Blood and War—Lest We Forget

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Early theories in medicine
The goals of treatment as a target for blood transfusion have evolved over time and included volume resuscitation, oxygen delivery, and hemostasis. These have accounted for the targets of a spectrum of volume resuscitation efforts, from saline to fresh whole blood.

Early surgery consisted of trephination, treatment of trauma, and bloodletting for the treatment of many syndromes. The Iliad describes 147 wounds, three-quarters of which led to death at the scene; treatment consisted of bandaging with herbs and bloodletting. At the peak of Greek civilization, Alexander the Great conquered what we now know as the Middle East and was the first to take scientists along with him because his teacher, Aristotle, was interested in the study of natural history. Alexander accommodated him by bringing leading worldly discoveries home.

In doing so, he collected new information and spread Greek medicine. The concept of research study during conflict was also established. Galen, a dominant figure during Roman domination of the world, started his medical training in the second century AD and studied at Alexandria. He dissected animals and established his observations based on misinterpretation of objective animal data. His writings became gospel and determined much of medical care for the next 1,500 years.1

Galen’s theory of circulation described food going to the liver, blood emerging from the liver going into arteries, and blood crossing the heart and continuing into veins with pulsatile flow. Draining blood was viewed as therapeutic and applied for multiple conditions. The basis of bloodletting was established, consistent with the current understanding of cardiovascular physiology at the time.

Roman domination included most of the Middle East and Europe, and the concept of far-forward care was first demonstrated in early depictions of Roman military care, in frescoes of the time. The seat of Roman power ultimately shifted from Rome to Constantinople (Istanbul), and with this, Europe and Rome ultimately fell.

Over the next 200 years, what was known as the Roman Empire shifted to the influence of Islam. Latin turned into Arabic, Galen’s readings and writings were endorsed by Avicenna, and bleeding continued to be the therapeutic treatment of choice.

Medicine returned to Europe in 1010 AD, when Constantine of Carthage, having studied medicine in Arabia, returned to Carthage and after being shunned, escaped to Salerno, where his Arabic was translated back into Latin. He sought refuge in a monastery and this established the first known medical school in Europe. With this, dissection reemerged and the term chairman evolved from the master disector overseeing pupils.1

The emergence of circulatory theory
Despite these advances the incidence of injury and significant surgical bleeding was low. Public registry data from the 14th century shows infection overwhelmingly responsible for mortality and bleeding as a minor cause of mortality.1 In the 16th century, the Barbers Company and Surgeons Guild were joined under a doctrine approved by Henry VIII and bloodletting, having been prohibited by monks during the previous two centuries, became the core business of barber surgeons. Reflecting the importance of this technique at the time, the second publication from the famous Guttenberg Press was a bloodletting calendar for practitioners at the time. In addition, they were given four executed criminals a year for dissection, and anatomic study was reestablished.

Paré described early involvement with gunshot wounds, and the practice of cautery for wounds was replaced by treatment with open dressings of turpentine and rosehips.1 The basis of transfusion emerged with a better understanding of anatomy, as described by Vesalius, who used human dissection to create the De Fabrica Humani Corporis. This effort led to his subsequent professional ostracism, but established the basis of anatomy as we know it today and set the stage for additional research in circulatory physiology.

Galileo, known for his description of the universe and the relationships between planets orbiting the sun, originally studied medical school and was the first to describe the timing of the pulse. This observation allowed Harvey to subsequently calculate the ejection volume per hour of blood. He realized that if Galen’s theory of blood flow was correct, the human body would create 16 tons of blood in...
By the early 20th century, William Osler continued the practice of bloodletting before his death, and William Osler continued this practice during his treatment of the malaria epidemic of 1799. George Washington was bled four times in the last 2 days during his treatment of the malaria epidemic of 1799. Benjamin Rush was sued for this practice in Philadelphia, and the practice continued to be controversial and Denys' patient returned for two subsequent transfusions; the third led to his death and caused the patient's wife to sue Denys. Denys was absolved at trial but the French Parliament banned the practice and the Pope subsequently followed suit. As a result, transfusion as a medical practice went dark for 150 years.

Bloodletting returned and ruled, and the Lancet journal is named after the instruments used for this treatment. Benjamin Rush was sued for this practice in Philadelphia, during his treatment of the malaria epidemic of 1799. George Washington was bled four times in the last 2 days before his death, and William Osler continued this practice into the early 20th century.

**Early transfusion**

Blundell, an obstetrician at Guy's Hospital, transfused patients after obstetric hemorrhage. His first four patients died, but in 1829 he had an initial survivor and blood transfusion was reestablished. There was little record of blood transfusion during the Civil War.

The history of saline solution as a volume replacement began developing in the early 19th century. The use of saline resuscitation evolved from observations during cholera epidemics, which described concentrated dark blood that suggested loss of fluid and electrolytes. In 1832 the infusion of normal saline was associated with a reduction in mortality. This was followed 50 years later by Ringer, who described subcomponents of electrolytes and their effect on myocardial activity in an in vitro heart model. The first use of saline in a resuscitation effort instead of blood for obstetric hemorrhage was in 1898.

The use of acacia, a carbohydrate colloid, with saline and hypertonic saline solutions emerged during World War I. The concept of a postoperative or perioperative drip was introduced by Matas in 1924. Hartman described the addition of lactate and the debate regarding sodium chloride and lactated Ringers emerged during the 1950s and 1960s.

**Beginning of rapid progress**

The first transfusion in the United States was probably carried out by Alex Carrel working at the Rockefeller Institute, having been recruited by Flexner to investigate techniques of vascular anastomosis. Carrel had concerned himself with this when, as a medical student in France, he witnessed the death of a patient with a portal vein injury. In 1908 he was summoned by Lambert (who had brothers who were surgeons) and asked to help with Lambert's child, who suffered from acute anemia associated with childbirth. Carrel, despite having no license, went to Lambert's apartment and sewed the father's radial artery to the baby's saphenous vein and they witnessed father-to-daughter transfusion, which subsequently saved the baby's life. He celebrated the child's birthday 21 years later.

Transfusion was popularized, and direct transfusion (a surgical procedure) was required because anticoagulation and technical problems precluded successful use of any other technique. Dr George Crile established the most commonly used technique, but it was still accompanied by a 35% hemolytic transfusion reaction. It was, by today's standards, one of the most expensive surgical procedures performed at the time.

A landmark in making transfusions more widely available occurred through Landsteiner's discovery of ABO compatibility and simplification of testing by Ottenberg at Mount Sinai. This reduced hemolysis to essentially zero when blood was adequately tested. At the same time, Lewisohn, in 1915, demonstrated that anticoagulation with sodium citrate allowed the technique of blood transfusion to be as simple as, and equal to, saline infusion. This opened the door for longterm storage. It was the critical reason that blood could, for the first time, be widely used toward the end of World War I.

**Use of blood during war**

During the beginning of World War I, the etiology of shock was debated. The prevailing theory was that circulating shock factors, as part of the neuroendocrine response, were responsible for the shock syndrome, as
advocated by Cannon and Crile. Volume resuscitation was
done primarily with crystalloid and acacia. Robertson was
the first to introduce citrated type O blood in curing casu-
alties well after the start of World War I.3 Cannon, a phy-
sician and physiologist at Harvard, subsequently published
extensive literature on traumatic shock, based on his theory
that a dilated capillary region led to entrapment and this
causd hypovolemia. In addition, Cannon and colleagues16
observed that the injection of fluid increased blood pres-
sure, which was dangerous in itself, and they demonstrated
that blood pressure could “pop the clot” and aggravate
bleeding, begging the question whether volume resuscita-
tion was appropriate at all.

In 1918 the US adopted citrated blood and a postwar
evaluation demonstrated that blood was better than gum
acacia and salt solution. It was noted that if blood was
grouped using techniques of Ottenberg, no serum reaction
occurred. To quote a battlefield surgeon at the time “slight
as my experience has been with this method of blood trans-
fusion, I know that at this hospital we save lives by its use,
which would have otherwise have been lost.”13

An interesting quote by Walter Cannon after an analysis
of his experience in World War I noted that fundamentally,
research in this area had been accompanied by ignorance.
“One reason for our ignorance is the relative irregularity of
the appearance of shock ensuing in life and the consequent
difficulty of pursuing persistent studies. The circumstances
of war however, are such to permit at times systematic
examination of large numbers of shock cases instead of
infrequent single cases as in civilian life. With such oppor-
tunity theoretic consideration should be set aside.”16

After World War I, Keynes, the brother of the famous
economist, set up a blood bank at St Bartholomew’s hos-
pital in London, and the US had several similar efforts,
using the concept of “donors on the hoof,” in which citi-
zens were on call to donate blood based a prescreening
system.17

Meanwhile, Alfred Blaylock was beginning his career,
joined Harrison at Vanderbilt, where both were chief resi-
dents, and studied the relationship of blood loss and car-
diogenic shock. He collaborated with Vivian Thomas and
did definitive shock studies before World War II, demon-
strating the importance of volume loss as the most impor-
tant cause of hypovolemic shock.18

In 1936 Elliott, a surgeon in North Carolina, demon-
strated after separating blood into plasma and red cells, that
plasma transfusion of a stab wound victim was life saving.
He approached John Scudder, who was known for his stud-
ies of shock at Columbia and had been responsible for
resuscitating the German pilots and crew with hypertonic
saline solutions after the Hindenburg disaster in Lake-
hurst, NJ.19 Dr Scudder was an advocate of the Blood
Betterment Association in New York City and based on
Dr Scudder’s recommendations, Dr Charles Drew was
asked to design a program for plasma therapy, which led
to the collection of 9 million units for plasma prepara-
dation during World War II.20

Started initially as a program for Britain, which was ini-
tiated by Carrel, who moved back to France after retire-
ment, the Americans were approached to help with the
need for blood. It was realized that blood would not survive
the journey to Europe because transatlantic flights at that
time were not routine and the delay associated with trans-
atlantic shipping would cause increased infection of the
units shipped. As such, a shift to focus on plasma to sup-
port blood pressure was established.

Dr Edwin Cohn, concerned about infection risk of
blood, had also embarked on a program known as Cohn
fractionation and this led to the isolation of albumin. Dr IS
Radvin was commissioned to take the first 50 bottles of
albumin and test them 4 days after the invasion of Pearl
Harbor. As such, plasma and albumin therapy was the fluid
resuscitation of choice at the beginning of World War II.2

The National Research Council established the Com-
mittee on Transfusion, chaired by Walter Cannon toward
the end of his career, and they concluded that shock is really
a form of hemoconcentration and that plasma would, in
fact, be more effective than blood. Despite this, the Sub-
committee on Blood Substitutes had the contrary opinion
that whole blood would be best as resuscitation during
World War II. This was omitted from their minutes in their
meeting in 1941 and was subsequently placed into meeting
minutes 2 years later.2

It was Dr Churchill, a thoracic surgeon from Harvard, as
part of an in-theater evaluation team, who studied resusci-
tation during his deployment and concluded that plasma
was not the best blood substitute. He described the early
effects of overzealous shock resuscitation and concluded
that whole blood was necessary for someone to endure an
operation. He attempted to convince command that a
movement to blood was important. But this request was
denied and as a result, he improvised and started a local
blood bank in North Africa. His partner at Harvard in
general surgery, Elliott Cutler, was also part of a study team
deployed to study resuscitation and he shared the opinion
that blood was needed. He worked to change the com-
mand’s view. By the end of World War II blood transfusion
had been established.20

Five years later, during the Korean conflict, the military
blood program of World War II had collapsed and there
was no blood available for the first 70 days in Korea. It was
during this time, however, that the first changes in coagu-
loration were reported, but these had little impact on resuscitation efforts.21

**Civilian practice**

Subsequent to Korea, the classic studies of Shires and Carrico described using a three isotope model that extracellular fluid repletion with crystalloid was essential for survival. Many studies compared crystalloid with colloid resuscitation and established that crystalloid solutions appeared superior.15,22,23

During the 1960s, blood was influenced significantly by economic factors. This was a time when collection was unregulated and fractionation was aimed at a market for drug use. Inappropriate collection became rampant and the result was that hepatitis emerged as a threat. Garrett Allen at Stanford demonstrated that slow heating killed hepatitis, and he collected plasma samples in Haight Ashbury to demonstrate how this could be prepared. He also lobbied the federal government about blood banking and ultimately was responsible for making a national agenda to control blood banking as we know it today.7

During this time, the use of fresh blood was described by George Sheldon and associates24 under a model of the Irwin Blood Bank in San Francisco. He believed that the routine use of whole blood to meet transfusion needs was inappropriate and unnecessary. However, they maintained a population available for fresh whole blood use after massive transfusion.

**Modern warfare**

During the Vietnam War, the use of blood included early use of fresh whole blood. This was replaced with red cells and fresh frozen plasma, and at the peak of 1969, the blood program provided 36,000 units of blood per month to 100 surgical teams. Universal donor red cells in more than 100,000 transfusions showed no fatal transfusion reaction and this practice was moved into civilian practice after the war.

The first complete description of coagulopathy after massive trauma related to shock came from classic work by Simmons and colleagues;25 they described the relationship of coagulopathy to shock and acidosis in 9% of massive transfusions. Many studies compared crystalloid with colloid resuscitation and established that crystalloid solutions appeared superior.15,22,23

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ter damage control methods and suggested the importance of the FFP to RBC ratio. Similarly, Brohi and associates described the existence of early coagulopathy and suggested the importance of screening.

The Iraqi conflict
By the beginning of the war in Iraq, far-forward surgical care, including damage control surgery, was introduced and the use of fresh whole blood initially for massive transfusion was practiced. This precipitated a subsequent movement to "virtual" fresh whole blood and a commitment was made to study this in the battlefield. Early analysis demonstrated that incremental improvements in mortality were associated with a movement of a transfusion strategy that achieved an FFP to RBC ratio of 1:1. There have been several studies to confirm this observation and a more recent evaluation in civilian trauma centers showed more plasma and platelets are associated with better survival. Selecting patients to undergo this type of therapy remains a challenge, but some recent studies suggest prehospital physiologic and laboratory factors can be used to predict the patient at risk.

In summary, moving back toward reconstituted whole blood seems very promising in select patients and represents a return to a practice almost 350 years old. A recent initiative for critical bleeding in trauma evaluated animal models and the mechanism behind this problem. This has led to a multidisciplinary consensus statement about current knowledge in this area.

A world survey of trauma centers in the US and Europe evaluating senior clinicians’ current practice protocols has demonstrated that a protocol to address these specific factors, including an RBC to FFP ratio, are currently used in only about one-third of trauma centers. A prospective randomized trial is warranted and plans are underway to test this important hypothesis.

The act of transfusion has gone from being feasible to being concerning over infectious complications and potential fears about toxicity. It is known that trauma leading to hemorrhage and shock is associated with an acute coagulopathy of trauma because of factor consumption, fibrinolysis, and augmentation by acidosis and hyperthermia. For some patients, this is critical to survival and early repletion with reconstitution toward whole blood may be critical.

Although we have traditionally resuscitated over the last 50 years with crystalloid, it may be more appropriate to think of resuscitation with reconstituted whole blood. This still needs to be worked out.

There is a subgroup of patients that has been present throughout wars, which we have trouble seeing in civilian practice, and for which we need better indicators of early coagulopathy. Protocols for identifying these patients and for treating these patients are inconsistent within and across trauma centers, but targeting correction may increase survival. Current practice with incremental coagulopathy component correction is probably out of date and out of fashion. Reconstitution of blood and the use of adjuvant therapy are likely to save lives, and research and evaluation of protocols are needed so this is done correctly.

REFERENCES