of 50 per cent glucose in water containing 2 gm. of vitamin C, 25 mg. of vitamin K, and 10 mg. of thiamine were given daily by intravenous catheter.

Hyperkalemia was well controlled, the plasma level dropping from 7.6 mEq./L. on admission to 5.8 by the next morning. The toxic effects of potassium were also counteracted later with intravenous calcium gluconate.

Throughout his course, this patient was in good fluid balance. Diuresis occurred immediately and, thereafter, the urinary output was about 2,000 cc. daily, but the plasma NPN continued to rise, reaching a peak of 430 mg. per 100 cc. on the seventh post-wound day. He was uremic, icteric and septic (pneumonia, wound infections and bacteremia). At this time, he underwent extracorporeal dialysis by an artificial kidney of the Kolff type because of uremia, drowsiness, nausea, tremulousness, occasional periods of disorientation, and a severe hemorrhagic diathesis. The results of the dialysis were satisfactory chemically, but the clinical condition of the patient did not improve and in retrospect the symptoms probably were due to sepsis rather than to uremia. Just prior to dialysis, plasma Na was 130 mEq./L.; K, 6.8 mEq/L.; Cl, 98 mEq/L.; CO_2, 13 mEq/L. The plasma urea nitrogen was 377 mg. per 100 cc. Creatine plus creatinine, purine and uric acid nitrogen were also much elevated, while total amino nitrogen was slightly high. Phenylalanine, histidine, aspartic acid, methionine, tyrosine, leucine, isoleucine and lysine were high. All the rest were normal except taurine, which was low. Following dialysis, all the NPN components other

Table 3. Ultrafilterable Nitrogen Components of Plasma (Patient A. K.)

Day Post-injury	½	1	1½	2	7 Pre-dialysis	7 Post-dialysis	8	Normal
	mg. N/100 ml. Plasma Ultrafiltrate							
Urea N	36. 4	91. 0	111. 0	132. 0	377. 0	113. 0	177. 0	15. 4
Creatine + Creatinine N	2. 3	4. 9	8. 0	10. 9	9. 8	5. 4	11. 3	2. 5
Uric Acid N	1. 5	2. 1	3. 2	3. 7	7. 1	3. 3	4. 6	1. 5
Purine N	0. 4	0. 9	1. 5	2. 8	4. 3	1. 8	3. 2	1. 0
Amino Conjugate N	0. 33			0. 64	2. 10		1. 32	0. 2
Amino N	3. 2	5. 8	5. 1	2. 7	4. 1	4. 8	4. 5	3. 5
	μM./100 ml. Plasma Ultrafiltrate							
Aspartic Acid	0. 8		4. 9	2. 3	5. 4	5. 6	9. 9	2. 4±1
Threonine	10. 4	24. 7	22. 7	8. 1	13. 6	24. 0	14. 4	13. 1±2
Glutamic Acid	29. 5	20. 6	15. 0	6. 1	18. 0	14. 1	10. 4	13. 8±8
Proline	10. 4	28. 1	31. 5	15. 2	29. 8	33. 0	29. 0	23. 0±4
Glycine	16. 4	32. 1	33. 8	10. 4	22. 2	29. 5	25. 0	24. 0±2
Alanine	49. 0	104. 0	70. 0	31. 0	28. 2	55. 1	56. 5	31. 9±4
Valine	25. 0	20. 5	28. 2	16. 9	22. 9	27. 3	21. 0	23. 0±0. 5
Methionine	1. 1	6. 1	5. 1	5. 8	6. 6	7. 5	7. 4	2. 2±0. 5
Isoleucine	1. 3	8. 5	7. 4	7. 8	11. 7	7. 4	6. 7	7. 5±0. 5
Leucine	17. 3	21. 6	17. 4	13. 8	17. 7	19. 1	14. 4	11. 6±0. 5
Tyrosine	4. 8	11. 4	9. 7	6. 8	8. 6	11. 2	8. 0	6. 0±0. 5
Phenylalanine	9. 8	28. 2	20. 0	10. 6	12. 1	14. 7	7. 3	7. 1±0. 5
Histidine	15. 5	22. 7	33. 3	17. 2	22. 0	28. 0	3. 8	14. 1±2
Lysine		33. 3	23. 4	13. 2	29. 6	36. 2	16. 6	16. 1±2
Taurine	10. 1	3. 6	5. 3	9. 3	1. 7	trace	0. 5	4. 8±1
Glutamine + Serine + Asparagine	16. 0	43. 4	35. 3	14. 8	40. 0	30. 3	39. 5	49. 8±3

than the amino acids dropped sharply. (A detailed description of the chemical findings will be found in the section on "Extracorporeal Dialysis.")

During the next day the patient continued running a septic course. He had lost 30 pounds. Plasma Na was 146 mEq./L.; K, 6.2 mEq./L.; CO_2, 20 mEq./L. There was a rise in urea, uric acid, purine and creatine plus creatinine nitrogen. The total amino acids stayed slightly elevated. Aspartic acid, alanine, leucine, methionine and tyrosine were elevated; histidine and taurine were low; all the rest were normal. No subsequent plasma samples were analyzed.

Bleeding into the nasopharynx, bowel and skin occurred and persisted in spite of fresh blood transfusions and large doses of vitamin K. Frequent hypotensive episodes occurred but could be controlled with blood. Noradrenalin in increasing amounts was required to maintain blood pressure, but finally the patient became refractory to the drug and transfusion and he died in circulatory collapse on the twelfth post-wound day. The clinical impression was that the uremia was reasonably well controlled and that death was due to overwhelming sepsis.

Pathologic findings included pulmonary infarcts of the left lower lobe, acute phlebitis of the inferior vena cava, septicemia (*B. proteus*), fibrinopurulent peritonitis, diffuse mucosal hemorrhages of the small intestine, gunshot wound

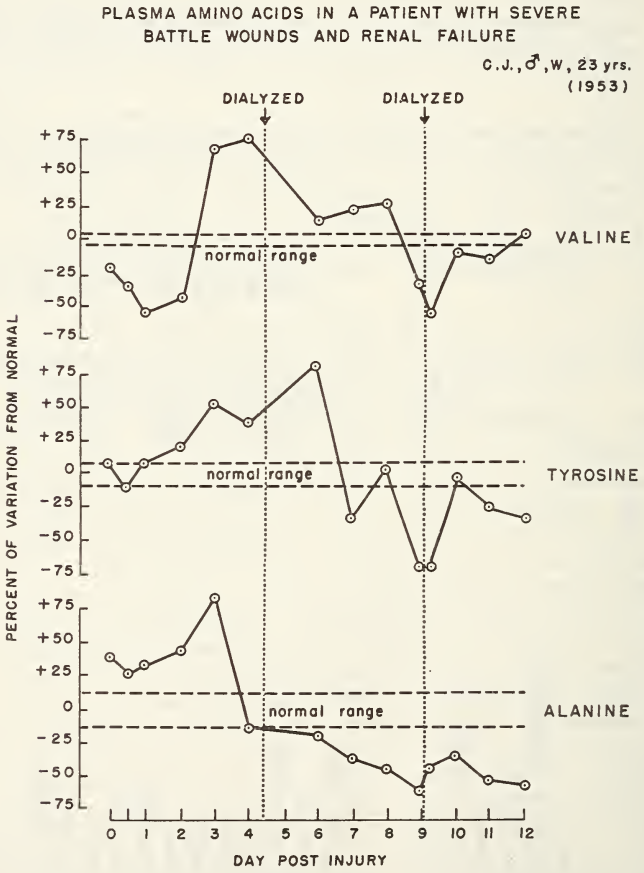

FIGURE 1.

of the right lobe of the liver, an abscess containing *B. proteus* in the liver, and central necrosis of the right lobe of the liver. There was mild lower nephron nephrosis, a few areas of focal glomerulitis, traumatic destruction of the lower pole of the right kidney, and multiple abscesses of the right kidney containing *B. proteus*.

Patient No. 5, C. J. This 26-year-old American soldier was wounded by mortar shell fragments. The wounds included laceration of the scalp, perforations of the liver and kidney, traumatic amputation of the right thigh, and multiple soft tissue injuries.

On arrival at battalion aid station shortly after injury, he was unconscious and his blood pressure was unobtainable. After the intravenous infusion of 320 cc. of albumin and 1,500 cc. of isotonic saline his blood pressure was 80/40. He was then evacuated by helicopter to a Mobile Army Surgical Hospital.

On arrival (2 hours after injury) he was still unconscious (cerebral concussion) and his blood pressure and pulse were unobtainable. Within 25 minutes, he was given 2,500 cc. of blood, but his blood pressure remained unobtainable. His pulse was barely palpable at a rate of 110 per minute. His right leg was amputated without anesthesia in the emergency room. In the next 4 hours, he was given 2,500 cc. more blood. His blood pressure was 128/80; pulse rate, 120 to 130, and respiratory rate, 20. Our first analyses were done on a plasma sample obtained at this time (Figs. 1 to 8). NPN, urea nitrogen and uric acid

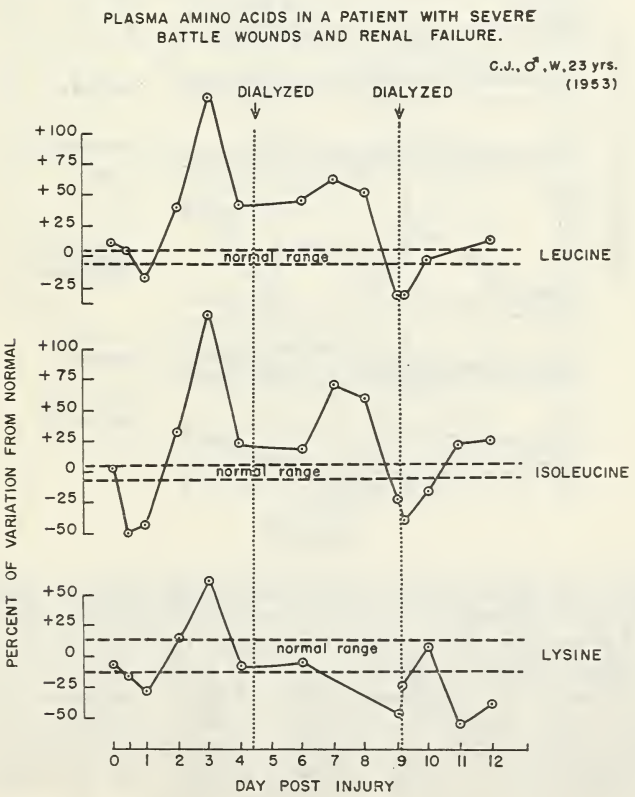

FIGURE 2.

nitrogen were already elevated, while creatine plus creatinine nitrogen, purine nitrogen and total amino nitrogen were normal. Glutamic acid was twice normal; alanine and phenylalanine were slightly elevated; threonine, glycine, valine and histidine were slightly low; all the rest were normal. Plasma Na was 158 mEq./L.; K, 3.8 mEq./L.

Operation was delayed for 3 more hours because he had not regained consciousness. During this time he received another 1,000 cc. of blood. His blood pressure had remained stable at about 130/80 and his pulse between 120 and 130 per minute.

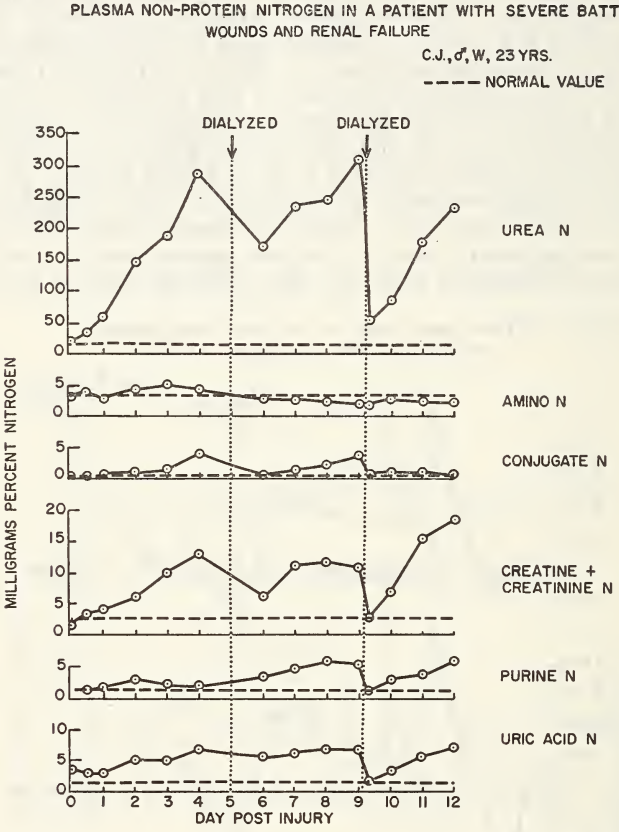

FIGURE 3.

Operation was begun 10 hours after injury, under atropine, pentothal and nitrous oxide-ether anesthesia. His blood pressure immediately fell from 140/80 to 90/60, but his pulse rate remained unchanged. His blood pressure remained low throughout most of the operative procedure (which lasted 3 hours) despite the administration of an additional 3,500 cc. of blood. Operative blood loss, by the washed sponge technic, was 3,030 cc. Operation consisted of exploratory laparotomy, drainage of the liver and kidney perforations, re-amputation of the thigh and débridement of many soft tissue injuries. He was found to have fractures of the femur proximal to the line of amputation.

Towards the end of the operation, noradrenalin was added to the infused blood. A rise in blood pressure was immediate. Plasma NPN and urea had risen still further; creatine and creatinine nitrogen, uric acid and purine nitrogen were slightly elevated, while the total amino nitrogen was still normal. Glutamic acid, phenylalanine and alanine were still elevated; taurine and aspartic acid had risen; all the others were normal except methionine, glycine and valine, which were low. Plasma Na was 146 mEq./L.; K, 5.4 mEq./L.

Noradrenalin was used throughout the night after injury to maintain his systolic pressure between 105 and 120. The rate of noradrenalin administration was gradually decreased and successfully stopped 24 hours after operation. On

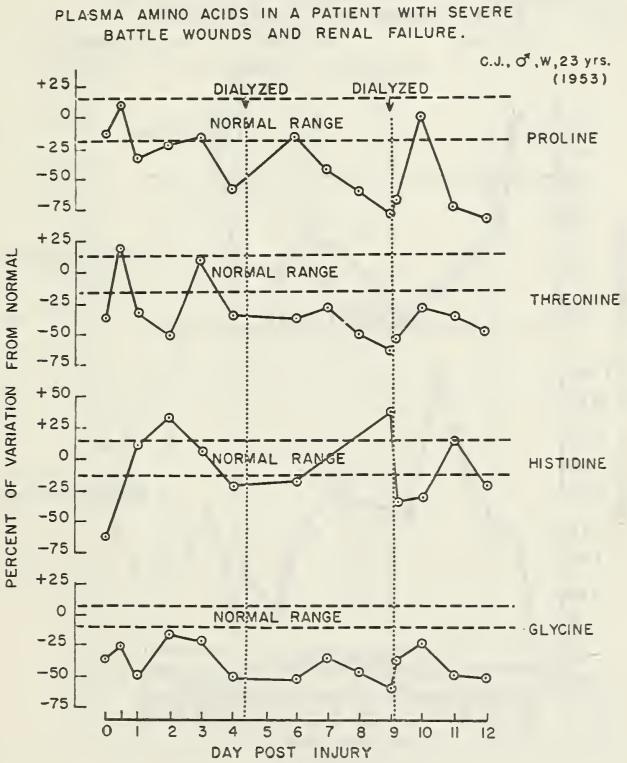

FIGURE 4.

the morning of the first postoperative day, the various NPN components, other than amino N, were still elevated. NPN, urea and uric acid were rising. The total amino nitrogen, on the other hand, had fallen below normal. Phenylalanine and alanine were still elevated while valine, glycine, proline, threonine, methionine, leucine, isoleucine and lysine were below normal. The other amino acids were normal. Plasma Na was 167 mEq./L.; K, 5.1 mEq./L.

By noon of the second day post injury, he was still unconscious; his blood pressure had risen to 140 to 160 systolic; pulse rate was 110 to 120; respiratory rate, 24 to 32. His temperature ranged from normal to 102° orally. He had received 500 mg. of terramycin, 1,000 cc. of 5 per cent glucose and water, 100

mg. of thiamine and 1,000 mg. of vitamin C. His 12-hour urine output was only 115 cc.

On admission at the Renal Center, he was semicomatose; blood pressure was 140/80; temperature, 101°. His serum potassium was 7.1 mEq./L.; sodium, 131; CO_2, 30; chloride, 86; hematocrit, 37 per cent NPN, 114 mg. per 100 cc. Because of the probability of pulmonary complications, he was tracheotomized and put on a Stryker frame on the third day after injury. His NPN components rose progressively during the next few days and all except the amino nitrogen reached very high levels. The latter was only moderately elevated. Taurine was an

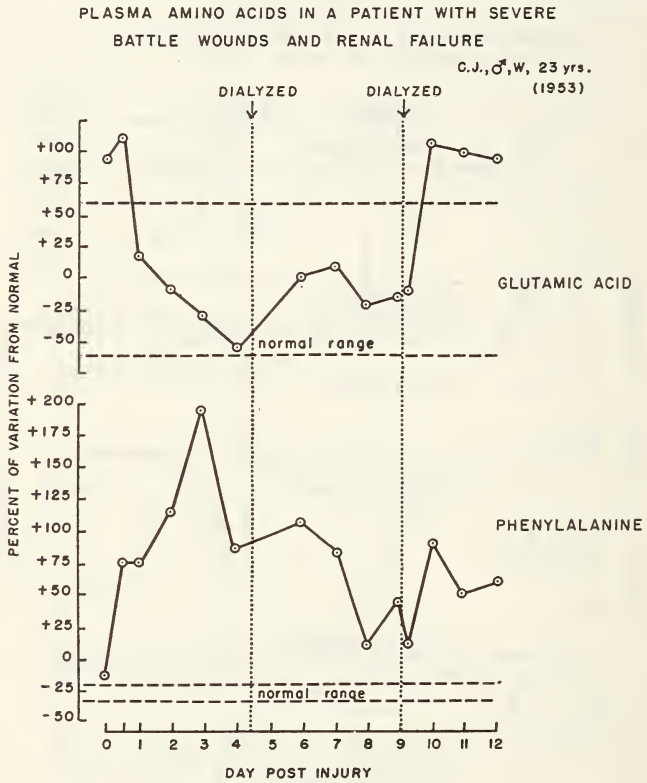

FIGURE 5.

exception among the amino acids, rising to 12 times normal on the fourth post-injury day. Methionine, leucine, isoleucine, lysine, phenylalanine, valine, tyrosine and alanine all rose progressively through the third post-injury day; all but valine fell the next day. Glutamic acid, proline, threonine and histidine had remained normal or slightly low, while glycine was persistently low. Aspartic acid fluctuated above and below normal.

There was an initial drop in his serum K concentration, but then a progressive increase to 8.2 mEq./L. on the fourth post-injury day with broadening of the QRS component on EKG. The serum Na, initially 131 mEq./L., rose to 139 mEq./L. Chlorides stayed constant at about 85 mEq./L., and CO_2 gradually

dropped from 29.6 to 15.7 mEq./L. After emergency infusion of calcium gluconate, he was dialyzed by the artificial kidney (Kolff-type) with an excellent chemical result, but with little change in his general condition. The chemical effects of the dialysis will be discussed in the section "Extracorporeal Dialysis."

During the next 5 days he was periodically conscious. He became increasingly jaundiced. Some of his wounds were grossly infected and bled excessively following débridement. He was still oliguric, and the plasma NPN components

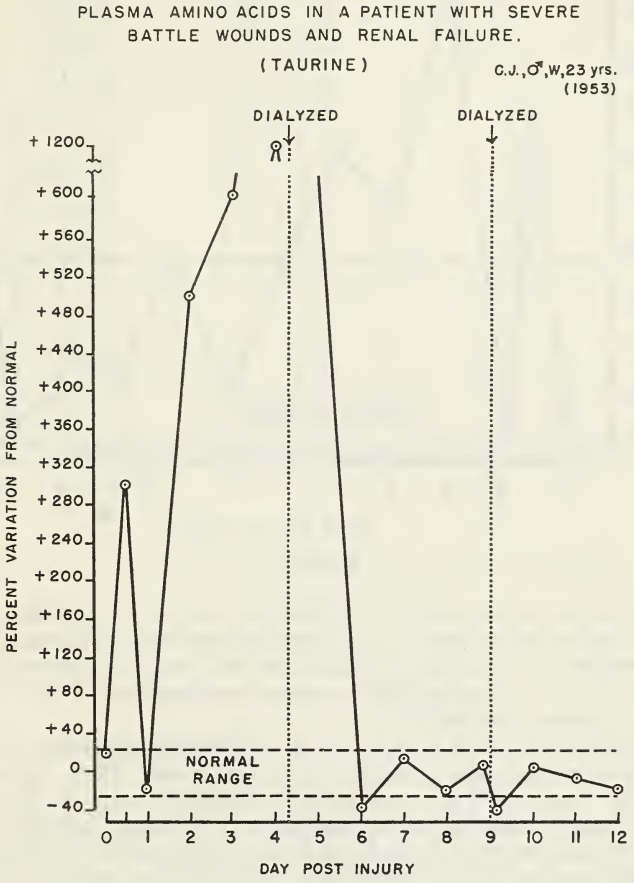

FIGURE 6.

other than amino nitrogen rose steadily to levels similar to those just prior to the first dialysis. In contrast, the total amino nitrogen steadily decreased and reached the very low level of 2 mg. per 100 cc. on the ninth post-injury day. Valine, tyrosine, alanine, aspartic acid, leucine, isoleucine, proline and threonine all fell, while taurine remained normal and glycine persistently low. Plasma K concentration which was 4.2 mEq./L. immediately after dialysis, on the fifth post-wound day, rose progressively to 8.6 mEq./L. by the ninth day. Plasma sodium was 139 mEq./L. after the first dialysis, and rose to 149 mEq./L.; chlo-

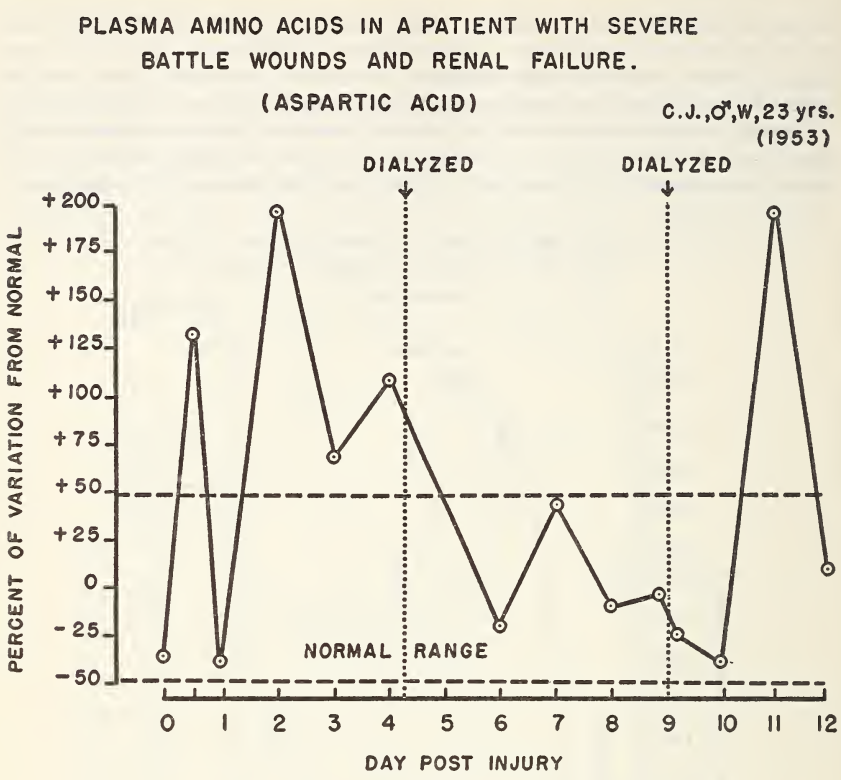

FIGURE 7.

ride fell from 104 to 93 mEq./L., and CO_2 fell from 26 to 18 mEq./L. On the ninth post-injury day, because of continuing hyperkalemia, he was again dialyzed, with correction of the potassium intoxication and transient improvement in his general condition. (Details of the chemical results will be found in the section on "Extracorporeal Dialysis.")

He continued febrile and oliguric. The plasma NPN fractions, except for amino nitrogen, rose steadily again to very high levels. On day 12, urea nitrogen was 234 mg. per 100 cc., other purine nitrogen, 5.7 mg. per 100 cc. On the contrary, amino nitrogen again fell progressively. Leucine and isoleucine became slightly elevated; proline, threonine, glycine, lysine, tyrosine and alanine, were low; valine, aspartic acid, taurine, methionine, and histidine were normal. At this time plasma K was 6.9 mEq./L. A few days later, because of recurrent potassium intoxication, he was dialyzed for the third time, with correction of the hyperkalemia, but with no change in his very poor general condition. He continued to deteriorate and died on the nineteenth post-injury day.

At autopsy his entire body showed evidence of marked wasting. The amputation site of the right thigh showed extensive necrosis and infection of the skin flaps, muscle and fascia. There was a severe bacterial pericarditis, focal edema and necrosis of the myocardium, bronchiolar pneumonia, central necrosis (severe) of the liver, hyperthopy of the parathyroids, acute cystitis, necrosis of the occipital poles of the cerebral cortex, and lower nephron nephrosis.

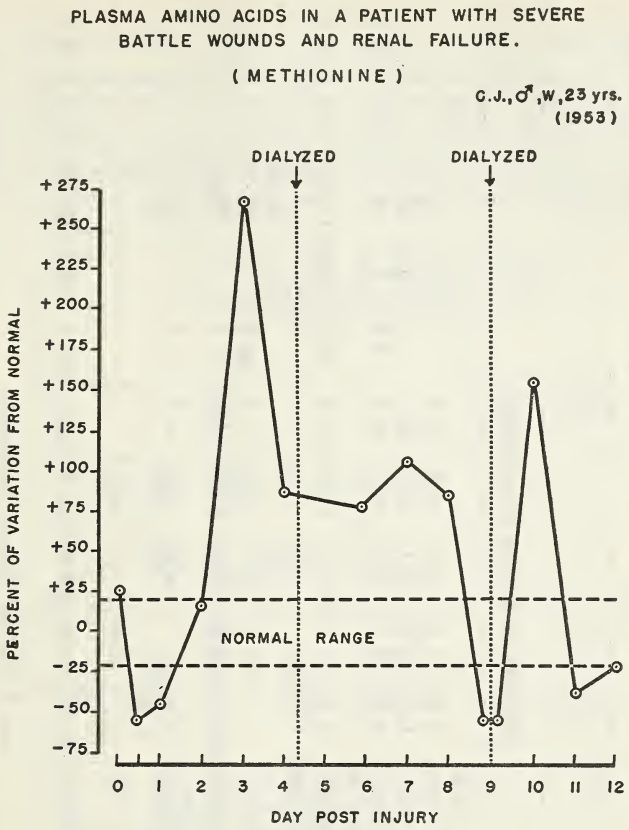

FIGURE 8.

Plasma Amino Conjugate

Early in our work on the plasma ultrafiltrates of human subjects, we noticed that one chromatographically distinct ninhydrin reactive component is unstable to acid hydrolysis. We isolated this component chromatographically, from a number of plasma samples, and rechromatographed them. The results are shown in Table 4 and Figure 9. The striking central fact is the quantitative and qualitative variability of the composition of this fraction among the patients.

The two normal subjects were young, healthy, male laboratory technicians. In both, glutamic acid and glycine comprised almost all of the conjugate; a small amount of threonine was also found in one. The plasma of the patients, however, contained the conjugate in greater quantity, and the component amino acids in greater variety. In patients C. J. and A. K., the plasma conjugate levels of the patients rose with the plasma urea levels, though not proportionately. As the

Table 4. Amino Acid Composition of Plasma Ultrafilterable Amino Conjugate

Patient Day Post-wound	½	C. J.				A. K.				K. D.			F. H.	Normals	
		1	2	11	12	½	2	7	8	3	8	11	10	A	B
	μM./100 ml. Plasma Ultrafiltrate														
Aspartic Acid			4. 0	3. 4	2. 5									1. 7	
Threonine			1. 8	3. 2	2. 0	3. 6	2. 3	7. 9	2. 3	15. 8		0. 8	13. 3		
Serine			2. 6	1. 3	2. 2	1. 8	2. 2	11. 1	3. 6	17. 7		6. 0	12. 1		
Glutamic Acid	6. 4		10. 8	13. 0	20. 8	6. 6	2. 1	9. 5	6. 7	18. 5	8. 0	4. 7	44. 2	8. 7	5. 5
Proline				10. 1	0. 8										
Glycine	18. 1	5. 3	18. 0	26. 0	10. 0	15. 1	8. 8	29. 5	14. 6	37. 5	23. 5	74. 4	145. 0	6. 6	8. 8
Alanine	4. 9	1. 7		2. 6	0. 8	1. 0		4. 6					8. 8		
Valine		2. 0		2. 5	1. 5			9. 5					44. 2		
Leucine	4. 8	4. 0	10. 0	14. 5	10. 0		21. 7	45. 6	34. 0	5. 4	45. 2		57. 2		
Tyrosine			4. 8	6. 0	5. 2		5. 3	23. 4	10. 6	4. 2	19. 1		36. 4		
Phenylalanine				2. 5											
Histidine			3. 1	2. 6	5. 1	3. 6		8. 5	13. 0	6. 3	5. 7		23. 6		
Lysine						1. 9									
Unknown			12. 9		6. 0		3. 6		9. 2						
Total	34. 2	13. 0	68. 0	87. 7	66. 9	33. 6	46. 0	149. 6	94. 0	105. 4	101. 5	85. 9	384. 8	17. 0	14. 3
	mg. N/100 ml. Plasma Ultrafiltrate														
Conjugate N	0. 5	0. 3	1. 0	1. 2	0. 9	0. 3	0. 6	2. 1	1. 3	1. 5	1. 4	1. 2	5. 4	0. 2	0. 2
Urea N	32	57	145	177	234	36. 4	132	377	178	84	122	42	364	20	17

level of the plasma conjugate fraction rose, more and more different amino acids were found within the component; the quantitative relations of the amino acids within the conjugate showed an ever shifting pattern, with first one amino acid becoming predominant then another. By the eleventh post-wound day, in patient C. J. (Fig. 9), 12 of the naturally occurring amino acids were present in the conjugate, with leucine and proline in addition to glycine and glutamic acid occupying

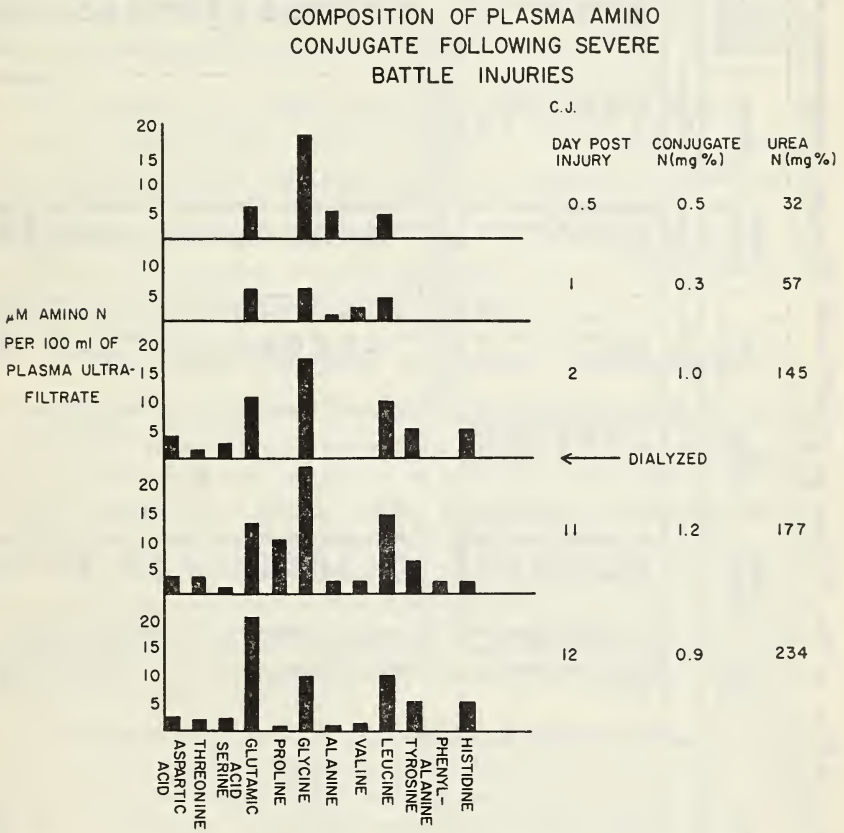

FIGURE 9.

quantitatively important positions. Patient A. K. showed the same sort of shifts in amino acid composition, but with different amino acids involved; leucine became even more predominant.

In patient K. D., whose plasma urea never reached the extreme heights of either C. J. or A. K., the amino conjugate concentration stayed at a relatively constant (but elevated) level. The quantitative relationships of the component amino acids gradually decreased in

Table 5. Effect of 6-Hour in Vivo Dialysis on Ultrafilterable Nitrogen Components of Plasma

Patient Day Post-injury	T. L. 12 Pre-dialysis	Post-dialysis	% Change	A. K. 7 Pre-dialysis	Post-dialysis	Change	C. J. 9 Pre-dialysis	Post-dialysis	% Change
	mg. N/100 ml. Plasma Ultrafiltrate								
NPN	392. 0	118. 0	−70	462. 0	208. 0	−55	383. 0	76. 0	−80
Urea N	336. 0	97. 5	−71	377. 0	113. 0	−70	311. 0	54. 0	−83
Creatine + Creatinine N	9. 7	5. 5	−43	9. 8	5. 4	−45	10. 8	3. 0	−72
Uric Acid N	6. 7	2. 5	−63	7. 1	3. 3	−54	6. 9	1. 6	−77
Purine N	3. 8	0. 9	−76	4. 3	1. 8	−55	5. 2	1. 1	−79
Amino Conjugate N	3. 1	0. 8	−74	2. 1	1. 3	−40	4. 0	0. 3	−92
Amino N	2. 7	2. 8	+3	4. 1	4. 8	+17	2. 0	1. 9	−5
	μM./100 ml. Plasma Ultrafiltrate								
Aspartic Acid	3. 7	2. 9		5. 4	5. 6		2. 3	1. 8	
Threonine	6. 2	6. 6		13. 6	24. 0		4. 8	6. 2	
Glutamic Acid	8. 5	10. 4		18. 0	14. 1		11. 8	12. 5	
Proline	14. 4	16. 0		29. 8	33. 0		5. 3	8. 0	
Glycine	15. 8	16. 6		22. 2	29. 5		10. 1	14. 7	
Alanine	20. 7	26. 8		28. 2	55. 1		10. 4	17. 2	
Valine	17. 0	19. 2		22. 9	27. 3		14. 6	9. 2	
Methionine	3. 5	2. 2		6. 6	7. 5		Trace	Trace	
Isoleucine	6. 8	5. 2		11. 7	7. 4		5. 8	4. 5	
Leucine	9. 6	12. 3		17. 7	19. 1		8. 0	8. 0	
Tyrosine	4. 0	5. 1		8. 6	11. 2		1. 7	1. 7	
Phenylalanine	12. 0	11. 3		12. 1	14. 7		10. 0	8. 0	
Histidine	28. 2	18. 7		22. 0	28. 0		19. 5	9. 3	
Lysine	11. 4	13. 0		29. 6	36. 2		8. 3	12. 6	
Taurine	1. 7	3. 0		1. 7	Trace		5. 2	2. 2	
Glutamine + Serine + Asparagine	29. 1	26. 1		40. 0	30. 3		22. 0	18. 4	

number, while glycine increased in concentration until it comprised some 85 per cent of the conjugate on the ninth day after injury.

These observations suggested that the amino conjugate fraction is not homogeneous. Accordingly, we chromatographed the intact conjugate on paper by the "circular" technic, using butanol—acetic acid—water (6:1:1) as the solvent. The conjugate of C. J. 2 days post injury was thereby separated into four ninhydrin-reactive components and that of K. D. 5 days post injury, into three. A specific chromatographic analysis was made in one subject (C. J.) for the peptides carnosine and anserine, normal intracellular constituents. Neither was found.

The conjugate, as a whole, acted as a metabolic end product with respect to extracorporeal dialysis (Table 5). The plasma concentration of the conjugate fraction was reduced after 6-hour dialyses in approximately the same ratios as urea, uric acid, other purines and the creatine plus creatinine fraction. This is in marked contrast to the behavior of the plasma free amino acids, whose concentrations, in general, were little changed by the dialyses.

Ultraviolet Absorption of Plasma Ultrafiltrates

On Figure 11 is depicted the absorption spectral pattern of a normal plasma ultrafiltrate. The peak at 290 mμ. is almost entirely due to the purine, uric acid, which has a molecular extinction coefficient, at this wavelength, of about 12,500. Absorption in the region of 240 to 260 mμ. is due to other prines, but also included a second peak of uric acid. The aromatic amino acids, with considerably lower extinction coefficients (around 3,000 to 4,000) have their absorption maxima at about 280 mμ. Absorption below these wavelengths is termed "nonspecific," and is characteristic of many nitrogenous compounds, including most of the amino acids.

The data for patient C. J. are shown in Figures 10 and 11. There was an insistent and progressive rise in absorption at all wavelengths, the rise being only temporarily halted by extracorporeal dialysis. The spectral absorption was highest when the plasma NPN levels were highest.

Similar observations were made in patients A. K. and K. D.

Effects of Extracorporeal Dialysis on the Plasma Nonprotein Nitrogen Components

Extracorporeal hemodialysis of the patients with severe renal dysfunction was carried out to reduce hyperpotassemia or relieve uremia. We studied the plasma of three patients, obtained before and after

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ULTRA VIOLET ABSORPTION SPECTRUM OF PLASMA ULTRAFILTRATE
OF A SEVERELY WOUNDED SOLDIER
Diluted 1-20
C.J., ♂ ,26 yrs.
Day Post injury
Normal
6
5 (dialyzed)
4
3
2
1
1/2
0
OPTICAL DENSITY
1.0
.6
.2
220
240
260
280
300
320
WAVE LENGTH mμ

FIGURE 10.

ULTRA VIOLET ABSORPTION SPECTRUM OF PLASMA ULTRAFILTRATE
OF A SEVERELY WOUNDED SOLDIER.

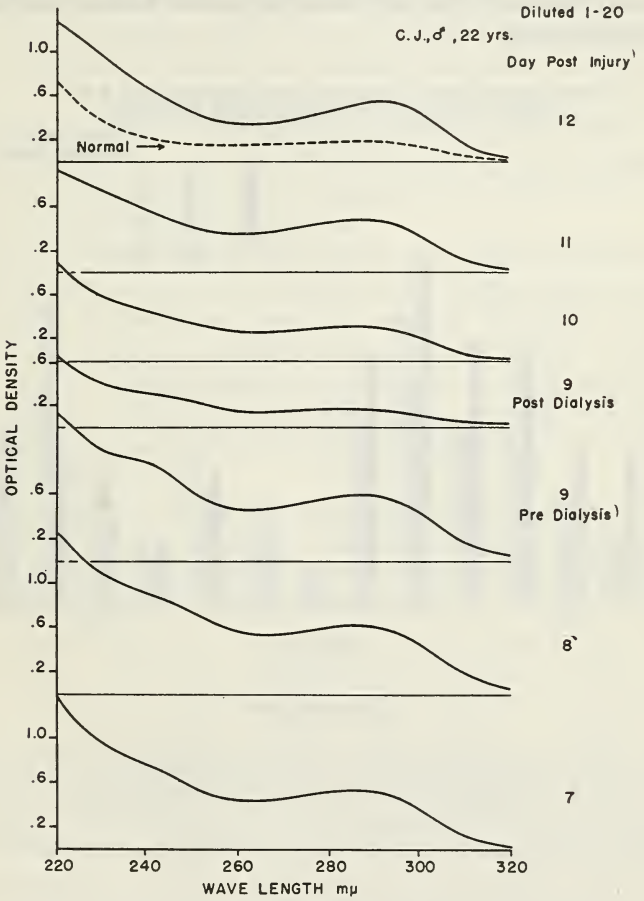

FIGURE 11.

6-hour dialyses, with a view toward establishing the pattern of change in the nonprotein nitrogen portion of the plasma, ostensibly that part readily diffusible through a cellophane membrane. The data set forth in Table 5 and Figure 12 show that there is a discernible pattern. With the notable exception of the amino acids, all the small nitrogenous compounds, including the amino conjugate, were sharply reduced in concentration after dialysis. In contrast, the plasma concentrations of the amino acids were changed little, despite the 6-hour "washouts" on the artificial kidney.

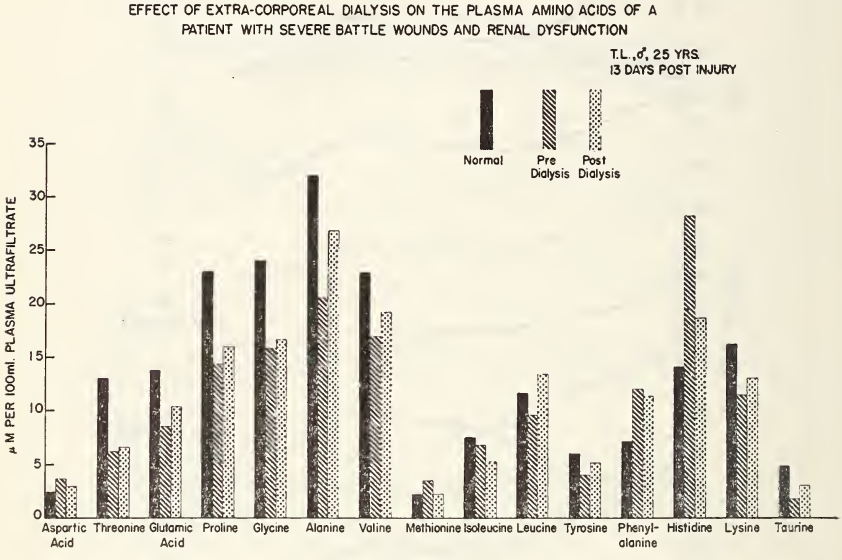

FIGURE 12.

Discussion

When 19 plasma amino acids are measured by ion exchange chromatography in a random group of healthy individuals, it is found that the total amino acid N measures close to 3.5 mg. per 100 cc. This figure practically never goes above 3.8 (except for a short time after a high-protein meal) or below 3.1 mg. per 100 cc. There is considerable variation in concentration among the amino acids, e. g., aspartic acid is present in a concentration of about 2.5 μM per 100 cc. while the concentration of alanine is about 32 μM per 100 cc. Speculations can be indulged in to explain this, but there is, at present, inadequate experimental evidence to support any theories. However, each amino acid is present in about the same relative concentration in the plasma of healthy men. Among the factors which have a possible connection

with maintaining the plasma amino acids relatively constant in normal individuals are: dietary intake, absorption of ingested amino acids from the gut; deamination, transamination, and decarboxylation primarily in the liver; excretion and reabsorption by the kidney; and dynamic transcapillary exchange. The plasma amino acids are in active metabolic exchange with tissue amino acids, tissue and plasma proteins, and body carbohydrate and fat.

One of the main objects of this study was to discover if any quantitative trend in plasma amino acids manifested itself in previously healthy young men who had been seriously wounded. At the present time, there is little hope of pinpointing the causes for any noted amino acid alterations, since (a) the plasma specimens were obtained from men undergoing many and varied stresses and (b) as mentioned, the basis for the differences in plasma concentrations of the various amino acids in normal individuals is unknown.

Among the stresses which the patients we studied underwent, the following might be expected to influence the plasma amino acids: the initial injury, hemorrhage, shock, intravenous infusions (blood, albumin, dextran, gelatin, glucose, saline, etc.), anesthesia, operation, liver dysfunction, renal dysfunction, fluid and electrolyte imbalance, fever, infection, antibiotics and malnutrition. Also to be considered are the paths along which the stresses may affect the amino acid levels, i. e., humoral, neural, etc.

Before discussing our results, the work already done on the effects of some of the stresses mentioned may be summarized. Most of the work done in this field concerned only the total plasma amino nitrogen concentration and not individual amino acids.

A prolonged decrease in the plasma concentration of total alpha-amino nitrogen following operation was reported by Man and coworkers.[21] They felt that the degree and duration of the decline in plasma total alpha-amino nitrogen concentration is related to the severity of the operative procedure. Less change postoperatively was observed in malnourished patients with low plasma amino nitrogen levels preoperatively than in those patients with normal preoperative levels.

Recently, Everson and Fritschel [8] have studied, in 16 patients (specific diagnoses not tabulated), the effect of major surgical operations (in magnitude, cholecystectomy to gastrectomy) on the plasma levels of 10 individual amino acids. Fourteen of the patients were stated to be in good nutritional status at the time of operation. Two presumably were not, but the authors do not specifically characterize the nutritional status of these two patients.

Statistically significant decreases in plasma concentration immediately after operation were observed for all but leucine and histidine. By the morning of the first postoperative day, only the values for threonine, arginine and lysine were still significantly lower than the preoperative levels. The plasma lysine concentration rose to the preoperative level by the third postoperative day, while the values for arginine and threonine rose to normal somewhere between the third and seventh postoperative days. They observed no obvious relationship among the type and duration of the operation and the plasma concentration of the 10 individual amino acids measured by them. However, the number of patients studied by them is small for comparisons of this nature. Presumably, none of the patients in the study of Everson and Fritschel was in shock. No details of fluid or blood administration during or after operation, however, are given.

To determine whether anesthesia, per se, might influence the plasma amino acids, 10 dogs were subjected by Everson and Fritschel to 2 hours of ether anesthesia. A lowering of the plasma level of the individual essential amino acids equal to or greater than the depression of plasma levels in patients produced by anesthesia plus operation was observed. No data were reported on dogs anesthesized and subjected to operation.

It is generally held that the total plasma amino nitrogen increases during severe shock. Thus, an increase in plasma amino nitrogen has been observed in rats with severe hemorrhagic shock [7, 33] and in rats [15] calves [12] and patients [17] with shock following severe burns. Engel, Winton, and Long [7] observed that the rise in plasma alpha-amino nitrogen in hemorrhagic shock in rats was accompanied by a fall in red cell alpha-amino nitrogen.

The effect on plasma amino acids of ether anesthesia and severe burns in untreated rats was studied by Rosen and Levenson [28] who found minimal rise in the total amino acids 12 hours after burn. A marked increase in taurine and an amino conjugate was observed; alanine, histidine, phenyl-alanine, tyrosine, leucine, isoleucine, serine and asparagine were somewhat elevated; threonine, glutamic acid, proline, glycine and valine were decreased.

In view of these results, the reported rises in total amino nitrogen during shock may reflect rises in substances other than, but similar to, free amino acids.

Among the explanations offered for the rise of total amino nitrogen in shock is increased production of amino acids from tissues and impairment of liver function. In this regard, it has been demonstrated by in vitro methods that the ability of liver slices from shocked ani-

mals to deaminate certain amino acids, viz., alanine, is impaired.[1, 33] In some patients with severe liver disease, Walshe [32] found little abnormalities in the plasma concentrations of individual amino acids until the last stages of hepatic failure.

Another factor bearing on the interpretation of plasma concentration data is the size of the plasma compartment; "false-high" or "false-low" levels might be obtained consequent to certain fluid and electrolyte shifts. It has recently been shown by Christensen,[2] that some, and possibly all amino acids can be concentrated to some degree by various cells; that this concentrative process is related to processes which control electrolyte balance; and that amino acids can displace potassium from cells and vice versa. Sodium ion fluctuations also affect amino acids; Wolf and McDowell [34] have observed that a 30 per cent increase in the plasma sodium concentration by sodium chloride infusion in dogs caused a roughly twofold increase in the concentrations of the plasma amino acids.

Decreases in plasma total alpha-amino nitrogen concentration have been reported during certain infectious diseases.[10]

The influence, if any, of fever, blood transfusions, and infusions of other fluids, and antibiotics on the plasma amino acids is unknown.

In regard to the effect of nutrition on plasma amino acids, Man *et al.*,[21] found lower than normal concentrations of total amino nitrogen (measured chemically) in the plasma of malnourished patients. Everson and Fritschel [9] measured, by microbiologic technics, the fasting plasma levels of the 8 amino acids considered essential for man and of histidine and arginine in surgical patients prior to operation. Thirty-eight of the patients were considered to be in poor nutritional state, while the other 25 were in good nutritional status. The two groups were made of patients having approximately the same pathologic conditions. The mean value of each of the amino acids except arginine was significantly lower in the plasma of the poorly nourished patients. They found that the decreased levels of the free amino acids in plasma of five malnourished patients were not restored to normal by only a few days of high-protein (level not stated) diets.

Kirsner, Sheffner, and Palmer [16] found in one human subject that the oral administration of a peptone solution treated with hydrogen peroxide and containing markedly reduced quantities of methionine, lysine, histidine, leucine, isoleucine, valine and threonine, was accompanied by definite decreases in the free levels of these amino acids in the plasma. During the same periods, the amino acid outputs in the urine increase considerably. These findings point to the importance of considering recent dietary intake and urine output in evaluating plasma concentrations.

Christensen and his co-workers [2, 3] have shown that high plasma levels of some amino acids (e. g., proline), brought about by feeding, appeared to interfere, perhaps on a competitive basis, with the cellular activity for concentrating other amino acids. When glutamic acid was fed in excess, however, the concentrating activity of liver and muscle for certain amino acids appeared to be increased and there was a concomitant fall in the plasma levels of these amino acids. From this point of view, decreased plasma levels of amino acids may result from increased concentrative assimilation by the cells. Elevated levels may occur when there is inhibition of the concentration process.

Regarding our own data, reference to Tables 1 to 5 and Figures 1 to 8 will give some idea as to the amino acid trends. It is significant that in no patient, at any time, are all the amino acids depressed or elevated. Rather, they seem to group themselves. Thus, in patient K. D., (a) glycine, histidine, threonine, proline and glutamic acid stayed near normal throughout the course of study; (b) leucine, isoleucine, lysine, valine, tyrosine and alanine rose moderately between days 3 and 9 post injury and then fell, (c) phenylalanine, aspartic acid and methionine showed the same picture of elevation, but to a greater degree. Taurine, the sulfonic amino acid, may not be handled by the organism as a metabolic intermediate, and bore little or no relationship to the other amino acids.

Patient C. J. showed, in general, the same picture, with the amino acids of group (a) normal or slightly low, group (b) becoming moderately elevated between days 1 and 8 post-injury and then falling, and group (c) becoming very elevated and then falling. In this patient, taurine reached a level of 1,200 per cent above normal on day 4; dialysis corrected this, and taurine thereafter stayed normal. The data of patient A. K. are less complete, but the same picture of grouping can be seen.

Can these trends be related to the injuries of these men, and to their subsequent clinical course? It is obvious that the separate effects of injury, shock and extensive transfusions cannot very well be delineated, since they occurred within so small a time interval. However, in none of our patients did the total of the 19 amino acids which we analyzed rise to excessive heights in the plasma. Whereas we have obtained a normal average value of 3.5 mg. per 100 cc., the highest values for the patients studied serially were 5.8 mg. (A. K., day 1 post injury), 5.0 mg. (C. J., day 3 post-injury) and 4.8 mg. (K. D., 6 days post-injury). These values, although not excessively high, are significantly so. A. K. had received a penetrating abdominal wound, with resultant perforations of the liver, kidney and colon. He apparently

was not in shock prior to operation (7 hours after injury). During the operation, however, his blood pressure became imperceptible for about a half hour and remained low for some time during operation. Immediately after operation, his plasma total amino acids were normal. During his first post-wound day, he received 10,000 cc. of blood, 2,000 cc. of gelatin and 500 cc. of dextran. At the end of this day his total amino nitrogen was 5.8 mg. per 100 cc.

Neither C. J. nor K. D. had elevated total amino acids on day 1 after injury. Both K. D. and C. J. were even more severely wounded than A. K. Both had been in severe shock; C. J., like A. K., had perforating wounds of the liver and kidney; all received large quantities of blood, but A. K. had also received gelatin. Glycine, occurring in relatively large quantities in gelatin, might be expected to appear in the plasma if the metabolism of gelatin were contributing to the rise in the total plasma amino acid concentration seen in this patient at the end of the day of injury. However, the rise in glycine was only slight. Other data indicate that relatively little gelatin is metabolized in the first post-infusion day. The rise in total amino nitrogen was, in fact, due principally to alanine, phenylalanine, leucine, lysine, tyrosine, threonine and glutamic acid.

In patient C. J. the plasma amino nitrogen fell gradually from its peak of 5 mg. per 100 cc. to 2 mg. per 100 cc. by the ninth post-injury day, and stayed low to the end of study. At the lowest point (day 9), all the amino acids, other than aspartic acid, glutamic acid, histidine and phenylalanine, were low. This patient's course was complicated by cerebral concussion, renal failure, jaundice, wound infection, pneumonia, pericarditis and marked weight loss. He had no oral food until the last day of study. Parenterally, he received some blood, glucose, electrolytes and vitamins. His caloric intake was grossly inadequate; his only nitrogen source was his transfusions. In this regard, it will be recalled that Man *et al.*,[21] and Everson and Fritschel [9] found decreased plasma amino acids in malnourished patients.

Patient T. L., who also had renal failure and an inadequate dietary intake, also had a slightly low amino nitrogen on the one sample we studied (12 days post-injury).

Patient A. K.'s dietary protein intake was also very low, but his parenteral caloric intake was significantly higher than C. J.'s. A. K.'s total plasma amino nitrogen was slightly low on only one occasion, the second post-injury day. His course had also been complicated by persistent renal failure, jaundice, pneumonia, bacteremia, liver abscess and liver necrosis.

Patient K. D.'s dietary intake was probably higher than that of the other patients and included moderate amounts of oral protein.

His total plasma amino nitrogen was only slightly low on the tenth and eleventh post-injury days.

Patient F. H. had a normal amino nitrogen on day 9 post-injury, and slightly elevated amino nitrogen on day 10. No data of his dietary intake up to this time are available, but it is likely that he, too, ate moderately during the first week post-injury since his renal failure occurred late, on the eighth day after injury, and 1 day after a secondary operative procedure.

After injury, activation of various endocrine glands (particularly the hypothalamic-pituitary-adrenal axis) occurs. Many of the metabolic changes seen following injury have been ascribed, in part, to the increased activity of this system. Crimson, Hanvey, and Luck [4] have shown that injections of adrenalin will produce lowering of plasma amino nitrogen in fasting dogs. Others have made similar observations in other species.[25] Since increased excretion of adrenalin during anesthesia and operation is well established, Everson and Fritschel have suggested that the decrease in the levels of plasma amino acids following anesthesia or operation observed by them may be consequent to increased adrenalin secretion. On the other hand, there is considerable evidence to indicate an increased secretion of adrenocorticotropic hormone after injury and operation. Li, Geschwind, and Evans [18] have observed an increase in plasma amino nitrogen following the repeated administration of adrenocorticotropic hormone to rats. On the other hand, neither Li *et al.*,[18] nor Luck and his associates [14, 20] observed this increase following a single injection of adrenocorticotropic hormone to rats. The latter investigators found no change, or a lowering, of the blood amino acid concentration following single injections of various commercial adrenocorticotropin preparations. Cortisone, desoxycorticosterone, norepinephrine and testosterone did not affect the level of the blood amino acids in normal rats.

Li *et al.*,[18] have demonstrated that the administration of anterior pituitary growth hormone causes a significant decrease in the blood amino acid content in rats. Luck and his associates have confirmed this and have also noted that thyrotropin has a similar effect.[14, 20] Although injection of insulin will lower the concentration of amino nitrogen in the plasma, the amount of insulin required is enough to produce signs and symptoms of hypoglycemia.[19] There is no evidence to suggest this degree of insulin secretion in the postoperative or post-injury period.

Urinary excretion of amino acids may reflect, or induce, changes in plasma amino acid concentrations. Everson and Fritschel state that they failed to find an increased urinary excretion of individual amino

acids during operation in five patients sufficient to account for the lowering of the plasma levels of the amino acids observed. Nardi [24] has recently applied the technic of paper chromatography to study the urinary excretion of amino acids in surgical patients. It should be emphasized that this is not a quantitative technic. He noted an apparent increase in the number and quantity of amino acids excreted by patients with burns or patients undergoing major operations. This increase began in the first days after injury and was roughly proportional to the severity of the burn or operation. The increased urinary output of amino acid did not necessarily coincide with the period of greatest negative nitrogen balance, but in some cases extended beyond the period of negative nitrogen balance. However, no data of intake or total urinary nitrogen or amino acid outputs are given. He also observed an increased urinary excretion of amino acids in patients with Cushing's syndrome. Following bilateral adrenalectomy, the amino acid excretion became normal, the patient being maintained with cortisone.

In seeking an explanation for the amino aciduria observed in these patients, Nardi considers the possibility that the amino aciduria is a reflection of an increase in the plasma concentration of the amino acids or consequent to a decrease in renal tubular reabsorption of the amino acids. (No measurements of the plasma amino acids were made.) He suggests the possibility that a disorderly, albeit not elevated, pattern of amino acids are presented to the kidney leading to a disturbance of tubular reabsorption. He also suggests the possibility of an increased secretion of an adrenocorticosteroid, probably other than cortisone, which would decrease tubular reabsorption of amino acids.

When renal function is normal, large increases in the plasma levels of amino acids may not occur, since a rise in their concentration, above the renal threshold may result in a large increase in their excretion.

We have had the opportunity to study the plasma amino acid in patients with persistent renal failure. While the biochemical picture of these patients is complicated by other pathologic conditions, our general impression is that renal failure has little specific effect on plasma amino acid levels. In spite of radically high plasma levels of other NPN components (urea nitrogen concentrations up to 400 mg. per 100 cc.), there was very little change in total plasma amino acid levels. The probability is that other, more powerful, regulatory processes can or do control amino acid levels in the plasma in the absence of renal function. Particularly dramatic is the failure of 6-hour plasma "washouts" of anuric patients on the artificial kidney, noticeably to affect plasma amino acid levels. The regulatory mechanism,

or complex of regulatory mechanisms, can obviously operate independently of the kidney. This does not exclude the kidney as one of the regulatory organs of amino acids in normal individuals, but indicates that other processes can intervene in the homeostatic task when the kidneys fail.

As a consequence of our use of the ion exchange technic for the analysis of amino acids, we have noted the presence, in all plasma samples analyzed, of an ultrafilterable, ninhydrin-reactive compound which is unstable to hot acid, and which, on hydrolysis, yields identifiable amino acids. We interpret these experimental findings to mean that this compound has a molecular weight of below 15,000 to 20,000, and that it is comprised of amino acids held in peptide or peptide-like linkages. Paper chromatography has revealed that this component is heterogeneous, since it is readily resolvable into three or more fractions. Further evidence of this heterogeneity is indicated by these findings: In the two normal plasmas analyzed for this substance, only glycine and glutamic acid could be found, with a small amount of threonine in one. Plasma ultrafiltrates from patients with renal dysfunction, however, showed larger quantities of the substance; degradation with hydrochloric acid, moreover, revealed many more amino acids, e. g., leucine, valine, proline, tyrosine, histidine, etc. Furthermore, the amino acid composition varied from patient to patient, and from day to day in the same patient. In general, those patients with the higher NPN's had the substance in greatest concentration. In these cases, analysis showed maximum numbers of different constituent amino acids.

Extracorporeal dialysis reduced the plasma level of this substance or substances like it in roughly the same ratio as the other NPN components other than the free amino acids. No amino-acid-like, homeostatic mechanism, therefore, regulates the level of the fraction.

The absorption of ultraviolet light by plasma ultrafiltrates gives information concerning certain small molecular compounds. In particular, uric acid, at pH 7, has a strong absorption peak at 290 mμ, and most of the other naturally occurring purines, including uric acid absorb in the region 240 to 260 mμ. The aromatic amino acids absorb in the 280 mμ. region. In general, the entire ultrafiltrate absorption spectral pattern from 220 mμ. to 320 mμ. is elevated when plasma NPN is high. The elevation of the various portions of the spectrum, however, only roughly parallels the NPN rise. Figures 10 and 11, for example, show progressive rises in spectral pattern in a patient becoming progressively more azotemic. On day 8 post-injury, the pattern is grossly elevated, at which time the NPN was 288 mg. per 100 cc. On day 9, when the NPN had risen to 383 mg. per 100 cc., the elevation of

the spectrum is no greater than it was on the previous day. This observation, together with the observable differences in the shape of some of the patterns, makes it seem probable that the components contributing to the spectral absorption vary in their relative concentrations. Since by far the largest contribution to absorption in the ultraviolet region is due to purines, these compounds are implicated in the high NPN levels.

Summary

Serious metabolic derangements are common after severe injury. In particular, nitrogen metabolism may become abnormal. Accordingly, we have studied changes in the pattern of the nonprotein nitrogen components in the plasma of five critically wounded soldiers.

The following quantitative data are presented: NPN creatine plus creatinine, uric acid, other purines and urea. In addition, 19 individual amino acids were quantitatively analyzed by ion exchange chromatography.

Of the five patients studied, four died. Shock and renal failure were present in all varying degrees. No plasma amino nitrogen level over 5.8 mg. per 100 cc. was found. Renal failure was persistent in four of the patients. Although plasma urea concentrations were as much as 30 times normal, the total free plasma amino acid nitrogen remained near normal.

In those patients studied for periods extending from the day of injury to 2 weeks post-injury, the plasma amino acids followed a pattern. At no time were all the amino acids depressed or elevated. Rather, they grouped themselves as follows: (a) glycine, histidine, threonine, proline and glutamic acid stayed near normal; (b) leucine, isoleucine, lysine, valine, tyrosine and alanine rose moderately during the first week and then fell; (c) phenylalanine, aspartic acid and methionine also rose during the first week, but to a greater degree. Taurine bore little or no relation to the other amino acids. At times, it was extremely high.

In two patients, who became markedly malnourished, the total plasma amino nitrogen fell to low levels.

In all plasmas analyzed, a heterogeneous amino conjugate was found. The amino acid composition varied from patient to patient, and in the same patient from day to day. In general, those patients with the highest NPN's had the substance in greatest concentration. In these cases, acid hydrolysis revealed maximum numbers of different constituent amino acids.

Analysis of the ultraviolet absorption spectra of the plasma ultrafiltrate of these patients indicates that there was an increase in purines, free or bound.

Extracorporeal dialysis with a Kolff-type artificial kidney was performed on three patients. Temporary biochemical and/or clinical improvement followed the dialyses. With the notable exception of the amino acids, all the small nitrogenous compounds (including the plasma amino conjugates) were sharply reduced after dialysis. In contrast, the plasma concentrations of the amino acids were little changed, despite the 6-hour "washouts" on the artificial kidney.

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Chapter 14

The Electrocardiographic Effects of Alterations in Concentration of Plasma Chemicals*

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The naturally occurring alterations in concentration of plasma chemicals which are known to produce configurational electrocardiographic changes are hypocalcemia,[1-3] hyperkalemia [1-41] and hypokalemia.[2, 3, 12] Experimental evidence suggests that extracellular, not intracellular concentration is the factor producing electrocardiographic abnormality.[13, 15, 16] Other electrolytes which may have an electrocardiographic effect are hydrogen ion, sodium, and bicarbonate, but it is not clear whether they have a direct effect upon cell polarization, or whether they influence chemicals which have a direct effect, or whether they are merely associated with changes in concentration of substances with direct effect.[1-3, 12]

Simultaneous changes in several electrolytes may interact to influence cardiac function. An isolated change in concentration of a single electrolyte cannot occur, because chemical equilibrium must be maintained, and various combinations of excess and deficiency of electrolyte concentration have been observed. Potassium excess, for instance, has been shown to exert exaggerated toxicity in the presence of calcium deficit, and replacement of the calcium deficit instantly modifies the cardiotoxic effects of the hyperkalemia.[6, 7, 9-11, 17, 18] The present study is designed to reveal or define further the influence of certain plasma chemicals upon the electrocardiogram.

Materials and Methods

This is a study of 663 electrocardiograms recorded on 61 patients; at the same time venous blood was drawn for chemical analyses. The patients were combat casualties with acute renal insufficiency. The examinations were performed at the Renal Insufficiency Center, Korea, as an activity of the Surgical Research Team, Army Medical Service Graduate School, Washington, D. C. The electrocardiograms were

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made at the bedside with the Sanborn Visocardiette. Chemical determinations were performed by the following methods: nonprotein nitrogen by the method of Folin and Wu;[19] chloride by the method of Sendroy;[20] carbon dioxide content by the manometric method of Van Slyke;[21] calcium* by the Clark and Collip modification of the method of Kramer and Tisdall;[22] inorganic phosphorus by the method of Fiske and Subbarow;[23] and sodium and potassium by the internal standard flame photometer.[24]

In the data and discussion to follow, QRS duration is measured in seconds, the QT interval (QTc) in seconds corrected for rate, where normal is 0.39 ± 0.02 second,[25] and T-wave height in millimeters from the isoelectric line of the tallest precordial T-wave.

Results

Part One: The QTc interval

A. Total plasma calcium is plotted against QTc interval in Figure 1. There is a tendency for the longer intervals to be associated with lower calcium values; that the relationship is not absolute and would stand little statistical tension is evident. The plasmas yielding these calcium values showed considerable variation in their potassium concentration, and the mutual antagonism between these ions may have affected the electrocardiographic response to variations in the calcium level. In Figure 2 the effect of variations of the concentration of plasma calcium is more clearly seen in four individual patients. An association betweeen hypocalcemia and prolongation of the QTc interval has frequently been observed,[1, 4, 8, 14] and if ionized calcium had been measured this relationship might have been more apparent in the composite chart. The high plasma calcium values were produced therapeutically with intravenous infusions of 10 per cent calcium gluconate in distilled water.

B. Inorganic phosphorus is plotted against QTc interval in Figure 3. A determination was not used if the patient had received calcium in the previous 24 hours. Again a rough correlation is observed. The relationship is due not to an effect of phosphorus elevation, but to the hypocalcemia with which it is associated in acute renal insufficiency.[4, 17, 18] Figure 3 is, thus, a rough mirror image of Figure 1.

C. No consistent relationship was found between the QTc interval and the plasma levels of sodium, potassium, chloride, bicarbonate or nonprotein nitrogen.

*Ionized calcium was not measured.

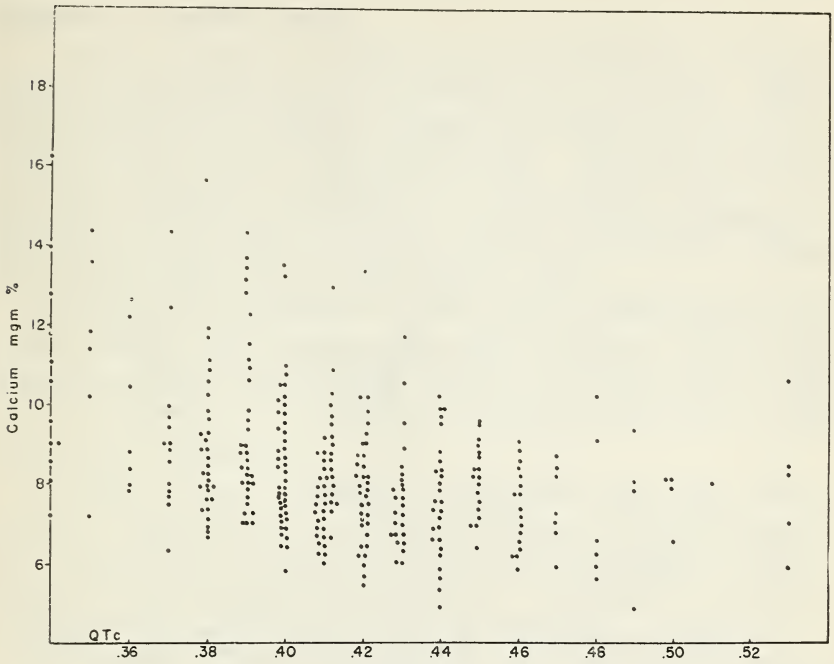


FIGURE 1.

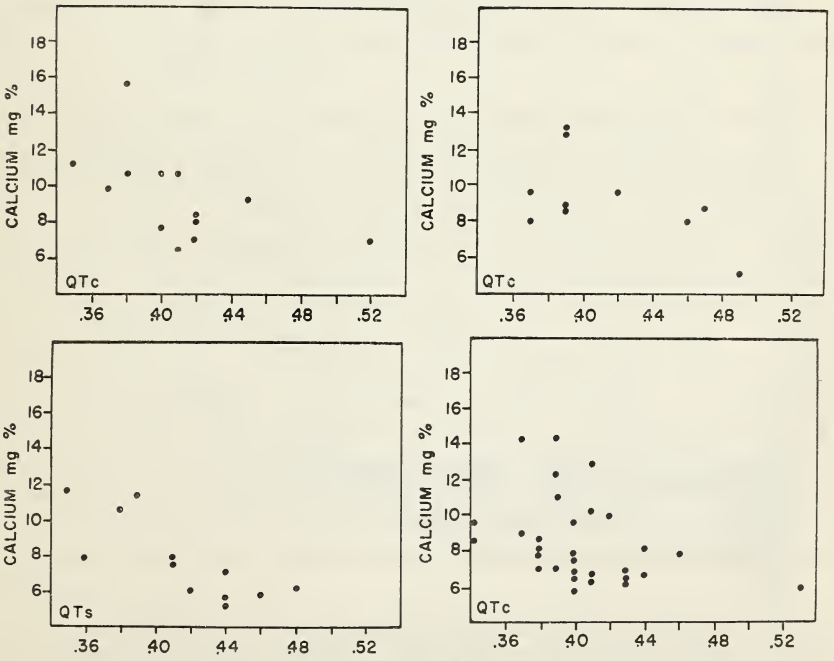


FIGURE 2.

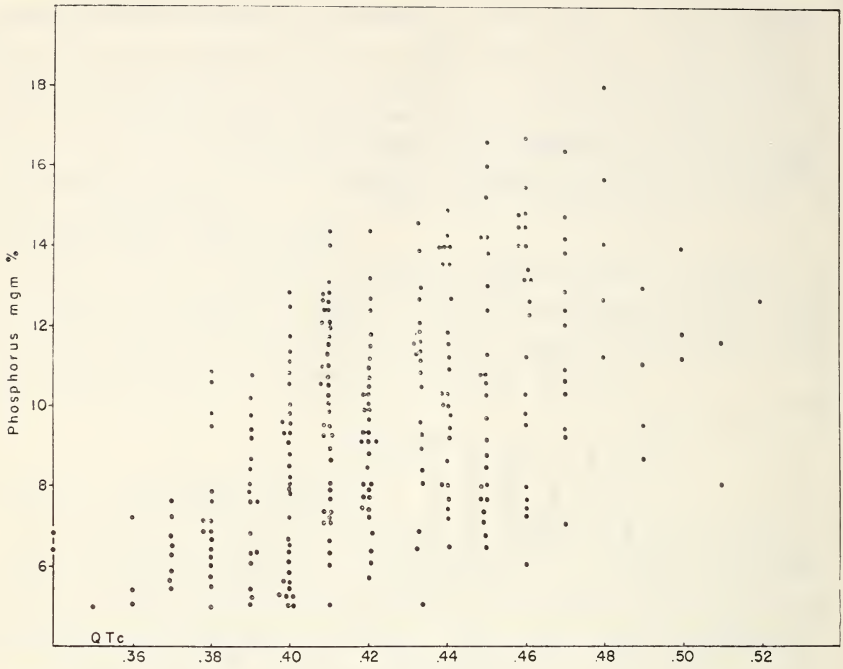


FIGURE 3.

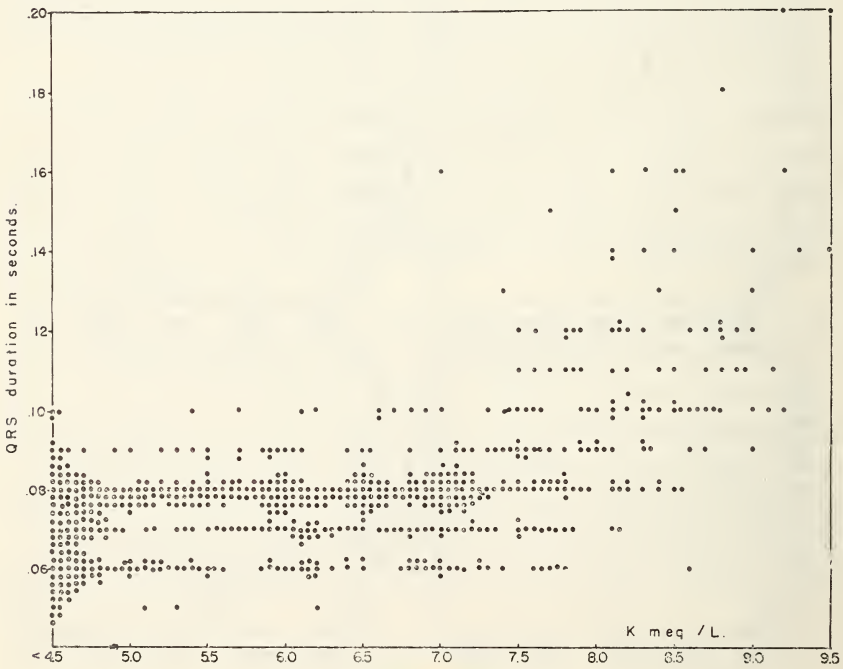


FIGURE 4.

Part Two: The QRS complex.

A. Plasma potassium is plotted against QRS duration in Figure 4. Figure 5 is a plot of the same relationship in four individuals. Figure 6 is a plot of the relationship in patients who had not received calcium within 24 hours prior to the determinations. All charts show QRS duration to be normal until plasma potassium reaches 7.0 mEq./L. As potassium levels exceed 7.0 mEq./L. the QRS duration is usually prolonged. This is not constant since the QRS duration is at times normal even in the presence of a very high potassium level.

B. Potassium concentration was the only factor showing any consistent pattern when plotted against QRS duration. No such relationship was found between QRS duration and calcium, sodium, chloride, bicarbonate, phosphorus or nonprotein nitrogen plasma levels.

Part Three: The T-wave.

A. Figure 7 shows the relation of potassium to the height of the T-wave. Figure 8 shows the same in four patients. T-wave abnormality was rarely seen at potassium levels of less than 6.5 mEq./L., but became marked as hyperkalemia progressed. A comparison of patients in Figure 8 shows wide patient-to-patient variation.

B. A plot of T-wave height against the plasma concentration of either calcium, sodium, chloride, bicarbonate, phosphorus or nonprotein nitrogen did not show a consistent pattern.

Part Four: The composite electrocardiographic effects of progressive hyperkalemia.

There is a step-wise evolution of electrocardiographic abnormality in progressive hyperkalemia when calcium concentration is normal. This is shown in Figures 9 and 10. At plasma levels of less than 6.5 mEq./L. there is no effect on the electrocardiogram. The earliest electrocardiographic change is elevation and peaking of the T-waves, especialy in the precordial leads, first seen at a plasma potassium level of about 6.5 mEq./L. As plasma potassium rises, this becomes more marked until the T-waves are very high, narrow and peaked.

The next change is a widening of the "S–ST" angle. The terminal portion of the QRS complex becomes wider and deeper. The initial portion of the QRS complex is unchanged. Overlapping this is a gradual loss of the ST segment. The end point of this effect is the most advanced hyperkalemic alteration. ST segment loss begins with a slight angulation of the ST segment from the iso-electric line. Angulation becomes more severe until the ST segment completely disappears.

As hyperkalemia progresses, a late electrocardiographic abnormality is gradual QRS broadening. This begins with S–ST angle widen-

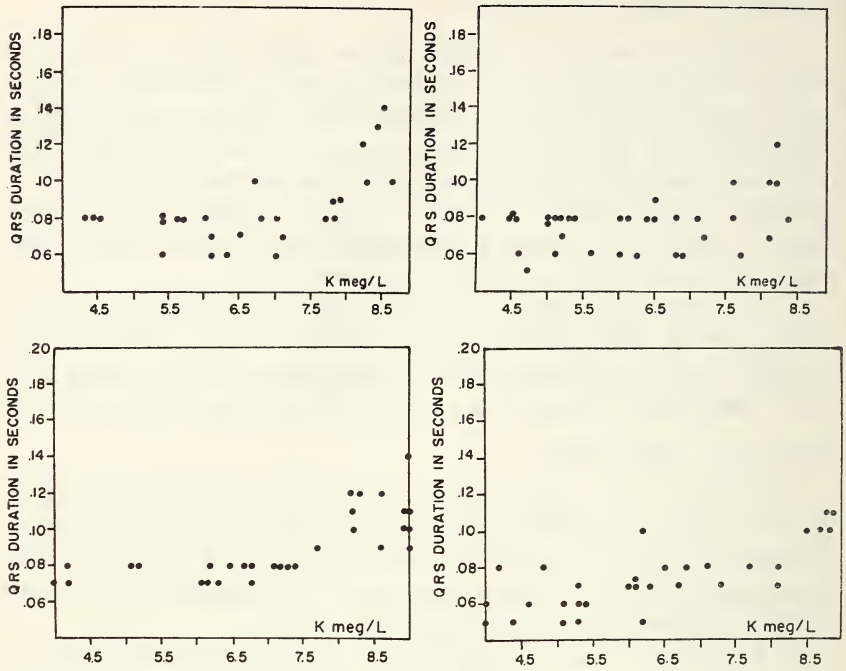


FIGURE 5.

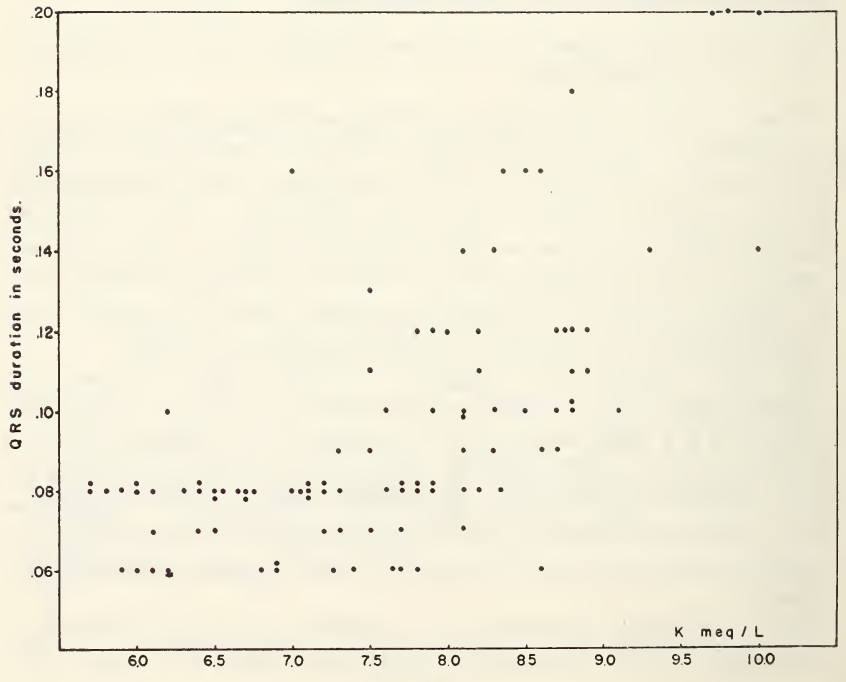


FIGURE 6.

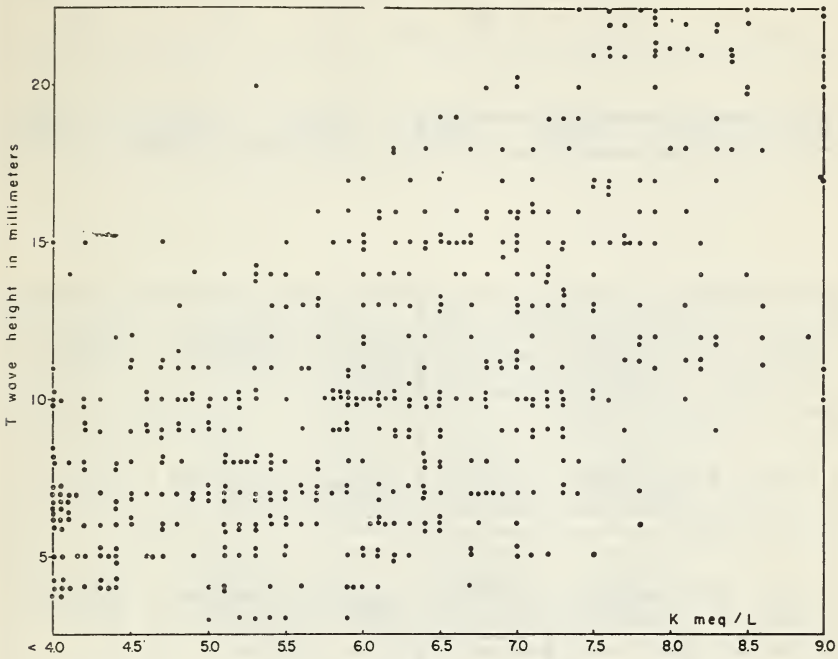


FIGURE 7.

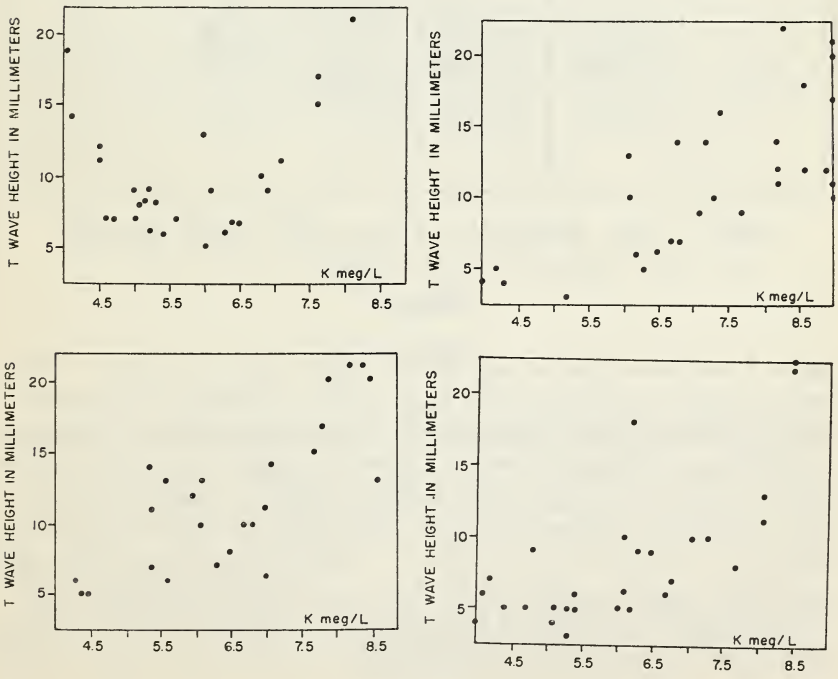


FIGURE 8.

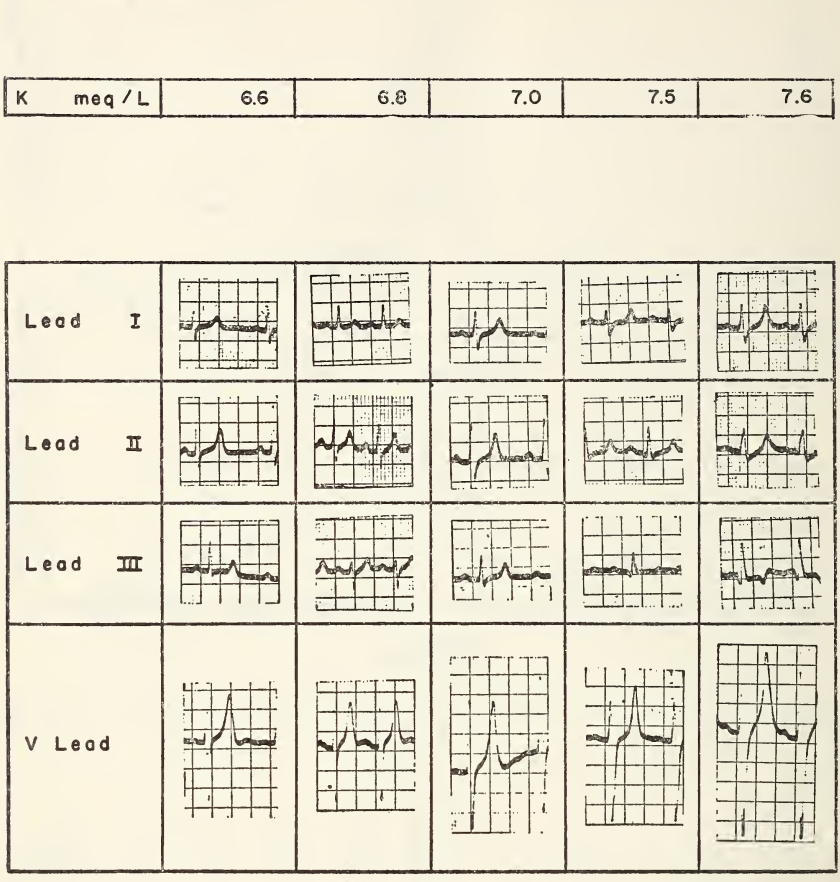
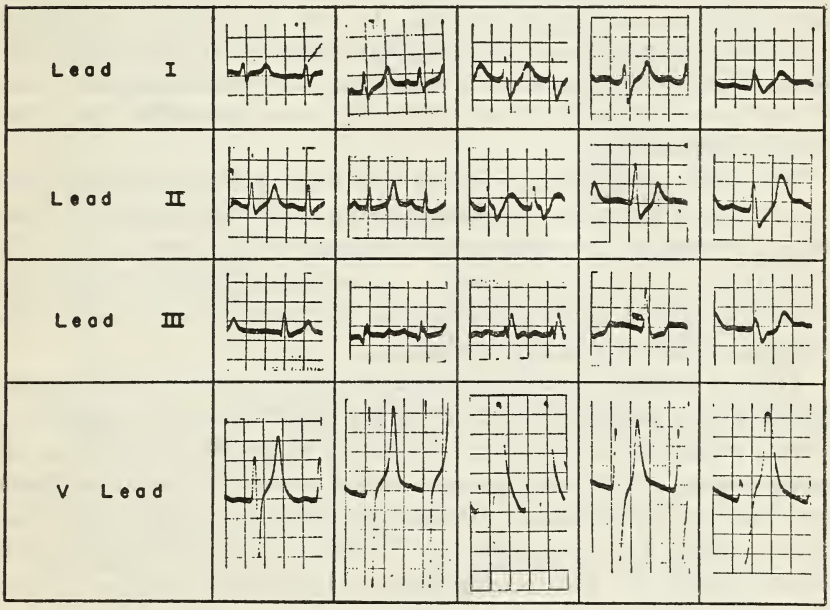


FIGURE 9.

ing and is a prolongation only to the upper limits of normal. This increase appears to be largely a delay in the activation of the base of the right ventricle and is reminiscent of what is traditionally known as "right bundle-branch block." Later the initial vector of the QRS complex is also prolonged and the QRS resembles a rather indeterminate ventricular conduction defect. Here there may be rhythm disturbances, especially nodal rhythm. The PR interval may become prolonged, so much so that the P-wave is lost in the preceding T-wave.

Lastly, the lethal result of uninterrupted progressive hyperkalemia is the "sine" wave of ventricular fibrillation.

	f.	g.	h.	i	j
K meq / L	7.8	8.0	8.5	9.0	9.3



The V Lead above is the precordial lead showing the most marked T wave change.

FIGURE 10.

Comment

These data show wide variation in the relationships between the concentration of plasma chemicals and the pattern of the simultaneously recorded electrocardiograms. We believe the explanation for this lies in the multiplicity of chemical abnormalities measured (and we did not measure them all), rather than in the factors embodied in the term "individual variation."

The electrocardiogram is an accurate, sensitive instrument for measurement of depolarization and repolarization of myocardial muscle cells. It is affected by various plasma electrolytes. The vari-

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ation in concentration of a single electrolyte may be reflected with considerable precision by the electrocardiogram. However, it is impossible to vary a single electrolyte even experimentally for chemical equilibrium must be maintained.

Clinical situations are even more complicated. We have shown that if calcium concentration is normal, the electrocardiogram reflects the potassium level with considerable accuracy. The electrocardiographic changes produced by progressive increments of plasma potassium are rather predictable and consistent provided the additive effects of hypocalcemia are not superimposed. In our cases other concomitant changes in electrolyte concentration have not shown an appreciable effect. Our inability to show a consistent electrocardiographic reflection of alternations in concentration of plasma sodium has been especially disappointing.

The electrocardiogram does not lend itself well to the comparison of duration and amplitude measurements in different patients. Positional variations are difficult to eliminate; QRS duration and QT interval vary in normal persons. In addition, there are variations from the normal in our patients that defy measurement, such as the peaking of T-waves in hyperkalemia.

Often a changing pattern in serial tracings has been of more significance than a single tracing. We have observed several episodes of severe potassium intoxication interrupted by artificial dialysis in the same patient. Electrocardiograms serially taken in separate episodes recorded similar patterns at similar levels of hyperkalemia when other abnormalities had been corrected.[26] Others have made like observations, finding the electrocardiogram to be an index of the level of hyperkalemia,[8, 14] and that the electrocardiogram shows definite evidence of hyperkalemia when serum potassium exceeds 7.4 mEq./L.[13] Other observers[1, 8, 14] have found QT duration to be prolonged in hyperkalemia. We have been unable to do so. Hypocalcemia associated with hyperphosphatemia may account for the discrepancy.

Summary and Conclusions

1. Data from 663 electrocardiograms and blood chemical determinations in 61 patients are presented.

2. The relationships between the configuration of the electrocardiogram and the plasma concentration of potassium, calcium, sodium, phosphorus, chloride, bicarbonate and nonprotein nitrogen are discussed. Only potassium and calcium are demonstrated to have potent effect on the electrocardiogram in our series.

3. QTc interval is prolonged in hypocalcemia and hyperphosphatemia. QRS duration is prolonged in hyperkalemia. T-wave amplitude is increased in hyperkalemia.

4. These data show wide variation in the electrocardiographic reflection of multiple electrolyte abnormalities. However, there is a step-wise evolution of electrocardiographic abnormality in progressive hyperkalemia when calcium concentration is normal.

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Chapter 15

Staphylococcal Bacteremia: Report of a Case Successfully Treated With Erythromycin*

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Recent data indicate that there is an increasing number of staphylococcus strains resistant to chemotherapeutic agents. Two cases of acute bacterial endocarditis due to hemolytic *Staphylococcus aureus*, which ended fatally despite treatment with virtually all the antibiotics except erythromycin, were reported by Carmichael.[1] In Boston City Hospital, about 75 per cent of the 500 strains of hemolytic, coagulase-positive staphylococci were resistant to penicillin, 25 per cent to aureomycin and 33 per cent to oxytetracycline (Terramycin). Finland and Haight [2] felt that the widespread use of antibiotics is probably of great importance in this increase of resistant staphylococci and other bacteria. Pulaski *et al.*[3] have noted that a decrease in penicillin-sensitive strains of *Staphylococcus aureus* closely parallels uncontrolled cross infection. Sherris and Florey [4] observed a distinct correlation between the clinical manifestations and the penicillin sensitivity of the causative staphylococci. While deep-seated infections were usually associated with penicillin-sensitive staphylococci, penicillin-resistant staphylococci were principally found in superficial lesions.

The problem of drug-resistant pathogenic staphylococci was recently encountered by us in a seriously injured man, who had in addition to multiple fractures and renal insufficiency, a bacteremia due to a staphylococcus which proved to be resistant to all of the routinely used antibiotics. It is our distinct impression that the improvement in his clinical course coincided with the administration of a new antibiotic, erythromycin,[5] and because of this we feel justified in accrediting to this agent a major share in his ultimate survival. Erythromycin is derived from *Streptomyces erythreus*, and is a broad-spectrum antibiotic, most active against gram-positive and less against gram-negative or-

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* From the Renal Insufficiency Center, 11th Evacuation Hospital, Wonju, Korea. Reprinted from *American Practitioner and Digest of Treatment*, July 1954, Vol. 5, No. 7.

ganisms.[6] It is also said to be effective against rickettsioses, viral pneumonia and infections with *Corynebacteria* and *Clostridia.* Its spectrum in general parallels that of penicillin, but its high effectiveness against staphylococci, including those resistant to other antibiotics, may make it a valuable adjunct to the antibiotic armamentarium.

Case Report

A 25-year-old soldier was injured in a truck accident in Korea on the night of April 1, 1953. When taken to a clearing company, he was in shock. Despite treatment, he was still in shock when admitted to the 46th Army Surgical Hospital. There he was given 3,000 cc. of blood, 500 cc. of dextran, and norepinephrine. His blood pressure gradually rose to 100/40 mm. Hg. and following an additional 1,500 cc. of blood the pressure stabilized near 150/98 mm. Hg. The urinary output for the first 12 hours after admission was only 11 cc., despite the maintenance of an adequate blood pressure.

Thus, on April 3, 36 hours after injury, he was transferred to the renal insufficiency unit of the 11th Evacuation Hospital. The surgical diagnosis was a simple fracture of the left humerus and a compound fracture of the left mid-femur. A hip-spica was applied to the latter which was treated as a closed fracture because the open wound was thought to have been produced by bone puncture from within.

Initial antibiotic treatment consisted of 600,000 units of penicillin and 0.5 gm. streptomycin daily. The temperature ranged from 99 to 101° F. Renal insufficiency persisted and uremia and hyperpotassemia became progressively more severe. On April 8 he was subjected to dialysis on the artificial kidney for 6 hours. Uremia and serum potassium elevation, however, rapidly recurred, now with 347 mg. per cent serum nonprotein nitrogen and 8.8 mEq. per liter serum potassium. A second hemodialysis was performed on April 12. Following this he developed acute pulmonary edema and signs of a pulmonary process, probably of infectious nature, in the left upper lobe. At this time streptomycin was discontinued and chloramphenicol, 2 gm. daily, started along with penicillin.

A third dialysis on the artificial kidney became necessary and was successfully performed on April 17. Following this diuresis began, and on April 20 exceeded for the first time, 1,000 cc. per day. There were no further signs of renal dysfunction. Due to the critical state, no attempts were made until then to deal with the fracture sites despite the realization that the surrounding necrotic tissue was playing a part in the recurrent rapid elevation of the serum nonprotein nitrogen and potassium. The patient appeared to be progressing satis-

factorily when on April 20 he developed a chill and fever, and his temperature rose to 104° F. A blood culture at this time yielded a hemolytic staphylococcus. Six more blood cultures taken during the next 7 days also yielded the same organism. A chest roentgenogram at this time showed a cystic pneumonitis with probable abscess formation in the left upper lobe. The site of the fracture of the left thigh was swollen and tender. Cultures taken from the bloody drainage revealed a hemolytic staphylococcus and *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*).

The staphylococcus was tested for its susceptibility to six antibiotics, using Difco discs and by the serial tube dilution method. It was resistant to terramycin, 60 mcg.; dihydrostreptomycin, 100 mcg.; aureomycin, 60 mcg,; and bacitracin, 20 units; with both methods. In the tube tests, it was resistant to penicillin, 50 units; and sensitive to chloramphenicol, 10 mcg., as well as to 2 mcg. erythromycin per cc. medium.

Thus, on April 24, 1953, penicillin was discontinued and chloramphenicol (0.5 gm. intravenously b. i. d. and 0.5 gm. orally q. i. d.) was given. The patient's condition, however, continued to be more and more critical, despite the large amounts of chloramphenicol received. The temperature ranged between 103° and 105° F. and a toxic psychosis developed. Severe dyspnea and tachycardia persisted. All daily blood cultures taken during this period revealed hemolytic staphylococci.

On April 27, 1953, a supply of erythromycin was obtained.* The patient was immediately started on 2 gm. and later given 4 gm. per day, while chloramphenicol was discontinued. The daily blood cultures taken thereafter were negative, and continued to be so throughout the remainder of the patient's illness. On April 30, aqueous penicillin, one million units every 2 hours (12 million units daily), was begun and later Gantrisin was also added. Following this the fever fell gradually, the toxic psychosis slowly cleared, and the roentgenologic evidence of pneumonitis lessened. Recovery was slow.

At no time during the course of the patient's illness was there a definitive cardiac murmur heard, but at the height of illness a coarse, pericardial friction rub was detected. On May 10, the clinical condition had improved sufficiently so that the patient was evacuated to Japan, continuing on the previous antibiotic regime at the Tokyo Army Hospital, where for about 45 days the patient was on an antibiotic schedule of erythromycin, 2 gm. daily; penicillin, 15 to 32

*The erythromycin was obtained through the courtesy of Dr. J. W. Smith of the Medical Department, Eli Lilly and Company.

million units daily (given by combined intravenous and intramuscular routes); streptomycin, 2 gm. daily; and Gantrisin orally, 6 gm. daily. Between May 10 and June 4 the temperature ranged from 98.6° to 100.4° F., and subsequently remained normal for 30 days. Blood cultures taken during this period remained sterile. On May 23, a culture of the necrotic material near the fracture of the femur revealed *Pseudomonas aeruginosa* but no staphylococci. On May 27, the necrotic tissues were débrided. This was followed by a brief period of shock. Upon recovery, more rapid improvement ensued, although a tachycardia persisted. On June 30, all antibiotics were discontinued and the patient remained afebrile. The fracture sites were healing; his appetite had returned and he is beginning to regain some of his considerable weight loss.

Discussion

In this case, *Staphylococcus aureus* bacteremia persisted for 7 days in spite of treatment with penicillin and chloramphenicol. The blood cultures became sterile, however, immediately after the beginning of erythromycin medication. *In vitro* sensitivity testing confirmed the clinical impression that erythromycin was the most effective antibiotic against this strain of staphylococcus. The origin of the staphylococcal bacteremia remained in doubt, but it is likely that there were multiple infected foci in the lung and in the necrotic tissues about the fractured left femur. An acute bacterial endocarditis was neither ruled out nor confirmed.

It is impossible to ascertain what effect the additional antibiotics, given later in the illness in conjunction with erythromycin, had on the ultimate recovery. Certainly, there was no evidence of antibiotic antagonism. On the contrary, a synergistic effect may be suspected in this case. Because of the close similarity in the antibacterial spectra of penicillin and erythromycin, it seems logical to presume that each may have played some role in the suppression of this infection, especially in view of the large doses of penicillin that were utilized.

Summary

A seriously injured man who suffered from multiple fractures, blood loss, shock, and severe renal insufficiency necessitating three artificial hemodialyses, with a virulent staphylococcal bacteremia, was eventually brought back to health by a prolonged series of therapeutic procedures. The hemolytic *Staphylococcus aureus* isolated from this case was resistant to the routinely used antibiotics *in vitro*, but was very sensitive to erythromycin. Recovery, although slow, could be dated from the time that treatment with erythromycin was begun.

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Chapter 16

A Survey of the Hemostatic Mechanisms in Acute Post-traumatic Renal Insufficiency

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(This information has been abstracted from a longer report prepared by Pfc Deaver.)

Hemorrhagic disease often appears in patients with severe renal insufficiency of whatever etiology. In medical cases it may manifest itself only by the appearance of large bruises at points of venipuncture, but in the battle casualty the disease is more serious because of the presence of wounds.

In December 1952 Captain Paul Teschan made a survey of the patients at the Renal Insufficiency Center and reported the following manifestations of hemorrhagic disease:

Patient 1—Gingival bleeding on the fourth post-wound day.

Patient 2—Tarry stools on post-wound days 9 to 15.

Patient 3—Bloody diarrhea on post-wound days 14 to 24.

Patient 4—Profuse bleeding from cut-downs and from wounds when dressings were changed.

Patient 5—Bleeding from drains in the right upper quadrant on the thirteenth day. Laparotomy showed a generalized oozing from the bed of the right kidney.

Patient 6—Bloody vomitus, bloody diarrhea and bleeding through his incision. A laparotomy revealed generalized oozing from the traumatized areas.

Patient 7—Brisk bleeding from the wound on the eleventh day.

The tendency to bleed in these patients may sometimes threaten their lives. It was for this reason that a study was undertaken to learn if possible the reason for this bleeding disease in battle casualties with post-traumatic renal insufficiency.

Materials and Methods. The study was carried out in the first half of the year 1953 at the Renal Insufficiency Center, 11th Evacuation Hospital, operating in support of the U. S. Eighth Army at Wonju in Korea. The work was carried out under the supervision of Captain Paul E. Teschan and Major William H. Meroney following a protocol that had been prepared by Lieutenant Russell Scott and Lieutenant Colonel William H. Crosby. The methods for tests of the hemostatic system have been described by Scott and Crosby.[1] The

chemical procedures were performed in the laboratory of the Renal Insufficiency Center. The methods have been described elsewhere.[2] A battery of tests was made serially in each case from the time the casualty was admitted to the Center until he died or was evacuated to Japan. Twenty-seven patients with severe renal insufficiency were included in the investigation.

Results. Table 1 shows the results of the battery of tests performed on several patients at times when marked abnormalities of one or more tests were evident. Table 2 shows the results of the serial testing done on a single patient during the first 2 weeks of his convalescence. This demonstrates the extent of the battery of tests and the interval at which the tests were performed in each of the subjects. An abstract of the results in all patients follows.

Coagulation time determined in 27 patients was usually prolonged in those with hemorrhagic disease and the prolongation seemed proportional to the severity of the disease. Patients with abdominal wounds seemed more severely affected than patients with wounds of the extremities but in general those with abdominal wounds were in a more critical condition than the others.

Clot retraction was often grossly abnormal and when it occurred in a patient it usually remained abnormal for several days. This was observed in two patients with thrombocytopenia, but it also occurred where the platelet count was adequate (Table 1, patient 102).

Platelet count (or an estimation of platelets made by examining a stained smear) demonstrated an adequate number in all patients excepting the two who had a temporary (5 or 6 days) but significant thrombocytopenia.

Tourniquet test for capillary fragility was abnormal in the two men with thrombocytopenia. The test was not performed consistently in all patients but it was usually negative when done. A few positive results were encountered in some patients during the time of hemorrhagic disease.

Fibrinogen levels were measured serially in 17 patients. Elevated levels were encountered almost invariably during the first 5 days after wounding and in some cases persisted for as long as 39 days. Fibrinogenopenia was not encountered.

Fibrinolytic activity was measured in 10 cases and the amount of lysis ranged from zero to 15 per cent, which values are not abnormal. In one patient only was there sufficient fibrinolytic activity to lyse completely the whole-blood clot in 24 hours.

Plasma prothrombin activity as determined by the one-stage method was usually moderately reduced. It was never so low that it alone would have caused abnormal bleeding.

Table 1. Hemostatic Tests in Acute Post-traumatic Renal Insufficiency

Patient	81			102		104		
Site of Wound	Abdomen and Extremities			Extremities		Extremities		
Day post-wound	6	11	12	23	26	17	23	27
Coagulation time (min.)	61	120s	120s	35	19	18	19	21
Clot retraction (1 hour)	poor	poor	complete	poor	poor	poor	complete	complete
Plasma prothrombin (% of normal)	25	35	50	70	95	95	73	95
Prothrombin consumption (% of plasma prothrombin)				0	90	65	95	95
Fibrinogen (mg./100 ml.)	610			439	556		572	590
Fibrinolysis		complete	complete					12
Bleeding time (min.)	4.5			35	2.5	1.5		
Platelets	low		adeq.	low	140,000	adeq.	adeq.	adeq.
Tourniquet test	pos.	pos.	pos.	pos.	neg.		pos.	sl. pos.
Nonprotein nitrogen (mg./100 ml.)	390	282	348	285	193	216	247	188
Plasma sodium (mEq./L.)	135	151	146	139	148	134	170	149
Plasma potassium	6.3	6.0	6.1	4.3	3.8	6.1	5.1	5.2
Carbon dioxide (vol. %)		12.7		20	27	25	22	23
Plasma calcium (mg./100 ml.)				8.2	9.4	6.2		12.3
Plasma bilirubin (mg./100 ml.)	11.3	5.0	5.4	1.25	0.66		1.1	0.66
Urine output (ml./day)	1400			4085	2870	295	1570	2695

Table 2. Hemostatic Tests in Acute Post-traumatic Renal Insufficiency

Patient 102—Wounds of the Extremities.

Dialyzed on the Artificial Kidney on Post-wound Days 5, 9 and 13.

Day post-wound	2	3	4	6	7	8	9	10	11	12	13	14
Coagulation time (min.)	23	29	15	40	22	18	19	15	16	16	16	16
Clot retraction (1 hour)	poor	poor	poor	poor	poor	poor	poor	poor	good	good	good	good
Plasma prothrombin (% of normal)	95	90		74	100	95	85	85	90	80		80
Prothrombin consumption (% of plasma prothrombin)	90	95	95	80	85	95		80	40	75	60	50
Fibrinogen (mg./100 ml.)	775											
Bleeding time (min.)	3.5	3										
Platelets	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.	adeq.
Tourniquet test	neg.	neg.										
Hematocrit		40	34				37				28	27
Nonprotein nitrogen (mg./100 ml.)	64	121	189	114	132	182	265	153	200	212	292	116
Sodium (mEq./L.)	129	127	147	144	146	135	130	141	151	132	146	136
Potassium (mEq./L.)	6.7	7.4	6.7	5.5	7.1	7.0	7.5	5.9	6.1	6.4	7.8	3.6
Carbon dioxide (vol. %)	27	27	26	27.5		21.0	19	24	22.0	22	14	22.5
Calcium (mg./100 ml.)	7.7	8.4	8.7	7.0		8.0	7.2	6.7		6.3	6.0	11.0
Bilirubin (mg./100 ml.)	1.78	1.44	0.54	1.00	0.76	1.00	0.51	0.49	0.71	0.76		3.44
Urine output (ml./day)	385	135	50	85	150	105	135	85	140	195	240	100

Serum prothrombin activity (prothrombin consumption) was studied in 13 patients. It was not often abnormal even when the coagulation time was grossly prolonged. Prothrombin consumption was sometimes deficient, even in the presence of an adequate number of platelets (Table 1, patient 104). When this was found in a patient it occurred consistently day after day for several days.

Discussion. The battery of tests performed on patients with acute post-traumatic renal insufficiency revealed no consistent single defect that would account for their tendency to bleed. In some patients there was transient thrombocytopenia of a degree capable of causing thrombocytopenic purpura. In others faulty clot retraction in the presence of adequate numbers of platelets suggested a qualitative deficiency in platelets. However, prothrombin consumption was not consistently decreased, suggesting that the platelets were not deficient in their ability to form thromboplastin even though the effect of clot retraction was diminished. The prolongation of clotting time remains unexplained. This was the most consistent abnormality and it is one that deserves further study.

Notable in the over-all results in these many patients is the presence of multiple small defects in the coagulation mechanism, differing in kind and degree from one patient to another. It is possible that the tendency to bleed results from the summation of small defects none of which would by itself interfere with hemostasis.

Summary

1. Patients with severe renal insufficiency frequently develop an abnormal tendency to bleed. A battery of tests of the hemostatic system was performed serially on 27 battle casualties who had severe post-traumatic renal insufficiency.

2. There was no consistent fault found by these tests excepting prolongation of coagulation time and moderate deficiency of prothrombin activity. Most of the patients showed other abnormalities but the time and degree were not consistent.

3. The cause of the bleeding disease in severe renal insufficiency has not been identified.

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