The history of anti-D
La storia dell'anti-D

Steven L. Spitalnik, M.D.

Laboratory of Transfusion Biology

COLUMBIA UNIVERSITY

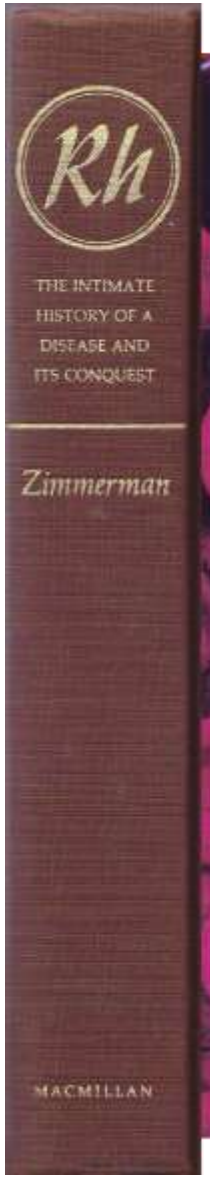
College of Physicians and Surgeons

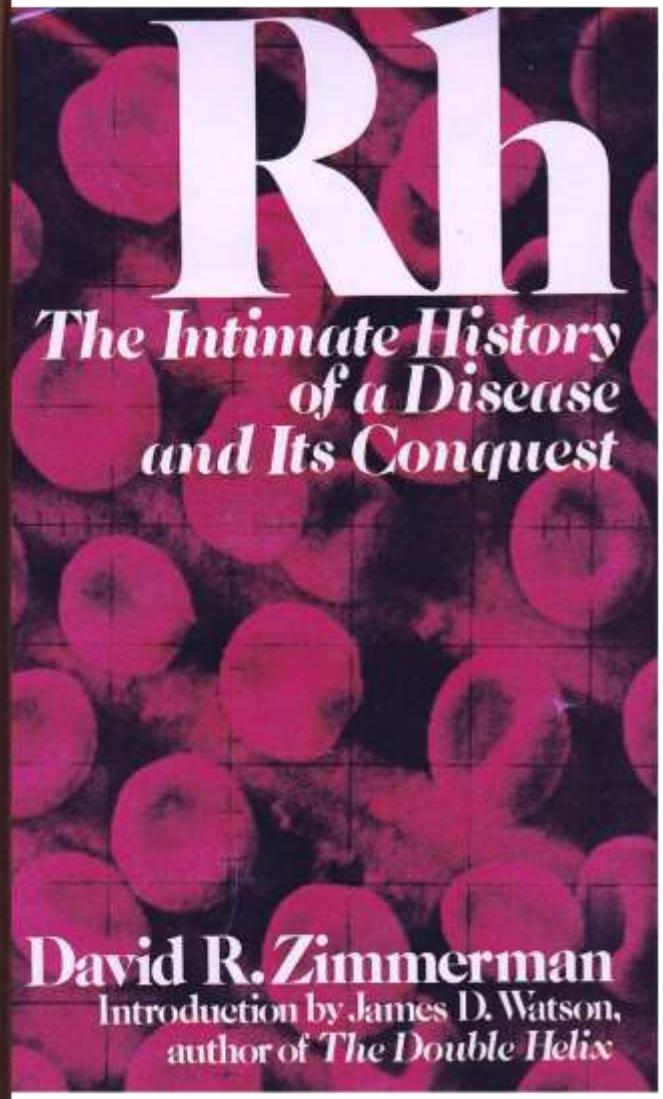
NewYork-Presbyterian
The University Hospitals of Columbia and Cornell

Potential Conflicts of Interest

Hemanext:	**Advisory Board**
New York Genome Center:	**Consultant**
Tioma, Inc:	**Consultant**
Theranos, Inc.:	**Advisory Board**
BloodWorks Research Inst.:	**Advisory Board**
Kedrion Biopharma	**Consultant**

David Zimmerman





(Continued from front flap)

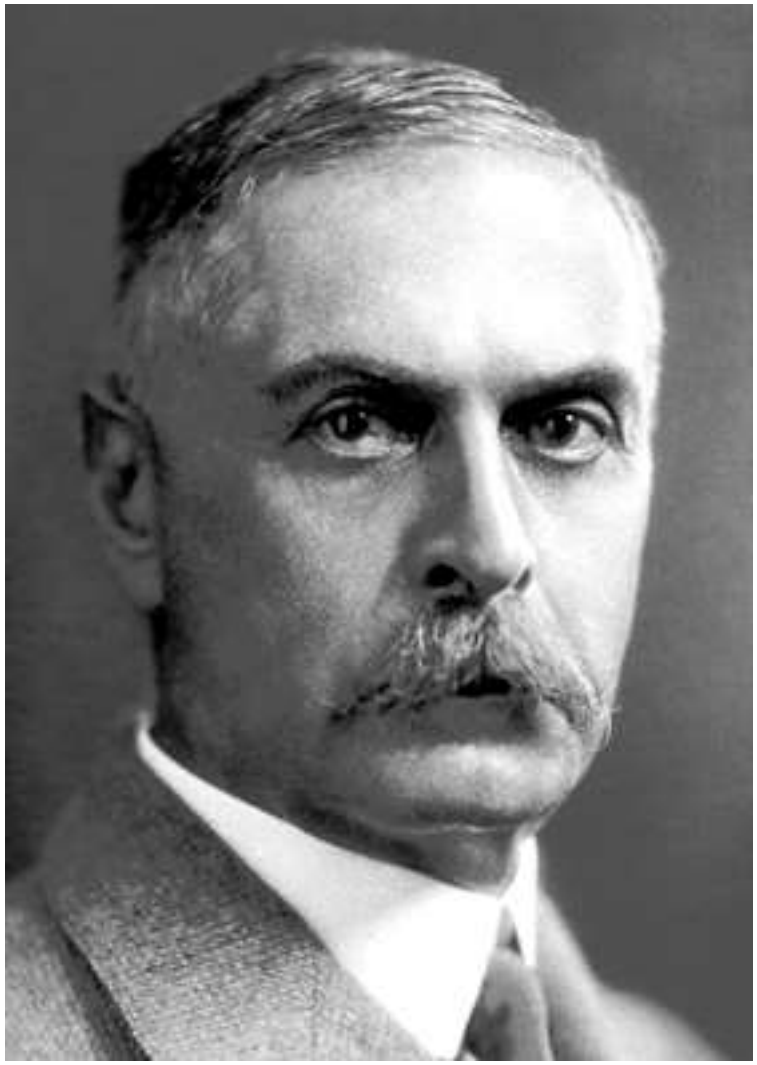
other endeavors." On the basis of his investigation, the author resolves the hotly contested question of who deserves credit for the development of the Rh vaccine.

Rh was—and is—a good story. It is also the most accurate, the most informative, and most "inside" account of creative scientists at work since *The Double Helix*.

Photo by Henry Grossman (ASMP)

DAVID R. ZIMMERMAN is a medical and science writer who contributes regularly to *Ladies' Home Journal*, *The New York Times Magazine*, and *Medical World News*. He is a member of the Society of Magazine Writers and the National Association of Science Writers. He lives in New York City.

Karl Landsteiner



ABO: Vienna, 1900

M, N, P: New York, early 20th century

Philip Levine

Alexander Wiener

Landsteiner's students
Co-discoverers of Rh

Hemolytic Disease of the Fetus & Newborn

Erythroblastosis fetalis

Fetal hydrops

Neonatal anemia and jaundice

Kernicterus

Maternal IgG to an RBC alloantigen crosses placenta, binds to fetal RBCs, and destroys them.

Diamond, Chown, et al.

Rh immune globulin to protect against maternal alloimmunization to D

1980 Albert Lasker Clinical Medical Research Award

Vaccine for preventing Rh incompatibility in newborns

Cyril A. Clarke
The University of Liverpool

Ronald Finn
Royal Liverpool Hospital

Vincent J. Freda
Columbia University

John G. Gorman
Columbia University

William Pollack
Ortho Diagnostics

Columbia University/Presbyterian Hospital

Vincent Freda, MD: Obstetrics & Gynecology
John Gorman, MD: Pathology (Blood Bank)

John Gorman in 2016

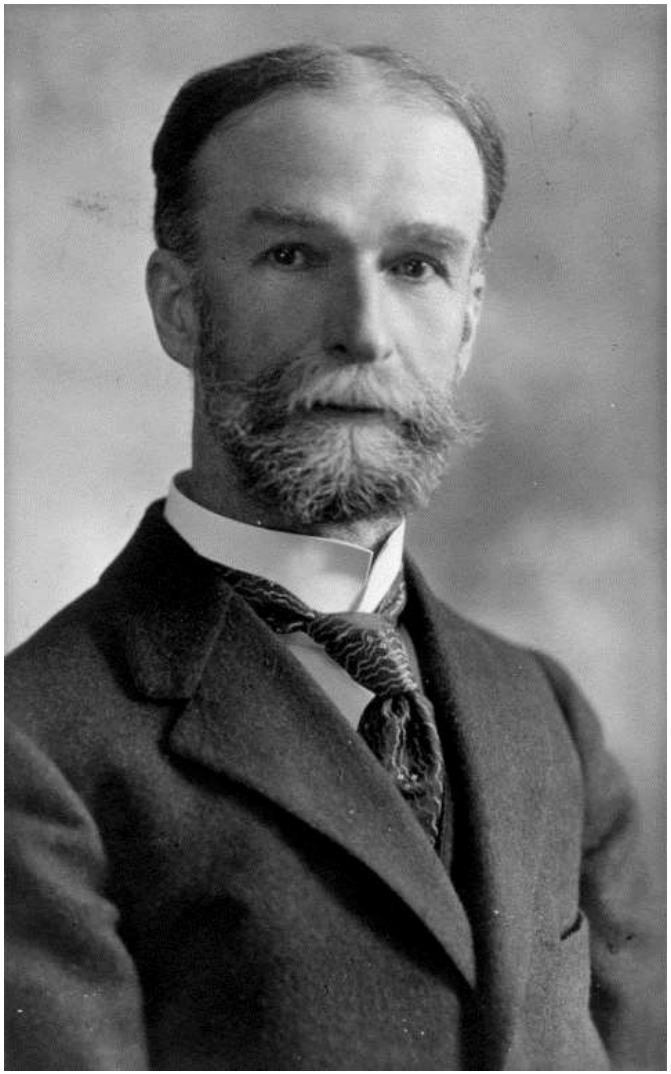
First clear glass Heinz ketchup bottle introduced in 1871, the squeezable in 1983, the upside down in 2002. It took 131 years before the upside-down idea was thought of and implemented.

131 Years

This upside-down idea was entirely “doable” in 1871.

It just didn’t occur to anyone for 131 years.

Theobald Smith



ACTIVE IMMUNITY PRODUCED BY SO-CALLED BALANCED OR NEUTRAL MIXTURES OF DIPHTHERIA TOXIN AND ANTITOXIN.[1]

By THEOBALD SMITH, M.D.,

George Fabyan Professor of Comparative Pathology in the Harvard University Medical School.

(*From the Antitoxin and Vaccine Laboratory of the Massachusetts State Board of Health.*)

Journal of Experimental Medicine 11:241-256, 1909

Theobald Smith

INTERPRETATIONS AND CONCLUSIONS.

The foregoing and earlier data taken together demonstrate that an active immunity lasting several years can be produced in guinea-pigs, by the injection of toxin-antitoxin mixtures which have no recognizable harmful effect either immediate or remote. They also show, what might have been anticipated, that under the same conditions mixtures which produce local lesions and which, therefore, contain an excess of toxin produce a much higher degree of immunity than the neutral mixtures, and that an excess of antitoxin reduces the possibility of producing an active immunity, and may extinguish it altogether. There is, therefore, a certain definite rela-

Ideas that were circulating at the time

Alloimmunization and Rh disease rarely seen in first pregnancy (different than ABO HDFN)

Fetal outcomes get progressively worse with subsequent Rh-incompatible pregnancies

Maternal-fetal ABO incompatibility is protective (e.g. Group A fetus & Group O mother)

When do fetal RBCs enter the maternal circulation?

The plan (NYC & Liverpool)

Inject all Rh(D)-negative primigravidas at delivery with a source of IgG anti-D (hyperimmune plasma, purified gamma globulin, etc.)

Do not treat with IgG anti-D before delivery

Monitor the health of the first neonate, the development of anti-D, and the outcome of the next pregnancy

The plan (NYC & Liverpool)

Rh Factor: Prevention of Isoimmunization and Clinical Trial on Mothers

Abstract. *The results on the use of γG-immunoglobulin to Rh factor for the prevention of active immunization of Rh-negative mothers at risk appear most promising. One hundred and seven mothers in the clinical trial have been followed for periods of about 6 months to 1½ years after delivery. Of these, 48 were treated mothers who received 5 ml γG-immunoglobulin to Rh, and 59 were untreated mothers. Of the 48 treated mothers none are actively immunized; seven of the 59 control mothers have become actively immunized to Rh.*

VINCENT J. FREDA
JOHN G. GORMAN
Departments of Obstetrics and Gynecology and *Pathology, Columbia University, New York*
WILLIAM POLLACK
Ortho Research Foundation, Raritan, New Jersey

Science 151:828-830, 1966

The plan (NYC & Liverpool)

Suppression of the Primary Rh Immune Response with Passive Rh IgG Immunoglobulin*

VINCENT J. FREDA, M.D.,
JOHN G. GORMAN, M.D., AND
WILLIAM POLLACK, PH.D.

TABLE 1. *Rh-Immunoglobulin Trial — Combined Results.*

STUDY	MOTHERS RH SENSITIZED			
	BY 6 MO. AFTER DELIVERY		AT SUBSEQUENT DELIVERY	
	Rh-immuno-globulin treated	*not treated*	*Rh-immuno-globulin treated*	*not treated*
Columbia[23]	0/180	14/117	0/27	4/16
Long Beach[24]	0/176	21/176	0/13	1/14
Cornell[25]	0/41	5/58	0/2	1/1
Edinburgh[26]	0/15	0/12	0/0	0/0
Liverpool – Baltimore[27]	0/94	22/98	0/21	4/26
Freiburg[28]	0/76	3/76	0/9	3/7
Totals	0/582	65/537	0/72	13/64

New Engl J Med 277:1022-1023, 1967

How does it really work?

Antibody-mediated immunosuppression (AMIS)

Clearing RBCs before immune system can "see" them

Cloaking the Rh antigen

Fc receptor-mediated mechanism

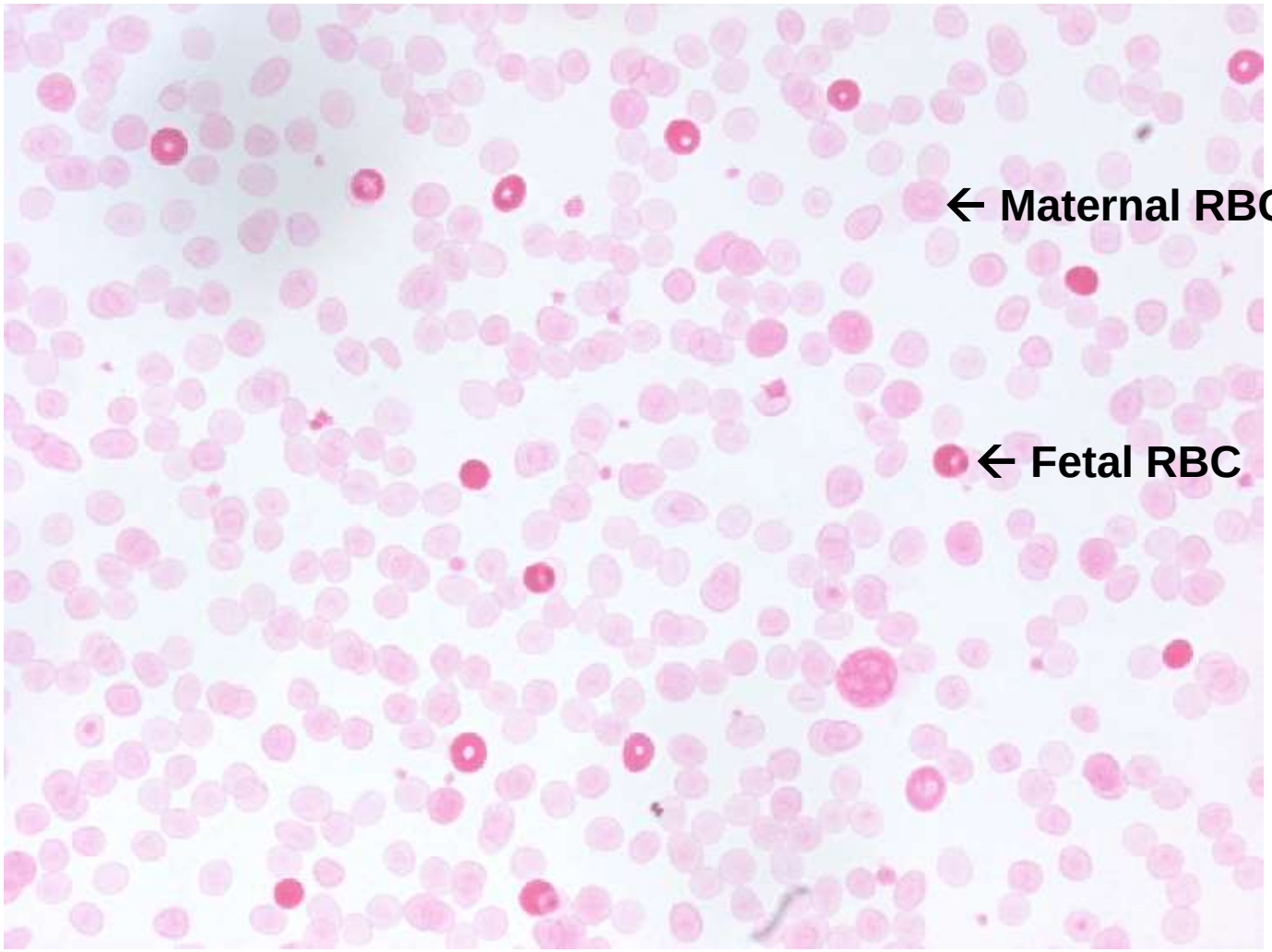
Other?

Remains unknown

When do fetal RBCs enter the maternal circulation?

Alvin Zipursky

Kleihauer-Betke test



Post GR et al. Laboratory Hematology 18:11-13, 2012

FŒTAL ERYTHROCYTES IN THE MATERNAL CIRCULATION

ALVIN ZIPURSKY
M.D. Manitoba
RESEARCH FELLOW IN DEPARTMENT OF PÆDIATRICS

ALAN HULL
B.Sc. Manitoba
RESEARCH ASSISTANT, DEPARTMENT OF BIOCHEMISTRY

F. D. WHITE
Ph.D. Edin., F.R.I.C.
PROFESSOR OF BIOCHEMISTRY

L. G. ISRAELS
M.D., M.Sc. Manitoba, F.R.C.P.(C.)
ASSISTANT PROFESSOR OF BIOCHEMISTRY

From the Faculty of Medicine, University of Manitoba, Winnipeg, Canada

Lancet February 29, 1959, pages 451-452

Fetal RBCs in maternal circulation during pregnancy

Bruce Chown

John Bowman

Rh isoimmunization during pregnancy: antenatal prophylaxis

J.M. Bowman, MD; B. Chown, MD; M. Lewis; J.M. Pollock

A clinical trial of antenatal administration of Rh immune globulin, initially at 34 weeks' and subsequently at 28 and 34 weeks' gestation, in 1357 Rh-negative pregnant women who were delivered of Rh-positive babies, was effective in preventing the development of Rh isoimmunization during pregnancy or within 3 days after delivery. Antenatal prophylaxis with Rh immune globulin will be necessary if the incidence of Rh isoimmunization is to be reduced to its lowest possible level. Antenatal prophylaxis at 28 weeks' gestation is now an insured service in Manitoba.

Canadian Medical Association Journal 118:623-627, 1978

Antenatal RhIg: "surprising" results

IgG anti-D (RhIg) does cross the placenta

Anti-D is detected in fetal plasma

Anti-D does bind to fetal RBCs (i.e., DAT+)

No hyperbilirubinemia → no "disease"

Enhances effectiveness in preventing alloimmunization to Rh(D)

More fruits of Rh disease research

Amniocentesis

Liley curve

Fetal blood sampling

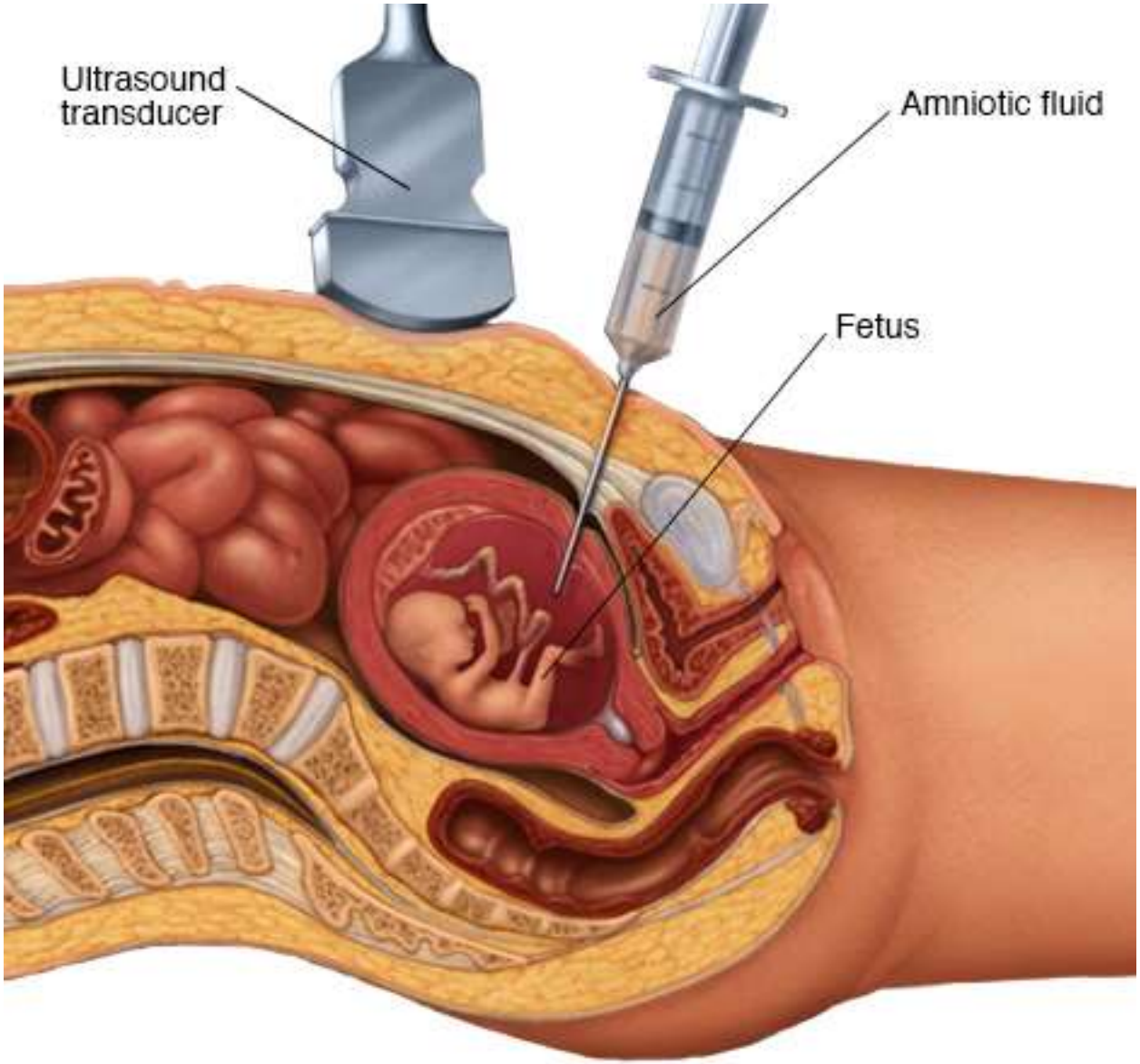
Intrauterine transfusion

Exchange transfusion

“Bili-lights”

Prenatal diagnosis with cell-free DNA

Amniocentesis



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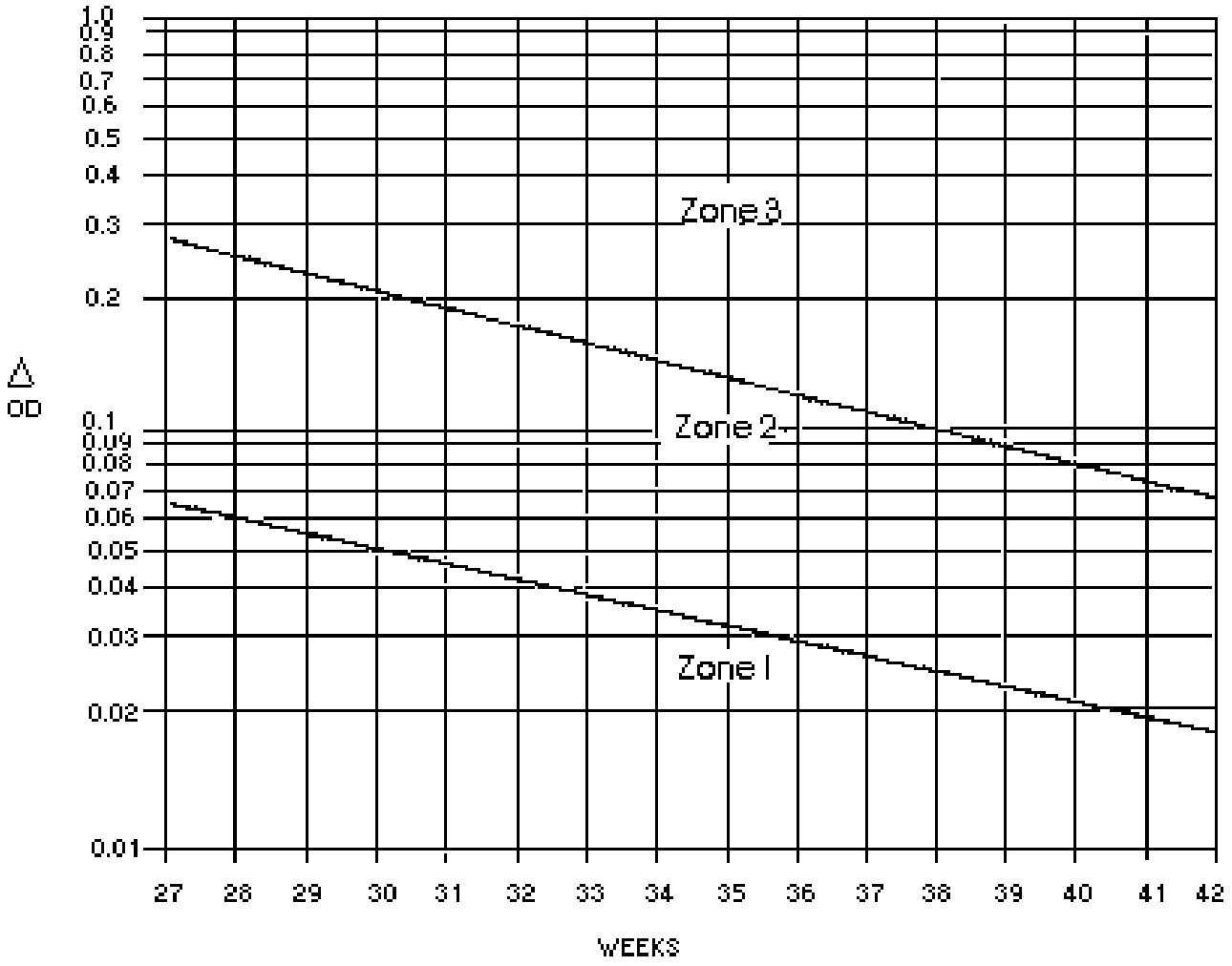
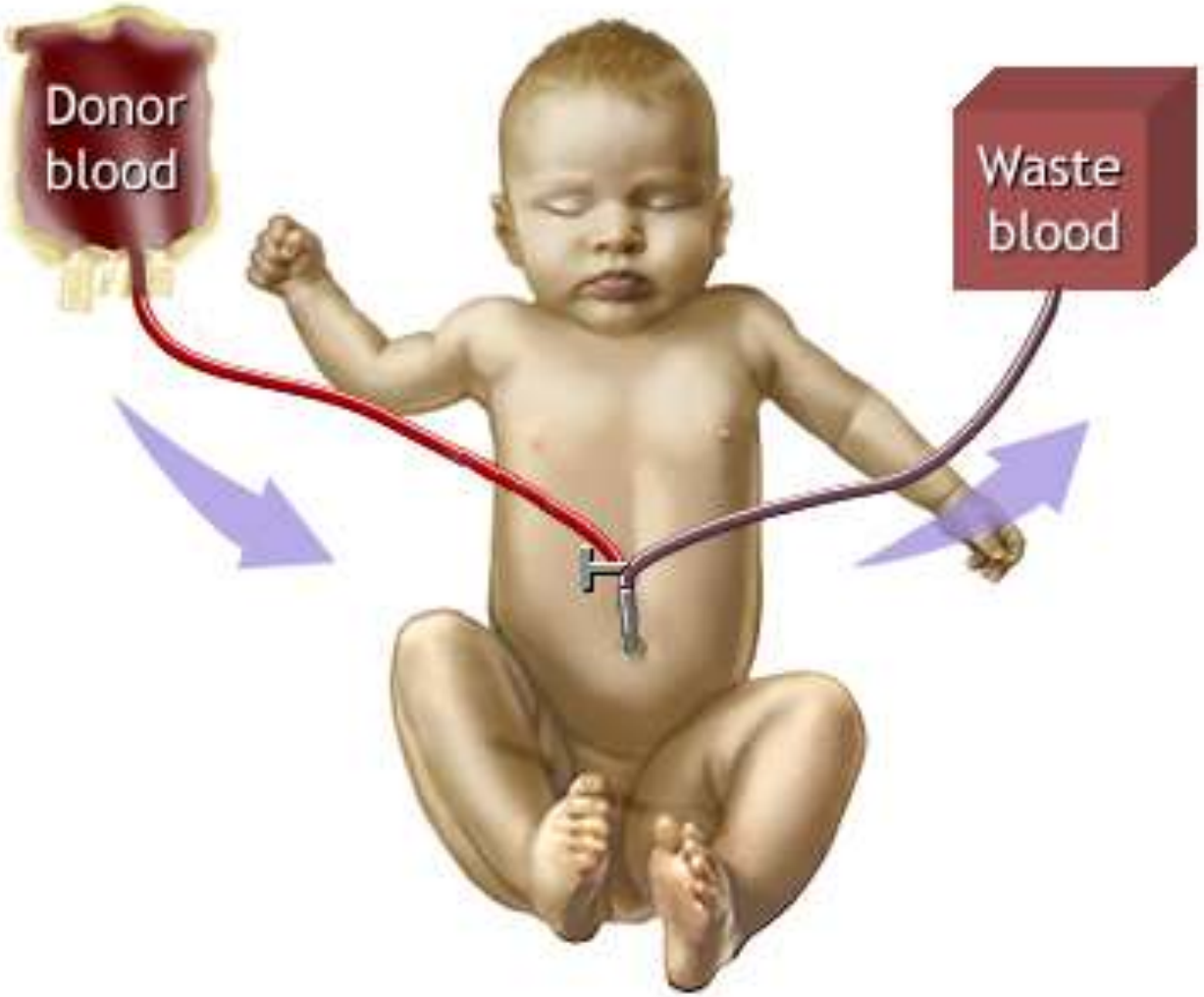
Liley curve with amniotic fluid



Exchange transfusion (post-natal)



“Cell-free” DNA

PRENATAL DIAGNOSIS OF FETAL RhD STATUS BY MOLECULAR ANALYSIS OF MATERNAL PLASMA

Y.M. Dennis Lo, M.R.C.P., N. Magnus Hjelm, F.R.C.Path., Carrie Fidler, Ph.D., Ian L. Sargent, Ph.D., Michael F. Murphy, F.R.C.Path., Paul F. Chamberlain, M.D., Priscilla M.K. Poon, Ph.D., Christopher W.G. Redman, F.R.C.P., and James S. Wainscoat, F.R.C.Path.

Conclusions Noninvasive fetal RhD genotyping can be performed rapidly and reliably with the use of maternal plasma beginning in the second trimester of pregnancy. (N Engl J Med 1998;339:1734-8.)

Modern approach: "Personalized Medicine"

Genotyping to prevent Rh disease: has the time come?

C. Ellen van der Schoot[a,b], *Masja de Haas*[c,d], *and Frederik Banch Clausen*[e]

Purpose of review
In this review, we analyzed the current literature on noninvasive fetal *RHD* typing to answer the question whether the administration of RhIg to prevent D-alloimmunization during pregnancy can be safely guided by fetal *RHD* typing.

Recent findings
Recently the first centers that implemented large-scale nationwide fetal *RHD* typing in the second trimester for targeted RhIg administration have published their studies evaluating the diagnostic accuracy of their screening programs. These data show that fetal *RHD* typing in a routine setting is, at least in a population of European descent, accurate enough to guide both antenatal and postnatal immunoprophylaxis.

Summary
Depending on the ethnic background and the organization of pregnancy care the decisions regarding RhIg can be safely and cost-effectively based on fetal *RHD* typing by a duplex real-time PCR. As a result, the unnecessary administration of 40% of antenatal RhIg can be prevented, and cord blood serology can be omitted.

Current Opinion in Hematology 24:544-550, 2017

Modern approach: "Personalized Medicine"

Other causes of HDFN are more prevalent

ABO	Low[b] risk for disease, in general mild[a], incidentally severe[a]
Rh	
D	High[b] risk for disease, often (very) severe, otherwise mild
c	High risk for disease, (very) severe or mild
E	Medium[b] risk for disease, sometimes severe, but mostly mild
Other Rh antigens	Medium risk for disease, incidentally severe, but mostly mild
Kell	
K	High risk for disease, (very) severe or mild
Other Kell antigens	Medium risk mild to severe disease
Duffy	
Fy^a/Fy^b	Medium risk for disease, mostly mild
Kidd	
Jk^a/Jk^b	Low risk[b] for disease, only mild
MNS	
M, N, S, s	Low risk[b] for disease, mostly mild disease, very rarely severe

de Haas et al. Vox Sanguinis 109:99-113, 2015

New activities at Columbia
&
New York-Presbyterian Hospital

Columbia University Medical Center

Columbia University
Department of Pathology and Cell Biology

Inaugural Dr. John G. Gorman Lectureship for Excellence in Transfusion Medicine

Lecture and Reception

Friday, September 23rd, 2016

Columbia University Medical Center
Fenoglio Library PH15W
630 West 168th Street
New York, NY 10032

Reception 4:00 p.m.
Lecture 5:00 p.m.

"From Type-and-Screen to Type-and-Gene: Everyday Uses of RBC Blood Group Genotyping"

Dr. Glenn Ramsey, M.D.
Director of Transfusion Medicine, Northwestern University, Chicago, IL

Dr. John G. Gorman
Co-Creator – RhoGAM ®
Former Professor of Pathology, Columbia University
Former Director, Blood Bank at Presbyterian Hospital

Dr. Glenn Ramsey
Professor of Pathology
Northwestern University Feinberg School of Medicine


From Type-and-Screen to Type-and-Gene:
veryday Uses of RBC Blood Group Genotyping
The 2016 John G. Gorman Lecture
Department of Pathology and Cell Biology
Columbia University

The Department of Pathology and Cell Biology invites you to the

2nd Annual Dr. John G. Gorman

Lectureship for Excellence in Transfusion Medicine

Lecture and Reception

Friday, September 15th, 2017

Reception 4:00pm
Lecture 5:00pm
Columbia University Medical Center
Roy & Diane Vagelos Education Center
104 Haven Ave, 4th Floor Room VEC401, New York, NY 10032

Dinner 7:00pm
Gabriel's Bar & Restaurant
11 W. 60th Street, New York, NY, 10023

"IgG Subtype Affects the Immune Regulatory Properties of Anti-RBC Immunoglobulin; Implications for Mechanism of Anti-D Immune Prophylaxis"

Dr. James C. Zimring, MD, PhD

Director and Chief Scientific Officer, BloodworksNW Research Institute
Professor, Department of Laboratory Medicine and Department of Medicine,
University of Washington School of Medicine
Seattle, WA

Connie Westoff/Christine Lomas-Francis/Jim Zimring

The Department of Pathology and Cell Biology
at Columbia University Medical Center

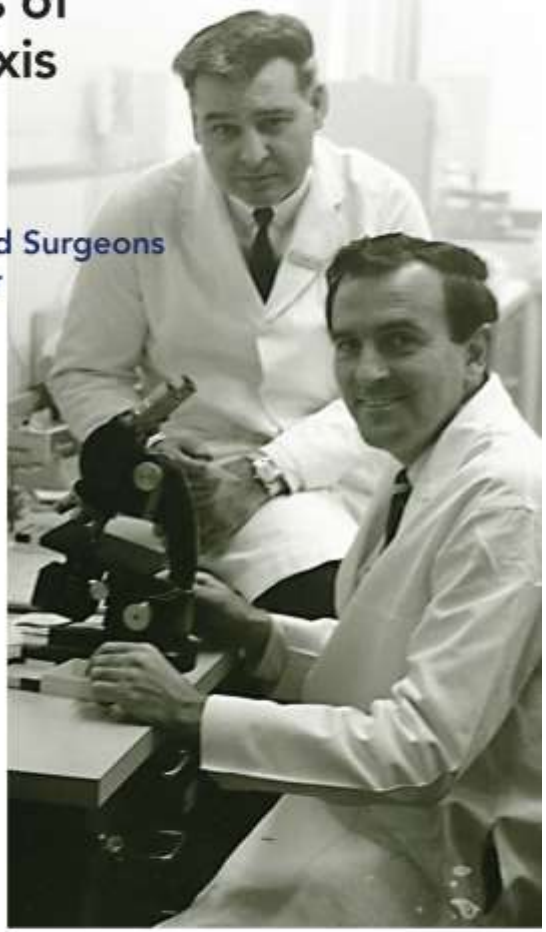
Invites you to join us

Celebrating 50 Years of Rh Disease Prophylaxis

Monday, February 5, 2018

The Faculty Club
Vagelos College of Physicians and Surgeons
630 West 168th Street, 4th Floor
New York City

For more information and to RSVP, please contact Marquett Kennely at mk4067@cumc.columbia.edu or at (212) 305-2204.



MORNING PROGRAM: 10:30–11:30 AM

Celebrating a Half Century of Success and Looking Ahead

Rh disease once claimed the lives of approximately 10,000 babies each year in the United States alone. In the 1960s, Dr. Vincent Freda, an obstetrician, and Dr. John Gorman, the Director of the Blood Bank, both at Columbia, conducted pioneering research that led to a breakthrough in disease prophylaxis (RhoGAM®), effectively eradicating hemolytic disease of the newborn due to anti-Rh antibodies. Today, alongside patients and their families, we celebrate the 50th anniversary of that innovation with a special program that will address the success of this standard of care and the vision for making this therapy available to moms and babies around the world. Notable panel members will include pioneers in the history of this achievement as well as representatives of major international organizations dedicated to spreading its benefits worldwide.

AFTERNOON PROGRAM: 2:00–3:00 PM *Grand Rounds*

Immunoprophylaxis Against Red Blood Cell Antigens: Successes and Failures

Featured speaker:
Jeanne Hendrickson, MD; Associate Professor of Laboratory Medicine and of Pediatrics;
Associate Director, Transfusion Medicine Service, Yale University School of Medicine

Dr. Hendrickson is a pediatric hematologist and transfusion medicine specialist. Her research interests include investigating the induction and consequences of red blood cell alloantibodies in transfusion and pregnancy situations, in murine models and in human clinical settings.

The panel (with Gorman looming)

Paolo Marcucci (Kedrion Biopharma)

The International Group

The first patient

Dr. David Landers/Marianne Cummins/Alvin Zipursky

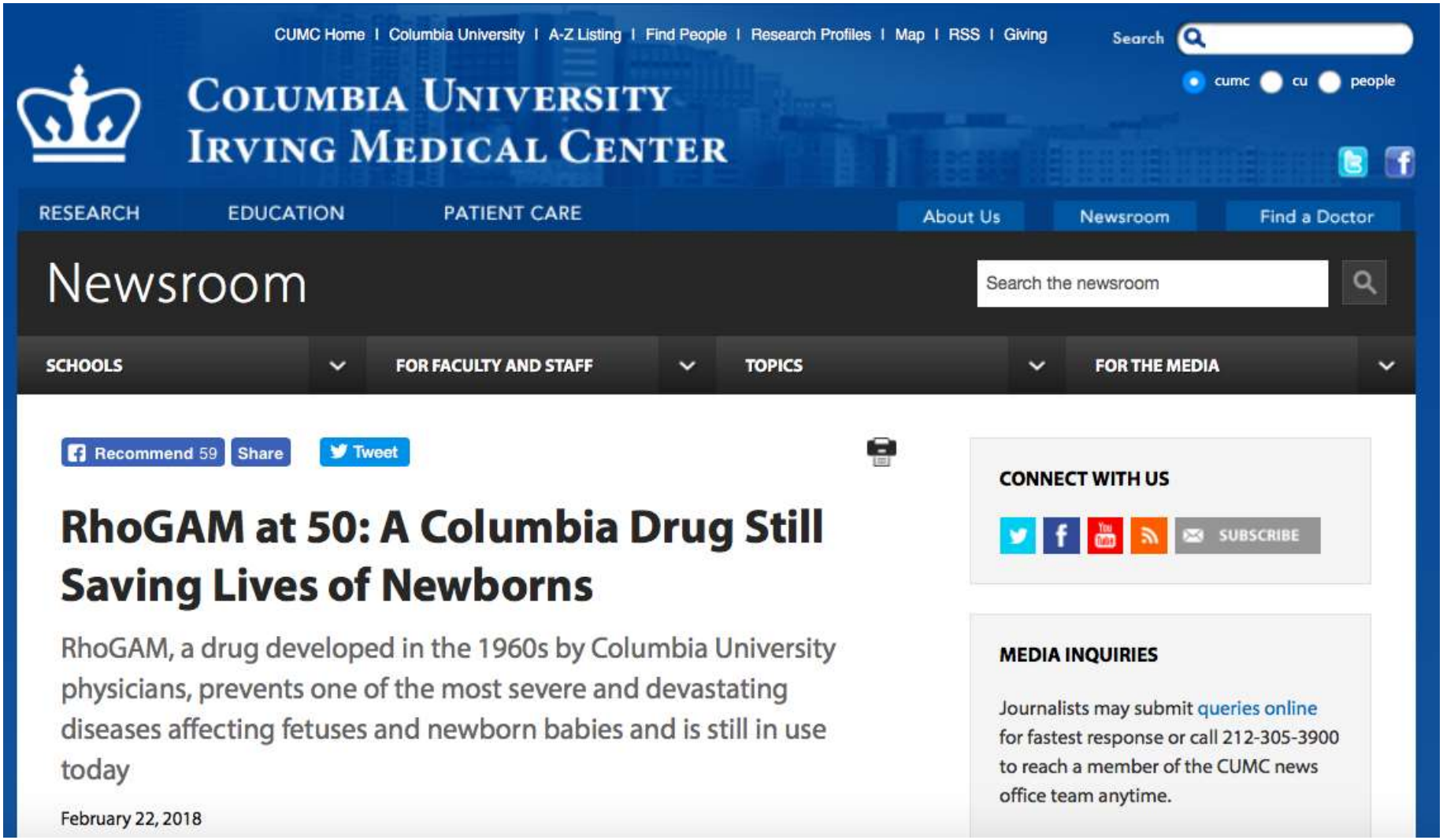
Next generation

Malcolm Pollack/Charlie Clark/Pam Freda

Lady Clarke, Sir Cyril Clarke, and Charlie Clark

Marcela Contreras/Alvin Zipursky

Jeanne Hendrickson (Yale): Keynote Speaker



http://newsroom.cumc.columbia.edu/blog/2018/02/22/rhogam-at-50-a-columbia-drug-still-saving-lives-of-newborns/

https://vimeo.com/254747528

Food for thought?

How does RhIg actually work?

ABO incompatibility protects against immunization to D:
- **IgM anti-A and/or anti-B induces “cross protection”**

But, IgG anti-D protects against only against immunization to D (?)
- **IgG anti-D provides no “cross protection” (?)**

Thus, would IgM anti-D (or anti-?) provide general protection against other RBC alloantigens?

Can these RhIg-like approaches be exploited to suppress or prevent other immune-mediated diseases?

There is “no” immunization to D during first pregnancy.
- **Why is that, really?**
- **Is there something special about fetal antigens during pregnancy?**

Rh disease: Are we done?

Not yet…

Thank you