Photo by Jack Pearce, reproduced with permission

Year	Discovery	Key Authors
1954	DNA carries genetic information	Crick, Franklin, Watson, Wilkins
1956	Human karyotype agreed as 46	Tijo, levan, Ford, Hamerton, Levan, Tijo
1958-62	Totipotentiality of nuclei established by nuclear transfer	Gurdon
1958-61	mRNA described and confirmed	Jacob, Monod and Woolf
1959	chromosomal basis of Down and Klinefelter syndrome established	Jacobs, Lejeune
1960	Chromosome numbering agreed	Denver conference

J. Endocrin. (1957) 15, 374–384

INDUCTION OF SUPEROVULATION AND PREGNANCY IN MATURE MICE BY GONADOTROPHINS

By RUTH E. FOWLER and R. G. EDWARDS

From the Institute of Animal Genetics, West Mains Road, Edinburgh 9

(*Received* 21 *March* 1957)

SUMMARY

1. The injection of 1 i.u. pregnant mares' serum (PMS) followed after 40 hr by 2 i.u. human chorionic gonadotrophin (HCG), or of 3 i.u. PMS followed by 3 i.u. HCG into mature female mice selected at random with regard to their oestrous cycle induces oestrus and mating in approximately 75 %, and ovulation in 99 % of them.

2. The induction of superovulation depends on the amount of PMS injected and on the strain of mice used.

3. Two types of egg are ovulated, one being normal and with a cumulus, the other degenerated and without cumulus. 93 % of the normal eggs were fertilized and 98 % of the pronucleate eggs possessed two pronuclei.

4. Approximately three-quarters of the females which mate in response to the injected gonadotrophins become pregnant, although this number was less than the number becoming pregnant after mating during natural oestrus. Many of the treated females carried their embryos to term and some gave birth to large litters, although resorptions, irregular distribution of embryos in the uterus, and difficulty during parturition occurred in some females. Mean litter size of the treated females was similar to that found after natural mating.

5. After more than one treatment with gonadotrophins, fewer females mated, ovulated, and became pregnant than after the first treatment. This reduction in response may have been due to the greater age of the females or to their decreased sensitivity to the hormones.

6. The value of the method as a technique for inducing oestrus, ovulation, and pregnancy in mature female mice is considered.

J. Endocrin. (1959) 18, 292–304

TIMING OF THE STAGES OF THE MATURATION DIVISIONS, OVULATION, FERTILIZATION AND THE FIRST CLEAVAGE OF EGGS OF ADULT MICE TREATED WITH GONADOTROPHINS

By R. G. EDWARDS and A. H. GATES

From the Institute of Animal Genetics, West Mains Road, Edinburgh 9

Year	Oocyte maturation & ovulation induction	Aneuploidy generation	Sperm studies	Genetics of development
1954		2		
1955			2	
1956			2	
1957	1	3	1	
1958	1	5	4	
1959	4		2	
1960	2			1
1961	1	1		2
1962	1			1
1963	1			1
Totals	**11**	**11**	**11**	**5**

Edwards' papers from Edinburgh days

Year	Discovery	Key Authors
1956	Human karyotype agreed as 46	Tijo, levan, Ford, Hamerton, Levan, Tijo
1959	Down and Klinefelter syndrome chromosomal basis established	Jacobs, Lejeune
1960	Chromosome numbering agreed	Denver conference

MEIOSIS IN OVARIAN OOCYTES OF ADULT MAMMALS

By R. G. EDWARDS

National Institute for Medical Research, Mill Hill, London, N.W.7

MANY of the chromosomal anomalies in man and animals arise through non-disjunction or lagging chromosomes during meiosis in the oocyte. Investigations of the origin and primary incidence of such anomalies would be greatly facilitated if meiotic stages in the mammalian oocyte were easily available. Unfortunately, this has not been the case. Oocytes undergo the prophase stages of meiosis until diplotene just before or shortly after birth in the majority of mammalian species[1,2]. DNA synthesis occurs in the oocytes before birth, no further synthesis occurring in the oocyte until after fertilization[3]. The total number of oocytes per female is thus determined at birth in most species, no oocytes being formed thereafter. After diplotene, oocytes enter the dictyate stage and remain nucleated for the long period from diplotene until shortly before ovulation. In most mammalian species the stages of meiosis between diakinesis and the metaphase of the second maturation division occur in the brief period between the stimulation of the Graafian follicle by luteinizing hormone and ovulation a few hours later. Anaphase and telophase of the second meiotic division occur after penetration of the egg by the fertilizing spermatozoon. Thus, to find the early stages of meiosis, oocytes must be taken from late fœtuses or newly-born animals, for example, mouse and man[4]. The later stages of meiosis will be found in oocytes taken from adult ovaries.

Much fundamental information on non-disjunction, lagging chromosomes, crossing-over, and associations between normal and structurally altered chromosomes will be provided by studies on meiotic stages after diplotene. The present article is primarily concerned with methods designed to obtain these stages. Oocytes which are naturally in diakinesis or later stages of their meiotic divisions can be recovered from the ovaries just prior to ovulation[5,6]. But the number of such oocytes recovered is meagre, and the stage of meiosis can vary widely between different animals. Under appropriate endocrinological conditions the dictyate stage in oocytes of adult mammals can be terminated, and the resumption of meiosis can be induced. The exact stage of meiosis at a particular time can often be predicted with considerable accuracy.

In the rabbit, an injection of a luteinizing hormone or the coital stimulus initiates the resumption of meiosis, and ovulation occurs 8–9 h later[7]. In man and other species, a single or multiple injection of a luteinizing hormone, with or without previous follicular priming by a follicle-stimulating hormone, induces

Landmark paper 1

CYTODIFFERENTIATION IN CELL COLONIES AND CELL STRAINS DERIVED FROM CLEAVING OVA AND BLASTOCYSTS OF THE RABBIT[1]

R. J. COLE, R. G. EDWARDS[2] and J. PAUL

Department of Biochemistry, The University, Glasgow, Scotland

Received November 9, 1964

The embryonic potentialities of these cells are being actively investigated to determine to what extent they have retained a capacity for further cytodifferentiation, with a view to their possible usefulness in embryological studies.

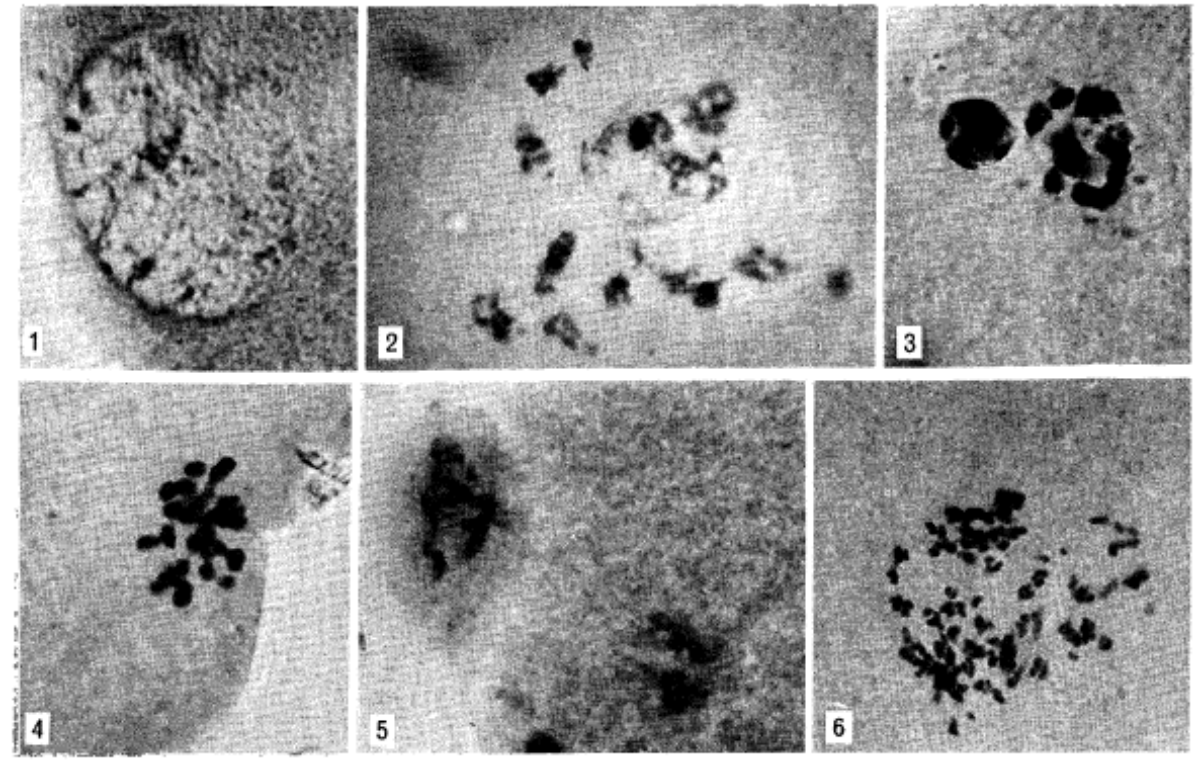
Landmark paper 2

THE LANCET NOVEMBER 6, 1965

MATURATION IN VITRO OF HUMAN OVARIAN OÖCYTES

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 *



Perhaps the greatest challenges of the present work lie in the prospect of obtaining fertilised human eggs

Another difficulty …. the culture of human eggs through early cleavage stages

by using priming doses of follicular stimulating hormone it should be possible to obtain many more oocytes per ovary

The transfer of eggs into the uterus via the cervix would successfully bypass a faulty fallopian tube.

The multiple pregnancies found after injecting gonadotrophins into sterile women would be avoided by transferring single eggs into the uterus

It is obviously necessary to ensure that embryos developed in vitro are normal, first by culturing oocytes from domestic and experimental animals

allow us to control some of the genetic disorders of man

If the sex of the blastocysts could be determined, some control over sex-linked recessives could be achieved by transferring a female embryo into the mother, thus avoiding the birth of affected boys.

Landmark paper 3

NATURE. VOL. 218. APRIL 27. 1968

Control of the Sex Ratio at Full Term in the Rabbit by transferring Sexed Blastocysts

by
R. L. GARDNER
R. G. EDWARDS
Physiological Laboratory,
University of Cambridge

An important step forward has been made in controlling the sex of rabbits by sexing pre-implantation embryos and transferring the sexed embryos into recipient females. In the experiments, foetuses were surgically delivered and their sex was found to have been correctly predicted at the blastocyst stage.

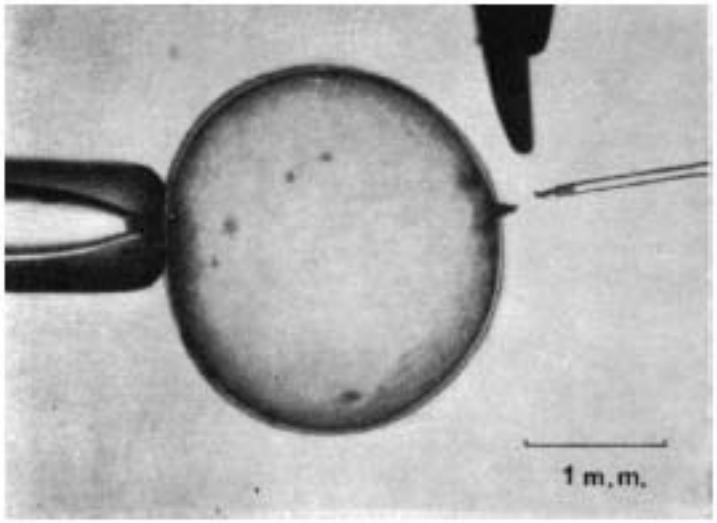


Fig. 1. Blastocyst immediately after excision of trophoblast. The holding pipette of internal diameter approximately 0·15 mm can be seen on the left, the scissor-tips top right, and the excised fragment in the suction pipette (internal diameter approx. 0·05 mm).

Landmark paper 4

Early Stages of Fertilization *in vitro* of Human Oocytes Matured *in vitro*

by

R. G. EDWARDS
B. D. BAVISTER
Physiological Laboratory, University of Cambridge

P. C. STEPTOE
Oldham General Hospital, Oldham

Human oocytes have been matured and fertilized by spermatozoa *in vitro*. There may be certain clinical and scientific uses for human eggs fertilized by this procedure.

NATURE. VOL. 221. FEBRUARY 15. 1969

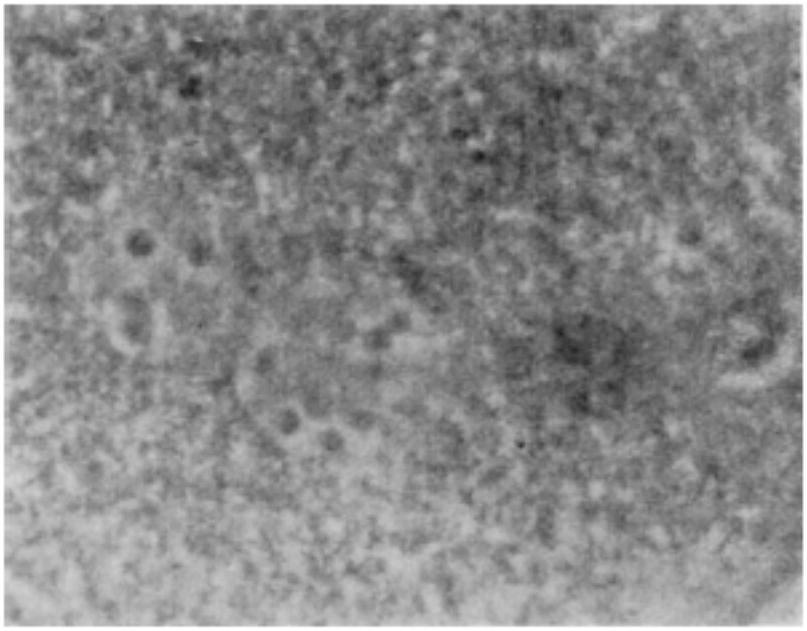


Fig. 3. Two pronuclei in a living human egg examined 22 h after insemination. Polar bodies were seen in this egg, but a sperm mid-piece could not be unequivocally identified. (×*c*. 675.)

DIFFUSION CHAMBER FOR EXPOSING SPERMATOZOA TO HUMAN UTERINE SECRETIONS

R. G. EDWARDS, PH.D., D.SC.
LUTHER TALBERT, M.D.
D. ISRAELSTAM, M.B., CH.B.
H. V. NINO, PH.D.
M. H. JOHNSON, B.A.
Cambridge and London, England
and
Chapel Hill, North Carolina

From the Physiological Laboratory, Cambridge University, Departments of Obstetrics, Gynecology, and Biophysics, University of North Carolina at Chapel Hill, and Department of Obstetrics and Gynaecology, Hammersmith Hospital

Reprinted from

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY
St. Louis

Vol. 102, No. 3, Pages 388-396, October 1, 1968

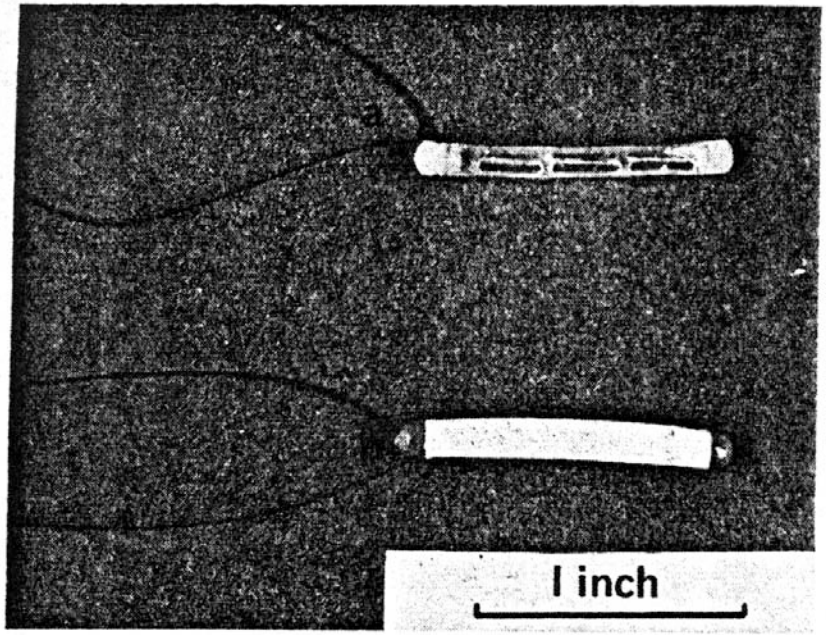
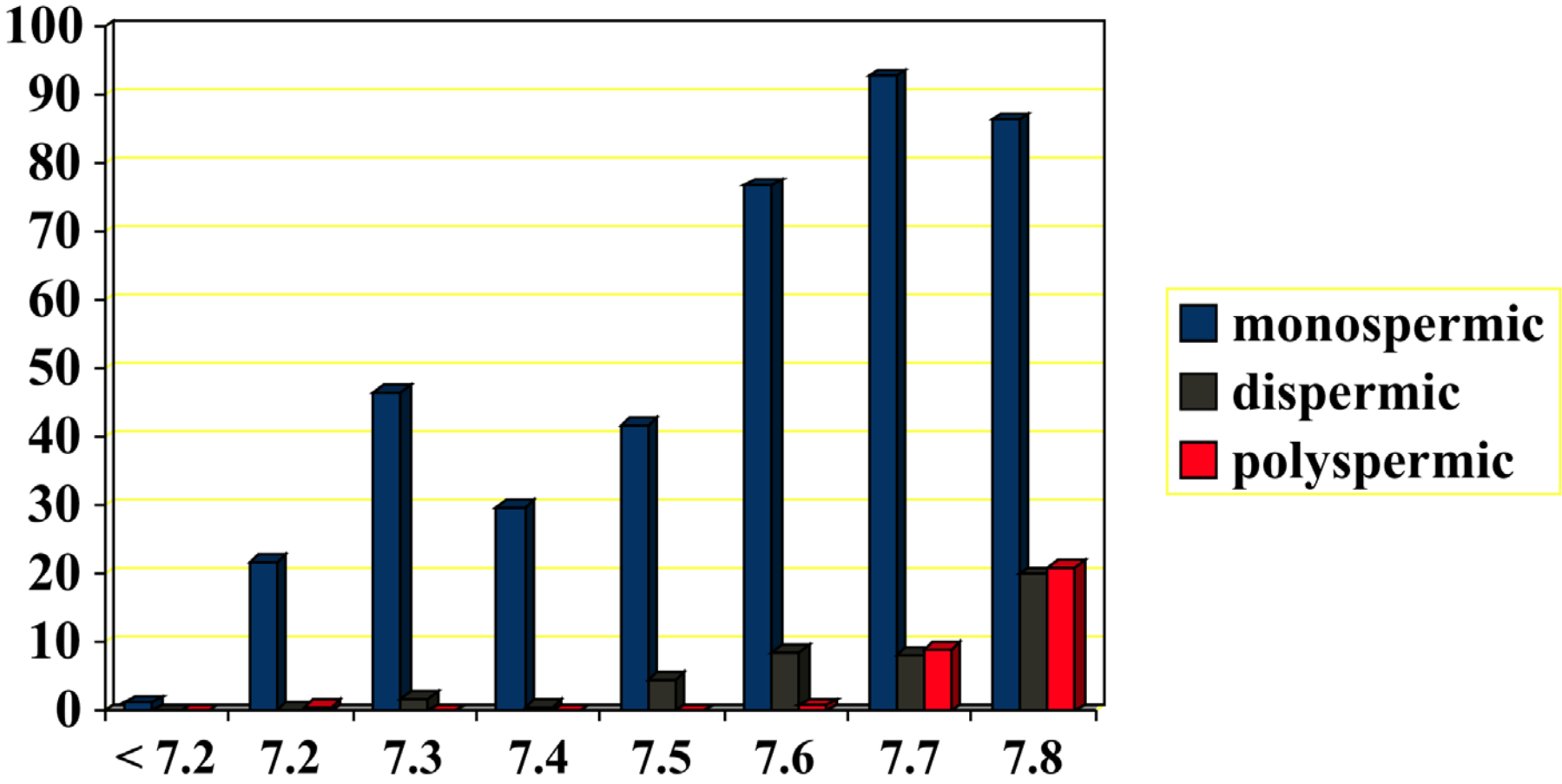


Fig. 1. *a*, The upper illustration shows the nylon tubing plugged at each end, and with the windows drilled through it. The transverse channel through one of the plugs is used for attaching the thread for withdrawing the chamber from the uterus. A longitudinal channel through the other plug is used for filling the chamber; it cannot be seen through the nylon. *b*, The lower illustration shows the completed chamber after the membrane has been stuck to the nylon tubing.

pH-Dependence of Hamster IVF



Bavister 1969 *J. Reprod. Fertil.*

We thank especially Professor C. R. Austin for his encouragement and advice, and Drs C. Abberley, G. Garrett and L. Davies for their help. One of us (R. G. E.) is indebted to the Ford Foundation and another (B. D. B.) to the Medical Research Council for financial assistance.

We thank Professor N. Morris and Drs M. Rose, J. Bottomley and S. Markham for ovarian tissue.

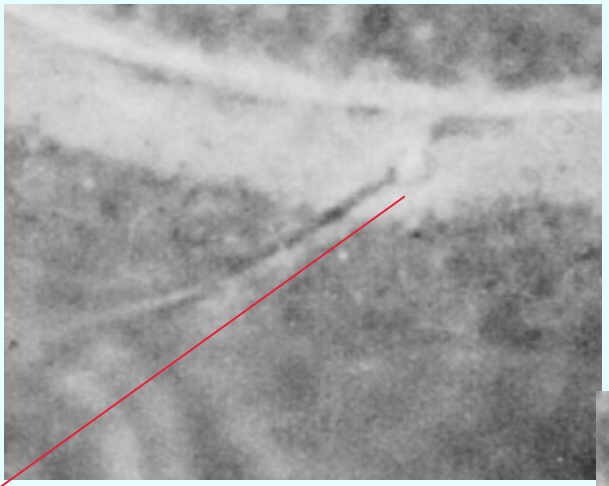
Addenbrooke's Hospital, Cambridge

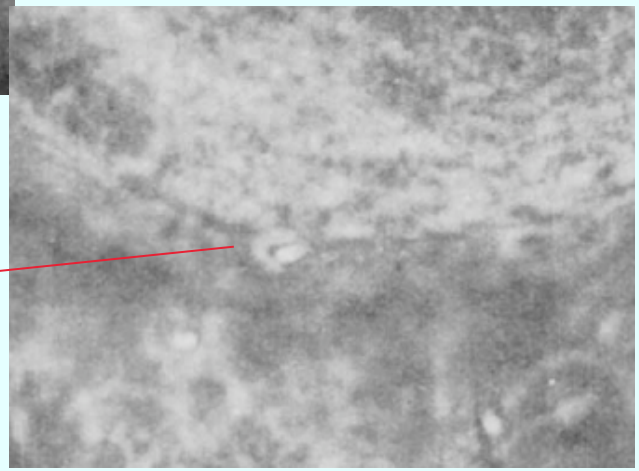
US Air Force, South Ruislip

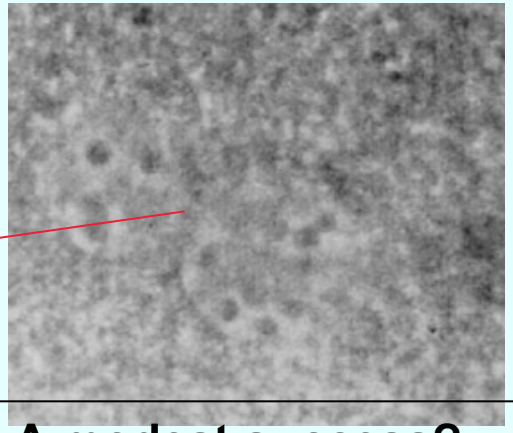
Charing Cross Hospital, London

Edgeware General Hospital, London

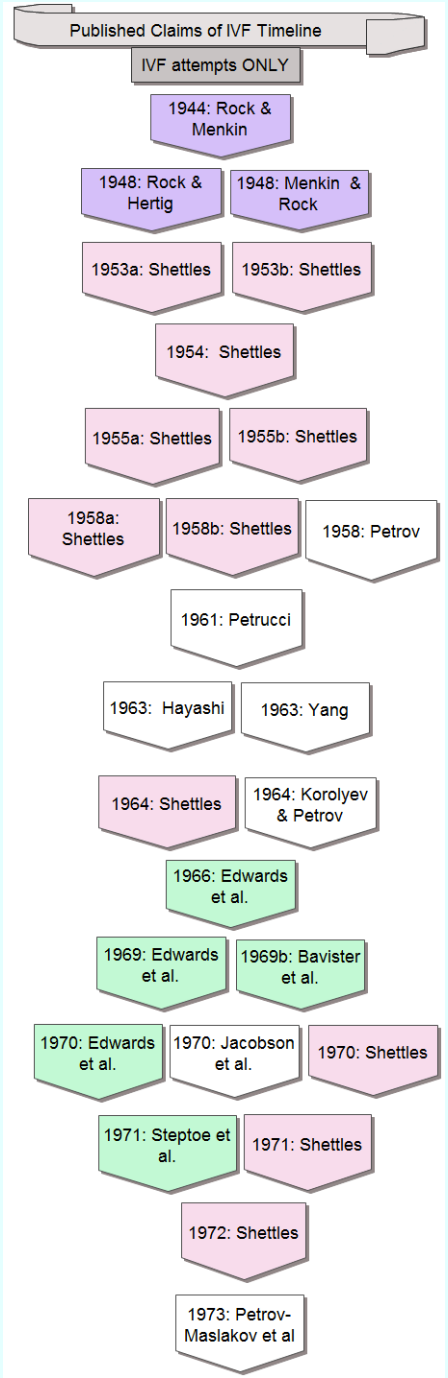
No. of eggs	56
No. surviving	54
No. that matured	34
No. with some evidence of sperm penetration	18
No. with sperm within the zona pellucida	6
No. with sperm inside zona pellucida	5
No. with evidence of spem penetration into oocyte	7
No. normally fertilised	*2*







A modest success?


Published Claims of IVF Timeline
IVF attempts ONLY
1944: Rock & Menkin
1948: Rock & Hertig
1948: Menkin & Rock
1953a: Shettles
1953b: Shettles
1954: Shettles
1955a: Shettles
1955b: Shettles
1958a: Shettles
1958b: Shettles
1958: Petrov
1961: Petrucci
1963: Hayashi
1963: Yang
1964: Shettles
1964: Korolyev & Petrov
1966: Edwards et al.
1969: Edwards et al.
1969b: Bavister et al.
1970: Edwards et al.
1970: Jacobson et al.
1970: Shettles
1971: Steptoe et al.
1971: Shettles
1972: Shettles
1973: Petrov-Maslakov et al

Landmark paper 5

The Lancet · Saturday 4 April 1970

LAPAROSCOPIC RECOVERY OF PREOVULATORY HUMAN OOCYTES AFTER PRIMING OF OVARIES WITH GONADOTROPHINS

P. C. STEPTOE
Oldham and District General Hospital, Lancashire
R. G. EDWARDS
Physiological Laboratory, Cambridge University

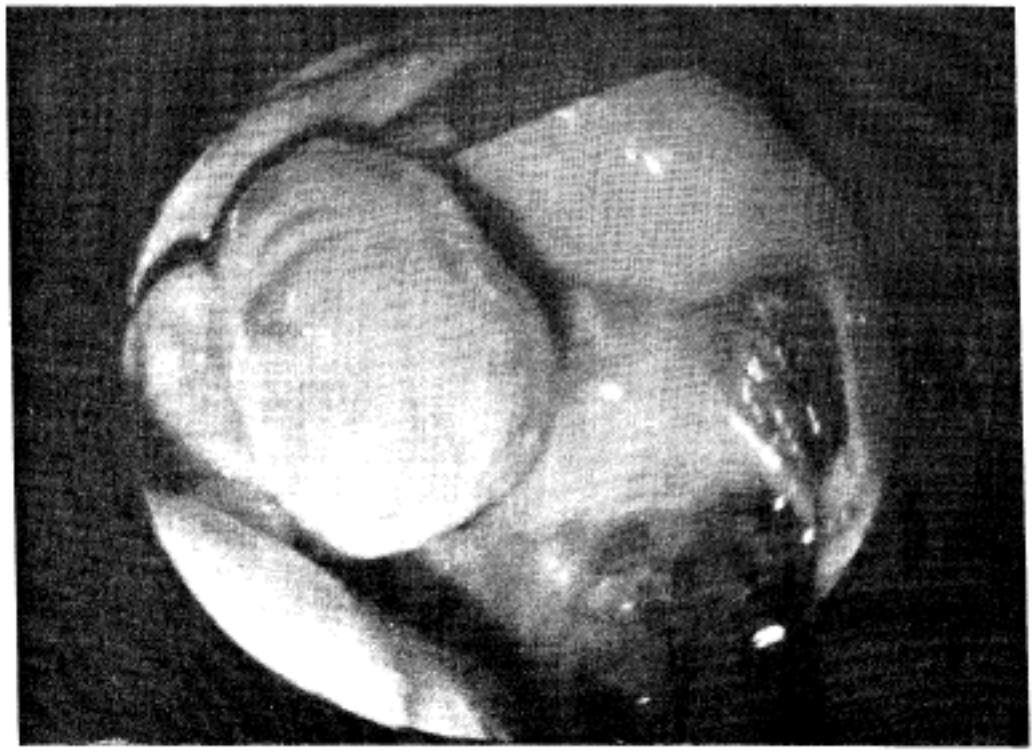


Fig. 1—Ovary showing a good response to gonadotrophins.
The follicles can be seen as swellings on the surface of the ovary; at least 6 follicles were found in this ovary. The actual maximum diameter of the ovary shown here was 3 cm.

Landmark paper 6

Human Blastocysts grown in Culture

We have already described the culture of cleaving human embryos to the sixteen celled stage[1], and we now wish to give details of a few embryos that have developed much further, including two that reached fully developed blastocysts. Methods were similar to those described before. Preovulatory oocytes recovered by laparoscopy[2] were fertilized in Bavister's medium[3], and transferred after 12–15 h into Ham's F 10

P. C. Steptoe
R. G. Edwards
J. M. Purdy

Oldham General Hospital, Lancashire, and Physiological Laboratory, University of Cambridge

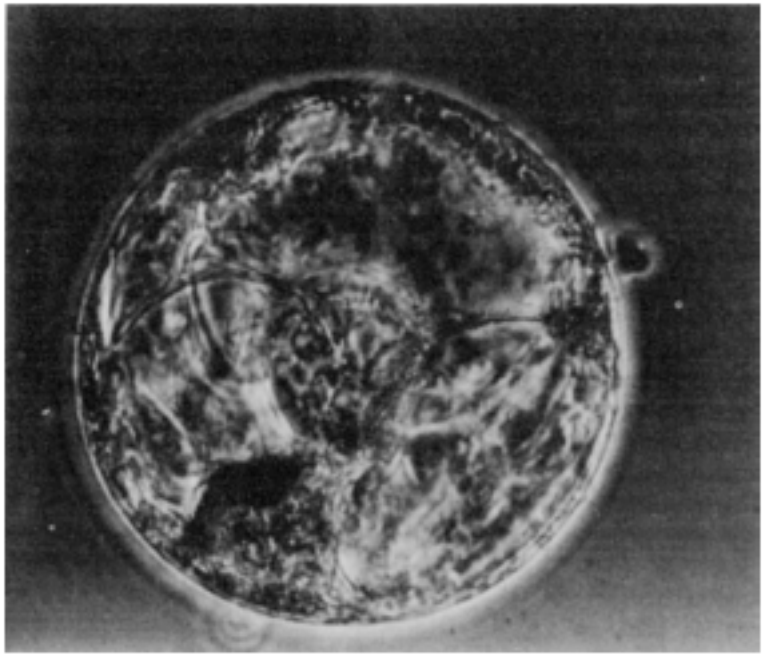


Fig. 2 Blastocyst 2 before it was fixed and stained. The thin zona pellucida and the underlying trophoblast can be seen; an extension is evidently emerging through the zona (at right). The inner cell mass (lower part of the embryo) is distinct. The cellular membranes persisting across the blastocoel can be seen.

NATURE VOL. 229 JANUARY 8 1971

On the 10th February 1971, a grant application from Bob Edwards and Patrick Steptoe was sent to the MRC

"Studies on Human Reproduction - application for long term support"

"*We believe it is fundamentally important to pursue studies on human reproduction at both the scientific and clinical level, to relate knowledge obtained from animals to man and to apply our results clinically where it is possible. Special applications of knowledge would be to problems concerned with contraception, infertility and inherited defects in man*."

Quotation taken from

Human Reproduction, Vol.25, No.9 pp. 2157–2174, 2010
Advanced Access publication on July 24, 2010 doi:10.1093/humrep/deq155

human reproduction ORIGINAL ARTICLE *Historical contribution*

Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971

Martin H. Johnson[1,*], Sarah B. Franklin[2], Matthew Cottingham[2], and Nick Hopwood[3]

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Martin H. Johnson[1,*], Sarah B. Franklin[2], Matthew Cottingham[2], and Nick Hopwood[3]

Royal College of Obstetricians & Gynaecologists

Macafee Report of 1962

Training Report of 1967

Medical Research Council

Report by Secretary to Annual Review Meeting of Council, November 1968

Report prepared in-house, July 1969

Discussed by Council, November 1969

Summary of talk by Prof PJ Huntingford to Clinical Research Board January 1970

Comment from an MRC referee on the 1971 grant application aiming to treat infertility

"..it would be wrong to place a major emphasis on techniques for augmenting fertility in infertile patients when we desperately need methods for limiting fertility in the normal population."

Quotation taken from


Human Reproduction, Vol.25, No.9 pp. 2157–2174, 2010
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Landmark paper 7

NATURE VOL. 231 MAY 14 1971

Social Values and Research in Human Embryology

ROBERT G. EDWARDS
Physiological Laboratory, University of Cambridge

DAVID J. SHARPE
The National Law Center, George Washington University, Washington DC

"Scientists may have to make disclosures of their work and its consequences that run against their immediate interests; they may have to stir up public opinion, even lobby for laws before legislatures, in the hope that the attitudes of society as evinced in its laws will mature at a rate not too far behind the transition of scientific discovery into technological achievement"

Edwards & Sharpe (1971) Social values and research in human embryology. *Nature 231:87-91*

Prescient statement in light of later events

One scientific referee begins his report –

"Dr Edwards feels the need to publicise his work on radio and television, and in the press, so that he can change public attitudes. I do not feel that an ill-informed general public is capable of evaluating the work and seeing it in its proper perspective. This publicity has antagonised a large number of Dr. Edwards' scientific colleagues, of whom I am one."

Quotation taken from

Human Reproduction, Vol.25, No.9 pp. 2157–2174, 2010
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human reproduction

ORIGINAL ARTICLE *Historical contribution*

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Martin H. Johnson[1,*], Sarah B. Franklin[2], Matthew Cottingham[2], and Nick Hopwood[3]

Landmark paper 8

BIRTH AFTER THE REIMPLANTATION OF A HUMAN EMBRYO

SIR,—We wish to report that one of our patients, a 30-year-old nulliparous married woman, was safely delivered by cæsarean section on July 25, 1978, of a normal healthy infant girl weighing 2700 g. The patient had been referred to one of us (P.C.S.) in 1976 with a history of 9 years' infertility, tubal occlusions, and unsuccessful salpingostomies done in 1970 with excision of the ampullæ of both oviducts followed by persistent tubal blockages. Laparoscopy in February, 1977, revealed grossly distorted tubal remnants with occlusion and peritubal and ovarian adhesions. Laparotomy in August, 1977, was done with excision of the remains of both tubes, adhesolysis, and suspension of the ovaries in good position for oocyte recovery.

Pregnancy was established after laparoscopic recovery of an oocyte on Nov. 10, 1977, in-vitro fertilisation and normal cleavage in culture media, and the reimplantation of the 8-cell embryo into the uterus 2½ days later. Amniocentesis at 16 weeks' pregnancy revealed normal α-fetoprotein levels, with no chromosome abnormalities in a 46 XX fetus. On the day of delivery the mother was 38 weeks and 5 days by dates from her last menstrual period, and she had pre-eclamptic toxæmia. Blood-pressure was fluctuating around 140/95, œdema involved both legs up to knee level together with the abdomen, back, hands, and face; the blood-uric-acid was 390 μmol/l, and albumin 0·5 g/l of urine. Ultrasonic scanning and radiographic appearances showed that the fetus had grown slowly for several weeks from week 30. Blood-œstriols and human placental lactogen levels also dropped below the normal levels during this period. However, the fetus grew considerably during the last 10 days before delivery while placental function improved greatly. On the day of delivery the biparietal diameter had reached 9·6 cm, and 5 ml of amniotic fluid was removed safely under sonic control. The lecithin: sphingomyelin ratio was 3·9:1, indicative of maturity and a low risk of the respiratory-distress syndrome.

We hope to publish further medical and scientific details in your columns at a later date.

Department of
Obstetrics and Gynæcology,
General Hospital,
Oldham OL1 2JH

P. C. STEPTOE

University Physiology Laboratory,
Cambridge CB2 3EG

R. G. EDWARDS

THE LANCET, AUGUST 12, 1978

Cole RJ, ***Edwards RG***, Paul J. (1965) Cytodifferentiation in cell colonies and cell strains derived from cleaving ova and blastocysts of the rabbit. *Exp. Cell Res.* 37:501–4.

Edwards RG. (1965) Maturation in vitro of human ovarian oöcytes. *Lancet* 2(7419):926-9.

Gardner RL, ***Edwards RG***. (1968) Control of the sex ratio at full term in the rabbit by transferring sexed blastocysts. *Nature* 218:346-9.

Edwards RG, Bavister BD, Steptoe PC. (1969) Early stages of fertilization in vitro of human oocytes matured in vitro. *Nature* 221:632–5.

Steptoe PC, ***Edwards RG***. (1970) Laparoscopic recovery of preovulatory human oocytes after priming of ovaries with gonadotrophins. *Lancet* i:683–9.

Steptoe PC, ***Edwards RG***, Purdy JM. (1971) Human blastocysts grown in culture. *Nature* 229:132–3.

Edwards RG, Sharpe DJ. (1971) Social values and research in human embryology. *Nature* 231:87–91.

Steptoe PC, ***Edwards RG***. (1978) Birth after the reimplantation of a human embryo. *Lancet,* ii:366.

Bob Edwards, Jean Purdy and Patrick Steptoe, Bourn Hall, 1981

Bob and Ruth Edwards wish to express their deep gratitude to Peter Williams for allowing us to show these four clips from two of his productions

To Mrs. Brown a daughter: for TV Eye on Thames Television 1980

Test Tube explosion: for Television South 1982