Knowing Where We Came From: History of Clinical IVF

Thomas B. Pool, Ph.D., HCLD
Fertility Center of San Antonio
San Antonio, Texas
“The vast majority of human beings dislike and even actually dread all notions with which they are not familiar...Hence, it comes about that at their first appearance, innovators have generally been persecuted, and always, derided as fools and madmen.”

Aldous Huxley
author
Brave New World, 1932
“Most human beings have an almost infinite capacity for taking things for granted”.
Acknowledgements

I want to thank the following individuals for their altruism and assistance in preparing this presentation for the College of Reproductive Biology:
Peter Brinsden (l) with James Watson and Bob Edwards
Kay Elder
Professor Sir Richard L. Gardner
Jacques Cohen

Henry Leese
Aristotle (384-322 BC) proposed the theory that children are a product of “the mingling of male and female seed”. This opposed the prevailing theory that children were from the male seed and women merely the “receptacle for the child”.

William Harvey (1578-1657) studied the fertility of the King’s herd of deer, and wrote: “De generatione animalium” in 1651, in which occurs the well known phrase: “Ex ovo omnia” – “from the egg is everything”.

Antonj van Leeuwenhoek (1632-1723) carried out the first studies on human sperm with the newly invented microscope.

Report of homunculus (miniature human within a sperm) by Dalenpatius (1699) turns out to be a hoax!

Van Leeuwenhoek’s drawings of sperm
The early history of IVF

• Spallanzani (1729-1799), an Italian Scientist, studied semen in mammals. He performed artificial insemination (AI) in a spaniel bitch – the first recorded instance of AI. He is also credited with the first freezing of sperm in 1776.

• John Hunter in c.1790 performed the first successful human AI for a man with hypospadias.

• Carl Ernst von Baer (1792-1876). In 1826 he identified mammalian oocytes in the ovaries of a bitch. He is credited with being “the father of modern embryology”.

• Henry Nelson (1852), Newport (1853), van Beneden (1854) and Hertwig (1876) all report observing the process of fertilization in ascaris, amphibians and mammals, respectively.
The early history of IVF

• Theodor Boveri (1880’s – 1912)

Reduction of chromosome number during egg maturation.

Along with Sutton, advanced the chromosome model of inheritance.

Discovered the centriole.

Nominated for Nobel Prize.

Work done with *Ascaris* and sea urchins; Sutton, with grasshoppers.
The early history of IVF

• Walter Heape (c. 1890) of Cambridge, UK, transplanted embryos into rabbits.

Embryos were washed from the oviducts and transferred to the recipient with little laboratory exposure – first transfer of a “segmented ova” (cleaved embryo).

Siblings were mixed as the Belgian had been bred.

Of interest, experiments were performed either in his laboratory in Cambridge or in Prestwick near Manchester, his home – parallels the trek of Bob Edwards during the pioneering days of human IVF with Steptoe.
The early years of human IVF

Events leading to human IVF:

• Pincus and Enzman (1934) propose that human oocytes could develop normally in vitro.
• Dr. John Rock (1937) suggested “ectogenesis” as a means of treating tubal disease in women.
• M.F. Menkin and J. Rock (1948) attempt in vitro fertilization of human oocytes with modest results.
• Polge (1949) reports the first practical freezing of animal spermatozoa using glycerol.
• Chang and Austin (1951) independently identify capacitation.
• McLaren and Biggers (1958) produced young from the transfer of blastocysts grown in Whitten’s medium to recipient mouse.
• Chang (1959) performs successful IVF in the rabbit.
Some major events and findings in the history of IVF*

384-322 BC Aristotle writes the first account of embryology
1561 Fallopius provides first correct anatomical description of the Fallopian tube
1677 Discovery of mammalian spermatozoa: A van Leeuwenhoek
1797 Recovery of embryos from rabbit Fallopian tube: W C Cruikshank
1827 Identification of an egg in a mammalian ovarian follicle: von Baer
1878 Understanding that fertilisation requires the fusion of one sperm with one egg: Hertwik (sea urchin), Van Beneden (rabbit) & Fol (starfish)
1890 First embryo transfer (in rabbit) W. Heape
1912 First culture of mammalian embryos: Brachet
1930 First experiments on IVF (rabbits): Pincus
1932 Publication of *Brave New World*: A Huxley
1944 First attempt at IVF using human oocytes: Rock & Menkin
1949 Culture medium in which 8 cell mouse embryos developed to blastocysts J Hammond Jr
1951 Capacitation in sperm: Chang : Austin
1958 Transfer of cultured mouse blastocyst to the uterus of another female followed by birth of live young (McLaren & Biggers)
1959 Unequivocal demonstration of IVF in the rabbit (Chang)
1969 Demonstration of human oocyte fertilisation in vitro: Edwards, Bavister & Steptoe
1972 Successful freezing of mammalian embryos (mouse): Wilmut : Whittingham
1976 First human pregnancy (ectopic) after IVF and embryo transfer: Steptoe & Edwards
1978 Birth of first child following IVF and embryo transfer: Steptoe & Edwards

*courtesy of Henry Leese*
The Development of Human IVF
Father of *In Vitro* Fertilization, Bob Edwards

Bob with Kay Elder, Bourn Hall, Louise Brown’s 30\textsuperscript{th} birthday party, 2008
SIR ROBERT GEOFFREY EDWARDS C.B.E
27 September 1925 – 10 April 2013
Elected F.R.S 1984
By SIR RICHARD GARDNER F.R.S
Department of Biology, University of York,
York, YO10 5YW
Bob Edwards – the early years

• Born in 1925 in Batley to Samuel, an engineer’s laborer and Margaret Edwards, a machinist

• Two brothers, Samuel and Harry Raymond

• Local school evacuated to Blackpool due to WWII but returned home in 6 mos. – hiatus from school put him into agriculture

• Entered Army in 1943 – instructor in driving tracked vehicles

• 1948, entered University College of North Wales studying agriculture but lost interest and turned to zoology (Zoology was headed by F.W. Rogers Brambell, FRS 1949).

• Accepted to Edinburgh but took menial jobs to pay for first three months (harvest laborer, dock laborer unloading bananas, hauled heavy flour sacks at mills, office boy at newspaper)
C.H. Waddington, FRS 1947
Head – Institute of Animal Genetics
Edinburgh University
• Bob performed well in the Postgraduate Diploma course and Waddington invited him to stay for his Ph.D.

• Studied the modification of chromosomal complement of the mouse embryo under Dr. Alan Beatty

• Made numerous observations of the timing of the events of oocyte maturation, fertilization and early embryonic development under normal and abnormal chromosomal conditions

• Tutored postdoctoral fellow at Edinburgh, Mary Lyon, on reproductive physiology of the mouse.
• Bob met and married geneticist Ruth Fowler at while at Edinburgh in 1954. Pioneered concept of ovulation induction in the mouse.

• Spent one year at Cal Tech with Albert Tyler in reproductive immunology

• Five years as a postdoctoral fellow at Mill Hill (NIMR) with Sir A.S. Parkes (FRS1933) and studied maturation in vitro of mouse, rat, hamster, etc.

• Parkes moves to Cambridge in 1961 and invites Bob to join him in 1963 – committed to fertilizing human oocytes in vitro, but no source of oocytes.
Parameters of spontaneous human meiosis

Capacitation – the key to fertilization
- Washed sperm (swim up)
- Cervical mucus
- Endometrium
- Fallopian tube
- Rabbit
- Cynomolgus monkey
Howard Jones and Bob Edwards
MATURATION IN VITRO OF HUMAN OVARIAN OOCYTES

R. G. EDWARDS
Ph.D. Edin., D.Sc. Wales

From the Division of Medical Genetics, School of Medicine, The Johns Hopkins Hospital, Baltimore, U.S.A., and the Physiological Laboratory, University of Cambridge*
• Raoul Palmer of France, a pioneer in laparoscopy, developed a technique to collect oocytes laparoscopically in 1961. Patrick Steptoe of the UK learns this technique from Palmer.

• Edwards and Steptoe begin collaboration in 1968.
Barry Bavister and Bob Edwards, Cambridge
pH-Dependence of Hamster IVF

Final Road to Success

In 1973, a group from Australia, led by Professors Carl Wood and John Leeton reported the first human IVF pregnancy, but it turns out to be a “biochemical pregnancy”.

Steptoe and Edwards in 1976 announce the first clinical IVF pregnancy – but it is found to be an ectopic pregnancy.

After 102 failed embryo transfers (ET), Steptoe and Edwards achieve the first ongoing human IVF pregnancy in Mrs Lesley Brown, who had severe tubal factor infertility.
The World’s First IVF Baby is Born – 25 July 1978

On 25 July 1978, Louise Brown was born by Caesarean section at Oldham General Hospital, England – the first baby to be born as a result of IVF in a human.
Born safe—the world’s first test-tube baby weighs in at 5lb 12oz and mother’s delighted

By Harry Pugh

It’s a girl! The world’s first test-tube baby was born late last night. She was born near midnight, both mother and baby are well.

They’re very much alive, the mother, 32-year-old Mrs Lesley Brown, is “doing well” and the baby is perfectly formed. A living miracle weighing in at 5lb 12oz.

The birth will bring world acclaim for Britain’s medical profession, after 12 years of research.

The two men who have created life in a test tube, gynaecologist Mr Patrick Steptoe and scientist Dr Robert Edwards, were said to be “overjoyed.” They had taken an egg from the patient’s ovary, fertilised it with her husband’s sperm, and inserted it back into her womb.

It’s a great moment in medical history. The baby is the first to be conceived outside the womb and carried to term. The technique is known as in vitro fertilisation.

They worked with ‘test tube’ scientist

Birth breakthrough thrills new EVMS profs

By Julia Wallace

Norfolk — Two new Eastern Virginia Medical School professors who worked with a member of the English test-tube baby team were thrilled with the Wednesday birth.

“We’ve just delighted,” said Dr. Howard Jones, 67, former head of the genetics lab at Johns Hopkins University in Baltimore. “We know how hard he had worked.”

Jones and his Minneapolis wife, Corresponding author, both geneticists, worked with Dr. Don Edwards at Baltimore during the summer of 1986.

Edwards, a basic scientist, is on the English team. They worked with ‘test tube’ scientist Dr. Robert Edwards, who was in the United States for the first time in 12 years.

The egg was fertilised outside the womb, and the embryo was then allowed to develop in the womb of a surrogate mother.

The baby is the first to be conceived outside the womb and carried to term. The technique is known as in vitro fertilisation.

Howard and Georgeanna Jones
Bourn Hall Clinic, Bourn, England
Dr. Peter Robert Brinsden, MBBS, MRCS, LRCP, FRCOG

Medical Director, Bourn Hall Clinic, 1989-2006;
Consultant Medical Director, 2006-present
HONOURS AND AWARDS

Medals and Prizes

1970  Medal of the American Fertility Society
1971  Darwin Medal, Institute of Biology, UK
1973  Adair Award, American Gynecological Society
1980  Serono Prize, American Fertility Society
1985  Spanish Fertility Society Gold Medal
1987  Gold Medal, City of Toulouse, France
1988  CBE
1989  Co-winner of the King Faisal International Prize for Medicine
1991  Steptoe Memorial Medal and Prize, British Fertility Society
       Marshall Medal, Society for the Study of Fertility, UK
Barbara Eck Manning Award, Resolve, USA
1994  Berthold-Gedachtnis Medal, German Society of Endocrinology
1996  Pierre Soupart Lecture, Axel Munthe Award, Naples
1998  Gold Medal, University of Sassari, Sardinia
1999  Gold Medal Award of the International Federation of Associations of
       Anatomists Malpighi Symposium, University of Rome
2000  Bertarelli Foundation Award in Reproductive healthcare
       FIGO Recognition Award to non-Obstetricians/Gynecologists
       Rotary Club Chennai “For the Sake of Honour Award”
2001  Albert Lasker Award for Clinical Medical Research
       Nature Medicine Prize
2002  Distinguished Lifetime Achievement Award, Reproductive Biology
       Professional Group ASRM
       Robert Edwards Award, American Infertility Association, New York
       The Grand Hamdan International Award for Obstetrics and Gynecology
       (Infertility), Dubai
2003  Award of the Egyptian Ministry of Health
2004  Pioneer in Stem Cell Award, Pittsburgh Development Center
2005  Eardley Holland Gold Medal, Royal College of Obstetrics and Gynaecology,
       London, UK
2006  30th Joseph Bolivar DeLee Humanitarian Award, Chicago Lying-in Hospital
       Board of Directors & Departement of Obstetrics and Gynecology, University
       of Chicago

Courtesy of Sir Richard Gardner
2007 Chevalier dans l’Ordre National de la Legion d’Honneur, Paris
    Jacques Salat-Baroux Prize, Paris
    Life Achievement Award, the German Society for Reproductive Medicine
2008 Pride of Britain Award- Lifetime Achievement
2010 Nobel Prize in Physiology or Medicine
2011 Knighthood

Membership of Academies, etc.

1983 Honorary Member of the French Society for Infertility
1984 Fellow of the Royal Society
1985 Founder member of the European Society for Human Reproduction and
    Embryology (ESHRE)
    Honorary Citizen, Bordeaux, France
    Life Fellow of Australian Fertility Society
    Fellow ad eundem, Royal College of Obstetricians and Gynaecologists
1986 Honorary Member of the Royal College of Physicians
1988-1990 President, Ribblehead Sheep Show
    Honorary President  British Fertility Society
1990 Honorary Member , Pacific Coast fertility Society
1992 Honorary Fellow, German Society of Gynecology and Obstetrics
    Honorary President, French Gynecological Society
    Keys of San Diego City
1993 Honorary Fellow, Royal Society of Medicine
    Honorary Fellow , European Society of Human Reproduction and Embryology
1995 Honorary Member, Italian Society of Anatomy
1998 Honorary Member, Association of Clinical Embryologists, UK
    Honorary President , Alpha – International Society for Scientists in
    Reproductive Medicine
    Honorary Member, Greek Fertility Society
    Honorary Fellow, International Federation of Fertility Societies, San Francisco
1999 Honorary Member of the Middle East Fertility Society
    Patron, UK National Gamete Donation Trust

Courtesy of Sir Richard Gardner
2000  Life membership, Indian Society for the Study of Reproduction and Fertility
2001  Honorary Membership, Society for Reproductive Endocrinology and Infertility, American Society for reproductive Medicine

Courtesy of Sir Richard Gardner
Robert G. Edwards, September 27, 1925 – April 10, 2013

2010 Nobel Prize, Physiology or Medicine
The early years of Human IVF

• 1980. Candice Reed, the World’s third IVF baby is born in Melbourne, Australia, as a result of the pioneering work of Professors Carl Wood and Alex Lopata.

• Altruism and expertise of Dr. Alan Trounson helped new programs worldwide in the early 1980’s.
In Vitro Fertilization Comes to America
Memoir of a Medical Breakthrough

Howard W. Jones, Jr., M.D.
Howard and Georgeanna Jones

- Mandated retirement from Johns Hopkins in 1978

- Took positions at the Eastern Virginia Medical School in Norfolk, Virginia

- Moved to Norfolk the day Louise Brown born

- Based on television interview, previous patient used family foundation to donate $5,000 for microscope and incubator
The Team
1979 – 1980

- Howard and Georgeanna Jones
- Anibal Acosta
- Jairo Garcia
- Lucinda Veeck
- Two secretaries
- One office nurse
- Two O.R. nurses
- One clinical fellow/one computer wiz resident
- Four EVMS-ODU collaborators (Sandow, Wright, Witmyer, Wortham)
First Problems

• Certificate of Need

• Public hearing Oct. 31, 1979

• Extreme controversy

• General misunderstanding of the process
Test-tube baby lab OK'd; foes pledge court battle

By SANDY BAKSYS and JULIA WALLACE

Ledger-Star Staff Writers

NORFOLK — State Health Commissioner James Kenley today approved plans for an in vitro fertilization lab at Norfolk General Hospital, clearing the way for the first test-tube baby clinic in the United States.

Kenley, in a phone call to Norfolk General Hospital officials this morning, said the clinic violates no state or federal law.

Officials at the hospital and at Eastern Virginia Medical School, which is sponsoring the program, expressed delight with the decision. Doctors say they hope to try for the first pregnancy in March.

However, the president of the Tidewater Chapter of the Virginia Society for the initial stages of the program.

"We have great confidence that we will win the court battle if it goes that far," he said. The hospital, however, said it has not determined how far it will go in the courts.

Charles Dean, president of the Tidewater Chapter of the Virginia Society for Human Life, said he will appeal the decision.

"We'll never give up. That's exactly how we feel," Dean said.

"There's a lot of pressure against it. And a lot more is mounting. This isn't the end of it," Dean said.

He said the controversy was clouded by politics and no meaningful debates were held.

"The development and prestige of the Kenley would approve the clinic after so much public opinion against it.

He said the Virginia Society for Human Life will lead all court appeals. The funds for the appeals will come from individual donations, he added.

The lab, located next door to the obstetrics/gynecology unit at Norfolk General, is near completion. About $25,000 of hospital reserves were used to renovate and buy equipment.

During the in vitro process, a single egg will be removed from a woman within two hours of ovulation. The egg will then be fertilized with her husband's sperm in a glass dish. Any resulting embryo will be reimplanted in the woman's womb at the 8 or 16-cell stage, about two days after fertilization.
Injunction Sought on Baby Lab

By SUSAN LOCKAMY
Virginian-Pilot Staff Writer

NORFOLK—Opponents of the nation’s first “test-tube” baby project are asking state Atty. Gen. J. Marshall Coleman to help them block the opening of the project’s laboratory at Norfolk General Hospital.

The Tidewater Chapter of the Virginia Society for Human Life, Inc., claims that State Health Commissioner James B. Kenley violated state requirements in granting on Jan. 8 the certificate-of-public-need for the lab.
In-Vitro Clinic Is Still Facing Firm Opposition

By MARIANNE ROBERSON
Staff Reporter

NORFOLK — Right-to-life groups' means possible to have the clinic closed.

Some of their efforts, such as a public statement that the Norfolk clinic might be freezing human embryos.
Living With the LH Surge

• Midnight, 1:30 am, 4:00 am cases

• Small team gathered with scientific enthusiasm

• Often too late and patient had ovulated

• On call around-the-clock

• Snowstorms (36 inches), floods, and hurricanes
1980

41 Patients monitored
19 Oocytes from natural cycles
13 Transfers
0 Pregnancies

Decision made by Dr. Georgeanna Jones to attempt mild ovarian stimulation in 1981 despite lack of success with these methods in the U.K.

How to stimulate normally-ovulating patients?
How to time hCG administration?
1981

13 attempts, some without oocytes, some without fertilization . .
World’s First IVF Conference is held at Bourn Hall in 1981

The World’s leading pioneers in IVF meet at Bourn Hall in September 1981. Steptoe, Purdy and Edwards are seated on the right.
Test-tube baby born in Norfolk is first in U.S.

By TERRY CARTER and ANU OGDEN
Ledger-Star Staff Writers

NORFOLK — America's first "test-tube" baby was born at 1:30 a.m. today. The girl and her parents were delivered by Dr. Maureen C. Andrews, chairman of the Department of Obstetrics and Gynecology at EVMS.

"The baby is in good condition," Andrews said. "It is just a symbol of the process, and I think a very happy one.

"I am very pleased to announce that Mrs. Carr has had a successful outcome. She was delivered by cesarean section and is doing well. The baby is healthy and strong.

"The procedure was a success, and the mother and baby are both doing well.

Andrews emphasized that the baby's

This is just a symbol of the process, and I think a very happy one.

— Dr. Maureen C. Andrews

The baby was delivered by Cesarean section at 1:30 a.m. today. The mother, Mrs. Carr, was admitted to the hospital yesterday at 5 p.m. The child was born at 1:30 a.m. today, weighing 5 pounds, 10 ounces. The mother is doing well and will have a normal recovery.

The baby, who will be named Elizabeth, is the first "test-tube" baby born in the United States. The procedure was performed by Dr. Maureen C. Andrews, chairman of the Department of Obstetrics and Gynecology at EVMS.

Andrews said the procedure was successful and the baby is in good condition.

"The baby is in good condition," Andrews said. "It is just a symbol of the process, and I think a very happy one.

"I am very pleased to announce that Mrs. Carr has had a successful outcome. She was delivered by cesarean section and is doing well. The baby is healthy and strong.

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Andrews emphasized that the baby's
TEST-TUBE BABY BOOM

Elizabeth Carr, America's first in vitro baby, at the lab where she was conceived
Dr. Georgeanna Takes On The Norfolk Press

- Newspaper article published in the Virginian Pilot five days after Elizabeth’s birth stating that abortions were mandated without parental consent by our clinical staff for patients carrying abnormal IVF fetuses

- GSJ sues for libel and wins a settlement; this money was donated for developing research projects
Some Pioneers and Pioneering Events in the IVF Laboratory

1. Embryo Culture
2. Cryobiology
3. Micromanipulation for andrology
4. Reproductive Genetics
# Somatic Cell Media Used for Human IVF and Embryo Culture

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<th>Year</th>
<th>Investigator</th>
<th>Medium</th>
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<tr>
<td>1880</td>
<td>Ringer</td>
<td>salt soln</td>
<td>amphib. heart</td>
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<td>1907</td>
<td>Tyrode</td>
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<td>1950</td>
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<td>F-10</td>
<td>somatic</td>
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Prof. Yves Menezo
B-1, B-2 Media
Dr. Patrick Quinn
HTF, Quinn’s series media
Prof. Henry Leese

**Students:**

David Gardner  
Daniel Brison  
Joe Conaghan  
Karen Martin  
Nicki Boland  
Laura Hewitson  
Franchesca Houghton  
Roger Sturmey

**Visiting Scientists:**

Jeremy Thompson  
Steve Downs
The ‘new generation’ media

**The special importance of Amino Acids**
Bavister (hamster)
Rieger (bovine)
Gardner and Lane (mouse/sheep): formulation of ‘SOFaa’
Hardy and Devreker (human)
Glutamine: Ammonium

Menezo: biochemical studies on amino acids and role of BSA/serum as a source of amino acids (B2 medium)

Forerunner of work which related amino acid profiling to developmental outcome: human/bovine (Houghton, Brison, Sturmey) oocyte (Picton)

**Pivotal work on glucose** (Gardner and Lane)

In addition to growing more blastocysts – search for methods of embryo selection

slide courtesy of Henry Leese
Prof. David K. Gardner
SOFaa, G-series media

Gardner → Lane → Zander-Fox → McPherson
Let the embryo choose: Empirical optimisation

Simplex optimisation

- **John Biggers, Joel Lawitts** (1991)
- Use of engineering-based strategy to optimise constituents for mouse embryo culture (especially, overcoming the ‘2-cell block’)
- Requires very high numbers of embryos for testing
- Resulted in KSOM and KSOM aa: excellent, if unphysiological media for growing mouse embryos
- Impossible to optimise every component
- ‘No guarantee that the maximum response is the natural response’ (**Summers and Biggers 2003**)
- Inappropriate strategy for optimising human embryo culture media – **but**, an outstanding achievement!

slide courtesy of Henry Leese
Dr. Stanley P. Leibo
Dr. Masa Kuwayama
Dr. Peter Mazur

Dr. Greg Fahy and Dr. Bill Rall

B. Lassalle, J. Testart, J.P. Renard

Dr. Jacques Cohen

Dr. James Stachecki
Micromanipulation for Male Factor

Dr. Jacques Cohen, RBA lab
PZD

Dr. Michael Tucker, RBA
UZI, SUZI
Micromanipulation for Male Factor

Dr. Gianpero Palermo
ICSI

Dr. Michael Tucker
DSI
Preimplantation Genetic Diagnosis

Dr. Alan Handyside

Dr. Marcus Hughes
Preimplantation Genetic Diagnosis

Sir Richard Gardner

trophectoderm biopsy
Certification for US Embryologists

Dr. Brooks Keel

Dr. Richard Rawlins
Thank you.