SEPSIS, DISSEMINATED INTRAVASCULAR COAGULATION AND MULTIORGAN FAILURE: CATASTROPHIC EVENTS IN SEVERE BURNS

H.A. Linares

Shriners Burns Institute and The University of Texas Medical Branch,
Galveston, Texas 77551, USA

INTRODUCTION

A thermal burn is essentially an inflammatory process which, if severe enough, can elicite not only local damage but a wide spectrum of systemic manifestations accompanied by life-threatening complications.

The anatomical observations during the past two centuries have confirmed this vast ensemble of morphological multisystem lesions evolving from the severe physiopathological derangement which takes place in the severe burn patient(Cumin 1823; Dupuytren 1839; Long 1840). The ensuing complications rather than the burn itself, are the major causes of morbidity and mortality although they are closely related.

In most of the cases, assessment of the actual mechanism of death is a very difficult task. Thus, it is pertinent to remember Cohennheim (cited by Orth 1908) who stated that people do not die because they develop pulmonary edema, but that they develop pulmonary edema because they are about to die.

Frequently, the establishment of the cause of death is closer to the subjective judgement of the observer than to any other objective evidence and, in most cases, selecting a single cause of death for each burned patient is neither easy nor always possible (Argamaso 1967; Delarue 1962; Sevitt 1972). The only pathognomonic burn lesions are those occurring in tissues that are directly exposed to the thermal source. If the patient survives long enough, the autopsy findings will be related to the complications rather than to the burn itself. In these cases, representing the vast majority, death can be attributed to multiple causes that often are very difficult to interpret. Furthermore, studies during life and at autopsy do not always result in an adequate and satisfactory explanation of the events, and the pathophysiologic disturbances leading to death may leave no anatomical traces (Wartman 1962).

However, the contribution of autopsy material to the better understanding of the perplexities of the burn illness cannot be underestimated. A careful morphological evaluation of the anatomical histological lesions and their clinical correlation

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can provide an invaluable critical analysis and give relevant information about important complications, unsuspected lesions, therapeutic effects or previous diseases.

Sepsis remains one of the most dangerous complications and in most cases originates in the burn wound. The presence of large extensions of open areas of injured skin with a very high potential for colonization by microorganisms (bacteria, fungi, virus) is a common source for further invasion of viable tissue and subsequent septicemia.

The complex physiopathological responses elicited by a severe burn injury affect different tissues and organs which may react promoting a variety of changes leading to multiorgan dysfunction. Thus, a cummulative sequence of organ failures may involve vital areas such as the cardiorespiratory system, kidneys, liver, the gastrointestinal tract or the central nervous system.

The burn tissue may also release tissue thromboplastin and other cellular enzymes into the systemic circulation triggering a disseminated intravascular coagulation-like process which is almost always present to some degree at the early period of critical burns. The initiation of coagulation may also be triggered by bacterial, fungal or viral procoagulant activators. In fact, DIC and sepsis are a frequently described cause-effect mechanism. Similarly, sepsis and the development of multiorgan failure has been described as a frequent concurrence. Therefore, it would not be uncommon to find severe burn injuries associated with a series of complications including sepsis, disseminated intravascular coagulation (DIC) and multisystem organ failure (MOF). We have reviewed 100 consecutive autopsies performed in burned children from 1973 to 1989 in order to evaluate the combined presence of these three major complications.

MATERIAL AND METHODS

From 1973 to 1989, 105 autopsies were performed at the Shriners Burns Institute. For this study five autopsies were excluded because of the circumstances related to death (1 dislodged endotracheal tube, 1 intraoperative death, 2 died shortly after arrival from a foreign country and, 1 was a toxic epidermal necrolysis, not a burn). Of the 100 children, 57 were males and 43 were females with an age range of 5 months to 18 years and a mean age of 4.7 years. Fifty were white, 32 were black, 17 were latin-american and one was asiatic. In 86 of the cases the burns were caused by flame and in 14 cases the injuries were due to scalding.

The percentage of total body surface burned area (TBSA) ranged from 25 to 100% with a mean burn size of 69.2% ($\pm$18.6). The average extension of full-thickness injury was 59.1% ($\pm$24.5). The patients were divided in three groups according to the extension of the injury: less than 49% of surface area burned, from 50% to 79% and more than 80% of surface area burned (Table 1).

Twelve children died within 3 days postburn, seventeen died between 4 to 7 days post burn, 17 died between 8-14 days post burn, 25 died between 15 to 30 days post burn and 29 died more than 30 days after the burn injury.

Table 1. Distribution of % TBSA and % 3rd. degree burn

	< 49%	50-79%	> 80%
TBSA	n = 17	n = 44	n = 39
3rd. degree burn	n = 42	n = 28	n = 30

n= number of patients

Sepsis was diagnosed at autopsy when pathogenic microorganisms were seen invading viable tissues and yielded positive blood cultures. We define septicemia as a syndrome caused by the persistent presence of pathogenetic microorganisms and/or their toxic products in the blood and/or body tissues, resulting in physiologic derangement (Linares 1982).

The criteria for post mortem diagnosis of DIC was the presence of multiple intravascular microthrombi with or without perivascular hemorrhages or multifocal hemorrhages and/or laboratory confirmation based on Prothrombin Time (PT), Activated Partial Thromboplastine Time (APTT), Plasma Fibrinogen, Platelet Count, and Fibrin Degradation Products (FDP).

Five organs or systems were selected to evaluate the incidence of MOF. These were lung, heart, kidney, liver and the gastrointestinal tract (stomach, duodenum, small and large intestine). A variety of morphological lesions along with clinical abnormalities at the time of the autopsy were evaluated and assessed retrospectively for each case, but only those lesions considered to be of anatomical and/or clinical significance were tabulated. A complete autopsy review was published elsewhere (Linares 1982, 1988).

Respiratory failure is generally defined as the presence of inadequate gas exchange requiring mechanical assistance for longer than 48 hours. The pathological morphology includes congestion, edema, hemorrhages, necrosis, microthrombosis, atelectasis and hyaline membranes. All these lesions are a common component in lungs with the acute respiratory distress syndrome (ARDS), inhalation injuries or shock (burn, sepsis).

Cardiovascular failure is the inability of the heart to maintain an adequate blood flow without pharmacological and/or mechanical assistance, despite adequate preload. Morphologically, the most common lesions are related to hemodynamic alterations such as congestion, edema, hemorrhages, ischemia and necrosis.

Renal failure may be defined as the inability of the kidneys to maintain an adequate volume of fluids and electrolytes, and also the inability to eliminate waste products. The histological lesions are compatible with a vasomotor nephropathy, acute tubular necrosis being the most common feature.

The incapacity of the gastrointestinal tract to function adequately and to maintain a useful oral nutrition defines gastrointestinal failure and the anatomical lesions are compatible with serious hemodynamics alterations (congestion, edema, hemorrhages, erosions, ulcerations, necrosis).

Hepatic failure is the inability of the liver to maintain its metabolic and biochemical functions. The anatomic morphology reveals serious hemodynamic alterations including congestion, edema and hemorrhages, significant hepato- cellular necrosis, intrahepatic cholestasis and fatty changes.

Data were analyzed using Fisher's exact test for 2x2 frequency tables. Observed differences were considered statistically significant when p values less than 0.05 were obtained.

RESULTS

As assessed by our criteria, sepsis was a contributory cause of death in 73 cases. DIC was present in 69 cases. Two or more organ failures were present in 94 of the 100 autopsies. Of the 73 cases of sepsis, 53 cases (72.6%) also had a combination of DIC and MOF (Table 2).

Table 2. Incidence of sepsis, DIC, and MOF, alone and in combination

SEPSIS = 73 cases
Sepsis and DIC = 54 cases (73.9%)
Sepsis and MOF = 71 cases (97.2%)
Sepsis, DIC, and MOF = 53 cases (72.6%)
DIC = 69 cases
DIC and MOF = 66 cases (95.6%)
MOF = 94 cases
without sepsis or DIC = 12 cases (12.7%)

The most prominent organs involved in MOF were lung (100%), heart (79%), kidney (68%), GI tract (49%) and liver (31%). The most frequent organ failure combination involved lung, heart, kidney (21%) followed by the combined failure of lungs, heart, kidney and GI (19%), the combined failure of lung, heart, liver, kidney and GI (15%), the combined failure of lung,

heart, and GI (9%), the combined failure of heart and lung (8%), the combined failure of heart, lung, liver and kidney (6%), lung and kidney (4%), and lung, liver and kidney (3%). There were no differences in the incidence of Sepsis, DIC and MOF when age, sex, race, or etiology were taken in consideration. Also, there was no difference if the evaluation of the elapsed time between the time of the injury and the admission to our Institute was performed. This is possibly due to the fact that our hospital is a referral facility, therefore most of the victims already received first aid and emergency treatment in some other place.

There were no significant differences in the individual incidence of Sepsis, DIC and MOF according to the extension of the body surface area burned. However, when in combination (DIC, Sepsis and MOF), the group of patients with burns from 50% to 79% of TBSA burn had a lesser incidence. There is no clear explanation for this finding but in this group, although not statistically significant, the incidence of DIC was lower and the survival time was longer while the elapsed time until admission was significantly higher.

The only significant difference found when the extension of 3rd degree burn was taken into consideration was related to sepsis alone, with a lesser incidence in those cases with less than 49% of 3rd degree burn.

Patients dying within 3 days after injury had a lesser incidence of sepsis and DIC alone, or sepsis combined with DIC and MOF, but there was no difference in the incidence of MOF alone. The incidence of sepsis and DIC individually was significant after four days post-injury, as was the incidence of DIC preceding the development of sepsis when the two processes developed in combination.

The combination of three organ failures was the most frequent event in MOF and this incidence was highly significant in patients with less than 49% TBSA.

The microorganism (alone or in combination) more likely to be the agent for the development of the septicemia was Pseudomonas Aeruginosa (43%) followed by Staphylococcus aureus (20%), Klebsiella pn. (19%), E. coli (15%), Enterobacter sp. (13%), Candida sp. (13%), Serratia marscecens (1%), Aspergillus sp. (1%), and Phycomycetes sp. (1%).

COMMENTS

It is apparent that, in our series, the association among sepsis, DIC and MOF in severely burned children was a frequent finding at autopsy. Each one of these manifestations constitutes by itself a life-threatening complication.

Sepsis, a complex syndrome which progresses with marked hemodynamic alterations, remains the leading contributory cause of death in the burn population around the world (Karyoute 1989; Linares 1988). The risk of infection is proportional to the severity of burn, the time of initiation

of fluid therapy, the presence of metabolic alterations, the development of immunological deficiency, the concurrence of trauma, the local evolution of the wounds and the age of the patient. Also, the risk of infection increases parallel to the increase in virulence and resistance of microorganisms. The infection may begin in the burn wound, the respiratory system, the gastrointestinal tract (translocation?), the urinary tract, the blood vessels (catheters) and also from localized infections in any area of the body or by nosocomial contamination.

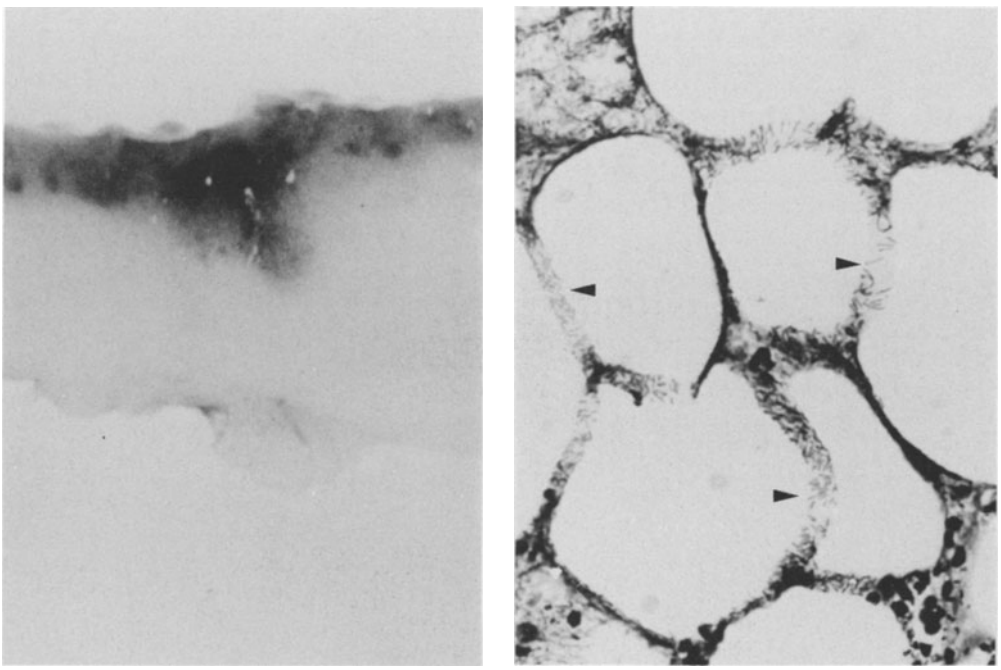

Fig. 1. Pseudomonas burn wound sepsis. Left, gross transversal section depicting the advance of the infection toward the subcutaneous tissue. Right, histological section showing the gram negative bacilli invasion (arrowhead) (hematoxylin-eosin, x 400)

Burn wound sepsis is suspected when the burn wound is the site of proliferating microorganisms exceeding 10^5/gm of tissue, and there is active invasion of subjacent unburned tissue (Teplitz 1964). The presence of microorganisms on or within the necrotic eschar cannot be considered sufficient evidence of burn wound sepsis, but as a site of primary colonization, it has potential capability for bacterial overgrowth and invasion of surrounding viable tissue (Fig. 1). Documented burn wound sepsis was the source of infection in most of our

cases of sepsis (80.8%) followed by air borne infections (16.4%).

Most of the physiopathological changes observed in sepsis seem to evolve from a variety of complex host dependent reactions and interactions still not completely understood (Marshall 1990; Wiles 1980). Increasing evidence accumulated by a number of investigators during the past several years shows that there is an ample variety of mediators both, beneficial and harmful, intervening in this fascinating process.

These many physiological responses convert to pathological reactions leading to a septic shock-like state or to a multiple organ failure (Marshall 1990). Bacterial products released into the circulation by gram-negative microorganisms (endotoxin lipopolysaccharides-lipid A) or by gram- positive bacteria (peptidoglycans) may produce severe damage of cell membranes (endothelial cells, blood cells, platelets, macrophages) inducing a variety of pathological responses

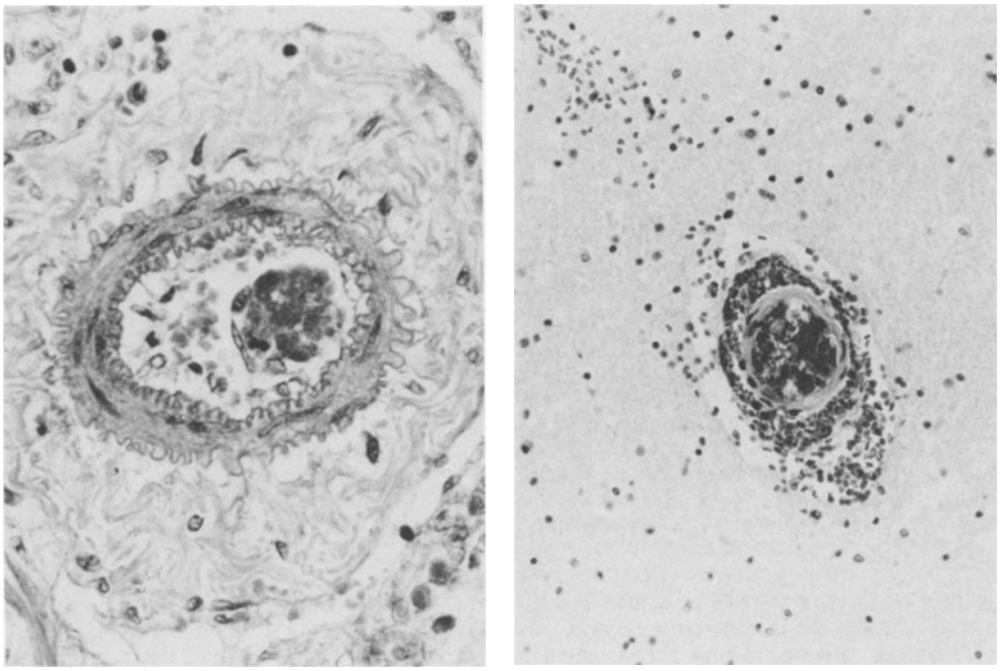

Fig. 2. DIC. Left, fibrin-platelet microthrombus in lung (hematoxylin-eosin, x 400). Right, fibrin microthrombus and perivascular hemorrhage in brain (hematoxylin-eosin, x 200)

potentially leading to the development of the septic shock syndrome. Thus, the activation of the coagulation system and

the complement (C3a, C5a), and the release of chemical mediators such as histamine, serotamine, prostaglandins, leukotrines, interleukin-1 or tumor necrosis factor will produce arteriolar dilatation, venous congestion and increased vascular permeability leading to a septic-shock state through a diminished cardiac output and cell perfusion (Cotran 1989).

This acute inflammatory response, however, may be elicited by factors other than bacteria as can frequently be seen in cases of burn (Demling 1988). Meakins (1980) for example, described a nonbacteremic clinical sepsis as sudden onset of worsening hypoxemia, hyperbilirubinemia, renal failure, thrombocytopenia, gastric bleeding and transient hypotension in the absence of positive blood cultures or clinical sites of infection.

Disseminated intravascular coagulation (DIC, microcirculatory thrombosis) is another serious complication in burn patients (Alkjaersig 1980; Curreri 1970; Eurenius 1974; McManus 1973). This thrombohemorrhagic disorder is characterized by the activation of the coagulation sequence with thrombotic and microemboli phenomena associated with bleeding (Effeney 1978; Hamilton 1978; Hardaway 1963).

The extensive tissue necrosis occurring in severe burns along with the inflammatory response, the erythrocytes, platelets and endothelial cell damage, or the exposure to subendothelial collagen can promote disseminated intravascular coagulation by the release of procoagulants or thromboplastin-like substances (extrinsic pathway). The systemic circulation of thrombin promotes the cleavage of fibrinopeptides from fibrinogen. The resultant fibrin monomers polymerize into fibrin aggregates leading to the intravascular thrombosis, tissural ischemia and in some cases, to a microangiopathic hemolytic anemia (red cells fragmentation). Thrombocytopenia may result from the entrapment of platelets within the fibrin clot and the systemic circulation of plasmin may promote the formation of fibrinogen degradation products (FDP). The FDP interference with fibrin monomer polymerization, as well as the consumption of blood coagulation factors, the depletion of platelets and fibrinogen, and the activation of plasminogen may lead to hemorrhages. The initiation of the Kallikrein pathway leads to an increased vascular permeability, hypotension and shock (Bick 1988).

In our series, there were 69 cases of verified DIC. In 64 of them, fibrin microthrombi were present at autopsy. The thrombi were observed most frequently in the lung (81%), followed by the skin (21.7%), kidneys (11.5%), gastrointestinal tract (11.5%), spleen (8.6%), heart (4.3%) and in lesser percentage, in other organs such as thymus, pancreas, liver, adrenals, ovaries, muscle, airways and gallbladder (Fig. 2,3).

Burned patients have supranormal in vitro clotting activity and may develop the syndrome of DIC coincidently with septicemia or hypotension (McManus 1973). Bleeding tendency in the early phase and hypercoagulability in the late phase of acute burn care are common clinical observations. During the

period of high coagulation (3 to 10 days after injury) in which acute burn patients may exhibit hyperfibrinogenemia and elevated fibrin-fibrinogen split products, DIC might be precipitated by shock or sepsis (Bartlett 1980;Eurenius 1974).

Also DIC can occur without depression of all the intrinsic clotting factors below the accepted normal values because of the common elevation in burns of factor VIII, fibrinogen or platelets. Therefore, the laboratory diagnosis of DIC may be masked. The diagnosis may be confirmed by the histological presence of fibrin thrombi, hyaline thrombi, platelet thrombi and/or hemorrhages, although these morphological features are not always present because microthrombi may be lysed by in vivo or post-mortem fibrinolysis (Curreri 1970; Neame 1973; Watanabe 1979).

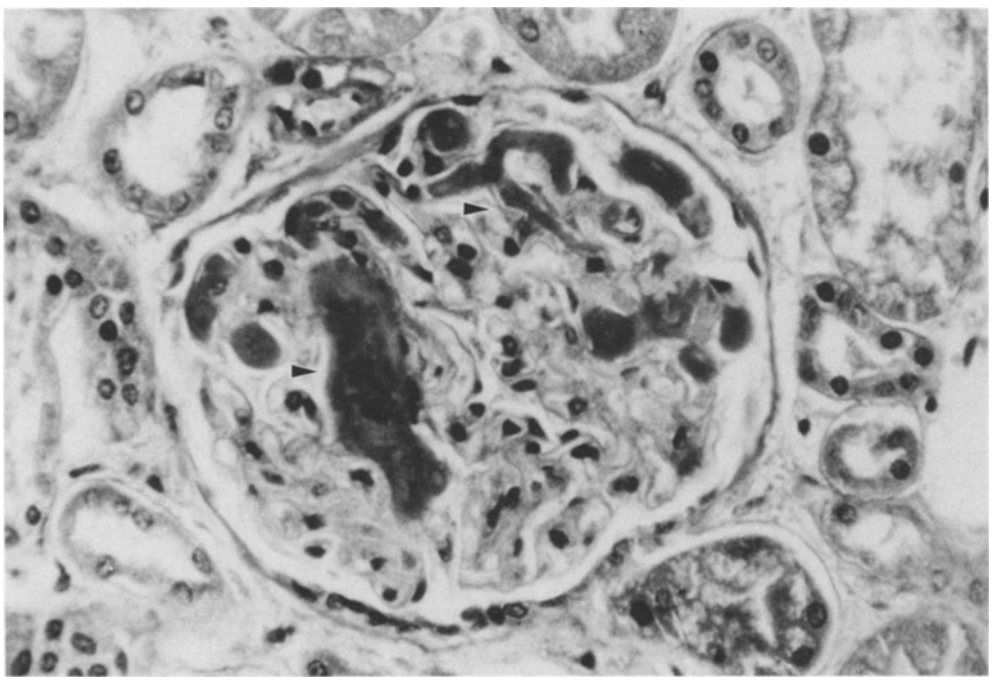

Fig. 3. DIC. Kidney, glomerular fibrin microthrombosis (arrowhead) (hematoxylin-eosin, x 400)

Platelet count in severe burn patients may vary widely from less than 100,000/mm^3 to more than 500,000/mm^3 but it is unusual to have a platelet count below 50,000/mm^3 unrelated to some degree of DIC. Thrombocytopenia is more likely to be caused by consumption during the genesis of the microthrombi rather than the inhibition of formation or release from the bone marrow (Sevitt 1974). In our series, of the 69 cases of

DIC, 38 patients (55%) had a platelet count that was less than 50,000/mm^3, in 11 patients (15.9%), the count was from 51,000 to 100,000/mm^3, in 9 cases (13%) from 101,000 to 200,000/mm^3 and in the remaining 11 cases (15%) the platelet count was over 200,000/mm^3.

Multiple system organ failure is a syndrome characterized by sequential rather than simultaneous failure of two or more organ systems and occurs when important organs such as lung, heart, liver or kidneys cannot spontaneously accomplish their functions (Baue 1975; De Camp 1988; Fry 1980).
This syndrome has a very high mortality rate and is the main cause of death in surgical and trauma patients in intensive care units (Goris 1985). Ironically, this syndrome has evolved under the shadow of the improvements occurred in the area of the intensive care units. The increased survival achieved by artificial support and monitoring of vital systems (i.e. cardio-respiratory, renal, gastrointestinal) has permitted the recognition of frequently fatal complications usually only indirectly related to the original illness.

The incidence of multisystem organ failure in burn patients is still unclear. In a four year review of 117 severe burns averaging 48.4% total body surface area, Mohan (1988), showed

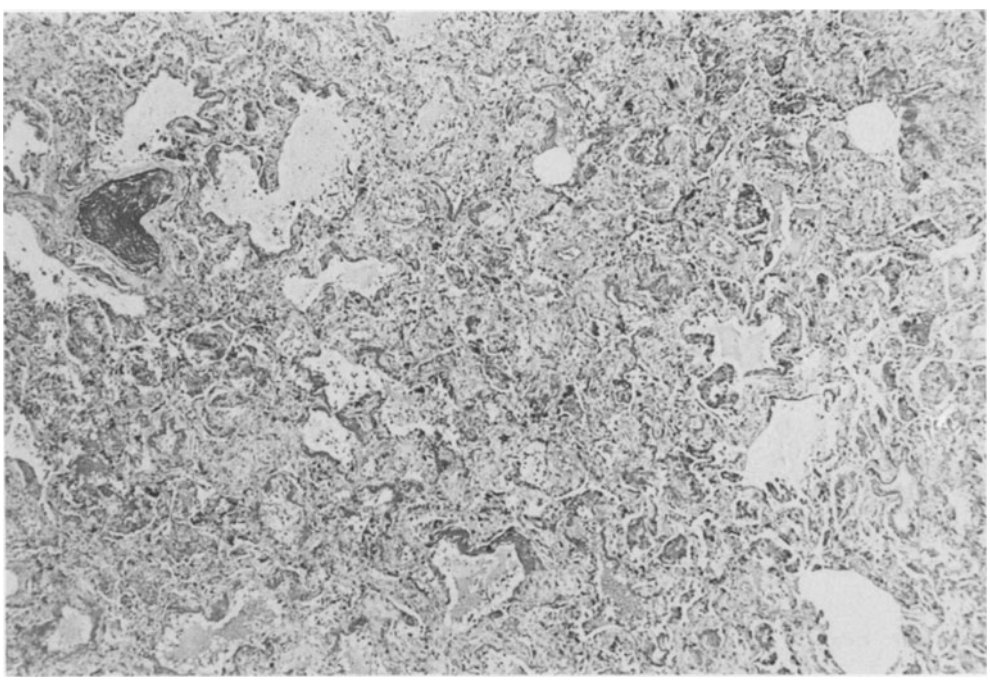

Fig. 4. Lung, ARDS. Interstitial and intraalveolar edema, fibrin microthrombosis, hemorrhages, hyaline membranes (hematoxylin-eosin, x 40)

a 67.5% of patients developing one or more organ system failure with a mortality rate of 72% for those with three or more organ system failure. The organ system most frequently affected was the respiratory followed by the immunological system, cardiovascular, hematologic, renal, hepatic and gastrointestinal. Aikawa (1987) reported an incidence of 16.5% MOF of 158 burned patients or 48.1% of the severe burns (more than 30% body surface area burned and/or inhalation injury). The mortality rate was 76.9% in MOF and 1.5% in non-MOF patients. The most frequently affected organ was the lung, followed by the heart, kidney, liver and the blood clotting system. In our series of autopsies, the incidence of MOF was very high (94%) and the organ system which most commonly failed was respiratory followed by heart, kidney, GI and liver.

As can be shown from our series, the lung is the main target organ, being respiratory failure the most conspicuous contributory cause of morbidity and death (Demling 1985; Petrof 1979). All the patients in this series had severe lung lesions ranging from the classical bacterial pneumonia to a distinctive acute respiratory distress syndrome. Sepsis, burn shock and inhalation injury were the most common determinants of respiratory system failure. A progressive deterioration of pulmonary function has been recognized as a frequent, and often fatal, complication in patients who have suffered severe

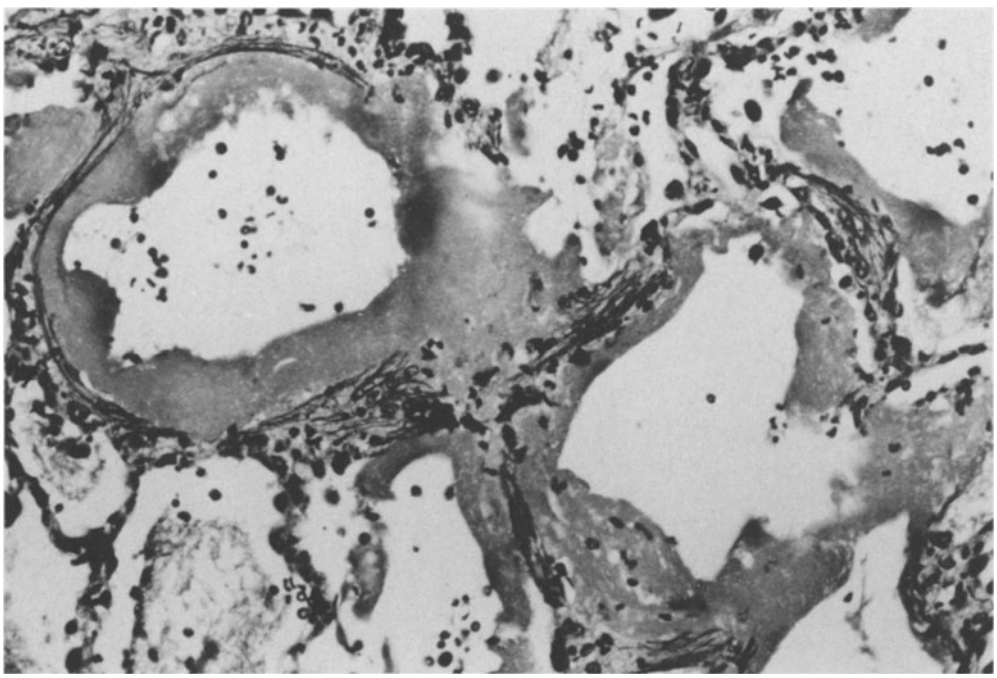

Fig. 5. Lung, ARDS. Hyaline membranes (hemat.-eosin x 400)

burns. The respiratory insufficiency is manifested by an increased respiratory effort followed by a progressive decrease in compliance, increased resistance, decreased arterial oxygen tension, and pulmonary arteriovenous shunting (Blaisdell 1973). This clinical syndrome and its variants has been described under a variety of terms such as posttraumatic pulmonary insufficiency, congestive atelectasis, traumatic wet lung, Da Nang lung and others (Blaisdell 1973; Fishman 1973). The lung has a limited reactional pattern and different types of injuries usually elicit a similar anatomical pathological response. Thus, this type of "pulmonary distress" (ARDS) may also result as a non specific pulmonary response to body tissue injury, inhalation injuries or sepsis (Clowes 1968). In this series 60% of the patients died with "pulmonary distress," 23% with bacterial pneumonia and the remaining 17% with a variety of other lesions such as aspiration pneumonia, pulmonary embolism, fluid and electrolyte imbalance, etc.

The more common morphological features seen in the patients dying with progressive respiratory insufficiency were interstitial and intra-alveolar edema and hemorrhages, atelectasis, intra-alveolar proteinaceous and cellular debris, hyaline membranes, leukostasis and fibrin microthrombi (Fig. 4, 5, 6). Although numerous factors have been implicated in the genesis of this type of lung damage, its pathogenetic

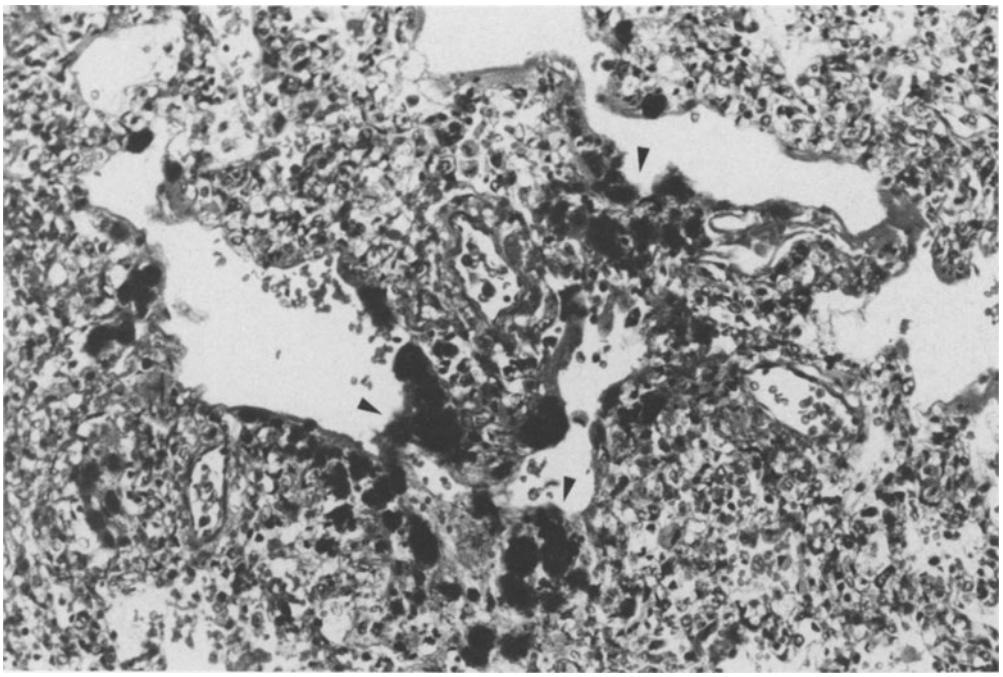

Fig. 6. Lung, ARDS. Hyaline membranes with bacterial infection (arrowhead) (hematoxylin-eosin, x 400)

mechanisms remain unclear (Demling 1987b). However, clinical and experimental evidence accumulated through the past several years seems to implicate the sequestration of polymorphonuclear leukocytes in the pulmonary microvasculature with the subsequent fragmentation and release of lysosomal enzymes (Craddock 1979; Henson 1981; Hosea 1980; Hyers 1981; Jacob 1980). Nevertheless, some reports indicate also the developing of ARDS without pulmonary leukostasis (Ognibene 1986; Swank 1989).

A common histologic feature in our series was the presence of leukostasis even in the presence of peripheral leukopenia (Table 3). (Fig. 7). The acute leukostasis observed in lung seems to be caused by the activation of the humoral systems particularly of the complement system (Craddock 1977). The activation of the sequestered leukocytes in the pulmonary circulation may originate multiple mediators which in turn may contribute to a variety of pathophysiological changes. However, although the neutrophil is a sufficient promoter of

Table 3. Leukocyte count/0.0645mm^2 in lung, liver, kidney and heart.

time post-burn	cause of death	sepsis	DIC	WBC (blood) (mm^3)	lung	liver	kidn.	heart
20 hrs.	Inhalation	no	no	3,500	>40*	5.1	2.1	1.3
21 hrs.	Inhalation	no	no	12,600	29.3*	8.4	2.6	1.5
32 days	Phycomycosis	yes	no	32,000	>40*	12.3	9.1	4.1
25 days	Inhalation	yes	no	19,900	>40*	9.1	4.9	3.2
3 days	Inhalation	no	yes	2,700	18.1*	4.2	1.4	1.2
22 days	Pseudomonas	yes	yes	10,000	18.6*	10.1	3.9	2.3
13 days	Pseudomonas	yes	yes	10,300	22.3*	6.1	1.3	0.6
5 days	Pseudomonas	yes	yes	1,800	>40*	8.2	5.1	3.1
normal values				5-10,000	5-10	3-6	3-6	1.3

*$p < 0.05$

the acute lung injury, the presence of activated neutrophils in the pulmonary vascular bed and interstitium may not signify tissue damage or make the neutrophil a necessary mediator of the tissue injury (Swank 1989).

Nevertheless, the general consensus among researchers is that leukocytes and their products are principal mediators of the pulmonary damage observed in the ARDS or related responses. Numerous local chemotactic agents (platelet-derived growth factor, lipoxygenase derivatives, hydroxyeicosatetraenoic acid, leukotrienes, C5a and others) along with the possible role of thromboxane A may contribute to the pulmonary leukosequestration (Hechtman 1984). A number of substances, both

useful or harmful depending on the biological circumstances, may be released by the polymorphonuclear leukocytes. Activated neutrophils not only release proteolytic enzymes but also generate a variety of oxygen metabolites (superoxide, hydrogen peroxide, hydroxyl radicals), cationic proteins, platelet activating factor or leukotrienes which have been shown to cause severe vascular injury (Vedder 1989). The damage of the capillary endothelium lead to permeability edema with further epithelial damage, alveolar collapse and many of the lesions above described (Schlag 1989).

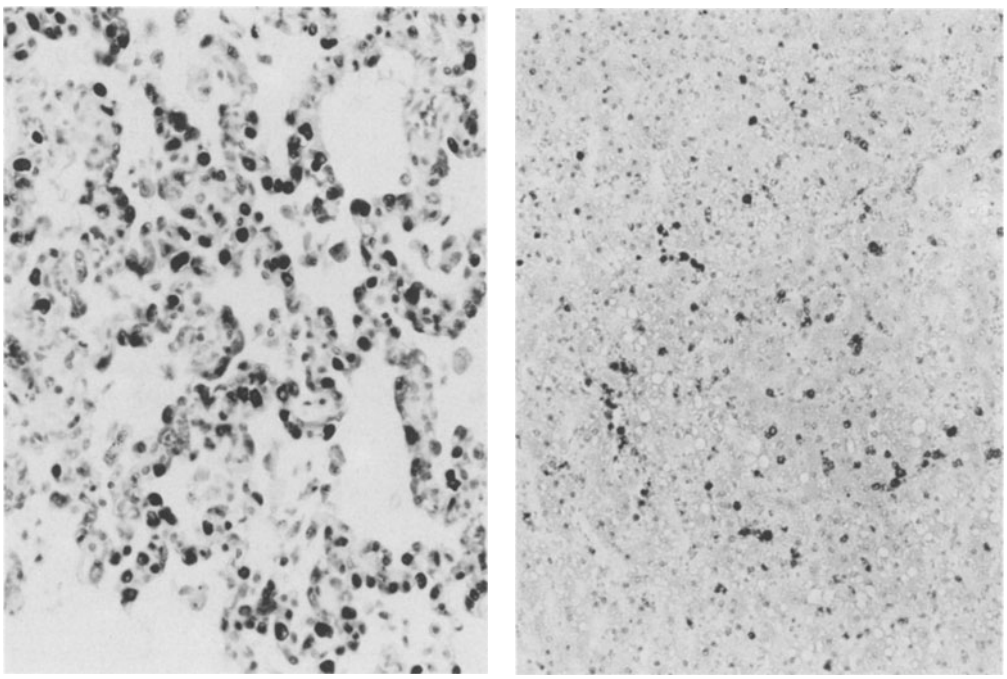

Fig. 7. Leukostasis. Left, lung, polymorphonuclear cells in septal capillaries (dark spots) (Leder, x 200). Right, liver, polymorphonuclear cells in sinusoids (dark spots) (Leder, x 100)

The post-burn hypovolemia due to the early loss of plasma volume (microvascular and cellular alterations) leads to a noticeable cardiovascular instability. It is still controversial if the postburn depression of the cardiac output is due to hypovolemia secondary to inadequate volume resuscitation or to a circulating myocardial depressant factor (Demling 1987a; Redl 1988). Most of the physiopathologic cardiovascular complications found in severe burned patients are secondary to sepsis or burn shock, usually related to inotropic disturbances (i.e. ischemia).

In our series, the heart disclosed anatomic lesions in 57% of the cases. Most of them consisting of subendocardial ischemia and to a very lesser degree, focal myocardial necrosis, hemorrhages or septic processes. Adding the anatomical lesions to the significant clinical symptoms within 48 hours of demise, the number of cardiovascular failures in our series reached 79%, and most of them, concommitantly with sepsis (Fig. 8).

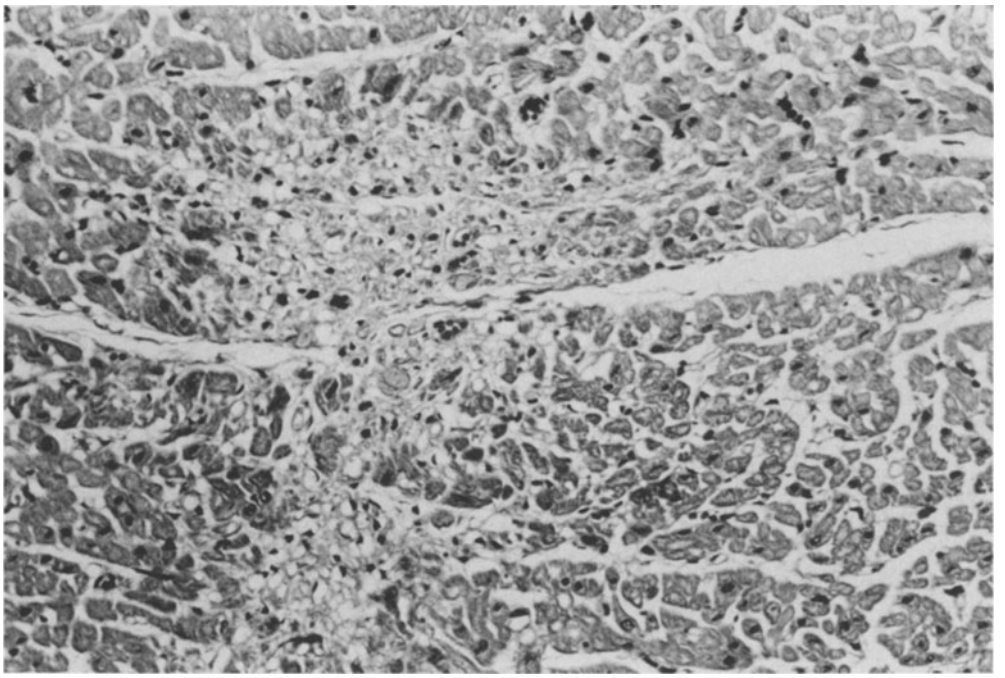

Fig. 8. Heart. Focal myocardial necrosis (hemat.-eosin x 200)

The kidneys are able to function properly even with only 20% of their normal capacity; however, this enormous reserve can be jeopardized because of the severe hemodynamic changes that occur during the shock phase. The cardiovascular disturbances, the neuroendocrine response, the electrolyte alterations, the tissue damage, the massive demands for exogenous fluid administration, and the subsequent reabsorption of burn edema form part of the complex mechanisms directly affecting the function of the kidneys. Thus, a state of kidney disfunction is frequently present in extensive burns during the immediate postburn period and in sepsis or shock from other causes.

The morphological lesions observed in the kidney not always coincide with the degree of the functional impairment, but

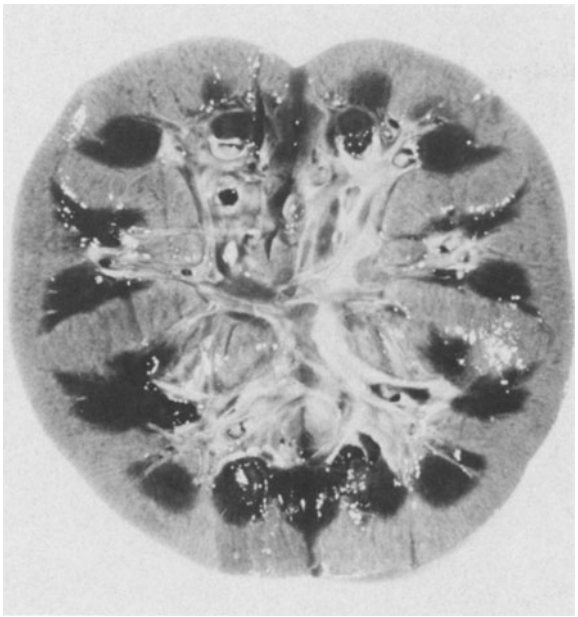

Fig. 9. Kidney, acute tubular necrosis, septic shock

an association between acute renal failure and the so-called "acute tubular necrosis" can usually be demonstrated. The later was the most common lesion in our series (68%) varying from focal to diffuse involvement of the tubules, sometimes affecting the proximal portion, sometimes the distal portion or both (Fig. 9).

A variable degree of liver dysfunction is often present in the burned patient and it is usually related to the severity of the injury. Fatty changes, a common finding, are per se reversible and their significance depends on the cause and severity of accumulation (Linares 1988).

The incidence of liver necrosis in our series (12%) did not differ significantly from other reports (Teplitz 1979; Yi-sheng 1985). It was generally focal or zonal (central or paracentral) and related to burn shock and sepsis. Intrahepatic cholestasis, which is one of the prime manifestations of hepatocellular injury, was present in 26% of our cases, all concurrent with sepsis (Fig. 10). The cellular damage observed in sepsis is most likely the result of decreased effective hepatic blood flow rather than direct cellular injury. (Hurd 1988).

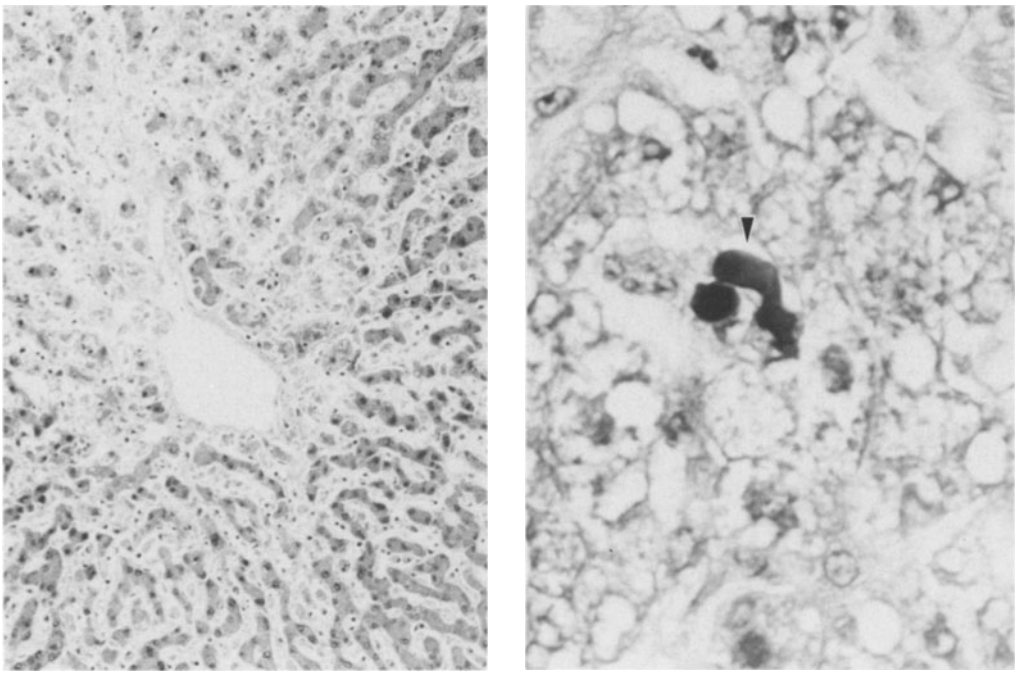

Fig. 10. Liver. Left, central ischemic necrosis (hematoxylin-eosin, x 100). Right, intrahepatic cholestasis, bile thrombus (arrow heads) (hematoxylin-eosin, x 400)

The criteria used in our anatomical assessment of liver failure for this particular review was to take into consideration only liver cell necrosis and intrahepatic cholestasis, excluding other common alterations seen in severe burned patients such as fatty metamorphosis and edema or congestion, and also the cases of DIC without anatomical alterations of the liver.

Cholestasis appears to be an important finding, and occurs without demonstrable extrahepatic obstruction. It has been described associated with a number of processes such as sepsis, hypoxia, drug toxicity or total parenteral nutrition (Cano 1983; Franson 1985; Phillips 1987). The mechanisms of intracholestasis remain uncertain and a variety of hypotheses have been proposed in the past several years. Among them, alterations in hepatocytes membrane (Kakis 1978; Reichen 1984), deficiencies in the bile secretory apparatus (Phillips 1980), blunting and distortion of microvilli (Erlinger 1978) microfilaments dysfunction (Phillips 1975) and alterations in tight intercellular junctions (Boyer 1983;, Elias 1980; Graf

1975). Because of the liver's innumerable functions, hepatic failure has many dimensions although the clinical features of hepatic failure are much the same, and the histological changes may not be conspicuous.

Acute digestive tract bleeding constitutes a relatively frequent gastrointestinal complication of severe burn injury. The initial postburn congestion and hyperemia of the mucosa frequently evolves into a diffuse bleeding, which can also originate not only a nonspecific, superficial and inflammatory process, but also erosion and/or ulcerations, with subsequent possibility of hemorrhage and perforation, a life-threatening complication. These lesions compatible with the so-called "stress ulcer syndrome" have been associated not only with burns, but also with several other conditions such as trauma, major surgery, sepsis, central nervous system lesions, respiratory disturbances, acute myocardial infarction, hepatic cirrhosis, and anti-inflammatory drugs.

Erosions and ulcers can be seen throughout the entire gastrointestinal tract, but the stomach and duodenum have been the sites of greatest predilection for this type of lesions; this may be due to the fact that gastroduodenal mucosa (especially stomach) is a labile tissue likely to be affected by any stressing stimulus.

The incidence of acute focal gastroduodenal necrosis in burns is very difficult to determine due to the multiple variables involved. In many cases, the gastrointestinal complains are minimal and are not even reported. Also, the results of the studies based on clinical cases or autopsy reports will differ considerably. Often, the gastroduodenal lesions of burned patients who have died are not detected because the autopsy is partially performed or is not performed at all. Significant variations can be observed if the pathologist differenciates between erosion and ulcerations or reports only lesions invading the muscularis mucosae. Some of the patients die in the first days after burn, before an erosion or ulceration can develop; on the other hand there are also a number of ulcerations that go on to healing without significant symptoms.

In our series, there were 7 ulcers and 2 gastroduodenal erosions, but the most frequent lesions involved the bowels, in which hemorrhages, erosions, ulceration or necrosis varying in depth from superficial to full-thickness wall of the organ were present in 44 cases (Fig. 11).

During the past decade an increasing number of reports are showing evidence, mostly based on animal experimentation, implying the gastrointestinal tract as a possible source of infection. In our series we were unable to show evidence of the gut as a source of sepsis. In 57% of the cases of sepsis there were digestive tract lesions but they appear to be more the consequence rather than the source of infection. Also in 25% of the cases without sepsis there were anatomical lesions in the digestive tract. Furthermore, in 80% of the cases of sepsis, documented burn wound sepsis was the source of the infection.

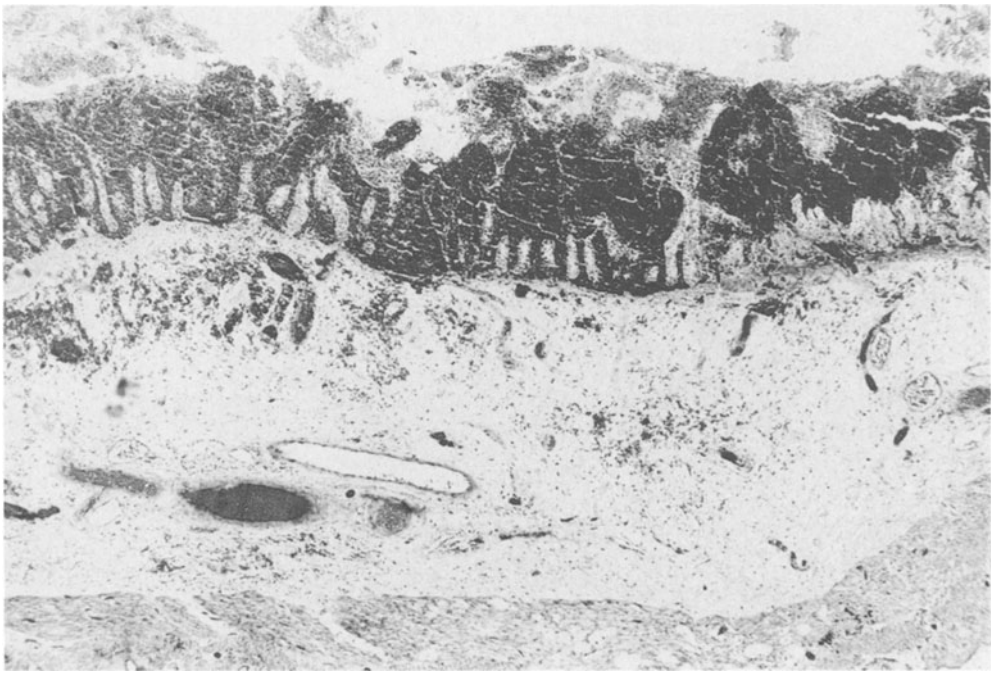

Fig. 11. Intestine. Hemorrhagic necrosis of the mucosa (hematoxylin-eosin, x 40)

As far back as the end of the last century, the presence of viable bacteria in the internal organs of humans and animals have been reported (Ford 1901). Furthermore it has been suggested that under certain conditions bacteria may pass through the intestinal wall and colonize internal organs (Arnold 1929).

This phenomenom is currently known as bacterial translocation and implies the passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa to mesenteric lymph nodes and other organs (Berg 1979). The translocation is promoted by disruption of the ecology of the indigenous gastrointestinal microflora resulting in bacterial overgrowth, impaired host defenses, or physical disruption of the gut mucosal barrier (Deitch 1987).

The mechanisms involved in this process remain obscure and numerous hypotheses have been proposed, such as the presence of a functional defect in the macrophages of the intestinal submucosa interfering in the intracellular bacterial killing (Wells 1988); the passage through the brush border or through the intercellular functional complex as it was described in

the case of the Salmonella typhimurium (Takeuchi 1967); through capture and transport of bacteria within host macrophages from the intestinal epithelium to the lamina propria (Popiel 1985); by disruption of the mucosal barrier due to increased local protease activity (Bounous 1977); the activity of the oxygen free radical generated during the period of intestinal reperfusion (Parks 1982); intestinal ischemia (Ahren 1973); hemorrhagic shock (Baker 1988); endotoxin and xanthine oxydase activity (Deitch 1989a); or immunosuppression and intestinal bacterial overgrowth (Berg 1988).

It is not clear if the term bacterial translocation means that viable indigenous bacteria pass through an intact intestinal mucosa (Berg 1979; Deitch 1985; Inoue 1988; Maejima 1984; Wolochow 1966), through an epithelium with alteration of its permeability (Berg 1983) or through necrotic mucosa (Ma 1989).

Obviously, if there is a necrosis of the mucosa, bacterial colonization with invasion of viable tissue is likely to occur, a mechanism similar to the bacterial infection in any tissue of the body.

Several mechanisms prevent potential pathogens from crossing the intestinal epithelium, among them a mucous interface between epithelium and intestinal lumen, secretory IgA, intestinal peristalsis and the periodical shedding of the mucosa (Deitch 1987). Disruption of the balance between the host defense mechanisms and the gastrointestinal flora can result in the passing of bacteria and its dissemination through the body. These mechanisms which protect healthy animals from bacterial translocation are impaired in severe burned patients and can promote lethal systemic infections (Deitch 1987; Maejima 1984).

Intestinal bacteria may normally cross the mucosal barriers to localize in the mesenteric lymph nodes (Deitch 1989b; Wells 1988). In healthy mice, these translocating bacteria are eliminated by host immune defense mechanisms, and therefore, are not usually cultured from this tissue. However, if bacteria overgrowth occurs in the intestines, greater numbers of bacteria translocate the mucosal barrier and these bacteria are then cultured from mesenteric lymph nodes. Although the translocated bacteria are present in the mesenteric lymph nodes, they do not spread to other organs unless the host is immuno-compromised or severely stressed as occurs after a major thermal injury. If the host cannot control the infection, as occurs in the burned mice, lethal sepsis results (Deitch 1989b).

BURNS, DIC, SEPSIS AND MOF

A commonality of biochemical actions, reactions and interactions seems to link many of the events occurring in severe burn patients and the development of DIC, the septic syndrome and the MOF. The common base seems to be the nonspecific acute activation of a generalized inflammatory response, and the cells more likely to be of prime

significance are leukocytes, macrophages and endothelial cells.

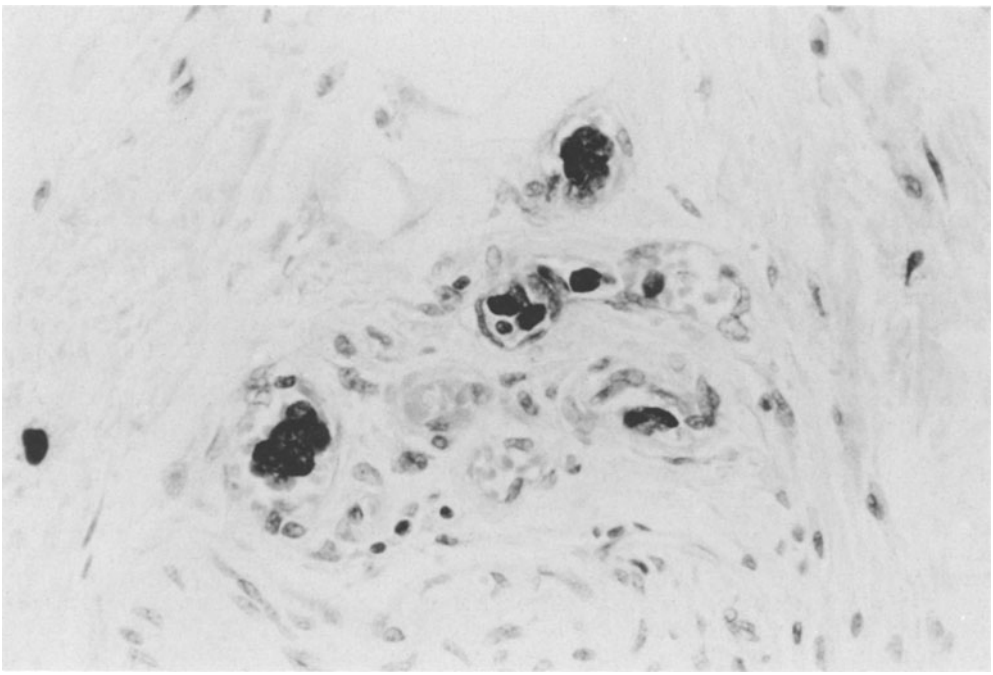

Fig. 12. Intravascular leukothrombosis (Leder, x 400)

Arturson (In press) describes five chronologic events of the inflammatory process after burns: 1) histamine release, 2) activation of the kallikrein-kinin system, 3) effects of arachidonic acid cascade, 4) activation of the coagulation and fibrinolytic systems, and 5) extravasation of leukocytes.

The histamine released from mast cells during the first hours of thermal injury lead to vasodilation and edema (Fredholm 1970; Horakova 1974). Furthermore, the intracellular proteases released as a result of the thermally induced cell damage seems to activate the kallikrein-kinin system leading to the synthesis of prostaglandins, vasodilation, and leukocyte migration (Olsson 1969). A marked increase in microvascular permeability and changes in the vasomotor control together with the margination of leukocytes and platelets, and the release of prostaglandins, prostacylins, thromboxanes, leukotrienes and lipoxins characterize a delayed phase which can be reproduced by a number of mediators especially those related to the arachidonic acid.

In close relation with DIC, the postburn inflammatory response

involves the activation of the coagulation and fibrinolitic systems which together with the kallikrein-kinin system may be activated by the Hageman factor. As a result, the fibrin polymerization in the burned tissue and the platelet aggregation, induce the formation of intravascular microthrombi which lead to ischemia and necrosis through perfusion blockage (Zimmerman 1984). The extravasation of leukocytes constitutes a very important event of the inflammatory response (Nuytinck 1988).

A number of mediators have been implicated in the neutrophil chemotaxis such as the components of complement cascade, metabolites derived from the arachidonic acid, lymphokines or those associated with the coagulation system (fibrinogen, kallikrein, platelet-derived growth factor, platelet activating factor, etc). The activation of the complement system, and particularly fragment C5a, not only results in widespread leukostasis but may constitute a source of potential pathogenic mediators of the hemodynamic disturbances related to sepsis and organ failure (Schirmer 1988). The chemotaxis agents produce aggregation, adherence, diapedesis and degranulation of the polymorphonuclear leukocytes (Fig. 12). This leukocyte activation generates metabolites of the arachidonic acid (prostanoids, thromboxan, leukotrienes), release proteolytic enzymes and forms products of the oxidative metabolism (superoxide, hydrogen peroxide, oxygen-free radicals, singlet oxygen) (Berringer 1985; Carmona 1984; Sprague 1989). These mediators produce severe endothelial damage with increased capillary permeability, tissural damage and further organ dysfunction.

The endothelial integrity is of paramount importance due to the complex and multifunctional activity of the endothelial cell which actively intervene in a ample variety of biological processes such as the production of vasoactive substances and procoagulants, immunoreactions, lipid metabolism, endocrinological interactions and others (Wagner 1989).

The integrity or failure of the reticuloendothelial system may also contribute to these complex mechanisms evolving from severe burns and its complications. Hypovolemia may significantly depress the activity of the hepatic reticuloendothelial system promoting not only an impaired clearance of microorganisms of intestinal origin and toxic substances from the gut but also the non-removal of circulating procoagulants and the activation of pulmonary macrophages establishing another link among burns, sepsis, DIC and MOF (Border 1988, Pardy 1977, Effeney 1978).

In summary, rather than consider DIC, MOF and the septic syndrome in severe burn patients as separate processes linked by a cause-effect relationship, it may be proper to consider them as frequently related events which share a commonality of actions, reactions and interactions with the relevant participation of polymorphonuclear leukocytes, macrophages and endothelial cells, within the broad spectrum of the inflammatory processes.

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D I S C U S S I O N

Traber:
I wanted to ask one question about the time sequence. In previous talks, the changes that were presented on the 1st day relative to bacterial translocation from the gut, were mostly experiments that were occurring a few hours after injury. Your histological data from the intestines were obtained several days later. I was wondering whether you might be able to see ischemia and reperfusion in a patient and yet by the time they came to autopsy whether they could have healed.

Linares:
I already said that. I said that some patients die before an erosion or ulceration can develop and also a number of gastrointestinal lesions may go on to healing without significant symptoms and leaving no anatomical traces.

Traber:
But what I was saying, they could have entered the system early on and been sequestered in cells. We have seen numerous cells that contain bacteria. Most antibodies do not penetrate.

Linares:
I was presenting autopsy material. Therefore, morphologically I can only correlate the changes presented at that moment. As I said also in my presentation, studies during life and at autopsy do not always result in an adequate and satisfactory explanation of the events.

Goris:
Your definition of MOF was a purely morphological definition. Is that right? You defined multiorgan failure purely from your morphology.

Linares:
You mean in this series? I used both, it is a combination of both. From my point of view I used a morphological evaluation, but for the purpose of the presentation I also defined and used the clinical and laboratory expressions of each particular system failure.

Goris:
Then in the patients who died early within 3 days you have already an incidence of 83% of multiple organ failure.
You have these patients with very early morphological signs of multiple organ failure. Some of them also have bacterial sepsis and some of them do not. Was there any difference looking at the morphology between these two subgroups?

Linares:
No, I did not find significant morphological differences between these two subgroups.

Deitch:
Just a quick question: I guess, I am concerned about the reliability of histologically defined burn wound sepsis as a cause of death in these patients. I think if you have an 80% burn and you take multiple biopsies, you are going to find some areas in which the bacteria have invaded viable tissue. But that degree of invasion may not be sufficient to cause the clinical syndrome of lethal sepsis. I think if you take a look at patients who have their burn wounds excised electively there are frequently areas of focal bacterial invasion, yet these patients are clinically well. So I think it takes a lot of bacterial invasion to get a lethal

septic syndrome based on bacterial invasion of the burn wound. So in making your diagnosis of burn wound sepsis, how much of the body did you have to find invaded with bacteria from the burn to establish that diagnosis?

Linares:
One place may be enough to start the invasion of different organs. But as a bacteremia is not synonymous with septicemia, also a burn wound sepsis does not necessarily end in a septic syndrome.

Kunkel:
You should publish your results showing that neutropenic patients can have significant infiltrates in the lung.

Linares:
Those results were obtained from 8 of this series of 100 autopsies, selected at random, and they are depicted in the table accompanying this paper.

Kunkel:
I need to quote that study!