



Tenth anniversary issue 1

www.sciencedirect.com
www.rbmonline.com



EDITORIAL

Bob Edwards and the first decade of *Reproductive BioMedicine Online*

Richard L. Gardner^a, Martin H. Johnson^b, *

^aDepartment of Biology, University of York, Heslington, York YO10 5YW, UK

^bAnatomy School and Trophoblast Research Centre, Department of Physiology, Development and Neuroscience, The University of Cambridge, Downing Street, Cambridge CB2 3DY, UK

*Corresponding author. Tel.: +44 (0) 1223 333777; fax: +44 (0) 1223 333840.

E-mail addresses: mhj21@cam.ac.uk (M.H. Johnson); gardner750@btinternet.com (R.L. Gardner).

Introduction

This special 10th anniversary issue of *Reproductive BioMedicine Online* celebrates the achievements of Bob Edwards – Founder of our journal, Editor Emeritus, and 2010 Nobel laureate for Physiology or Medicine. A glance through his life-time's publications from 1954 to 2008 (Appendix, p. 9) reveals the extraordinary range of Bob's intellectual curiosity and knowledge, and his at times almost mischievous determination to challenge conventional wisdom. We have selected 14 of his papers from the first decade of *Reproductive BioMedicine Online* by way of illustration. Nonetheless, whole areas of Bob's interests remain unrepresented – notably the immunology of reproduction, mutagenesis, spermatogenesis, sperm biology and implantation. Despite this, we hope that we have captured the polymathic enthusiasm and energy that Bob has brought to our subject, and which inspired both of us to commence our research careers with him in 1966.

Those difficult early years in the Cambridge Department of Physiology were remarkable. We would gather regularly at lunch time in the Fountain pub for a beer and a cheese and onion roll, and there would discuss and debate science, ethics, social values, and the latest papers. Bob was an avid journal reader and always ahead of the rest of us – something that he has persisted with throughout his career, as witnessed by the extraordinary range of material and ideas he has assembled in his papers chosen for this issue.

We have organised this preface to the papers thematically, and comment on each selected paper

in the context of his life-time achievements. We hope you enjoy – and are sure you will admire – this collection from a remarkable man who has transformed both of our lives, as he has those of so many people throughout the world.

Egg maturation

Bob's studies on oocyte maturation date back to the 1950s, when his wife Ruth and he described for the first time a protocol for inducing ovulation, oestrus and pregnancy in the adult mouse (Fowler and Edwards, 1957). Further papers with Ruth, and with Austin, Gates, Sirlin, Falconer and Wilson on the endocrinology, cell biology and genetics of egg maturation followed between 1958 and 1964, and in 1965 this work came together in two seminal papers on animal and human oocyte maturation *in vitro* (Edwards, 1965a,b). It is in these papers, building on observations on the rabbit by Pincus and Chang, that Bob defines the time from the release of human oocytes from the follicle (and thus time from the LH peak) to GV breakdown, 1st polar body extrusion and entry into 2nd metaphase. In the *Lancet* paper (1965b), Bob discusses the prospects for, and difficulties likely to be confronted by, IVF, embryo culture and transfer, pre-implantation genetic diagnosis (PGD) and the biochemistry of early human development. This visionary paper of 45 years ago takes one's breath away to read even now.

For this volume, we have selected a paper from 2005 (Edwards, 2005a), in which Bob traces the

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

intertwined histories of gonadotrophins and egg maturation from these early studies. The inadequacy of cytoplasmic maturation after egg release from the follicle prompted Bob and his colleague, Patrick Steptoe, to move to HMG and HCG stimulation, when they then engaged in the struggle to understand the relationship between the inducing hormones and the endocrinology of early pregnancy, in both natural and stimulated cycles. The move through natural cycles to GnRH analogues, to recombinant gonadotrophins and the return to in-vitro maturation (IVM) are surveyed. In this last section of the paper, Bob warms to the research possibilities that mass oocyte IVM will bring – for knowledge's sake but always tempered by the strictures of ethics and potential clinical utility. Bob's knowledge, imagination and intellectual energy are impressively at work as he peers into the future – at times almost wistfully as if he wishes he could start his career all over again – addressing many of the same questions as he was asking in the 1950s but now with such a rich new technology. He is not only 'green with envy', as he describes himself, he is also evergreen with ideas and enthusiasm.

IVF

It is clear when reading Bob's early papers that his intellectual interests lie primarily in the embryo. Oogenesis, spermatogenesis and fertilisation engage him, but his passion is the unfurling of the developmental programme that these events herald (see next section). His 1950's studies focussed on the role of genetic factors in early mouse development, either by studying embryos directly or by generating them after treating sperm or eggs in some way calculated to show developmental effects. In those days, technology was limiting and most of his studies investigated the impact developmentally of chromosomal anomalies by inducing aneuploidies through drugs, X-rays or parthenogenetic stimuli.

However, for human development to be studied, sufficient embryos had to be obtained, and so IVF had first to succeed. This was not a trivial problem in 1965, by when successful IVF was limited to rabbits (Chang, 1959) and hamsters (Yanagimachi and Chang, 1963), mice following in 1968 (Whittingham, 1968). Having made some progress with egg maturation, Bob was nonetheless worried about the normality of IVM eggs, and during one of his library sessions he encountered a paper by Patrick on laparoscopic egg recovery, and then subsequently met the man himself, with now famous consequences. However, there was still the problem of capacitation to solve, with which Bob had been wrestling using various approaches (Edwards et al., 1966, 1968). Fortuitously at the same time that Patrick and Bob

were getting together, a solution to the sperm problem was found close at hand. Experiments on hamster capacitation, undertaken by Barry Bavister, then a graduate student with Bunny Austin across the corridor in the Physiology Department, had revealed that the pH of the insemination medium was crucial and when his findings were applied to human sperm, a similar result ensued. The three published their key paper 41 years ago (Edwards et al., 1969), and the media response was massive!

One early concern about that 1969 paper was that parthenogenesis was being observed, a critique also levelled – perhaps with greater justification – at Rock and Menkin (1944). In fact, the 1969 paper was careful to address this problem, one to which Bob returned on a broader canvas in Edwards (2007b). Here he reviews recent evidence for parthenogenetic reproduction in the two vertebrates groups in which the phenomenon had not yet been demonstrated, namely elasmobranch fishes and eutherian mammals. He begins with the claim of its occurrence in a captive female bonnethead shark, which produced a pup despite being segregated from males for much longer than sperm are known to survive in the female reproductive tract in this species. The claim was clinched by the demonstration through DNA fingerprinting that the genome of the offspring lacked a paternal contribution, and could be assigned unambiguously to one of three possible candidate mothers.

He goes on to tell how parthenogenetic development in the mouse has been brought about by a complex oocyte fusion and genome transfer process, whereby maternal expression of the imprinted *Igf2* gene, which is normally paternally expressed, was obtained in the presence of a defective maternally-expressed *H19* gene in diploid unfertilized oocytes that were then activated artificially. This process resulted in the production of a single fertile adult, which was accompanied by considerable pre- and post-natal losses. The discussion evolves into a broader consideration of chromosomal disorders in mammalian development.

A concern that Bob has always shared with many of his critics was the normality of the embryos produced by IVF. His early experiences on the mouse had led him to believe that early pregnancy was an effective filter of abnormal embryos, and that it was post-implantation embryonic stages in the first trimester that were most at risk of surviving environmental insults despite being damaged. But the risk of proceeding to embryo transfer was too great until he had undertaken karyotypic and developmental research on IVF-generated embryos. From time to time, epidemiological scares have erupted in the literature, almost always picked up on and exaggerated by the media. Edwards and Ludwig (2003) address this issue with a forensic analysis of

the difficulties of interpreting epidemiological studies. The analysis concludes that IVF as a procedure is an unlikely cause of abnormality in off-spring. But whether he believes that it is the patient profile or some other feature of the treatment that might exert a small adverse effect on outcomes remains unclear.

Mechanisms of early development

In a paper with Chris Hansis (Edwards and Hansis, 2005), Bob's interest in development is made clear. In this paper, he develops the notion originally propounded in an earlier article co-authored with Helen Beard (Edwards and Beard, 1997), namely that blastomeres in eutherian mammals may already be allocated to different lineages by the 4-cell stage. This allocation was held to depend on early cleavage planes bearing a consistent relationship to the animal-vegetal axial organization of a polarized oocyte. Thus, in second cleavage one blastomere was assumed to divide meridionally to produce two daughters containing cytoplasm from all axial levels of the zygote and the other equatorially to produce one daughter with only vegetal and the other with only animal polar cytoplasm. In citing the work of Gulyas (1975) on cleavage in the rabbit in support of this contention, Bob, like most others, misinterprets the explanation this author gave for the predominantly 'regular tetrahedral' arrangement of blastomeres seen at the 4-cell stage in various mammals, including man. Gulyas actually describes second cleavage as 'rotational', meaning that the second 2-cell blastomere to divide underwent a 90° rotation of its polar axis relative to that of its sister before dividing so that both blastomeres actually divide meridionally. However, more recent blastomere marking experiments in the mouse support Bob's contention that one second-cleavage division is typically meridional and the other approximately equatorial (Gardner, 2002). Because the products of the meridional division contain both animal and vegetal polar cytoplasm, it is suggested that they represent precursors of the inner cell mass (ICM), while the animal polar product of the equatorial division founds the trophectoderm and its vegetal polar counterpart, the germline. The association of the germline with vegetal polar material is presumably inspired by the corresponding localization of the germ plasm in anuran amphibians. This view of early lineage is undoubtedly conditioned by intriguing observations regarding the expression and localization of β -HCG5 transcripts to a small minority of single blastomeres dissociated from non-clinical grade early cleavage stage human embryos (Hansis et al., 2002). Blastomeres were claimed to show exclusivity in either expressing transcripts of this gene or those of the pluripotential stem cell marker, Oct4.

It is important to note that in proposing a consistent and distinctive early lineage origin for the ICM, trophectoderm and germline, Bob is not claiming that the mammalian embryo is a fully determinate, mosaic system and thereby denying its well-established capacity for regulation. This is made clear by the following extract:

"The results of cell replacement may differ according to the characteristics of the substitute cell. Fully potent replacement cells may divide immediately after insertion to restore a normal cell complement. Replacement cells with mostly animal or vegetal cytoplasm may be unable to respond as quickly."

Nonetheless, this proposed lineage scheme remains speculative and much more incisive experiments would need to be done to give it credence. It would, for example, be necessary to show by *in situ* methods that β -HCG5 transcripts or protein were normally confined to descendants of the animal daughter of the equatorial second cleavage division and that ICM cell markers were eventually restricted to descendants of both products of the meridional division. There is then also the issue of relating germ cell markers to the vegetal product of the equatorial division. Of course, in favouring segregation of the germline, Bob's thinking is, as often the case, out of step with conventional wisdom, which holds that germ cells are induced rather than specified lineally in mammals.

Critical support for their induction comes from experiments in which distal epiblast cells, which do not normally give rise to primordial germ cells, can do so to some extent if grafted in place of the proximal epiblast cells, the normal source of germ cells (Tam and Zhou, 1996). However, as all the founder cells of the epiblast in the Inner Cell Mass are distributed throughout the epiblast by this developmental stage (Gardner and Cockcroft, 1998), it is impossible to exclude the possibility that the competence to respond to an inductive signal is itself lineage-dependent and so depends on early cell origins. If a strictly inductive mechanism, like that seen in urodele amphibians, really operates in mammals, then ALL epiblast cells should be susceptible to yielding primordial germ cells when exposed to appropriate induction conditions, which has yet to be demonstrated. Thus, the possibility of a lineage-based influence on germ cell formation cannot be discounted.

Woven into the various arguments in support of the proposed model of early development is consideration of its various implications for human assisted conception *in vitro*. For example, could the choice of blastomere for PGD affect the viability of biopsied embryos? Whether removal of one or two blastomeres from cleavage stage embryos has a negative impact on subsequent development or birth weight is still a contentious issue. Also, much more

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

tongue-in-cheek is Bob's pondering whether combining ICM tissue with high-quality trophectoderm could be a way of combating implantation failure in IVF.

Edwards (2005b) combines Bob's passion for understanding development with his original interest in genetics, and does so by addressing the significance and genetic basis of polarity. Here Bob draws from his knowledge of findings in genetically more tractable species, particularly *Drosophila* and *Caenorhabditis*, and places emphasis on the degree to which the various facets of polarity depend on evolutionary conservation of common genetic pathways. One area of controversy is whether polarity of the oocyte or zygote is significant for development in mammals, and another whether the sperm plays a role in early patterning. Regarding the latter, specification of the plane of first cleavage has been variously ascribed to the site of sperm entry, alignment of male and female pronuclei, or intrinsic organization of the oocyte. Bob is clearly of the view that polarity of the oocyte is important, and holds that the ooplasm of the entire zygote rotates in relation to the position of the fertilizing sperm or, more specifically, its expanding microtubular system. Here it is worth noting that whilst the coordinated rotation of paternal and maternal pronuclei has been recorded in human zygotes, it has not been reported in the mouse or, indeed, in any other mammal. Bob re-expresses the view that the pattern of early cleavage in which division of one 2-cell blastomere is meridional and the other equatorial is specified maternally and accounts for establishing the ICM, trophectoderm and germ cell lineages at the 4-cell stage. As noted earlier, the case for this depends largely on detecting β -HCG transcripts in some isolated 4-cell blastomeres, which, in contrast to others, do not contain those for the pluripotency marker, Oct4. However, he does note that such findings were made on blastomeres from embryos that were highly heteroploid.

Bob then extends his consideration to embrace further topical issues relating to morphogenesis, including timers, RNA interference and data on the shifting gene expression patterns in early embryogenesis deduced from the use of array technology. In this, as in his other writing, he shows an enviable capacity to keep up with the literature in very diverse fields of research.

Stem cells

Edwards (2002b) holds particular interest because, although much of the content features in other of Bob's writings in *Reproductive BioMedicine Online*, it looks at the theme of embryo-derived stem cells, both historically and in relation to their potential in regenerative medicine, very much from his own

personal perspective. Many may be unaware that he became engaged in trying to derive cell lines from both cleavage- and blastocyst-stage embryos in the early 1960s, concentrating on the rabbit and mouse (Cole et al., 1965). He undertook this work largely in collaboration with Robin Cole and John Paul, the latter being a very accomplished expert in tissue culture. It was clearly demonstrated that inner cell mass tissue in particular could go on to form a variety of differentiated cell types representative of the different germ layers. Moreover, cell lines were derived that could be maintained indefinitely in a proliferative state, even after cryopreservation, thereby demonstrating that 'Hayflick's Rule' was not of universal applicability. That this work has largely been ignored by those in the stem cell field is probably mainly attributable to its being too far ahead of its time, so that neither reliable markers for different types of cells were available nor were appropriate techniques for producing chimaeras with which to critically test the developmental potential of cultured cells. The work of one of Bob's research students, Peter Hollands (Hollands and Edwards, 1986; Edwards and Hollands, 1988), on the ability of intravenously injected cells from early post-implantation mouse embryos to rapidly restore the haematopoietic system of lethally irradiated or genetically anaemic mice, is reviewed in considerable detail. Some colonization of the adult haematopoietic tissue was also obtained following introduction of such cells into normal mice and, most surprisingly, restoration of haematopoiesis in mice could even be obtained with cells from early postimplantation rat embryos. That Bob discusses this work in such detail may be because he felt that it has not received the attention it warrants. Hopefully, someone will be seduced by Bob's inspirational track-record in original research to re-visit it.

Edwards and Hollands (2007), in contrast, is centred on stem cells from the full-term umbilical cord, notably their properties and potential compared with those from bone marrow or peripheral blood for treating a range of haematopoietic and other disorders, including stroke. Both the advantages and limitations of cells from this source are considered, as also is evidence of their versatility with regard to differentiating into a variety of other cell types, including neurones, hepatocytes, adipocytes, osteocytes and insulin-secreting pancreatic β cells. Mention is also made of their seemingly more ready acceptance as allografts compared with cells from adult sources. A further, then novel, source of stem cells, the amniotic fluid that is typically made available through amniocentesis, is also considered, as also are still controversial claims that bone marrow serves as a source of oocytes. The possibility that ectopic germline or embryonic stem-like cells may be

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

responsible for at least part of the versatility is also raised, a notion of considerable antiquity.

Edwards (2008) is the most recent of a series of Bob's contributions to the Journal that deal with stem cells in the context of their potential or actual application to regenerative medicine. In this review he takes a very broad view of this important subject, proceeding from an appraisal of the burgeoning number of sources of stem cells in addition to those of early embryonic origin before dealing at length with the very impressive intrinsic regenerative capacity of the salamander with regard to re-growing amputated legs or tail. This sets the stage for Bob's introduction of the Murphy Roths Large (MRL) inbred strain of mouse which seems to show the most marked ability to regenerate of any mammal that has been studied thus far. MRL mice first attracted attention through the fairly rapid, complete sealing of holes punched in their ears for identification purposes. Subsequently, it was shown that newborns of this strain showed faster and more complete restoration of amputated terminal phalanges of digits than other mouse strains. Claims for more spectacular degrees of regeneration, such as damaged myocardium and CNS, that feature in the review have, disappointingly, not been upheld by more recent work from other laboratories.

A most interesting point to emerge from this review is Bob's strong advocacy for stem cells from sources other than very early embryos, especially since he was the first to argue explicitly in print for use in regenerative medicine of those that were surplus to the requirements of IVF (Edwards, 1982).

Epigenetics and imprinting

Edwards (2006) echoes with his very early exposure to the concept of 'epigenetics' from his Edinburgh days in the laboratory of Conrad Waddington, who was responsible for coining the term. In this review, Bob considers the phenomenon at both cell and molecular levels in various contexts starting with oogenesis and early embryogenesis, then proceeding to a discussion of imprinting syndromes, X-chromosome inactivation, reproductive and therapeutic cloning by nuclear transfer, before finally focussing on haematopoietic stem cells and the question of the elusive haemangioblast.

He also takes this opportunity to hit back at critics of his view that germ cells segregate during cleavage rather than being induced later during gastrulation. This is an issue that will remain open until a satisfactory explanation is provided as to why mice produced by pronuclear transgenesis or retroviral infection of cleavage stages not infrequently show marked disparities in mosaicism between their soma and germline (Soriano and Jaenisch, 1986; Wilkie et al.,

1986). Such disparities are unexpected given the very fine-grained mixing of founder-cell clones observed in epiblast shortly after its early post-implantation epithelialization (Gardner and Cockcroft, 1998) and the correspondingly impressive degree of equilibration of component cell populations throughout somatic tissues in adult mosaics and chimaeras. However, one way in which these seemingly conflicting findings can be reconciled is, as noted earlier, if only a sub-set of founder clones yield descendants that are competent to be induced to form primordial germ cells.

Yet again, Bob is concerned not only with basic biology relating to genomic re-programming and imprinting, but also possible practical implications of errors in these processes with respect to assisted reproduction. Here, particular concern centres on intracytoplasmic sperm injection (ICSI), where otherwise rare abnormalities have been encountered, raising the possibility of their being linked to errors in genomic imprinting. Similarly, errors of re-programming or imprinting are of concern in the possible use of therapeutic cloning to generate patient-compatible grafts. However, given the recent dramatic success in the re-programming of adult cells to a pluripotent state, there can now be few adherents to the view that therapeutic cloning has any future practically for making histocompatible grafts.

Also evident in this review is that while Bob is cautious in presenting his view on establishment of distinct cell lineages by the 4-cell stage, he seems very receptive to the claim that new oocytes can be formed in the adult from human stem cells in bone marrow. This rather undermines his argument that early segregation of the germline would be important in avoiding exposure of its cells to "massive genetic changes occurring in blastocysts ...". However, the critical issue of whether such neo-formed oocytes are competent to support embryonic development has still to be settled.

Developmental and reproductive timing

Edwards (2002a) provides further testimony to the breadth of Bob's interests and reading, in this wide-ranging review of biological timers and circadian rhythms – beginning with a consideration of genetic, dietary and other factors relating to longevity in organisms ranging from yeast to mammals before focussing more specifically on the basis of rhythmicity and its involvement in a wide range of life processes. It finally homes in on reproduction, with consideration of the LH surge (Edwards and Fowler, 1960), and the existence of a production line for oocytes (Henderson and Edwards, 1968), both subjects to which Bob has contributed, before considering what determines luteal cell life-span and our present lack of understanding of timing of events in embryogenesis.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

PGD and embryo sexing

Bob Edwards 'invented' the idea of PGD in the mid-sixties (Edwards, 1965b). He helped supervise Anne Vickers (1967), who sexed fixed whole mouse blastocysts by karyotyping. A potentially easier method of sexing was to use the 'Barr body', or sex chromatin, originally described in neurones (Barr and Bartrum, 1949), but then only recently observed in fixed embryos of rabbit (Melander, 1962) and hamster (Sundell, 1962). Encouraged by these findings, Edwards and Gardner (1967) vitally stained rabbit blastocyst sex chromatin with euchrysin 2GNX, visualised by fluorescence microscopy, but the technique, being potentially mutagenic, was not compatible with embryo transfer. So Gardner and Edwards (1968) micro-surgically biopsied small pieces of trophoblast to recover 200–300 cells that were stained and sexed. The 'sexed' biopsied blastocysts were then transferred to a pseudo-pregnant female rabbit, and the sex of the developed fetuses was confirmed anatomically and histologically at full term. Edwards and Gardner (1968) explicitly pointed out the potential for clinical application, including its use to identify autosomally inherited disease. Despite several attempts by Edwards to pursue this work subsequently in human embryos, the UK Medical Research Council (MRC) declined to fund it as being of unlikely and marginal value (Johnson et al., 2010). It was only in 1986 that interest in PGD took off within the medical science community, largely ignited by political events, and, characteristically, Bob Edwards was at the fore-front of activities (Theodosiou and Johnson, 2010). When the clinical application of PGD finally came, fittingly the lead author was a scientific 'grand-son' to Bob, Alan Handyside being MHJ's first graduate student (Handyside et al., 1989, 1990). As in so many other areas of reproductive medicine, Bob was years ahead of his time! Bob has returned in print to PGD on many occasions, and we have selected his paper on the ethics of PGD for inclusion here (Edwards, 2004).

Ethics

In a paper selected from 2007, Bob reflects on how his own ethical thinking evolved (Edwards, 2007a). Ethics first featured as the central element of an Edwards' paper in 1971 (Edwards and Sharpe, 1971). This remarkable paper rewards a read for its foresight, not only into the possibilities that producing human embryos *in vitro* brought, but also for its analysis of why such work was ethically challenging and how these challenges might possibly be met through regulation. In 1971, bioethics as a discipline was in its infancy (Cooter, 2000), research ethics committees were a novelty (Hedgecoe, 2009), and most scientists

and clinicians were remarkably unconscious of bio-ethical considerations as we would understand them today. In contrast, Bob Edwards was well aware of the problematic ethical dimension posed by his work – indeed earlier in 1971 he had been effectively censured by the MRC, which, in rejecting a grant application to fund the work that would eventually lead to the birth of Louise Brown, had ethically shredded the proposal (Johnson et al., 2010). This wounding rejection by his scientific and medical colleagues had been foreshadowed in the press coverage that had greeted his IVF paper with Bavister and Steptoe in 1969 (Edwards et al., 1969), and in the reactions of many churchmen, politicians and fellow scientists to it. It was a taste of the ethical and legal challenges to come over the next ten or so years. It hit Bob hard, because his politics, which were unashamedly leftist and humanistic, were for him rooted in the ethics of social justice. Bob wrestled with these ethical challenges, questioned his own moral position, and sought out a diverse range of ethical thinkers to test it through discourse and disputation. In the selected PGD article (Edwards, 2004), one can see how Bob rejects both the 'yuk factor' (Kass and Glass, 1971) and claims to 'authority', whether of church or state, as reactionary and irrational. The process of reasoned argument, challenge and discussion displayed in what is almost a self-dialogue, is something most of us now understand as being what ethics is about, but back in the 1960's and 70's this was ground-breaking stuff that few of us at the time truly understood. There is much in his paper that we disagree with – which delights Bob of course, because argument is how he honed his own ethical thinking for over 40 years.

Bob's commitment to ethics is seen perhaps most concretely in the biannual issues of *Ethics, Bioscience and Life* published as supplements to this journal. The first of these issues was an outcome of an international conference *Ethics, Law and Moral Philosophy of Reproductive Biomedicine* organised by Bob and held at the Royal Society of London in 2004.

Public engagement

Bob's arguments are often conducted publicly and always robustly. He is a great believer in the common sense of the public – as long as they are engaged and informed. Attempts to suppress discussion of controversial bioethical issues are anathema to him, as illustrated in an Editorial by Simpson and Edwards (2002). This Editorial explores the conflict between scientific paternalism and public values. To some, the paper may seem naïve – scientists can often see potential dangers not obvious to Joe public, who, if things do go wrong, will be the first to

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

turn on scientists for their cavalier lack of caution! The successes of IVF, ICSI, surrogacy and PGD can be set against the disasters of thalidomide and diethylstilboestrol. To take Bob to task for naivety is, however, to miss the point. Bob is well aware that experimental caution is needed. The focus of this Editorial is on the suppression of ideas, of the discussion of possibilities, probabilities and potential outcomes. It is only through such discussion that scientific and ethical thinking will develop and practical ways forward will become clear. Bob has long understood this, as we both know from our challenging conversations over lunches as graduate students and post docs, when Bob would come out with the most infuriating and apparently absurd ideas to tease, stimulate and test us – many of them now accepted wisdoms. Indeed, often we would be sent away to read up a topic and produce a short précis of it for *Research in Reproduction*, a quarterly news-sheet of science and science-related topics that had wide and valued currency among students and scholars in many disciplines. Bob's catholicity of interests and ideas is matched by his zeal to disseminate, whether within science, within academe or amongst the public. And anything was up for discussion, hence this selected Editorial's passionate defence of general education against the dangers of suppression and censorship.

Journals and societies

Research in Reproduction was Bob's first venture into publishing, started in 1969. It was a glossy (and for its day stylish), double-sided, hot-metal printed affair, usually of just one A3 sheet folded to give four pages. Its front page had a green banner head proclaiming its title and publishers – the International Planned Parenthood Federation (IPPF). Once *R-in-R* was in production we became somewhat guarded about discussing notable newly published papers in peer review journals with Bob, because this all too often resulted in his asking us to write a review of them! Aside from news items, there were special-issue wall charts on reproductive topics. *R-in-R* continued in production through 22 volumes until 1990, by which time his new journal *Human Reproduction* was well underway. Having started in 1986, this journal was followed in 1995 by *Human Reproduction Update* and *Molecular Human Reproduction*. All three titles are owned by the European Society for Human Reproduction and Embryology (ESHRE), of which Bob was a founding member in 1984 with Jean Cohen. However, it was Bob who is acknowledged as the driving force behind both the Society and the journals with his indefatigable energy and enthusiasm (Brown, 2005).

Sadly, disagreements over publishing policy for the ESHRE stable of journals, with Bob characteristically

wishing to push forward innovatively, led to a falling out between him and the committee. But triumphantly, Bob's vision of the future rose like a phoenix in 2000 when he, then well into his 70s but with no diminution of energy, enthusiasm and catholicity of interests, initiated his next new publishing venture – *Reproductive BioMedicine Online*. Recently, Fiona Bennett (2010) has chronicled some of the history of this, Bob's latest journal venture. He is an impossibly hard act to follow – as several editors of the ESHRE journals and of *Reproductive BioMedicine Online* can testify!

People

Many people, too numerous to mention by name, have worked with Bob and have been influenced by him and his work. Bob was a gregarious, enthusiastic and affable presence at meetings throughout the world. There are however, some in his extended network of colleagues whom we must mention. Prior to Patrick's involvement, with exceptions like Molly Rose of the Edgeware General Hospital, the medical profession in the UK was not only unhelpful, but generally extremely hostile towards Bob's work on IVF. During these very difficult early years, Bob traversed the Atlantic to find people in the field of obstetrics and gynaecology who really understood and approved of what he was trying to do. Those kindred spirits, who were happy to assist him in every possible way, were a husband and wife team, Howard and Georgeanna Jones, then at Johns Hopkins in Baltimore. Just how important they were to Bob is evident from the very fulsome tribute he pays to the couple (Edwards, 2002c), which is, in its own right, a fascinating document about the early history of IVF. Howard Jones, now a centenarian, reciprocated in an interview he gave following the announcement of Bob's Nobel Prize (<http://www.medscape.com/viewarticle/730305>). Sadly, Georgeanna Jones died five years ago at the age of 92.

Two other people played a crucial role in Bob's work on IVF, but did not live to see him justly rewarded for his extraordinary determination and achievements. One was, of course, Patrick who worked in Oldham in Greater Manchester prior to his retirement and contributed his vitally relevant skills in laparoscopic surgery. This key role was acknowledged in the year before his death in 1988 by his election to the Royal Society, for which Bob wrote a moving memoir (Edwards, 1996). The other person was Jean Purdy, who joined Bob's team as a fully qualified nurse some time before his involvement with Patrick began. RLG shared Bob's laboratory with Jean and benefited greatly from her technical assistance until the collaboration with Patrick started in earnest. Thereafter, she accompanied Bob plus

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

mobile laboratory to Oldham, usually at short notice and for unpredictable intervals, as and when patient volunteers became available there. 'Jeannie' brought to the work not only her nursing and laboratory skills, but a most impressive ability to organize Bob and focus his attention where it was needed, which all those who know Bob well will acknowledge as no mean feat! Sadly, Jean died in 1985 when only 39 (Edwards and Steptoe, 1985).

Conclusion

We hope through our selection of Bob's writings for *Reproductive BioMedicine Online*, and our commentaries on them, that we have been able to provide readers with some insight into the extraordinary prescience, originality and restless energy of an outstanding scientist. Bob, whose first degree was in agriculture and second in mouse genetics, was not only responsible for the greatest revolution in the treatment of infertility, but also pointed the way to other clinical advances including PGD and use of stem cells for regenerative purposes. It is through his work on IVF that we are now in a position to gain a real understanding of our own embryonic origins. Moreover, he never lost sight of addressing the ethical and social implications of his work. Altogether, his career has been remarkable and thoroughly deserving of recognition by the award of a Nobel Prize.

References

- Barr, M.L., Bertram, E.G., 1949. A morphological distinction between neurones of the male and female, and the behaviour of the nucleolar satellite during accelerated nucleoprotein synthesis. *Nature* 163, 676.
- Bennett, F., 2010. Birth of a journal: a personal memoir. *Reprod. BioMed. Online* 21, 727–728.
- Brown, S., 2005. ESHRE: the first 21 years. ESHRE, Bruxelles.
- Chang, M.C., 1959. Fertilization of rabbit ova in vitro. *Nature* 184 (Suppl. 7), 466–467.
- Cole, R.J., Edwards, R.G., Paul, J., 1965. Cytodifferentiation in cell colonies and cell strains derived from cleaving ova and blastocysts of the rabbit. *Exp. Cell Res.* 37, 501–504.
- Cooter, R., 2000. The ethical body. In: Cooter, R., Pickstone, J., eds., *Medicine in the twentieth century*. Amsterdam: Harwood, pp. 451–468.
- Edwards, R.G., 1965a. Maturation in vitro of mouse, sheep, cow, pig, rhesus monkey and human ovarian oocytes. *Nature* 208, 349–351.
- Edwards, R.G., 1965b. Maturation in vitro of human ovarian oocytes. *Lancet* ii, 926–929.
- Edwards, R.G., 1982. The case for studying human embryos and their constituent tissues in vitro. In: Edwards, R.G., Purdy, J.M., eds., *Human Conception in Vitro*. London: Academic Press,) pp. 371–388.
- Edwards, R.G., 1996. Patrick Christopher Steptoe, C.B.E.: 9 June 1913 – 22 March 1988. *Biogr. Mem. Fellows R. Soc.* 42, 435–452.
- Edwards, R.G., 2002a. Reproductive rhythms, longevity and cancer. *Reprod. BioMed. Online* 4, 93–96.
- Edwards, R.G., 2002b. Personal pathways to embryonic stem cells. *Reprod. BioMed. Online* 4, 263–278.
- Edwards, R.G. 2002c. Tribute to Georgeanna and Howard Jones. *Reprod. BioMed. Online* 6, 352–360.
- Edwards, R.G. 2004. Ethics of PGD: Thoughts on the consequences of typing HLA in embryos. *Reprod. BioMed. Online* 9, 222–224.
- Edwards, R.G., 2005a. Historical significance of gonadotrophins in assisted reproduction. *Reprod. BioMed. Online* 10 (Suppl. 3), 3–10.
- Edwards, R.G., 2005b. Genetics of polarity in mammalian embryos. *Reprod. BioMed. Online* 11, 104–114.
- Edwards, R.G., 2006. Genetics, epigenetics and gene silencing in differentiating mammalian embryos. *Reprod. BioMed. Online* 13, 732–753.
- Edwards, R.G., 2007a. Reminiscences on learning about morals and ethics in biomedicine. *Reprod. BioMed. Online* 14 (Suppl. 1), 7–11.
- Edwards, R.G., 2007b. The significance of parthenogenetic virgin mothers in bonnet head sharks and mice. *Reprod. BioMed. Online* 15, 12–15.
- Edwards, R.G., 2008. From embryo stem cells to blastema and MRL mice. *Reprod. BioMed. Online* 16, 425–461.
- Edwards, R.G., Beard, H., 1997. Oocyte polarity and cell determination in early mammalian embryos. *Mol. Hum. Reprod.* 3, 863–905.
- Edwards, R.G., Fowler, R.E., 1960. Superovulation treatment of adult mice: their subsequent natural fertility and response to further treatment. *J. Endocrinol.* 21, 147–154.
- Edwards, R.G., Gardner, R.L., 1967. Sexing of live rabbit blastocysts. *Nature* 214, 576–577.
- Edwards, R.G., Gardner, R.L., 1968. Choosing sex before birth. *New Scientist* 38, 218–220.
- Edwards, R.G., Hansis, C., 2005. Initial differentiation of blastomeres in 4-cell human embryos and its significance for early embryogenesis and implantation. *Reprod. BioMed. Online* 11, 206–218.
- Edwards, R.G., Hollands, P., 1988. New advances in human embryology: implications of the preimplantation diagnosis of genetic disease. *Hum. Reprod.* 3, 549–556.
- Edwards, R.G., Hollands, P., 2007. Will stem cells in cord blood, amniotic fluid, bone marrow and peripheral blood soon be unnecessary in transplantation? *Reprod. BioMed. Online* 14, 396–401.
- Edwards, R.G., Ludwig, M., 2003. Are major defects in children conceived in vitro due to innate problems in patients or to induced genetic damage? *Reprod. BioMed. Online* 7, 131–138.
- Edwards, R.G., Sharpe, D.J., 1971. Social values and research in human embryology. *Nature* 231, 87–91.
- Edwards, R.G., Steptoe, P.C., 1985. Preface. In: Edwards, R.G., Purdy, J.M., Steptoe, P.C., eds., *Implantation of the Human Embryo*. London: Academic Press, pp. vii–viii.
- Edwards, R.G., Donahue, R., Bramki, T., Jones Jr, H., 1966. Preliminary attempts to fertilise human oocytes matured in vitro. *Am. J. Obstet. Gynecol.* 96, 192–200.
- Edwards, R.G., Talbert, L., Israelstam, D., Nino, H.V., Johnson, M.H., 1968. Diffusion chamber for exposing spermatozoa to human uterine secretions. *Am. J. Obstet. Gynecol.* 102, 388–396.
- Edwards, R.G., Bavister, B.D., Steptoe, P.C., 1969. Early stages of fertilization in vitro of human oocytes matured in vitro. *Nature* 221, 632–635.
- Fowler, R.E., Edwards, R.G., 1957. Induction of superovulation and pregnancy in mature mice by gonadotrophins. *J. Endocrinol.* 15, 374–384.
- Gardner, R.L., 2002. Experimental analysis of second cleavage in the mouse. *Hum. Reprod.* 17, 3178–3189.
- Gardner, R.L. Cockroft, D.L., 1998. Complete dissipation of coherent clonal growth occurs before gastrulation in mouse epiblast. *Development* 125, 2397–2402.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Gardner, R.L., Edwards, R.G., 1968. Control of the sex ratio at full term in the rabbit by transferring sexed blastocysts. *Nature* 218, 346–349.
- Gulyas, B., 1975. A reexamination of cleavage patterns in eutherian mammalian eggs: rotation of blastomere pairs during second cleavage in the rabbit. *J. Exp. Zool.* 193, 235–248.
- Handyside, A.H., Pattinson, J.K., Penketh, R.J., Delhanty, J.D., Winston, R.M., Tuddenham, E.G., 1989. Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet* 1 (8634), 347–349.
- Handyside, A.H., Kontogianni, E.H., Hardy, K., Winston, R.M., 1990. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. *Nature* 344, 768–770.
- Hansis, C., Grifo, J.A., Tang, Y., Krey, L.C., 2002. Assessment of beta-HCH, beta-LH mRNA and ploidy in individual human blastomeres. *Reprod. Biomed. Online* 5, 156–161.
- Hedgecoe, A., 2009. 'A form of practical machinery': the origins of research ethics committees in the UK, 1967–1972. *Med. Hist.* 53, 331–350.
- Henderson, S.A., Edwards, R.G., 1968. Chiasma frequency and maternal age in mammals. *Nature* 218, 22–28.
- Hollands, P., Edwards, R.G., 1986. The fate of embryonic cells grafted into X-irradiated recipients. *Hum. Reprod.* 1 (Suppl. 2), 40.
- Johnson, M.H., Franklin, S.B., Cottingham, M., Hopwood, N., 2010. Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971. *Hum. Reprod.* 25, 2157–2174.
- Kass, L.R., Glass, B., 1971. What price the perfect baby? *Science* 173, 103–104.
- Melander, Y., 1962. Chromosomal behaviour during the origin of sex chromatin in the rabbit. *Hereditas* 48, 645–661.
- Rock, J., Menkin, M.F., 1944. In vitro fertilization and cleavage of human ovarian eggs. *Science* 100, 105–107.
- Simpson, J.L., Edwards, R.G., 2002. Objections to designer babies and cloning in the USA: not quite what was expected. *Reprod. BioMed. Online* 6, 147–148.
- Soriano, P., Jaenisch, R., 1986. Retroviruses as probes for mammalian development: allocation of cells to the somatic and germ cell lineages. *Cell* 46, 19–29.
- Sundell, G., 1962. The sex ratio before uterine implantation in the golden hamster. *Development* 10, 58–63.
- Tam, P.P.L., Zhou, S.X., 1996. The allocation of epiblast cells to ectodermal and germ-line lineages is influenced by the position of cells in the gastrulating mouse embryo. *Dev. Biol.* 178, 124–132.
- Theodosiou, A., Johnson, M.H. 2010. The politics of human embryo research and the motivation to achieve PGD. *Reprod. BioMed. Online*, submitted.
- Vickers, A.D., 1967. A direct measurement of the sex-ratio in mouse blastocysts. *Reproduction* 13, 375–376.
- Whittingham, D.G., 1968. Fertilization of mouse eggs in vitro. *Nature* 220, 592–593.
- Wilkie, T.M., Brinster, R.L., Palmiter, R.D., 1986. Germline and somatic mosaicism in transgenic mice. *Dev. Biol.* 118, 9–18.
- Yanagimachi, R., Chang, M.C., 1963. Fertilization of hamster eggs in vitro. *Nature* 200, 281–282.

Acknowledgements: MHJ is supported by the Wellcome Trust [084418 and 088708], which otherwise had no involvement in the publication other than to require it be made open access.

Declaration: The authors report no financial or commercial conflicts of interest.

Appendix. Robert G. Edwards: List of publications

1954

- Edwards, RG. The experimental induction of pseudogamy in early mouse embryos. *Experimenta* 10, 499–500.
- Edwards, RG. Colchicine induced heteroploidy in early mouse embryos. *Nature* 174, 276–278.

1955

- Edwards, RG. Selective fertilization following the use of sperm mixtures in the mouse. *Nature* 175, 429.
- Sirlin, JL and Edwards, RG. The labelling of mouse sperm by adenine-8-C-14. *Experimental Cell Research* 9, 596–599.

1956

- Edwards, RG and Sirlin, JL. Labelled pronuclei in mouse eggs fertilised by labelled sperm. *Nature* 177, 429.
- Edwards, RG and Sirlin, JL. Studies in gametogenesis, fertilization and early development in the mouse using radioactive tracers. *Proceedings of the 2nd World Congress of Fertility and Sterility, Naples.*

1957

- Edwards, RG. The experimental induction of gynogenesis in the mouse I. Irradiation of the sperm by X-rays. *Proceeding of the Royal Society of London B* 146, 469–487.
- Edwards, RG. The experimental induction of gynogenesis in the mouse II. Ultraviolet irradiation of the sperm. *Proceeding of the Royal Society of London B* 146, 488–504.
- Fowler, RE and Edwards, RG. Induction of superovulation and pregnancy in mature mice by gonadotrophins. *Journal of Endocrinology* 15, 374–384.
- Sirlin, JL and Edwards, RG. Sensitivity of immature mouse sperm to the mutagenic effects of X-rays. *Nature* 179, 725–727.
- Sirlin, JL and Edwards, RG. Duration of spermatogenesis in the mouse. *Nature* 180, 1137–1139.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*. *Reprod. BioMed. Online*, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

1958

- Cattanach, BM and Edwards, RG. The effects of triethylenemelamine on the fertility of male mice. *Proceedings of the Royal Society of Edinburgh B* 67, 54–64.
- Edwards, RG. The number of cells and cleavages in haploid, diploid, polyploid and other heteroploid embryos at 3½ days gestation. *Journal of Experimental Zoology* 138, 189–207.
- Edwards, RG. Colchicine-induced heteroploidy in the mouse. I. The induction of triploidy by treatment of the gametes. *Journal of Experimental Zoology* 137, 317–348.
- Edwards, RG. Colchicine-induced heteroploidy in the mouse. II. The induction of tetraploidy and other types of heteroploidy. *Journal of Experimental Zoology* 137, 349–362.
- Edwards, RG. The experimental induction of gynogenesis in the mouse. III. Treatment of sperm with trypaflavine, toluidine blue, and nitrogen mustard. *Proceedings of the Royal Society of London B* 149, 117–129.
- Edwards, RG and Fowler, RE. The experimental induction of superfoetation in the mouse. *Journal of Endocrinology* 17, 223–236.
- Edwards, RG and Sirlin, JL. Radioactive tracers and fertilization in mammals. *Endeavour* 17, 42–47.
- Edwards, RG and Sirlin, JL. The effect of 200 r of X-rays on the rate of spermatogenesis and spermiogenesis in the mouse. *Experimental Cell Research* 15, 522–528.
- Sirlin, JL and Edwards, RG. The labelling of mammalian spermatozoa with radioactive tracers. *Journal of Experimental Zoology* 137, 363–388.
- Sirlin, JL and Edwards, RG. Studies with labelled spermatozoa in mice. *XVth International Congress of Zoology, Naples*.

1959

- Edwards, RG and Austin, CR. Induction of oestrus and ovulation in adult rats. *Journal of Endocrinology* 18, vii–viii.
- Edwards, RG and Fowler, RE. Fetal mortality in adult mice after superovulation with gonadotrophins. *Journal of Experimental Zoology* 141, 299–322.
- Edwards, RG and Gates, AH. Embryonic development in superovulated mice not receiving the coital stimulus. *Anatomical Research* 135, 291–301.
- Edwards, RG and Gates, AH. Timing of the stages of the maturation divisions, ovulation, fertilization and the first cleavage of eggs of adult mice treated with gonadotrophins. *Journal of Endocrinology* 18, 292–304.
- Edwards, RG and Sirlin, JL. Identification of C14-labelled male chromatin at fertilization in colchicine-treated mouse eggs. *Journal of Experimental Zoology* 140, 19–27.
- Edwards, RG and Sirlin, JL. Fate of spermatozoa penetrating into the tissue of the fallopian tube. *Nature* 183, 1744–1745.
- Sirlin, JL and Edwards, RG. Timing of DNA synthesis in ovarian oocyte nuclei and pronuclei of the mouse. *Experimental Cell Research* 18, 190–194.

1960

- Edwards, RG. Complement-fixing activity of normal rabbit serum with rabbit spermatozoa and seminal plasma. *Journal of Reproduction and Fertility* 1, 268–282.
- Edwards, RG. Antigenicity of rabbit semen, bull semen and egg yolk after intravaginal or intramuscular injections into female rabbits. *Journal of Reproduction and Fertility* 1, 385–401.
- Edwards, RG. Isoantibodies against semen in rabbits. *Symposium on Germ Cells and Development, Pallanza*, pp. 197–201.
- Edwards, RG and Fowler, RE. Superovulation treatment of adult mice: their subsequent natural fertility and response to further treatment. *Journal of Endocrinology* 21, 147–154.
- Fowler, RE and Edwards, RG. The fertility of mice selected for large or small body size. *Genetical Research* 1, 393–407.
- Fowler, RE and Edwards, RG. Effect of progesterone and oestrogen on pregnancy and embryonic mortality in adult mice following superovulation treatment. *Journal of Endocrinology* 20, 1–8.

1961

- Edwards, RG. Induced heteroploidy in mice: the effect of deacetylmethylcolchicine on eggs at fertilization. *Experimental Cell Research* 24, 615–617.
- Edwards, RG. Identification of the chromosome complements of newborn and adult living mice. *Nature* 192, 1316–1317.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

Falcolner, DS, Edwards, RG, Fowler, RE and Roberts, RC. Analysis of differences in the numbers of eggs shed by the two ovaries of mice during natural oestrus or after superovulation. *Journal of Reproduction and Fertility* 2, 418–437.

Fowler, RE and Edwards, RG. *Midget*, a new dwarfing gene in the house mouse dependent on a genetic background of small body size for its expression. *Genetical Research* 2, 272–282.

1962

Beck, JS, Edwards, RG and Young, MR. Immune fluorescence technique and the isoantigenicity of mammalian spermatozoa. *Journal of Reproduction and Fertility* 4, 103–110.

Edwards, RG. The size and endocrine activity of the pituitary in mice selected for large and small body size. *Genetical Research* 3, 428–443.

Edwards, RG. Antibodies against spermatozoa. *Journal of Reproduction and Fertility* 4, 225.

Edwards, RG. Meiosis in ovarian oocytes of adult mammals. *Nature* 196, 446–450.

1963

Edwards, RG. The antigenicity of mammalian spermatozoa and its relationship to induced infertility. *Proceedings of the Eighth International Conference of the International Planned Parenthood Federation, Singapore*. International Planned Parenthood Federation, London, pp. 539–543.

Edwards, RG and Searle, AG. Genetic radiosensitivity of specific post-dictyate stages in mouse oocytes. *Genetical Research* 4, 389–398.

Edwards, RG and Valentine, RH. Cytochemical demonstration of succinic dehydrogenase in intact rabbit spermatozoa. *Experimental Cell Research* 31, 508–516.

Edwards, RG, Wilson, ED and Fowler, RE. Genetic and hormonal influences on ovulation and implantation in adult mice treated with gonadotrophins. *Journal of Endocrinology* 26, 389–399.

Wilson, ED and Edwards, RG. Parturition and increased litter size in mice after superovulation. *Journal of Reproduction and Fertility* 5, 179–186.

Young, MR and Edwards, RG. Ultraviolet microscopy and the detection of formazan deposits. *Journal of Histochemistry and Cytochemistry* 11, 444–446.

1964

Edwards, RG. Maturation, fertilization and congenital malformations. *Congenital Malformations. International Medical Congress, New York*, pp. 70–73.

Edwards, RG. Cleavage of one- or two-celled rabbit eggs *in vitro* after removal of the zona pellucida. *Journal of Reproduction and Fertility* 7, 413–415.

Edwards, RG. Multipronucleate eggs and chromosome number in mouse embryos. *Second International Congress of Human Genetics, Rome*. Mendel Institute, Rome, pp. 1223–1226.

Edwards, RG. Immunological control of fertility in female mice. *Nature* 203, 50–53.

Edwards, RG, Ferguson, LC and Coombs, RRA. Blood group antigens on human spermatozoa. *Journal of Reproduction and Fertility* 7, 153–161.

1965

Cole, RJ, Edwards, RG and Paul, J. Cytodifferentiation in cell colonies and cell strains derived from cleaving ova and blastocysts of the rabbit. *Experimental Cell Research* 37, 501–504.

Edwards, RG. Maturation *in vitro* of human ovarian oocytes. *Lancet* ii, 926–929.

Edwards, RG. Maturation *in vitro* of mouse, sheep, cow, pig, rhesus monkey and human ovarian oocytes. *Nature* 208, 349–351.

1966

Cole, RJ, Edwards, RG and Paul, J. Cytodifferentiation and embryogenesis in cell colonies and tissue cultures derived from ova and blastocysts of the rabbit. *Developmental Biology* 13, 385–407.

Edwards, RG. Immunological approaches to the control of fertility. *Preventive Medicine and Family Planning. Proceedings of the Fifth ENE Region*. International Planned Parenthood Federation, London, pp. 37–43.

Edwards, RG. Mammalian eggs in the laboratory. *Scientific American* 215, 72–81.

Edwards, RG, Donahue, R, Bramki, T and Jones, Jr, H. Preliminary attempts to fertilise human oocytes matured *in vitro*. *American Journal of Obstetrics and Gynecology* 96, 192–200.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

1967

- Edwards, RG. The beginnings of human development. *Proceedings of the Eighth International Conference, International Planned Parenthood Federation, Santiago*. International Planned Parenthood Federation, London, pp. 381–385.
- Edwards, RG. Antibodies and fertility. *Science* 1, 68–74; and *Atomes* 240, 80–86.
- Edwards, RG and Gardner, RL. Sexing of live rabbit blastocysts. *Nature* 214, 576–577.

1968

- Edwards, RG and Gardner, RL. Choosing sex before birth. *New Scientist* 38 (595), 218–220.
- Edwards, RG, Talbert, L, Israelstam, D, Nino, HV and Johnson, MH. Diffusion chamber for exposing spermatozoa to human uterine secretions. *American Journal of Obstetrics and Gynecology* 102, 388–396.
- Gardner, RL and Edwards, RG. Control of the sex ratio at full term in the rabbit by transferring sexed blastocysts. *Nature* 218, 346–348.
- Henderson, SA and Edwards, RG. Chiasma frequency and maternal age in mammals. *Nature* 218, 22–28.

1969

- Bavister, BD, Edwards, RG and Steptoe, PC. Identification of the midpiece and tail of the spermatozoon during fertilization of human eggs *in vitro*. *Journal of Reproduction and Fertility* 20, 159–160.
- Edwards, RG. Stages of the development of the human egg. In Raspe, G (ed). *Advances in the Biosciences* 4. Schering Symposium on Mechanisms Involved in Conception, Berlin. Pergamon Press, Vieweg, pp. 235–254.
- Edwards, RE and Edwards, RG. *Control of Early Mammalian Development*. Abbottempo Book 3, pp. 20–25.
- Edwards, RG. Reproduction: Chance or Choice. In Paterson, D (ed), *Genetic Engineering*. BBC, London, pp. 25–32.
- Edwards, RG. Transmission of antibodies across membranes of the reproductive tracts. In Edwards, RG (ed), *Immunology and Reproduction. Proceedings of the First Symposium of the International Coordination Committee for the Immunology of Reproduction, Geneva, 1968*. International Planned Parenthood Federation, London, pp. 28–48.
- Edwards, RG. Antigenicity of spermatozoa with respect to fertility and infertility. In Bratanov, K (ed), *Immunology of Spermatozoa and Fertilization. Proceedings of the International Symposium on Immunology of Spermatozoa and Fertilization, Varna, 1967*. Bulgarian Academy of Sciences, Sofia, pp. 22–34.
- Edwards, RG. Analyse chromosomique des ovocytes des mammifères et de l'homme, et origine de la trisomie chez l'homme. In *L'Ovulation, Méiose et Ouverture Folliculaire – Traitements de l'Anovulation*, pp. 111–121.
- Edwards, RG. Immunological aspects of infertility. *Proceedings of the Royal Society of Medicine* 62, 25–26.
- Edwards, RG. The culture of pre-implantation mammalian embryos. *Proceedings of the Royal Society of Medicine* 62, 143–144.
- Edwards, RG. Basic science and human reproduction. In *Social Demography and Medical Responsibility. Proceedings of the Sixth Conference of International Planned Parenthood Federation Europe and Near East Region*. International Planned Parenthood Federation, London, pp. 93–97.
- Edwards, RG, Bavister, BD and Steptoe, PC. Early stages of fertilization *in vitro* of human oocytes matured *in vitro*. *Nature* 221, 632–635.

1970

- Abraham, GE, Odel, WD, Edwards, RG and Purdy, JM. Solid-phase radio-immunoassay of estrogens in biological fluids. In Diczfalusy, E and Diczfalusy, A (eds), *Steroid Assay by Protein Binding. Second Karolinska Symposium on Research Methods in Reproductive Endocrinology, Geneva*. Karolinska Institutet, Stockholm, p. 332–343.
- Austin, CR, Bavister, BD and Edwards, RG. Components of capacitation. In Segal, SJ, Crozier, R, Corfman, P and Condliffe, P (eds), *The Regulation of Mammalian Reproduction. Proceedings of NIH Conference*. CC Thomas, Springfield, Illinois, pp. 247–256.
- Edwards, RG. Immunology of conception and pregnancy. *British Medical Bulletin* 26, 72–78.
- Edwards, RG. Observations of meiosis in normal males and females. In Jacobs, PA, Price, WH and Law, P (eds), *Human Population Cytogenetics*. Pfizer Medical Monographs, 5, 10–21. Edinburgh University Press.
- Edwards, RG. Fertilization of human eggs *in vitro*. *Ontogenesis, USSR* 1, 138–142.
- Edwards, RG. Are oocytes formed and used sequentially in the mammalian ovary? *Philosophical Transactions of the Royal Society of London B* 259, 103–105.
- Edwards, RG. Meiosis in oocytes and the origin of mongolism and infertility in older mothers. In *Sixth World Congress on Fertility and Sterility, Tel Aviv 1968*. Israel Academy of Sciences and Humanities, pp. 64–71.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*. *Reprod. BioMed. Online*, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Edwards, RG. Genetic aspects of early mammalian development. In Gibian, H and Plotz, EJ (eds), *Sonderdruck ans 21. Colloquium der Gesellschaft für Biologische Chemie*. Mosbach, pp. 315–323.
- Edwards, RG and Edwards, R. Maturazione e fecondazione di uove umane *in vitro*. In *Enciclopedia della Scienze e della Tecnica Modadori*. S&T/70, pp. 360–366.
- Edwards, RG and Fowler, RE. The genetics of human pre-implantation development. In Emery, AEH (ed), *Modern Trends in Human Genetics*. Butterworths, London, pp. 181–213.
- Edwards, RG and Fowler, RE. Human embryos in the laboratory. *Scientific American* 223, 44–54.
- Edwards, RG, Steptoe, PC and Purdy, JM. Fertilization and cleavage *in vitro* of preovulatory human oocytes. *Nature* 227, 1307–1309.
- Fowler, RE and Edwards, RG. Contraception today. In Allison, A (ed), *Population Control*. Penguin Books, Harmondsworth, pp. 181–203.
- Sawyer, GIM, Edwards, RG, Morris, NF, Paton, WDM and Pirie, MW. The scientific basis of contraception. Report of a Royal Society Study Group. *Population Studies*, Supplement.
- Steptoe, PC and Edwards, RG. Laparoscopic recovery of preovulatory human oocytes after priming of ovaries with gonadotrophins. *Lancet* i, 683–689.

1971

- Edwards, RG. Human conception. 11th Darwin Lecture. *Biologist* 18, 106–113.
- Edwards, RG. Discussion on the use of blastocysts in human and veterinary medicine. In Ingleman-Sundberg, A and Lunell, NO (eds), *Current Problems in Infertility*. Plenum Press, New York, pp. 103–112.
- Edwards, RG. First stages of the development of the human ovum. In Tuchmann-Duplessis, H (ed), *Malformations Congénitales de Mammifères*. Masson et C^{ie}, Paris, pp. 1–12.
- Edwards, RG. Problems of artificial fertilization. *Nature* 223, 23–25.
- Edwards, RG. Fertilization and development of preovulatory human oocytes *in vitro*. *Proceedings of the Eighth International Conference of Fertility and Sterility, Tokyo*, pp. 45–55.
- Edwards, RG. Aspects of human reproduction. In Watson Fuller (ed), *The Social Impact of Modern Biology*. Routledge and Kegan Paul, London. pp. 108–121.
- Edwards, RG and Sharpe, DJ. Social values and research in human embryology. *Nature* 231, 87–91.
- Steptoe, PC, Edwards, RG and Purdy, JM. Human blastocysts grown in culture. *Nature* 229, 132–133.

1972

- Edwards, RG. *Judging the Social Values of Scientific Advances*. World Council of Churches, Geneva.
- Edwards, RG. Maturation, fertilization, and cleavage of embryos *in vitro*. In Wright, SW, Crandall, BF and Boyer, L (eds), *Perspectives in Cytogenetics*. Charles C Thomas, Springfield, Illinois, pp. 55–66.
- Edwards, RG. Immunological influences. In Austin, CR and Short, RV (eds), *Reproduction in Mammals 4, Reproductive Patterns*. Cambridge University Press, Cambridge, pp. 94–127.
- Edwards, RG. Control of human development. In Austin, CR and Short, RV (eds), *Reproduction in Mammals 5, Artificial Control of Reproduction*. Cambridge University Press, Cambridge, pp. 87–113.
- Edwards, RG. Culture of human embryos *in vitro*. In Diczfalusy, E and Standley, CC (eds), *The Use of Non-Human Primates in Research on Human Reproduction*. Karolinska Institutet, Stockholm, pp. 131–134.
- Edwards, RG. Immunology of pregnancy. In Diczfalusy, E and Standley, CC (eds), *The Use of Non-Human Primates in Research on Human Reproduction*. Karolinska Institutet, Stockholm, pp. 506–511.
- Edwards, RG, Steptoe, PC, Abraham, GE, Walters, E, Purdy, JM and Fotherby, K. Steroid assays and preovulatory follicular development in human ovaries primed with gonadotrophins. *Lancet* ii, 611–615.
- Steptoe, PC and Edwards, RG. The research of today and the ethics of tomorrow. BMA Scientific Meeting, Southampton. *British Medical Journal* 3, 342–343.
- YoungLai, EV, Edwards, RG and Steptoe, PC. The enzymatic activity of aspirates of preovulatory follicles. *Canadian Journal of Biochemistry* 50, 233–236.

1973

- Coombs, RRA, Rümke, Ph and Edwards, RG. Immunoglobulin classes reactive with spermatozoa in the serum and seminal plasma of vasectomised and infertile men. In Bratanov, K, Edwards, RG, Vulchanov, VH, Dikov, V and Somlev, B (eds), *Immunology of Reproduction*. Bulgarian Academy of Sciences Press, Sofia, pp. 354–358.
- Edwards, RG. Studies on human conception. *American Journal of Obstetrics and Gynecology* 117, 587–601.
- Edwards, RG. Advances in reproductive biology and their implication for studies on human congenital defects. In Motulsky, AG and Lentz, W (eds), *Birth Defects. Proceedings of the Fourth International Medical Conference, Vienna*. Excerpta Medica, Amsterdam, pp. 92–104.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Edwards, RG. Current concepts of the growth of ovarian follicles. *International Planned Parenthood Federation Medical Bulletin* 7, no. 4.
- Edwards, RG. Physiological aspects of human ovulation, fertilization and cleavage. *Journal of Reproduction and Fertility* (Supplement) 18, 87–101.
- Edwards, RG. The problem of compensation for antenatal injuries. *Nature* 246, 54–55.
- Edwards, RG and Steptoe, PC. Biological aspects of embryo transfer. In *Law and Ethics of A.I.D. and Embryo Transfer. Ciba Foundation Symposium 17*. ASP Amsterdam, pp. 11–18.
- Fowler, RE and Edwards, RG. The genetics of early human development. *Progress in Medical Genetics* IX, 49–112.
- Gardner, RL, Johnson, MH and Edwards, RG. Are H-2 antigens expressed in the preimplantation blastocyst? In Bratanov, K, Edwards, RG, Vulchanov, VH, Dikov, V and Somlev, B (eds), *Immunology of Reproduction*. Bulgarian Academy of Sciences Press, Sofia, pp. 480–486.

1974

- Edwards, RG. Follicular fluid. *Journal of Reproduction and Fertility* 37, 189–219.
- Edwards, RG. Fertilization of human eggs *in vitro*: morals, ethics and the law. *The Quarterly Review of Biology* 49, 3–26; and In *Genetic Engineering – Its Applications and Limitations*. Davos, Switzerland, pp. 73–113.
- Edwards, RG and Steptoe, PC. Control of human ovulation, fertilization and implantation. *Proceedings of the Royal Society of Medicine* 67, 932–936. (Section: Obstetrics and Gynaecology), pp. 30–34.
- Readhead, C and Edwards, RG. Antibodies against hormones. In Centaro, A and Carretti, N (eds), *Immunology in Obstetrics and Gynaecology. Proceedings of the First International Congress, Padua*. Excerpta Medica, Amsterdam, pp. 78–86.

1975

- Edwards, RG. Judging the social values of scientific advances. In Birch, C and Abrecht, P (eds), *Genetics and the Quality of Life*. Pergamon Press, Oxford. Organized by the World Council of Churches, pp. 41–49.
- Edwards, RG and Coombs, RRA. Immunological interactions between mother and fetus. In Gell, PGH, Coombs, RRA and Lachmann, PJ (eds), *Clinical Aspects of Immunology*. Blackwell Scientific Publications, Oxford, pp. 561–598.
- Edwards, RG and Fowler, RE. Oogenesis, fertilization, cleavage and development of the preimplantation blastocyst. In Taymor, ML and Green, Jr, TH (eds), *Progress in Gynaecology*. Grune & Stratton, New York. V1, pp. 3–29.
- Edwards, RG and Johnson, MH. Introduction. In Edwards, RG and Johnson, MH (eds), *Physiological Effects of Immunity Against Reproductive Hormones*. Cambridge University Press, Cambridge, pp. 1–4.
- Edwards, RG and Steptoe, PC. Induction of follicular growth, ovulation and luteinization in the human ovary. *Journal of Reproduction and Fertility* (Supplement) 22, 121–163.
- Edwards, RG and Steptoe, PC. Physiological aspects of embryo transfer. In Behrman, SJ and Kistner, RW (eds), *Progress in Infertility*. Little, Brown, Boston, pp. 377–409.
- Edwards, RG, Howe, CWS and Johnson, MH. Introduction. In Edwards, RG, Howe, CWS and Johnson, MH (eds), *Immunobiology of Trophoblast*. Cambridge University Press, Cambridge, pp. 1–3.
- Kennedy, I and Edwards, RG. A critique of the Law Commission report on injuries to unborn children and the proposed Congenital Disabilities (Civil Liability) Bill. *Journal of Medical Ethics* 1, 116–121.
- Tekelioglu-Uysal, M, Edwards, RG and Kisnisci, HA. Ultrastructural relationships between decidua, trophoblast and lymphocytes at the beginning of human pregnancy. *Journal of Reproduction and Fertility* 42, 431–438.

1976

- Edwards, RG. Responsibility and decision making in the orientation and genetic control of human procreation. *Biology and the Future of Man*. Universities of Paris, pp. 377–394.
- Edwards, RG. Immunity and the control of human fertility. In Scott, JS and Jones, WR (eds), *Immunology of Human Reproduction*. Academic Press, London, pp. 415–470.
- Edwards, RG. Immunization against HCG- β for suppressing human fertility. *Research in Reproduction* 8, no. 3.
- Faddy, MJ, Jones, EC and Edwards, RG. An analytical model for ovarian follicle dynamics. *Journal of Experimental Zoology* 197, 173–185.
- Setchell, BP and Edwards, RG. The effect of immunisation against gonadotrophins on the testis and male reproductive tract. In Edwards, RG and Johnson, MH (eds), *Physiological Effects of Immunity Against Reproductive Hormones*. Cambridge University Press, Cambridge, pp. 167–186.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*. *Reprod. BioMed. Online*, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

Step toe, PC and Edwards, RG. Reimplantation of a human embryo with subsequent tubal pregnancy. *Lancet* i, 880–882.

Step toe, PC, Edwards, RG and Purdy, JM. The recovery of human preovulatory oocytes, fertilization *in vitro*, cleavage and embryo transfer. In *Recent Advances in Human Reproduction. Proceedings of the First International Congress on Human Reproduction, Rio de Janeiro*. Excerpta Medica, Amsterdam, pp. 285–295.

Wallace, ME, MacSwiney, FJ and Edwards, RG. Parental age and recombination frequency in the house mouse. *Genetical Research* 28, 241–251.

1977

Edwards, RG. Early human development: From the oocyte to implantation. In Philipp, EE, Barnes, J and Newton, M (eds), *Scientific Foundations of Obstetrics and Gynaecology*, 2nd edn. Heinemann Medical Books Limited, London, pp. 175–252.

Edwards, RG and Step toe, PC. The relevance of the frozen storage of human embryos. In *The Freezing of Mammalian Embryos*. Ciba Foundation Symposium 52. Elsevier, Excerpta Medica, North-Holland, pp. 235–250.

Edwards, RG, Fowler, RE, Gore-Langton, RE, Gosden, RG, Jones, EC, Readhead, C and Step toe, PC. Normal and abnormal follicular growth in mouse, rat and human ovaries. *Journal of Reproduction and Fertility* 51, 237–263.

Fowler, RE, Chat, STH, Walters, DE, Edwards, RG and Step toe, PC. Steroidogenesis in human follicles approaching ovulation as judged from assays of follicular fluid. *Journal of Endocrinology* 72, 259–271.

1978

Edwards, RG and Surani, MAH. The primate blastocyst and its environment. *Uppsala Journal of Medical Sciences Supplement* 22, 39–50.

Fowler, RE, Edwards, RG, Walters, DE, Chan, STH and Step toe, PC. Steroidogenesis in preovulatory follicles of patients given human menopausal and chorionic gonadotrophins as judged by the radioimmunoassay of steroids in follicular fluid. *Journal of Endocrinology* 77, 161–169.

Fowler, RE, Fox, NL, Edwards, RG, Walters, DE and Step toe, PC. Steroidogenesis by cultured granulosa cells aspirated from human follicles using pregnenolone and androgens as precursors. *Journal of Endocrinology* 77, 171–183.

Fowler, RE, Fox, NL, Edwards, RG and Step toe, PC. Steroid production from 17^{*}-hydroxypregnenolone and dehydroepiandrosterone by human granulosa cells *in vitro*. *Journal of Reproduction and Fertility* 54, 109–117.

Step toe, PC and Edwards, RG. Birth after the reimplantation of a human embryo. *Lancet* ii, 366.

1979

Edwards, RG and Step toe, PC. Honorary Symposium, *Pregnancies After the Reimplantation of Human Embryos*. Royal College of Obstetricians and Gynaecologists, London. Issued as a tape/slide set.

Edwards, RG, Fowler, RE and Jones, EC. The ovary and the control of ovulation. In Jacobs, HS (ed), *Advances in Gynaecological Endocrinology. Proceedings of the sixth study group of the Royal College of Obstetricians and Gynaecologists, London*, pp. 1–34.

1980

Dennis, F and Edwards, RG. A difficult time for contraceptive research. *Research in Reproduction* 12, no. 1.

Edwards, RG, Step toe, PC and Purdy, JM. Establishing full term human pregnancies using cleaving embryos grown *in vitro*. *British Journal of Obstetrics and Gynaecology* 87, 737–756.

Edwards, RG, Step toe, PC, Fowler, RE and Baillie, J. Observations on preovulatory human ovarian follicles and their aspirates. *British Journal of Obstetrics and Gynaecology* 87, 769–779.

Step toe, PC, Edwards, RG and Purdy, JM. Clinical aspects of pregnancies established with embryos grown *in vitro*. *British Journal of Obstetrics and Gynaecology* 87, 757–768.

1981

Austin, CR and Edwards, RG (eds). *Mechanisms of Sex Differentiation in Animals and Man*. Academic Press, London.

Edwards, RG. Test-Tube Babies. *Carolina Biology Readers* 89, Head, JJ (ed.). Scientific Publications Division, Carolina Biological Supply Company, Burlington.

Edwards, RG. The Beginnings of Human Life. *Carolina Biology Readers* 135. Head, JJ (ed.). Scientific Publications Division, Carolina Biological Supply Company, Burlington.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

Edwards, RG. Test-tube babies. *Nature* 293, 253–256.

Edwards, RG, Purdy, JM, Steptoe, PC and Walters, DE. The growth of human preimplantation embryos *in vitro*. *American Journal of Obstetrics and Gynecology* 141, 408–416.

Edwards, RG, Steptoe, PC and Purdy, JM. Beginnings of life *in vivo* and *in vitro*. In Semm, K and Mettler, L (eds), *Human Reproduction. Proceedings of III World Congress on Human Reproduction, Berlin*. Excerpta Medica, Amsterdam, pp. 148–153.

1982

Edwards, RG. The case for studying human embryos and their constituent tissues *in vitro*. In Edwards, RG and Purdy, JM (eds), *Human Conception in Vitro*. Academic Press, London, pp. 371–387.

Edwards, RG. The initiation of life *in vitro*. In Porter, G and Williams, IA (eds), *Proceedings of the Royal Institution of Great Britain* 54, 260–287.

Edwards, RG and Fishel, SB. The human uterus in the luteal phase and early pregnancy. In Edwards, RG and Purdy, JM (eds), *Human Conception in Vitro*. Academic Press, London, pp. 256–287.

Edwards, RG, Anderson, G, Pickering, J and Purdy, JM. Rapid assay of urinary LH in women using a simplified method of Hi-Gonavis. In Edwards, RG and Purdy, JM (eds), *Human Conception in Vitro*. Academic Press, London, pp. 19–34.

Fishel, SB and Edwards, RG. Essentials of fertilization. In Edwards, RG and Purdy, JM (eds), *Human Conception in Vitro*. Academic Press, London, pp. 157–179.

Fishel, SB, Steptoe, PC, Webster, J, Edwards, RG and Purdy, JM. Establishing and maintaining pregnancy by in-vitro fertilization. In Crosignani, PG and Rubin, BL (eds), *Proceedings of the Sero Symposium on In-Vitro Fertilization and Embryo Transfer*. Academic Press, p. 30.

1983

Edwards, RG. Contraception *in vitro*, Adresse du Président. *Contraception, fertilité, sexualité* (Supplement), 11, 303–309.

Edwards, RG. The current clinical and ethical situation of human conception *in vitro*. Galton Lecture of the Eugenic Society. In Carter, SC (ed), *Developments in Human Reproduction and their Eugenic Ethical Implications*. Academic Press London, pp. 53–115.

Edwards, RG. Chromosomal abnormalities in human embryos. *Nature* 303, 283.

Edwards, RG. Ethics of fertilization of human eggs *in vitro*. *Second International Conference on In Vitro Fertilization, Annecy*. European Society of Embryo Transfer.

Edwards, RG. Test-tube babies: the ethical debate. BBC Television Horizon Lecture. *The Listener*. British Broadcasting Corporation, London, 27 October, pp. 10–19.

Edwards, RG and Steptoe, PC. Current status of in-vitro fertilization and implantation of human embryos. *Lancet* ii, 1265–1270.

Edwards, RG, Fishel, SB and Purdy, JM. *In vitro* fertilization of human eggs: Analysis of follicular growth, ovulation and fertilization. In Beier, HH and Lindner, HR (eds), *Fertilization of the Human Egg in Vitro*. Springer-Verlag, Berlin, p. 169–188.

Faddy, MJ, Gosden, RG and Edwards, RG. Ovarian follicle dynamics in mice: a comparative study of three inbred strains and an F₁ hybrid. *Journal of Endocrinology* 96, 23–33.

Fishel, SB, Edwards, RG and Purdy, JM. *In vitro* fertilization of human oocytes: Factors associated with embryonic development *in vitro*, replacement of embryos and pregnancy. In Beier, HH and Lindner, HR (eds), *Fertilization of the Human Egg in Vitro*. Springer-Verlag, Berlin, pp. 251–269.

Fishel, SB, Edwards, RG and Walters, DE. Follicular steroids as a prognosticator of successful fertilization of human oocytes *in vitro*. *Journal of Endocrinology* 99, 335–344.

Steptoe, PC and Edwards, RG. Pregnancy in an infertile patient after transfer of an embryo fertilized *in vitro*: an ethical question. *British Medical Journal* 286, 1351.

Steptoe, PC, Webster, J, Fishel, S, Edwards, RG and Purdy, JM. *In vitro* fertilization and embryo transfer. In Crosignani, PC and Rubin, BL (eds), *Serono Clinical Colloquia on Reproduction* 4. Academic Press, London.

1984

Cohen, J, Fehilly, CB, Fishel, SB, Edwards, RG, Hewitt, J, Rowland, GF, Steptoe, PC, and Webster, J. Male infertility successfully treated by in-vitro fertilization. *Lancet* i, 1239–1240.

Edwards, RG. Current status of human in-vitro fertilization. In Harrison, RF, Bonnar, J and Thompson, W (eds), *Fertility and Sterility. Proceedings of the XI World Congress on Fertility, International Federation of Fertility Societies, Dublin*. MTP Press Limited, Lancaster, pp. 109–120.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Edwards, RG. Human conception *in vitro*: new opportunities in medicine and research. In Wood, C and Trounson, A (eds), *In-vitro Fertilization and Embryo Transfer*. Churchill, Livingstone, London, pp. 217–250.
- Edwards, RG. Test-tube babies: the ethical debate. *Proceedings of the Belgian Society of Medical Ethics and Morals*, pp. 14–26.
- Edwards, RG. The current clinical success of human in-vitro fertilization. In Feichtinger, W and Kemeter, P (eds), *Recent Progress in Human In Vitro Fertilization*. Cofese, Palermo, pp. 9–22.
- Edwards, RG. The ethical, scientific and medical implications of human conception *in vitro*. In *Study Week on Modern Biological Experimentation. Pontificiae Academiae Scientiarum Scripta Varia* 51, 193–249.
- Edwards, RG and Puxon, M. Parental consent over embryos. *Nature* 310, 179.
- Edwards, RG, Fishel, SB, Cohen, J, Fehilly, CB, Purdy, JM, Steptoe, PC and Webster, J. New physiological considerations resulting from the experience of fertilization *in vitro*. In *Actualités Gynécologiques* 5th Series. Masson, Paris, pp. 135–154.
- Edwards, RG, Fishel, SB, Cohen, J, Fehilly, CB, Purdy, JM, Slater, JM, Steptoe, PC and Webster, J. Factors influencing the success of *in vitro* fertilization for alleviating human infertility. *Journal of In-vitro Fertilization and Embryo Transfer* 1, 3–23.
- Forman, R, Cohen, J, Fehilly, CB, Fishel, SB and Edwards, RG. The application of the zona-free hamster egg test for the prognosis of human *in vitro* fertilization. *Journal of In-vitro Fertilization and Embryo Transfer* 1, 166–171.
- Fishel, SB, Edwards, RG and Purdy, JM. Analysis of 25 infertile patients treated consecutively by *in vitro* fertilization at Bourn Hall. *Fertility and Sterility* 42, 191–197.
- Fishel, SB, Edwards, RG and Purdy, JM. Births after a prolonged delay between oocyte recovery and fertilization *in vitro*. *Gamete Research* 9, 175–181.
- Fishel, SB, Edwards, RG and Evans, CJ. Human chorionic gonadotropin secreted by preimplantation embryos cultured *in vitro*. *Science* 223, 816–818.

1985

- Cohen, J, Edwards, RG, Fehilly, CB, Fishel, SB, Hewitt, J, Rolland, GF, Steptoe, PC and Webster, J. Treatment of male infertility by in-vitro fertilization; factors affecting fertilization and pregnancy. *European Journal of Fertility and Sterility* 43, 321–432.
- Cohen, J, Edwards, RG, Fehilly, CB, Fishel, SB, Hewitt, J, Rowland, GF, Steptoe, PC, Walters, DE and Webster, J. *In vitro* fertilization using cryo-preserved donor semen in cases where both partners are infertile. *Fertility and Sterility* 43, 570–574.
- Cohen, J, Edwards, RG, Fehilly, CB, Fishel, SB, Hewitt, J, Purdy, JM, Rowland, G, Steptoe, PC and Webster, J. In-vitro fertilization: a treatment for male infertility. *Fertility and Sterility* 43, 422–432.
- Cohen, J, Simons, RF, Edwards, RG, Fehilly, CB and Fishel, SB. Pregnancies following the frozen-storage of expanding human blastocysts. *Journal of In Vitro Fertilization and Embryo Transfer* 2, 59–64.
- Edwards, RG. Normal and abnormal implantation in animals and man. In Edwards, RG, Purdy, JM and Steptoe, PC (eds), *Human Implantation*. Academic Press, London, pp. 303–333.
- Edwards, RG. New advances in therapy and research through *in vitro* fertilization. In Testart, J and Frydman, R (eds), *Human in Vitro Fertilization, Actual Problems and Prospects, INSERM Symposium, Cargese*. Elsevier Science Publishers (Biomedical Division), 24, pp. 293–307.
- Edwards, RG. Major problems in IVF. In Thompson, W, Joyce, DN and Jewton, JR (eds), *In-Vitro Fertilization and Donor Insemination. Proceedings of the 12th Study Group of the Royal College of Obstetricians and Gynaecologists*, pp. 79–92.
- Edwards, RG. *In vitro* fertilization and embryo replacement. Opening lecture, Third International Conference on In Vitro Fertilization, Helsinki. In Seppälä, M and Edwards, RG (eds), *In Vitro Fertilization and Embryo Transfer. Annals of the New York Academy of Sciences* 442, 1–22.
- Edwards, RG. Introduction: the scientific basis of ethics. In Seppälä, M and Edwards, RG (eds), *In Vitro Fertilization and Embryo Transfer. Annals of the New York Academy of Sciences* 442, 564–576.
- Edwards, RG. Current status of human conception *in vitro*. Review Lecture. *Proceedings of the Royal Society of London B* 223, 417–448.
- Edwards, RG and Fishel, SB. Ovulation, fertilization, embryo cleavage and implantation. In Barnes, J, Newton, M and Phillipp, E (eds), *Scientific Foundations of Obstetrics and Gynaecology*. Heinemann, London.
- Edwards, RG, Purdy, JM and Steptoe, PC. *Implantation of the Human Embryo*. Academic Press, London.
- Fehilly, CB, Cohen, J, Simons, RF, Fishel, SB and Edwards, RG. Cryopreservation of cleaving embryos and expanded blastocysts in the human: a comparative study. *Fertility and Sterility* 44, 638–644.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*. *Reprod. BioMed. Online*, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Fehilly, CB, Cohen, J and Edwards, RG. Conception *in vitro*. In Austin, CR and Short, R (eds), *Reproduction in Mammals*. Cambridge University Press, Cambridge.
- Fishel, SB, Cohen, J, Fehilly, C, Purdy, JM, Walters, DE and Edwards, RG. Factors influencing human embryonic development *in vitro*. In Seppälä, M and Edwards, RG (eds), *In Vitro Fertilization and Embryo Transfer. Annals of the New York Academy of Sciences* 442, 342–356.
- Fishel, SB, Edwards, RG, Purdy, JM, Steptoe, PC, Webster, J, Walters, E, Cohen, J, Fehilly, C, Hewitt, C and Rowland, GF. Implantation, abortion, and birth after *in vitro* fertilization using the natural menstrual cycle or follicular stimulation with clomiphene citrate and human menopausal gonadotrophin. *Journal of In Vitro Fertilization and Embryo Transfer* 2, 123–131.
- Fishel, SB, Walters, DE, Yodyingvad, V and Edwards, RG. Time-dependent motility changes of human spermatozoa after preparation for *in vitro* fertilization. *Journal of In Vitro Fertilization and Embryo Transfer* 2, 233–236.
- Forman, R, Fishel, SB, Edwards, RG and Walters, DE. The influence of transient hyperprolactinaemia on in-vitro fertilization in humans. *Journal of Clinical Endocrinology & Metabolism* 60, 517–522.
- Hewitt, J, Cohen, J, Fehilly, CB, Rowland, G, Steptoe, PC, Webster, J, Edwards, RG and Fishel, SB. Seminal bacterial pathogens and *in vitro* fertilization. *Journal of In Vitro Fertilization and Embryo Transfer* 2, 105–107.
- Walters, DE, Edwards, RG and Meistrich, MC. A statistical evaluation of implantation after replacing one or more human embryos. *Journal of Reproduction and Fertility* 74, 557–563.

1986

- Cohen, J and Edwards, RG. Responses to nine questions concerning research on human embryos. *Human Reproduction* 1, 263–269.
- Cohen, J, Simon, RS, Fehilly, CB and Edwards, RG. Factors affecting survival and implantation of cryopreserved human embryos. *Journal of In Vitro Fertilization and Embryo Transfer* 3, 46–52.
- Edwards, RG. The science and ethics of the cleavage of human embryos *in vitro*. *Contraception, Fertility and Sexuality* 14, 313–318.
- Edwards, RG. Clinical aspects of in-vitro fertilization. In Bock, G and O'Conner, M (eds), *Embryo Research, Yes or No?* Ciba Foundation, London.
- Edwards, RG, Howles, C and Macnamee, M. The endocrinology of human conception. *Gynaecological Endocrinology* 1.
- Edwards, RG. Use and abuse of research on human embryos. In Ludwig, H and Thomsen, K (eds), *Gynaecology and Obstetrics. Proceedings of the XI World Congress of Gynaecology and Obstetrics, Berlin*. Springer-Verlag, Berlin, Heidelberg, pp. 689–704.
- Edwards, RG. Causes of early embryonic loss in human pregnancies. *Human Reproduction* 1, 185–198.
- Edwards, RG. *Use of human embryos for therapeutic, scientific, industrial and commercial purposes*. Council of Europe, Parliamentary Assembly: Paris, March 4, 1986. *Human Reproduction* 1, 271–276.
- Edwards, RG. New ethical implications of human embryology. *Human Reproduction* 1, 277–278.
- Edwards, RG. Joint hearing of the Legal Affairs Committee, the Sub-Committee on Bio-Ethics of the Committee on Social and Health Questions, and the Committee on Science and Technology. Council of Europe, Parliamentary Assembly. *Human Reproduction* 1, 463–491.
- Edwards, RG. Current clinical, scientific and ethical situation of human in-vitro fertilization. Bartholomew Mosse Memorial Lecture, Dublin. *Irish Journal of Medical Science* 155, 275–285.
- Edwards, RG. The beginning of life *in vitro* and *in vivo*. *Proceedings of the 5th World Congress on Human Reproduction, Athens*.
- Edwards, RG, Mettler, LE and Walters, DE. Identical twins and in-vitro fertilization. *Journal of In Vitro Fertilization and Embryo Transfer* 3, 114–117.
- Hollands, P and Edwards, RG. The fate of embryonic cells grafted into X-irradiated recipients. *Human Reproduction* 1 (supplement 2), 40.
- Howles, CM, Macnamee, MC, Edwards, RG, Goswamy, RK and Steptoe, PC. Effect of high tonic levels of luteinizing hormone on incidence of in-vitro fertilization. *Lancet* ii, 521–522.
- Leese, HJ, Hooper, MAK, Edwards, RG and Ashwood-Smith, MJ. Uptake of pyruvate by early human embryos determined by a non-invasive technique. *Human Reproduction* 1, 181–182.
- Steptoe, P and Edwards, RG. European experience of *in vitro* fertilization and embryo replacement. Advantages of embryo storage by freezing. *Acta Europaea Fertilitatis* 17, 181–186.
- Steptoe, PC, Edwards, RG and Walters, DE. Observations on 767 clinical pregnancies and 500 births after human in-vitro fertilization. *Human Reproduction* 1, 89–94.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

1987

- Crosignani, PG and Edwards, RG. Current treatments with LHRH and its analogues. *Human Reproduction* 2, 95–97.
- Edwards, RG. La 3^e Conférence annuelle de la Société Européenne de Reproduction et d'Embryologie Humaine (ESHRE), Cambridge, Royaume-Uni, 28 juin–1^{er} juillet 1987. *Contraception, fertilité, sexualité* 15, 981–984.
- Edwards, RG. Potential of research on human embryos. In Feichtinger, W and Kemeter, P (eds), *Future Aspects of In-Vitro Fertilization*. Springer-Verlag, Berlin, pp. 245–250.
- Edwards, RG. Diagnostic methods for human gametes and embryos. *Human Reproduction* 2, 415–420.
- Edwards, RG. *In vitro* fertilization – past and future. *III International Symposium on Human Infertility, Bruges. Annales de Biologie Clinique* 45, 321–329.
- Edwards, RG. Ethics of human conception *in vitro*. *Joint meeting of the Royal Society and the American Philosophical Society*. American Philosophical Society, Philadelphia, pp. 11–24.
- Howles, CM, Macnamee, MC and Edwards, RG. Follicular development and early luteal function of conception and non-conceptual cycles after human in-vitro fertilization: endocrine correlates. *Human Reproduction* 2, 17–21.
- Howles, CM, Macnamee, MC and Edwards, RG. The effect of progesterone supplementation prior to the induction of ovulation in women treated for *in vitro* fertilization. *Human Reproduction* 2, 91–94.
- Howles, CM, Macnamee, MC and Edwards, RG. Short-term use of an LHRH agonist to treat poor responders entering in an in-vitro fertilization programme. *Human Reproduction* 2, 655–656.
- Jones, KW, Singh, L and Edwards, RG. The use of probes for the Y chromosome in preimplantation embryo cells. *Human Reproduction* 2, 439–455.
- Macnamee, MC, Howles, CM and Edwards, RG. Pregnancies after IVF when high tonic LH is reduced by long-term treatment with GnRH agonists. *Human Reproduction* 2, 569–571.
- Macnamee, MC, Howles, CM and Edwards, RG. The effects of ovarian stimulation on endogenous endocrine rhythms. In Naftolin, F and DeCherney, AH (eds), *The Control of Follicle Development, Ovulation and Luteal Functions: Lessons from In-Vitro Fertilization*. Raven Press, New York, p. 121–134.

1988

- Edwards, RG. The role of the individual and organisations in the ethical decision-making process. *Human Reproduction* 3, 11–19.
- Edwards, RG. Human uterine endocrinology and the implantation window. In Jones, Jr, HW and Schrader, C (eds), *In Vitro Fertilization and Other Assisted Reproduction. Annals of the New York Academy of Sciences* 541, 445–454.
- Edwards, RG. Obituary – Patrick Steptoe, *Independent* 30 March, 1988.
- Edwards, RG. Obituary – Patrick Steptoe 1913–1988. *Human Reproduction* 3, 821–822.
- Edwards, RG. Tribute to IVF pioneer Patrick Steptoe. *IVF Congress Magazine* 1988, 5.
- Edwards, RG and Hollands, P. New advances in human embryology: implications of the preimplantation diagnosis of genetic disease. *Human Reproduction* 3, 549–556.
- Edwards, RG and Taylor, PG. Obituary – Patrick Christopher Steptoe, CBE, MB Lond, FRCSE, FRCOG, FRS. *Lancet* i, 782.
- Howles, CM and Edwards, RG. *Wallchart on Assisted Conception*. International Planned Parenthood Federation, London.
- Howles, CM, Macnamee, MC and Edwards, RG. Progesterone supplementation in the late follicular phase of an in-vitro fertilization cycle: a 'natural' way to time oocyte recovery? *Human Reproduction* 3, 409–412.
- Macnamee, MC, Howles, CM and Edwards, RG. The influence of stimulation regimes and luteal phase support on the outcome of IVF. *Human Reproduction* 3, 43–52.

1989

- Ashwood-Smith, MJ, Hollands, P and Edwards, RG. The use of Albuminar 5TM as a media supplement in clinical in-vitro fertilization. *Human Reproduction* 4, 702–705.
- Edwards, RG. Early embryos and the fundamentals of embryology. In Motta, PN (ed), *Developments in Ultrastructure of Reproduction*. Alan R Liss Inc, New York, pp. 7–10.
- Edwards, RG. A tribute to Patrick Steptoe: beginnings of laparoscopy and in-vitro fertilization. *Human Reproduction* 4, Supplement 1, 1–9.
- Edwards, RG. *Life Before Birth: Reflections on the Embryo Debate*. Century-Hutchinson, London.
- Edwards, RG. The current ethical situation on in-vitro fertilization. In Nicholas, JN (ed), *Moral Priorities in Medical Research: The Second Hannah Conference, 1984, London, Canada*. Graphic Services, Ontario, Canada, pp. 199–212.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*. *Reprod. BioMed. Online*, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Edwards, RG, Plachot, M, Renard, JP, Questiaux, N and Testart, J. Discussion on ethical and judicial aspects of embryo research. *Human Reproduction* 4, 206–217.
- Macnamee, MC, Howles, CM, Edwards, RG, Taylor, PJ and Elder, KT. Short-term luteinising hormone-releasing hormone agonist treatment: prospective trial of a novel ovarian stimulation regimen for in-vitro fertilization. *Fertility and Sterility* 52, 264–269.

1990

- Edwards, RG. Making bioethical decisions in today's society: an individual facing many organisations. *Essay Series, Bonhoeffer Institute (Queensland)*.
- Edwards, RG. Ethics and embryology: the case for experimentation. In Dyson, A and Harris, J (eds), *Experiments on embryos. Proceedings of Research on Human Embryos Conference, Manchester*. Social Ethics and Policy series. Routledge, London, 42–54.
- Edwards, RG. Science and Society, *Proceedings of the European bioethics Conference on Human Embryos and Research, Mainz*.
- Edwards, RG and Craft, I. Development of assisted conception. *British Medical Bulletin* 46, 565–579.
- Edwards, RG and Handyside, A. Future developments in IVF. *British Medical Bulletin* 46, 769–782.
- Edwards, RG, Crow, J, Dale, S, Macnamee, M, Hartshorne, GM and Brinsden, P. Preimplantation diagnosis and recurrent hydatidiform mole. *Lancet* i, 1030–1031.
- Elder, KT, Wick, KL and Edwards, RG. Seminal plasma antisperm antibodies and IVF: the effect of semen sample collection into 50% serum. *Human Reproduction* 5, 179–184.
- Kingsland, C, Edwards, RG, Mason, BA and Davis, M. Analysis of twins, triplet and quadruplet births after in-vitro fertilization. *European Journal of Obstetrics and Gynaecology* 34, 197–203.
- Rizk, B, Lachelin, GCL, Davies, MC, Hartshorne, GM and Edwards, RG. Ovarian pregnancy following in-vitro fertilization and embryo transfer. *Human Reproduction* 5, 763–764.
- Rizk, B, Marcos, S, Avery, S, Elder, K, Brinsden, P, Mason, B and Edwards, R. Rare ectopic pregnancies after in-vitro fertilization: one unilateral twin and four bilateral tubal pregnancies. *Human Reproduction* 5, 1025–1028.

1991

- Edwards, RG, Morcos, S, Macnamee, M, Balmaceda, JP, Walters, DE and Asch, R. High fecundity of amenorrhoeic women in embryo-transfer programmes. *Lancet* 338, 292–294.
- Hartshorne, GM and Edwards, RG. Role of embryonic factors in development: recent developments. In Seppälä, M (ed), *Factors of Importance for Implantation, Bailliere's Clinical Obstetrics and Gynecology*, vol. 5. Bailliere Tindall, London, p. 133.
- Rizk, B, Tan, SL, Morcos, S, Riddle, A, Brinsden, P, Mason, BA and Edwards, RG. Heterotopic pregnancies after in-vitro fertilisation and embryo transfer. *American Journal of Obstetrics and Gynecology* 164, 161–164.
- Rizk, B, Doyle, P, Tan, Rainsbury, P, Betts, Brinsden, P and Edwards, R. Perinatal outcome and congenital malformations in in-vitro fertilization babies from the Bourn-Hallam group. *Human Reproduction* 6, 1259–1264.
- Sathanandan, M, Macnamee, MC, Rainsbury, P, Wick, K, Brinsden, P and Edwards, RG. Replacement of frozen-thawed embryos in artificial and natural cycles – a semi-randomized study. *Human Reproduction* 6, 685–687.

1992

- Edwards, RG. Embryonic stem cells. *Bone Marrow Transplantation* 9, 4–6.
- Edwards, RG. Human embryos as a source of cells. *Bone Marrow Transplantation* 9, 90–92.
- Edwards, RG. Why are agonadal and amenorrhoeic women so fertile? *Human Reproduction* 7, 733–734.
- Edwards, RG, Crow, J, Dale, S, Macnamee, MC, Hartshorne, GM and Brinsden, P. Pronuclear, cleavage and blastocyst histories in the attempted preimplantation diagnosis of the human hydatidiform mole. *Human Reproduction* 7, 994–998.
- Rizk, B, Edwards, RG, Nicolini, U, Maugher, S and Lamont, RF. Edwards syndrome after the replacement of cryo-preserved thawed embryos. *Fertility and Sterility* 55, 208–210.
- Rizk, B, Manners, CV, Davies, MC, Steer, CV, Bell, SC, Dillon, D and Edwards, RG. Immunohistochemical expression of endometrial proteins and pregnancy outcome in frozen embryo replacements. *Human Reproduction* 7, 413–417.
- Sharpe, DJ and Edwards, RG. The fraud conviction of Cecil B. Jacobson. *Human Reproduction* 7, 897–898.
- Steer, CV, Mills, CL, Tan, SL, Campbell, S and Edwards, RG. The cumulative embryo score. *Human Reproduction* 7, 117–119.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

Tan, SL, Doyle, P, Campbell, S, Veral, V, Rizk, B, Brinsden, P, Mason, B and Edwards, RG. Obstetric outcome of in-vitro fertilization pregnancies compared with normally conceived pregnancies. *American Journal of Obstetrics and Gynecology* 167, 778–784.

Tan, SL, Royston, P, Campbell, S, Jacobs, HS, Betts, J, Mason, B and Edwards, RG. Cumulative conception and livebirth rates after in-vitro fertilisation. *Lancet* 1, 1390–1394.

1993

Edwards, RG. Pregnancies are acceptable in post-menopausal women. *Human Reproduction* 1542–1544.

Edwards, RG. The early days of in-vitro fertilization. In Alberda, ATh, Gan, RA and Vemer, HM (eds), *Pioneers in In-vitro Fertilization*. Studies in Profertility Series, 7–23.

Edwards, RG, Van Steirteghem, AC. Intracytoplasmic sperm injection (ICSI) and human fertilization: does calcium hold the key to success? *Human Reproduction* 8, 988–989.

Edwards, RG, Van Steirteghem, AC and Richardson, MJ. Impact factors – more misleading than ever. *Human Reproduction* 8, 983–985.

Marcus, SF, Brinsden, PR, Macnamee, M, Rainsbury, PA, Elder, KA and Edwards, RG. Comparative trial between an ultra-short and long protocol of luteinizing-hormone releasing hormone agonist for ovarian stimulation in in-vitro fertilization. *Human Reproduction* 8, 238–243.

1994

Dean, NL and Edwards, RG. Oocyte donation – implications for fertility treatment in the nineties. *Current Opinion in Obstetrics and Gynecology* 6, 160–165.

Edwards, RG. Implantation, interception and contraception. *Human Reproduction* 9, 985–995.

Edwards, RG. Hydatidiform moles. *Human Reproduction* 9, 1783–4 (letter).

Edwards, RG, Tarin, JJ, Dean, N, Hirsh, A and Tan, SL. Are spermatid injections into human oocytes now mandatory? *Human Reproduction* 9, 2217–2219.

Jones, Jr, HW, Edwards, RG and Seidel, Jr, GE. On attempts at cloning in the human. *Fertility and Sterility* 61, 423–426.

Marcus, S and Edwards, RG. High rates of pregnancy after a long-term down regulation of women with severe endometriosis. *American Journal of Obstetrics and Gynecology* 171, 812–817.

Massey, JB, Kort, HI, Tucker, MJ, Elsner, CW, Nisker, JA, Baylis, F, Jones, Jr, HW, Edwards, RG, Seidel, GE and McDonough, PG. The best of us. *Fertility and Sterility* 62, 893–896.

Tan, SL, Doyle, P, Maconochie, Edwards, RG, Balen, A, Bekir, J, Brinsden, P and Campbell, S. Pregnancy and birth rates after in-vitro fertilization in women with and without previous in-vitro pregnancies: A study of 8,000 cycles at one centre. *American Journal of Obstetrics and Gynecology* 170, 34–40.

1995

Edwards, RG. Truth and veracity in science. *Fertility and Sterility*.

Edwards, RG. Georgeanna and Howard: Two of a kind. Tribute to Drs Georgeanna and Howard Jones. *Human Reproduction Update* 1, CD-ROM disk item 17.

Edwards, RG and Beard, HK. Sexing human spermatozoa to control sex ratios at birth is now a reality. *Molecular Human Reproduction* 1, 977–978.

Edwards, RG. Cell cycle factors in the human oocyte and the intracytoplasmic injection of spermatozoa. *Reproduction, Fertility and Development* 7, 143–153.

Edwards, RG, Jauniaux, E, Binns, RM, Layton, M, Jovkovic, D, Grillo, TAI and Campbell, S. Induced tolerance and chimaerism in human fetuses using coelocentesis – a medical opportunity to avert genetic disease. *Human Reproduction Update* 1, 419–427.

1996

Ashwood-Smith, MJ and Edwards, RG. DNA repair by oocytes. *Molecular Human Reproduction* 2, 46–51.

Crosignani, PG, Rubin, B, Acosta, A, Baird, DT, Benagiano, G, Cohen, J, Collins, J, Cooke, I, Diczfalussy, E, Diedrich, K, Edwards, RG, Farley, T, Filicori, M, Glasier, A, Hargreave, T, Jager, S, Mishell, DR, Nieschlag, E and Ragni, G. Guidelines to the prevalence, diagnosis, treatment and management of infertility. *Human Reproduction* 11, 1775–1807.

Edwards, RG. Art and Science: Two cosy bedfellows. In Einstein Meets Magritte. *Anniversary Symposium of the Vrije Universiteit Brussels*.

Edwards, RG. The history of assisted human conception with especial reference to endocrinology. *Experimental and Clinical Endocrinology and Diabetes* 104, 183–204.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

- Edwards, RG. Biography, Patrick Steptoe, CBE, MBChB, DSc, FRCS (Edin), FRCOG, FRS. *Philosophical Transactions of the Royal Society* 435–452.
- Edwards, RG. Human conception *in vitro*: a summing up. *Proceedings of the 3rd Bourn Hall Symposium. Human Reproduction Supplement* 1, 199–211.
- Edwards, RG and McDonough, PG. Integrity and IVF. *Fertility and Sterility* 65, 678–679.
- Edwards, RG, Lobo, R and Bouchard, P. Time to revolutionise ovarian stimulation. *Human Reproduction* 11, 917–919.
- Schulman, JD and Edwards, RG. Preimplantation diagnosis is disease control, not eugenics. *Human Reproduction* 11, 463–464.

1997

- Edwards, RG. Recent scientific and medical advances in assisted human conception. *International Journal of Developmental Biology* 41, 255–262.
- Edwards, RG. Introduction and development of IVF and its ethical regulation. In Hildt, E and Mieth, D (eds), *IVF in the Nineties – Towards a Medical, Social and Ethical Evaluation*. An EU Publication. Ashgate, pp. 1–17.
- Edwards, RG and Beard, HK. UK law dictated the destruction of 3000 cryopreserved human embryos. *Human Reproduction* 12, 3–5.
- Edwards, RG and Beard, HK. Oocyte polarity and cell determination in early mammalian embryos, *Molecular Human Reproduction* 3, 863–906.
- Edwards, RG and Beard, HK. Human cloning and monozygotic twinning: how similar will they be? In Shenfield, F (ed) *Societal, Medical and Ethical Implications of Animal Cloning*. Royal Society, London.
- Edwards, RG and Bishop, C. On the origin and frequency of Y chromosome deletions responsible for severe male infertility. *Molecular Human Reproduction* 3, 549–554.
- Edwards, RG, Lobo, RA and Bouchard, P. Why delay the obvious need for milder forms of ovarian stimulation? *Human Reproduction* 12, 399–400.
- Edwards, RG, Beard, HK and Bradshaw, JP. Balancing risks and benefits of oral contraception, *Human Reproduction* 12, 2339–2340.

1998

- Edwards, RG. New approaches to achieving human fertilization: a resume. *Human Reproduction* 13, Supplement 3, 127–136.
- Edwards, RG. New concepts in embryonic growth and implantation. *Human Reproduction* 13, Supplement 3, 271–282.
- Edwards, RG. Recent analyses on implantation in mammals. In Filicori, M and Flamigni, C (eds), *Treatment of Infertility: The New Frontiers*. Communication Media for Education Inc., Princeton Junction, New Jersey, pp. 29–35.
- Edwards, RG and Beard, HK. A simple new source of human follicles and oocytes. *Human Reproduction* 13, 2337.
- Edwards, RG and Beard, HK. How identical would cloned children be? An understanding essential to the ethical debate. *Human Reproduction Update* 4, 791–811.
- Edwards, RG and Beard, HK. Les clones, des copies parfaites? *La Revue de la Confédération française démocratique du travail* 14, 26–31.
- Kupker, W, Diedrich, K and Edwards, RG. Major principles of mammalian fertilization. *Human Reproduction* 13, Supplement 1, 20–32.

1999

- Ahuja, KK, Simons, EG and Edwards, RG. Money, morals and medical risks: conflicting notions underlying the recruitment of egg donors. *Human Reproduction* 14, no. 2, 279–284.
- Cohen, J and Edwards, RG. Conclusions: the relative safety of modern oral contraceptives. *Human Reproduction Update* 5, 756–771.
- Edwards, RG. Widening perspectives of intracytoplasmic sperm injection (ICSI). *Nature Medicine* 5, no. 4, 377–378.
- Edwards, RG and Beard, HK. Is the success of human IVF more a matter of molecular genetics than growing blastocysts? Debate. *Human Reproduction*, 14, 1–4.
- Edwards, RG and Beard, HK. Hypothesis: Sex-determination and germ-line formation in mammalian embryos originates at the pronucleate stage. *Molecular Human Reproduction* 5, 596–606.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

Edwards, RG and Cohen, J. The recent saga of cardiovascular disease and safety of oral contraceptives. *Human Reproduction Update* 5, 565–620.

2000

Edwards, RG. Human embryos in-vitro: pioneer illustrations of oocyte maturation, fertilization, cleavage and blastulation. *Human Reproduction Supplement*, Volume 15, no. 4, 1–9.

Edwards, RG. The role of embryonic polarities in preimplantation growth and implantation of mammalian embryos. *Human Reproduction Supplement*, Volume 15, no. 6, 1–8.

Edwards, RG. A well-taken opportunity for double blessing. *Reproductive BioMedicine Online* 1, 31–32.

Edwards, RG. Exciting times for gene knockout and homologous recombination in mammalian embryos. *Reproductive BioMedicine Online* 1, 123–125.

Edwards, RG. Restoring and repairing human organs: cloning embryos and embryo stem cells versus reconstructive surgery. In *Le clonage, la thérapie cellulaire et l'utilisation thérapeutique des cellules embryonnaires*. Assemblée Nationale, France, 123–127.

2001

Edwards, RG. Gentler alternatives to modern forms of ovarian stimulation are necessary. *Current Issues in Obstetrics and Gynaecology*.

Edwards, RG. Regulatory systems in early mammalian development, with especial reference to polarity and totipotency. *Italian Journal of Anatomy and Embryology* 106 (supplement 2), 85–100.

Edwards, RG. IVF and the history of stem cells. *Nature* 413, 349–351.

Edwards, RG. The bumpy road to human in-vitro fertilization. *Nature Medicine* 7, 10.

Edwards, RG. Ovarian differentiation and human embryo quality. 1. Molecular and morphogenetic homologies between *Drosophila*, *C. elegans*, *Xenopus* and mammals. *Reproductive BioMedicine Online* 3, 53–74.

Edwards, RG. Is scientific history cloning itself? Comment on the Washington conference. *Reproductive BioMedicine Online* 3, 136–137.

Edwards, RG. Ethics of preimplantation genetic diagnosis combined with histocompatibility selection to repair sick siblings. *Reproductive BioMedicine Online* 3, 176.

Edwards, RG and Ahuja, KK. Legal cases against IVF embryologists spell big trouble and great opportunities. *Reproductive BioMedicine Online* 2, 70–71.

2002

Boiso, I, Veiga, A and Edwards, RG. Fundamentals of human embryonic growth *in-vitro* and the selection of high-quality embryos for transfer. *Reproductive BioMedicine Online* 5, 328–350.

Edwards, RG. The scientific and clinical journey to modern IVF. *Emirates Medical Journal* 20, no. 3, 1–16.

Edwards, RG. Exciting times in modern gynaecological endocrinology. *Gynäkologische Endokrinologie*, Volume 1.

Edwards, RG. Reproductive rhythms, longevity and cancer. *Reproductive BioMedicine Online* 4, 93–96.

Edwards, RG. Personal pathways to embryonic stem cells. *Reproductive BioMedicine Online* 4, 263–278.

Hardarson, T, Löfman, C, Coull, G, Sjogren, S, Hamberger, L and Edwards, RG. Internalization of cellular fragments in a human embryo: time-lapse recordings, *Reproductive BioMedicine Online* 5, 36–38.

2003

Edwards, RG. Aspects of the molecular regulation of early mammalian development. *Reproductive BioMedicine Online* 6, 97–113.

Edwards, RG and Ludwig, M. Are major defects in children conceived *in vitro* due to innate problems in patients or to induced genetic damage? *Reproductive BioMedicine Online* 7, 131–138.

Edwards, RG, Angastiniotis, M, Antinori, S, Braude, P, Simpson, L, Willadsen, SM and Wilton, L. Ethics of preimplantation diagnosis: recordings from the Fourth International Symposium on Preimplantation Genetics. *Reproductive BioMedicine Online* 6, 170–180.

Hansis, C and Edwards, RG. Cell differentiation in the preimplantation human embryo. *Reproductive BioMedicine Online* 6, 215–220.

Simpson, JL and Edwards, RG. Public objections to designer babies and cloning in USA: not quite what was expected. *Reproductive BioMedicine Online* 6, 147–148.

Walters, E and Edwards, RG. On a fallacious invocation of the Barker hypothesis of anomalies in newborn rats due to mothers' food restriction in preimplantation phases. *Reproductive BioMedicine Online* 7, 580–582.

Please cite this article in press as:

Gardner RL, Johnson MH. Bob Edwards and the first decade of *Reproductive BioMedicine Online*.

Reprod. BioMed. Online, in press. doi: 10.1016/j.rbmo.2010.11.010. © 2010, Reproductive Healthcare Ltd. Published by Elsevier Ltd.

2004

- Edwards, RG. History of embryo stem cells. In Lanza, R (ed), *Handbook of Stem Cells, Volume 2, Embryonic Stem Cells*. Elsevier Inc., pp. 1–14.
- Edwards, RG. Stem cells today: A. Origin and potential of embryo stem cells. *Reproductive BioMedicine Online* 8, 275–306.
- Edwards, RG. Stem cells today: B1. Bone marrow stem cells. *Reproductive BioMedicine Online* 9, 541–583.
- Empeaire, JC and Edwards, RG. Time to revolutionize the triggering of ovulation. *Reproductive BioMedicine Online* 9, 480–483.
- Thrasher, AJ and Edwards, RG. Averting abnormal inheritance: potential of gene therapy and preimplantation diagnosis. *Reproductive BioMedicine Online* 8, 99–106.
- Walters, E and Edwards, RG. Further thoughts regarding the evidence in support of the 'Barker Hypothesis'. *Reproductive BioMedicine Online* 9, 129–131.

2005

- Edwards, RG. The Lasker Foundation and Recognition of Scientific Excellence. *Journal of the American Medical Association* 294, no. 11, 1–2.
- Edwards, RG. An astonishing journey into reproductive genetics since the 1950's. *Reproduction, Nutrition, Development* 45, 299–306.
- Edwards, RG. Ethics and moral philosophy in the initiation of IVF, preimplantation diagnosis and stem cells. *Reproductive BioMedicine Online* 10 (supplement 1), 1–8.
- Edwards, RG. Genetics of polarity in mammalian embryos. *Reproductive BioMedicine Online* 11, 104–114.
- Edwards, RG. Changing genetic world of IVF, stem cells and PGD. A. Early methods in research. *Reproductive BioMedicine Online* 11, 750–760.
- Edwards, RG. Changing genetic world of IVF, stem cells and PGD. B. Polarities and gene expression in differentiating embryo cells and stem cells. *Reproductive BioMedicine Online* 11, 761–776.
- Edwards, RG. Changing genetic world of IVF, stem cells and PGD. C. Embryogenesis and the differentiation of the haemopoietic system. *Reproductive BioMedicine Online* 11, 777–785.
- Edwards, RG. The biomedical background to Bourn Hall Clinic. In Brinsden, P (ed), *Textbook of In-vitro Fertilization and Assisted Reproduction*, 3rd edn. Parthenon Press.
- Edwards, RG and Hansis, C. Initial differentiation of blastomeres in 4-cell human embryos and its significance for early embryogenesis and implantation. *Reproductive BioMedicine Online* 11, 206–218.

2006

- Edwards, RG. Genetics, epigenetics and gene silencing in differentiating mammalian embryos. *Reproductive BioMedicine Online* 13, 732–753.
- Edwards, RG. Human implantation: the last barrier in assisted reproduction technologies? *Reproductive BioMedicine Online* 13, 887–904.
- Edwards, RG and Ahuja, KK. Ethics and science of stem cells: are ES cell lines outdated? *Reproductive BioMedicine Online* 13, 309–310.

2007

- Edwards, RG. IVF, IVM, natural cycle IVF, minimal stimulation IVF – time for a rethink. *Reproductive BioMedicine Online* 15, 106–119.
- Edwards, RG and Hollands, P. Will stem cells in cord blood, amniotic fluid, bone marrow and peripheral blood soon be unnecessary in transplantation? *Reproductive BioMedicine Online* 14, 396–401.

2008

- Edwards, RG. From embryo stem cells to blastema and MRL mice. *Reproductive BioMedicine Online* 16, 425–461.