Chapter 8

Research Activities

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Formal surgical research efforts at forward military hospitals during combat could perhaps be considered to have started during the American Civil War, when the Surgeon General of the United States Army issued an order for regimental surgeons to send to the newly established Army Medical Museum in Washington (now the Armed Forces Institute of Pathology) such pathology specimens as amputated limbs for the study of wounds and infection in the combat wounded. Formal surgical research efforts in subsequent wars in which the United States has been involved were essentially nil until early in World War II, when the English were able to conduct investigations in some kinds of fresh battle casualties in established English hospitals — because of the effectiveness of the air war in bringing combat literally right on top of these hospitals. Valuable observations were made of the relationship of blood-volume changes to shock and the susceptibility of the kidneys to delayed derangement following crushing or severely hemorrhagic injuries. Battlefield investigations were formalized halfway through the war into the British Traumatic Shock Team No. 1 (Italy) and No. 2 (Northwest Europe), with emphasis on studies on the etiology and treatment of shock.

Several different countries attempted forward area evaluations of the use of topical chemotherapy in war wounds early in World War II. Of all these attempts, including those of the United States, England, Germany, and Russia, the English appear to have had the best-designed approach. However, they reached the conclusion that adequate data probably could not be obtained under circumstances of combat.

The American military position on our entry into World War II was one of extreme instability and desperate delaying actions in the Pacific, often incompatible with decent medical support, much less formal research. The position in Africa was more tenable, but little more stable. The primary emphasis at this time, fortunately for the American fighting man, was on a workable system of organization, distribution, and feedback to active medical units of clinical experiences of positive and negative value. The method involved the use of fulltime surgical consultants, not burdened with direct patient care and administrative details. The approach was well described by Dr. E. D. Churchill, who was a surgical consultant, Mediterranean Theater, World War II (see Volume 2 of the U.S. Army Medical Department's *Surgery in World War II,* 1955):

> [The surgical consultants] were searching for surgical evidence by direct observation and discussion. . . . The Mediterranean Theater of Operations provided a favorable environment for such undertakings. It was an experimental laboratory not only for surgery but also for medicine as a whole; for ordinance; for equipment. . . . It was vital that wound surgery be carried on within a framework of inquiry, for this theater was the proving ground for the greater task that was to come.

This effort to formalize clinical experience in combat surgery in order to improve its evaluation and distribution yielded enormous benefits in the organization of medical support, the quality of wound surgery, and, to a certain extent, resuscitative practices. With some stabilization of the combat area and improvement in personnel, supplies, and equipment in the Italian campaign, formal surgical research teams in forward areas made their first appearances in the American Army. Such teams assumed several characteristics which have persisted to the present time: personnel, organization, and

equipment independent of immediate patient-care organizations; medical officers not responsible for routine patient care; a laboratory facility for studies not usually performed in a combat area; and a mission primarily involving the accumulation of data relating to certain specific questions regarding surgical care of the soldier injured in combat. These teams, then, have had limited missions, independent laboratory support, and a significant degree of autonomy.

From small, scattered efforts, the formal surgical research effort evolved into the larger, better-equipped "Board for the Study of the Severely Wounded, North African-Mediterranean Theatre of Operations." Investigations were carried out centering about the clinical picture of shock, biochemical changes in shock, organ-function studies in the severely wounded, especially liver and kidney, and a clinical-chemical-pathological correlation of what was subsequently called acute renal failure. These studies continued until the capitulation of the German forces in Italy near the end of the war. Formal research activities of like nature were not set up in the American sectors in northern Europe.

Efforts to establish formal surgical research units in the Pacific Theater were less successful. The comments of Dr. Frank Glenn, surgical consultant to the U.S. Army in the Southwest Pacific, are informative and somewhat prophetic (see *Activities of the Surgical Consultants)*:

> Clinical and laboratory investigation should have been considered an integral part and function of the Medical Department during service in a foreign theater. Knowledge of tropical surgery as well as tropical medicine could have been increased with profit much earlier, had the proper organization been available. Because there was no official organization of this type provided for, the construction and securing of one was met by a great deal of resistance. One ranking medical officer in the theater chief surgeon's office bitterly opposed "research in the jungle." A base surgeon of equal rank was insistent that such an organization would deprive the wounded of proper care. Such attitudes were relics of the dark ages, and they delayed progress.

Fortunately, these attitudes were not characteristic of the Army Medical Corps in general. When the battle lines in Korea finally reached some form of stability, a well-staffed and moderately well-equipped formal research team was set up within 8 to 10 miles of the fighting. The impetus for this project came from high levels within the Medical Corps; it was not based on a local effort as in World War II. An unusual military circumstance soon developed: continuous, prolonged negotiations for a ceasefire. This resulted in stable lines with continued fighting, a situation almost ideal for a combat surgical research effort.

The team in Korea evolved into several specialized components in separate areas dealing with specific problems: the renal-insufficiency center, the vascular-surgery study group, the front-line metabolic surveys, and the main study group. The functions of the detached groups is self-evident. The main study group concentrated on studies in the systemic response to injury, the sequelae of shock and wounding, an evaluation of resuscitative tools and techniques, and the wound itself, especially the bacteriologic aspects. The team eventually was of sufficient size and well-enough supplied to become directly responsible for patient care to a large extent.

It is generally agreed that no two wars are really alike, but the war in Vietnam was about as unlike previous wars involving the United States as it is possible to conceive. The absence of front lines and large functioning units of enemy forces resulted in poor predictability and wide fluctuations of casualty location and density, and created a very real problem regarding when and where to set up a research team. The terrain was predominantly jungle and swamp, usually with a hostile potential. The few adequate roads were insecure.

Medical units and military bases were essentially islands in hostile surroundings. New facilities had to be constructed, and an extensive (and expensive) system of supply by air spanning 12,000 miles had to be established. The climate itself was a major obstacle. The ambient temperature in Vietnam often exceeds body temperature, and humidity is always high. Sophisticated instruments that were considered essential for modern surgical research had never been tested under these conditions.

Many new techniques were available for trial in the Combat Zone. The "oxygen electrode" had been rapidly developed to a clinically useful state, and a small, reliable, relatively simple equipment for

measuring hydrogen ion concentration and carbon dioxode partial pressures became available. In addition, interest had been reawakened in lactic acid metabolism. Enzymatic assay methods prepackaged in kit forms for simplicity became available. These were ideally suited to field application. Concepts of intravascular coagulation in the natural history of shock had received considerable attention, placing a new emphasis on studies of clotting function in severe injury. Once again, a recent laboratory innovation was pertinent: the use of the activated partial thromboplastin time as a simple, sensitive, and reproducible screening test for the activity of the "intrinsic" clotting factors.

During a survey trip of all medical installations in Vietnam during the rapid United States Army buildup in November and December of 1965, it was decided that it was possible, in fact necessary, to study surgical problems of the combat wounded in forward military hospitals. Immediate steps were taken to recruit, train, and make Vietnam arrangements for a surgical research team.

Fortified with recent advances in concept and technology, a small team of one officer and six enlisted men arrived in Vietnam in April 1966. To have arrived much sooner would have been largely a waste of time, because supply, transportation, and communications were just stabilizing after the initial rapid buildup in late 1965. As it was, the lack of airconditioning, power failures, and unstable voltage problems in the hospitals, all relying on outdoor portable field generators working in intense heat and dust or frequent severe rain and mud, caused significant problems and the loss of a number of opportunities to gather pertinent data. Most of our laboratory determinations, for example, are performed at 37°C, but our equipment was all designed to heat up to this level, not cool down to it. The equipment itself performed better than expected, but it was essentially inoperative after six months in a laboratory where the afternoon temperature before the rainy season exceeded 120°F. These problems were later diminished by the availability of airconditioning units and improved generator arrangements.

The research team consisted of a surgeon, Capt. John A. Collins, and six technicians. They were members of the Division of Surgery, Walter Reed Army Institute of Research, and were attached to the 93d Evacuation Hospital, Long Binh. The 93d Evacuation Hospital was a 400-bed, well-staffed and well-equipped hospital of semi-

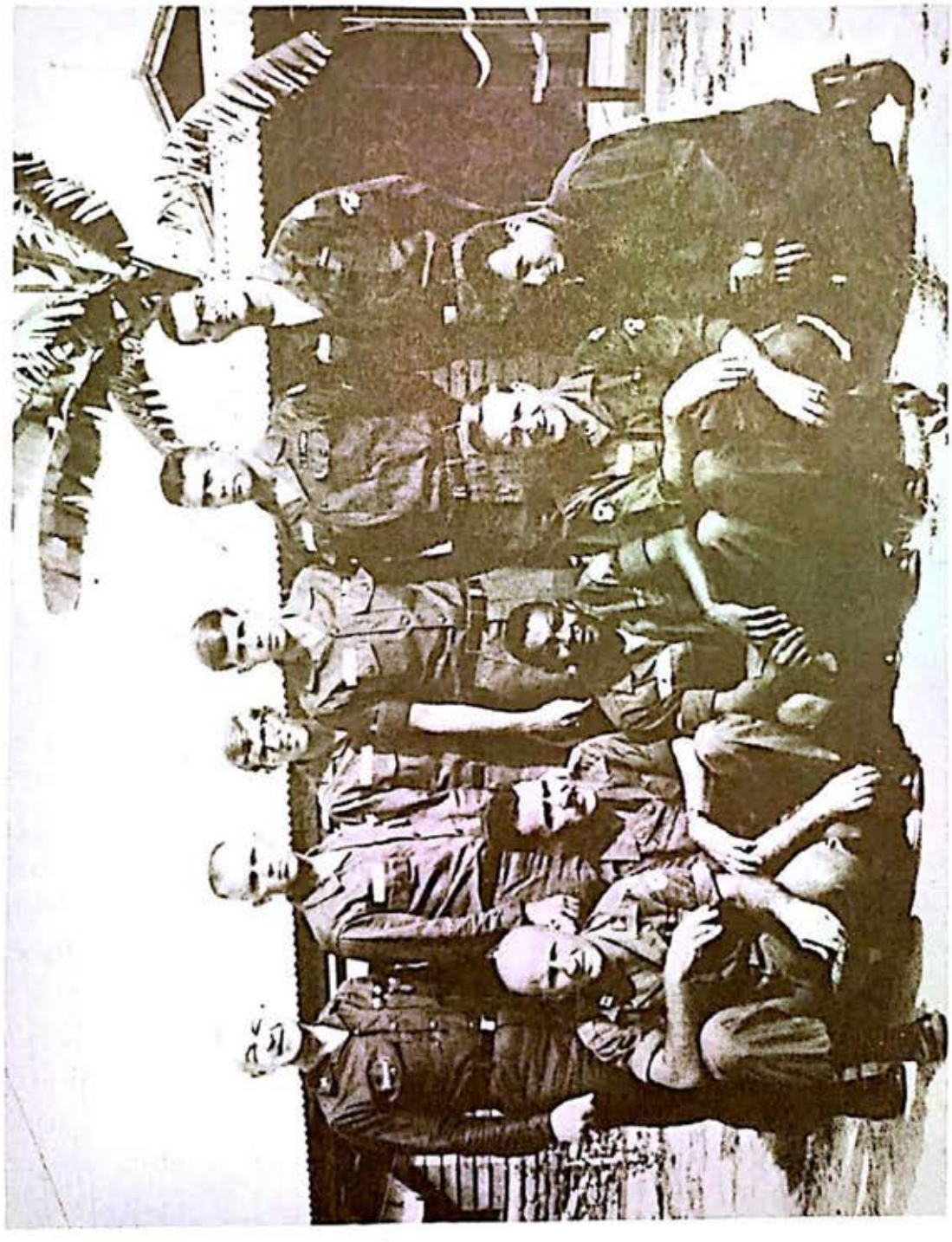

Figure 1. Shock research team at Third Surgical Hospital. Front row (left to right): Capt. Paul James, Sfc. Cecil Pugh, Sp. 5 Aaron Grace, Sp. 5 William Monahan, Capt. Carl Bredenberg. Second row: Col. Robert Hardaway, 1st Lt. Gene Phillipps, Sp. 4 Mitchell Caldwell, Pfc. Robert Fink, Sp. 5 Michael Elliott, Sp. 5 Eric Lundberg.

permanent construction. It supported the United States First Infantry Division, deployed just to the north of Saigon. The team members were selected and trained at the Division of Surgery Laboratory and Shock Unit of Walter Reed Army Medical Center. The team's primary mission was to study severely injured patients, particularly those in shock. Its facilities were in the same building as the regular hospital laboratory and consisted of instruments to measure blood gases and pH, lactate, and pyruvate, and make a variety of coagulation tests such as prothrombin time, partial thromboplastic time, and fibrinogen, and other tests. Tissue and blood samples were sent back to the main surgical facility at Walter Reed Army Institute of Research.

In October 1966 an expanded surgical research team under the leadership of Capt. Paul M. James, Jr., was sent to Vietnam to continue and expand the studies started by the first team and to conduct patient care of some of the patients to be studied. The new team consisted of three general surgeons, a male nurse, and seven technicians. Their equipment and supplies were somewhat more extensive than that of the first team and included a two-channel recorder for monitoring arterial and central venous pressures, instruments for measuring cardiac output by the Cardio-Green dye dilution method, and a counter for measuring red-cell mass, plasma volume, and extracellular fluid.

In order to study the most seriously wounded casualties, the unit was moved in November 1966 to the Third Surgical Hospital at Bien Hoa, 30 miles north of Saigon. This was a 60-bed surgical hospital close to the heavy fighting in the "Iron Triangle"; it treated those wounded who needed to be cared for most promptly. It was well set up with airconditioned buildings. The surgical research team had an adequate laboratory equipped with apparatus for doing blood gases, pH's, lactates, and pyruvates. It also had a flame photometer and facilities for coagulation studies. A four-channel beta gamma counter for doing red-cell mass, plasma volume, extracellular fluid and total body water was available. Patients, brought by helicopter, were studied in the preoperative ward, in the operating room, and in the postoperative ward. In addition, a special one-bed shock unit was equipped with facilities to measure cardiac output and record arterial and venous pressure, with a volume-cycled respirator, with a defibrillator, and with other special equipment.

Figure 2. The shock unit at Third Surgical Hospital contained a two-channel recorder for recording arterial and central venous pressure and a suction pump for chest tube suction.

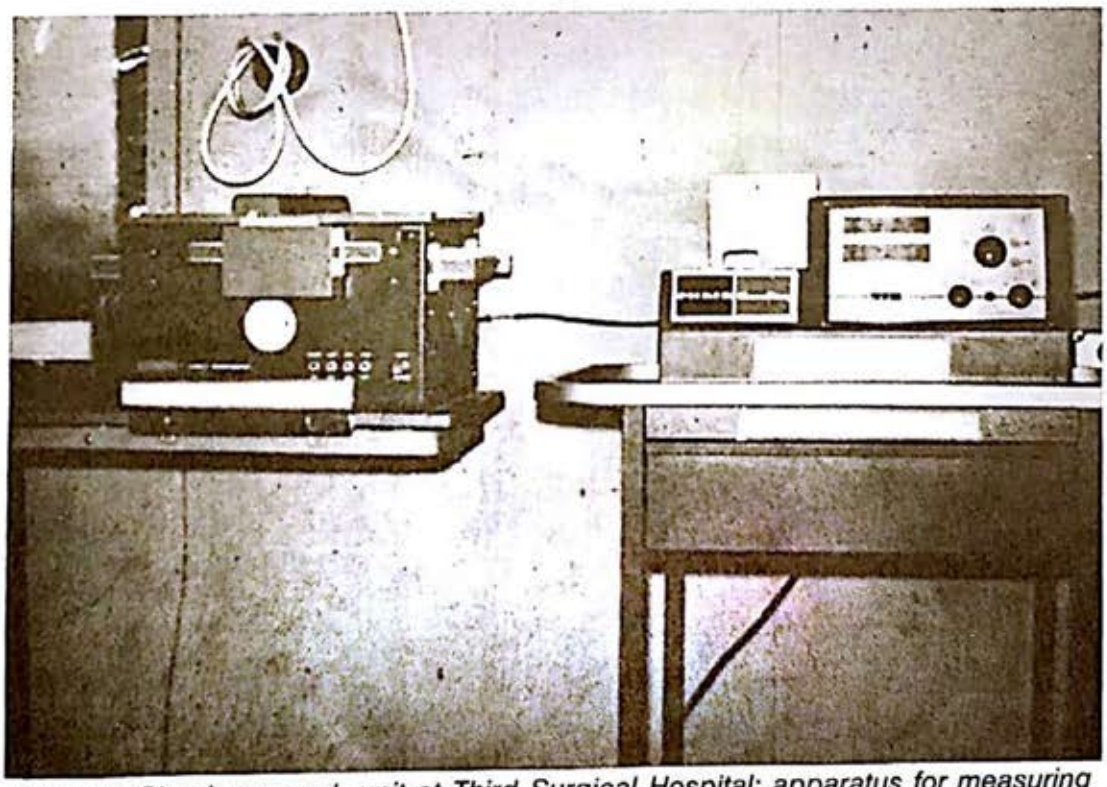

Figure 3. Shock research unit at Third Surgical Hospital: apparatus for measuring cardiac output, red-cell mass, and plasma volume.

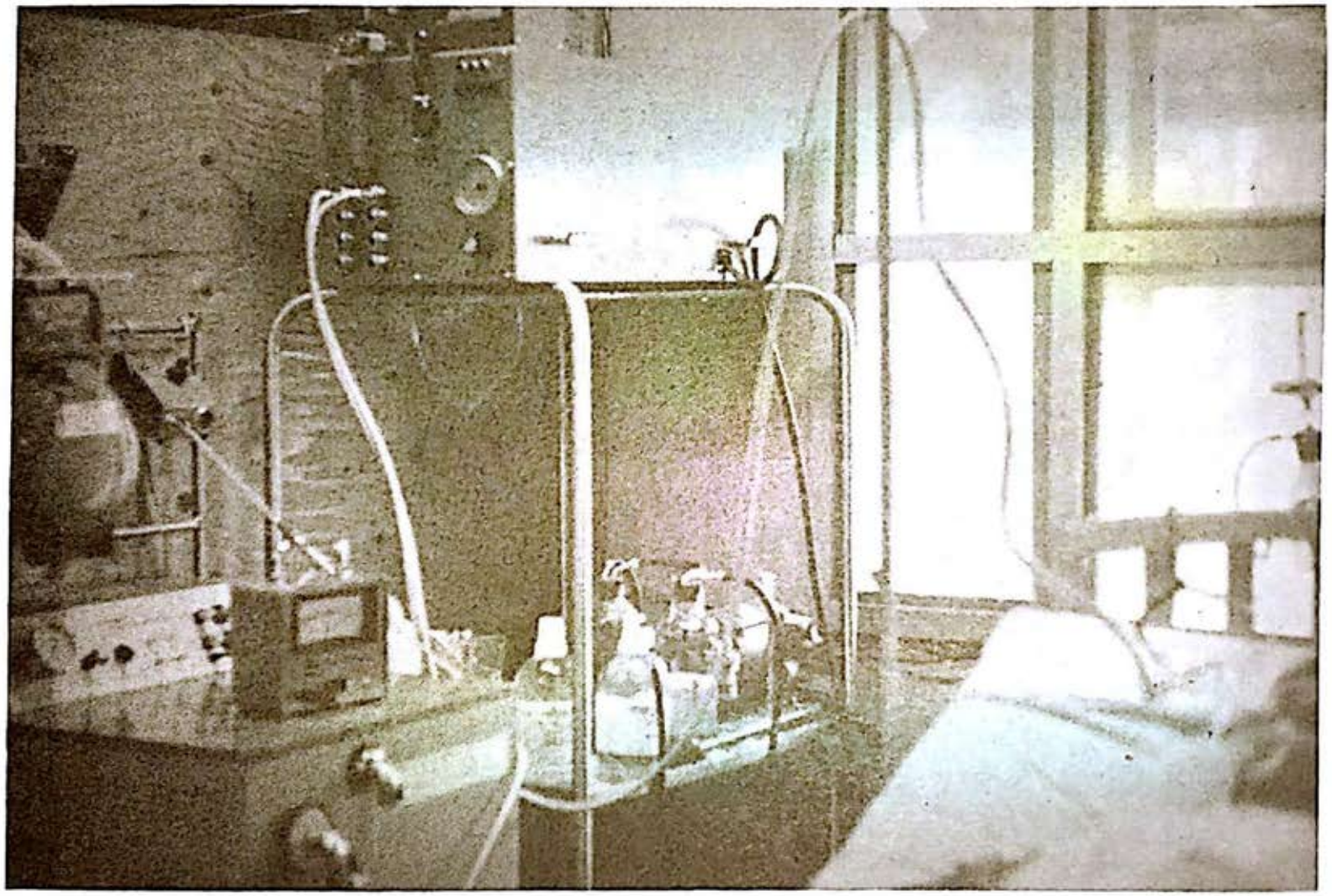

Figure 4. Shock unit at Third Surgical Hospital: a volume-cycled respirator for treating shock lung (Adult Respiratory Distress Syndrome) is on the left. Above is a K thermia unit for automatic regulation of patient's temperature.

Figure 5. Shock patient being treated in shock unit at Third Surgical Hospital.

The surgical research team was entirely dependent on the hospital to which it was attached for shelter, power, and other support. It soon became evident that in many circumstances this support might not be possible. Therefore, in late 1966 and early 1967 one expandable unit and one inflatable unit of the Army MUST facilities were adapted to provide laboratory and shock treatment capabilities in a unit that could be packed and towed behind a truck or transported by air. This portable unit consisted of a laboratory and a one-bed ward.

The expandable unit was utilized for the laboratory, and the inflatable unit was used for patient-care and study. A generator and an airconditioner were adapted to serve the unit. The surgical research team under the leadership of Lt. Col. John J. Kovaric used this facility when it accompanied the Third Surgical Hospial to the Mekong Delta in May 1967.

The techniques employed by the Vietnam Shock Research Unit were essentially the same as those used at Walter Reed. Certain minor changes were required. Central venous pressure was recorded ordinarily by a water manometer instead of by a transducer and recorder,

Figure 6. Road delivery of shock research unit laboratory.

but the technique of its insertion into the subclavian vein was unchanged. There was no facility to accurately record the patient's weight by metabolic scale. There was no facility for inserting a pulmonary-artery catheter and for recording pulmonary artery pressure. Otherwise, studies and treatment were carried out in a manner identical to the Walter Reed studies.

This marked the first time that such sophisticated studies had been carried on under such conditions of war, primitive surroundings, high humidity, mud, and dust, and at the end of a supply line stretching halfway around the world. During the first few months in Vietnam the team's laboratory facilities were in a congested building that had no airconditioning. As a consequence all instruments were rusted and unserviceable at the end of six months and required replacement. Ice was required to keep the temperature of a body-temperature water bath for coagulation studies down to 98°F. Some instruments and supplies never arrived; others were damaged. Maintenance without factory service or skilled help was a problem, but with more experience, persistence, and ingenuity, and with provision of an adequate

Figure 7. Helicopter delivery of shock research unit laboratory.

airconditioned shelter and the wholehearted support and cooperation of the Third Surgical Hospital under the command of Lt. Col. Theodore Sadler, the many problems were successfully dealt with and much valuable data obtained.

(Some of the following material was written in 1967, as a report on research being conducted during the war.)

The primary concern of the surgical research team in Vietnam has been the intensive treatment and study of shock. The same philosophy, instrumentation, skills, and even the same people have been used in this effort in Vietnam that have been so successful in our shock research unit at Walter Reed General Hospital. Treatment and study of shock go hand in hand. They cannot be separated if the best results are to be obtained. Shock is of paramount importance in Vietnam; it is what kills patients after they reach the hospital. Mortality of casualties reaching a hospital in Vietnam is a little less than in Korea, where it was 2.4 percent. However, this does not tell

the true story of the treatment of shock in Vietnam. Patients reaching hospitals in Vietnam include many who would have died on the battlefield in Korea. The killed-to-wounded ratio in Korea was one to three. There were, up to March 1967, about 50,000 soldiers wounded in Vietnam. If this same ratio were applied, there should have been about 17,000 killed; however, only 8,500 were killed. About 8,500 were saved by more prompt and efficient treatment.

The new type of surgical patient that has appeared in Vietnam is of great importance to surgical research and shock treatment: the critically wounded patient, suffering rapid blood loss from vascular or organ injury, who under any other circumstances would have died shortly after injury. He is now delivered to a hospital within a few minutes after injury; he arrives with unobtainable blood pressure, lactate levels of 200 mg% or more, and severe metabolic disturbances; he is at the point of death, and if effective treatment is not forthcoming immediately he will die. This patient has never before been faced in any military or civilian hospital. The resuscitation of these patients requires sophisticated laboratory and treat-

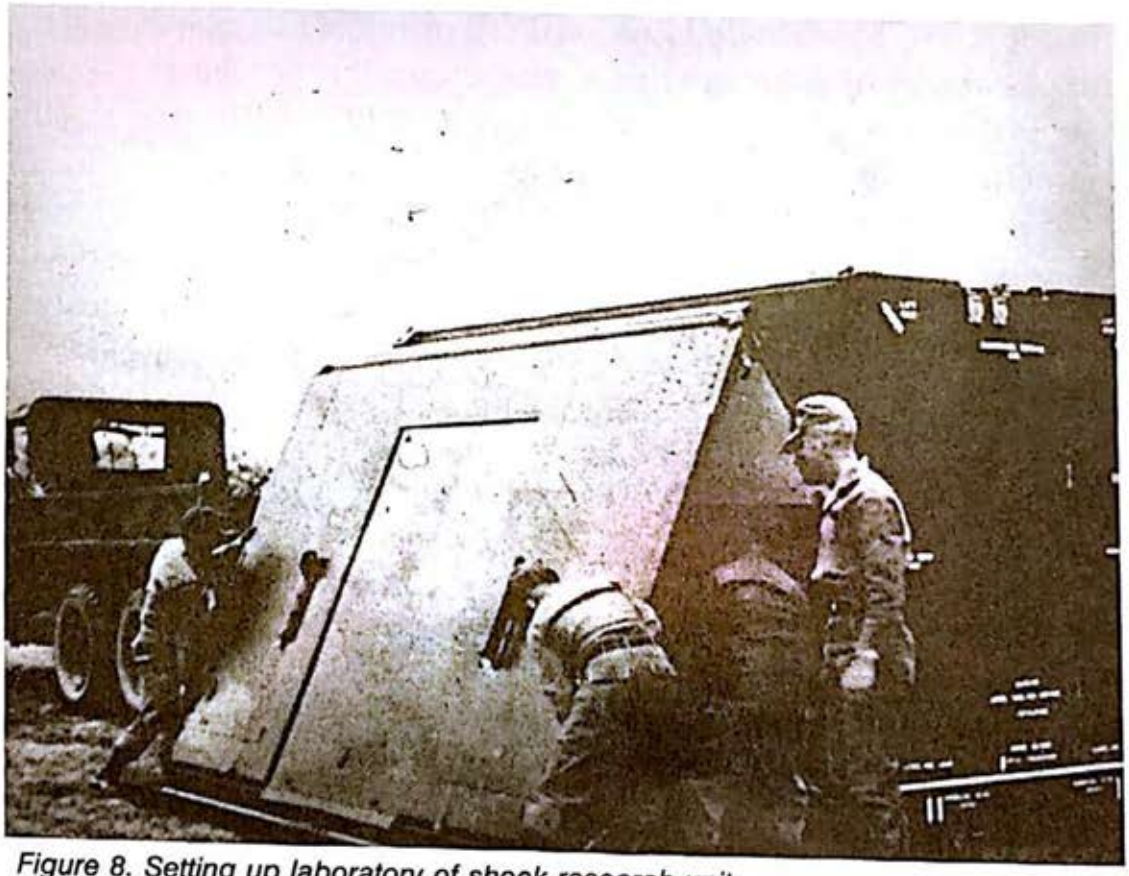

Figure 8. Setting up laboratory of shock research unit.

ment facilities, and those of the Surgical Research Team at the Third Surgical Hospital are ideal for the treatment and study of these cases.

The relationship of medical-research personnel to the hospital staff is an extremely important one. The research team should not be an organic part of the staff or they will be drawn into the routine patient care and not be able to carry out their prime purpose. On the other hand, the research team must not be allowed to divorce itself from clinical care and become complete strangers begging blood samples from someone else's patients. It is important that the shock team establish a close relationship with the staff of the hospital, participating in patient care of those patients who are being studied but not bearing clinical responsibility for large numbers of patients. This relationship is a difficult one to achieve, but it has been enormously successful both at Walter Reed General Hospital and in Vietnam.

Studies Carried Out at the 93d Evacuation Hospital

The first shock studies were carried out by a team headed by Capt. John A. Collins at the 93d Evacuation Hospital at Long Binh, starting in April 1966.

Perhaps most immediately evident to all concerned was the high incidence of hypoxemia in seriously ill or injured casualties and the impossibility of estimating this value clinically. Similar to this was the inability on clinical grounds to predict acid-base balance and the sometimes surprisingly large differences between clinical estimates and objectively determined values. Interestingly, these differences were almost always in the form of clinical overestimation of acidosis. Many patients were alkalotic with pH's of 7.5 or more. Previously it had been thought that all of these patients were acidotic and would benefit from sodium bicarbonate. This alkalosis was largely respiratory, but other factors may have been involved.

We were not able to document the existence of "transfusion acidosis." Although bank blood, particularly relatively old bank blood, is markedly acid (pH 6.5 or less) and high in lactate (130 mg%), it may decrease acidosis and lower lactate levels by promoting blood flow and capillary perfusion. Many of the rapidly transfused patients quickly underwent general anesthesia in order to obtain adequate control of hemorrhage. General anesthesia in itself had a significant effect on arterial pH because of the abolition of respiratory compensation, but we obtained data on three casualties rapidly

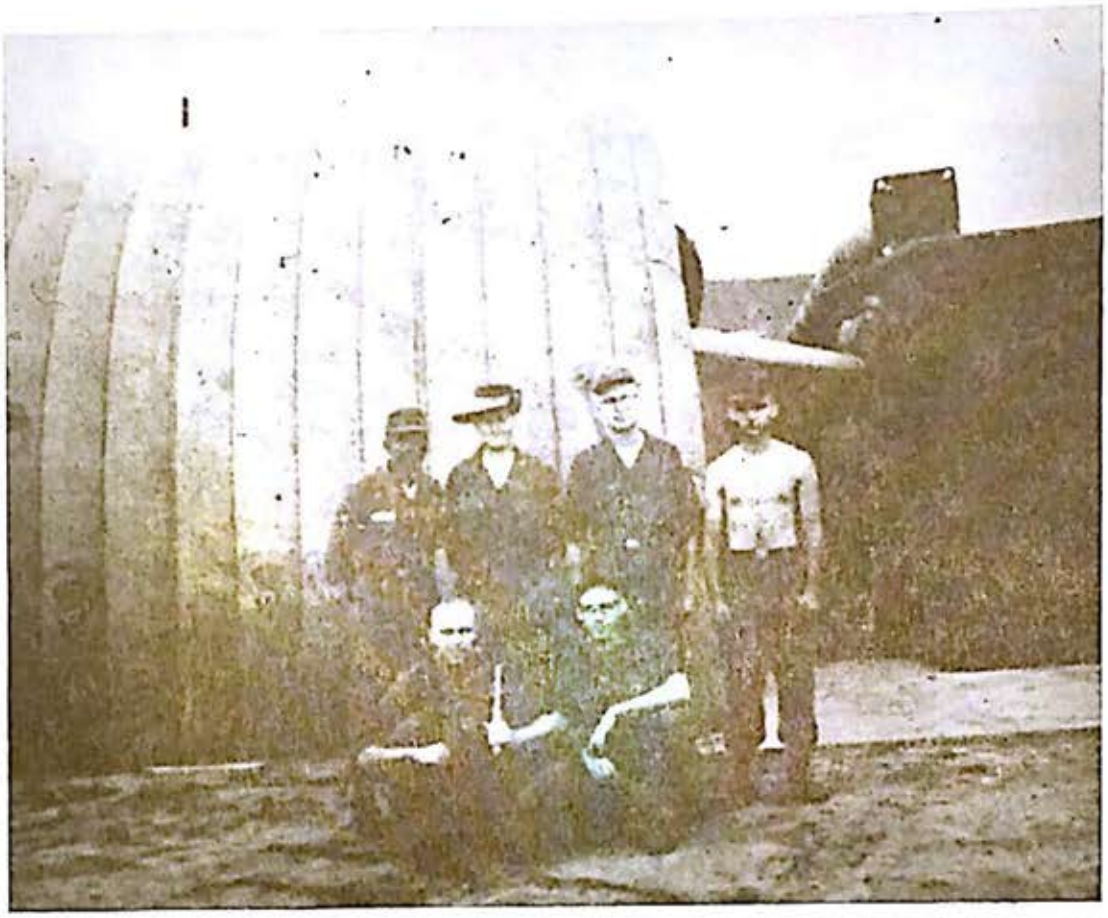

Figure 9. Shock unit ward and laboratory in operation with the Third Surgical Hospital on the Mekong Delta. This kind of inflatable tent and prefabricated building was used in the construction of the experimental ***MUST*** *units.*

transfused before anesthesia and not given alkalinizing agents. One was admitted without palpable peripheral pulses, with an arterial pH of 7.27, pCO_2 of 23.5 mm Hg, and a lactate of 78 mgm per 100 ml blood. He received nine units of blood in 60 minutes with restoration of blood pressure (150/80) and restoration of arterial pH to 7.36, pCO_2 to 36.5, and decrease in lactate to 51 mgm%. A second patient received eight units of blood and two liters of saline in the first 35 minutes in the hospial without restoration of an audible blood pressure, but with correction of arterial pH from 7.12 to 7.29, pCO_2 from 32 to 34, and lactate from 140 to 63 mgm%. A third patient was a civilian war casualty in hemorrhagic shock given an unknown amount of norepinephrine at a civilian hospital before arrival. Her pH on arrival was the lowest recorded series, 6.78, her pCO_2 at 30, lactate at 139 mgm%. After receiving 11 units of blood and no alkalinizing solutions in 110 minutes, and despite continued bleeding

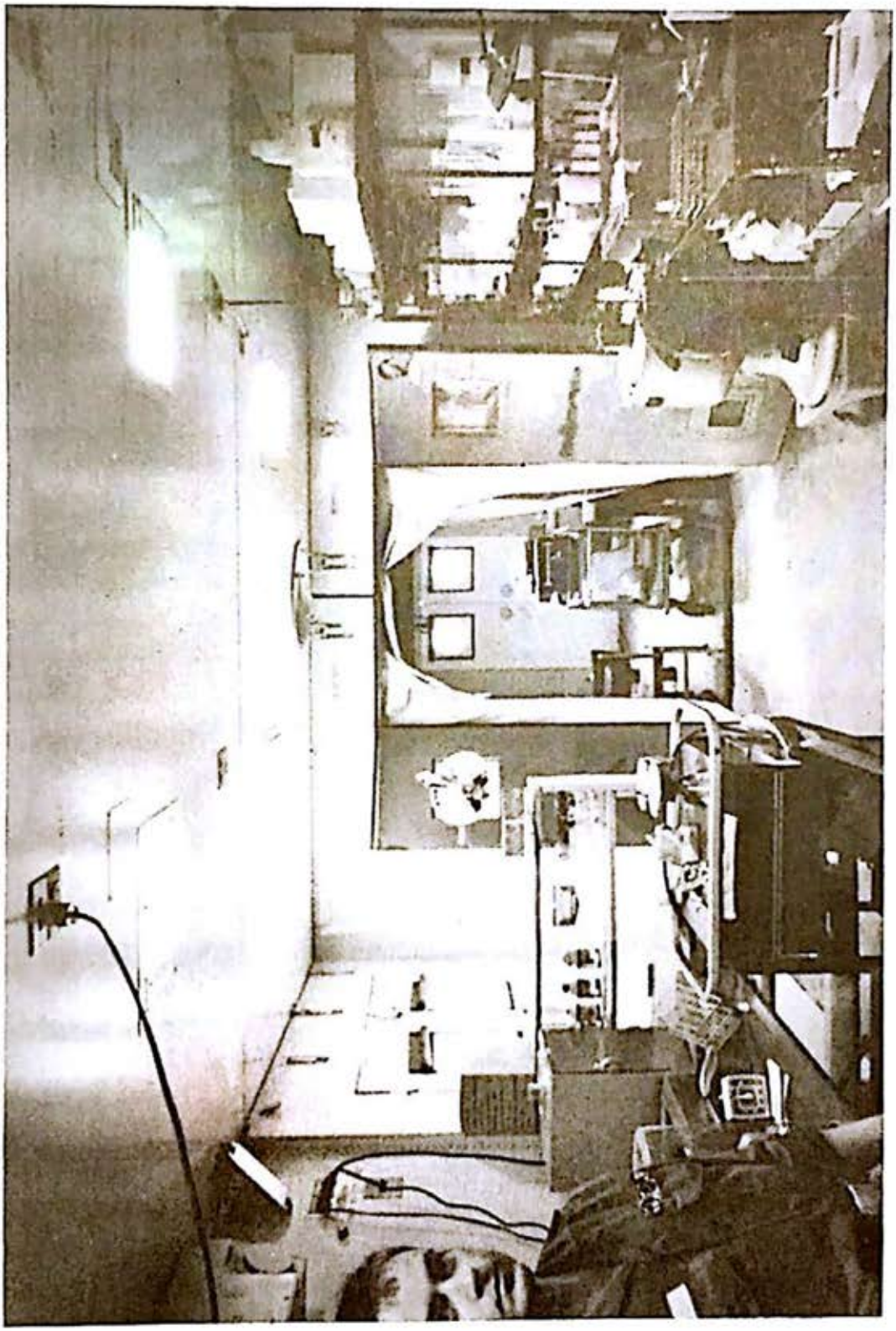

Figure 10. Laboratory and ward of shock research unit.

and hypotension, her pH was 7.09, pCO_2 was 34, lactate was 106 mgm%.

The excess acidity of bank blood in Vietnam appears to be due to the initial citrate preservative solution and to the accumulation of lactate during storage. The lactate level in bank blood varied up to one full gram per unit. Despite this, most rapidly transfused patients showed a rapid fall in lactate level as circulatory status improved toward the end of a period of rapid transfusion. Only two patients exhibited continuing rises in lactate level during rapid transfusion without hypotension, and both of these were undergoing bloody debridements and may have been hypovolemic. The volume-expanding effect of stored blood in this population in Vietnam apparently far outweighed its "excess acid load."

Arterial lactate levels were studied serially in the postoperative period on 60 seriously injured casualties with peak recorded lactate levels of 25 mgm% or more. All patients were normotensive with pulse rates below 120 but usually greater than 90, and urinary output sustained in excess of 100 ml per hour. In 43 of the 60 patients, the lactate level remained below 10 mgm% after 12 hours in the hospital. In 17 the level either remained elevated or rose significantly after returning to normal. The most likely explanation for the persistent or recurrent elevation is hypovolemia and poor capillary perfusion. This is compensated shock, but a true shock.

Patients with delayed lactate clearance tended to develop coagulation defects. This is another hallmark of persistent shock. (See Table 1).

We were impressed with the high frequency of alkalosis during recovery in seriously injured casualties. We encountered 40 such patients with an arterial pH of 7.45 or greater after correction of body

TABLE 1. Relationship Between Lactate Clearance and Clotting

Return of Lactate to Normal	Pattern of Clotting Tests	
	No Clotting Defect	Presence of Clotting Defect
	(number of patients)	
Rapid	16	7
Delayed	1	16

temperature. All were breathing spontaneously at the time of sampling. Sixteen patients had a predominantly metabolic alkalosis, 17 had predominantly respiratory alkalosis, and 7 had both at different times. The patients with metabolic alkalosis formed two groups, those with early onset (9/11 within 48 hours) and those with late onset (4/5 more than four days after injury). The group with early onset had the more severely alkalotic metabolic component by the "base excess" and "whole blood buffer base" criteria. Respiratory alkalosis usually occurred soon after injury (15/23 within 48 hours). Four of the remaining eight exhibited a severe systemic fat embolism syndrome. More of these patients had evidence of pulmonary damage (18/23 as opposed to 8/16 of those with only metabolic alkalosis). The alkalosis persisted after oxygen enrichment of the atmosphere raised arterial oxygen tensions to levels of 90 percent saturation or better.

The cause of the metabolic alkalosis is not clear. Hypokalemia is the usually invoked cause, but none of these patients had significant enteric-fluid losses, half were retaining potassium-containing fluids by mouth when the alkalosis appeared, and three of the remaining six had serum potassium levels over 3.4 mEq/liver while alkalotic. Perhaps more significant is a consideration of the alkalinizing effect of citrated blood, which contains 15.2 mEq sodium citrate per unit. After metabolic conversion of this citrate, three units of blood contributed approximately the same alkalinizing effect as one commonly used ampule of sodium bicarbonate. Most of our patients were extensively transfused, but not all exhibited metabolic alkalosis, or even a rise in the calculated metabolic alkaline components. Also, such alkalosis should be maximum soon after transfusion and gradually diminish. Nevertheless, this "excess alkaline load" must certainly contribute to the alkalosis.

There was a current vogue for the liberal use of sodium bicarbonate in almost any injured or extensively transfused patient, based on implications of a high incidence of metabolic acidosis in injury, or hypovolemia of such a degree as to impair cardiovascular function. We were unable to document such a situation or support such practices.

We found no instance in which the "excess lactate" yielded information beyond the simple lactate level. Moreover, we found wide variation and significant instability of the resting lactate/

pyruvate in convalescent patients, despite a routine technique of mixing the sample with premeasured cold perchloric acid at the bedside immediately after obtaining the sample. In patients with respiratory alkalosis and hypocapnia, lactate elevations were always accompanied by elevated excess lactate values, so that even in the situation where the calculation should perhaps be of greatest clinical usefulness, no advantage was found.

Clotting Studies: clotting studies on combat casualties were interesting. The routine tests performed were the prothrombin time, activated partial thromboplastin time, and salt-precipitable fibrinogen level. The last rarely varied acutely, but significant variations in the first two values did occur in the first 24 hours. We have arbitrarily called a numerical elevation of more than one-third in these values a clotting defect. In serial studies on 45 severely injured casualties, a clotting defect in the first 24 hours was associated with large levels of transfusion (15 or more units), significant prolonged hypotension in the unanesthetized state, unexplained arterial hypoxemia and therefore presumed embolization (discussed later), and extensive local tissue damage, although this was also common in those with a normal coagulation mechanism (Tables 2, 3). Most of these variables occurred in combinations in the same patient, making statistical evaluation difficult, but one interesting fact emerged. Of 15 patients with significant hypotension in combination with either embolization or extensive transfusion, all had clotting defects. In another study of 29 patients in severe refractory shock, mostly septic shock, all but one developed a clotting defect (Table 4). In another study of normal people, early severe hemorrhagic shock patients, patients not in shock, and patients in severe refractory shock it was found that the early severe hemorrhagic shock patients had a shortened prothrombin time and partial thromboplastin time, while the refractory shock patients had prolonged clotting times (Fig. 11). Fibrinogen levels were normal or above, but all other clotting factors were depleted (Fig. 12). These coagulation changes were documented by means of thromboelastograms (Figs. 13, 14).

The response to rapid transfusion formed no consistent pattern, and certainly did not support the time-honored concept that abnormal bleeding in a severely injured patient is often due to replacement of the patient's blood with factor-poor stored bank blood. One patient

TABLE 2-A. Distribution of Patients Demonstrating No Defect and Having a Clotting Defect According to Transfusion Requirement

Units of Blood	No Defect (Number of Patients)	Clotting Defect (Number of Patients)
1 - 9	14	13
10 - 19	4	5
20 - 30	0	4
30 +	0	5

TABLE 2-B. Distribution of Patients with Clotting Defects According to Occurrence of Hypotension

	No Defect (Number of Patients)	Clotting Defect (Number of Patients)
Hypotensive before anesthesia	3/18	20/27
Hypotensive only during anesthesia	4/18	2/27
Never hypotensive	11/18	5/27

TABLE 2-C. Distribution of Patients' Clotting Tests According to Extensive Transfusion Therapy

Units of Blood	No Defect (Number of Patients)	Clotting Defect (Number of Patients)
0 - 15	18	16
15 +	0	11*

**Also hypotensive and hypoxemic*

received 15 units of blood in three hours but retained a remarkable stability of clotting values. This patient, in addition, had extensive tissue damage and presumed embolization, but was never significantly hypotensive. This pattern of stability during rapid prolonged transfusion was seen in seven patients. However, another patient entered the hospital hypotensive and with abnormal clotting values before transfusion. During administration of five units of

TABLE 3-A. Distribution of Patients With and Without Clotting Defects According to Occurrence of Important Variables, Excluding Tissue Damage

	No Defect	Clotting Defect
	(Number of Patients)	
None	11	7
"Shock"	3	3
Transfusion greater than 10 units	1	0
Presumed Embolization	2	1
Shock + Transfusion	0	10
Shock + Embolization	0	3
Embolization + Transfusion	1	1
Shock + Embolization + Transfusion	0	2

TABLE 3-B. Distribution of Patients With and Without Clotting Defects, Excluding Those With Chest or Abdominal Injury, According to the Occurrence of Presumed Embolization (Preoperative Hypoxemia)

Arterial Hypoxemia	No Defect	Clotting Defect
	(Number of Patients)	
Preoperative	3/12	7/19
Postoperative only	2/12	8/19
No hypoxemia	7/12	4/19

blood his values returned toward normal, but rose again when transfusion stopped, suggesting a pattern of preexisting factor deficiency being partly replaced by stored bank blood transfusion. This pattern was seen in eight patients, but all were hypotensive.

Most patients with abnormal clotting values at some time exhibited values much higher than the surprisingly respectable means for 40 units of 11- to 22-day-old bank blood in Vietnam (prothrombin time 17.1/12.7 seconds, activated partial thromboplastin time 64/48 seconds). Two patients who died after prolonged uncontrolled hemorrhage illustrate that in a very general way the most severe clotting changes were observed in the patients with the most profound and prolonged hypotension.

TABLE 4. Clotting Factor Depletions Noted in Severe Shock Patients

Patient	Fibrinogen	Platelets	Patient		Control		Factor Assays						
			PT*	PTT**	PT*	PTT**	II	V	VII	IX	X	XI	XII
1	238 mg%	16,500	19.0	60.4	13.2	38.4							
2	228 mg%	31,000	16.2	72.8	12.5	37.6	46	59	100	57	54		
3	347 mg%	111,000	15.6	49.4	12.5	41.6							
4	359 mg%	102,000	18.0	215.8	13.2	42.5	45	66	48	2	17		95
5	542 mg%	265,000	14.5	120.5	13.0	55.0							
6	318 mg%	24,000	15.8	255.0	12.3	43.0	50	32	10	37			77
7	400 mg%	99,500	15.8	75.0	13.4	47.4	100	86	59	56			48
8	235 mg%	97,500	17.9	71.6	13.9	44.3							
9	280 mg%	16,500	19.3	61.9	14.5	48.2							
10	290 mg%	154,000	120.0	180.0	14.9	42.0							
11	650 mg%	101,500	25.4	93.4	13.5	48.3	100	63	35			26	15
12	320 mg%	8,000	22.0	86.2	12.5	41.0							
13	355 mg%	8,000	19.0	72.6	13.0	44.3	45	35	67			23	90
14	160 mg%	29,000	16.2	132.0	13.6	41.6							
15	165 mg%	3,000	37.0	263.4	13.3	46.2	23	5	3			6	18
16	150 mg%	57,000	17.8	277.0	14.3	55.9							
17	355 mg%	116,000	15.2	49.0	13.7	44.7							
18	184 mg%	13,000	26.4	207.0	13.3	44.9	6	12	54			23	29
19	355 mg%	110,000	15.2	49.0	14.5	44.8							
20	184 mg%	12,500	26.4	207.0	13.5	46.8	6	12	54			23	29
21	50 mg%	18,000	33.0	240.0	14.1	40.5							
22	605 mg%	83,000	14.9	50.5	14.3	46.5							
23	367 mg%	3,500	16.0	116.9	13.1	48.2							
24	240 mg%	15,500	52.5	107.4	12.9	35.7							
25	525 mg%	29,500	16.6	76.6	14.6	48.5							
26	325 mg%	140,000	14.4	44.9	14.2	54.7							
27	465 mg%	31,000	22.2	86.6	12.8	47.1							
28	436 mg%	33,500	17.4	52.0	12.7	47.3							
29	310 mg%	12.000	30.6	94.2	14.5	55.5							
Average	305 mg%	59,000	24.5	119	13.5	43.9	46%	41%	48%	38%	35%	20%	50%

* *Prothrombin Time* ** *Partial Thromboplastin Time*

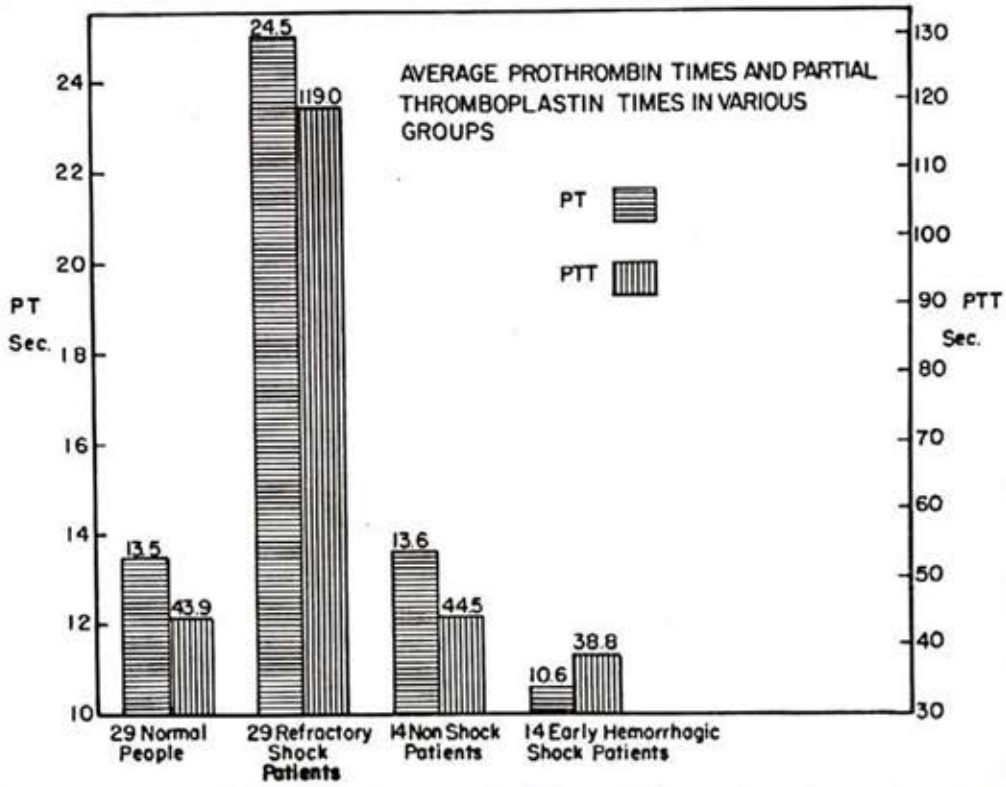

Figure 11. Average prothrombin time and partial thromboplastin time of several groups of people. Normal individuals and patients not in shock had normal times. Early severe hemorrhagic shock patients had very short times (hypercoagulability). Patients in severe refractory shock, primarily septic shock, had very prolonged times, secondary to the development of disseminated intravascular coagulation.

Blood pO_2 Studies: an interesting pattern emerged when the arterial oxygen tension on admission of a series of seriously wounded casualties without lung injury or ventilatory impairment was examined. Seventeen of 69 such casualties, almost all with limb injuries, had arterial oxygen tensions below 80 mm Hg on admission. The interval between wounding and study (all became recumbent when wounded), the amount of blood transfused before study, morphine administration, and the lactate level of the same arterial sample, as an approximation of the degree of shock, were all examined independently and did not seem to be associated with the observed hypoxemia. A positive association was found when the site and etiology of wounding were considered: 50 percent of those with high velocity missile-type wounds of the thigh with comminuted femoral-shaft fractures exhibited the phenomenon, and none of a group of 22

AVERAGE LOWEST LEVEL OF CLOTTING FACTORS PTS. IN REFRACTORY SHOCK

FIBRINOGEN—309 mg%
PLATELETS—69,583
PT—24.9 CONTROL PT—13.2
PTT—123.8 CONTROL PTT—45.5

FACTOR ASSAYS

II—51%
V—44%
VIII—39%
IX—38%
X—35%
XI—19%
XII—46%

Figure 12. Average lowest level of clotting factors pts. in refractory shock.

casualties with wounds apparently from low velocity missiles but with significant blood loss were hypoxemic. Major blast amputations of limbs were not associated with hypoxemia to the same degree (1/7). We think this is circumstantial evidence of physiologically significant tissue embolization occurring at the time of injury, when a high energy projectile produces a blast cavity with severe and sudden increase in pressure in a large closed tissue space and transmits a shattering force to a dense cylindrical shaft of cortical bone filled with soft fat and marrow. Major blast amputations were not associated with the same incidence of hypoxemia (1/7), but the force in these casualties may have been largely shearing in nature, tearing off the limb in a lateral direction and with immediate decompression of the medullary cavity and early reversal of flow in main venous channels. The one fatality in the series occurred in a patient exhibiting both blast and missile effects in the injured limb, with truly massive tissue destruction of the thigh. This patient arrived with an arterial pO_2 of 34 mm Hg, but was not apparently cyanotic or in unusual respiratory

distress. He was already anuric and had marked hemoglobinemia before transfusion. Despite fairly adequate control of hemorrhage, transfusion of 19 units of blood to replace loss, and survival for almost two hours after arrival at the hospital, he died without any apparent response to volume restoration. He was, on the surface, an apparent example of "irreversible shock" (a concept not accepted at any military hospital in Vietnam), or "resuscitative failure," or "refractoriness to transfusion." At autopsy his main pulmonary vessels appeared normal, but microscopically the terminal pulmonary arterioles and capillaries contained abundant debris, some of which looked like fibrin and platelet clots, and stainable fat globules. No organized bone or bone marrow could be found. Pulmonary embolization or thrombosis certainly contributed to this patient's death, but its true impact would not have been suspected on clinical grounds. This was our experience repeatedly: arterial hypoxemia down to 40 mm Hg or even below can be clinically inapparent.

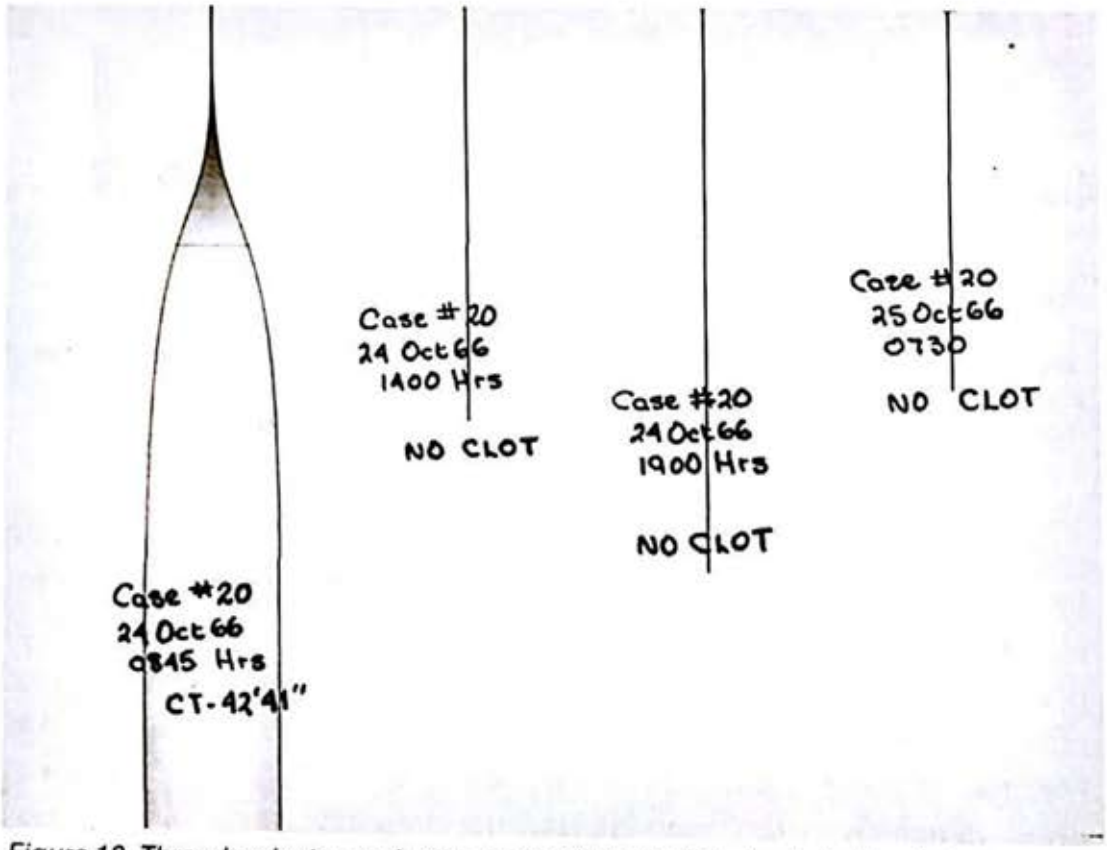

Figure 13. Thromboelastographs on a case of irreversible shock. Left, relatively normal clotting mechanism as indicated by torpedo shape with spike. Subsequent tests showed development of complete incoagulability secondary to disseminated intravascular coagulation as denoted by straight line. Development and persistence of a clotting defect is a bad prognostic sign.

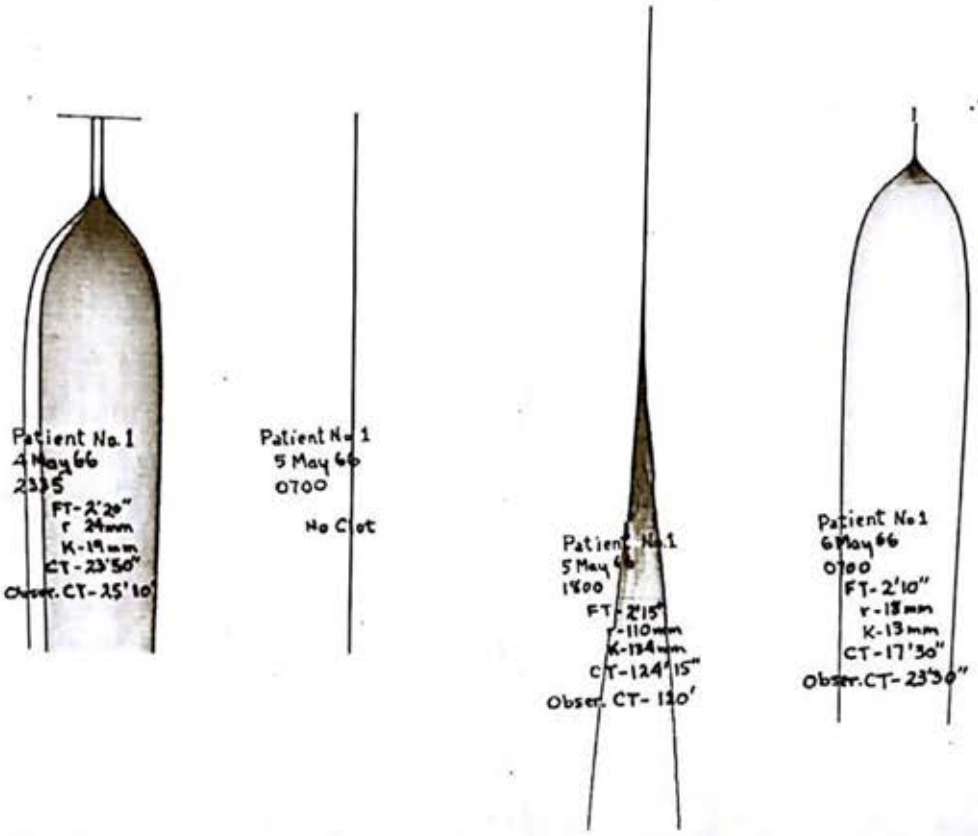

Figure 14. Thromboelastographs of patient going into and recovering from episode of disseminated intravascular coagulation. On left, note normal thromboelastograph on 4 May, which changed to a straight line on 5 May, indicating complete incoagulability. This development of clotting defect is associated with disseminated intravascular coagulation and refractory shock. The third figure, taken a few hours later on same day, indicates partial recovery from clotting defect. The last figure, taken the following day, shows normal thromboelastrograph indicating recovery from clotting defect and was associated with recovery from shock. This illustrates correlation between a clotting defect and refractory shock.

Autopsy series from both World War II and Korea have given an incidence of 20 percent for moderate or severe pulmonary fat embolism in casualties who died after reaching the hospital, and 4 percent for significant systemic fat embolism. Because of the lack of clinically apparent effects of such embolization, the conclusion was reached from the Korean study reported by C. P. Artz that "there was no evidence from the analysis that the presence of fat in the lungs causes pulmonary dysfunction or death." We think we are accumulating evidence to the contrary.

Penetrating missile wounds of the chest have caused a significant percentage of the wounds of all wars in this century. We

are documenting the serial changes in arterial pO_2 following missile wounds of the chest, excluding those with major associated wounds which might in themselves interfere with ventilation. Early results indicate that the degree of impairment is related to the apparent velocity or kinetic energy of the wounding missile, indicating that even the lung, which is thought to be the tissue least susceptible to high velocity missile effects, is more severely damaged by such a missile. The difference is not striking but appears to be real. A series of patients with high velocity missile-type wounds in whom exploration of the wound indicated that the missile did not itself penetrate the pleural cavity, but who had significant pulmonary damage, by X-ray exhibited changes similar to those with penetrating high velocity missile wounds, with perhaps a trend to earlier recovery. Correlation with X-ray changes indicates that improvement in arterial pO_2 accompanies or precedes — never follows — radiologic improvement. This may prove to be a useful rule of thumb in selecting patients for prolonged air evacuation at reduced cabin pressures when oxygen tension-measuring equipment is not available.

Tissue Adhesives: the surgical research team also evaluated various very rapidly polymerizing adhesives, cyanoacrylates, for use as a hemostatic spray to stop bleeding from bleeding surfaces where conventional suture methods have failed. The results on 10 casualties were very encouraging; in seven, bleeding from large wounds of the liver, and in one, bleeding from a single-functioning kidney remnant, were obtained when life was seriously threatened by failure to control hemorrhage. Two died of associated injuries, but the others have made good recoveries. The compounds wer developed at the United States Army Medical Biomechanical Research Laboratory, and are distinct improvements over the previously available tissue adhesive in terms of tissue reaction and effective polymerization. Search for a biodegradable adhesive continues, since this would avoid the potential problems of permanent indwelling foreign bodies.

Local Antibiotics: laboratory studies on rabbits at WRAIR had shown that an antibiotic spray to areas of dead muscle produced by a crushing wound would delay the otherwise rapid multiplication of bacteria and prevent death from sepsis (Fig. 15). This would be useful if debridement of the dead tissue could not be carried out

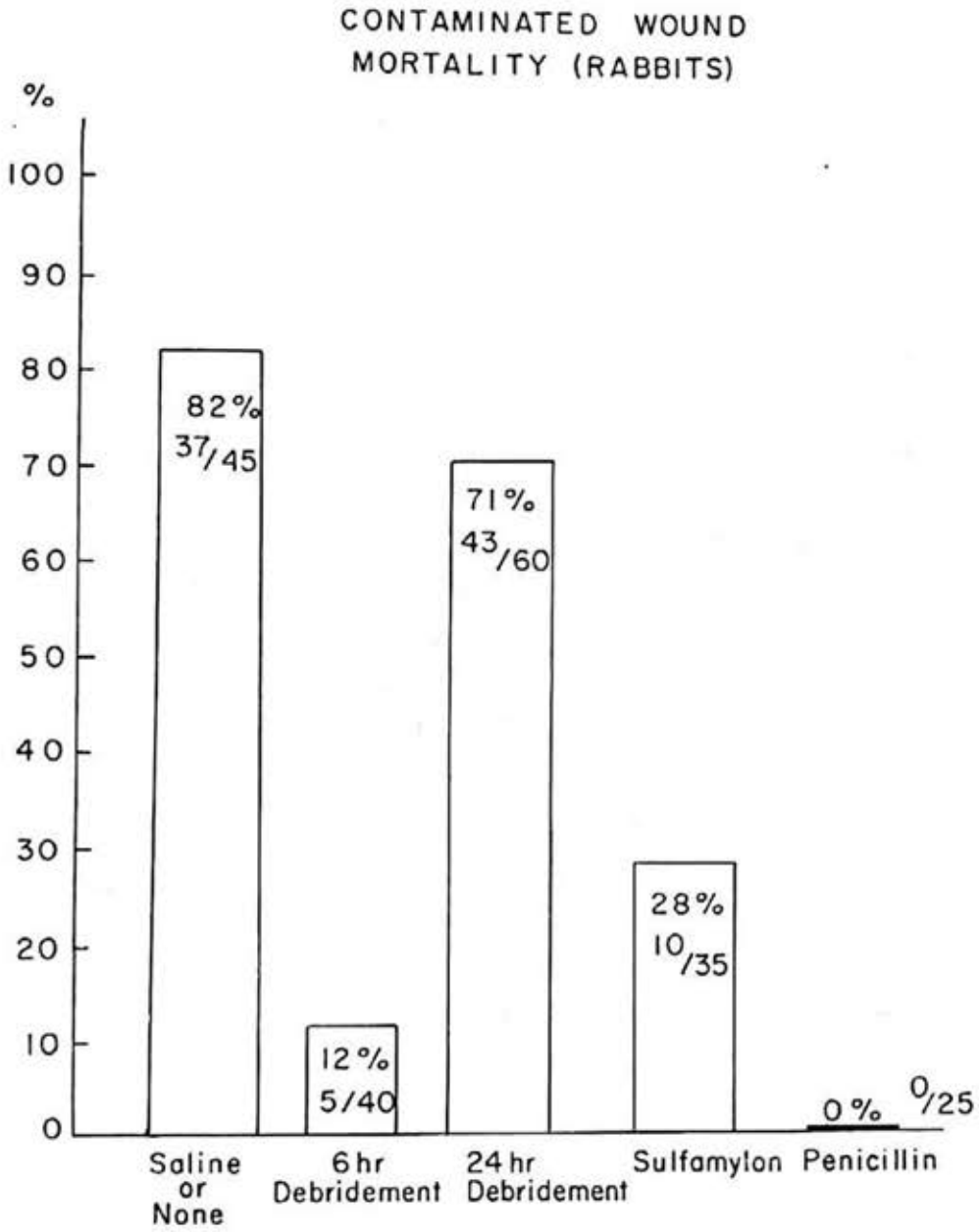

Figure 15. Crushing wounds in rabbits treated by saline spray, at 6- or 24-hour debridement, or antibiotic spray.

promptly. A systemic antibiotic would not be useful because the dead tissue is not perfused. Accordingly an antibiotic spray was tested on a limited scale in Vietnam. It consisted of Bacitracin Polymyxin-B Neomycin and Penicillin in a small spray unit (Fig. 16). Although promising, the research could not be carried out adequately because of administrative difficulties.

Bank Blood: most patients studied by the team received stored

Figure 16. Antibiotic wound spray used in Vietnam.

bank blood for the treatment of hypovolemia and during surgery. It is known to differ from circulating normal blood in all the parameters measured. In contrast to large civilian hospitals, the blood used in a field medical unit in a combat zone necessarily travels long distances and usually undergoes several short periods of time with little or no active refrigeration. Generator failures, especially during the monsoon season, are expected occurrences and are accompanied by unavoidable variations in blood bank refrigerator temperatures. For these reasons it was of interest to define the parameters of the study in bank blood at its point of usage. Blood was drawn from the IV tubing during the last half of a transfusion and handled exactly as for arterial samples except that additional citrate was not added for the clotting studies. All the blood studied was in Fenwal plastic bags said to contain 450 cc blood plus 67.5 cc NIH solution A. All the units of blood were administered through disposable field-type blood recipient sets (Fenwal or Burron).

The results of the study are summarized in Table 5. It is seen that bank blood, even old bank blood, has a relatively normal coagulation profile. In most cases it should not contribute to a coagulation defect, but should actually help to correct it.

On the basis of our studies one conclusion can be drawn: definite

TABLE 5. Measurements of Bank Blood Administered at the 93d Evacuation Hospital*

	pH	pO_2 mm Hg	pCO_2 mm Hg	PTT** Secs.	PT*** Secs.	Fibrinogen mg %	Lactate mg %
Old Blood (Mean)	6.50	33	144	65	18	390	130
Old Blood (Range)	6.41-6.56	24-36	110-180	55-91	14-23	290-510	106-167
Fresh Blood	6.82	44	101	47	13.8	365	13

**"Old Blood" represents 15 units of blood within five days of expiration, 8 units usually on the day of expiration. "Fresh Blood" represents a single unit of blood given four hours after shedding. All blood used was supplied through the 406th Medical Laboratory (Japan) and its mobile element in Vietnam.*

***Partial Thromboplastin Time*

****Prothrombin Time*

changes occur in the clotting values of this population of young, acutely injured adults who require blood replacement, but these changes cannot be attributed simply to the replacement of the patient's blood with bank blood.

Occult Fluid Deficits: twenty-six battle casualties were studied to determine their response to an additional fluid load given after their condition had stabilized postoperatively and their wounds had been repaired.

Two groups were included in the study. Group I never showed hypotension of excess lactate. Group II, prior to surgery, demonstrated various degrees of excess lactate accumulation, and all had systolic blood pressures of 90 mm Hg or less.

Group I consisted of 10 patients: 5 received 800 cc low molecular weight Dextran in normal saline, 5 received 1000 cc Ringer's lactate over a period of one hour. Group II consisted of 16 patients; 10 received low molecular weight Dextran in normal saline, and 6 received 1000 cc of lactated Ringer's solution.

Studies performed for the eight hours during and following infusions consisted of serial hematocrits, serum sodium, potassium, and protein, cardiac index, stroke index, blood pressure, pulse, central venous pressure, urine output, serum osmolarity, blood

volume (Cr^{51}, I^{125}) and extracellular fluid space (SO_4^{35}) measurements. Group I showed minimal elevation in central venous pressure and cardiac output. Urine output increased markedly and plasma volume increased. The changes were the same for both solutions but lasted two and one-half hours average for the Ringer's lactate, and four hours using low molecular weight Dextran in saline. Group II showed rather marked changes. Initially these patients had low central venous pressure measurements and decreased extracellular fluid volume. On infusion of the test solution, cardiac index, stroke index, central venous pressure, and blood pressure increased markedly. Serum sodium and osmolarity decreased, and plasma and extracellular fluid compartments increased significantly. Hematocrit levels decreased. The Ringer's lactate group maintained changes for four hours, except for extracellular fluid, which remained elevated during the eight hours the patients were followed. The Dextran group maintained their new state for an average of six and one-half hours, although three of the group were still showing increased values at eight hours; again the extracellular fluid compartment remained enlarged.

From this study it was concluded that the "stable" patient, previously hypotensive even though apparently stable postoperatively, often has occult extracellular fluid or plasma volume deficits which need replacement.

According to the Surgical Consultant of the United States Army in Vietnam, two of the most common immediate causes of death among shock cases in Vietnam were pulmonary edema and cardiac arrest. It is interesting to speculate on the reason for this in light of the findings of our shock-research team both in Vietnam and at Walter Reed. Military hospitals in Vietnam were very well equipped for modern surgical treatment as practiced currently in the United States. However, they did not have the facilities of the shock unit at the Third Surgical Hospital. With the exception of the shock-research unit, routine central venous pressure measurements were usually not made previous to 1967; or if they were, they often registered pressures of 10 cm of H_2O or below at the time of development of pulmonary edema. As measured clinically in the Walter Reed Shock Unit, pulmonary artery pressure may rise before the central venous pressure as volume is being administered. Based on findings in the surgical laboratory at Walter Reed Army Institute of Research and the shock unit at Walter

Reed General Hospital, the reason for this may be as follows: volume administration ordinarily results in a fall in the level of catecholamines (Fig. 17). This results in the physiologic vasodilation of pulmonary arterioles. With the rise in central venous pressure from 0 to 6 or 8 cm H_2O, venous return to the right heart becomes adequate. The adequate right heart takes this adequate venous return and pumps it into the pulmonary artery. If the pulmonary arterioles are open, the blood surges through into the left heart, where it is pumped out, giving a higher systemic blood pressure. However, if the catecholamine level remains high because of severe trauma, infection, or other cause, pulmonary arterioles may remain constricted. The pulmonary microcirculation may also be partially obstructed by microthrombi and sludged blood. In this case the increased right-heart output produces a rather sudden rise in pulmonary artery pressure with the onset of pulmonary edema. A high pulmonary

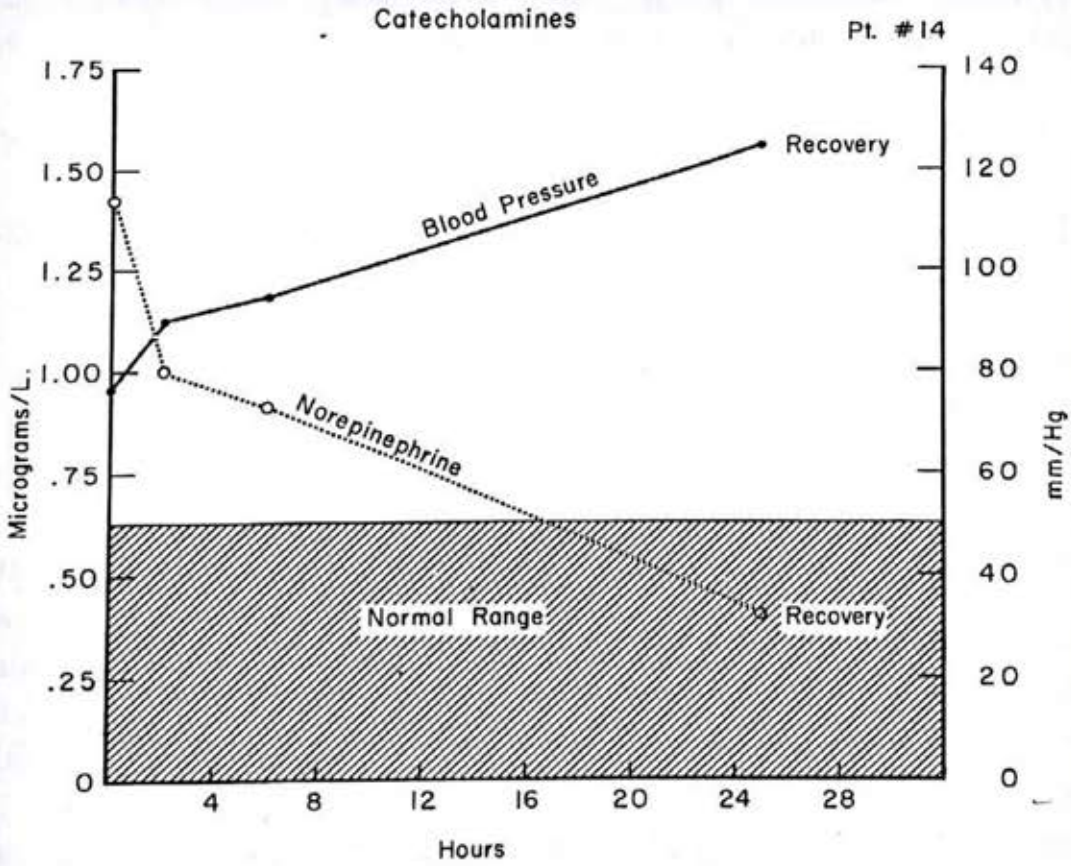

*Figure 17. Wounded soldier in shock has a high endogenous norepinephrine level causing peripheral vasoconstriction. With adequate IV fluid administration, epinephrine level returns to normal, arterial pressure rises to normal, and peripheral vasoconstriction subsides. Reprinted with permission from R. M. Hardaway, "Wartime Treatment of Shock," **Military Medicine,** 147 (1982): 1011-1017.*

artery pressure is associated with the development of pulmonary edema (Fig. 18). Central venous pressure may remain with normal limits until right-heart failure intervenes and the high pulmonary artery pressure backs up into the right atrium, elevating the central venous pressure. If central venous pressure is not monitored, or even if it is and great care is taken, pulmonary edema may arise rapidly and cause death of the patient.

Another possibility for the cause of this pulmonary edema is the contraction of the vascular space that occurs after adequate perfusion has been attained. This contraction creates a relative excess of blood volume over that needed during shock. If the entire volume need has been filled with whole blood, the excess cannot be urinated out as it could with fluids other than blood. Even if too much blood has not been given, fluid may not be excreted if renal output is poor because of kidney damage. In this case the volume is retained, a relative hypervolemia occurs, and pulmonary edema results. A third possibility is the excessive use of Ringer's lactate as the prime resuscitative fluid for prolonged periods. Any electrolyte solution tends to leak from the vascular space, and excessive amounts of it cause edema of all organs if given to the exclusion of colloids over a period of time.

The occurrence of numerous cases of cardiac arrest may well be correlated to a low pO_2, hypothermia, low blood volume or low blood pressure, or other factors. Military hospitals in Vietnam do not have facilities for the measurement of blood gases (with the exception of the shock unit at the Third Surgical Hospital). It is impossible to clinically diagnose a low pO_2. Patients in shock may seem clinically in relatively good shape with little if any respiratory distress. But pO_2 taken may prove to be very low. Certainly extremely low pO_2 not corrected results in cardiac arrest. This has been seen frequently. Although most casualties in early shock have a relatively normal pO_2 when studied in the shock unit, three categories may have a low pO_2.

First, patients who have experienced a high velocity bullet wound of the thigh frequently have a low pO_2. This may be due to multiple pulmonary microemboli and microthrombi. The sudden increase of pressure in the closed fascial space of the thigh may drive tissue into the veins and embolize the lungs. Fibrin thrombi develop from this. These emboli and thrombi interfere with O_2 absorption, may cause arteriovenous shunting, or lack of surfactant, all produced by pul-

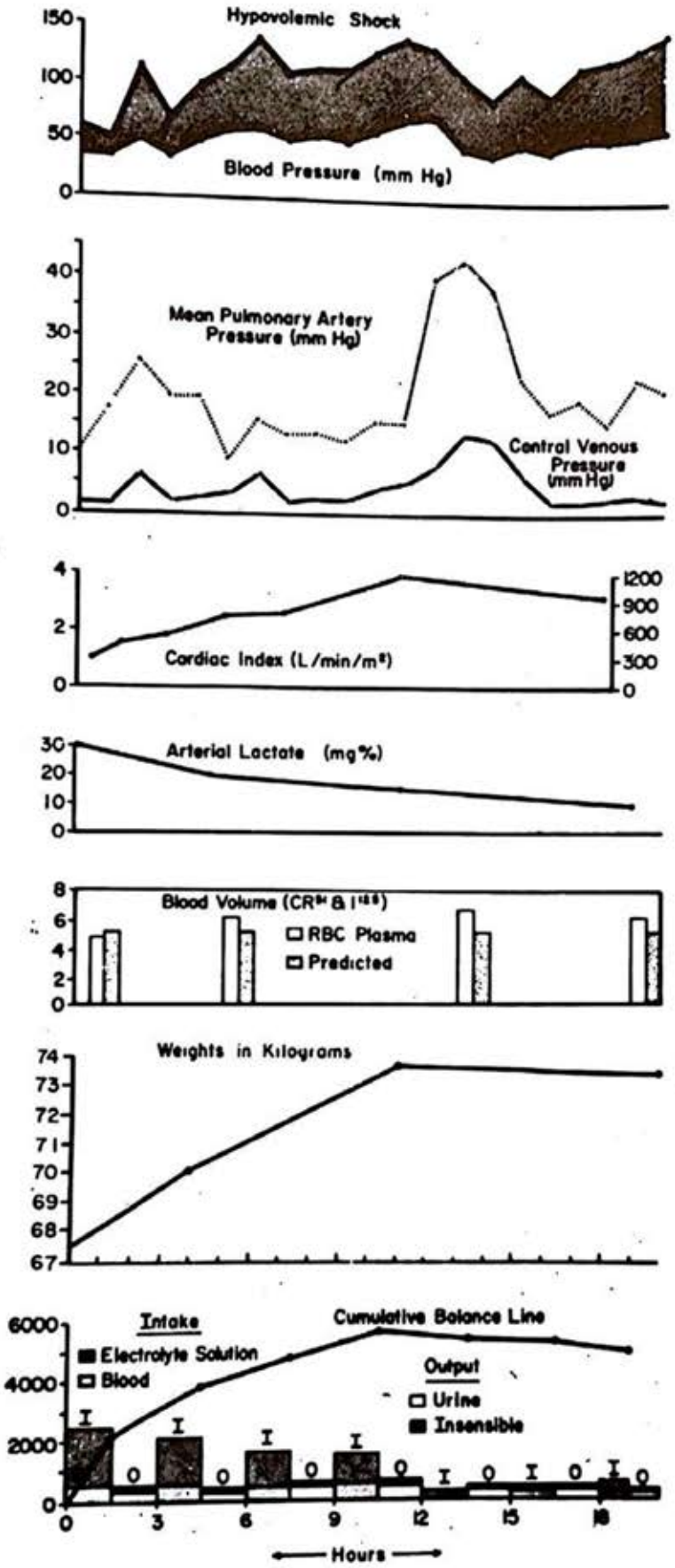

Figure 18. Patient in hypovolemic shock being given IV fluids. With just a mild rise in central venous pressure, pulmonary edema developed and systemic arterial pressure fell. At the same time, pulmonary artery pressure rose to high levels. A pulmonary artery catheter is a more accurate monitor for IV fluid administration in severe cases of shock, especially septic shock. Reprinted with permission from R. M. Hardaway, "Wartime Treatment of Shock," ***Military Medicine,*** *147 (1982): 1011-1017.*

monary circulation blockage. Second, any wound involving the respiratory tract may interfere with oxygenation. Third, all severe shock is accompanied by a low pO_2 perhaps due to any or all of the above and disseminated intravascular coagulation. If a low arterial pO_2 is not soon reversed or becomes worse, cardiac arrest will result. If pO_2 is not measured, a low level will probably go unrecognized.

Of course, other reasons for cardiac arrest may exist. Hyperkalemia due to catabolism, massive transfusion with old blood, or anuria may cause cardiac arrest. Hypokalemia may occur secondary to alkalosis. The sudden administration of large amounts of cold blood or other fluids may cause a severe hypothermia which might result in ventricular fibrillation. Low blood pressure and hypovolemia, especially as accentuated by the vasodilation caused by anesthesia, are frequent causes. These and other causes cannot be diagnosed without adequate study.

Studies Carried Out at the Third Surgical Hospital

The second six-months study was carried out by the surgical research team at the Third Surgical Hospital under Capt. Paul M. James, Jr. In this period, 186 shock patients were intensively studied and treated by the surgical research team. The following laboratory tests were performed on these patients: pH, 1,470; pO_2, 1,436; pCO_2, 1,453; prothrombin time, 606; partial thromboplastin time, 606; hematocrit, 1,213; hemoglobin, 890; fibrinogen, 693; total protein, 477; lactate, 1,552; pyruvate, 716; SGOT, 162; SGPT, 150; LDH, 195; factor V, 60; and many others. Many other patients were treated and studied less completely.

Results of these studies may be summarized in part as follows:

1. Arterial and venous pressure studies as a guide to volume administration. The routine use of the supraclavicular approach to the subclavian vein, utilizing a disposable sterile catheter and disposable sterile-water manometer, has proved to be an extremely valuable guide to volume administration. In well over 400 cases, only two complications were encountered. These were both minor pneumothoraxes which did not affect the clinical course of the patient. One of these patients also had a chest wound on that side, and the pneumothorax could have been due to the wound rather than the insertion of the central venous catheter. Approximately 20 radial-

artery catheters were placed to study direct readings of arterial pressure with cuff pressures. No complications have arisen. It is possible to record both central venous and radial artery pressures on our two-channel recorder for documentation.

2. Determinations of blood gases and pH. This has proved to be one of the most valuable procedures in both patient care and research. Although it had previously been assumed that all casualties are acidotic, it has been found that many are quite alkalotic due to a respiratory alkalosis probably secondary to high catecholamine levels and hyperventilation. This is in spite of a high lactate level. It has been found that some patients were treated with bicarbonate for a supposed acidosis when in fact they were alkalotic. In some cases a severe hypernatremia was produced because of the administration of too much bicarbonate which was not needed in the first place. The pO_2 is sometimes found to be extremely low and requires immediate oxygen treatment. It is impossible to clinically determine which patient will need this. The low pO_2's are frequently found in cases without any respiratory-tract injury. They may be secondary to tissue embolism in the lungs or other pulmonary changes. It has been found that remarkable degrees of arteriovenous shunting (up to 90 percent) are frequent so that arterial oxygen pressure may be extremely low in spite of oxygen therapy. The pCO_2 is often extremely low producing a relative respiratory alkalosis. These determinations plus those in paragraph 4 below would be valuable in evaluating patient for air evacuation and for anesthesia.

3. Lactate and pyruvate levels. Although pyruvate levels do not change particularly, lactate levels may be extremely high. They have been measured over 200 mg% in some cases which come in without blood pressure and in extremis (normal of 10 mg%). In spite of the extremely high lactate levels, these patients are frequently reversible with proper treatment. Lactate reflects the present state of perfusion and cellular anoxia. One of the highest lactate levels was observed in a patient transferred from a civilian hospital in hypovolemic hypotension treated with norepinephrine. This probably reflects the danger of treating this syndrome with vasoconstrictor agents. This patient died.

4. Red-cell mass, plasma volumes, and extracellular fluid. This work so far has been limited because of the loss in transit of one machine and the damage to another. However, it has been determined

that the administration of 500 ml of low molecular weight Dextran will result in the immediate but transient increase in blood volume of more than twice that volume given as a result of pulling in of extracellular fluid. This dramatically increases cardiac output and blood pressure, but further depletes extracellular fluid which must be replaced. It is contemplated that in the future we will be able to measure not only red-cell mass and plasma volume, but also extracellular fluid and total body water in Vietnam. These latter determinations have been done in the past by sending frozen specimens back to our lab at Walter Reed. It has been found that extracellular fluid is decreased along with the blood volume in hemorrhagic and traumatic shock. Both blood volume and extracellular fluid require replacement.

Soldiers wounded in Vietnam were found to be dehydrated when studied immediately after a minor injury. This was particularly noticeable if they were wearing heavy body armor. Their extracellular fluid was decreased, as compared with other soldiers not in combat and doing routine duties. This partial dehydration may increase their susceptibility to shock if they should be wounded. The sulfur-35 space-equilibration time for patients in shock is prolonged, and the use of a single 18-minute sample, as recommended by Shires *et al.*, is questioned. Thirty minutes or more is required. The extracellular (sulfur-35) deficits found in our patients are attributable to dehydration and hemorrhage. We are unable to confirm the existence of a "functional extracellular fluid deficit."

5. Cardiac output. Cardiac outputs were measured for the first time in a combat zone. They were very low in hemorrhagic shock. They markedly increased as a result of administration of intravenous fluids. Cardiac output determinations after low molecular weight Dextran administration show dramatic increases in cardiac output.

6. Catecholamine levels. Elevation of catecholamines in shock has been documented. This rapidly decreases with volume administration and rise in blood pressure. This produces a physiologic vasodilatation and fall in peripheral resistance.

7. Osmolarity studies of blood and urine. Osmolarity of both blood and urine varied markedly with the treatment given the patient and with his condition. Too much electrolyte tended to lower osmolarity of both blood and urine. When capillary perfusion was restored and excess fluid was being mobilized and excreted as urine,

there was a tendency for both blood and urine osmolarity to decrease.

8. Respiratory studies involving use and effects of volume-cycled respirator. The volume-cycled respirator has been found to be extremely useful in ensuring adequate air and oxygen exchange. It has definite advantages over pressure-cycled respirators. Respiratory problems have been found to be perhaps the most difficult problem in severe shock.

9. Platelet counts, prothrombin times, partial thromboplastin times, clotting factor assays. Severe and refractory shock cases have shown a clotting defect characterized by deficiencies in all of these factors secondary to disseminated intravascular coagulation. These clotting defects cannot be accounted for on the basis of dilution with large quantities of transfused factor-poor blood, since the transfused blood is often of better clotting quality than the patient's and should help rather than cause the clotting defect. In addition, early reversible shock has shown a hypercoagulable phase with decrease in prothrombin time and partial thromboplastin time. This is the first documentation of this in humans.

10. Effect of low molecular weight Dextran on blood volume, cardiac output, and shock. Low molecular weight Dextran and clinical Dextran have been used with good effect. Increases in blood volume and cardiac output have been documented. As many as four units of Dextran will not affect the coagulation mechanism. However, increase in blood volume over and above the volume of the Dextran administered is obtained from the already depleted interstitial fluid. Little advantage of Dextran over saline is seen. Dextran, however, decreases blood viscosity and was used with good effect in preventing clotting after vascular repair.

11. Use of plastic bags for intravenous fluids of various types. The packaging of these fluids in bags seems to be extremely valuable and innocuous. Any fluid seems to be initially equally helpful in producing a normal blood pressure.

12. Effect of Ringer's lactate solution on blood lactate. It has been found that Ringer's lactate will in most cases actually lower blood lactate levels because of the increased perfusion produced. The ability to metabolize lactate in shock seems not to be impaired unless there is severe liver damage. However, Ringer's lactate along with any other fluid is very effective in raising blood pressure, increasing capillary perfusion, and thereby lowering lactate levels. It is thought

that although Ringer's solution is excellent, the potassium and lactate ions it contributes are already in excess in the blood and are not needed. Saline is just as good.

Sixty percent of all casualties admitted to the Third Surgical Hospital needed intravenous fluids. This means perhaps 268 of a group of 447 admitted in one three-month period would have been in shock without treatment. All were young males. Most were Americans, although there were a number of Vietnamese, both friendly and otherwise, and some Koreans. Many had had blood or Dextran given at divisional and station hospitals before admission. This undoubtedly saved many lives and prevented or treated shock. Ten percent of all wounded in Vietnam required blood. The average amount of blood given was seven units per patient. About 12 percent of those receiving blood received 11 or more units and up to 90 units.

Typically these cases of shock were of the early, hypovolemic reversible type. Wounds and acute blood loss had resulted in a high level of catecholamines. This caused a pale, cold, sweaty skin. Many patients hyperventilated because of sympathetic stimulation and apprehension. This sometimes caused a respiratory alkalosis of up to pH 7.68 or more with a low pCO_2 and a rather high pO_2. At the same time vasoconstriction and a low venous return to the heart (central venous pressure zero or below) had resulted in a low cardiac output and an extremely low blood pressure (often zero by cuff). This resulted in a poor tissue perfusion and markedly elevated blood lactate levels. Thus there was a metabolic acidosis and a respiratory alkalosis. Early, this whole sequence of events could be easily reversed by a relatively small amount of any fluid. Within an hour and with 1,000 or 2,000 ml of intravenous fluid, the blood pressure could be returned to normal as could pH, lactate, and other measurements. This early and at times severe alkalosis was unexpected. It had been the policy in many hospitals to assume a severe acidosis and give large quantities of sodium bicarbonate empirically. This often resulted in very high sodium levels when actually the bicarbonate was contraindicated because of the alkalosis. Later in shock the lactate levels may rise so high that the alkalosis is replaced by a severe acidosis. The pH may fall from 7.68 to 6.68. Although in this case sodium bicarbonate is indicated, the best treatment is volume administration to restore perfusion.

Of course, with the severe wounds and varying amounts of hemor-

rhage, blood volumes on admission were low. With volume administration this was easily brought up to normal or above; stroke volume and cardiac output followed this.

Patients responded as well to Ringer's lactate, saline, Dextran, or other fluid as to blood, even though the hematocrit became quite low. As long as the hematocrit did not fall too low, 30 or less, patients did well. Of course, this is an expedient. The hematocrit should be brought up when adequate good blood is available. However, this points out that it is better to give any intravenous fluid rather than delay and wait for blood. Uncrossmatched O blood is often given and is life-saving. Although no "formal" hemolytic transfusion reactions occurred using type O blood in Vietnam and Korea, several patients were noted in the hundreds of patients given O uncrossmatched blood who developed renal failure and demonstrated hemoglobinemia and hemoglobinuria. These might have been avoided by using other solutions while blood was being crossmatched.

The administration of several units of O uncrossmatched blood makes the patient difficult if not impossible to crossmatch, and more uncrossmatched blood may be all that can be given. Frozen blood, actually a suspension of red cells in saline, may be given instead. Uncrossmatched group O blood is often life-saving, but should only be used when crossmatching facilities are either unavailable or overcrowded.

Extracellular fluid was also measured and showed evidence of being transferred to the blood to help make up the blood volume deficit leaving the extracellular space dehydrated. Deficient extracellular fluid had to be made up by electrolyte administration over and above blood volume requirements. In the early days of the Vietnam War, patients were treated only in field aid stations and then evacuated quickly to Clark Air Force Base Hospital in the Philippine Islands. There they were found to be dehydrated, even though they had a normal blood pressure. If these patients were anesthetized in this condition they immediately went into shock. They required intravenous fluids before anesthesia.

A slightly different problem was found in Vietnam casualties transferred to Walter Reed General Hospital. Here some of the patients remained ill because of infection or other complications. If these patients were taken to the operating room and anesthetized,

some of them developed a marked fall in blood pressure and some even had cardiac arrests. In a study of these patients the blood volume and extracellular fluid were found to be normal. However, there was often a red-cell-mass deficit. It is probable that these patients were in a chronic state of vasoconstriction due to stress and high catecholamine level. Central venous pressure may be low. When the vasoconstriction was abolished by anesthesia, the blood pressure dropped precipitously. This might be prevented by making sure the central venous pressure is normal before anesthesia.

A study of the effectiveness of low molecular weight Dextran was conducted. It was found that 500 ml expanded the blood volume about 1,000 to 1,200 ml, thus being the equivalent of 1,000 to 1,200 ml of electrolyte solution in restoring blood volume. Of course, this extra volume came from the extracellular space and must be restored. Also, low molecular weight Dextran rapidly escapes from the blood, as does electrolyte, and is only a temporary volume expander.

Another interesting phenomenon was that sometimes shock patients had a hypercoagulable blood with prothrombin time of less than 11 seconds and partial thromboplastin time of less than 30 seconds. In 85 early shocked patients from combat wounds, 14 or 16 percent had low prothrombin times averaging 9.7 seconds, and low partial thromboplastin times averaging 35 seconds. Controls averaged 13 to 14 seconds and 50 to 55 seconds. This is similar to the findings of hypercoagulability in dogs immediately after severe hemorrhage. It is probably a protective mechanism to help the body stop the hemorrhage from wounds and is therefore very helpful. However, if allowed to persist this hypercoagulability becomes detrimental instead of helpful and may predispose to disseminated intravascular coagulation.

Initial fibrinogens soon after wounding were a high normal, averaging about 380 mg%, but over the course of the next one to four days rose to unusually high levels averaging 710 mg% and in many cases exceeding 1,000 mg%. One case had 1,270 mg% fibrinogen. Stress stimulates fibrinogen production. It was rare to have an abnormally low fibrinogen, even in the presence of disseminated intravascular coagulation and a coagulation defect. This was also found to be true in the more severely shocked patients studied at Walter Reed. In other words, a clotting defect was usually due to a deficiency in something other than fibrinogen. If prompt treatment by

intravenous volume administration was not forthcoming, this early stage of vasoconstriction would progress to the later stage of vascular space expansion. Although this stage was also easily reversible, much more fluid volume was required. Often a volume of many thousands of milliliters of blood and other fluid was needed. During this stage lactate levels climbed to 200 mg% or more and pH fell to low levels of 7.0 or less in spite of low pCO_2. Prothrombin time and partial thromboplastin time climbed back to normal and perhaps above.

In only a few cases in which treatment was either delayed or in which shock was unusually severe did the shock advance to the refractory stage and show evidence of disseminated intravascular coagulation with elevated prothrombin time and partial thromboplastin time levels. Of 87 casualties in shock, 17 (20 percent) developed prolonged prothrombin times averaging 18.3 seconds and prolonged partial thromboplastin times averaging 126 seconds. In some of these cases volume administration was relatively ineffective, and in one case vasodilators were required. Usually the cases were complicated by infection.

A number of cases developed extremely high Na levels, up to 160 mEq. This seemed in many cases to be associated with the administration of a great many ampules of $NaHCO_3$ to combat real or assumed acidosis. However, as described above, it was not uncommon to find high pH's early in shock secondary to a respiratory alkalosis.

Some cases developed unexpectedly high venous pO_2 levels in relation to the arterial pO_2. The venous blood may even appear arterial in color. This could be due to perfusion of dead cells which cannot utilize oxygen. However, more likely it is due to the opening of arteriovenous shunts, which is characteristic of severe shock.

Coagulation Studies: thromboelastography. The formation of a clot by whole blood was followed visually and recorded by a thromboelastograph. If a clot formed, it was observed for two hours in order that lysis might be detected.

Twenty-nine patients in refractory shock were studied. Twenty-eight of these developed a coagulation defect. (See Table 4.)

One hundred and thirty cases of shock were studied in Vietnam in relation to the coagulation mechanism. The general character of these

patients was different from those at Walter Reed. In general the Vietnam cases were severe hypovolemic shock due to battle wounds. Most, however, were easily brought to normal condition with volume administration. Only a few could be called "refractory" shock, as were practically all the cases studied at Walter Reed.

Of 130 cases studied at the Third Surgical Hospital, 60 demonstrated coagulation abnormalities. In general these were of two types, hypercoagulability and hypocoagulability. Fourteen demonstrated a hypercoagulability as evidenced by a prothrombin time below 11 seconds or a partial thromboplastin time below 30 seconds. Forty-six patients showed a hypocoagulability as evidenced by a prolonged prothrombin time (over 16 seconds) or a prolonged partial thromboplastin time (over 75 seconds). These, in general, were the most severely shocked patients. Increasing severity of clotting defects was associated with death. A rapid spontaneous repair of the clotting defect was associated with recovery.

Another group of 45 seriously wounded patients was studied at the 93d Evacuation Hospital. Twenty-seven of these showed some clotting defect. All of these patients required transfusion, but multiple transfusions could not account for the development of a clotting defect in most cases.

The fibrinogen levels did not vary greatly during the acute phase of injury and transfusion, and formed no recognizable pattern or correlations, except for a steady increase beginning one or two days following injury.

At least four different factors influencing clotting mechanisms were active in these patients: "shock," multiple transfusions of stored citrated blood, extensive local tissue damage, and tissue (and possibly thromboplastin) embolization. Each of these factors appears to correlate positively with the occurrence of a clotting defect.

Significant hypotension (systolic pressure by cuff less than 90 mm Hg for more than 20 minutes) was associated with a clotting defect in this group. Hypotension during anesthesia did not seem to bear the same significance (vasodilation). It was also noted that the rise in lactate during a hypotensive episode under anesthesia was often minimal, indicating that hypotension during anesthesis is associated with better tissue perfusion than a corresponding numerical blood pressure value in an awake patient.

Thirty-four patients received 15 or fewer units of blood. Eighteen

had normal clotting studies, and 16 had abnormal. Eleven patients received more than 15 units of blood, and all had clotting abnormalities in the postinjury period. Unfortunately, all had also been hypotensive before anesthesia and none had normal postoperative oxygen tensions, so other major variables cannot be separated from this group.

Twenty-one of the 27 patients with clotting defects had sustained injuries from blasts or high velocity missiles with major long-bone fractures. One of the remaining six had sustained a severe closed-abdominal injury and cardiac arrest during operation. In the group of 18 patients with no clotting defects, 14 sustained injuries from blasts or high velocity missiles, but only 6 of these involved major long-bone fractures, possibly indicating less extensive local damage in the group with no clotting defects.

There was no definite evidence for an association between embolization and a clotting defect. Excluding patients with chest and abdominal injuries, 7 of 19 patients with clotting defects had unexplained preoperative arterial hypoxemia, and therefore presumed embolization. Only 3 of 12 such patients with no clotting defect had evidence of embolization. If postoperative hypoxemia is also considered, which includes many more variables, only 3 of the 19 with clotting defects retained normal oxygen tensions throughout, while 7 of the 12 with no clotting defect remained normal.

Most of the patients studied had a combination of the four factors discussed. Extensive tissue damage was common in both groups, but the other three factors were less common. Each of these factors, "shock," extensive transfusion (more than 10 units of blood in the first 24 hours), and embolization (unexplained preoperative hypoxemia) rarely occurred in the absence of the other two. No apparent association wth a clotting defect is seen in these few patients. All combinations which included "shock," however, were associated with a clotting defect.

A definite pattern of change associated with rapid transfusion did not occur in this series. Clotting studies remained normal during administration of 15 units of blood in three hours to a patient who was never severely hypotensive. Such stability was seen in six patients given 6 to 15 units of blood in a few hours. There was a shortening of clotting time from initially elevated values during rapid transfusion, with a return of the elevations several hours after cessation of

transfusion. This pattern is seen during temporary replacement of depleted clotting factors by administered blood or blood products. It is not what one would expect if bank blood were responsible for the bleeding problems often attributed to its use. This pattern of shortening clotting times during rapid transfusion and later elevation was seen in eight patients.

The more-expected change, a rise in clotting times with rapid transfusion, was seen in six patients. However, with continued transfusion the clotting times decreased.

Finally, no definite pattern of change of the fibrinogen levels could be detected. In general, changes in fibrinogen levels were relatively small in the acute phase. Complicating these studies, of course, is the fact that all patients were transfused with blood that had normal fibrinogen levels. On the second or third day following injury, especially with high velocity missiles, fibrinogen levels often reached close to 1,000 mg per 100 ml, and at this time the prothrombin time and partial thromboplastin time were usually below normal.

In spite of the uncontrolled nature and multiplicity of the variables in this study, several conclusions seemed warranted. Severely injured combat casualties often exhibit clotting abnormalities during the acute phase of injury. This appeared to be associated with extensive tissue damage, extensive transfusion of stored blood, presumed embolization at the time of injury, and hemorrhagic hypotension. Of all these factors, hypotension seems to be the most important. Combinations of these factors, especially with prolonged hypotension, increase the likelihood for a clotting defect. The etiology of these changes was not indicated in these studies. The clinical significance of these changes was also not apparent, except the association with the more severely injured patient. Extremely abnormal clotting values were seen only in those few patients who died. Clinical bleeding problems were rare. When they occur, we feel it is not justified to attribute the clotting aberrations to replacement of the patient's blood with bank blood, as has often been the tendency. Hypoperfusion appears to be more important in our study and also experimentally. The suggestive relationship of a clotting defect to presumed embolization (unexplained hypoxemia), especially if associated with shock, is interesting in view of a recent demonstration of

frequent pulmonary microthromboembolization following vascular operations involving prolonged regional hypoperfusion.

Characteristics of the Coagulation Abnormality: the clotting abnormality of shock is manifested by a prolongation of one-stage prothrombin time and partial thromboplastin time. Of all the coagulation screening tests, these two provided the most reliable means for detecting an abnormality of the plasma clotting factors involved in forming a fibrin clot. Thrombocytopenia was present in most cases. The degree of depression of the platelet count varied. In many it was severe — down to 3,000.

Quantitative assays for fibrinogen were performed on the plasma of each patient. None of the patients had an extremely low fibrinogen concentration and no examples of the "defibrination syndrome" were encountered.

Assays of the quantitative activity of known plasma-clotting factors were performed. Because of non availability of known-deficient plasma, it was not possible to do quantitative assays for all known plasma-clotting factors in each case. The plasmas selected for assay were from patients who had an unequivocal coagulation abnormality associated with shock. The results are shown in Table 4. In the presence of normal fibrinogen concentration, prolongation of both the PT and PTT indicates one or a combination of the following: (1) deficiency of activity of Factors II, V, or X; (2) deficiency of activity of several of the known factors, or (3) presence of a circulating anticoagulant. In the patient studied in detail, no evidence of circulating anticoagulant was found. The assays of factor activity were consistent with a mild depression of the activity of several of the known factors. In a few assays, severe depression of one to two of the known factors was encountered.

In three cases (patients 2, 16, and 29) evidence of fibrinolysin was found.

Fibrinolysis: disseminated intravascular coagulation which accompanies refractory shock can result in profound changes in the coagulation and fibrinolytic systems. The process of coagulation will usually produce an extreme depletion of platelets and moderate to severe drops in fibrinogen and other clotting factors. All of these changes result from utilization of the substance during coagulation.

There may be a concomitant activation of the fibrinolytic system. If there is, many of these changes will be accentuated, since fibrinolysin can hydrolyze and thus destroy the biological activity of Factor V and fibrinogen, and to a lesser extent Factors II and VIII. In addition to destruction of these coagulation factors, active fibrinolysin also lyses any clots formed from the remaining coagulants. The breakdown products from hydrolysis of fibrinogen and fibrin can further reduce the coagulability of the blood by acting as antithrombic materials and by impairing fibrin polymerization. The total picture can then be one of intractable hemorrhage.

Activation of the fibrinolytic system can be a fulminating process, as is frequently seen in abruptio placentae, open heart operations, or surgery connected with liver cirrhosis or chest wounds. In these cases the active fibrinolysis is often demonstrable by such insensitive methods as lysis of a whole blood clot or serially diluted plasma clots, and is usually accompanied by excessive bleeding. Profibrinolysin (plasminogen) levels and fibrinolytic inhibitor levels are greatly reduced.

In other cases, activation of the fibrinolytic system may be a slow response to fibrin deposition in the vasculature and hemorrhage may be minimal, in spite of low levels of many coagulation factors. Activation of the fibrinolytic system occurred in only a minority of our shock cases. A thromboelastogram on Case No. 2 illustrated the presence of thrombolysin when the patient was first admitted, but this spontaneously disappeared on subsequent days. Active fibrinolysis may be difficult to detect, and the presence of previous activation may be indicated only by elevation of plasma or euglobulin thrombin times as evidence of fibrinogen breakdown products, or by depleted profibrinolysin and inhibitor levels showing that the precursor of the active enzyme has been utilized. Three of 29 cases of refractory shock had determinations made of fibrinolysin precursor. In all three cases profibrinolysin was depleted, indicating conversion to fibrinolysin.

Respiratory Studies

The initial application of modern rapid techniques of blood gas analysis at a forward military hospital in Vietnam documented two fundamental observations. Hypoxemia was a frequent finding and often was seen without clinical evidence of respiratory distress or

cyanosis. Hypercarbia, on the other hand, was rarely found except in specific instances of head injury, upper airway obstruction, or oversedation. Upon grouping patients in categories to provide an explanation of this hypoxemia, it became apparent that the wound itself was the major determinant of the degree and course of hypoxemia. The two critical factors in the wound were (1) location (Fig. 19) and (2) velocity of wounding agent. High velocity missiles are highly destructive of tissue and in whatever location cause a far more severe injury. Thus any effect of wounds in a given location on respiratory function is apt to be amplified by the more destructive high velocity injury. The high velocity wound, so common to war injuries, is rarely seen in civilian trauma.

It was found most useful, therefore, to review post-traumatic hypoxemia by relating it to wound location, keeping in mind the vastly greater destructive powers of high velocity missiles, and to include the impact of complications on the convalescent course of hypoxemia.

Limb Injuries: the first studies selected patients with extensive limb injuries. This group was deliberately selected as one without obvious cause for hypoxemia. Patients with central nervous system, chest, or abdominal wounds, and burns were excluded. Twenty percent of these limb injuries studied had an admission arterial pO_2 less than 80 mm Hg. The data suggested a direct relationship of hypoxemia to the presence of fractures and high velocity wounds. Femoral fractures had the highest incidence of hypoxemia. Blast amputations of lower extremity, particularly the foot, also had a high incidence of hypoxemia.

Subsequent studies on a larger group of patients with limb wounds confirmed a statistically significant increase in hypoxemia associated with fracture. Eighteen percent with fractures had a pO_2 less than 80, 2 percent without fractures were hypoxemic. Patients in this later series were selected to exclude those in shock.

In studying patients with limb injuries, the Army Surgical Research Team, led by Capt. John Collins, established the fundamental observation that hypoxemia could occur in patients without primary injury to the chest, lungs, or central nervous system and could be present, at times to a severe degree, without overt clinical signs. In four patients reviewed in detail by Collins the

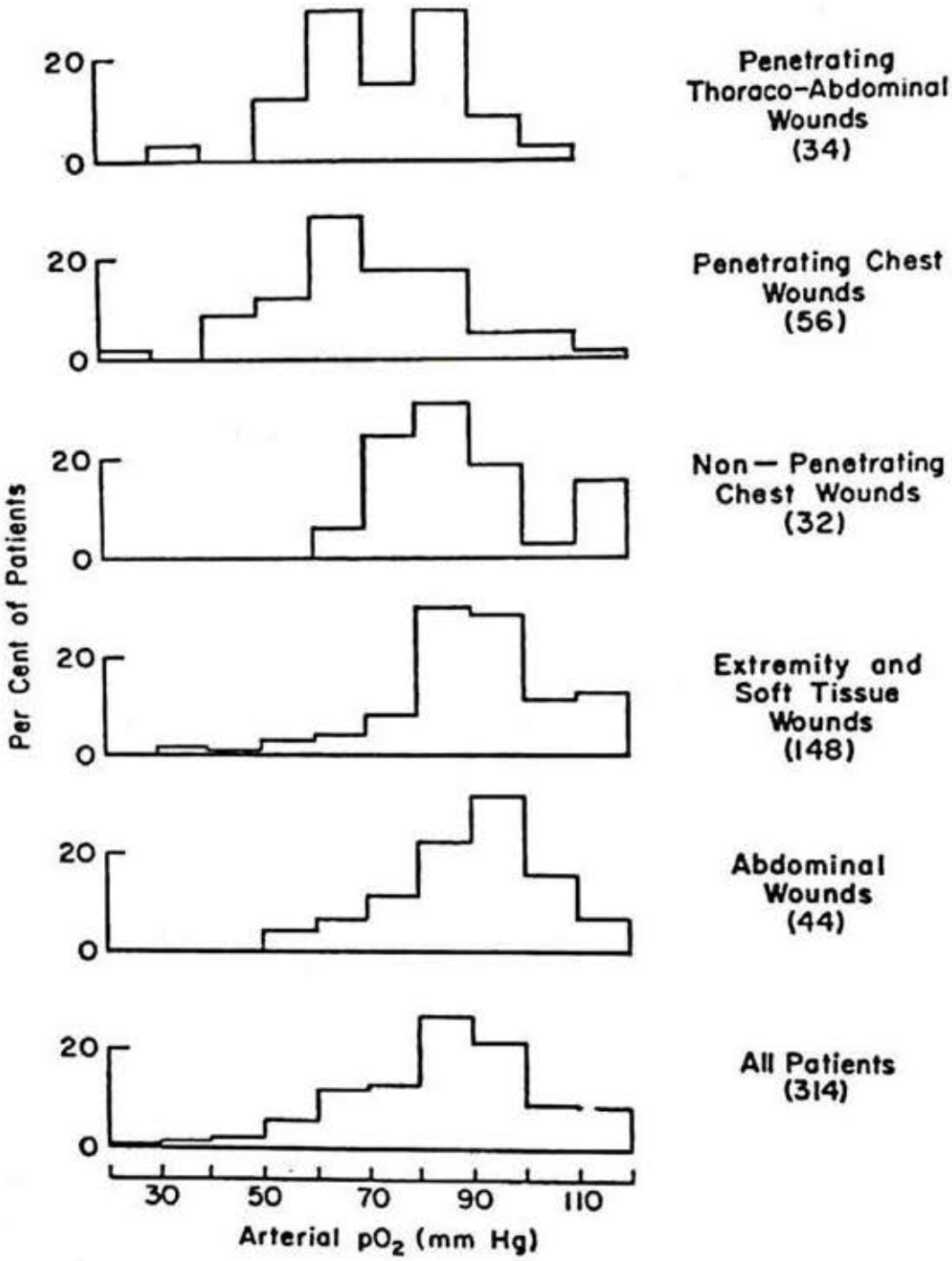

*Figure 19. Effect of wound location in 314 patients on arterial oxygen tension at time of admission to hospital. By permission: Simmons, R. L., **et al.**, "Respiratory Insufficiency in Combat Casualties. III. Arterial Hypoxemia after Wounding," **Ann. Surg.**, 170 (1969): 45.*

explanation offered for the hypoxemia in limb injuries was that they were secondary to fat embolism from the medullary cavity of long bones. It was suggested that the fatty marrow was dislodged by the blast or "internal explosion" of a high velocity wound and embolized to the pulmonary capillary bed. Blast injuries to the foot, it was suggested, may cause such a severe jolt to the entire limb as to dislodge the marrow fat from the limb. Blast amputations somewhat higher in the leg seemed to cause hypoxemia less frequently. The explanation offered was that the shearing action of the blast amputating the proximal limb left a decompressed medullary cavity with early reversal of flow in the veins. In contrast, the lack of any open decompression was suggested as the reason for the high frequency of fat embolism seen in a small group of closed comminuted femoral shaft fractures from blunt trauma.

The four patients with fat emboli, studied in detail, all had a pO_2 of less than 50, breathing room air spontaneously. None of the patients was hypercarbic. In two patients the hypoxemia clearly preceded any neurologic change or clinical signs of embolization and the hypoxemia was progressive over several hours following injury. Neurologic recovery occurred from five to ten days following injury and the hypoxemia gradually improved concomitant with neurologic recovery.

Fig. 20 shows a course of arterial pO_2 in two patients with clinical fat embolism compared with two other patients with limb injury without clinical evidence of fat embolism. General supportive measures were used in treating this respiratory insufficiency; small doses of Heparin were used in some patients but not in a manner to allow conclusions as to their specific efficacy. In several cases tracheal intubation with controlled ventilation with a volume-cycled respirator was required.

Subsequent studies by Moseley and Doty confirmed the association of hypoxemia with long bone fractures. The hypoxemia was accompanied by an increased pulmonary shunt on 100 percent oxygen (Fig. 21, Table 6). Though eventually a pulmonary infiltrate developed, hypoxemia usually preceded X-ray changes. That embolization may be more frequent than originally assumed was noted by many research teams and all confirmed the original observation that the first manifestation may be unsuspected, clinically inapparent hypoxemia.

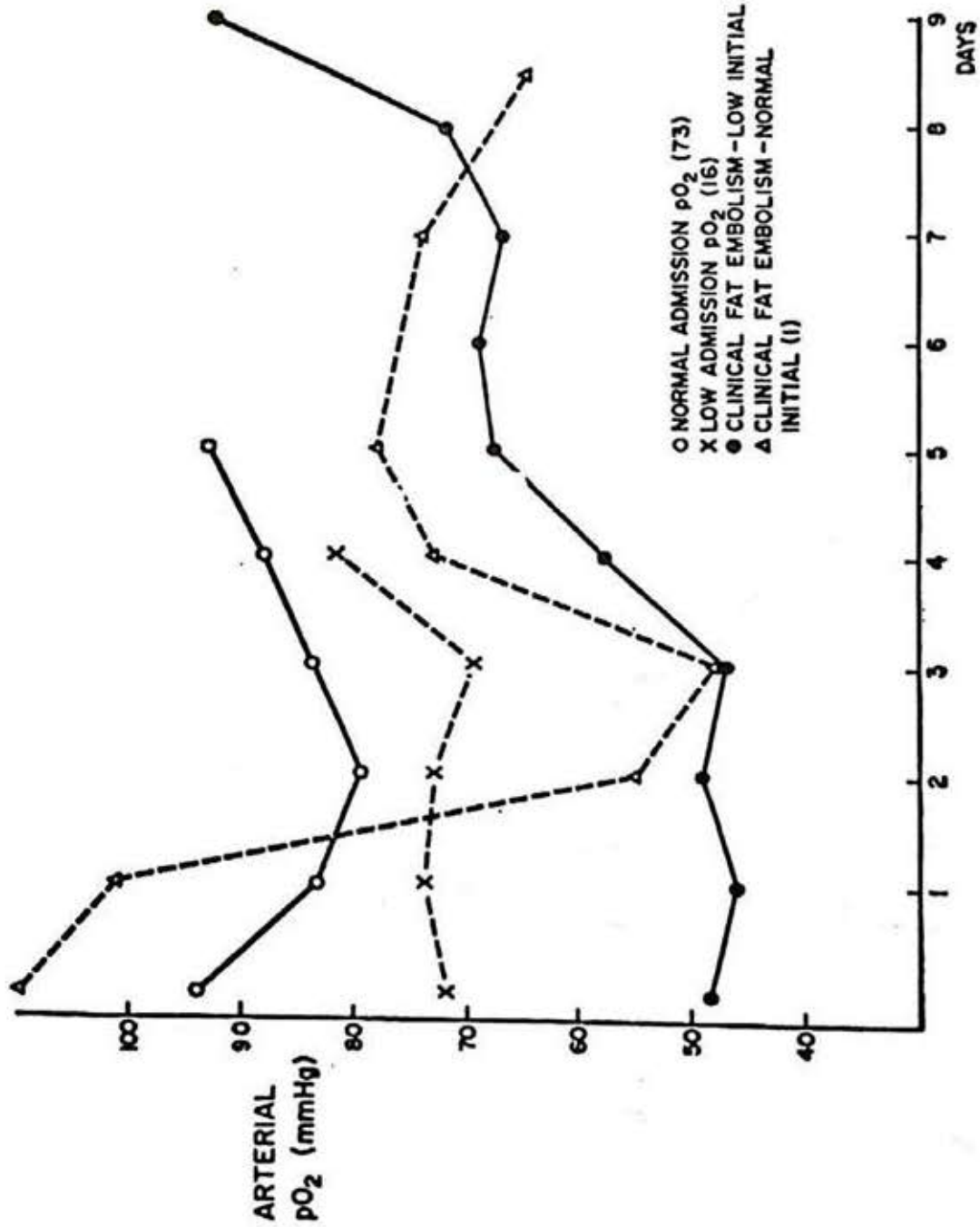

*Figure 20. Mean daily arterial oxygen tension in four patients with limb wounds — two with clinical evidence of fat emboli, two without. By permission: Simmons, R. L., **et al.**, "Respiratory Insufficiency in Combat Casualties. IV. Hypoxemia during Convalescence." **Ann. Surg.**, 170 (1969): 53.*

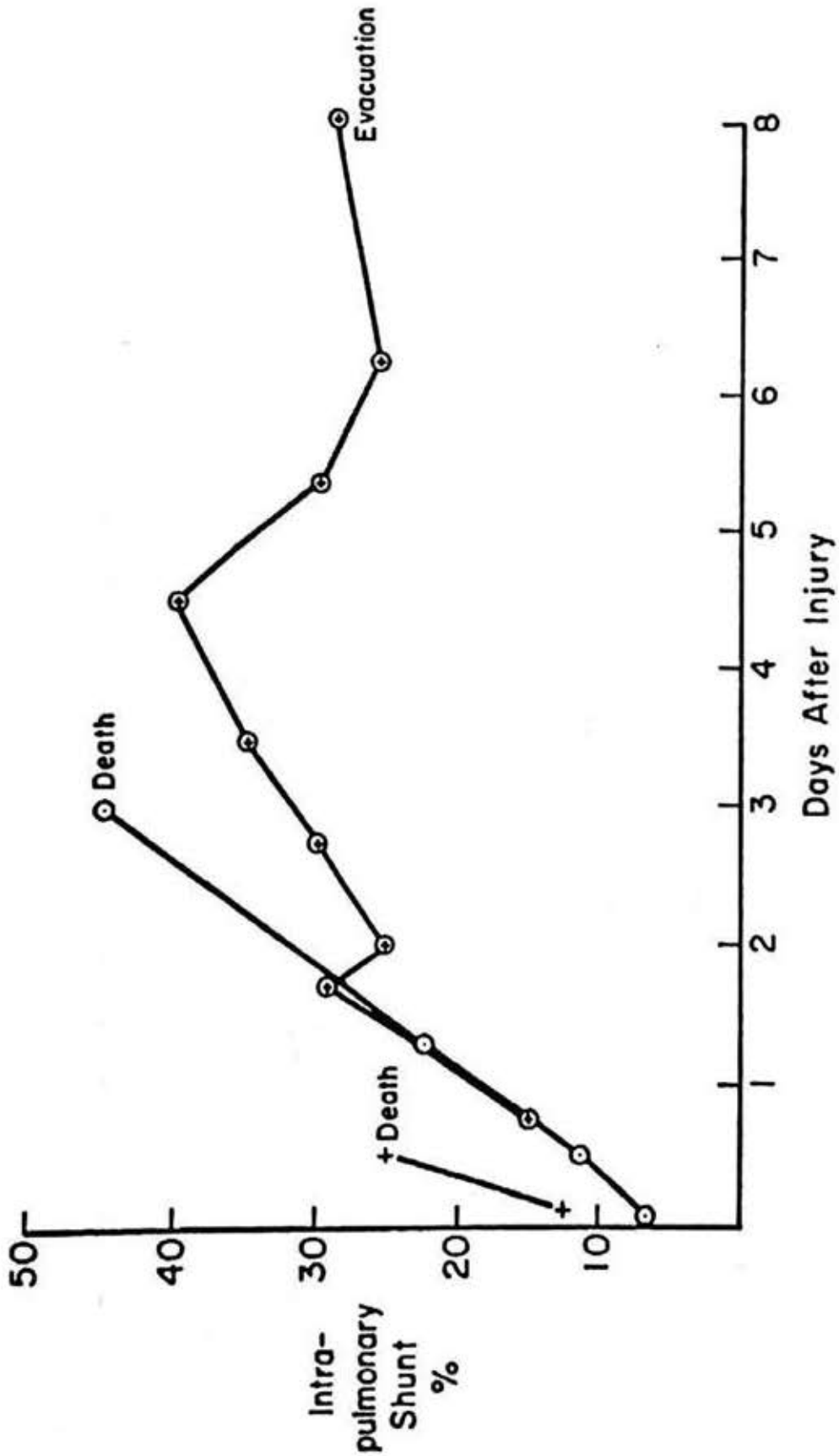

*Figure 21. Pulmonary shunting in three patients with severe limb wounds and clinical fat emboli. By permission: Moseley, R. V., and D. B. Doty. "Hypoxemia during the First 12 Hours After Battle Injury." **Surgery**, 67 (1970): 765.*

TABLE 6. Respiratory Function Studies in Six Patients Following Presumed Fat Embolism

Patient	Injury	Arterial pO_2 (mm Hg)	Resp. rate (breath/ min.)	Min. vol. (L/ min.)	Shunt (%)	VD/VT	Temp. (max. °F)	Petechia	Cerebral symp-toms
1	Fracture femur and tibia, bilateral	50	44	25.7	21	0.55	103	−	+
2	Fracture right femur and tibia	42	44	58.4	15	0.50	103	+	+
3	Traumatic ampu-tation legs, bilateral	50	30	11.3	17	0.48	103	+	+
4	Traumatic ampu-tation left arm and leg	51	12	—	31	—	103	−	+
5	Fracture femur and ulna	70	15	—	—	—	100	−	−
6	Fracture pelvis with extensive soft tissue destruction	66	26	—	30	—	101	−	−

By Permission: Moseley, R.V., and D.B. Doty. "Hypoxemia during the First 12 Hours after Battle Injury." ***Surgery,*** 67 (1970): 765.

Chest Injuries: in a series reported by Simmons *et al.*, two-thirds of patients with penetrating thoracic or thoracoabdominal wounds were hypoxemic on admission (Fig. 19). High velocity chest wounds had a 90% incidence of hypoxemia (pO_2 less than 80), almost always associated with the appearance of pulmonary contusion on X-ray. Low velocity chest wounds had a 57% incidence of hypoxemia.

A detailed study of 43 patients with chest injuries by Moseley, Doty, and Pruitt found an average admission pO_2 of 63 (Fig. 22). Hemopneumothorax alone caused a relatively mild hypoxemia (average pO_2, 75). The common finding of several teams was that the degree of hypoxemia with chest injury generally paralleled the degree of pulmonary contusion seen on X-ray. CO_2 retention was found only with oversedation or concomitant head injury. In chest injuries alone a low pCO_2 was frequent.

Studies by Moseley *et al.* of pulmonary shunting on admission in eight patients with penetrating chest injuries revealed an average shunt of 45 percent of cardiac output while spontaneously breathing room air. The average shunt was reduced to 27 percent with 100 percent oxygen administered by a tightly fitting face mask, and to 14 percent with oxygen given by assisted ventilation. The progressive reduction in pulmonary shunting by both high oxygen concentrations and assisted ventilation suggest that the admission hypoxemia is a product of both true shunting and venous admixture. The shunt reduction from that breathing room air to that breathing spontaneously 100 percent oxygen reflects the "venous admixture" contributed by pulmonary blood passing underventilated alveoli. The shunt that remains on 100 percent oxygen is that from alveoli that are truly nonventilated for whatever reason, *e.g.*, atelectasis or fluid accumulation. The obvious clinical significance of this is that in these patients on admission a useful increase in arterial pO_2 and hemoglobin saturation could be obtained simply by the administration of supplemental oxygen by mask.

The further reduction in shunt by intermittent positive pressure indicates the recruitment of previously collapsed alveoli obtained by increased tidal volume and positive ventilation.

All of this suggests a readily reversible process at this stage (admission to hospital); this indeed, was most often the case. Clinical

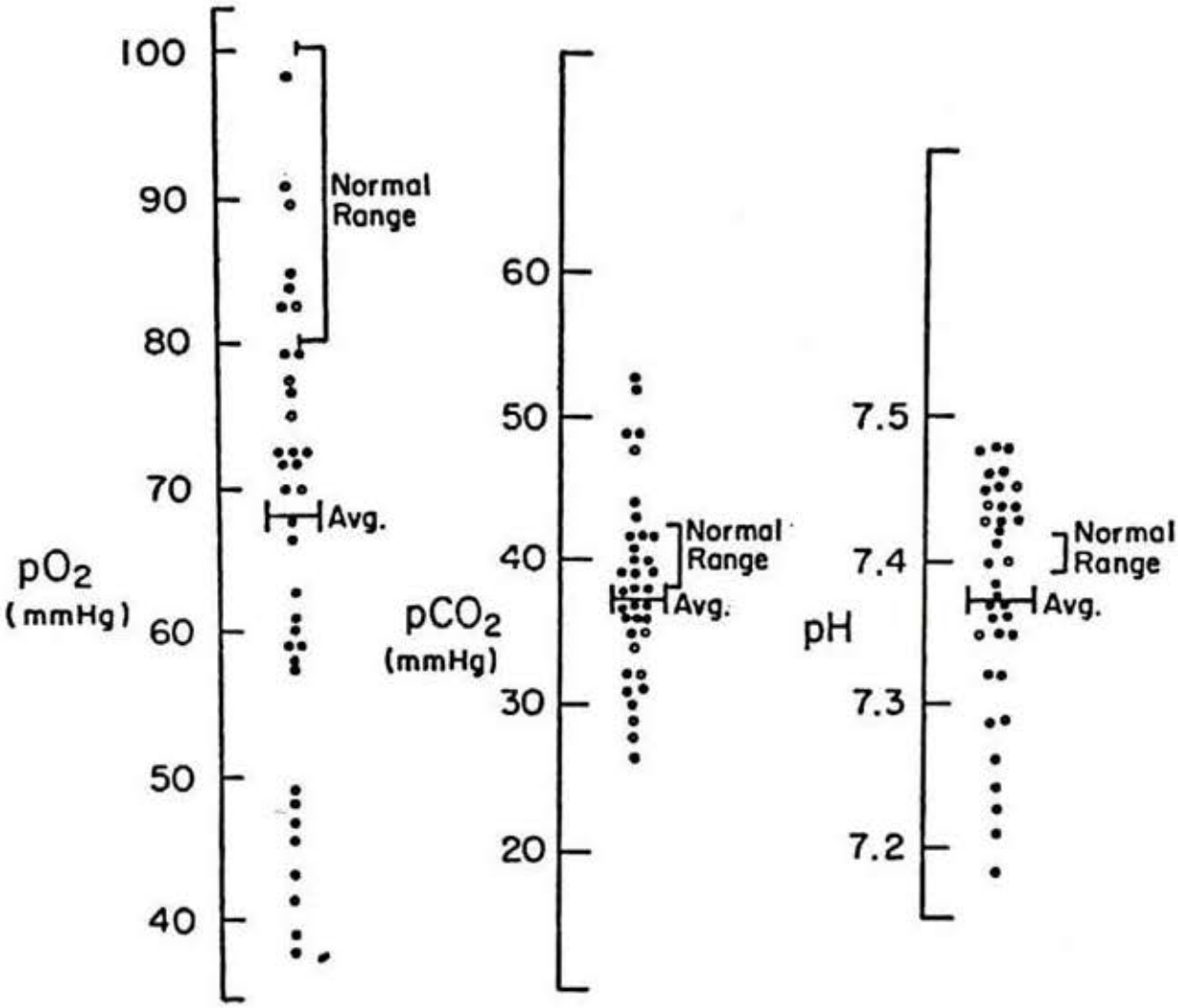

Figure 22. Arterial blood gas studies at the time of hospital admission immediately after chest injury. Note wide variability of oxygen tension and frequency of normal or low pCO_2. • indicates penetrating injury; ○ indicates nonpenetrating injury. By permission: Moseley, R. V., D. B. Doty, and B. A. Pruitt, "Physiologic Changes following Chest Injury in Combat Casualties," **Surg. Gynec. Obstet.,** *129 (1969): 233.*

recovery of the patient was marked by a steady reduction of pulmonary shunting (Fig. 23). During convalescence from chest injury, however, severe hypoxemia and slow recovery were associated with low admission pO_2 and with severe pulmonary contusion on X-ray.

Studies in ventilatory patterns in chest wounds revealed considerable variation. In general, there was an increase in respiratory rate relative to normal tidal volume, giving increased minute volumes in association with the increased alveolar dead space. On admission the ratio of dead space to tidal volume (V.d/V.t.) was 0.6 (0.4 upper limit of normal). During convalescence the pattern of recovery

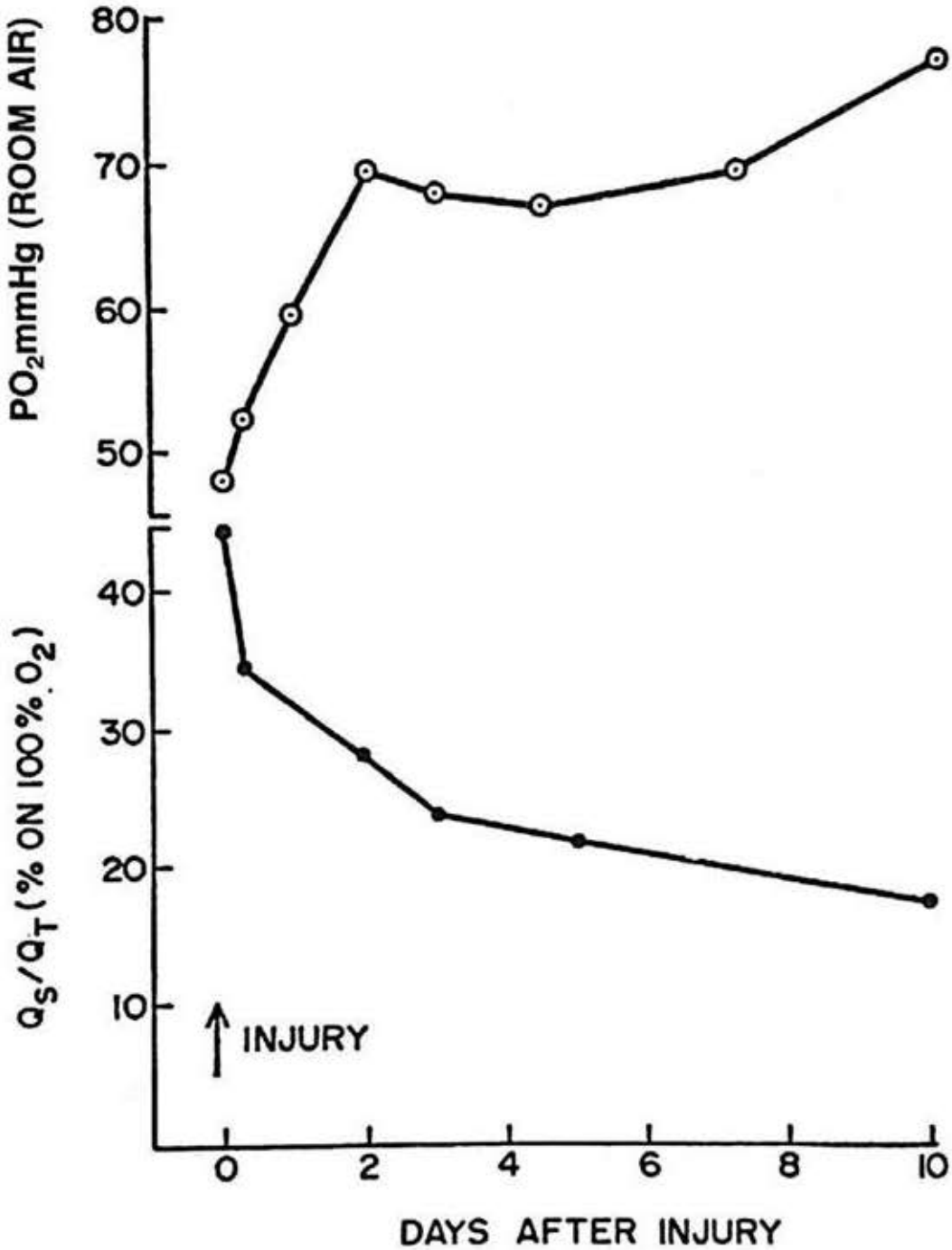

Figure 23. Arterial pO_2 and percent pulmonary shunt on 100 percent oxygen in one patient recovering from bilateral pulmonary contusion. By permission: Moseley, R. V., D. B. Doty, and B. A. Pruitt, "Physiologic Changes following Chest Injury in Combat Casualties," ***Surg. Gynec. Obstet.****, 129 (1969): 233.*

showed a lowering of respiratory rate and a progressive lowering of the V.d./V.t. ratio towards normal as patients clinically improved (Fig. 24). The ventilatory consequences of chest injuries were thus an increase in alveoli underperfused relative to their ventilation, *i.e.*,

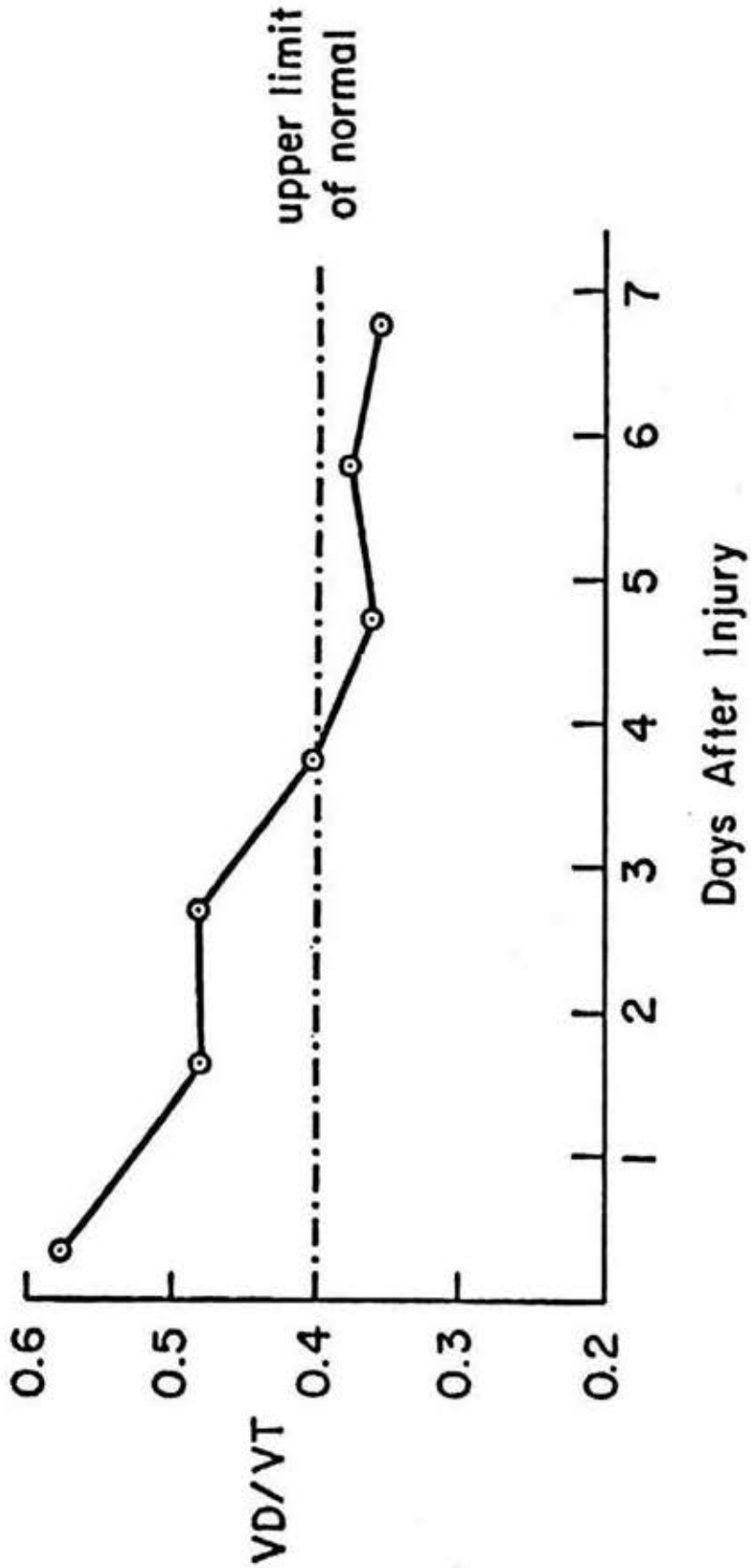

Figure 24. Dead space/tidal volume ration (V.d./V.t.) in eight patients with unilateral pulmonary contusion. A gradually decreasing dead space/tidal volume ration accompanied clinical improvement.

increased alveolar dead space compensated for by increased minute volume. Minute volume increase was achieved largely by the increase in respiratory rate. That compensation was usually such as to keep the pCO_2 at normal or more often at subnormal levels.

In these young, strong patients sustaining penetrating trauma with essentially stable chest walls, the increased respiratory rate was usually well tolerated. Isolated problems of ventilation manifest by elevated pCO_2 usually were not severe enough to require mechanical ventilatory assistance unless there was accompanying oversedation or central nervous system injury. In the severely injured patient, however, a combination of these ventilatory derangements along with hypoxemia from contusion, edema, or pneumonia required tracheal intubation and mechanical ventilatory support with the volume-cycled respirator.

Abdominal Wounds: in a review of admission hypoxemia following abdominal wounds by Simmons *et al.* about one-quarter (10/44) patients had admission pO_2 less than 80 mm Hg. (See Table 7.) Nearly all of these patients had concomitant chest injury or major long bone fracture or were in shock, making it difficult to prove a mechanism for this early hypoxemia unique to abdominal trauma. Studies by subsequent research teams confirmed the observation that admission hypoxemia in patients with abdominal wounds occurred most frequently in those patients who had other wounds known to be associated with hypoxemia.

Serial studies in the convalescence period following abdominal trauma, however, revealed hypoxemia to appear accompanying either intra-abdominal or pulmonary complications. Table 7 summarizes a group of patients with abdominal wounds who had, in general, a satisfactory admission pO_2 but who developed rather severe hypoxemia (pO_2 less than 60 mm Hg. on room air) postoperatively. Convalescent hypoxemia was associated with pulmonary complications including atelectasis, pneumonia, or contusion. Intra-abdominal complications associated with convalescent hypoxemia ranged from prolonged ileus to peritonitis and intra-abdominal abscesses. The frequent association of sepsis, particularly peritonitis with hypoxemia, has been noted by Collins in a recent review and has been emphasized by Clowes. In the absence of pulmonary or intra-abdominal complications the typical pattern was a

TABLE 7. Respiratory Insufficiency and Postoperative Complications Following Abdominal Wounds

Patient No.	Wound	pO_2 Admission	Lowest pO_2 Convalescence	Complications
C-52	MFW extremities Unrecognized abd wound	98	34	Peritonitis Intra-abdominal abscess
C-84	MFW abd Small intestine	76.5	51	Basal atelectasis
62	MFW abd, chest wall Axillary artery	51	53	Nonpenetrating wound chest wall with underlying pulmonary contusion
85	MFW abd, liver Lt femoral fx Bilateral tibial fx Bilateral popliteal artery	84	55	Bilateral lower extremity traction in Trendelenberg position Prolonged intestinal ileus
205	GSW abd Small intestine	96	55	Abd wound disruption Intestinal obstruction
206	GSW abd Small intestine	105	58	Bilateral pulmonary atelectasis Prolonged ileus
245	GSU abd Small intestine Colon	82	49	GI bleeding Intestinal obstruction Wound infection
256	GSW abd Kidney, liver hepatic flexure colon, duodenum	90	54	Bilateral pneumonitis
279	GSW abd Colon, jejunum, liver, kidney	96	48	Intestinal obstruction Wound infection Pneumonia

By Permission: Simmons, R.L., et al. "Respiratory Insufficiency in Combat Casualties. IV. Hypoxemia during Convalescence." Ann. Surg., 170 (1969): 53.

mild hypoxemia postoperatively, with progressive recovery over the ensuing two to five days very similar to that seen following major civilian abdominal surgery.

Head Wounds: respiratory depression secondary to head injury is a generally recognized complication and was observed in Vietnam. Patients with cranial and maxillary facial injury are also liable to upper airway obstruction and aspiration.

The role of pulmonary edema appearing in patients dying of head injuries was specifically examined by reviewing autopsy records of patients dying with head wounds. Fifty routine autopsies done on patients dying from head injury were reviewed, and six additional autopsies were performed by a pathologist of the Walter Reed Surgical Research Team. Pulmonary edema was found in nearly all patients dying of head trauma. Only two patients had normal weights. Thirty-seven patients had combined lung weights between 800 and 1,500 grams; twelve had lungs weighing 1,500 to 2,000 grams; and there were five whose combined lung weights were greater than 2,000 grams. Gross examination usually revealed wet lungs with gross frothy pulmonary edema fluid in the bronchi. Pulmonary congestion and edema were confirmed on histologic examination.

These findings were seen even in patients dying "instantly" or within minutes of injury. Two other patients convalescing satisfactorily several days following head injury died suddenly — one from acute subdural hematoma and the other with a rupture of the cerebral aneurysm. Despite death within minutes of the acute insult, severe pulmonary edema and congestion were present with lung weights of 1,200 to 1,500 grams.

In other patients who survived for long periods of time, factors such as prolonged shock, overtransfusion, aspiration, or pneumonia may have contributed to the increased lung weight.

One patient who died with severe head injury and herniated brain and penetrating chest trauma and lower leg fractures also had a C-6 cord transection. This patient's lungs weighed 640 grams and pulmonary edema was absent grossly and histologically.

This pathologic investigation in Vietnam stimulated experimental work in animals at Walter Reed Army Institute of Research. From the related work in animals at WRAIR, the proposed explanation for the acute pulmonary edema was that head injury invokes a massive

autonomic discharge causing a marked increase in peripheral arterial resistance, a decrease in systemic venous capacitance, and a loss of left ventricular compliance, leading to left ventricular failure; this leads to acute left ventricular failure, pulmonary edema, and increased pulmonary blood volume. The later work in animals revealed that chordotomy or adrenergic blocking agents could protect against this edema with experimental head injury. Based on this experimental work, it was felt the cervical cord transsection in the patient reported in the pathologic series from Vietnam blocked the transmission of the sympathetic discharge, thereby protecting the lung from edema. The possible therapeutic benefits from the use of adrenergic blocking agents in patients with head injuries were discussed related to the patient series from Vietnam, but adrenergic blocking agents were not used clinically.

Later clinical studies in Vietnam on five patients with severe head injuries dying within hours of admission confirmed the finding of severe potentially life-threatening hypoxemia. Arterial pO_2 ranged from 36 to 65, with pulmonary shunting ranging from 26 percent to 50 percent of cardiac output. Increased minute volumes with low arterial pCO_2 were present in four of the five. The ratio of dead space to tidal volume was generally increased. One patient was in overt clinical pulmonary edema. Autopsies were not performed to ascertain lesser degrees of lung edema. Again, the fact that this hypoxemia was severe enough to be potentially life-threatening itself, and yet clinically inapparent in most cases, underlined the value of blood gas analyses in patients with head injuries.

Non-wound Factors Related to Hypoxemia:

1. *Analgesia*

The influence of narcotics as a known respiratory depressant was studied on admission hypoxemia. There was no correlation of interval from narcotic administration to hospital admission with arterial pO_2, nor was the distribution of arterial pO_2 in those patients receiving narcotics any different from those not receiving analgesia. The usual narcotic was morphine given IV or IM (Intra-muscularly) in 15 mg doses. Typically, this was given once prior to admission or not at all. In these doses narcotics did not significantly influence arterial pO_2 or pCO_2 in patients on admission to hospital. During the hospital

course, isolated examples of oversedation with respiratory depression were seen, however.

2. *Recumbency*

Atelectasis in dependent areas of the lung, consequent to an injured patient's remaining in the recumbent position for long periods of time following wounding and during transportation to hospital, was considered as one of the possible causes of admission hypoxemia. However, in a group of limb injuries, plotting interval from wounding until sampling versus arterial pO_2 showed no correlation of this interval of recumbency with hypoxemia. The routine transport of patients by helicopter directly from the immediate tactical area to a fixed hospital tended to minimize this interval.

3. *Transfusion Volume*

Initial studies on a group of patients with injured limbs plotted arterial pO_2 versus volume of blood administered. No correlation was found between volume of bank blood administered with the degree of hypoxemia on admission.

Studies extending into the convalescent period, however, showed that in a group of patients sustaining a variety of injuries but receiving over 4,000 cc of whole blood transfusion there tended to be a slightly greater drop in arterial pO_2 during the postoperative, post-resuscitation period (Fig. 25). Recovery of a normal pO_2 in this group of heavily transfused patients was delayed an average of a day or two. These differences, however, were not statistically significant.

A later team studied in detail two patients who died of progressive pulmonary insufficiency while receiving 32,500 and 13,500 cc of blood respectively. At autopsy, these two patients were found to have clots in multiple small pulmonary vessels. In these two patients, reported by Moseley and Doty, it was felt that the rapid transfusion of huge quantities of bank blood had resulted in particulate embolization from the bank blood, despite the presence of the usual filters on blood administration sets. In both patients, lung weights at autopsy were elevated; and although gross description is lacking, the possibility of edema and congestion secondary to unrelieved hypotension as an explanation for the hypoxemia is unanswered.

The group effect of greater hypoxemia with large transfusions (greater than 4,000 cc) may result from two factors. Patients transfused with large volumes will obviously tend to be the most severely injured and thus are apt to have multiple factors contributing to

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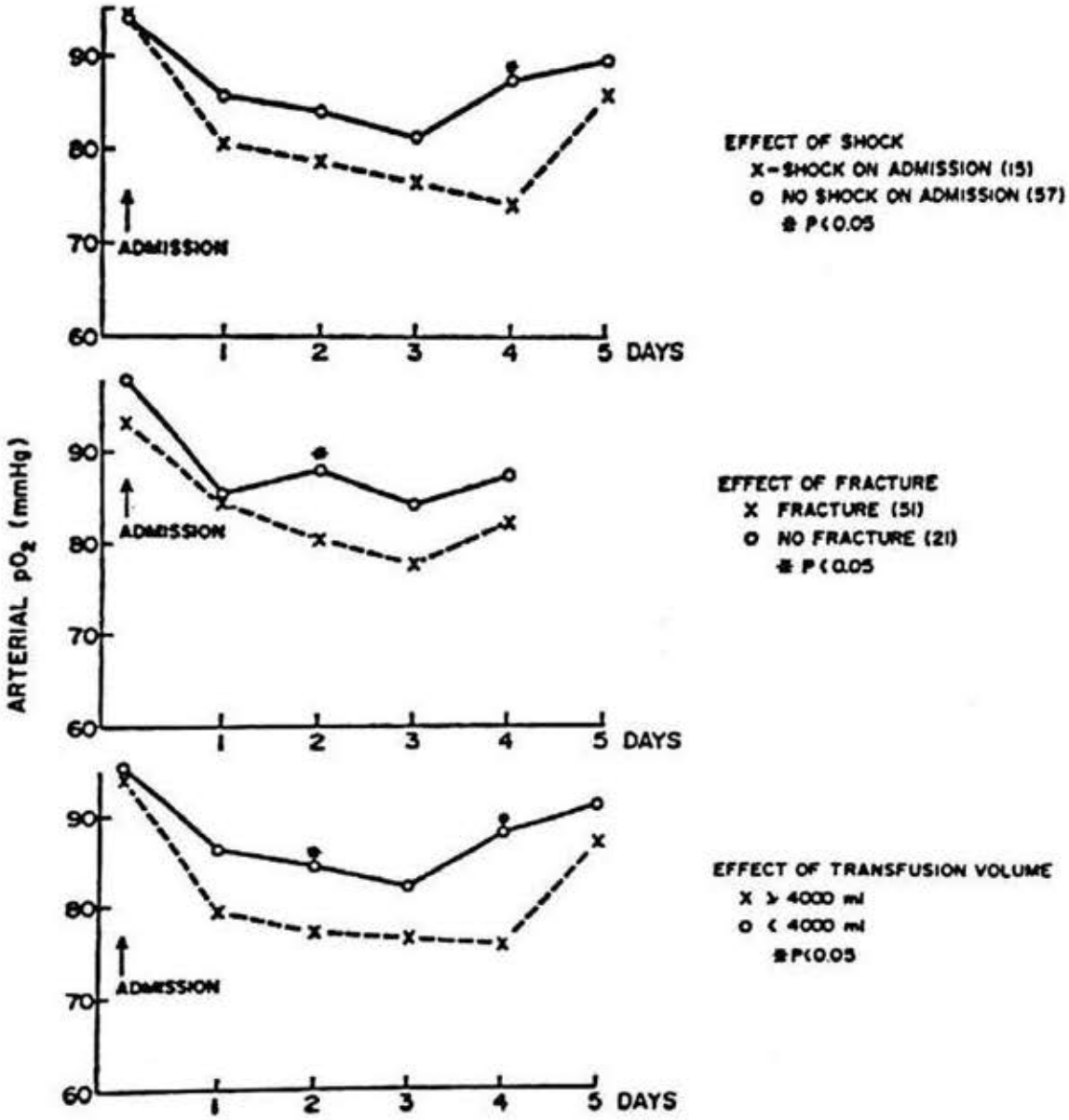

Figure 25. Mean daily oxygen tension in patients with injuries confined to limbs and soft tissues and with admission pO_2 above 80 mg Hg. A slightly greater degree of hypoxemia during convalescence is associated with a fracture, over 4,000 ml transfusion, or shock. Asterisks indicate days on which statistically significantly different mean values were obtained. By permission: Simmons, R. L., ***et al.****, "Respiratory Insufficiency in Combat Casualties. IV. Hypoxemia during Convalescence."* ***Ann. Surg.****, 170 (1969): 53.*

hypoxemia. The second possibility is that particulate embolization to the lungs in the bank blood contributes to or initiates progressive pulmonary insufficiency. The difference in degree of hypoxemia between two groups transfused greater or less than four liters was not dramatic, and may represent a nonspecific response to more severe

injury. The massive volumes of blood given to two patients in whom particulate embolization was seen at autopsy, on the other hand, suggests that a much greater volume than the four liters may be required before the effects of particulate embolization become significant.

4. *Aspiration*

Moseley and Doty reported that in a series of 58 patients, drawn from a group of severely injured patients simply by the interest of the investigating team, there were 14 patients with hypoxemia attributable to aspiration. Seven were due to aspiration of gastric contents, seven due to aspiration of blood. Those aspirating gastric contents had a more severe disease with severe arterial hypoxemia: arterial pO_2 range 26 to 53 mm Hg, average 40; tachypnea; increased ratio of dead space to tidal volume (range V.d./V.t. 0.42 to 0.90, average 0.58); and high intrapulmonary shunting (range 12 percent to 55 percent, average 36 percent). All seven required tracheostomy and controlled ventilation, and two died. Those aspirating blood from severe maximal facial wounds had an average pO_2 of 66, and an average pulmonary shunt of 25%.

Detailed study by those authors of a single patient with documented gastric aspiration is of interest. This patient demonstrated striking loss of circulating plasma secondary to severe pulmonary edema from gastric aspiration. The hematocrit rose to 62 with a measured plasma volume deficit (I-125 tag) of 1,000 ml. At this time cardiac output was 2.0 liters/minute, blood pressure 60, and central pressure 13.5.

This response was interpreted as a "pulmonary burn" with all the carefully documented sequelae of extravascular plasma loss seen with a dermal burn or peritonitis but with the added characteristics of profuse, frothy sputum, as this fluid flooded the alveoli and airway. Severe hypoxemia with increased intrapulmonary shunting (maximum 50 percent of cardiac output) required controlled ventilation with the volume-cycle respirator through a tracheotomy. Fluid deficits were corrected with Ringer's lactate and albumin, the pulmonary inflammatory response treated with steroids and antibiotics, and the patient supported with a volume-cycled respirator. Intrapulmonary shunting declined as the patient clinically improved. By day five the patient was ambulatory and breathing spontaneously, and he had completely recovered by day ten.

5. *Overtransfusion*

As in any group of patients whose treatment required administration of large volumes of fluid and whole blood, a few cases of classic pulmonary edema secondary to overtransfusion were seen. Overtransfusion, however, did not play a role in the etiology of hypoxemia present on admission to the hospital. Although some patients received Ringer's lactate, albumin, or whole blood during the interval from wounding to hospitalization, this was never in sufficient volumes relative to the magnitude of the wound and blood loss to ever approach overtransfusion. The frequent use of central venous pressure catheters by the research teams and others was a great aid in preventing overtransfusion though it could not be followed blindly.

Autopsy Data: one hundred autopsy records of patients dying following combat wounds after reaching hospital were reviewed by members of a surgical research team, including a surgical pathologist. These excluded head injuries. The most notable findings reported by Martin *et al.* were the frequency of pulmonary edema, congestion, and hemorrhage in patients dying within a few days of injury. Pleural effusion, pneumonia, and pulmonary hyaline members occurred most frequently in patients who died at a later interval. Fat emboli were found in four of the 100 reports — all of whom had extremity fractures, though fat emboli were not specifically searched for in these routine autopsies.

Increased lung weight indicating excess fluid in the lungs was present in nearly all of the cases. Sixty-five percent had a combined lung weight of 1,000 to 2,000 gm, 30 percent had a combined weight greater than 2,000 gm, and only 5 percent less than 1,000 gm.

The increased lung-weights incline, increased lung water and a frequent finding of edema, congestion, and hemorrhage in the lungs of patients dying early after injury, suggests the common reaction in the lung prior to death. Clinical records were not extensive enough to allow specific correlation of shock with lung weight. The frequency of these pathologic findings was noted, and it was suggested that one of the etiologic factors might be hemodynamic collapse prior to death. A separate review of pulmonary edema and head injuries was conducted (described previously under *Head Injuries).*

Hemodynamic Consequences of Respiratory Insufficiency: twenty-one critically injured patients were serially studied by Doty, Moseley, and Pruitt for the hemodynamic consequences of respiratory insufficiency. One-third were hypoxemic from direct chest trauma. Overtransfusion, aspiration pneumonitis, fat embolism, and atelectasis contributed to hypoxemia in a total of ten. One patient had gram-negative septic shock and another a transfusion reaction.

Table 8 summarizes the average values of hemodynamic and respiratory parameters on these patients after completion of resuscitation and definitive surgery. The patients were hypoxemic (average pO_2 on room air 47 mm Hg) with an average pulmonary shunt on 100 percent oxygen of 26 percent cardiac output. The common hemodynamic response in these patients with major trauma and hypoxemia was an elevated cardiac output, normal arterial pressure, and slightly lowered calculated peripheral resistance. Those with normal blood volume averaged higher cardiac outputs than those with moderately contracted blood volumes (less than 80 percent of predicted). A cardiac index less than 2.0 liters/minute/M^2 was found only in patients whose measured blood volume was less than 65 percent of predicted normal, or as a preterminal event.

TABLE 8. Cardiopulmonary, Metabolic, and Blood Volume Status in 21 Patients with Respiratory Insufficiency

	Mean value ± SD
Arterial pO_2 (mm Hg)	47.3 ± 13.4
Physiologic intrapulmonary shunt (%)	26.4 ± 11.2
A-V oxygen content (vol. %)	4.11 ± 1.74
Arterial pressure (mean mm Hg)	92.5 ± 19.5
Cardiac index (L/min./M^2)	4.01 ± 1.88
Stroke index (ml/beat/M^2)	37.1 ± 16.2
Stroke work (Gm-M/beat)	88.7 ± 38.4
Mean transit time (sec.)	9.4 ± 3.5
Resistance (dyne-sec./cm^5)	1035 ± 447
Lactate (mg %)	41.4 ± 24.5
Blood volume (ratio measured/predicted)	0.86 ± 0.20

*By Permission: Doty, D.B., R.V. Moseley, and B.A. Pruitt. "Hemodynamic Consequences of Respiratory Insufficiency following Trauma. "**J. Thorac. Cardiovasc. Surg.**, 58 (1969): 374.*

In those patients with elevated cardiac indices, oxygen and respirator support tended to reduce cardiac index towards normal, while arterial pressure and oxygen consumption remained the same (Table 9). Decrease of cardiac index towards normal on 100 percent oxygen and on the respirator suggests that the elevated cardiac output is compensating for decreased oxygenation of blood and, possibly, increased work of breathing.

Increased pulmonary shunting was associated with increased cardiac index. In patients with shunts greater than 30 percent, 87 percent of the cardiac index measurements were greater than 3.0 l/min./M^2. In the group with pulmonary shunting from 10 to 18 percent of cardiac output only 20 percent of cardiac index measurements were greater than 3.0 l/min./M^2 (Table 10).

TABLE 9. Effect of Oxygen and Respiratory Therapy on Hemodynamic Effects of Respiratory Insufficiency. Average of 13 Observations in Six Patients.

	Cardiac index (L/min./M^2)	Arterial pressure (mean mm Hg)	Resistance (dyne-sec./cm^5)	Stroke work (Gm-M/beat)	Oxygen consumption (cc/min.)
Room air	4.38	91	1,033	85	240
100% oxygen	3.97	95	1,166	84	260
Respirator	3.42	86	1,293	70	250

By Permission: Doty, D.B., R.V. Moseley, and B.A. Pruitt. "Hemodynamic Consequences of Respiratory Insufficiency following Trauma." J. Thorac. Cardiovasc. Surg., 58 (1969): 374.

TABLE 10. Relationship of Pulmonary Shunting with Elevated Cardiac Index

Physiologic intrapulmonary shunt (%)	Cardiac index (% of observations greater than 3.0 L/min./M^2)
10-18	20
19-30	60
> 30	87

By Permission: Doty, D.B., R.V. Moseley, and B.A. Pruitt. "Hemodynamic Consequences of Respiratory Insufficiency following Trauma." J. Thorac. Cardiovasc. Surg., 58 (1969): 374.

It was suggested that decreased A-V oxygen content difference might be an indication of peripheral "functional" shunting *i.e.*, actual anatomic shunting and/or capillary transit of blood too rapid for total oxygen transfer. Increased frequency of elevated cardiac indices was associated with decreased A-V oxygen content difference (Table 11). This suggested that increased peripheral shunting as well as increased pulmonary shunting was associated with elevated cardiac output.

The course of a patient with aspiration pneumonitis demonstrates the pattern in patients who recovered (Fig. 26). Initially cardiac index rose, as did pulmonary shunting. A-V O_2 content difference concomitantly fell, suggesting increased functional peripheral shunting. As clinical recovery ensued and the pneumonitis cleared, pulmonary shunting fell, A-V oxygen content difference increased toward normal, and cardiac index fell towards normal.

In patients who died, cardiac index usually rose progressively (as high as 6 l/min./M^2) with progressive increase in pulmonary shunting and a progressive decrease in A-V oxygen difference. Lactic acid progressively elevated, indicating poor tissue perfusion despite high cardiac output (Fig. 27).

In the patient who did well, increased cardiac output adequately compensated for hypoxemia and poor gas transport in the lung and possible peripheral shunting. In the patient who failed to recover, not only was gas transport in the lung severely deranged, but tissue perfusion was inadequate despite elevated cardiac output and progressive lactic acidosis developed.

TABLE 11. Relationship of Frequency of Elevated Cardiac Index Measurements with A-V Oxygen Content Difference

A-V oxygen content (vol. %)	Cardiac index (% of observations greater than 3.0 L/min./M^2)
> 6.0	35
6.0-3.0	76
< 3.0	87

By Permission: Doty, D.B., R.V. Moseley, and B.A. Pruitt. "Hemodynamic Consequences of Respiratory Insufficiency following Trauma." ***J. Thorac. Cardiovasc. Surg.****, 58 (1969): 374.*

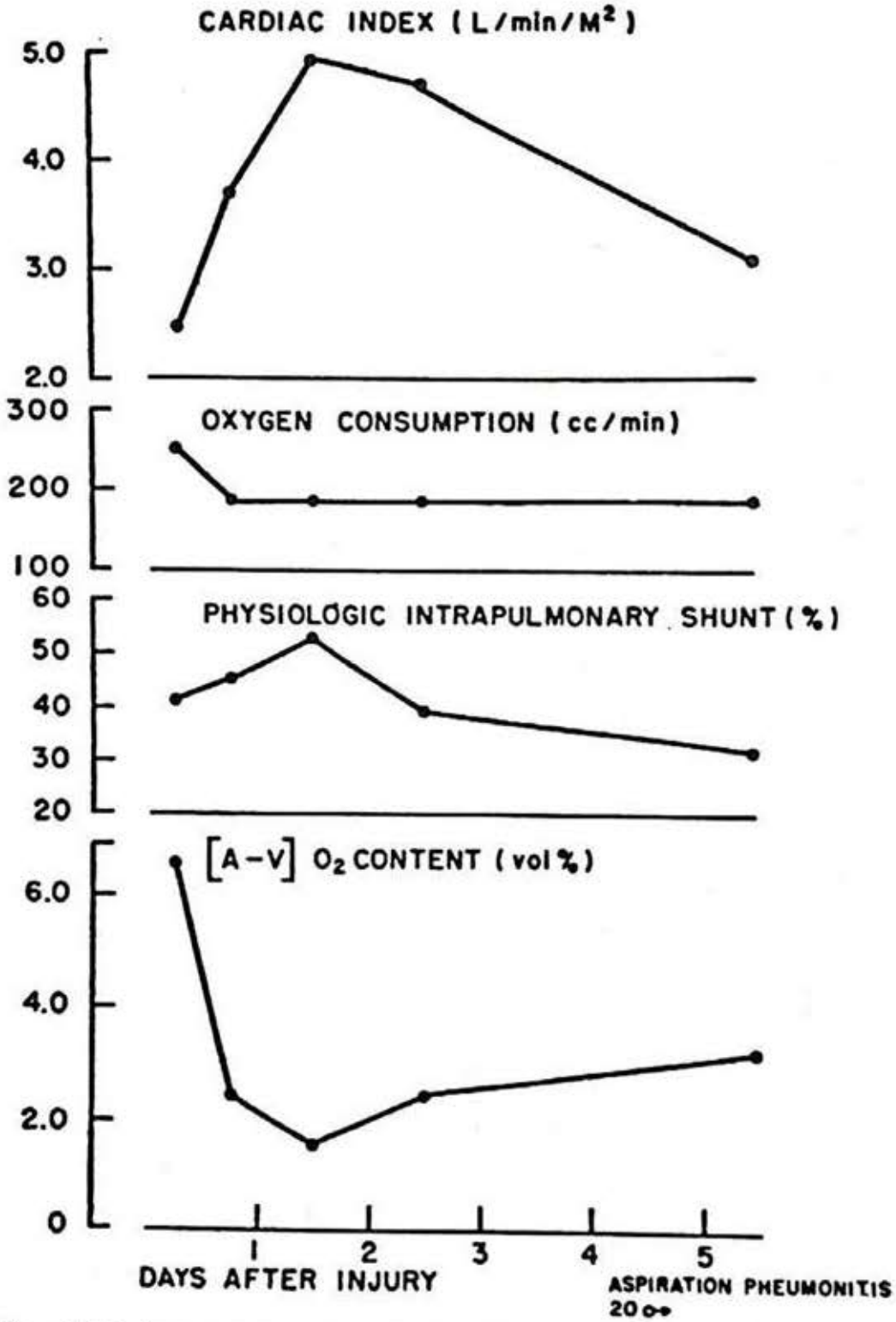

Figure 26. Patient recovery from aspiration pneumonitis. Note parallel rise in cardiac index and pulmonary shunting, followed by concomitant fall with recovery. A-V oxygen content bears reciprocal relationship with cardiac index and intrapulmonary shunting. By permission: Doty, D. B., R. V. Moseley, and B. A. Pruitt. "Hemodynamic Consequences of Respiratory Insufficiency following Trauma." **J. Thorac. Cardiovasc. Surg.,** *58 (1969): 374.*

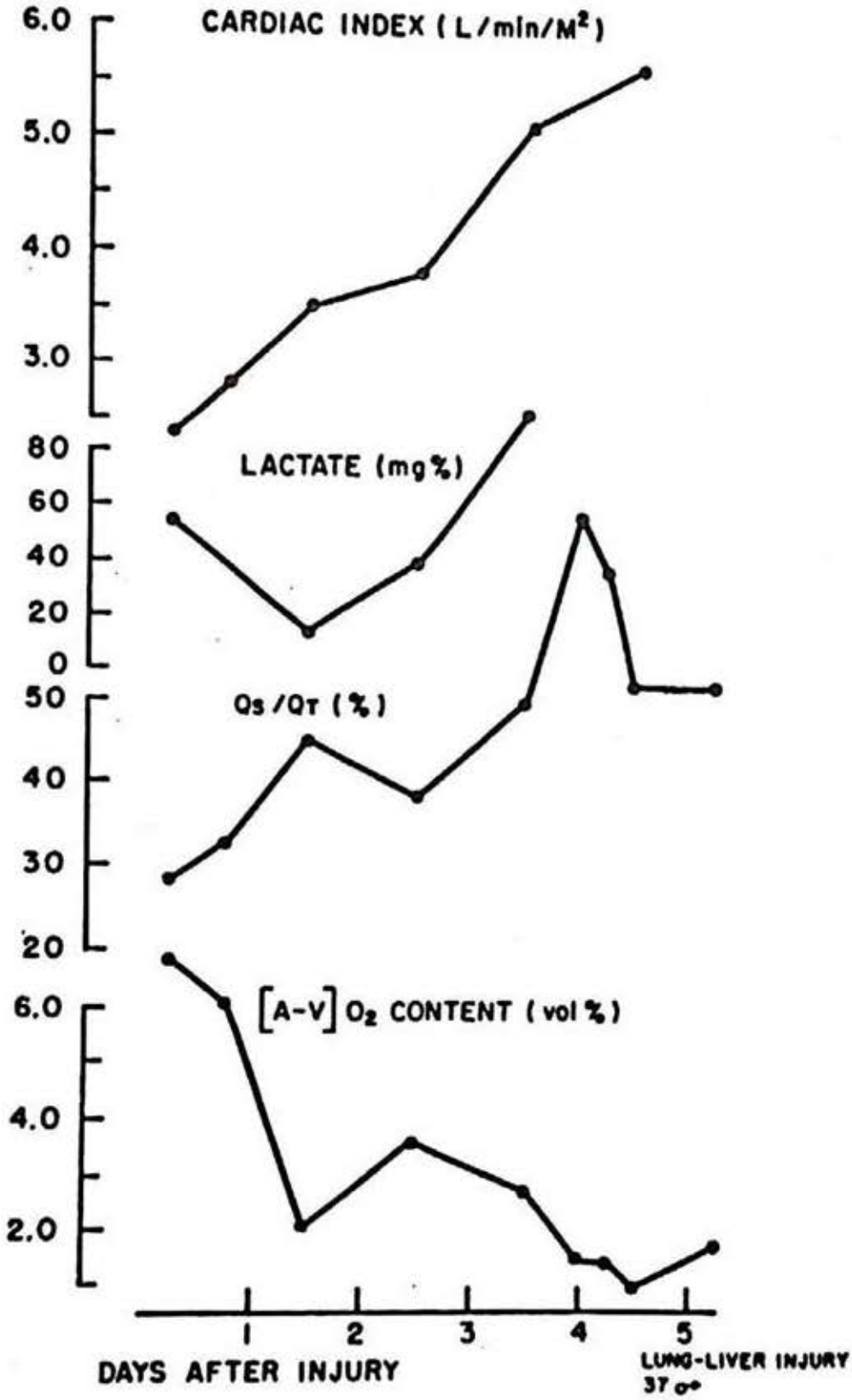

Figure 27. Patient dying of thoracoabdominal wound. Not progressive rise in cardiac index, pulmonary shunt (Qs/Qt %), and arterial lactate, and decrease in A-V oxygen content difference. By permission: Doty, D. B., R. V. Moseley, and B. A. Pruitt. "Hemodynamic Conseq;uences of Respiratory Insufficiency following Trauma." ***J. Thorac. Cardiovasc. Surg.****, 58 (1969): 374.*

The youth and previous good health of these patients accounted for their ability to tolerate the high cardiac outputs for long intervals. If, however, cardiac reserve is decreased, the ability to compensate for increased shunting and poor oxygenation will be limited. Or, if the extent of injury is too great, that alone can overwhelm even the relatively strong heart and death ensues.

Shock Lung: the frequency of severe, often lethal hypoxemia in a series of patients treated in the Walter Reed Shock Unit in Washington led to attempts by several research teams in Vietnam to correlate shock with hypoxemia. An expanding series of patients with limb wounds was studied for effects of shock on hypoxemia. These wounds were chosen because they seemed least likely to cause direct injuries to the lungs or airway.

In the first series, reported by Collins, shock was defined as an arterial lactate elevated above 20 mg.%. No correlation of elevated arterial lactate with hypoxemia on admission was found. Subsequently, this series was expanded by that of two other research teams and was reviewed by Simmons *et al.* This expanded group of patients did suggest an effect of shock on convalescent hypoxemia. Shock in this expanded series was defined as patients having one of the following criteria: arterial systolic pressure less than 60; arterial pH less than 7.30 without hypercarbia; or arterial lactate greater than 20 mg.%. In the group of limb injuries without shock, an average drop in postoperative pO_2, to a moderate degree, was noted persisting for approximately three days with recovery to near normal or normal pO_2 by the fourth and fifth day. Patients in shock with limb injuries had a similar pattern but showed a more severe drop in pO_2 which lasted for one to two days longer than those patients not in shock. These differences, however, were not statistically significant. A larger group, consisting of 34 patients with limb injuries in shock and 114 patients with limb injuries without shock, did show a statistically significant greater incidence of hypoxemia on admission, contradicting the earlier work of Collins. In this series 33 percent of patients with limb injuries in shock had pO_2 less than 80 whereas only 12 percent without shock had pO_2 less than 80. Similarly, 12 percent of those in shock had pO_2 less than 60, whereas only 3 percent had pO_2 less than 60 without shock. The contradictions of this last series with the original work of Collins, whose patients were included in the

enlarged group, is perhaps explainable by the larger size of the later group as well as by the expanded criteria of shock.

However, the problem of attempting the statistical correlation of shock with hypoxemia is complicated by the often more dramatic effect of the wound itself. This is apparent in the influence of pulmonary contusion in chest injury. However, while these studies were going on, cases of obvious fat embolism from limb wounds were becoming apparent, as well as the overall statistical association of major long bone fractures with increased incidence of hypoxemia. These findings suggested that subclinical fat embolism may frequently accompany long bone fractures. Thus, even in limb injuries, complications of the wound itself apart from shock are present. The correlation with shock, however, disregards incidence of fractures. Since both are apt to be caused by a more severe injury, they are apt to coexist in a high percentage of cases making statistical separation of the effects of each difficult.

In establishing a perspective for considering the possibility of "shock lung" it is necessary to emphasize that the patients studied by the various surgical research teams were selected primarily because of the presence of severe injury from a total patient population numbering several thousands. In reviewing these patients, it became apparent that the location of the wound and severity of wound, particularly those from high velocity missiles, were the most frequent determinants of the course of respiratory function. In nearly all cases a specific cause of hypoxemia could be found. It was also a common experience to see patients in profound shock who were quickly and completely resuscitated to go on to develop no more severe pulmonary problem beyond the mild hypoxemia common to the postoperative period following major surgery. Thus though there was a loose association of shock with more severe hypoxemia, and though we would not seek in any sense to deny the possible contributing influence of shock in the course of this hypoxemia, we were able to find otherwise unexplained, severe, progressive, pulmonary insufficiency clearly related in only five patients.

Case Summary: a 30-year old captain received a single fragment wound of the left lower chest traversing the diaphragm and entering the abdomen. He was admitted to Third Surgical Hospital by helicopter at 11:30 a.m., 12 February 1967, 55 minutes after wounding,

with unobtainable blood pressure and weak pulse. Cardiac arrest occurred on admission, responding to immediate intubation and two minutes of external cardiac message. Preoperative arterial blood gases after resuscitation from arrest while receiving manual ventilation through endotracheal tube with supplemental oxygen: pH 6.90, pCO_2 85, HCO_3 2O, pO_2 75.

At operation prolonged difficulty was encountered in getting control of hemorrhage, and a left nephrectomy, repair of inferior vena cava laceration, left colectomy with exteriorization of colostomy and mucous fistula, and small bowel resection were carried out. A left thoracotomy was performed to control intrapleural bleeding from the chest wall and diaphragm. Tracheostomy was performed at the conclusion of these procedures. The patient was hypotensive and anuric during the entire 11-hour procedure and received 98 units of blood, 75 of which were freshly drawn. Postoperatively at 2100 hours, 12 February, on Emerson Volume Cycle Respirator with 20 liter/minute volume: arterial pH 7.41, pCO_2 42, HCO_3 25.

A course of fluid limitation was started postoperatively with a central venous pressure of 10-15 cm of water and arterial blood pressure 90-100 systolic. Twenty-five grams of Mannitol was given and urine output occurred for the first time, averaging 40 cc per hour for five hours, with central venous pressure rising to 20 after Mannitol. The patient regained consciousness and communicated by writing on a pad. Digitalization was begun with 0.75 Digoxin IV in the operating room during active hemorrhage, and 1.5 mg Digoxin, divided doses, was given postoperatively with central venous pressure falling to 13.

Subsequently, recurring hemodynamic instability developed, manifested by frequent falls in blood pressure and urine output accompanied by a slight drop in central venous pressure. All parameters responded with the administration of intravenous fluids. This cycle of temporary improvement in response to intravenous fluid administration was repeated numerous times with a general trend to the falling blood pressure and urine output.

By 2000 hours, 13 February, approximately 36 hours from admission, the patient had received postoperatively 9,000 cc of normal saline, 500 cc of low molecular weight Dextran, 1,500 cc of blood, and 4,000 cc of D5W (the last because of hypernatremia secondary to large volumes of hypertonic sodium bicarbonate given intra-

operably). Blood pressure by this time had fallen to 60-80 systolic, central venous pressure 10-15, radial artery flow inadequate for cardiac output recording, lungs were clear to auscultation, trachea was dry to suctioning. Concern over the large volumes of fluid given was recognized at the time. These volumes were given only because the patient seemed to get a good hemodynamic response, albeit a temporary one.

Subsequently, CVP increased to 20 cc of water and Isuprel was started, and urine output fell to nil. At 0830, 14 February, blood pressure was inaudible, pulse was weak, patient was anuric, CVP 20. On the Emerson ventilator with 20 liter/minute volume and 80 percent inspired oxygen, arterial pH 7.38, pCO_2 26, pO_2 58, HCO_3 15, sodium 138, potassium 5.4, creatinine 3.2 mg%. The patient expired 1036 hours, 14 February, approximately 48 hours after wounding.

Autopsy revealed bilateral pleural effusions 500 cc each, severely congested and edematous lungs with a liverlike carniform appearance, and very slight "frothy fluids" in the bronchi. The heart was grossly unremarkable. No fat emboli or particular emboli were found. The primary missile injury to the lung was confirmed to the small lappet in the costophrenic sulcus.

Comments: this patient illustrates prolonged hypotension, cardiac arrest early in the course, massive transfusion and crystalloid administration, and severe hypoxemia despite controlled respirations with volume-cycle respirator using high inspired oxygen concentrations. Autopsy revealed lungs with the typical appearance associated with the term "shock lung."

Discussion: this patient illustrates many of the features of otherwise unexplained progressive hypoxemia associated with shock as seen in the small number of patients by the WRAIR surgical research teams in Vietnam. The hypoxemia was severe and incompletely improved by high concentrations of inspired oxygen, indicating greatly increased intrapulmonary shunting. Shunts ranged from 50 percent to 80 percent of cardiac output.

Obviously, the patient's survival depends upon the use of a respirator for ventilatory support. Though not part of the surgical or evacuation hospital TOE, the surgical research teams had their own

electrically driven volume-limited piston respirator. This type of respirator proved most satisfactory for ventilatory support of patients with severe post-traumatic respiratory insufficiency from all causes. Control of the respirator was greatly enhanced by measuring and recording tidal volume and rate to calculate minute ventilation, and by measuring and recording inspired oxygen concentration. These measurements are simple to make, but often overlooked. With them, blood gas measurements became far more relevant and useful. Adequate ventilation can be assured without gross overventilation and alkalosis, and inspired oxygen concentrations can be adjusted without simply relying on inordinately high levels which can be potentially dangerous. Changes in serial blood gases were most significant when minute ventilation and inspired oxygen concentrations were accurately measured and carefully recorded. Patient care can be greatly improved if respirators and facilities for blood gas analysis are made available to forward military hospitals when the tactical and logistical situation allows it.

The other conclusion illustrated by this patient is that shock is severe. In fact, the dominant feature of the patient illustrated is that hemorrhage, hypotension, and lactic acidosis continued over a prolonged interval and were severe enough to cause cardiac arrest at the beginning of resuscitation. Without other specific causes of respiratory insufficiency, the common response of patients admitted in severe shock who were resuscitated quickly was a mild postoperative hypoxemia with recovery of virtually normal blood gases within a few days. There seems little doubt that prolonged hypotension is more likely to lead to acute respiratory insufficiency than that which can be promptly relieved.

How much massive transfusion *per se* contributed to this problem, and how much it is merely the innocent concomitant of prolonged hemorrhage, is not entirely clear. No particulate embolization was seen in the patient illustrated, though it has been present in other patients.

In reviewing the patient's postoperative course, one is struck by the paradox of large volumes of intravenous crystalloid given after the arrest of hemorrhage. In each case a transient hemodynamic improvement was encountered followed by a recurrence of hypotension and oliguria. Although the dangers of fluid overload were

recognized, fluid was given because it seemed to correct (albeit temporarily) the momentary problem.

Studies by the WRAIR Surgical Research Teams as well as civilian groups suggest that there is no mystical loss of salt or water from the ECF (Extra Cellular Fluid) consequent to shock. On the other hand, diluting plasma protein by infusion of crystalloid solution has known edema-producing results. In the patient illustrated, in common with the others in Vietnam, the parameters being followed and corrected were hemodynamic ones. It seems logical, then, in the absence of excessive crystalloid losses to use the fluid which is hemodynamically most effective. For all these reasons, blood as a colloid solution, such as plasma or 5 percent albumin and saline or Ringer's lactate, may be more appropriate in this setting. This should reduce the volume necessary to obtain a hemodynamic result and lessen plasma protein dilution. Both of these results should reduce the tendency of water to leave the pulmonary capillaries and thereby lend some protection to the development of interstitial edema and congestion.

Though not available to the research teams at the time the illustrated patient was treated, new diuretics — Furosemide and Ethacrynic Acid — have been useful in maintaining urine flow when treating shock. They will function only if renal perfusion is sufficient to develop a glomerular filtrate. However, when concern over a low urine output may be greater than that of a borderline blood pressure, and central venous pressure is adequate or slightly elevated, use of these diuretics may augment and preserve renal tubular flow without the necessity of increased fluid administration.

The response of the illustrated patient, though not uniformly applicable to all patients with respiratory insufficiency and shock, suggests poor cardiac performance — low cardiac output with high filling pressure (as reflected by high CVP). Digitalization and perhaps earlier use of adrenergic drugs — specifically Isuprel — may be useful in improving cardiac performance and limiting the volume of fluid required. Increasing cardiac output by increasing cardiac filling pressure is not without potential harmful effects on the lungs. Other patients, however, with respiratory insufficiency associated with hemorrhage and shock have had high cardiac output, making this therapy less appropriate in those cases.

It is not suggested by this that pulmonary insufficiency in shock is

simply pulmonary edema and congestive heart failure. The clinical data and pathologic observations deny that. Nevertheless, one cannot deny that lungs were heavy with water at autopsy and that large volumes of water and salt were given on clinical indications.

We should like to suggest, however, that in the patient who has had profound hemodynamic collapse and a prolonged period of poor perfusion following trauma and hemorrhage, the therapy of subsequent hemodynamic instability be reevaluated in the light of the potential harm of that therapy to the lungs.

Specifically, it seems appropriate to reexamine the mechanisms controlling water transport from capillary to pulmonary interstitium and alveoli. In this setting of continued hemodynamic instability following arrest of hemorrhage, it may be wise to consider alternative or supplements to intravenous fluid administration and to reconsider the contents of the fluids given.

We would summarize our current feelings by emphasizing the use of new potent diuretics in instituting and maintaining urine output, use of direct cardiac stimulation with digitalis preparations or Isuprel when appropriate, and use of colloid-containing fluid (plasmanate, albumin) when treating patients for hemodynamic instability, rather than continuing fluid losses. Positive and expiratory pressure applied to a ventilator seems to have therapeutic promise of protecting the lungs in these situations, although it was not tried systematically in Vietnam.

It is not imagined that these suggestions are a panacea. It is reasonable to assume, for example, in the illustrated patient that the pathologic picture in the lung was already well established by the time hemorrhage was controlled at the end of the operation. In less severe cases, however, attention to these details may be useful.

The mechanisms linking shock with progressive respiratory insufficiency and with the heavy, wet, carniform lungs seen at autopsy are as yet unclear. It is clear, however, that prompt and definitive resuscitation from shock by rapid blood transfusion and definitive control of hemorrhage are the most effective ways yet known to prevent this problem.

Summary: studies by WRAIR Surgical Research Teams in Vietnam have documented a significant incidence of respiratory problems and hypoxemia following major combat injury. Appropriate detec-

tion and management required particular reliance on blood gas analysis and use of an electrically driven, piston respirator for ventilatory support. Both these technical features worked well in Army surgical, evacuation, and field hospitals as constructed, maintained, and supplied in Vietnam.

The hypoxemia is often clinically inapparent and, except in specific cases, usually unaccompanied by hypercarbia. Hypoxemia may be severe, associated with increased pulmonary shunting, and severe pulmonary changes are a frequent concomitant of the terminal course, as seen at autopsy.

The highest incidence of respiratory problems was associated with chest injuries and correlated with high velocity wounds with X-ray evidence of pulmonary contusion.

Limb wounds demonstrated unexpected hypoxemia thought to be from subclinical fat emboli and related to high velocity missiles and long bone fractures.

Lethal head injury was almost always associated with severe pulmonary edema thought to result from the cardiovascular response to a massive autonomic discharge from the injured brain.

Abdominal wounds, aside from associated injuries, developed hypoxemia most significantly as an accompaniment of intra-abdominal or pulmonary complications in the convalescent period.

Aspiration of blood and/or gastric contents, particulate embolization from massive transfusion, and fat emboli received particular studies as etiologies of hypoxemia. Though unequivocally present to a severe degree in the patients reported, the implication was quite clear that these complications may be present to a less obvious degree — and may alone or synergistically with other factors be the source of much hitherto "unexplained" hypoxemia.

Hemodynamic studies of patients with respiratory difficulties showed a parallel increase in pulmonary shunting and cardiac output as the patient deteriorated. In those patients who survived, both pulmonary shunting and cardiac output returned toward normal levels coincident with clinical recovery. A-V oxygen content difference had a reciprocal relationship to pulmonary shunting and cardiac output, suggesting the possibility that "functional" peripheral shunting may accompany an increase in pulmonary shunting and cardiac output.

Statistical studies attempting to correlate shock with hypoxemia

suggested a correlation but found it difficult to separate the effects of shock from the effects of the wound itself. In a handful of patients where shock was severe and prolonged, an interval of hemodynamic instability after arrest of hemorrhage was associated with progressive deterioration of pulmonary function. At autopsy heavy, wet, carniform lungs were found. Though not at all typical in autopsy appearance or clinical course of pulmonary edema as conventionally viewed, it is thought that the mechanism of water transfer between pulmonary capillary and alveolus should be reexamined and hemodynamic management be reevaluated for its effects on the lung. Preliminary experience suggests a dye for fluid limitation and diuresis in the postoperative period, following resuscitation with large volume of fluid and blood.

Addendum: a 1972 report by a team from WRAIR has shown examples of the efficacy of diuretics (Furosemide and Ethacrynic Acid) in the treatment of a "wet lung syndrome" occurring 2 to 15 days following injury. From the evidence presented in this report it would appear that this syndrome developed when the large volumes of fluid required during resuscitation were being mobilized and excreted. This report amplifies our feeling that though fluid administration, particularly of whole blood, during resuscitation must continue to be aggressive, there does come a time during the postoperative phase when we ought to be more aggressive in diuresing this fluid.

From all these studies evolved the recognition that significant numbers of wounded soldiers have been benefited from focusing on principles and details of respiratory care. Clearly the benefits gained warrant continued investigation toward greater physiologic understanding and improved patient care.

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