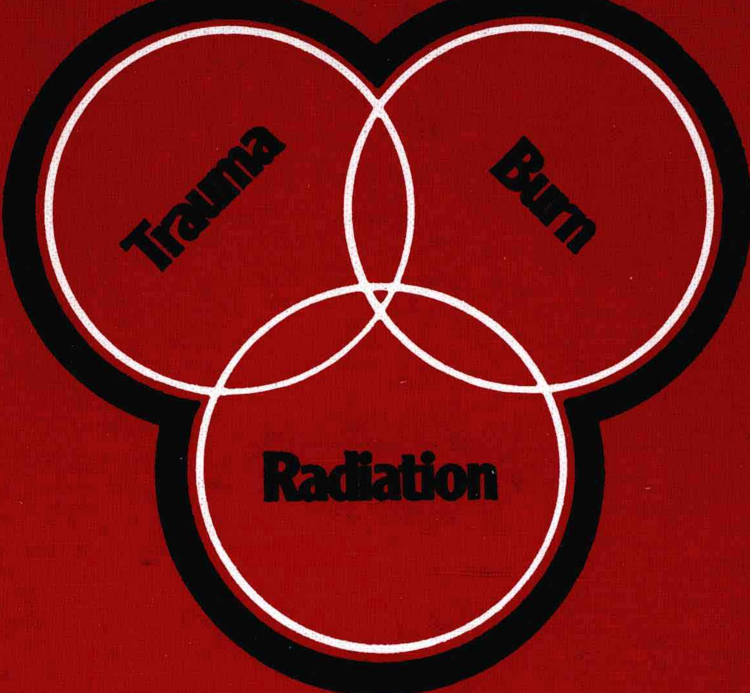
The Pathophysiology of Combined Injury and Trauma



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University Park Press • Baltimore

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Radiation, Burn, and Trauma

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University Park Press
International Publishers in Medicine and Allied Health
300 North Charles Street
Baltimore, Maryland 21201

Sponsoring Editor: Ruby Richardson
Production Editor: Michael Treadway
Cover and text design by: Caliber Design Planning, Inc.
Typeset by: BG Composition, Inc.
Manufactured in the United States by: Halliday Lithograph

Work presented in Chapters 1, 13, 14, and 23 of this volume was supported by the Armed Forces Radiobiology Research Institute, Defense Nuclear Agency. Views presented in the papers are those of the authors; no endorsement by the Defense Nuclear Agency has been given or should be inferred. Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council.

Library of Congress Cataloging in Publication Data

Main entry under title:

The pathophysiology of combined injury and trauma.

"Based on the proceedings of the First International Symposium on the Pathophysiology of Combined Injury and Trauma, which was sponsored by the Armed Forces Radiobiology Research Institute, Bethesda, Maryland, and held April 27–29, 1983, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland"—Introd.
Includes bibliographies and index.
1. Wounds and injuries—Congresses. 2. Physiology, Pathological—Congresses. 3. Traumatology—Congresses. I. Walker, Richard I. II. Armed Forces Radiobiology Research Institute (U.S.) III. International Symposium on the Pathophysiology of Combined Injury and Trauma (1st : 1983 : Uniformed Services University of the Health Sciences) [DNLM: 1. Wounds and Injuries—physiopathology—congresses. 2. Wounds and Injuries—therapy—congresses. WO 700 P297 1983]
RD92.2.P38 1985 617'.1 85-6128
ISBN 0-8391-2077-X

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Acknowledgments

The editors are very grateful to many people who contributed their time and talents to the production of this Proceedings. Particularly, we wish to acknowledge the excellent support and services of Donna Boyle, Janet Pierpont, Betty Markovich, Junith Van Deusen, Terri Hunt, and Tom Davis.

Introduction

The general medical term "trauma" is a simple six-letter word that is capable of conjuring up almost as many dreadful scenarios as there are individuals. The direct and ancillary effects of traumatic circumstances are staggering to comprehend. Trauma includes both accidental and intentional injuries, and it is the principal cause of death in Americans between the ages of 1 and 39 years. In 1982 alone, 165,000 trauma deaths occurred. The economic impact of trauma was more than $88 billion in 1980. A simple word? Yes. Tragic? Yes. Wide-reaching and expensive? Yes.

Deaths due to trauma have been noted as presenting a trimodal distribution pattern. The first peak has been characterized as "immediate death," representing persons who die very soon after injury. These deaths are typically caused by lacerations of the brain or brain stem, upper spinal cord, heart, or one or more of the major blood vessels. The second peak, "early deaths," represents that segment of the population who die within a few hours of the injury, typically from major internal hemorrhages and/or severe blood loss. The third peak is characterized by patients that die days or weeks after the original injury. In 80% of these "late deaths," the cause is infection and/or multiple organ failure. This area may be one of the few in which interdiction is possible, and it is, in all likelihood, where our efforts should be applied.

This volume is based on the Proceedings of the First International Symposium on the Pathophysiology of Combined Injury and Trauma, which was sponsored by the Armed Forces Radiobiology Research Institute, Bethesda, Maryland, and held April 27–29, 1983, at the Uniformed Services University of the Health Sciences, Bethesda, Maryland. This symposium has brought together the diverse backgrounds of over 100 physicians and scientists to focus on the complex problems engendered by injuries of a combined nature. It may be possible to develop a holistic approach to the management and therapy of combined injuries by marshaling the many talents of these investigators.

At the symposium, speakers and discussants attempted to define derangements in homeostasis following polytrauma, including radiation injury. Different types of trauma were examined for pathogenic commonality. Potential methodologies that were identified and examined included technical surgical problems and immunologic and biochemical alterations. These factors apparently predispose the patient to devastating infectious complications during the post-trauma period.

Trauma is a recognized fact of life in our highly industrialized and technical society. A pervasive problem in our nuclear era is the possibility of nuclear disaster. Such an event could produce injuries of a nature and scale almost too horrible to contemplate. However, they must be contemplated, and we as physicians and scientists must be ready, even while making every effort to reduce the likelihood of that event.

Surgery in Combined Injury

The chance of survival for a patient increases with the speed with which he or she is moved to a definitive care facility for further treatment. In spite of rapid treatment, sepsis and multiple organ failure often occur as late consequences of severe injury. The importance of debridement and wound closure in traumatic injury has been demonstrated experimentally in mice by Messerschmidt, who found that closure of a sublethal wound in mice given minimally lethal doses (LD) of radiation reduced mortality from 90% to 18%.

Whole-body irradiation ($LD_{50/30}$) is not a contraindication for intestinal or retroperitoneal surgery if the surgery is carried out at the end of the period of acute radiation sickness. Early excision grafts are recommended in irradiated and burned subjects. It appears that surgical corrections should be performed within the first 48 hours, and elective procedures should be postponed until later in the convalescent period (i.e., 2–3 months).

Good trauma management necessitates the rapid removal of necrotic tissue and then wound closure. Wound closure is one of the most challenging of surgical areas in the combined injury patient. Increased mortality occurs in the absence of wound closure. The problem appears to be that any anticipated surgery must be performed within a very narrow time frame after injury. Conversely, we have learned only too well that closing contaminated wounds will have lethal consequences.

Many questions remain for future research consideration. Among them are: Should an effort be made at splenic repair rather than extirpation? What is the effectiveness of healing in a site of anastomosis after irradiation? Will different types of dressings or wound covers be more advantageous? Are there other methodologies that may be used in debridement procedures? Burn management in combined injury patients is in itself a formidable task. Mass casualty situations will present unique problems in which accuracy of triage is essential. Patients with third-degree burns in excess of 40% of the body surface area or total burns in excess of 60% of the body surface area require massive support. Ringer's lactate is recommended as the resuscitation fluid in patients having less than a 60% body surface burn. Combined injury situations in which radiation is involved present a very different picture. Survival is difficult in patients with 30% body burns coupled with radiation. That is why triage and personal dosimetry are vitally important with radiation casualties. Any contemplated dosimetry system for personnel must be simple, self-reading, and issued to everyone. A patient whose dosimetry shows survival potential should begin receiving treatment that has been adapted for initiation by untrained personnel, if necessary.

The British Falkland Islands crisis demonstrated very low mortality rates and only limited infections in 730 patients. This may be due to the use of early surgery and antimicrobial agents. Patients were given prophylactic doses of penicillin and tetanus toxoid, and wounds and burns were excised early and covered with dressings and silver sulfadiazine. Resuscitation fluid, when required, was Hartman's solution (1 liter) followed by the administration of colloid.

Renal failure often occurs with ischemia-induced trauma. This is due to an increased concentration of mitochondrial calcium. It may be prevented by calcium blockers such as verapamil.

Nutritional support is essential for effective recovery in the injured patient. Some attention was given to these nutritional effects by participants of the meeting. However, it is obvious that future meetings should examine more fully the multifaceted aspects of nutritional support.

Mediator Systems

Combined injuries are associated with changes in levels or activities of many substances, including acute-phase proteins, immunosuppressive factors, prostaglandins, and coagulation factors. The reticuloendothelial system (RES) may be a common pathway in different forms of circulatory shock and trauma, and it may explain similar host responses. Macrophages and endothelial cells are known to be major sources of mediator molecules. The pharmacologic manipulation of these cellular systems represents a possible therapeutic opportunity, which remains to be exploited.

Infection

Antimicrobial agents have had limited impact on Gram-negative infection. Because of their limited impact, new approaches are needed for the effective management of complications concomitant with states of infection. Passive immunotherapy is one promising approach to the control of infection. Antiserum against core glycolipid of the J5 mutant of *E.coli,* common to many Gram-negative organisms, gives some protection against subsequent challenge with other Gram-negative organisms. Specific monoclonal antibodies directed against exotoxin A of *Pseudomonas aeruginosa* are known to enhance survivability in a murine burn model.

Identification of the effector and mediator molecules of immunosuppression and shock associated with infection are much needed. Treatment of patients could then include the administration of pharmacologic agents to regulate mediator substances. Other promising agents include calcium channel-blocking agents, antibiotics, and nonsteroidal anti-inflammatory drugs.

Survival from shock has been noted as paralleling progressively improving RES phagocytic indices. For that reason, modulation of the RES system may be a worthwhile pursuit. Various natural and synthetic immunomodulators now available may prove useful for stimulating the RES. Immunomodulatory agents may not demonstrate the resistance problem particularly associated with antibiotics, since they are broad-spectrum.

Prevention of the abnormal colonization of mucosal surfaces of immunosuppressed hosts by opportunistic pathogens may significantly reduce infectious complications post-trauma. One of the most promising means now available for controlling colonization is the use of selective decontamination procedures. Selective decontamination uses poorly absorbed antibiotics to preserve anaerobic flora but eliminate potential pathogens. When systemic infection does occur, it is usually due to a mixture of organisms. Therefore it is advantageous to develop synergistic antimicrobial combinations to be directed against all components of mixed infections.

The low incidence of infections in patients injured in the Falklands crisis may be due to the fact that they were maintained in newly commissioned hospital ships. Nosocomial agents were either absent or were in extremely low concentrations. Our meetings in the future should consider how these conditions may affect the ultimate outcome of the patient.

Use of Blood Products

Fibronectin is purported to increase RES function and protect vascular beds. Decreased levels of fibronectin have been noted in instances of trauma. However, the significance of fibronectin to the well-being of the septic/trauma patient remains to be investigated.

Serum from burn patients is known to contain factors that are toxic to cellular functions. The technique of plasmapheresis has been used for this reason, and it has resulted in marked improvements in a number of patients. It too appears to be a technique deserving of more study.

Blood products and resuscitative solutions are vitally important in the treatment of shock patients. Red blood cells in combination with crystalloid/colloid solutions have produced satisfactory responses in some shock patients. Platelet concentrates and fresh frozen plasma have also shown results worthy of further investigation. Infusion of hematopoietic stem cell fractions may also prove to be of value. The goal is to have supplies of these frozen blood components readily available at central blood banks to supplement supplies of fresh blood, for use in emergency situations.

Model Systems for Study

It is imperative that correct models be selected for the questions being asked. No system can be considered to be exactly similar to human systems, and because human studies are so limited, the appropriate animal models must be selected.

Better animal models for infection need to be developed. Rather than challenging healthy animals with massive doses of bacteria, compromised models are needed in which infection can be initiated with a small amount of inoculum, resulting in progressive infection. One such model, which is very promising, uses a plasma clot that contains bacteria; it is inserted into canines to mimic a progressively lethal infection. Similarly, rodent burn and radiation models have been established that may offer realistic models for the study of infections in an immunocompromised host.

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Keynote Address

The Pressing Need for New Knowledge on Radiation Injury with Physical Trauma

Francis D. Moore

The care of military and civilian casualties in the wars of the past century has defined new problems in pathophysiology, surgery, and medicine. These new problems have demanded new solutions. In almost every case, these new solutions have reacted to the benefit of humanity throughout the world. New understandings of changes in the human body produced by various forms of injury have resulted in improved treatment of a whole variety of human illnesses. In addition, and rather unexpectedly, many of these advances have involved the development of wholly new concepts and methods in the biosciences.

This type of advance, occurring in conjunction with military casualties, has often given the erroneous impression to amateur historians that "surgical advance thrives on war." Nothing could be further from the case. It is merely that the accumulation of pressing problems in one place and at one time results in the pressures that drives human ingenuity: "Necessity is the mother of invention." Civilian disasters, be they earthquakes, fires, or explosions, have often resulted in the same sort of remarkable breakthroughs. It would be a shame if anyone hearing of this conference were to get the wrong idea that biomedical advances arising from massive nuclear warfare would in any sense counterbalance the human and global disasters resulting from such an occurrence.

The history of new advances arising from the recognition of new patterns of injury need not be belabored for a well-informed audience such as this. It was Bywaters, during the London blitz, who perceived that, after the weight was removed from seriously crushed limbs, individuals developed renal failure. The "crush syndrome" became the model upon which all of our early knowledge of post-traumatic renal failure (later called lower nephron nephrosis) was built. It is an amusing irony of history that it was the lifting of weight from crushed limbs that led Walter Cannon, in World War I, to the conclusion that fluid loss in injured tissue was at the basis of the then newly recognized syndrome of "shock."

Willem Kolff, working under the very eyes of the Nazis in the Netherlands at about the same time that Bywaters was making his observations on renal failure, was developing a dialysis machine based on winding sausage casing on old tomato cans. This machine was destined to save the life of thousands of people with post-traumatic renal insufficiency over the next few decades. This artificial kidney, as we understand so clearly now, was to become the leading alternative to kidney transplantation for patients with end-stage renal failure throughout the world.

Transplantation itself received a remarkable boost during World War II. Confronted with the problem of severe burns in their air force pilots, the British government undertook new research on methods of skin graft covering in burns. Gibson, an accomplished plastic surgeon in Glasgow, sought the help of a brilliant young biologist named Peter Medawar. The two of them published their first paper on skin homograft survival and clearly described the "second set" response. If a skin graft from one donor is placed on a recipient, it is rejected after a few days. If a second set of grafts is then taken from the same donor and put on the same recipient, it is rejected much more rapidly. Often the brilliance of a biologist is his or her ability to recognize in an unexpected finding the quintessential model of an important response.

Peter Medawar, later to be knighted for this work and to receive the Nobel Prize, recognized in the "second set" response an immunologic model for the study of immunogenetics and histocompatibility. From that knowledge came kidney transplantation as we know it today, but most importantly there also came a tremendous explosion in the biochemistry of molecular genetics and molecular immunology.

Although shock was extensively studied in World War I and between the wars, it was its much clearer definition during World War II that led Professor E. J. Cohn to start fractionating blood. His discovery that alcohol precipitation would allow him to fractionate human plasma without denaturing the protein was a major advance of this century. Although concentrated human albumin saved many lives in World War II, it has almost disappeared from the scene save for occasional usage in liver failure. Yet, when anyone asks me about it, I cannot help but tell them the wonderful story of the day that I was having lunch with Professor Cohn. I was only a lowly research fellow at the time, and the data came in showing that each gram of concentrated albumin pulled into the circulation was exactly the amount of fluid that he had predicted from the differential osmotic pressure. At that moment Professor Cohn realized that concentrated albumin, hanging in a little vial from the belt of a corpsman, could do the work of five times its volume of plasma. From this work also came fibrin foam, fibrinogen, the clotting factors, and then later the separation of platelets, white cells, immune globulins, and a whole bevy of important functions from either whole blood or plasma. Another amusing story of the era involves a meeting of the National Research Council held in Washington in about 1945, where a distinguished professor reported that, after many months of work, he had found that red cells were best suspended, and survived best, when all of the known fractions of plasma were added to the mixture. I am sure that someone with an evolutionary turn of mind might have said, "Well, blood evolved that way. Why did you have to waste so much time rediscovering it?"

The first use of chlorine gas as a mass toxin was carried out at Ypres in Belgium in 1915. It produced an exudative bronchopulmonary secretory response that resulted in flooding of the lung with body fluids and death in severe cases. At the time, not much could be made of this, and no treatment could be evolved. The gas mask was made available and became standard equipment. It is another historical irony of this century that the lesson of how to handle low-pressure pulmonary edema was not really learned for another 40 years, and that even today we are not sure how best to adjust respiratory assistance apparatus for this type of exudative response. But the response was recognized. At several civilian disasters (the Coconut Grove Fire in Boston in 1942 being a spectacular example), pathologists recognized changes in the lungs of those who died in the fire (and were totally unburned) as showing the exudative changes of poisoning during World War I. It is also a remarkable fact of this century that poison gas was not used at all in World War II; its use was either zero or so localized as to have attracted no historical attention. In our anxiety to avoid an exchange of nuclear weapons in some future conflict, we should try to understand the military decision-making process and the political pressures that led to the avoidance of the use of gas in World War II, when it had been one of the most terrifying weapons of World War I.

The development of the submarine might never have been considered to have anything to do with pulmonary function. However, it was the deep water submarine tank at the Naval Research Institute that led Otto Behnke to his gravimetric methods of analyzing body composition, and then later a long series of studies (many of them carried out at the submarine bases at New London and Groton, Connecticut) on pulmonary physiology. The particular challenges of sudden changes in pressure in the airway were felt by the submariners just as they were also felt on explosive decompression during air warfare.

The development of vascular surgery must be added to this list. The extensive vascular surgery of World War II, so carefully analyzed by Michael DeBakey and his colleagues, would now be regarded as primitive. Direct replacement of arteries by homografts, allografts, and prostheses came along within months of the end of World War II. By 1950, Professor Charles Rob, at Saint Mary's Hospital in London, had dozens of patients with aortic replacement. Direct replacement of arteries and veins formed major surgical advances that were useful to patients throughout the world, and of course they were of major military application in the conflicts of Korea and Vietnam.

Mixed Radiobiologic and Physical Injury

The foregoing account of past achievements could be expanded historically, but we are on the verge of a new challenge, and it is certainly more appropriate to look to the future than the past, especially for a seminar such as this.

Mixed radiobiologic and physical injury has been seen on a grand scale only twice in the history of our planet: at Hiroshima and Nagasaki. Most of the data developed from those episodes were brought together by the Atomic Bomb Casualty Commission of the United States in collaboration with the Japanese, and later were taken over with increasing authority by the Japanese themselves. Most of the information deals with late effects. Data on early management are very scarce largely because early medical management was almost nonexistent. The hospitals and other medical facilities of both cities were destroyed, and many of the physicians were killed by the initial explosions.

Much has been made of these devastating effects in a medical context. One school holds them up as an example to the world, demonstrating that atomic warfare should never occur again, a point of view with which few could disagree, whatever its predictive significance.

Others have drawn a different conclusion, namely, that if individuals could protect themselves from blast heat and radiation by a shallow earth shelter and minor coverage, injury would be avoided. This view, together with the idea of massive relocation of population, is, in my opinion, equally unrealistic. The exact timing of an attack or an explosion is never known for sure. Exactly when are you to dig your grave and lie in it? The proposal for massive relocation of people neglects completely the problems of food, water, sewage, civilian crime, and municipal organization. It also neglects the fact that, in the outer perimeter of the blasts at Hiroshima and Nagasaki, the people who were least injured were those who were deep in cellars or in their own homes, protected at the margin of blast and radiation injury by the very structures that they would be forced to leave if relocation had been the policy.

Despite the limitation of our knowledge from those two episodes, their further study and computer projections of blast and radiation effects are of basic importance to the mission of this meeting, although in a logistical sense rather than physiological.

On a microscale, combined radiobiologic and physical injury has been seen in two categorical circumstances since 1945. The first of these is the occasional radiation accident. Most of these have been incidental to the management of atomic fuels and fission energy, usually in an industrial or manufacturing center, and usually of the atomic pile variety rather than a cyclotron or an explosion. These industrial accidents have been important experiences and will doubtless be reviewed at this meeting. The lessons of Three Mile Island and the nuclear industry are yet to be learned.

The second category includes those in which whole-body irradiation has been given intentionally, either as a feature of the treatment of lymphoma, leukemia, or Hodgkin's disease, or as a preparation for the transplantation of kidneys, liver, or bone marrow. In the former instance (that is, the use of whole-body irradiation or, at the very least, widespread bodily radiation in the treatment of lymphoma), many effects have been seen that have been helpful and valuable in understanding radiobiologic injury and its combination with physical trauma. However, in the kidney and bone marrow transplant setting, a surgical procedure that is major in the former and rather minor in the latter has sometimes been superimposed upon radiation at a varying time interval. Speaking from my own experience, it was this combination of whole-body irradiation with the surgery required for kidney transplantation that first alerted me to the biologic challenge imposed by the combination. Our patients were few in number. Whole-body irradiation was given in a very simple geometrical arrangement. The radiation dose was loosely calculated without the accurate measurements available today. The dosages were between 300 and 800 rads given in either one, two, or three sittings.

The operative procedure for transplantation occurred within a matter of days after the radiotherapy. The original concept was that the valley of immunosuppression due to radiation might coincide roughly with the predicted first rejection episode of the kidney, and that the improvement in kidney function would help the patient "weather through" the second wave of radiation injury consisting of bone marrow suppression.

To the extent that kidney rejection was abated by radiotherapy, the effect was reasonably successful. As you probably know, other experiments were carried out, and have been since, in which the local kidney or other specific anatomical regions (specifically those involved with lymph nodes) have been radiated, with less drastic systemic effects. However, whole-body irradiation then proceeded to take its disastrous toll, and over the course of the next days, weeks, or months, the patient began to pay the price of this massive continuing injury.

In one patient, success was achieved. The whole-body irradiation dose was a little less than the others, estimated at 450 rads. The donor was closely related, a fraternal twin. Although this genetic similarity would favor acceptance of the transplant (but would fail to guarantee it as in identical twins), it would have little effect on the severity of the irradiation-induced illness. By whatever combination of surgical care and good luck, success was achieved despite the awesome combination of whole-body irradiation and a major operation.

Death was due in all cases to a terminal infection. We have long since learned to recognize in critical care medicine and in severely injured patients that the terminal infection that finally carries the patient off should not in any sense be regarded as the proximate cause of death. The problem always is one of antecedents: Why is the infection there, and what makes the patient prone to the infection? The mere diagnosis of multiple organ failure tells us absolutely nothing. The question is, "What has gone wrong with the immune defenses or the biochemical feedback regulators that normally govern the body?"

The decline in formed elements of the blood was obvious. Less apparent were the subtle changes in immune function, many of which could not be measured or quantified in 1956 with the elegance that they are now, almost 30 years later. Without trying to reconstruct these cases in detail, the fact remains that a breakdown in immunity and an apparent defect in healing, as well as a tendency to very early deterioration in lung and liver function, could certainly not be abated by the rapidly improving kidney function, even though the patient had chronic renal failure. Whole-body irradiation has been used since that time for a number of different purposes. The very large fields used in the treatment of Hodgkin's disease cannot be equated with massive whole-body irradiation, even though there are doubtless many changes in common. The use of whole-body irradiation for bone marrow transplantation with or without immunosuppressive drugs always supplies a model.

Civilian and Military Projections and Settings

This conference has been called to review not only the known effects but the development of suitable laboratory models for the study of combined injury of this type. The pathophysiologic scope of the problem is evident from the program of this conference, and to review it further here would be redundant.

From what little we know, civilian settings of combined radiobiologic and physical injury are chiefly confined to workers in the nuclear energy field or, in the case of a nuclear energy industrial plant disaster, some of the local residents of the area. A second possible vulnerable group would be those engaged in the production, management, deployment, transportation, maintenance, or supervision of nuclear missiles, particularly those involving the element plutonium.

From the military side, others here today can predict the setting far better than I. It seems superficially evident that we should consider as distinct the settings and epidemiology of combined injury on the battlefield: tactical situations where geographical scope might be limited, and the nature of the radiation might in some cases be almost monovalent, consisting, for example, largely of neutrons. Whatever the details, there will be a central core of hopeless injury, an outer periphery of readily salvaged persons, and a critical torus, or doughnut-shaped zone, where injury is very severe, often combined, and survival unlikely but conceivable. It is to that group of patients that this conference is particularly directed.

In the event of the ultimate intercontinental ballistic missile catastrophe that we all apprehend, should there be a major world conflict involving nuclear exchanges, there will be far more destruction. However, we will be faced with the same triphasic zone arrangement of an inner lethal area, an outer fringe of salvageability, and a torus of medical challenge. We will have the additional problem, possibly not so evident in the battlefield situation, that the medical facilities of the area will be largely destroyed. Therefore, somewhere down the line, we are going to be thinking about first aid or measures that might be taken by unskilled personnel, self-help, and public education.

It is a tribute to the Department of Defense and to the preparedness plans of our nation that this conference has been called. There are many pessimists, activists, and propagandists who feel that a conference of this type somehow by its very nature admits the possibility of and therefore encourages atomic warfare. I could not disagree more wholeheartedly with such a Madison Avenue or media view. It is our job to look after the sick and injured, either of the military or civilian populations, and of all ages and all occupations or degrees of vulnerability, whatever the public relations impact may be. We must do our job even if people say it is misleading to indicate its necessity. If some say that a conference such as this invites nuclear war, then we are entitled to ask if the writings of Ambroise Paré brought on the invention of dynamite. In the words of the Prophet, let us "Hew to the line, let the chips fall where they may."