Invention and Development of the Blood Bag

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Until the 20th century, the complications inherent in transfusion of blood restricted its use to bold physicians treating patients with a desperate clinical problem. Incompatibility, complex technology, clotting, hemolysis, air embolism, microbial contamination, particulate emboli and identity of aliquots epitomize problems that have been successfully addressed to make transfusion convenient, safe and dependable for donor, recipient and physician. Blood banking made transfusion timely therapy for acute blood loss. Improved apparatus for handling blood played the major role in providing blood or its components on demand in industrialized societies around the world.

The concept of a content-compliant system for the collection, processing, storage and infusion of blood or its components in a closed liquid system evolved from 15 years of experience in a pioneer bank at the Peter Bent Brigham Hospital, and managing the collection of 900,000 units of blood for the American National Red Cross in the World War II era. A hermetically sealed bag and its appendages replaced the heavy glass bottle and its perforated bung; the hazards of bacterial contamination and air embolism were eliminated for both donor and recipient. Hemorepellent surfaces and physiologic pressures minimized trauma to the blood cells and suppressed clotting and hemolysis [1]. The logistics of transfusion therapy were enhanced. The system became the ultimate symphony for blood bankers!

The search for appropriate plastic film and tubing began in the fall of 1947. Over the Thanksgiving Holidays I fashioned hot wire platens to join the parts of the system – bag, donor tube, and delivery ports – into a hand-
some reduction to practice (fig. 1). The following Monday, my patent counsel was elated and the patent application was drafted – beginning with the claims! A patent was issued 12 years later with those claims intact. A parent claim, one of the eventual 37, reads [2]:

‘Apparatus for the contamination and coagulation-free collection, storage and infusing of whole blood, comprising a deformable hermetically sealed bag to contain the blood, a diaphragm-sealed delivery tube on the bag and adapted to receive a seal-piercing coupling needle to afford egress from the bag, and a collecting line comprising flexible tubing admitting at one end to the bag and having a phlebotomy needle at the other end, said bag and tubes being fabricated from a hermetically sealable impermeable material of good tissue tolerance, stable to sterilization and presenting to the blood only chemically clean inert glossy and hemorepellent surfaces.’

The prototype bags worked well with water and outdated blood. The compressible compliant bags could be filled and emptied by gravity and withstood centrifugation. Plasma could be extracted and the formed elements separated. Pressure infusion could be done. But bags of plasma fractured when frozen. The bags containing anticoagulant burst during sterilization despite my expertise at steam sterilization. Worse – fungi grew in the ‘sterilized’ plastic itself after shelf storage for 1 week. Only the functional idea of a device made in the surgical research laboratory proved sound.

Developing that design into a commercial product presented an increasingly complex series of technical, tooling, manufacturing, educational, political and financial problems. State of the art presented obstacles in the choice of material, fabrication, packaging, shelf-life and biologic validation. Professional resistance to change, consumer protection, and commercial disparagement and competition were difficult and persistent deterrents. When the American National Red Cross purchased 5,000 blood bags in June 1949, a nonacademic auspice for addressing the array of challenges became crucial.

After commercial firms with appropriate capabilities proved disinterested, I resorted to using resources available at Fenwal Incorporated of which I was a founder in 19351. Its products included temperature detection and control devices and a Pyrex™ glass system for the preparation of transfusion equipment and parenteral fluids widely used by teaching hospitals and the United States...
Navy [3]. Fenwal Incorporated’s four partners formed a subsidiary, Fenwal Laboratories, Inc., to develop the blood bag. A managerial staff was recruited from the hospital supply industry, and an engineer and a physician with experience in pertinent research and development were hired. Consultants were used freely, and a wide range of the parent corporation’s engineering and manufacturing expertise was called upon as required.

A series of development projects was defined by the state of the art in each category. Some 5 years and 1.5 million 1952 dollars later, blood bags were available for clinical trial. Parenteral solution bags followed within a year. These products were produced in a completely tooled prototype production facility including a clean room, which complied with the United States Food and Drug Administration’s Good Manufacturing Practices. Only sterility and pyrogen testing, toxicity studies, and in vivo red cell survival studies were done elsewhere.

The complexity of the development can be sensed by scanning the knowledge and talents of the array of people recruited to solve the major projects – mostly on an ad hoc basis (table I).

The search for a plastic that would permit sterilization by steam and yet be elastic and flexible enough to withstand freezing led to a surprise. The formulation of the plastic and the texture and charge of its surface affected clotting, hemolysis and longevity of red cells! Indeed, the plasticizer was key to these biologic properties. Polyvinylchloride copolymer plasticized with di-2-ethylhexylphthalate (DEHP) provided hemorepellence and protected the red cell membrane to preclude hemolysis and enhance the in vitro survival of erythrocytes.

Growth of microorganisms either in the plastic or that permeated it eliminated several promising formulations. Most plastics proved to be excellent barriers to bacterial incursion. The search for a suitable plastic that began with the industry’s giant in Philadelphia was successfully resolved in Los Angeles – a dozen stops and years later. The search ended through happenstance seatmate chatter on an airplane between strangers—a Fenwal Laboratories executive and an elastomer engineer who had just formulated a new copolymer.

Steam sterilization – a seemingly simple procedure – too often resulted in concentrated or discolored solution, burst bags, collapsed tubes or adherent surfaces. Ultimately a turbulent mixture of air and steam, the antithesis of conventional steam sterilization, was invented that would sterilize both empty bags and those containing liquid. A programmed sterilizing process shifted the partial pressures of air and steam during the sterilizing cycle to effect timely exchange of heat or air through the plastic without altering the contents or damaging the structure of the bag or its complex of pouches, tubes, satellites and cannulas.

The plastics with the desirable biologic properties transmitted water vapor that condensed inside the sealed container used to package the product. The condensate corroded tinned or lacquered cans. The advent of inexpensive aluminum cans and pouches, and eventually, plastics impervious to water vapor, solved the problem of packaging.

The choice of material for labels was dictated by the discovery that thermoduric fungal spores persist in paper made from southern pine. Labels made from pine grown in the State of Maine could be sterilized.
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Table I.

- **Biocompatible, hemorepellent, cryoelastic, non-toxic plastic**
  - Professor of organic chemistry
  - Professor of physics – cryophysics
  - Industrial polymer chemist
  - Elastomer engineer

- **Dielectric sealing**
  - Engineer-inventor
  - Electrical engineer ‘A’
  - Electronics engineer – inventor

- **Production methodology and tooling**
  - Electrical engineer ‘B’
  - Production engineer
  - Tool designer
  - Tool maker
  - Clean room designer

- **Sterilization**
  - Associate professor of surgery
  - Nurse, expert at compounding parenteral fluids
  - Electrical engineer-inventor
  - Mechanical engineer ‘A’
  - Microbiologist ‘A’

- **Bacterial barrier and sterility testing**
  - Microbiologist ‘B’

- **Labels, indelible, spore-free, moisture- and heat-resistant, heat-and moisture resistant plastic-compatible adhesive**
  - Mechanical engineer ‘A’
  - Industrial ink chemist

- **Industrial paper chemist**
  - Adhesives chemical engineer

- **Sterile packaging and shelf-life – water vapor barrier**
  - Aluminum can engineer
  - Aluminum pouch engineer
  - High-density polyethylene engineer

- **Stability of anticoagulant**
  - Microbiologist ‘A’
  - Microbiologist ‘B’
  - Isotope biologist

- **Red cell preservation**
  - Assistant professor of medicine
  - Isotope-physiologist
  - Hematologist
  - Associate professor of medicine
  - Engineer, isotope biologist

- **Blood bank practices**
  - Associate professor of surgery – blood banker
  - Associate professor of medicine – hematologist
  - Mechanical engineer ‘A’
  - Electrical engineer-inventor
  - Blood bank nurse
  - Blood bank technician
  - Nurse detailer and instructor
  - Physician – clinical trials

The mold and slime found in some packages of bags stored for several months was prevented by pasteurization of the sterilized bags promptly after packaging in a hermetically sealed container.

The white thread-like frond of platelets that formed in the donor tube during gravity collection was a final challenge. Development of a hemorepellent surface for stainless steel, and redesign of the phlebotomy needle tip facilitated phlebotomy; a flared connection with the donor tube preserved laminar flow. It became possible to collect blood by gravity into an empty blood bag and refrigerate it for 6–8 h without clotting [4]. The completed hemorepellent laminar flow system seemed ready for clinical trial.

A tamper-proof cover for the donor nee-
Dependable production of blood bags (fig. 2) permitted mounting the first clinical trial at the Peter Bent Brigham Hospital. There the team of experts who effected the development mingled with clinicians receptive to new ideas and devices. The hybridization of ideas that emerged produced a series of techniques and accessories that improved blood-banking practices and facilitated blood component therapy.

A special scale was devised to ensure collection of a prescribed amount of blood. Because phlebotomists often served several donors simultaneously, an automatic donor scale was developed to clamp off the donor tube and signal when a predetermined quantity of blood was drawn. To satisfy the demands of phlebotomists accustomed to vacuum collection, a machine was designed to speed the drawing of blood. The 'hemolator' applied controlled negative pressure to the outside of the bag, rocked the bag to mix the anticoagulant, and stopped collection at a predetermined volume.

Development of a portable dielectric sealer permitted the segmentation of aliquots of blood in the integral donor tube. Each segment, imprinted with an identifying number, eliminated error and facilitated culturing, typing, and cross-matching.

Disposable infusion sets were devised to satisfy a variety of clinical needs. Filters were developed to retain the inevitable agglomeration of proteins that occurred because of faulty phlebotomy or during prolonged storage.

Rapid infusion of blood by means of a pressure infusor was developed. A cleverly designed pouch to embrace the blood bag applied controlled pneumatic compression to effect a predetermined infusion rate.

An automatic exchange transfusion ma-
machine was produced to facilitate the incremental replacement of blood in the newborn.

Separation of the blood components was facilitated by a manual press that permitted the controlled expression of plasma and leukocytes. An automatic photoelectric version was developed that simultaneously separated plasma and the formed elements from several bags.

Blood packs featuring various anticoagulants were produced. The most novel was ion-exchange resin; the most noteworthy was CPD (citrate phosphate dextrose solution). Various configurations of bags and interconnecting tubes and enclosed pierceable diaphragms facilitated the separation of blood into its components and their infusion from a completely closed system.

Devices for thawing frozen plasma and warming blood to body temperature were designed and produced.

The introduction of blood bags by the American National Red Cross and blood banks in several teaching hospitals soon established the new technique. The attractions were: 84% in vivo survival of red cells after 20 days storage in ACD and 72% survival of 28 days; low rate of bacterial contamination, 0.53% in contrast to 6.7% in glass; and few pyrogen reactions, 0.83% in 6,659 transfusions [5]. There was no demonstrable leaching of toxic substances from the plastic after shelf storage of 10 months. Such data overpowered the prejudices of most blood bankers.

However, absurd requirements emerged. Bags of blood should withstand a drop of 2,000 feet onto an asphalt surface; bags must not splatter when tossed across an operating room or when stepped on; bags must not leak when vented; bags must be reusable in an emergency; and used bags must not explode when incinerated. An adverse aesthetic factor was that bags of blood 'looked and felt like liver'. And so it went.

Clinical trials in Korea during United States military involvement in the early 1950s resulted in the development of a disposable lightweight airborne liquefied gas expansion refrigerator for transporting blood from Boston to Seoul.

The advantages of transport of bags over bottles was striking. Shipments of bags or bags of blood were smaller and lighter—one-fifth the space or weight when empty, half the space or weight when full. Ease of infusion by tucking the bag beneath the wounded and the rapid infusion under pressure were advantageous [6]. The convenience of carrying a bag of blood in a pocket while crawling to resuscitate the wounded in the battlefield was extolled.

Thus, the 4-day Thanksgiving Holiday initiated a decade of productive research and development that melded the knowledge and skills of many disciplines and breached boundaries between professions. Many talented experts dedicated themselves to improving the technology of blood banking. The needs of the donor and the variety of specific requirements of each category of recipient were analyzed and satisfied.

Hurdles still persist after 30 years of success. The Conference of Phthalates [7] on June 9, 1981, considered that the biocompatible plastic formulated in 1950 might be mutagenic and carcinogenic. The toxicity studies were done under the same auspice that originally determined the increased half-life of red cells stored in that plastic. The laboratory demonstrated that the plasticizer, DEHP, is leached from the plastic by plasma. Recipients who receive multiple (20
or more) transfusions per year may accumulate DEHP in their livers. Comparable accumulation may cause hepatic cancer in rats and crystallize changes in hepatic cells in monkeys. The same laboratory has repeatedly shown that DEHP is the factor in polyvinyl chloride plastic that enhances the survival of red cells to a degree that it is the key to modern blood banking. What a dilemma – safe lives for the 99+\% for whom a transfusion is crucial and safe at the putative risk of the few with a chronic fatal disease whose lives are prolonged by transfusion!

The search for the ideal biocompatible plastic container for blood continues along with efforts to prolong and improve the storage of red cells to ensure the prompt exchange of oxygen in the tissues following infusion.

An invention seldom stands alone or finds its way to the marketplace in its pristine form. An invention furthers human welfare only through a complex program and development that usually involves the knowledge, skills, energy and resources of people willing to dedicate their special talents to bring a unique concept into public use. At that juncture, yet another resource is essential, access to the market. Masterful marketing by a competitive corporation resulted in the manufacture and use of 150 million Fenwal blood bags in the Free World since the Food and Drug Administration’s approval of ACD in plastic bags in 1963 [8].

References

7 United States Department of Health & Human Services, National Toxicology Program, Inter-Agency Regulatory Liaison Conference on Phthalates, June 9, 1981.