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40 years of IVF

14th February 1969 - 2009

In Vitro Human Embryos:
Interdisciplinary reflections on the first 4 decades

The Yusuf Hamied Centre
Christ's College, Cambridge

10.00-18.00 February 14th 2009

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Christ's College

UNIVERSITY OF CAMBRIDGE

Cover photograph: Bunny Austin, Barbara Rankin, Bob Edwards & Jean Purdy, in the Marshall Lab in the early 1970's

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Marina Warner - John Batten
Marilyn Strathern - Andrew Houston

Introduction

In Vitro Human Embryos: Interdisciplinary reflections on the first four decades

Welcome to a meeting that is both commemorative and historical. The juxtaposition of these two functions is full of tension. Commemorations are occasions for joyful celebration, but they can also be dangerous academically, helping to sustain or create myths. Histories aim to expose and destroy myths and replace them with new, albeit provisional, truths. For example, there is an often articulated belief that the 1969 Nature paper was, in a neat touch of "Natural" editorial irony, published on St Valentine's day - hence the date of this meeting. However, the actual date on the paper is 15th February 1969! A first myth destroyed?

This meeting seeks to examine both the importance of a particular scientific publication and a wider social process of coming to terms with the in vitro human embryo, the birth of IVF, and the rapid expansion of new assisted reproductive technologies (ARTs) worldwide that have emerged from it over the past 40 years. The questions we have asked our speakers to consider concern the ways in which different disciplines have responded to or been affected by this sea change in science and the accompanying social attitudes and values. How have they incorporated the significance of the changes associated with both IVF and assisted conception? What contributions have their various disciplines made to understanding the 'birth of ART'? Our hope is to discover and to stimulate empirical, conceptual, reflective and comparative responses to these questions.

However, the quest for historical truth does not preclude either joyfulness or celebration, for whatever myths may have developed around the 1969 Nature paper, we can assuredly celebrate the impact of a remarkable man in Bob Edwards. Sadly, Bob is too unwell to be able to join us today, but is looking forward to seeing the video. Barry Bavister is also unable to join us for family reasons, but sends his warmest greetings from the USA.

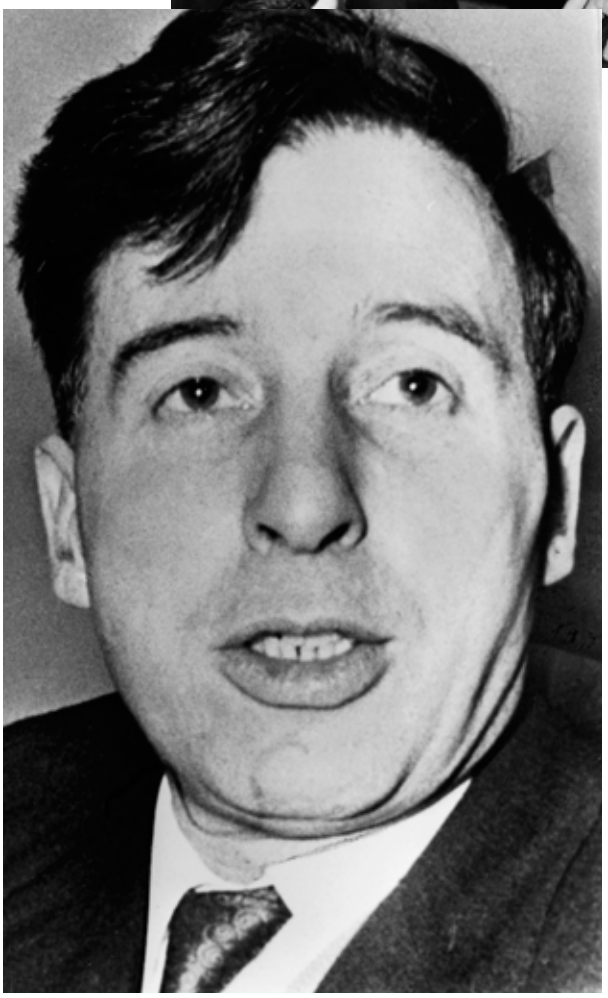
We hope you enjoy the day and are stimulated by it!

Sarah Franklin
Nick Hopwood
Martin Johnson

Acknowledgements

We would like to thank the ***Wellcome Trust*** for their constructive and generous support; ***Nature*** for sponsoring the programme and allowing us to reproduce papers; the journal founded by Bob Edwards, ***Human Reproduction***, for permission to reproduce a paper by Bunny Austin; ***Bourn Hall Clinic*** and the ***Edwards family*** for permission to reproduce photographs; The ***Department of Physiology, Development and Neuroscience*** (Bob Edward's old Department) for providing organisational support; ***Debbie Spikins*** for her untiring work dealing with the applications and administration; ***Ian, Adrian and John*** in the AVMG section of Anatomy for their unfailingly good humoured advice and support in assembling and producing the programme and posters; ***Genevieve Maul*** of the University Office of External Affairs and Communications for her advice and support; ***Christ's College*** for providing the venue free of charge; our student ushers ***Ali Almini, Isabella Felmer, Isabel Huang-Doran, Charlotte Jefferies, Ben Warne and Jamie Wilson*** for looking after us; and all the ***College staff*** for their careful attention to matters about College, particularly ***Clare Kitcat, Susan O'Donnell, Wayne Bell, Jeremy Taylor, Kevin Keohane*** *and their staffs*.

British physiologist Robert Edwards (front) and his team of scientists work in their laboratory at Cambridge University, Cambridge, England, March 28, 1969. Accompanying him in the lab are: (L-R) Barry Bavister, Richard Gardner and Dr. Alan Henderson. (Photo by Pictorial Parade/Getty Images)



Portrait of British physiologist Robert Edwards, one of the medical pioneers responsible for in vitro fertilization, late 1960s. The Cambridge scientist and his collaborator clinician Patrick Steptoe have ignited a firestorm of controversy over the ethical questions raised from their experiments. (Photo by Pictorial Parade/Getty Images)

Programme

9.15-10.00 Coffee (downstairs)

10.00-10.45 Welcome:	Martin Johnson
10.45-12.15	*Mary Warnock*
10.45 Ethics:	Onora O'Neill
11.30 Law:	Emily Jackson

12.15 Sandwich lunch (downstairs)

13.15-14.45	*Jacques Cohen*
13.15 Biology:	Richard Gardner
14.00 Medicine:	Peter Braude

14.45 Tea (downstairs)

15.15-16.45	*Sarah Franklin*
15.15 The Arts:	Marina Warner
16.00 Social anthropology:	Marilyn Strathern
16.45-18.00	*Lisa Jardine*
16.45 General discussion	
17.45 Summing up & closure:	Lisa Jardine

There will be a display of memorabilia curated by Dr Kay Elder

After the meeting, the Buttery Bar in 1st Court
will be available for informal discussions
(go back towards the Great Gate and Porter's Lodge; after passing through the Screens into 1st Court, the buttery bar is obvious through the glass door on the left)

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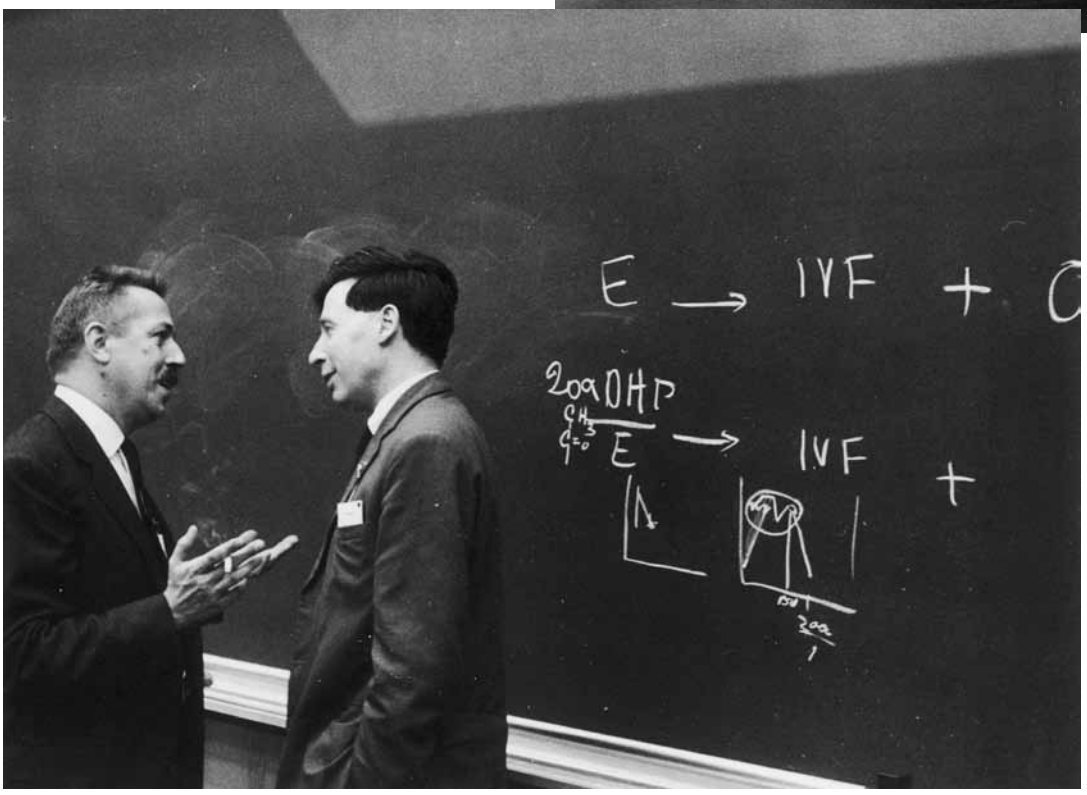
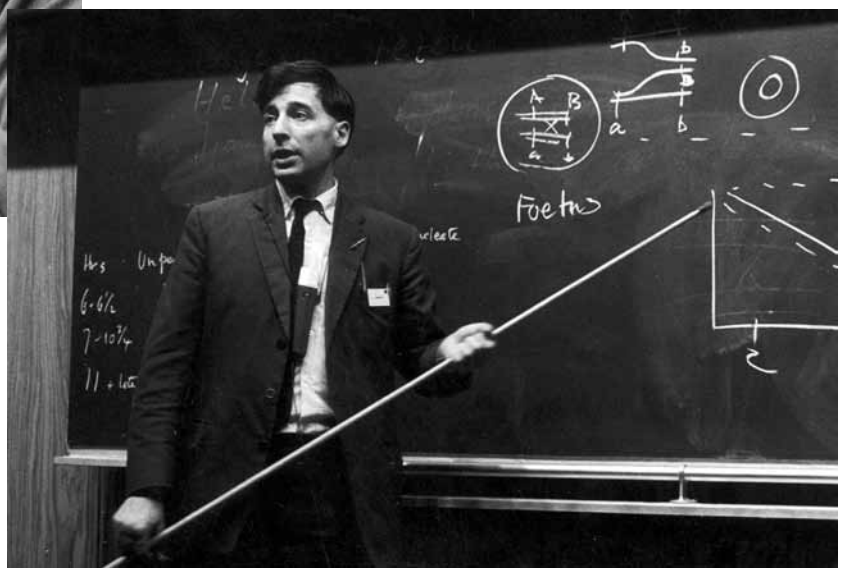
The chamber in which embryos were transported between Oldham and Cambridge during the 1960s and early 1970s



Bob Edwards and Pierre Soupart (1960s)

Bob Edwards (1960s)



40 Years ago

On February 15th 1969 the following paper appeared in Nature

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.

THE technique of maturing human oocytes *in vitro* after their removal from follicles provides many eggs for studies on fertilization[1]. Their fertilization *in vitro* would yield a supply of embryos for research or clinical use, but in previous attempts the incidence of fertilization was too low to be useful[2].

A possible solution to the problem of obtaining "capacitated" spermatozoa has recently emerged from experiments on hamster eggs, where the addition of epididymal spermatozoa to eggs in tubal[3] or follicular[4] secretions can lead to a high incidence of fertilization. Study of the conditions leading to capacitation of hamster spermatozoa and fertilization *in vitro*[5] has led to the use of a medium based on Tyrode's solution, but with extra bicarbonate (final concentration 3 mg/ml.); also added were sodium pyruvate (9·0 μg/ml.), bovine serum albumin (2·5 mg/ml.),

phenol red (20 μg/ml.) and penicillin (100 IU/ml.)[5]. After equilibration with 5 per cent CO_2 in air, the *p*H of this medium was 7·6. Bicarbonate has been shown to stimulate the respiration and motility of rabbit spermatozoa *in vivo* and *in vitro*[6].

We have adapted the conditions found successful in the hamster for work on the human oocyte. The preliminary results reported in this article indicate that human eggs can be fertilized in conditions similar to those found most suitable for the fertilization of hamster eggs *in vitro*.

Maturation of Eggs and Insemination

Oocytes were released from Graafian and smaller follicles into a medium composed of equal amounts of Hank's solution containing heparin, and medium 199 (Microbiological Associates, Inc.) supplemented with 15 per cent foetal calf serum (Microbiological Associates, Inc.) and buffered (*p*H 7·2) with phosphate buffer. Penicillin (100 IU/ml.) was added to these media. Some oocytes were transported from Oldham to Cambridge (a journey taking about 4 h), in medium 199 supplemented with 15 per cent foetal calf serum.

The oocytes were cultured soon after liberation from their follicles, or after transport to Cambridge, in follicular fluid obtained from the same or different ovaries. Where follicular fluid was in short supply it was supplemented by Hank's, Brinster's[7] or Bavister's[5] medium. Oocytes were cultured under a gas phase of 5 per cent CO_2 in air, in droplets of medium under liquid paraffin previously equilibrated with medium 199 containing 15 per cent foetal calf serum, and with the same gas mixture. After 38 h in culture many of the oocytes had extruded their first polar body and reached metaphase of the second meiotic division (metaphase-II).

Ejaculated spermatozoa were washed once with Bavister's medium to remove seminal plasma, and were then re-suspended at a concentration of 10^6/ml. in more of the same medium. Human follicular fluid was added to some samples of spermatozoa before they were added to the oocytes. Oocytes were washed through one or two droplets of Bavister's medium and then pipetted into the sperm suspension. At different intervals after insemination, living eggs were examined by phase contrast microscopy, and then fixed in acetic–saline (20 per cent acetic acid in normal saline solution) or acetic–alcohol (1 : 3), stained with aceto–orcein, and re-examined. In one-celled eggs, the occurrence of penetration was inferred from the presence of spermatozoa in the zona pellucida or in the perivitelline space; the presence in the vitellus of pronuclei, with mid-pieces or tails of spermatozoa, and the extrusion of the second polar body, were regarded as evidence of fertilization.

Fertilization

Fifty-six human eggs were inseminated. When examined for evidence of fertilization, twenty of them were found still to be in dictyotene, having failed to mature *in vitro*. In one of these eggs, a spermatozoon was seen in the perivitelline space. Two other eggs were degenerate.

The remaining thirty-four eggs had matured *in vitro*, as judged by the presence of chromosomes or polar bodies. Many of these eggs were so heavily coated with spermatozoa attached to the zona pellucida that it was difficult to discern internal details. Sixteen of them were in metaphase-II, and showed no evidence of penetration.

In eleven eggs spermatozoa had begun to move through the zona pellucida. One or more spermatozoa were deeply embedded in the zona pellucida in six eggs (Fig. 1). When fixed and stained, each of these eggs was found to be at metaphase-II. Spermatozoa were seen in the perivitelline space of the other five eggs (Fig. 2), and in four of them the spermatozoa were motile. When fixed and stained, four of these eggs were seen to be in metaphase-II, and one had a small nucleus.

Seven eggs had well formed pronuclei. Two of them possessed two pronuclei each (Fig. 3), four had three pronuclei and one had five. Spermatozoa were seen in the zona pellucida or perivitelline space of three of these eggs.

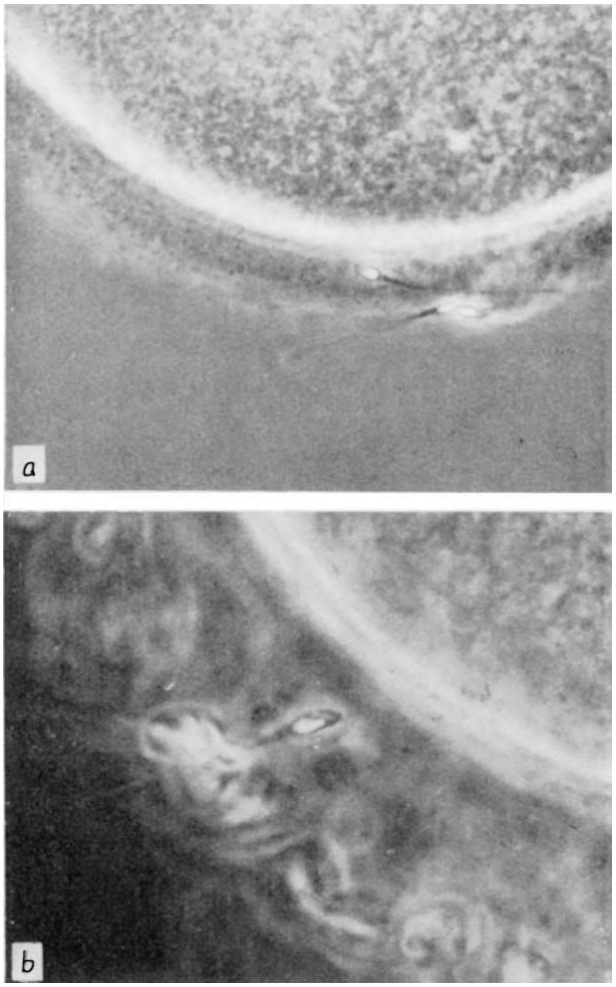


Fig. 1. Spermatozoa lying in the zona pellucida of living human eggs 24 h after insemination. (*a*, × 675; *b*, × 1,200.)

These observations are related to the time after insemination in Table 1. Penetration of spermatozoa into the perivitelline space was first seen in eggs examined 7–7·25 h after insemination, and pronuclei at 11·5 h. Spermatozoa were found in the zona pellucida or perivitelline space of eggs in metaphase-II as late as 27 h after insemination. Many of these spermatozoa were immotile, and it is doubtful whether they would have penetrated further.

Mid-pieces and tails of spermatozoa were not seen with certainty in any of the living eggs, but after fixation structures of a size similar to mid-pieces (as illustrated by other workers[8]) were recognizable in three eggs (Fig. 4). In two eggs, each with two pronuclei, the first and second polar bodies could be identified. In one of these eggs, the two pronuclei were lying close to each other (Fig. 3); on

Table 1. DETAILS OF HUMAN OOCYTES EXAMINED AT VARIOUS INTERVALS AFTER INSEMINATION *in vitro*

Time after insemination (h)	1. Failed to mature *in vitro*			2. Matured *in vitro*		
	Germinal vesicle	Vacuolated or degenerate	Unpenetrated	Spermatozoa in zona pellucida	Spermatozoa in perivitelline space	Pronucleate
6–6·5	1		3			
7–7·5	1				3	
8–9	1	1	2	1	1†	
9·5–10·75	3		3			
11·5	5		1	1		1
12·5–13·5	6*				1	1
22–31	3	1	7	4		5
	20	2	16	6	5	7

* In one of these eggs, a spermatozoon was present in the perivitelline space.
† This egg may have been in metaphase of the first meiotic division.

staining, a mass of coarser chromatin was observed in one pronucleus in a region where the two pronuclei were apposed.

As controls, seventeen eggs were cultured without the addition of spermatozoa. Eight of them failed to mature and displayed germinal vesicles. Of the remainder, one had a small mass of chromatin instead of metaphase chromosomes, seven had metaphase chromosomes, and in one the contents were obscured by overlying cumulus cells. Pronuclei were not seen in any of these eggs.

Of the seventy-three inseminated and control eggs, thirty-one failed to mature or degenerated. Thirteen of these failures occurred in one set of experiments involving a total of fifteen eggs. If this group of eggs is excluded, about 70 per cent of the oocytes matured in culture. After insemination, eighteen of the thirty-four oocytes that had matured *in vitro* had spermatozoa in the zona pellucida, spermatozoa in the perivitelline space, or pronuclei. Judged on the criteria of fertilization given, it is highly probable that most of these eighteen eggs were undergoing fertilization.

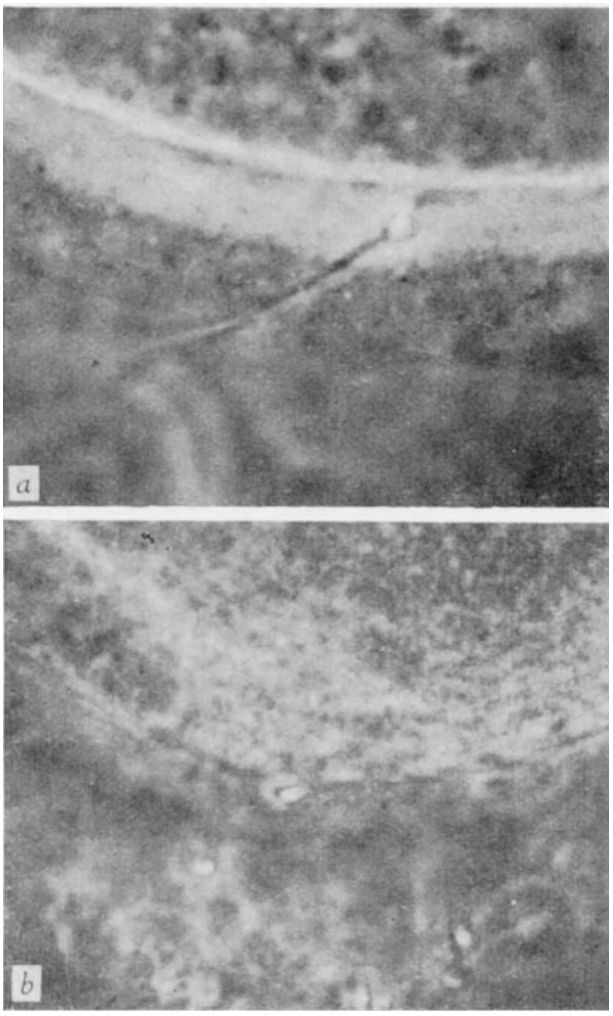


Fig. 2. Spermatozoa in the perivitelline space of human eggs. In *a*, the sperm head is lying in the vitellus, the mid-piece is still embedded in the zona pellucida, and the main piece lies outside the zona. This egg was examined 13 h after insemination; the spermatozoon was still active. (×1,650.) In *b*, the whole of the spermatozoon was in the perivitelline space, although only the sperm head can be seen in the illustration. This spermatozoon was still active. (×750.)

Capacitation and Embryonic Development

The possible function of follicular fluid in the capacitation of spermatozoa and the fertilization of human eggs *in vitro* requires further examination. All eggs in the present series were matured in follicular fluid obtained from the same or a different ovary, and then washed in order to reduce any deleterious effect of follicular fluid on spermatozoa. We have found that spermatozoa of some animal species can be immobilized or agglutinated by follicular fluid, and heat treatment of the fluid does not necessarily abolish these effects. In some of the present experiments, however, we pre-incubated spermatozoa in follicular fluid before adding them to the eggs. Our impression is that this pre-incubation led to the attachment of more spermatozoa to the zona pellucida, and to a higher incidence of penetrated and pronucleate eggs.

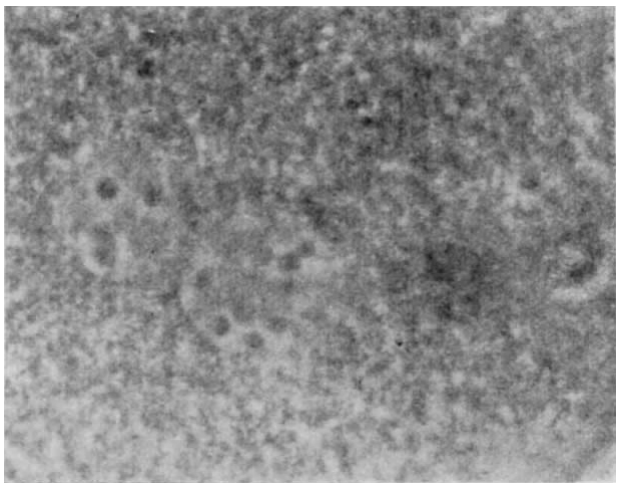


Fig. 3. Two pronuclei in a living human egg examined 22 h after insemination. Polar bodies were seen in this egg, but a sperm mid-piece could not be unequivocally identified. (×*c*. 675.)

The failure of spermatozoa to pass completely through the zona pellucida or into the vitellus may reflect the existence of different layers in the zona with different requirements for penetration, or it may signify that the final movement of spermatozoa through the zona pellucida depends to a large extent on sperm/egg association. Complete penetration might be achieved by conferring greater activity on spermatozoa; mouse eggs can be fertilized *in vitro* by uterine spermatozoa[9] in a medium richer in pyruvate and albumin[10] than our media. Delayed fertilization may well have occurred in the conditions of our culture, and led to anomalies in the eggs. Thus the egg with a spermatozoon in the perivitelline space, polar bodies and a single small nucleus might have been acti-

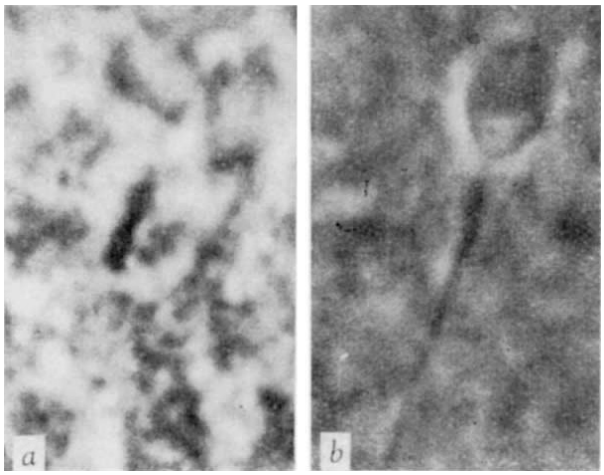


Fig. 4. In *a*, a small body resembling a sperm mid-piece was found in a stained egg which contained three pronuclei and at least one polar body. (× 3,300.) In *b*, a spermatozoon present in the perivitelline space of another egg has been photographed in a position illustrating the size of the mid-piece, for comparison with *a*. (×3,300.)

vated parthenogenetically. The presence of several pronuclei in some eggs may have arisen through polyspermy, but is more probably due to the abnormal movement of chromosomes along the spindle or to fragmentation of the female pronucleus; multipronucleate eggs are common after delayed fertilization *in vivo* of eggs of various mammalian species[11].

Problems of embryonic development are likely to accompany the use of human oocytes matured and fertilized *in vitro*. When oocytes of the rabbit and other species were matured *in vitro* and fertilized *in vivo*, the pronuclear stages appeared normal but many of the resulting embryos had sub-nuclei in their blastomeres, and almost all of them died during the early cleavage stages (ref. 12 and unpublished work of R. G. E.). Abnormal development might have been the result of incomplete RNA synthesis when oocytes are removed from follicles for maturation *in vitro*; small amounts of RNA are synthesized by *Xenopus* oocytes in response to luteinizing hormone (LH) during the final period of maturation[13]. When maturation of rabbit oocytes was started *in vivo* by injecting gonadotrophins into the mother, and completed in the oviduct or *in vitro*, full term rabbit foetuses were obtained (ref. 12 and unpublished work of R. G. E.). Another developmental problem could be that some oocytes blocked during maturation at anaphase of the first meiotic division[1,14] could yield polyploid or heteroploid embryos at fertilization. Fortunately human oocytes in the present and earlier[1] work were rarely blocked at this stage.

Clinical Use of Human Embryos

These potential difficulties with human embryos may be solved when the conditions necessary for maturation *in vitro* are better understood, or, as in rabbits, by initiating maturation *in vivo* by administering gonadotrophins or clomiphene to the mother. When women were injected with gonadotrophins, maturing oocytes were recovered from excised pieces of ovary[15]. The timing of the stages of oocyte maturation in this work[15] was very similar to that exhibited by oocytes matured *in vitro*[1], and should indicate the appropriate moment to remove oocytes in preparation for fertilization *in vitro*.

Fertilized human eggs could be useful in treating some forms of infertility, and many infertile patients will probably be older women. If the "production line" of eggs in the ovary, inferred from studies on mouse oocytes[16], also occurs in humans, the eggs of older women will have more anomalies of bivalent association than those of younger women. A higher incidence of trisomic and polysomic embryos, and hence of mongols and abortions, would thus be expected in these patients.

The clinical use of human embryos will require the development of operative techniques for the recovery of follicular oocytes and for the transfer of eggs into human oviducts and uteri. Preliminary work using laparoscopy has shown that oocytes can be recovered from ovaries by puncturing ripening follicles *in vivo*, and that a few of the eggs transferred into the oviducts can be recovered following salpingectomy (unpublished work of P. C. S. and R. G. E.). Improvements in equipment and techniques may give better results and avoid resorting to laparotomy.

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.

Received December 13, 1968.

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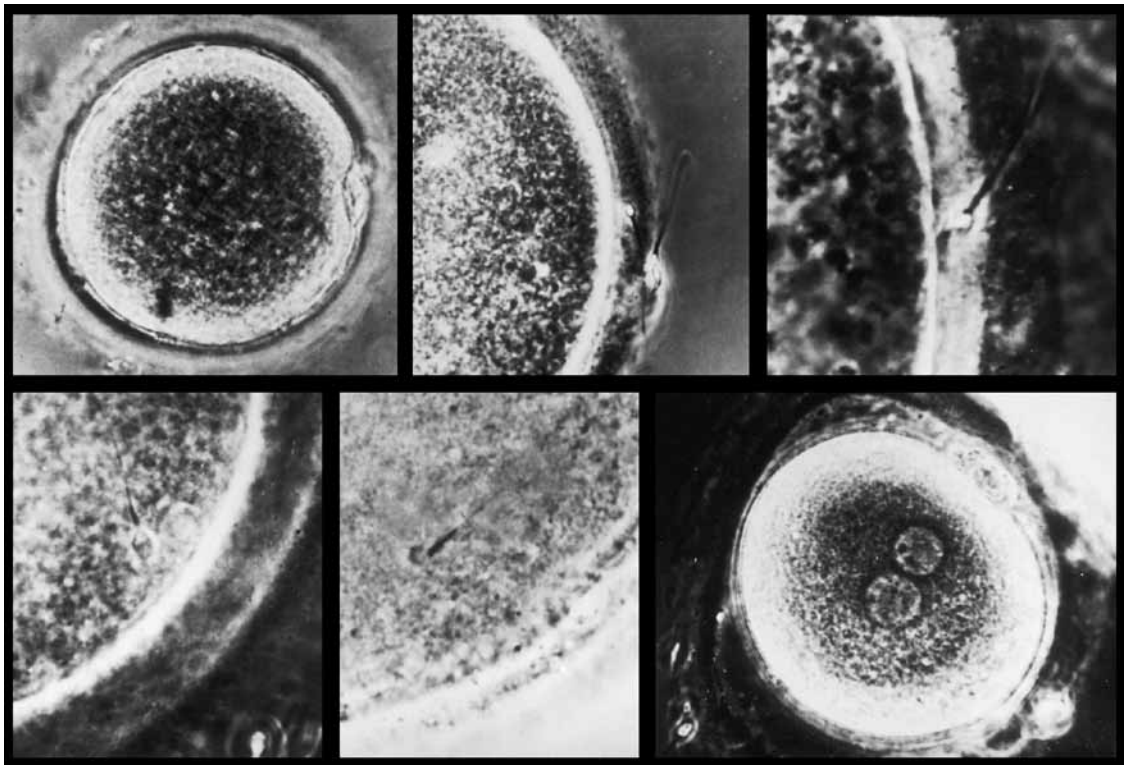
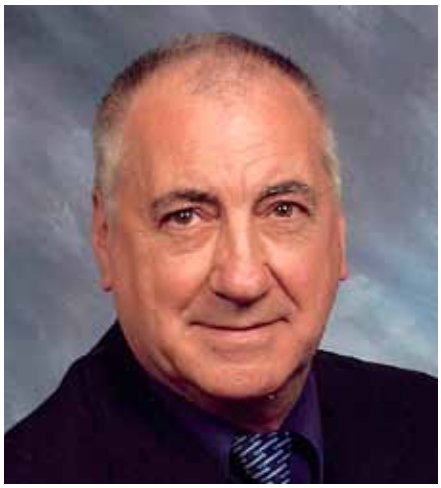


Reminiscences

A tribute to Bob Edwards from Barry Bavister

I first encountered Bob when I was an undergraduate studying Physiology at Cambridge University, in 1967. Unlike most of the lecturers, Bob had a dynamic style of teaching. He would stride up and down in front of the class, wildly gesturing and sometimes looking for notes that he had crammed into his pockets. I was excited by his enthusiasm for his topic and decided then and there to become a Reproductive Physiologist. Of course, Bob's basic themes were that we knew too little about human reproduction, and that infertility was a major problem that needed attention. In those days, the focus was on female infertility due to oviductal pathology, and the only realistic treatment was resection and re-anastomosis, which wasn't very successful. In his lectures, Bob proposed a radical idea: removing eggs from the infertile patient, fertilizing them in vitro and returning the resulting embryos to the uterus. There were some problems with this concept: no-one had ever fertilized human eggs in vitro, and at least in animals, placing early cleavage stage embryos into the uterus rather than the oviduct did not work!



I did not know it at the time, but Bob had worked for several years to mature eggs in vitro, first with animals and later with human material. For the latter, he was given portions of ovaries that had been removed for medical reasons at a local hospital. He had tried several times to fertilize human eggs in vitro but without success. So while Bob was enthusiastically discussing his IVF approach to human infertility, he knew that it was going to be difficult, or perhaps even impractical. It is a tribute to Bob's vision and determination, as in later stages of the human IVF saga, that he was not deterred.

In the summer of 1967, I became a graduate student in the famous Marshall Laboratory, which was located on the top floor of the Physiological Laboratory situated in the Downing Site where most of the Cambridge University laboratories were located. Bob was working there in a tiny laboratory with his two graduate students, Martin Johnson and Richard Gardner. My supervisor was Professor "Bunny" Austin, who had co-discovered sperm capacitation in 1951. That discovery laid the foundation for IVF in all species, so it was serendipitous that Bob, Bunny and I were all in the same small space in 1967. Strangely enough, although Bob was always very pleasant to me, he and I did not interact much because I was working on a project under Bunny's supervision, namely, sperm capacitation in the hamster. But it was Bob who had suggested that topic to me and to Bunny, no doubt hoping that some nugget of information from my efforts might be helpful to his attempts at human IVF! Incidentally, it was Bob who persuaded Bunny to take me on as his Ph.D. student, sight unseen.

I spent my first year in the Marshall Laboratory trying to duplicate the successful IVF in hamsters reported by Yanagimachi and Chang in 1963 and 1964. Without a consistently successful IVF system, I could not begin to study the changes undergone by spermatozoa during capacitation (and we still don't fully understand them!). After a year of frustratingly variable results, it dawned on me that the pH of the culture medium was critically important. In those days, I used a crude culture medium (Tyrode's solution) without any pH buffering. The sperm concentration was highly variable, so paradoxically very high numbers of motile spermatozoa depressed the culture medium pH and this blocked fertilization. Incidentally, research from other laboratories later showed that the acrosome reaction is pH-dependent, so a low extracellular pH reduces the transmembrane pH gradient and prevents the efflux of protons that is required to trigger the acrosome reaction. I had noted in my short report on hamster IVF in 1969 that at low pH (7.0 or less), none of the spermatozoa appeared to have undergone the acrosome reaction and they could not adhere to the zona pellucida [Bavister, 1969]. In contrast, at high extracellular pH (7.6 and above), acrosome-reacted spermatozoa were abundant and virtually all the eggs were fertilized, even polyspermic. I think this was the first report that mammalian fertilization is pH-dependent (and see Bavister, 2002, for more details). In view of this information, I formulated a culture medium (Tyrode-B) with a bicarbonate-CO2 buffer system and bovine serum albumin to protect the cells.

When Bob learned of this success with hamster gametes, he suggested applying it to support fertilization of in vitro matured human eggs. That was entirely Bob's idea. We started working together in the summer of 1968 and continued into autumn. As before, Bob obtained human ovarian fragments, from which he extracted immature eggs and matured them in vitro. Then we inseminated them in Tyrode-B. An immediate problem was that, while we believed that human spermatozoa needed capacitation, thanks to Bunny's work, we had no idea how long that process took. As a result, we inseminated batches of eggs then waited for 2, or 4, or 6 hours before examining them to see if they were fertilized. That usually meant inseminating the eggs in the early evening then going home for dinner and returning at night to check the results. On one occasion, we found we were locked out of the Downing Site because the huge gates across the entrance were locked for the night. Bob is fond of telling this story, that it was my fault because I had forgotten my keys. That is a bit unfair because to the best of my recollection, lowly graduate students were not entrusted with keys to those gates, and it was Bob who had forgotten his keys! Regardless, we had to boost ourselves over the 8- or 9-foot iron gates to get into the Downing Site. I wonder what would have happened to our work if the police had caught us breaking in! I really don't remember if that was the very night that we observed the first human IVF, but it is nice to think so.

Typically, Bob and I would take turns to examine the precious human eggs, one at a time, at varying intervals after insemination. This was laborious. Unlike the enormous hamster spermatozoa, human spermatozoa are tiny and, as it turned out, impossible to visualize within the egg cytoplasm without staining. So, we would take one egg, compress it gently under a microscope coverslip, then flood it with fixative followed by aceto-orcein stain. Under high magnification, it took a lot of searching in the egg cytoplasm to convince ourselves that there was no sperm penetration. After several fruitless inspections, one evening Bob was getting frustrated and said "Barry, you do the next one." So I had the privilege of examining the egg that proved to be the first one with evidence of sperm penetration. Within the egg cytoplasm was a hairlike structure that could only be a sperm tail, and at one end was a clearly recognizable expanding sperm nucleus. I remember sitting there at the microscope for just a few seconds, then turning to Bob and saying "there it is!" Bob rushed over, took one look and turned to me with a big grin and said "Barry, we've done it!" Later that night, as well as on subsequent nights, we found spermatozoa within the zona pellucida and two pronuclei in some of the eggs.

When Bob felt we had enough data, he wrote two manuscripts. One was sent to Nature and the other to the Journal of Reproduction and Fertility [Edwards et al., 1969; Bavister et al., 1969]. Patrick Steptoe was a co-author because all this time Bob had been collaborating with him to obtain in vivo matured eggs for IVF. Bob knew that the eggs he and I had been working with had no chance of developing into embryos because of the way they were obtained – in vitro maturation of eggs did not become a successful clinical practice until more than 20 years later. I have not forgotten the excitement of our discovery that night more than 40 years ago, nor the fact that Bob made me the first author on the JRF paper even though he wrote it and I was just a graduate student. This gesture is typical of Bob's generosity to his colleagues, as countless others will no doubt attest.

The Nature paper came out, as luck would have it, on Valentine's Day, 1969. This helped to fuel the excitement about the discovery in the press all over the world. Suddenly, Bob and Patrick were the focus of intense attention, and immediately Bob was asked to go to London for a press conference. He asked me to go, too, but Bunny wisely advised me not to get involved in the media frenzy so that I could concentrate on my studies. That turned out to be good advice! The Physiological Laboratory was invaded by hordes of press and television journalists, all clamoring for interviews with Bob. I was glad to be out of it! In those days, television cameras were huge boxes on tripods and giant cables snaking down five flights of stairs connected them to "outside broadcast" vans parked outside the building. Needless to say, the intrusion of all this equipment and invasive journalists was highly resented by some of the other professors in the building. I think that some of them also resented the fact that Bob was getting so much publicity, and for doing something of practical importance! In a classic understatement, on the face page of one of our publications, Edwards commented that '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.' [Edwards et al., 1969].

It should not be forgotten that other laboratories around the world were also working on human IVF, notably Lopata and Woods and their colleagues in Australia. But it was primarily Bob who argued forcefully for acceptance of the new technology of human IVF, defending it against the inevitable backlash from those who saw it in "Brave New World" terms instead of accepting its potential for solving infertility. He did this at many public and scientific meetings as well as in scholarly articles for years, until his collaboration with Patrick Steptoe resulted in the break-through birth of Louise Brown in 1978. Bob's vision and determination to develop human IVF technology have been paramount not only in its success but also in its acceptance by patients, by physicians and, for the most part, by society in general. After the birth of a normal, healthy baby using IVF technology, it became much harder to criticize the approach, and as we all know, today about one million previously infertile couples have been able to have children. And of course human ART now can treat infertile men as well as women. Bob's fundamental work on human IVF also stimulated a huge resurgence of interest in research on embryology, across a wide spectrum of species, with ramifications for progress in breeding domesticated animals and endangered species.

It has been my great privilege to work with Bob during those exhilarating few months of 1968, and to have my name associated with his ever since. As I have said before, Bob epitomizes the socially conscious, visionary scientist, and the legacy of his work speaks for itself.

Barry Bavister
New Orleans, USA
January 2009

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Bob Edwards – a profile

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Born 27 September 1925, Robert Geoffrey Edwards grew up in Batley, a small Yorkshire town, and in Manchester, where he was educated at the Central High School, going on to study Agriculture at the University College of North Wales in Bangor. Bob's university life was interrupted by a 4-year spell of army service in the Near East, during which he was awarded a commission. On returning, he realized sadly that he was not after all interested in crop planting rates and other things agricultural, so he transferred to the Department of Zoology, where the study of animal spermatozoa and eggs was much more to his fancy. Indeed, an interest in the biological aspects of reproduction had been with him since school days, and there was even a vague ambition that in the dim future he might be able to do something about the problems of human infertility. He graduated from UCNW in 1951; later on, this institution was to confer on him the degree of D.Sc.

After graduation, Bob was successful in winning a Studentship at the Institute of Animal Genetics in Edinburgh (1951–1957), where he worked for a Ph.D., initially under the supervision of the Director, C.H. ('Wad') Waddington, a geneticist of world renown, and then of Alan Beatty, well known for his research in the fields of reproduction and genetics. Wad earned Bob's special respect for the high moral and ethical standards he defended, qualities that Bob himself was to show in great measure during his professional life, as witness some of his later pronouncements on these issues (Edwards, 1971, 1974, 1980, 1983, 1988, 1989; Edwards and Sharpe, 1971; Edwards and Steptoe, 1980).

The early fifties were initially difficult years for Bob, for his family was not wealthy and his grants had been spent during the period at Bangor. So to begin with he had to set about accumulating a small reserve and to accept any employment that was offered – helping at hay-making, carrying loads on the wharves, doing menial work in a newspaper office, working in a flour mill and so on. But once launched into the life of the Institute, he soon became totally absorbed in research on reproduction in mice. Indeed, as Alan Beatty recalls, his enthusiasm drew him into innumerable experiments, so that his supervisors became concerned that work would not be completed and that time, animals and reagents would be wasted; but their fears were groundless, for the work was duly completed and useful results reported.

This interest was instrumental in Bob's meeting his future wife, Ruth Fowler, who was busy at the Institute with research on mouse genetics, and they became both friends and collaborators, studying among other things the maturation of mouse primary oocytes in culture, a highly important step to Bob's mind, should human embryos ever be produced *in vitro*, and the induction of superovulation and pregnancy by appropriate hormone treatment (Fowler and Edwards, 1957; Edwards and Gates, 1959). One evening, Bob remarked that among the people he most admired was Ernest Rutherford, the famous New Zealand physicist, and Ruth promptly floored him by remarking casually that she was in fact the granddaughter of Rutherford. For a while thereafter he concentrated on research and in due course achieved his Ph.D.

It was at the Institute in 1955 that I first met Bob – a memorable encounter for me because he demonstrated a technique for the artificial insemination of mice, a procedure I had thought hardly practicable, and he did this with speed and aplomb, using a hypodermic syringe and a dentist's speculum.

In 1956, Bob and Ruth were married, soon after she had received her Ph.D. in Edinburgh. Then, aided by a grant from the Population Council of New York, they went to spend a year at the California Institute of Technology, in Pasadena, where a lasting friendship was formed with Albert Tyler, well known for his work in immunology. It was of course in the immunology of reproduction that Bob was chiefly interested and a major step in this direction was made when they returned from the States and Bob entered upon a 5-year contract with the Medical Research Council to work on this topic at the National Institute for Medical Research in Mill Hill, London. Here he came under the leadership of Alan Parkes and it was my good fortune to also be one of his team at the time.

Bob continued his investigations on oocyte maturation in an extended range of animal species (Edwards, 1962, 1965a,b) and, later in Cambridge with Alan Henderson, made important observations on the mechanism of origin of trisomies (Henderson and Edwards, 1968). His work at the National Institute, however, primarily involved immunology, earning him a firm reputation in this field, and soon he was in demand for contributions at scientific meetings, both in the UK and abroad, as author of original reports, organizer of symposia and editor of proceedings. (Bob has always had a great capacity for appreciating the form and detail of a research field, being familiar with the work of a remarkable number of investigators, as is evident also in the coverage of his news-sheet, *Research in Reproduction*, produced from 1969 onwards, and as I was to discover later when we co-edited a book on sex differentiation – Austin and Edwards, 1981.) But he could never lose his enthusiasm for spermatozoa, eggs and the early stages of pregnancy – all this as yet (in the early sixties) in experimental animals. Increasingly, his real ambition was to work with human gametes and embryos, to do something

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about human infertility, perhaps by the simple expedient of implanting embryos in the reproductive tract, much as he had done frequently with success in mice.

Progress was also being made on the family side, for near the end of 1962, Bob and Ruth were blessed with the birth of their third daughter. They had indeed hoped for a son at this stage, and so they cheerfully initiated another pregnancy – surely this time it would be a boy. About now, my wife and I departed for a 3-year visit to the States, so we begged to be kept informed of the outcome – and we duly were, by a telegram announcing 'twin girls'! So Bob now has a special interest in methods for sex control in the human subject.

Fortunately, it now became possible for Bob to obtain human ovarian tissue, first from the nearby Edgware General Hospital and later from other hospitals, enabling him to start work with human eggs. An early observation of special significance was that human ovarian oocytes, removed from follicles without prior hormone treatment, and placed in culture in the laboratory, would begin to undergo maturation after an interval of some 28 h, with completion some 7 or 8 h later (Edwards, 1965b). For Bob, this opened the gates to his long-cherished dream of human clinical work, though in subsequent practice care was taken to use only eggs that had matured *in vivo*, because in-vitro maturation seemed all too frequently associated with anomalous development later.

With the spell at the National Institute coming to an end, a move became necessary and Alan Parkes, who had just previously been appointed Mary Marshall Professor of the Physiology of Reproduction at the Physiological Laboratory in Cambridge, invited Bob to join him there. Despite the many advantages of the new location, there were major problems, notably the fact that human ovarian tissue was difficult to come by. A 6-week visit to the Johns Hopkins Hospital in Baltimore, MD, USA, made possible by a grant from the Ford Foundation, provided greatly improved opportunities for work with human material and to try out new ideas, so Bob made several attempts to fertilize eggs with spermatozoa recovered from the cervix some hours after intercourse, but all to no avail. Then a year later, a visit was made to Chapel Hill, North Carolina, to test the possibility that spermatozoa enclosed within porous membrane chambers and placed in the uteri of volunteers might acquire the ability to fertilize, but again without success. So it looked very much like a case of 'back to the bench once more'.

Luck then took a turn for the better. Bob attended a meeting of the Royal Society of Medicine in London and heard Patrick Steptoe, an experienced clinician, describe the potential applications of laparoscopy and found himself deeply impressed with both the man and the method. They soon got together and agreed to collaborate, working towards the goal of establishing pregnancies by fertilizing eggs *in vitro* and transferring the embryos to suitable recipients, a programme in which laparoscopy would play an indispensable role. The logistic difficulty inherent in the proposition, that Patrick worked in Oldham which was some 4 h hard drive from Cambridge, was appreciated but not held to be insuperable. So, in 1968, Bob and an assistant set up a tiny laboratory near Patrick's operating theatre in Oldham General Hospital. Later that year, Bob's first assistant left and was replaced by Jean Purdy, whose nursing experience, general competence and great sense of dedication made her an invaluable member of the team, a function she fulfilled most admirably until her untimely death some 15 years later. In 1970, the little unit moved to Kershaw's Hospital in Royton, near Oldham, where they were allocated an operating theatre, culture and preparation rooms – and two beds!

A major advance in the research had been initiated the previous year, when Bob decided to attempt the fertilization of some human eggs, deriving from the Edgware General Hospital in London, with freshly collected human spermatozoa. The culture medium he used was of a composition that had been found suitable for the in-vitro fertilization of hamster eggs by one of our Ph.D. students, Barry Bavister (Bavister, 1969). To everyone's delight, this and subsequent experiments were entirely successful, the eggs not only undergoing fertilization but several cleavage divisions also (Bavister *et al.*, 1969; Edwards *et al.*, 1969, 1970; Steptoe *et al.*, 1971). Public reaction to these announcements was, however, somewhat mixed and Bob became involved in vigorous and often heated debate on moral and ethical issues, as well as on the medical and biological ones. (Barry Bavister is now a leading figure in the Department of Veterinary Science, University of Wisconsin, Madison, USA; he and his team were able to report the birth of the first non-human primate, a chimpanzee, from an egg fertilized *in vitro* – Bavister *et al.*, 1984.)

The intense public interest aroused by Bob and Patrick's success was steadfastly maintained. Indeed, it was augmented throughout the following years, when the team, proceeding past the cultivation of embryos, strove valiantly to obtain implantation in anxious patients. This proved a very hard nut to crack – time after time, beautiful healthy embryos were placed in recipients' tracts but all to no avail, despite numerous variations in the procedures followed. Prospects looked dim indeed with these persistent failures, and to make matters worse Patrick was suffering increasingly from arthritis of his hip joints, which were now so painful he could scarcely continue with his surgical work. Accordingly, he became a patient himself for hip replacement.

The realization then dawned on Bob and Jean that the hormonal treatment necessary to provoke ovulation of a useful number of eggs at a time convenient for the operative work could be having a wholly undesirable effect on the patients' endometrium, advancing its status too rapidly through the later stages of the cycle and into the next menstruation. The vital inference to be drawn was that Nature must be allowed to take her own course and the clinical work geared to accepting the number of oocytes naturally ovulated (commonly only one) at a time decreed by the hormones (generally a highly inconvenient one for the clinical and laboratory staff). A possible way around the problem was to continue with the ovulation-induction treatment, fertilize the eggs and culture the embryos as before, but now freeze the embryos until such time as the patients' cycle had settled down again, when the embryos could be transferred. David Whittingham, then a member of our group at the Physiological Laboratory, had devised a means for the cryopreservation of mouse embryos, which on transfer to recipient mice developed through to normal young at birth (Whittingham, 1971; Whittingham *et al.*, 1972). So a freezing machine was duly installed at Kershaw's and several embryos put through the process. Unfortunately, none survived the experience and it was

clear that human embryos required different conditions for freeze-storage, which implied the mounting of a separate research programme.

That seemed to leave the only practicable way ahead to fit in with natural cycle times and find the means to get prior warning of ovulation, so as to arrange for eggs to be collected just before that event. The answer turned out to lie with the simple yet dependable estimation of LH levels in patients' urine by the 'Hi-Gonavis' test, enabling the vital 'surge' of LH to be detected, marking the stimulation of the follicle and impending ovulation. Assay of urinary oestrogen was also useful, for this gave an even earlier warning of follicular activities. It was just before ovulation that Patrick had to find the leading follicle, and recover the egg it contained, so that Bob and Jean could proceed with the fertilization and culture. (Patrick was now 'back in circulation' again, his renewed hip joints allowing him to work in greater comfort and ease than he had done for years.) With the essentially new simple regimen, pregnancies were at last established. It was truly 'in the nick of time', for the available period of the clinical facilities at Kershaw's was nearly over, Patrick's contract at Oldham had only a few months to run and both Bob and Jean were at the end of their respective tethers. But now the team were finally able to announce the establishment and progress of an apparently normal pregnancy, and then the birth of the first test-tube baby – some 9 years after the first successful fertilization (Steptoe and Edwards, 1978). It had been a painfully long and rocky road, the full trauma of which is admirably revealed in the detailed account narrated by Bob and Patrick in their book (Edwards and Steptoe, 1980).

Curiously enough, during that gruelling period when all attempts to establish a pregnancy were futile, Bob developed a keen interest in local politics in Cambridge – he relished the disputation of social issues, such as the inequity of the education system and the persisting injustice of the housing shortage for low income groups, perhaps because these problems were so different from test-tube baby problems but certainly because of his innate moral and ethical sensitivity. For a while some of us feared that he might actually canvass for election to parliament! With the publicity arising from his research activities, that was a distinct possibility. In the event, he was elected to the Cambridge City Council, but fortunately (in our opinion) things did not go farther than that and the phase passed.

The next step for Bob and Patrick was to set up their own clinic in the neighbourhood of Cambridge and Jean was deputed to find a suitable place. After much tireless searching, she came upon Bourn Hall, which was a magnificent installation and ideal in many respects, though requiring the expenditure of a good deal of time and money to develop satisfactory biological and clinical facilities. Bourn Hall Clinic opened in October 1980 and in the ensuing years well over a thousand babies have seen the light of day after having been conceived there, and the staff have earned world-wide acclaim from their professional, including ethical, standards. (Advice just received is that the number of babies is now around 2500.) From 1980, Bob has been the Scientific Director of this clinic and Patrick was Medical Director until his death in March 1988.

During these very busy times, and despite the demands of his principal commitment, Bob yet managed to make important contributions in other directions. As Ford Foundation Reader in Physiology at the Physiological Laboratory, he was involved in an intensive teaching programme from 1965 onwards and carried as well the responsibility of supervising a succession of research students, most of whom have achieved notable reputations of their own. From 1969 on, Bob has edited (and largely written) the news-sheet *Research in Reproduction*, on behalf of the International Planned Parenthood Federation, for whom he also made numerous visits to developing countries in the company of Alan Parkes and E.C.Amoroso. In 1985, he was made Professor of Human Reproduction at Cambridge, retiring in 1989. He held the post of Chairman of the European Society of Human Reproduction and Embryology from 1985 to 1987 and he has been Chief Editor of the journal *Human Reproduction* since 1986. Numerous honours have come his way, including: Hon.D.Sc., Hull (1983), FRS (1984), Hon.FRCOG (1985), Hon.MRCP (1986) and CBE (1988). In addition, there have been international recognitions, notably Honorary Member of the French Society for Infertility (1983), Honorary Citizen of Bordeaux (1985), Life Member of the Australian Fertility Society (1985) and Gold Medal of the Spanish Fertility Society (1985).

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Peter Eckstein, **Bunny Austin** and Bob Edwards (1960s)

SEXING OF RABBIT BLASTOCYSTS BY TROPHECTODERM BIOPSY - PROOF OF PRINCPLE FOR PRE-IMPLANTATION GENETIC DIAGNOSIS
A memoir by Richard Gardner

When I joined the Marshall Laboratory as one of Bob Edwards' first two research students in September 1966, he suggested extending experimental embryology to the so-called blastocyst stage of early mammalian development as a worthwhile project. The rabbit seemed an obvious choice for this since its blastocyst attains a diameter of 5 mm while it can still be recovered from the uterus and returned to it without damage. Bob was already interested in the possibility of controlling the sex of offspring for which selection of sperm carrying male versus female determining chromosomes had so far proved very unpromising. Hence, typing pre-uterine attachment conceptuses seemed a more realistic option, particularly since the presence of the sex chromatin body, the condensed product of one of the two X chromosomes present in females, had been demonstrated in the outer trophectoderm (placental precursor) cells of the rabbit blastocyst.

Initially, we attempted to type intact living rabbit blastocysts for sex, having first exposed them to a chromosome-binding fluorescent dye called Euchrysine 2 2GNX. Our overall rate of success in sexing 48 blastocysts by fluorescence microscopy was 81% with all those classified as female being confirmed as such by conventional staining for sex chromatin after preservation. However, 4 females were wrongly scored as males, and no consensus could be reached on the sex chromatin status of a further 3. While this study showed that reasonably reliable sexing of living blastocysts was achievable in the rabbit, use of a potentially mutagenic

acridine dye for this purpose was clearly questionable. Unsurprisingly, none of a series of blastocysts that had been exposed to Euchrysine showed any sign of further development after transfer to uterine foster-mothers. We therefore looked to see if we could visualize sex chromatin reliably in living blastocysts by various types of microscopy that depended on exposing them to relatively harmless visible light Blastocysts were first stained with Euchrysine so that any candidate bodies identified thus could be checked by fluorescence microscopy. Disappointingly, sex chromatin could not be identified reliably in living trophectoderm by any of a range of light microscopic techniques even though this tissue was a thin monolayer like certain cells culture in which it could be visualized very clearly.

Encouragement not to abandon our goal of sexing living blastocysts without compromising their viability came from a timely publication in the Journal of Anatomy in which L.E.A. ('Tim') Rowson and R.M. ('Bob') Moor showed that late preimplantation sheep conceptuses could continue to develop normally following removal of several millimetres of trophectoderm. However, removing some of this tissue from the blastocyst without jeopardizing its further development posed a rather greater challenge in the rabbit than the sheep. This was partly because, as found by C. E. (('Dub') Adams, the ability of the rabbit blastocyst to implant depended crucially on the integrity of an investing coat called the zona pellucida.

The procedure we adopted was to immobilize the blastocyst by gently sucking it onto the flame-polished tip of a glass micropipette so that its inner cell mass, which includes the precursor cells of the future fetus, was away from a second much narrower pipette through which focal suction was applied to the zona pellucida. A hand-held sharp-tipped glass needle was then used to puncture the zona at the site of suction, thereby enabling a strand of trophectoderm to be drawn into the pipette. This pipette was then withdrawn from the surface of the blastocyst so that the exteriorized trophectoderm could be cut away with very fine iris scissors. Finally, the biopsied tissue was preserved and stained for scoring independently for sex chromatin by the two of us plus Christine Stadelmann, a temporary member of staff of the Marshall Laboratory from Europe.

Sexing blastocysts thus proved very reliable providing they were advanced enough for the majority of trophectoderm cells in females to have formed sex chromatin. However, simply avoiding more than very focal damage to the zona pellucida of biopsied blastocysts was not enough to ensure they developed normally following return to the uterus. For this, their cavity had also to be fully or nearly fully inflated so that the trophectoderm was pressed against the inner surface of the zona. This could be achieved providing the residual tuft of trophectoderm was securely trapped in the slit in the zona after the biopsy had been taken. Thus, it seems that successful uterine implantation of the rabbit blastocyst depends on its resisting deformation through the trophectoderm and zona behaving, respectively like an inner tube and tyre.

All of 18 blastocysts confidently typed in this way that developed to term were found by genital morphology and histology, as well a sex chromatin status of membranes, to have been sexed correctly at the blastocyst stage. However, one of them, a male, lacked all head structures anterior to the ears. This could possibly have been due to loss of part of the future fetal tissue during as a result of its herniating through the slit in the zona.

It took a considerable amount of time to perfect the microsurgery so that most blastocysts were fully expanded after a period of post-operative culture. The first 6 successfully typed blastocysts for which this was achieved were assigned to Bob to transfer to the uterus. Having put on a pristine white lab coat, anaesthetized the recipient doe, exposed its uterus, and then picked up the precious blastocysts in a glass pipette, he turned to me with an embarrassed grin. Glistening on the lapel of his lab coat were the fruits of my labour, 6 tiny pearls that were quite beyond recovery! I am told by Martin Johnson, Bob's other Ph.D student, that I marched straight out of the laboratory in a fulminatory state. Martin himself was instantly converted to working on sperm as being much more numerous and thus less readily mislaid.

Our blastocyst sexing studies, which were reported in two papers in Nature, engendered sufficient interest for us to be invited to write an article for New Scientist. Here we drew attention to some of the wider implications of transfer of typed blastocysts, not only in agriculture but also in offering an ethically more acceptable alternative to amniocentesis and abortion in avoiding the birth of children inflicted with serious genetic diseases. We suggested that sexing blastocysts could be used to deal with X-chromosome-linked diseases such as Duchenne type muscular dystrophy, and that extending typing to conditions due to defects in genes on other chromosomes might also be possible, depending on which are expressed during these early stage of development. Of course, all this was contingent on achieving human fertilization in vitro, which was still a 'pipe-dream' in 1968. Subsequent research has shown that Duchenne dystrophy was not a good choice of X-linked disease for this approach because many cases arise de novo and thus, unlike with cystic fibrosis, lack a predictable family history whereby parents at risk of producing an afflicted child can be identified. This is because its gene presents an unusually large target for mutation, being more than 1% of the entire length of the X-chromosome.

Of course, following introduction of recombinant DNA technology, the scope for typing preimplantation conceptuses as a way of tackling genetic disease has become potentially limitless. While the normal practice is to remove one or two cells from pre-blastocyst conceptuses, moves towards trophectoderm biopsy are now being advocated as the efficiency with which conceptuses produced by fertilization in vitro can be cultured to the blastocyst stage improves.

Richard Gardner 30/12/2008

Reminiscences

Extract (edited by Kay Elder) from an interview with Martin Johnson conducted by Sarah Franklin at the London School of Economics on the 20th February 2008

Sarah Franklin: You went up to Cambridge in 1963 to read Natural Sciences for Medicine. Did any of your teachers from that period stand out in particular?

Martin Johnson: In the third year I decided to do physiology Part II. In those days the Department was full of the most extraordinarily talented people, including two very influential personalities whose influence changed the course of my life, one of whom was Bob Edwards. He suddenly appeared in the second term, completely different from everybody else because he was open and easy-going and egalitarian, he laughed and he was amiable and he was wild and erratic and totally outrageous. He'd just come out with ideas which seemed patently nonsense - except most of them turned out not to be! We started challenging him, so he would also make you go away and read things and engage with him. It was Bob who made me consider very carefully whether I really wanted to go on to do medicine, because by this time I'd been offered a place at Charing Cross Hospital. When Bob asked me and Richard Gardner whether we would be interested in doing a PhD with him, I thought I would really like that. Partly because my whole thinking was moving away from the constraints of medical education, into what I saw as a more intellectually stimulating area, and partly because I was really unsure that I was mature enough to be going onto the wards. Bob was really exciting and stimulating, but it was a big risk - the whole of the physiology department said to Richard and me, well, if you want to do a PhD, why are you doing it in a stupid subject like reproduction with a maverick like Bob Edwards? This was the first intimation as to how the scientific community saw Bob, and of what was to come. It was almost a flashing red light really - I thought that Bob might be wild, maybe they're a bit right about him, but he's exciting. Richard and I discussed it together and decided that we were going to work with Bob - it was almost a rather awkward cussed streak coming out in us.

Sarah Franklin: Do you have any idea why Bob would have approached you and Richard? Was there something that you'd written, or some conversations you'd had with him?

Martin Johnson: We were clearly interested in the work he was doing and we did a little project, trying to stain cortical granules with lysosomal acridine orange vital dyes in hamster eggs to see whether we could visualise the cortical discharge at fertilisation. We did make some progress and got quite interested in that.

Sarah Franklin: Did Bob Edwards have his own lab?

Martin Johnson: Yes, a little place called the Marshall Lab, right up at the top of the Physiology department, next to the Animal House. Alan Parkes was the Marshall Professor then, and subsequently Bunny Austin came in as head. It was a smallish group, Bob had taken over partial supervision of a little project by someone else's student, Ann Vickers, or Ann Wallace as she then was, but he hadn't taken any students of his own yet. He'd only recently arrived in Cambridge from Mill Hill. It was a pretty small lab. Clare and Valerie were his formidable technicians and Barbara Rankin his secretary – she was great fun and prone to crises of various sorts! Dennis New was down the corridor, and Ruth Deansley ("Mrs Parkes") worked some of the time there and some of the time at Babraham. Dave Whittingham and John Marston came later. Alan Henderson from Genetics was around - he and Bob were developing their ideas on oocyte/follicle production lines at that time.

Sarah Franklin: Was he able to offer you a studentship there, financial support?

Martin Johnson: I think the department probably got studentships. Richard and I both got firsts at the end of our Part 2 year, so we were probably "shoo-ins". Also, there weren't that many graduate students in those days, it wasn't a factory like today and was not considered a 'training post' as it is now. It involved doing research, so Bob didn't say 'here's a project' - he said 'what do you want to do? What are you interested in?' We had to find our own project, work out what it was and then go and talk to him, and he'd get very excited! He treated us like scientists in our own right from the outset, but was always very supportive. I can't remember how I got to my PhD project, which was on the immunology of spermatozoa as a potential contraceptive vaccine. At some stage I got very interested in population control, which was very big in those days. I think it was probably the result of having spent the three summer months of 1966 before I started my PhD in a lab in Bombay with Dr Shanta Rao at Bob's suggestion (he was also very interested in this subject and admired Shanta a great deal). She had done work on the immunogenicity of semen and was another very influential person in my intellectual life.

Sarah Franklin: You must have been one of the earliest people who worked in what was becoming a new field, and inventing the techniques and the equipment would have been part of it?

Martin Johnson: To some extent - my second published paper was co-authored with Bob and three clinicians he had worked with in Baltimore during the previous summer, trying to capacitate sperm (R.G. Edwards, L. Talbert, D. Israelstam, H.N. Nino & M.H. Johnson 1968; Diffusion chamber for exposing spermatozoa to human uterine secretions. Am. J. Obstet. Gynec. **102**, 388-396). Bunny Austin and MC Chang had independently discovered the need for ejaculated sperm to be ripened before they could fertilise eggs, and at the time Bob thought that this was the step preventing the fertilisation of human eggs in vitro. He had been developing in vitro maturation of eggs, and I had been working with Brian Setchell in Babraham to analyse the protein content of testis fluid

(M.H. Johnson & B. P. Setchell 1968 Protein and immunoglobin content of rete testis fluid of rams. J. Reprod. Fert. **17**, 403-406.) We made a semi-permeable chamber, which we filled with human sperm and then inserted para-cervically into the uterus, like an IUD with an attached thread hanging out into the upper vagina. The idea was that exposure to the uterine fluids would ripen the sperm, so that you could then recover the chamber using the thread. I analysed the fluid collected when an empty chamber had been used to see what sort of equilibrated environment there was within it. Unfortunately I concluded that most probably the sperm were being exposed to inflammatory exudates – hardly conducive to capacitation, and not surprisingly this approach did not work and was abandoned.

Sarah Franklin: What other papers did you publish with Bob?

Martin Johnson: Remarkably few really, maybe a couple more in the 70s and some co-editing of books and the odd joint review - but that is not to say that he wasn't very influential. His principle was that he didn't put his name on a paper written by his students or post docs unless he had done a substantial amount of the practical experimental work. It was partly an honest regard for practical science and partly a desire to give his students the exposure they needed to make a career. Nowadays all senior investigators put their names on all papers whether they have contributed or not (or even know what's in it sometimes!). Indeed I adopted the same policy as Bob until 1995 when the University told me I couldn't continue doing that, because unless my name went on the paper it could not be counted for the Research Assessment Exercise. If I had adopted current policy earlier I would have another 100 papers to my name!!

Sarah Franklin: Going back to IVF and the 1969 paper, could you just say a little bit about your awareness of IVF in the offing as it were, and perhaps a little bit about Bob and the work he was doing?

Martin Johnson: If I'm honest, while we were doing our PhDs, and even into our postdoctoral time in the lab, both Richard and I were very unsure about whether what Bob was doing was appropriate, and we didn't want to get too involved in it. The reasons for that were partly because it was quite unsettling as graduate students and early postdocs to see the sheer level of hostility to the work - when Nobel Laureates and the Fellows of the Royal Society and the emerging bigwigs of the subject like Bob Winston and Roger Short were lambasting into Bob and saying, you shouldn't do it… you had to say, well, what's going on here? Can one man be right against this weight of authoritative opinion? From the perspective of a graduate student, although we were both fairly bolshie, nonetheless it made you wonder. The other thing was that I was not sufficiently sure ethically about whether it was right or wrong - and neither was Bob, in a way. We used to have discussions and arguments with him over lunch in a little pub, The Fountain on Regent Street. Bob would give us things to read and then suggest that we write articles – later they were published in Research in Reproduction, a sort of broadsheet News and Views that Bob edited, published by the IPPF. It was a wonderful exercise in being taught how to write concisely and logically on the job, like cub reporters! A great deal of this discussion was about the ethics as well as the science. Numerous people were saying, why is a man like Bob wasting his time on a trivial problem like infertility, which isn't really important to anyone? I remember this coming again and again and again from other scientists, people I respected could be totally dismissive and scathing about Bob, saying he's lovely man, but completely misguided …. he really shouldn't be doing this work because it's immoral as well as a waste of his talent. That was the general theme. We were in this sort of little ghetto at the top of Physiology, which was ringed with prejudice and hostility and antagonism. We thrived on one part of it, being a bit sort of obstinate, and on the other hand felt slightly ambivalent about the work. The other problem was that later most of the work was going on in Oldham, and we were really irritated because Bob wasn't there when we needed him a great deal. He used to arrive absolutely shattered at night, we'd still be working in the lab and then we'd run in and grab him and say, I've got this problem, what about this, what about that? And he was great, he would always respond - but Richard and I always moaned that Bob wasn't around more, why was he wasting his time up in Oldham doing this sort of thing? How short sighted we were! And what a remarkable visionary Bob was.

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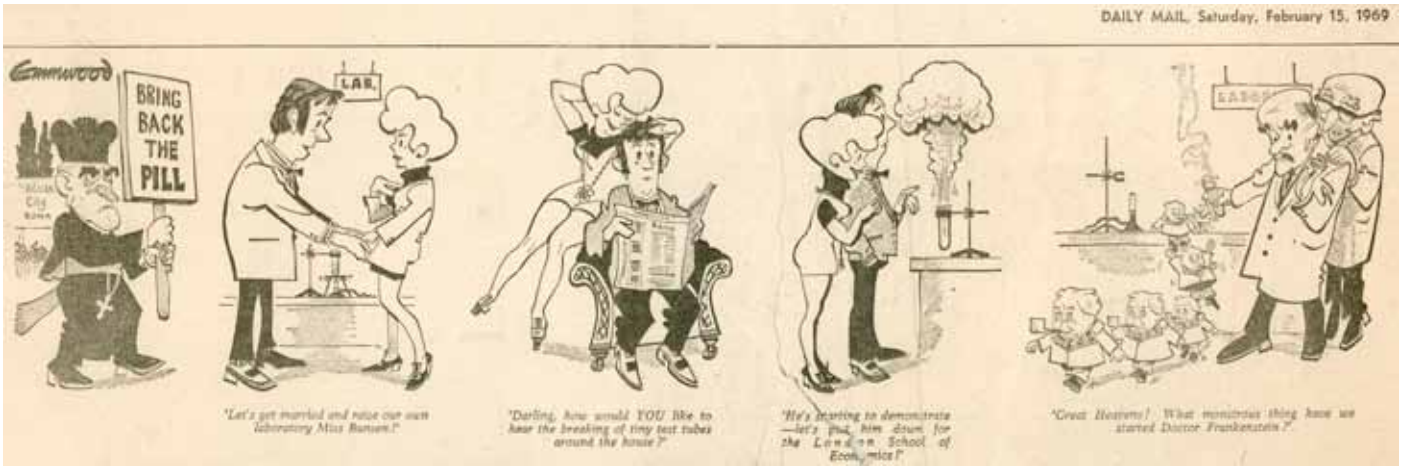

In September 2001, Bob Edwards received the Albert Lasker Award for Clinical Medical Science, often called the American Nobel prize, at a ceremony in New York. The following article is his account of his life's work.

Lasker Clinical Medical Research Award

The bumpy road to human *in vitro* fertilization

ROBERT G. EDWARDS

My first ideas of human *in vitro* fertilization (IVF) arose with my PhD in Edinburgh University in the early 1950s. Supervised by Alan Beatty, my research was based on his work on altering chromosomal complements in mouse embryos. All went very well, as haploid, triploid, tetraploid and more-bizarre embryos emerged[1], and I learned about mouse meiosis, fertilization, embryos, blastocysts and chromosomes as well as immense amounts of reproductive physiology. The arrival of Alan Gates in Edinburgh relieved my midnight labors. Also working with Alan Beatty, he brought the Organon preparations of gonadotrophins which induced immature mice to ovulate many eggs and mate with adult males. Transfer of their embryos to adult mice produced fully normal offspring in huge numbers.

Science in Edinburgh was incredibly fruitful. Another PhD student, Ruth Fowler (later my wife), and I decided to test these Organon hormones on adult mice. They again induced estrus and timed oocyte maturation, with erratic numbers of ovulated oocytes, fertilization, cleavage, implantation and fetal growth to full term[2]. Julio Sirlin and I[3] applied radioactive tracers to spermatogenesis, oogenesis and embryology, labeling DNA, RNA and proteins. My professor, Conrad Waddington, discussed ethics and genetics with senior churchmen, which proved invaluable for me, as ethics would feature immensely in my future work on human conception. After a year at the California Institute of Technology with Albert Tyler, a welcome from Alan Parkes and Bunny Austin to the National Institute for Medical Research, London, in 1958, shifted me from pure science to biomedicine. Emphasis on immunology gradually decreased as visiting lecturers described their work. Margaret Jackson ran a sperm donation program in Devon. Only 5 feet tall, her heart was double the normal size as she stoutly defended her work against a barrage of critical ethical questions. What could I do for patients? Literally nothing until human eggs were fertilized *in vitro*. Carl Gemzell in Sweden began treating infertile acyclic women with extracts of human anterior pituitaries[4] but, as in mice, oocyte numbers were erratic, so very high-order multiple pregnancies were established alongside patients with singletons or twins. Later, some of his patients died from Creutzfeldt–Jacob disease transmitted by those pituitaries, showing how clinical matters can go badly wrong. Donini *et al.*[5] extracted follicle-stimulating hormone from human menopausal urine and Bruno Lunenfeld[6] applied it clinically, so pituitary glands were no longer needed.

Increasingly committed to human studies, I sought to collect several immature human oocytes from pieces of excised ovarian tissue, mature and fertilize them *in vitro* and transfer the resulting embryos into infertile women to help them conceive. Some gynecologists approached about this project candidly responded they thought the idea preposterous. Molly Rose, a gynecologist who delivered two of my daughters, offered to send occasional slithers of human ovaries. Now I had a supply of oocytes, albeit very rare and precious. Pincus and Saunders[7] had liberated rabbit and human oocytes from their follicles *in vitro* and shown how both matured spontaneously in less than 12 hours. I hurried to apply these findings, and found that oocytes from mice, rats and hamsters did mature within 12 hours. Whatever I did, sheep, cow, rhesus monkey, baboon and human oocytes did not mature, despite my adding hormones, media constituents and feeder cells, changing gas phases, and even perfusing human ovaries *in vitro* with HCG before aspirating follicles. After 2 disappointing years, a slither of human ovary from Molly Rose provided several oocytes. This time I waited longer, for 18 hours, only to face disappointment—the oocyte nuclei were unchanged[8]. For the next three

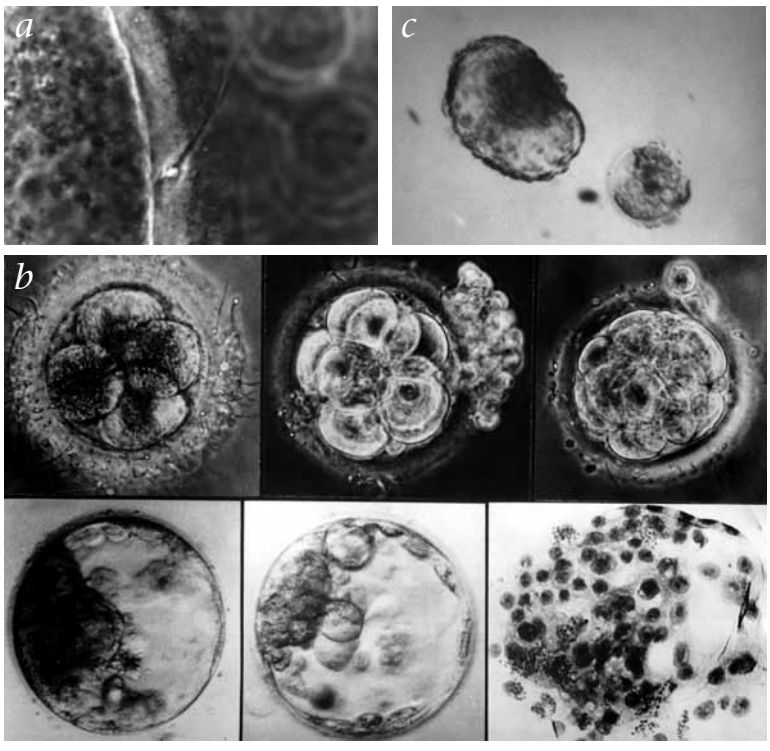

Fig. 1 Initial work in introducing human IVF. ***a***, An early stage of fertilization *in vitro* showing the spermatozoon making contact with the oolemma. ***b***, Living 4- and 8-cell human embryos, a compacting morula, two examples of live blastocysts, and a fixed blastocyst preparation with nuclei and chromosomes. ***c***, A hatched blastocyst at day 9, with a large embryonic disc and bilaminar membrane; the shed zona pellucida contains cells and debris.

oocytes,I waited for 25 hours, and—joy unbounding! A beautiful diakinesis with chiasmata, superb chromatids and nucleoli fading appeared[9]. Pincus's error cost me 2 years. Now, a definite future existed for human IVF. Oocytes had to develop *in vitro* to meiosis-2 arrest and expel a first polar body. These stages were inevitable once diakinesis had begun, and would require an estimated 12 hours.

The rarity of human oocytes left much time available for immunology and for another of my interests: isolating embryo stem cells from mammalian embryos. Stimulated by work with Julio Sirlin, I disaggregated four- and eight-cell rabbit embryos, which produced groups of single cells that persisted briefly in culture. Unexpectedly, John Paul at Glasgow University invited me to work with him and Robin Cole on cytodifferentiation in the early embryo. During that wonderful year, stem cells grew from inner cell mass of rabbit blastocysts to differentiate into blood islands, muscle and connective tissue. Long-lived (immortal) stem cells, stable karyotypically, enzymologically and morphologically, grew rapidly *in vitro* and after cryopreservation[10,11]. I followed these leads as clinical entities 20 years later. While in Glasgow, the first human oocyte matured *in vitro* to metaphase-2 with a polar body in 37 hours[9].

Cambridge beckoned, and I rejoined Parkes and Austin and resumed immunology and oocyte maturation. Cow, sheep, pig and monkey oocytes all matured *in vitro*, each with their own specific intervals[12]. Chris Polge and I found that pig oocytes required 37 hours *in vitro* and *in vivo*, just like human oocytes! Clinical collaboration was essential, with Molly Rose and Howard and Georgeanna Jones at Johns Hopkins, and Victor Lewis in London. Each stage in the maturation of human ovarian oocytes was timed[12]. A memorable 6 weeks at Hopkins included occasional pronuclei forming in inseminated human eggs *in vitro*, as happened again back in Cambridge. Tight controls on pH, osmotic pressure and constituents of medium were probably paying off. Molly Rose sent a piece of human ovary. Barry Bavister had devised a medium with high pH for hamster fertilization *in vitro*, already achieved by Yanagimachi and Chang[13]. Examining that small group of matured and inseminated oocytes was memorable: every stage of fertilization was recorded[14]. We found later that media of lower pH, and other variations, would support human fertilization.

Searching for a clinical partner capable of reaching the ovary using minimal surgery ended as I phoned Patrick Steptoe in 1968, having read of his laparoscopy in the Oldham and District General Hospital. Then the world's master of this method, he could easily aspirate oocytes from their follicles[15]. We teamed up for IVF, and discussed in detail the safety of our proposed procedures, and the underlying ethics. We agreed to work together as equals, pursue our work carefully, and stop if any danger emerged to patients or children, but not for vague religious or political reasons[16]. We stayed together for 20 years, until his death. I reckon he taught me medicine. At the time, he faced immense clinical criticism over his laparoscopy, even being isolated at clinical meetings in London. This disgraceful treatment led me to comment on this shabby treatment of a man opening new concepts in his field as I wrote his biography, just as it had angered many of his clinical colleagues in northern England. He is now regarded as a true pioneer of general endoscopy and, of course, of IVF.

Fig. 2 Reverend Gordon Dunstan talking with Robert Edwards some time in the 1980s. A senior ethicist of the Church of England, Dunstan knew more about the science and medicine of IVF than most scientists and clinicians at the time, having taught himself in detail about new approaches to infertility. His book *Artifice of Ethics*, published in 1974 (ref. 18), devoted several chapters to the science and medicine of IVF and its ethical issues.

Mild ovarian stimulation with human menopausal gonadotropin (HMG) and HCG produced several follicles. Steptoe's aspirations 36 hours after HCG treatment were superb, with the oocytes about to ovulate being surrounded by glistening cumulus cells. Fertilization and embryo growth *in vitro* proceeded excellently. Fascinated, I watched as two-cell, four-cell and eight-cell embryos, morulae, and beautiful blastocysts at 4–6 days grew *in vitro* in various media (Fig. 1). About half the embryos faltered as they approached the blastocyst stage[17]. Most had normal nuclei, even-sized blastomeres and approximately diploid chromosomes, developed to a strict timetable, compacted excellently, secreted blastocoelic fluid, and were obviously vibrant as blastocysts with 100 or more nuclei and many mitoses on day 5. Some blastocysts grew to 9 days, their expanding embryonic discs stuffed full of embryonic stem cells!

Ethicists decried us, forecasting abnormal babies, misleading the infertile and misrepresenting our work as really acquiring human embryos for research. They announced that IVF did not cure infertility, as women remained infertile after having an IVF baby. My response was to put forward spectacles, false teeth and heart transplants. Popes were critical and rigid Protestants were sometimes vicious. A new-found friend, Gordon Dunstan, senior ethicist of the Church of England, wrote his *The Artifice of Ethics*[18] with four chapters on IVF and a penetrating and ethical analysis (Fig. 2). Some years later, the Archbishop in Tiblisi, Georgia, responded identically, instantly making a collection in his cathedral to train Georgian IVF embryologists! It was time to transfer embryos to their mothers. We gained ethical consent from Cambridge and Oldham to open a clinic in Newmarket Hospital, near Cambridge, with a post for Steptoe. The Medical Research Council refused to fund it; at least one member of that committee has since apologized publicly. The Oldham authorities converted the small Kershaw's Hospital into the world's first IVF clinic. With colleagues, I had assessed in detail the teratological risks to babies, with a general consensus that our work was safe. We began transfers in 1972. I assumed human embryo implantation rates matched those of laboratory and farm animals, only realizing some time later that only 20% of them can implant successfully.

Ovarian stimulation with HMG and HCG led to severe endocrine deficiencies in the luteal phase of our patients. Some

patients menstruated 5–6 days after ovulation as their urinary pregnanediol fell abruptly. This disappointing discovery meant that endocrine support was essential until the placenta assumed its endocrine function at 8–10 weeks of gestation[19]. Daily injections of progesterone in oil were needed, but could cause serious scabbing. We substituted Primulot depot, an artificial progestagen given once every 5 days. This ethical decision produced transfer failures for 2 years. Ken Bagshawe in London assayed our patients' blood samples using a new HCG immunoassay, and identified some very short-lived pregnancies, later called 'biochemical pregnancies'. Primulot had acted as an abortifacient (confirmed a few years later), so we mostly abandoned it. To our delight, one clinical pregnancy began after a blastocyst was transferred[20]. Sadly, it was ectopic and had to be removed at 11 weeks or so. Still, my laboratory techniques had sustained a human embryo capable of implantation and early organogenesis.

Luteal-phase weakness had to be overcome. We tested different forms of stimulation: clomiphene and HMG produced excellent luteal phases, bromocryptine and HMG to reduce high prolactin levels in many stimulated patients, and HCG alone to control ovulation in natural menstrual cycles. We did the first gamete intra-Fallopian transfers (in our terms, oocyte recovery with tubal insemination), cryopreserved oocytes and embryos, accomplished oocyte donation to a recipient, and finally moved to natural-menstrual-cycle IVF by closely timing the urinary luteinizing hormone surge in our patients. Lesley Brown was the second natural-cycle patient; her single oocyte was aspirated within minutes, inseminated quickly and transferred exactly as it reached the eight-cell stage. I hoped earlier transfer would benefit from the embryos' spending less time *in vitro*. After an eventful pregnancy (Fig. 3), Louise Brown was born on 26 July 1978 on a momentous evening in Oldham. It is hard to put into words what the occasion of her birth meant to me, and to our wonderful supportive team. It was a purely routine Caesarean section, yes, but with a significance outstripping anything we had done before or were likely to achieve later. Surrounded by hundreds of members of the press, the birth was achieved in secret, to the delight of the parents, staff and ourselves. Details of all our work have been reported elsewhere[21–25]. A success rate of 4, possibly 5, pregnancies of 32 transfers using natural-cycle IVF alerted me to the weakness of human implantation compared with that of other species, which still restricts IVF benefits today.

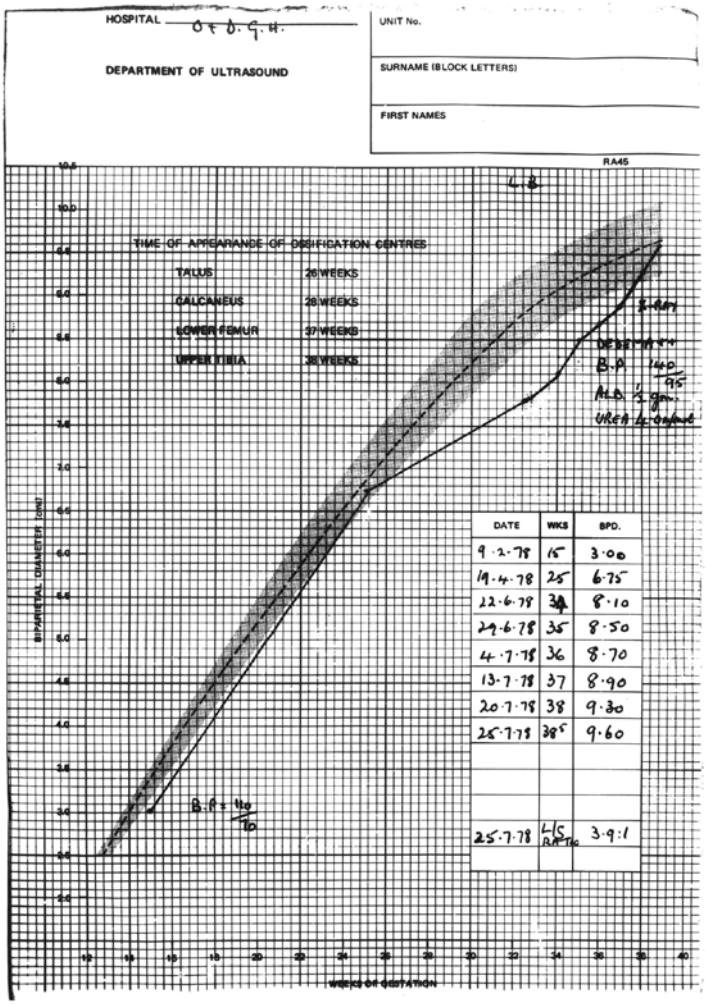

Fig. 3 Growth of the first IVF baby *in utero*, showing low biparietal diameter from week 26 to week 38, when a Caesarean section was done.

Louise Brown's birth marked the end of the beginning of human IVF, acclaimed at the Royal College of Obstetricians and Gynaecologists. This event was snubbed by some clinicians now styled as 'pioneers', who shouted that the test-tube claim was a fake! They did not matter. IVF had to become large-scale, in a center providing the necessary clinical, scientific, consultative, nursing and counseling back-up services, and even providing ward and dining facilities for the immense patient numbers on Steptoe's waiting list. No governmental support was forthcoming, so our work was halted for 2.5 years after Louise Brown's birth. Finally, venture capital was obtained and Bourn Hall opened in September 2000. This Jacobean mansion, with the motto 'Jour de ma Vie', became the world's second (and most beautiful) IVF clinic—and among the largest. So many patients passed through its doors to enable the many clinical trials of IVF success: treatments for infertile men, and for women responding poorly to ovarian stimulation or suffering from endometriosis. We carried out studies on embryos, better endocrine tools and transfer catheters, improved laparoscopy, embryo implantation, biochemical pregnancies, miscarriage, birth and early growth of children. Babies had to be conceived—dozens, fifties, hundreds and thousands—to assess the procedures and safety of IVF (ref. 26). Familiarity with the unexpected was routine, endless small events almost too strange to be true. Staff responded. More than 1,000 children were born by 1989, as normal as children conceived in vivo. Major ethical arguments in the press formed a constant background. I had to issue eight libel actions in the High Court of London on a single day, which is when ethics becomes very practical. I won them all, but the work and worry restricted research for several years.

Many papers were published. Preimplantation genetic diagnosis was resumed, as Jones, Singh and I[27] marked one-half of human spermatozoa and a few available human embryos unsuitable for transfer. This was the first indication of sex

selection of human spermatozoa and embryos *in vitro*. A year or so later, Alan Handyside succeeded with a birth after amplifying Y sequences in human embryos. Still working with PhD students in Cambridge, I supervised Richard Gardner and Peter Hollands, proposing they assessed embryo stem cells for making transgenic mice[28] or to repair damaged bone marrow in lethally irradiated mice[29]. Stem cells from mouse or rat embryos apparently followed fetal pathways through liver to bone marrow in irradiated mice. We moved to clinical development, as Simon Fishel, Chris Evans and I[30] measured HCG output in cultured human blastocysts and reported weak growth of inner cell mass cells. The field of therapeutic stem cells was wide open[30,31], when an ethical decision in Bourn Hall reserved all embryos for their parents, and this research ended[30].

Clinical topics were equally numerous. Male infertility, endometriosis and embryo transfer, cryopreservation of embryos and desperately low human embryo implantation rates were assessed. The essential need for ethicists and counselors to advise patients, and ourselves, was recognized. Gamete donation and surrogate pregnancies were introduced, and immense attention was paid to consent forms and legal aspects. Implantation rates remained stubbornly low despite various forms of ovarian stimulation, indicating embryo quality had been 'decided' long before transfer. The world now joined in IVF, with the introduction of intracytoplasmic sperm injection, improved maturation *in vitro*, sex selection and other items. These years saw the deaths of both Steptoe and Jean Purdy; by then, Steptoe's work had been widely recognized (Fig. 4)

Fig. 4 A happy moment as Robert Edwards and Patrick Steptoe receive an Honorary DSc From Hull University in 1983.

My genetic interests persist in the area of the control of human development. Something must be fundamentally flawed with a reproductive system that allows only 20% of embryos to implant, even in younger couples. Why are so many human spermatozoa immotile or formed abnormally, and why do up to one-half of embryos carry chromosomal anomalies? Such issues hold my interest today as I question our earlier concepts on embryonic differentiation in mammals, or search for functional embryonic homologies between human and *Drosophila, Caenorhabditis elegans* and *Xenopus laevis*[32].

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R.G. Edwards
Reproductive BioMedicine Online
Duck End Farm, Dry Drayton
Cambridge, UK

Pen Portraits

Professor Peter BRAUDE BSc MB BCh MA PhD FRCOG DPMSA FMedSci

Peter Braude is Head of the Department of Women's Health at King's College London, and directs the Centre for Preimplantation Genetic Diagnosis at Guy's and St Thomas Hospital, which is the most active of the HFEA licensed programmes in the UK. Trained as a doctor in South Africa, he moved to Cambridge in 1974 to become a member of the department of Anatomy where he read for his PhD. Whilst there, together with Professor Martin Johnson he lead one of the first groups to be funded by the UK Medical Research Council to carry out research using human embryos fertilised in vitro, to gain an understanding of the cellular and molecular mechanisms operating at these early stages of development. Having undertaken consultant training in obstetrics and gynaecology interspersed with research in embryology and reproduction, he was appointed to the chair of Obstetrics and Gynaecology at the United Medical and Dental Schools of Guy's and St Thomas' Hospitals, London, now incorporated within King's College London. There he set up a successful assisted conception and preimplantation genetic diagnosis programme, which continues today at Guy's Hospital. His research group at King's, funded by the Medical Research Council, established the first human embryonic stem cell lines in the UK, and the first internationally to contain the common ΔF508 cystic fibrosis deletion. These and the other lines established have been lodged in the UK Stem Cell Bank for use in international research. He served for five years as a member of the Human Fertilisation and Embryology Authority, and was chair of the Scientific Advisory Committee for the Royal College of Obstetricians and Gynaecologists. He chaired the RCOG expert committee on Umbilical Stem Cell Banking and the Expert Committee advising the HFEA on multiple pregnancies after IVF. He currently sits on the committee for the Safety of Blood, Tissues and Organs and the management committee of the UK Stem Cell Bank.

Professor Jacques COHEN BSc MSc PhD HCLD

Jacques Cohen is one of the founders and principals of Reprogenetics, one of the larger PGD service laboratories in the USA and founder and President of Tyho-Galileo Research Laboratories – an organization that promotes and conducts human fertilization and preimplantation research. He is also the Scientific Director of IVF-Online. He was trained at Erasmus University in Rotterdam, Holland as a Reproductive Scientist specialized in in vitro fertilization and cryobiology. His initial studies of human embryology occurred in the late 1970s. He was one of the first embryologists in Bourn Hall Clinic and moved to the USA in 1985 after having studied the application of IVF in male factor infertility and the cryopreservation of blastocysts. In Atlanta, Georgia (USA), he and colleagues developed methods for micro-surgically assisting human fertilization, precursor methods to ICSI. The same team was responsible for the development of assisted hatching and co-culture. In 1989 he became the Laboratory Director at Cornell University in New York City, where aneuploidy testing as well as fragment removal were added to the list of technologies. The same team has been responsible for new methods in cryobiology and preimplantation genetics when moved to Saint Barnabas in 1995, where he became the scientific Director until 2003; through Tyho-Galileo he is still responsible for research performed at The Institute of Reproductive Medicine and Science as consultant scientific director. He has authored more than 200 publications and several textbooks. He is the senior adjunct editor of Reproductive Biomedicine Online and the North-American editor of Zygote. He is associated with several laboratories involved in IVF and PGD both in Europe and the USA.

Professor Sir Richard GARDNER Kt, MA, PhD, FRS

Richard Gardner was Royal Society Henry Dale Research Professor (1978–2003), and since then Royal Society Edward Penley Abraham Research Professor at the Department of Zoology, University of Oxford. He read Natural Sciences at St Catharine's College Cambridge including Part 2 Physiology (1966) followed by a PhD in the Physiology Department (1971). He was Director of the ICRF Developmental Biology Unit in Oxford (1986–96), Member of the ABRC (1990–93), and President of the Institute of Biology (2006). He ha sbeen awarded the Scientific Medal by the Zoological Society of London (1977), March of Dimes Prize in Developmental Biology (1999), Royal Medal of the Royal Society (2001), and Albert Brachet Prize of the Royal Academy of Belgium (2004).

Dr Kay ELDER BSc, PhD, MB, Bchir, FRSM

Kay Elder joined Steptoe and Edwards' team at Bourn Hall Clinic in 1984. Her academic background began with a Diploma in Chemistry from Dundee (1966), followed by Biochemistry at the University of St Andrews (1970). A PhD thesis studying the molecular biology of oncogenic viruses at the University of Colorado Medical School in Denver (1971-74) then led to post-doctoral research at the Imperial Cancer Research Fund in London. In 1978 she was awarded a Foulkes Foundation Fellowship for the promotion of collaboration between medicine and science, and undertook a medical degree at Cambridge University, graduating in 1981. Her initial appointment at Bourn Hall was as Clinical Assistant to Patrick Steptoe; her scientific background soon led her to the science of IVF in the Embryology laboratory, and with these combined interests, her career evolved into education and teaching. From 1989 to 2005 she conducted regular workshops and seminars in Assisted Reproductive Technology at Bourn Hall for groups of doctors, scientists, nurses and other healthcare professionals. In 1994 she became a Founder Member and Executive Secretary

for Alpha, an International society for scientists in reproductive medicine, and edited and produced quarterly newsletters for Alpha from 1994 – 2001. As Visiting Professor at Danube University of Krems in Austria (1998), she initiated and directed a postgraduate training programme for IVF scientists, which was followed by the inauguration of an MSc in Clinical Embryology at the University of Leeds (2000). She continues to hold a post as Honorary Senior Lecturer in Leeds, as well as Senior Research Scientist at Bourn Hall Clinic, co-ordinating embryo research programmes in collaboration with academic research teams in Leeds, Cambridge and London. From July 2007 Kay has also acted as Deputy Editor to Professor Robert Edwards for the journal Reproductive Biomedicine Online. Her publications include senior authorship of three textbooks: In Vitro Fertilization (1998, 2000), Infections, Infertility and Assisted Reproduction (2004), and Human Preimplantation Embryo Selection (2007).

Professor Sarah FRANKLIN BA, MA, PhD

Sarah Franklin is Professor of Social Studies of Biomedicine and Associate Director of the BIOS Centre for the Study of Biomedicine, Bioscience, Biotechnology and Society in the Department of Sociology at the London School of Economics and Political Science (2004-). She was educated at Smith College (BA 1982), University of Kent (MA 1984), New York University (MA 1986), and the University of Birmingham (PhD 1992). Before joining the LSE she has had postitions at Lancaster University (1990-1997, 1997-2001), University of Manchester (1990-1993), New York University (1993), and University of California at Santa Cruz (1994-5). She has served on editorial Boards of Science as Culture (1992 -); Cultural Anthropology (1995-2001); Body and Society (1997-2003); Ethnos (1993-1998); Distinktion (2004-); Feminist Theory (2002-); and Biosocieties (2004-). Her publications include Off-Centre: feminism and cultural studies (1991, 2008); Procreation Stories (1993); Technologies of Procreation (1993, 1999); Sociology of Gender (1996); Embodied Progress: a cultural account of assisted conception (1997); Reproducing Reproduction (1998); Global Nature, Global Culture (2000); Relative Values: reconfiguring kinship theory (2001); Remaking Life and Death: toward an anthropology of the biosciences (2003); Born and Made: an ethnography of preimplantation genetic diagnosis (2006); Dolly Mixtures: the remaking of genealogy (2007).

Professor Emily JACKSON BA, MA

Emily Jackson is Professor of Law, London School of Economics and Political Science (2007-). She was educated at Brasenose College, Oxford (BA Jurisprudence 1989; MA 1991) and joined the Centre for Socio-Legal Studies, Wolfson College, Oxford (1989-1991) before becoming a Fellow and Lecturer in Law at St. Catharine's College, Cambridge (1991-1993), Lecturer in Law, Birkbeck College, London (1993-1997) and joining the Law Department at the London School of Economics (1998-2004) as Senior Lecturer. She was then Professor of Medical Law at Queen Mary, University of London, Barts and the Royal London Medical School (2004-2007). She has beeen a member of the HFEA since 2003 (Deputy Chair since 2008) and a member of the BMA Medical Ethics Committee since 2005, of the Royal College of Physicians Ethics Committee since 2006, and of the Royal College of Pathologists Ethics Committee since 2005. Her publications include Regulating Reproduction (2001; Winner of Society of Legal Scholars' Prize for Outstanding Legal Scholarship 2002), Medical Law (2006), and Individual Freedom, Autonomy and the State: The limits of intervention in private life (co-editor, 2009), plus articles in scholarly journals, including Modern Law Review, Current Legal Problems, Medical Law Review, Nature, Biosocieties.

Professor Lisa JARDINE CBE, MA, PhD FRHistS FRSA

Lisa Jardine has been Professor of Renaissance Studies, since 1989, Centenary Professor, since 2005, and Director, AHRC (formerly AHRB) Research Centre for Editing Lives and Letters, since 2002, at Queen Mary (formerly Queen Mary and Westfield College), University of London. Educated at Newnham College, Cambridge (BA Maths and English 1966; MA 1968; PhD 1973; Associate 1992) and University of Essex (MA 1967), her career has included periods at the Warburg Institute (1971–74), Lecturer in Renaissance Literature, University of Essex (1974), Cornell University (1974–75), University of Cambridge (1976-1989) where he has Hon. Fellowships at King's and Jesus Colleges. She has chaired the AHRB Working Party on public understanding of the arts and humanities (2002), the AHRC Museum and Collections Committee (2004–), the Judges for the Orange Prize for Fiction (1997), the Booker Prize for Fiction (2002), the Michael Faraday Prize Committee of the Royal Society (2003–), and the HFEA (2008-). Publications include Francis Bacon: discovery and the art of discourse (1974), Still Harping on Daughters: women and drama in the age of Shakespeare (1983), From Humanism to the Humanities: education and the liberal arts in fifteenth- and sixteenth-century Europe (jointly,1986), What's Left? Women In Culture and the Labour Movement (jointly,1989), Erasmus, Man of Letters (1993), Reading Shakespeare Historically (1996), Worldly Goods: a new history of the Renaissance (1996), Erasmus, the Education of a Christian Prince (1997), Hostage to Fortune: the troubled life of Francis Bacon (jointly,1998), Ingenious Pursuits: building the scientific revolution (1999), Francis Bacon, A New Organon and Other Writings (1999), Global Interests: Renaissance art between East and West (jointly, 2000), On a Grander Scale: the outstanding career of Sir Christopher Wren (2002), The Curious Life of Robert Hooke: the man who measured London (2003), London's Leonardo (jointly, 2003), and The Awful End of Prince William the Silent (2005).

Pen Portraits

Professor Martin JOHNSON MA, PhD, FRCOG

Martin Johnson is Professor of Reproductive Sciences, University of Cambridge and President of Christ's College. Educated at Christ's and the Department of Physiology, Cambridge, he and Richard Gardner were Bob Edwards' first graduate students. He held an MRC Junior Research Fellowship (1969-74) during which time he also was awarded a Harkness Fellowship held at Johns Hopkins University and the University of Colorado. He joined the Anatomy Department in Cambridge as lecturer (1974–84), Reader (1984–92) and Head of Department (1995–99), and has held honorary positions in Obstetrics and Gynaecology, UMDS (1991–95), Zoology and Law at La Trobe University (Melbourne, 1993, 2006), Physiology at Sydney University and St Paul's College (1999–2004), and the Indian Institute of Science, Bangalore (1984-89). He was chair of the British Society for Developmental Biology (1984–89), member of the HFEA (1994–99), the BMA Board of Medical Education (2002), specialist scientific advisor to the Joint Lords and Commons Committee scrutinizing the Draft Human Embryos and Tissue Bill (2007), and founding scientific member of the Cambridge Socio-legal group (2001-2008). Awards include the Albert Brachet Prize, Belgian Royal Academy of Sciences, Letters and Fine Arts (1989) and the King's Fund Prize for Innovation in Medical Education (1993). Publications include Essential Reproduction (6th edn 2007; winner of the BMA Obstetrics and Gynaecology prize, 2008), Sexuality Repositioned (jointly, 2004) and Death Rites and Rights (jointly, 2007) plus papers on reproductive science, ethics, law and medical education. He is currently studying the history of mammalian developmental biology in the UK since 1945.

Baroness Onora O'NEILL of Bengarve MA, PhD, CBE, PBA, Hon FRS, FmedSci

Onora O'Neill was Principal of Newnham (1992-2006), and teaches in the Faculty of Philosophy in Cambridge. Educated at Oxford and Harvard, she has also held positions at Columbia and Essex Universities, and has been awarded Honorary degrees from several other universities. She is currently President of the British Academy, chairs the Nuffield Foundation and is Professor of Philosophy in Cambridge. She been a member of and chaired the Nuffield Council on Bioethics and the Human Genetics Advisory Commission. She has worked on a number of reports on bio-medical issues, including recently the Kings Fund Inquiry into the Safety of Maternity Services. She was created a Life Peer in 1999, sits as a crossbencher, served on the House of Lords Select Committees on Stem Cell Research, BBC Charter Review and currently Genomic Medicine. She writes on ethics and political philosophy, with particular interests in questions of international justice, in the philosophy of Immanuel Kant and in bioethics. Her books include Faces of Hunger: An Essay on Poverty, Development and Justice (1986), Constructions of Reason: Exploration of Kant's Practical Philosophy (1989), Towards Justice and Virtue (1996) and Bounds of Justice (2000), Autonomy and Trust in Bioethics (2002) and A Question of Trust (the 2002 Reith Lectures) and Rethinking Informed Consent in Bioethics (jointly with Neil Manson, 2007). She currently works on practical judgement and normativity, on questions of trust and accountability in public life; and on the ethics of communication (including media ethics), while continuing to work on Kant's philosophy.

Dame Marilyn STRATHERN MA, PhD, FBA

Marilyn has been Mistress of Girton College since 1998, and William Wyse Professor of Social Anthropology, University of Cambridge (1993–2008). Educated at Girton College, her career has also included periods at the Museum of Ethnology, Cambridge (1966–68), the Australian National University (Canberra, 1970–72, 1974–75, 1983-84), Trinity College Cambridge (1984–85; Hon. Fellow, 1999) and Head of Department of Social Anthropology (Manchester University, 1985–93), plus a visiting professorship at the Univerisity of California, Berkeley (1984). She holds many honorary degrees and awards including Hon. Foreign Membership of the American Academy of Arts and Sciences, the. Rivers Memorial Medal (1976), Huxley Memorial Medal (2004) and Viking Fund Medal, Wenner-Gren Foundation for Anthropological Research (NY, 2003). Publications include Self-Decoration in Mt Hagen (jointly, 1971), Women In Between (1972), Nature, Culture and Gender (co-editor,1980), Kinship at the Core: an anthropology of Elmdon, Essex (1981), Dealing With Inequality (editor, 1987), The Gender of the Gift (1988), Partial Connections (1991), Big Men and Great Men in Melanesia (editor, 1991), After Nature (1992), Reproducing the Future (1992), (jtly) Technologies of Procreation (jointly, 1993), Shifting Contexts (editor, 1995), Property, Substance and Effect (1999), (ed) Audit Cultures (editor, 2000), Kinship, Law and the Unexpected (2005).

Professor Marina WARNER CBE, MA, FBA, FRSL

Marina Warner is a writer and critic, Professor, Department of Literature, Film and Theatre Studies, University of Essex (2004-), Distinguished Visiting Professor in the Humanities, Queen Mary College, and and Visiting Professor at the Royal College of Art, Department of Animation. She was educated at Margaret Hall, Oxford (Mod. Langs, French and Italian) where she has been an Hon. Fellow since 2000. Prior to her current position, she has been a Getty Scholar (California 1987–88), Visiting Fellow at the BFI (1992), Whitney J. Oakes Fellow (Princeton, 1996), Tinbergen Professor (Erasmus University 1991), Mellon Professor (Pittsburgh 1997), Visiting Professor/fellow at the University of Ulster (1995), Queen Mary and Westfield (1995–), York University (1996–), Paris XIII (2003), Stanford University (2000), Trinity College Cambridge (1998), the Humanities Research Centre, Warwick University (1999), All Souls, Oxford (2001), Birkbeck Collge London (1999–), and Erich Remarque Institute., NY University (2006). Her numerous honours include the Reith lectures (BBC, 1994), the Tanner Lectures (Yale, 1999), Clarendon Lectures (Oxford, 2001), and Robb lectures (Auckland, 2004). She has been a member inter alia of the Advisory Board, Royal Mint (1986–93), Council,

Charter 88 (1990–98), Advisory Council, British Library (1992–98), Literature Panel, Arts Council (1992–98), Council, Institute of Historical Research, University of London (1999–2000). She has curated Metamorphing (Wellcome Trust exhibition at the Science Museum (2002–03), Only Make- Believe: Ways of Playing (Compton Verney, 2004). She has numerous honorary degrees and awards including Chevalier de l'Ordre des Arts et des Lettres (France, 2000), Stella dell'Ordine della Solidarietà (Italy, 2005). Publications include The Dragon Empress (1972), Alone of All Her Sex: the myth and the cult of the Virgin Mary (1976), Queen Victoria's Sketchbook, (1980), Joan of Arc: the image of female heroism (1981), Monuments and Maidens: the allegory of the female form (1985), L'Atalante (1993), Managing Monsters: six myths of our time (Reith Lectures 1994), From the Beast to the Blonde: on fairy tales and their tellers (1994), The Inner Eye: art beyond the visible (1996), No Go the Bogeyman: scaring, lulling and making mock (1998), Fantastic Metamorphoses, Other Worlds (Clarendon Lectures; 2002), Signs and Wonders: essays on literature and culture (2003), Phantasmagoria: spirit visions, metaphors, and media into the twenty-first century (2006), In a Dark Wood (1977), The Skating Party (1983), The Lost Father (1988), Indigo (1992), The Mermaids in the Basement (1993), Wonder Tales (ed. 1994), The Leto Bundle (2001), Murderers I Have Known (short stories; 2002), and children's books: The Impossible Day (1981), The Impossible Night (1981), The Impossible Bath (1982), The Impossible Rocket (1982), The Wobbly Tooth (1984), The Crack in the Teacup (1979), and Libretti: The Legs of the Queen of Sheba (1991) and In the House of Crossed Desires (1996).

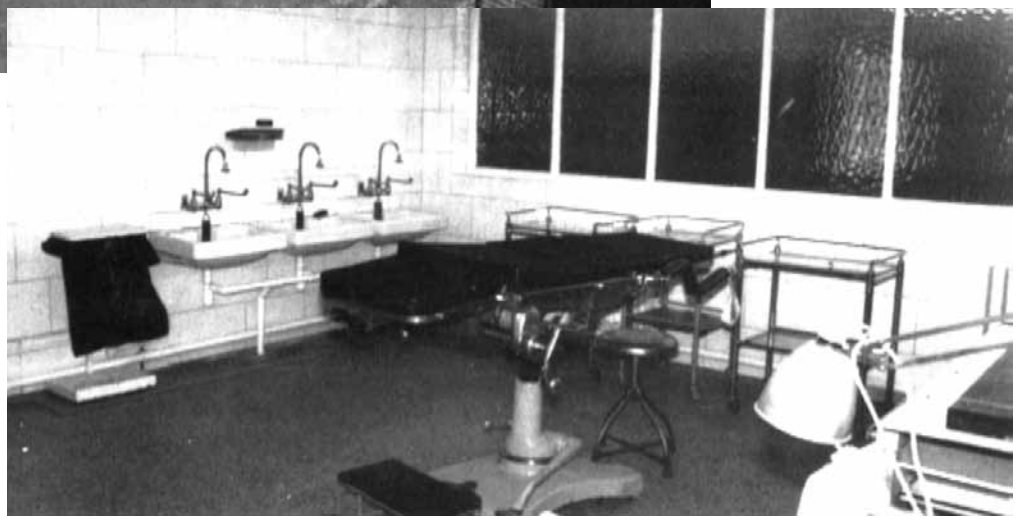
Baroness Mary WARNOCK of Weeke in the City of Winchester DBE, MA, DPhil, FRCP, FRSocMed

Mary Warnock was Mistress of Girton College (1985–91). Educated at Lady Margaret Hall, Oxford (Hon. Fellow 1984), her career included periods as Fellow and Tutor in Philosophy, St Hugh's College (Oxford, 1949–66), Headmistress, Oxford High School (1966–72), Talbot Res. Fellow, Lady Margaret Hall, Oxford, (1972–76), and Fellow, St Hugh's College (1976–84, Hon. Fellow, 1985). She chaired the Committee of Inquiry into Special Education (1974–78), the Royal Commission on Environmental Pollution (1979–84), the Advisory Committee on Animal Experiments (1979–85), the Committee of Inquiry into Human Fertilization (1982–84), the Committee on Teaching Quality (1990); She has also served on the Committee of Inquiry into Validation of Public Sector Higher Education (1984), the European Advisory Group on Bioethics (1992–94), the Archbishop of Canterbury's Advisory Group on Medical Ethics (1992–), the SSRC (1981–85), and the UK National Commission for Unesco. She holds many honorary degrees and awards. Publications include Ethics since 1900 (1960, 3rd edn 1978), J.-P. Sartre (1963), Existentialist Ethics (1966), Existentialism (1970), Imagination (1976), Schools of Thought (1977), What Must We Teach? (with T. Devlin, 1977) Education: a way forward (1979), A Question of Life (1985), Teacher Teach Thyself (Dimbleby Lecture, 1985), Memory (1987), A Common Policy for Education (1988), Universities: knowing our minds (1989), The Uses of Philosophy (1992), Imagination and Time (1994), Women Philosophers (editor, 1996), An Intelligent Person's Guide to Ethics (1998), A Memoir (2000), Making Babies (2002), Nature and Morality: recollections of a philosopher in public life (2003).

Gallery

The boy third from the left in the front row is Patrick Steptoe (circled) aged 12, taken at St Mary's School, Church Green, Witney

1978 Patrick Steptoe – musician,
and Bob Edwards - the bicycling don



Dr Kershaw's Cottage Hospital Oldham, where the work leading to Louise Brown's birth was carried out

1981 Group photo at Bourn Hall conference: "Human Conception In Vitro, Sept 3-5"

Front row: Bob, Jean, Patrick, John Webster, Simon Fischel (squatting) Who else can you recognise!

Can you help empirical research on the History of ARTs?

Sarah Franklin, Nick Hopwood and Martin Johnson are engaged in a Wellcome-funded project on the history of mammalian embryology in the UK since 1945. What we, and subsequent historians, are able to do will be crucially dependent on the materials available. We are conducting interviews with the pioneers of these major scientific and regulatory innovations and helping interested participants and organisations such as Bob Edwards, Anne Mclaren's executors, PROGRESS and PAGIGS, to donate important documents, photographs and even apparatus to publicly accessible collections. Only in such places can we be confident that items will be kept for posterity, catalogued, conserved, and made available for research. We would be delighted to hear from anyone with such materials in his or her possession, and we can advise or support you in locating the best archival home.

emails: ndh12@cam.ac.uk, S.Franklin@lse.ac.uk, or mhj21@cam.ac.uk

Art Installation by Issam Kourbaj

Artist in Residence and Bye-Fellow at Christ's College

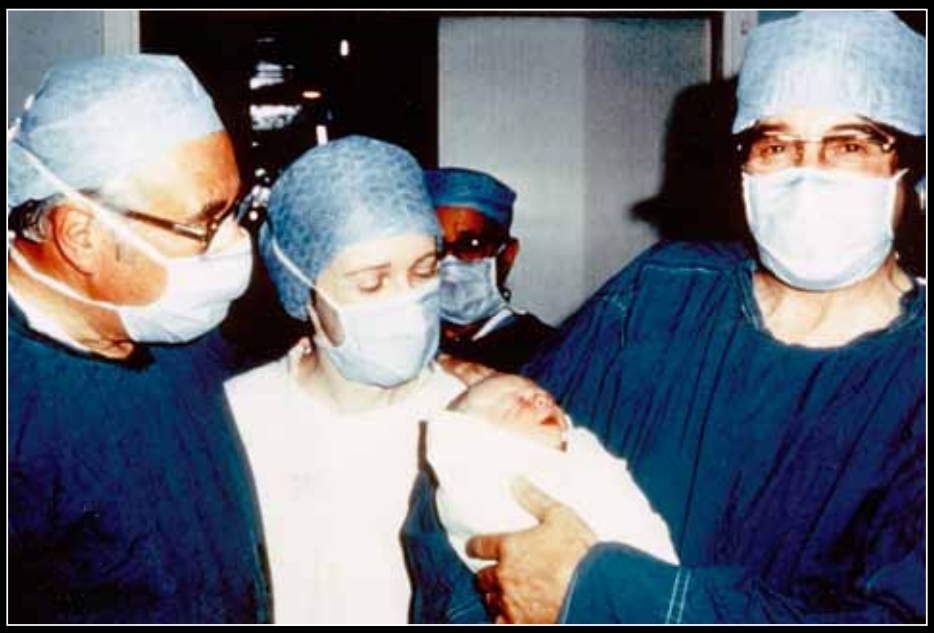
Light Reproduction

Light box with x-ray plate and Camera Obscura with multiple lenses - 2008

In 2003, at the time of the Iraq war, I worked on a project called Palimpsest, where I etched on hospital and veterinary x-ray plates. This project led me to search for further possibilities that light might offer. Subsequently, I came across the Camera Obscura, which provided me with a place where looking becomes seeing. Putting both, the x-ray plate and the Camera Obscura, together Light reproduction is an attempt to explore the performance of light and its reproduction of images.

Issam Kourbaj comes from a fine art, architecture and theatre design background. He was born in Syria, and trained in Damascus, Leningrad (St Petersburg) and London, and has been living and working in Cambridge since 1989. His work has been exhibited in three continents, and is in the Collection of the Department of the Middle East and of Prints and Drawings of the British Museum, as well as in College and private collections. His pieces 'Sound Palimpsest' is currently on show in the British Museum as part of the special display, 'Iraq's Past speaks to the Present', complementing the Museum's major historical exhibition, Babylon: Myth and Reality.

1986 Bob launches *Human Reproduction*



Louise Brown born 1978 – held by Bob as Jean and Patrick look on

1981 Bob and Jean Purdy at Bourn Hall

1987 Louise Brown holds Matthew – Bourn Hall's 1000th baby

2003, celebrating Louise's 25th birthday. Bob with Louise and Alastair MacDonald, - the first IVF boy

wellcome trust

Christ's College

nature

UNIVERSITY OF CAMBRIDGE