RBC Transfusion: Historical vs Best Practices

Jacob Pendergrast, MD, FRCPC

Associate Professor, Department of Laboratory Medicine and Pathobiology
University of Toronto

Medical Director, Blood Transfusion Service

University Health Network

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Disclosures

- None to declare

Objective

To understand the origins of traditional RBC transfusion practices and why these have changed

Pre/Post Transfusion Knowledge Question

1. A 50-year-old male alcoholic is admitted to the intensive care unit with a three day history of productive cough, fever and chills. His chest x-ray shows a right lower lobe pneumonia and he is septic. Shortly after arrival, he is intubated and mechanically ventilated with an arterial oxygen saturation of 99% on 50% oxygen. The patient is hemodynamically stable with no evidence of ongoing blood loss and he is euvolemic. However, his hemoglobin value has dropped.

Pre/Post Transfusion Knowledge Question

1. In the absence of symptoms of inadequate tissue oxygen delivery, at what hemoglobin level would you first consider a red cell transfusion?
   A. When less than 60 g/L
   B. When less than 70 g/L
   C. When less than 80 g/L
   D. When less than 90 g/L
   E. When less than 100 g/L

Pre/Post Transfusion Knowledge Question

2. An 87-year-old 50 kg woman presents with new onset autoimmune hemolytic anemia. She had a presyncopal episode and is short of breath with minimal exertion. Her hemoglobin is 55 g/L (baseline: 120 g/L last checked one month ago). Her vital signs are: Heart rate 105 beats per minute; Respiratory rate: 20 per minute; O_2 saturation 94% on room air.

Pre/Post Transfusion Knowledge Question

2. Which of the following would you recommend?
    A. Transfuse 1 red blood cell unit over 1 hour
    B. Transfuse 1 red blood cell unit over 3 hours
    C. Transfuse 2 red blood cells units, each over 1 hour
    D. Transfuse 2 red blood cells units, each over 3 hours
    E. Do not transfuse

Acute Hemolysis

- Early attempts at blood transfusion often went badly
  - Shock
  - Diffuse bleeding
  - Kidney failure
  - Death

Cause of these reactions unclear

“As soon as the blood began to enter into his veins, he felt the heat along his arm and under his armpits. His pulse rose and soon after we observed a plentiful sweat over his face. His pulse varied extremely at this instant and he complained of great pains in his kidneys, and that he was not well in his stomach, and that he was ready to choke unless given his liberty.”

Jean-Baptise Denis, 1668, describing use of calf blood transfusion to treat a patient suffering from phrenesy (mania)

"In pressing forward the piston, from moment to moment, fix your eye on the countenance, and if all is well, then proceed more boldly; but if the lip quiver, or the eye-lid flicker, or if there be restlessness or vomiting, though these are not fatal symptoms, yet it is better to suspend your operation until they subside, as in the present state of our information there is good cause for alarm."

James Blundell, 1834, describing the transfusion of blood from husband to wife as treatment for post-partum hemorrhage

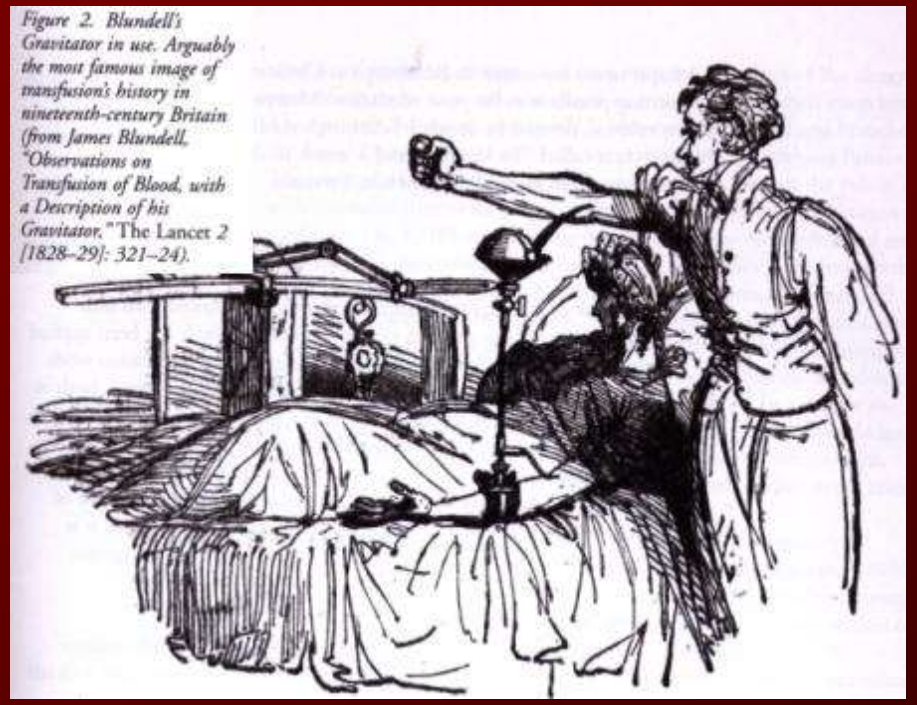
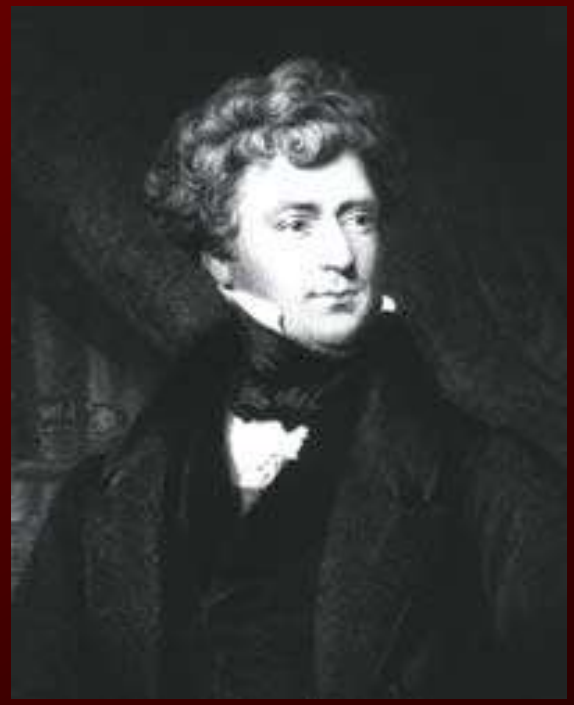


Figure 2. Blundell's Gravitator in use. Arguably the most famous image of transfusion's history in nineteenth-century Britain (from James Blundell, "Observations on Transfusion of Blood, with a Description of his Gravitator," The Lancet 2 [1828–29]: 321–24).



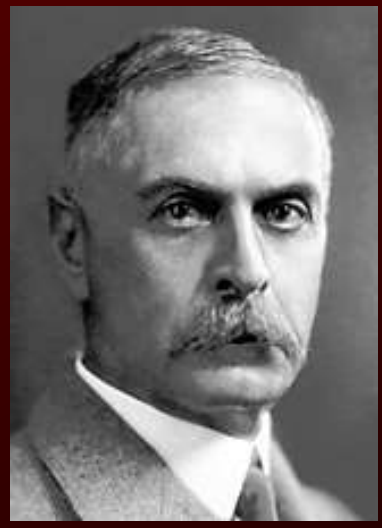
Discovery of Major Blood Groups

- 1900: Pathologist Karl Landsteiner notes that serum of apparently healthy individuals predictably agglutinates the red blood cells of some (but not all) other individuals; agglutinated cells eventually rupture
- Incompatibility between plasma and RBCs recognized as basis for hemolytic transfusion reactions (Nobel Prize awarded in 1930)

Blood grouping based on RBC agglutination (Landsteiner, 1900)

Serum \ RBC	Dr.St.Dr.	Plee.Dr.	Sturl. Dr.	Erdh. Mr.	Zar. Mr.	Land.
Dr. St.	-	+	+	+	+	-
Dr. Plee.	-	-	+	+	-	-
Dr. Sturl.	-	+	-	-	+	-
Dr. Erdh.	-	+	-	-	+	-
Mr. Zar.	-	-	+	+	-	-
Mr. Land.	-	+	+	+	+	-

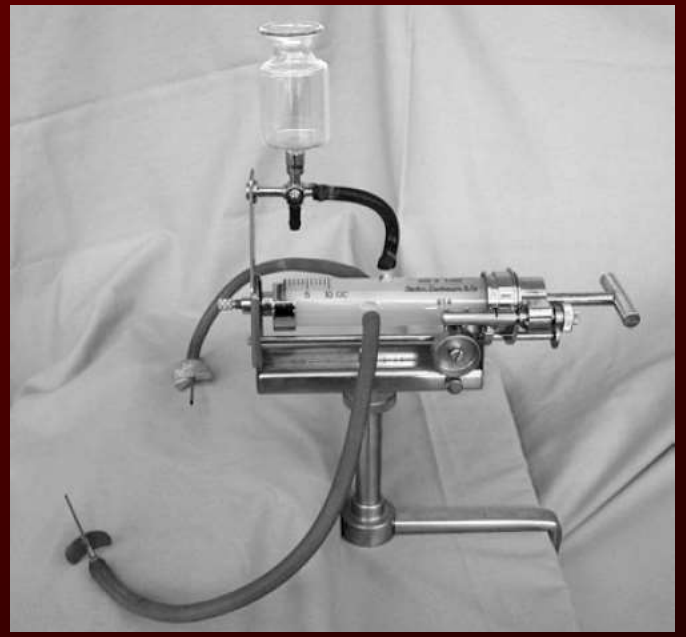
(+ agglutination - no agglutination)



Yanamoto, Immunohematology, 2004;20:3

Direct Donation

- Because blood quickly clots when removed from the body, earliest blood transfusions were direct from donor to recipient: surgical procedure
- Transfusions only performed to treat life-threatening anemia or hemorrhage
- **Quantities limited by donor's ability to tolerate phlebotomy**



The Discovery of Citrate Antcoagulation

- Clotting now prevented with citrate
  - Binds the calcium present in blood
  - Calcium required for the activation of the coagulation cascade
  - Only small volumes of citrate required, not toxic to transfusion recipient unless very large volumes of blood transfused
  - Citrated blood = blood that can be stored

First successful transfusion of citrated blood, credited to Argentinian MD Dr. Luis Agote, in Buenos Aires, November 9 1914

- Following WW2, blood donation now considered in many countries to be a civic duty
- Physicians returning to civilian service with new enthusiasm for benefits of transfusion
- Rapid growth in hospital blood banks
- **Question shifts from “what can the donor tolerate” to “what does the recipient need?”**

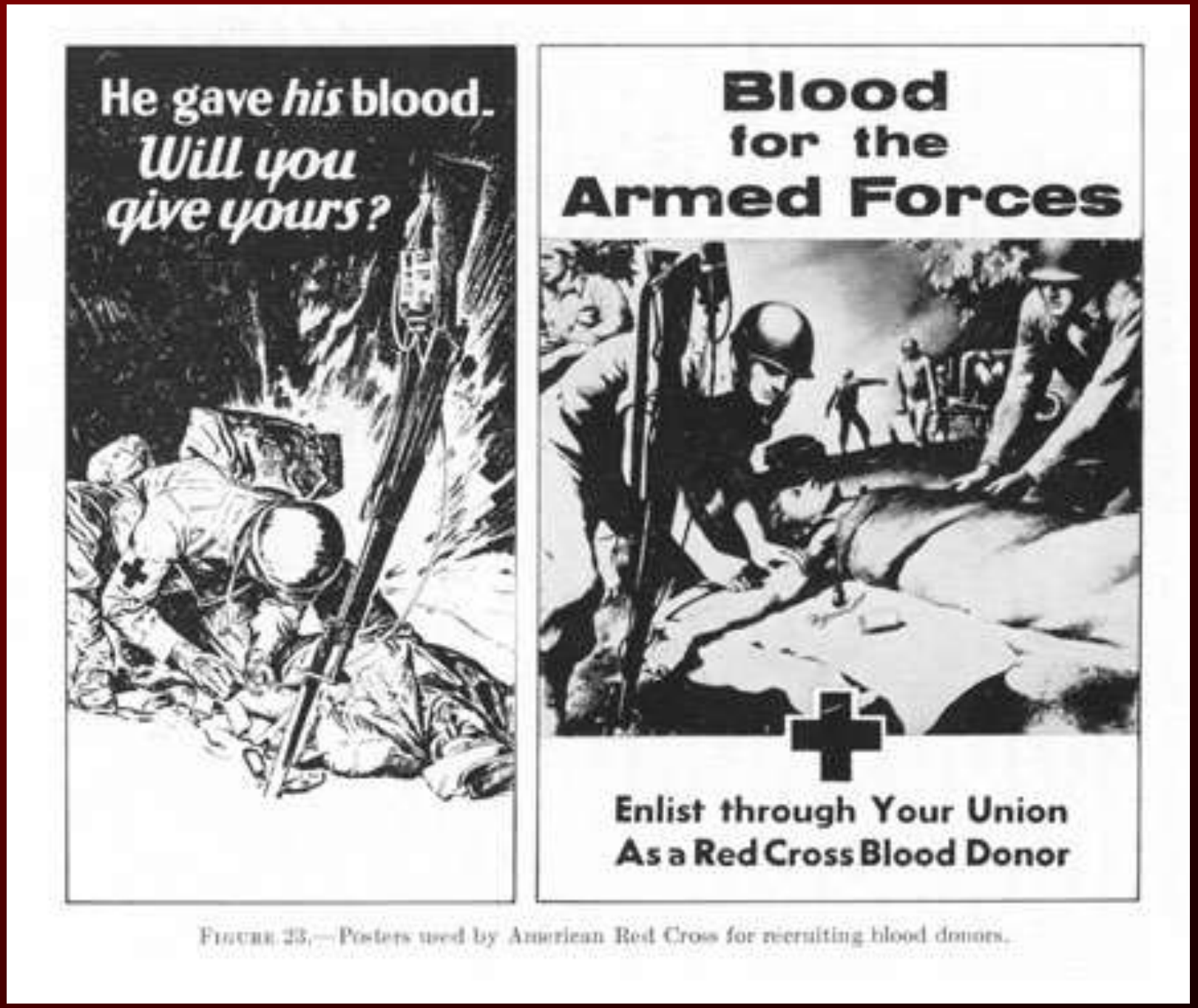
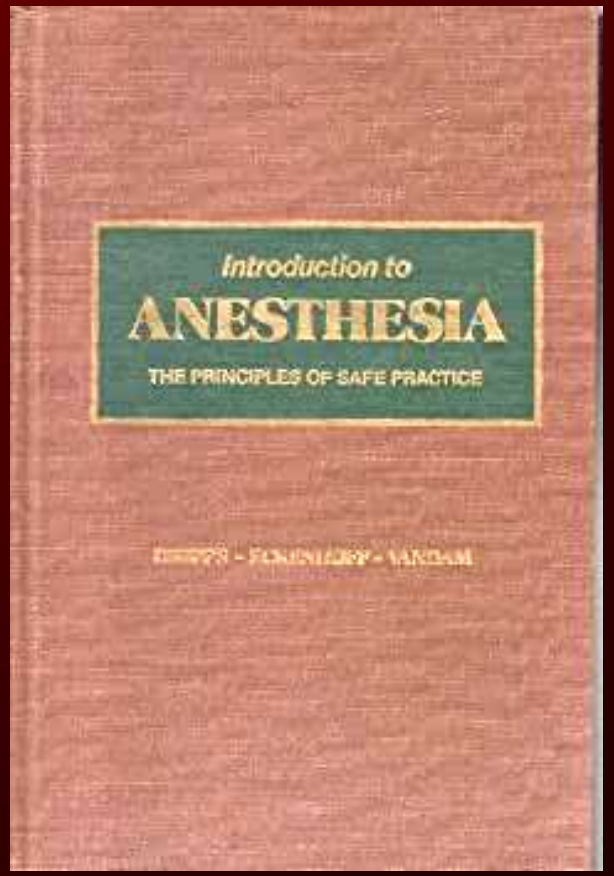


FIGURE 23.—Posters used by American Red Cross for recruiting blood donors.

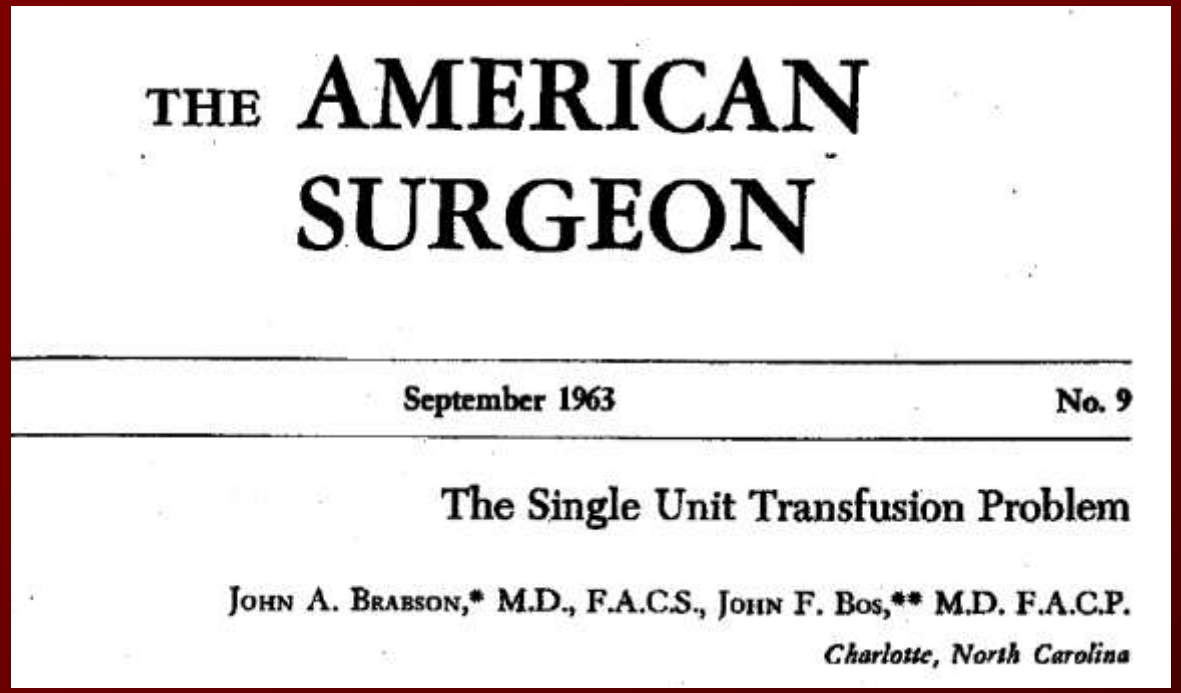
The 10/30 Rule

- 1941: Adams & Lundy (Mayo Clinic) advocate transfusing at hemoglobin 8-10 g/dL for high-risk surgical patients
- Attributed as the origin of the 10/30 “transfusion trigger”: all patients best served by being transfused to a hemoglobin of 100 g/L (10 g/dL) or a Hct of 30%
- Adopted as a general rule-of-thumb by standard surgery and anesthesiology textbooks for *decades* afterwards



Adams RC, Surg Gynecol Obstet. 1941;71:1011

The 2u Transfusion Rule



THE AMERICAN SURGEON

September 1963 No. 9

The Single Unit Transfusion Problem

JOHN A. BRABSON,* M.D., F.A.C.S., JOHN F. BOS,** M.D. F.A.C.P.

Charlotte, North Carolina

Published Under the Auspices of The Board of Trustees

THE JOURNAL of the American Medical Association

JAMA

VOL 195, NO 10, March 7, 1966

Epidemiology of Single-Unit Transfusion

A One-Year Experience in a Community Hospital

Richard L. Reece, MD, and Ronald S. Beckett, MD

The 2u Transfusion Rule

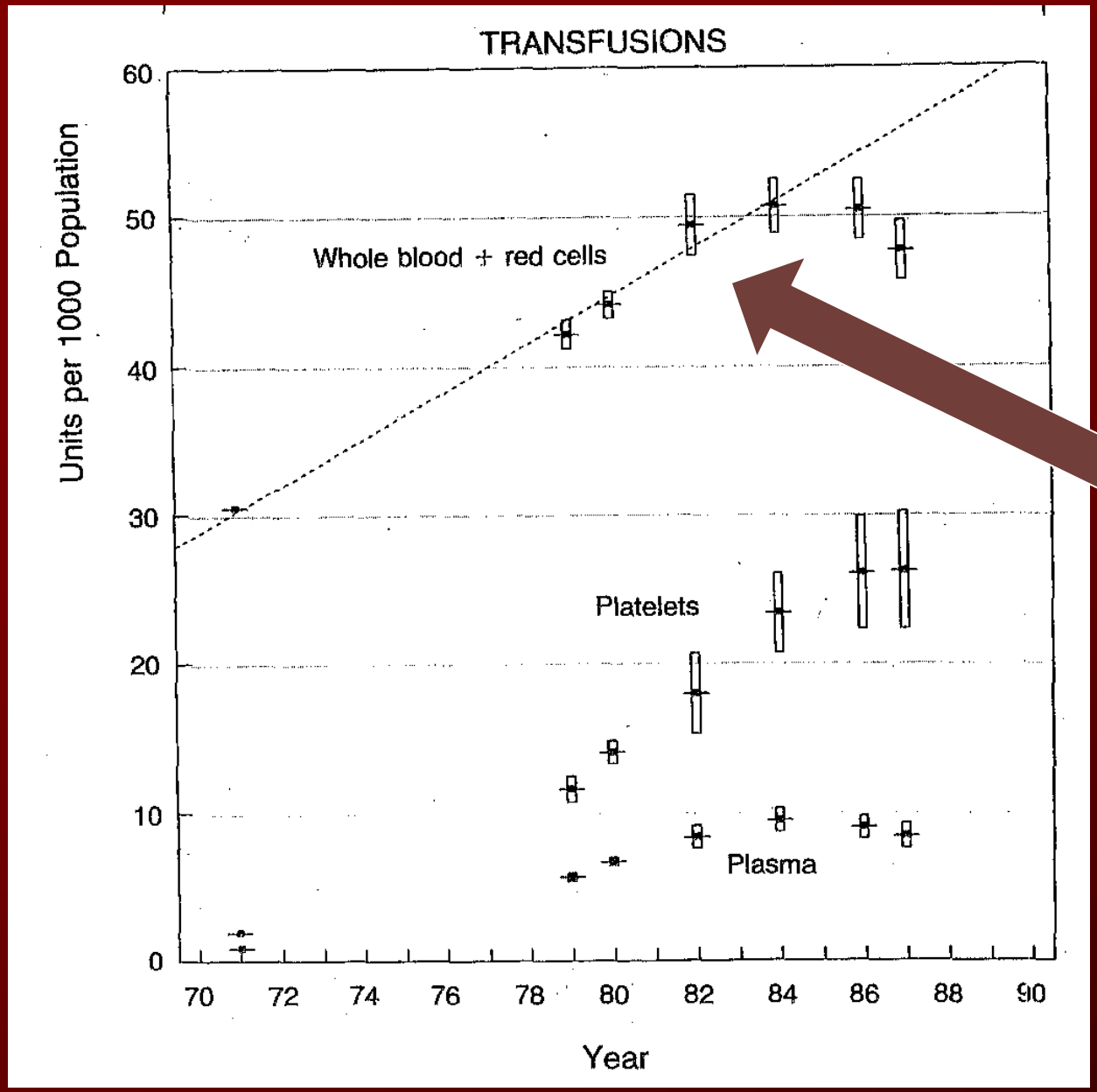
- Early reviews of transfusion practice did not challenge the 10/30 rule, but did note that 2/3 of transfusions ordered above this threshold were single-unit transfusions or were otherwise considered clinically unnecessary
- 1962: US Joint Blood Council (AABB, AHA, AMA, ARC, ASCP) issues statement calling for critical assessment of any hospital using predominantly single-unit transfusions
- JCAHO subsequently requires all HTCs to perform audits of single-unit transfusions

The 2u Transfusion Rule

- As feared, critical focus on single-unit transfusions resulted in new clinical heuristic: always order RBC transfusions 2 units at a time!
- 1983: authors of a NEJM publication on transfusion-transmitted hepatitis comment that single-unit transfusions "are generally acknowledged to be unnecessary": widespread misconception that appropriateness of transfusion was defined by the volume administered rather than the clinical indication

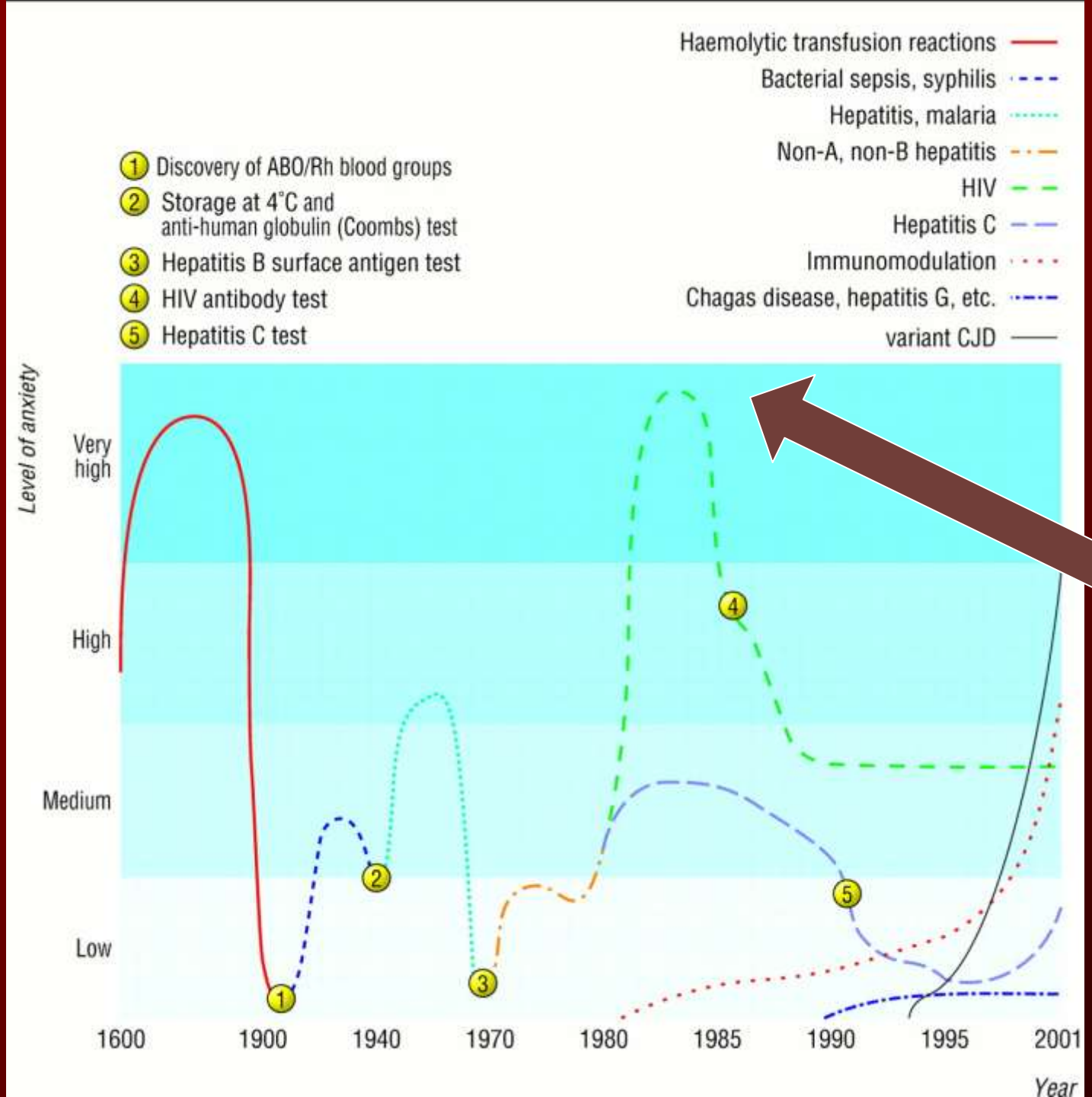
Hornbrook MC, NEJM. 1983:308:845

- These two rules of thumb are the backbone of “liberal transfusion practices”:
  1. Keeping the hemoglobin at 100 g/L is good for the patient
  2. Always transfuse 2 units at a time
- Both took root in the years preceding the expectation that medical practices be evidence-based rather than informed by expert opinion



Liberal transfusion practices first began to flag in the 1980s…

Surgenor DM, NEJM 1990;322:1646-51



… with emergence of HIV as a novel, transfusion-transmissible disease

Increased Scrutiny of Liberal Transfusion Practices

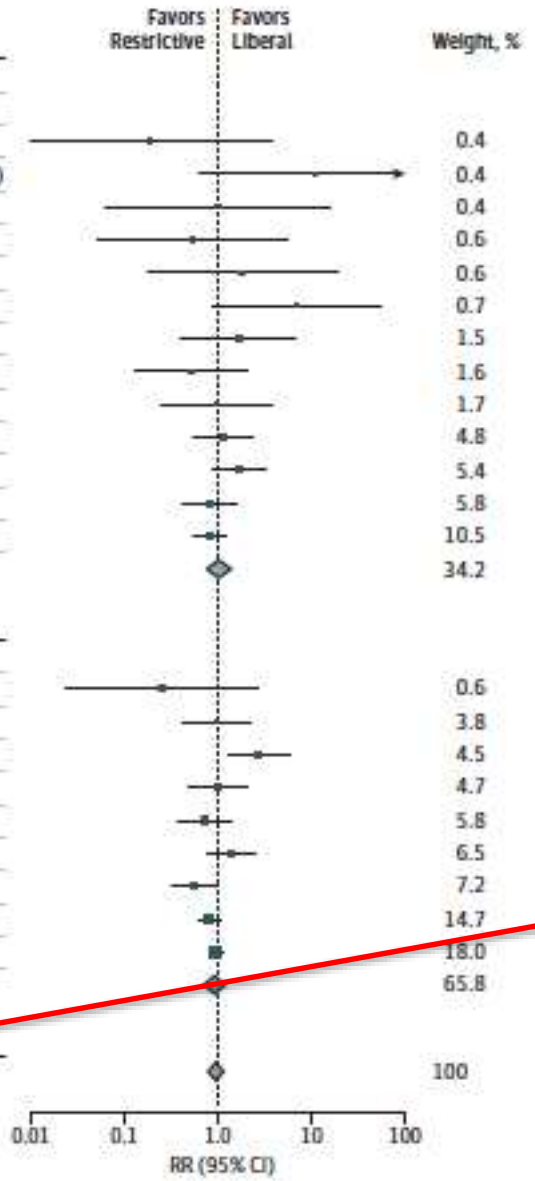
- 1983: risk of HIV transmission via transfusion in US estimated at **1:5000**
- 1988: US NIH/FDA convene 2-day conference on perioperative blood transfusion with goal of reducing use
- The 10/30 and 2-unit transfusion rules specifically challenged as unjustified
- *Call for clinical trials to determine best practices*

JAMA 1988; 260: 2700

Schreiber GB, N Engl J Med 1996; 334

Figure 1. Comparison of 30-Day Mortality Using Restrictive vs Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials

Source	Restrictive Transfusion Threshold: No. of Deaths	Restrictive Transfusion Threshold: Total No.	Liberal Transfusion Threshold: No. of Deaths	Liberal Transfusion Threshold: Total No.	RR (95% CI)	Weight, %
Restrictive threshold, hemoglobin <8 to 9 g/dL						
Lotke et al,[75] 1999	0	62	0	65	Not estimable	
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)	0.4
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)	0.4
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)	0.4
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)	0.6
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)	0.6
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)	0.7
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)	1.5
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)	1.6
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)	1.7
Hajjar et al,[68] 2010	15	249	13	253	1.17 (0.57-2.41)	4.8
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)	5.4
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)	5.8
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)	10.5
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)	34.2
Heterogeneity: $\tau^2=0.02$; $\chi^2_{12}=13.14$; $P=.36$; $I^2=9\%$						
Tests for overall effect: z score = 0.31; $P=.76$						
Restrictive threshold, hemoglobin <7 g/dL						
DeZern et al,[87] 2016	1	59	2	30	0.25 (0.02-2.69)	0.6
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)	3.8
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)	4.5
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)	4.7
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)	5.8
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)	6.5
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)	7.2
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)	14.7
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)	18.0
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)	65.8
Heterogeneity: $\tau^2=0.05$; $\chi^2_8=16.09$; $P=.04$; $I^2=50\%$						
Tests for overall effect: z score = 0.53; $P=.59$						
Overall	470	5221	497	5316	0.97 (0.81-1.16)	100
Heterogeneity: $\tau^2=0.04$; $\chi^2_{21}=29.75$; $P=.10$; $I^2=29\%$						
Tests for overall effect: z score = 0.29; $P=.77$						
Tests for subgroup differences: $\chi^2_1=0.34$; $P=.56$; $I^2=0\%$						



Multiple RCTs in variety of clinical settings have shown that restrictive transfusion practices (ie., transfusion trigger of 70-80 g/L) do not increase mortality rates vs traditional target of 100 g/L…

Important Secondary Outcomes

- Orthopedic surgery: *restrictive transfusion practices did not prolong hospital stay or functional recovery*
- Upper GI bleed: *…resulted in **less** recurrent hemorrhage*
- Stem cell transplantation*: …did not decrease quality of life*
- Acute coronary syndrome: *… did not increase major adverse cardiac events*
- All inpatients*: …resulted in **fewer** serious infections*

Carson , NEJM 2011;365:2453
Villanueva et al. NEJM Jan 2013;368:11
Rodhe, JAMA 2014;311:1317
Tay, J Clin Oncol 2020;38:1463
Ducroq, JAMA. 2021;325(6):552-560

Bottom Line

- RBCs should only be administered 1 unit at a time
  - Exception for chronically transfused outpatients or patients with massive blood loss
- RBCs should only be transfused to patients with Hgb > 70 g/L to treat symptoms of anemia
  - No evidence that different rules needed for the elderly, those with cardiac disease, or actively bleeding patients
  - Different rules for patients with hemoglobinopathies
- The above recommendations are supported by numerous practice guidelines and are mirrored in most hospital transfusion policies

The Battle Continues…

Pre/Post Transfusion Knowledge Question

1. A 50-year-old male alcoholic is admitted to the intensive care unit with a three day history of productive cough, fever and chills. His chest x-ray shows a right lower lobe pneumonia and he is septic. Shortly after arrival, he is intubated and mechanically ventilated with an arterial oxygen saturation of 99% on 50% oxygen. The patient is hemodynamically stable with no evidence of ongoing blood loss and he is euvolemic. However, his hemoglobin value has dropped.

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