

SYMPOSIUM: THE HISTORY OF THE FIRST IVF BIRTHS

The Oldham Notebooks: an analysis of the development of IVF 1969–1978. I. Introduction, materials and methods

Kay Elder^a, Martin H Johnson^{b,*}

^a Bourn Hall Clinic, Bourn, Cambridge CB23 2TN; ^b Anatomy School and Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge, Downing Street, Cambridge CB2 3DY, UK * Corresponding author. *E-mail addresses:* kay.elder@bourn-hall.com (K. Elder), mhj21@cam.ac.uk (M.H. Johnson).



Kay Elder joined Bourn Hall in 1984 as Clinical Assistant to Patrick Steptoe, directing the Out-Patient Department from 1985 – 1987. Her scientific background as a research scientist at Imperial Cancer Research Fund prior to a medical degree at Cambridge University naturally led her to Bob Edwards and the IVF laboratory, where she worked as a senior embryologist from 1987. A programme of Continuing Education for IVF doctors, scientists and nurses at Bourn Hall was established in 1989, which she directed for 16 years. During this period she also helped to set up and run two Master's degree programmes in Clinical Embryology, and she continues to mentor and tutor postgraduate students of Clinical Embryology at the University of Leeds. In her current role as Senior Research Scientist at Bourn Hall she co-ordinates research collaborations with the MRC Laboratory of Molecular Biology in Cambridge and the MRC National Institute for Medical Research in Mill Hill.

Abstract In this introductory paper, we describe the primary source material studied in this Symposium, namely a set of 21 notebooks and 571 pages of loose sheets and scraps of paper, which, on cross-referencing, have allowed us to reconstruct the sequence, timing and numbers of the laparoscopic cycles planned, attempted and undertaken between 9 January 1969 and 1 August 1978 by Robert Edwards, Patrick Steptoe and Jean Purdy in Oldham, UK, as well as to identify most of the patients involved. In addition, we describe the background to the five papers that follow, and the secondary sources and recorded interviews, which have provided useful ancillary material.

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Introduction

Louise Joy Brown was born on 25 July 1978. This event generated international excitement then, and its wider impact on science, medicine, and society in general continues to reverberate (Franklin, 2013). Little historical

research has been undertaken on the work conducted in Oldham and Cambridge that led to this birth, other than that concerning its very early stages up to 1972 (Johnson, 2011; Johnson et al., 2010). Our main sources of information about the later (1972–1978) work come from the scientific writings and lectures of Edwards and Steptoe, and from their

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narrative account, *A Matter of Life* (Edwards and Steptoe, 1980), which conveys the atmosphere of events from 1968 to 1978, but which contains several internal contradictions and inaccuracies.

The historical background to the evidence described in this series of papers draws largely on Johnson et al. (2010) and Johnson (2011). Thus, Johnson (2011) examines how and where Edwards and Steptoe first met in February of 1968 (p. 254-256) and when Purdy joined Edwards (p. 252). Prior to the meeting of these three, Edwards' primary interests lay in the study of the genetic basis of developmental diseases (p. 250-251), and of their possible alleviation by pre-implantation genetic diagnosis (p. 253 and Theodosiou and Johnson, 2011). These were the main reasons for studying the timing and control of oocyte maturation and IVF given by Edwards (1965) in his Lancet paper. It seems clear that infertility treatment only moved higher up Edwards' interests after he met Steptoe, who had a long-standing interest in trying to understand infertility and to treat the infertile (Johnson, 2011, p. 254). Indeed, one of the reasons that Steptoe pioneered laparoscopy (Steptoe, 1967) was so that he could investigate possible causes of infertility less invasively than had hitherto been the case (in addition to providing a safer and less invasive sterilization procedure for those who wished to limit further child bearing). Indeed, it was the claim that he could assess the state of post-coital sperm in the oviduct after their recovery laparoscopically that first attracted Edwards to contact him, given that sperm capacitation was the problem foremost on Edwards' mind in 1967-1968 (Johnson, 2011, p. 255-256).

Johnson et al. (2010) covers the slightly later period of 1971–1972, in which Edwards and Steptoe were initially offered institutional support by the Medical Research Council (MRC) at the Northwick Park Clinical Research Centre (Johnson et al., 2010, p. 2162-2163), and then, after Edwards declined this offer in the mistaken belief that it signalled that the MRC would look favourably on a grant application for a major project, the pair were refused funding on ostensibly ethical grounds (Johnson et al., 2010, p.2166-2168). This refusal had major consequences for the ethical approaches to their work taken subsequently by Edwards (Johnson and Elder, 2015a), as well as for how their research was funded (Johnson and Elder, 2015c).

The recent discovery of research notes from the period 1969 to 1978 amongst the papers of Edwards and at Bourn Hall Clinic has now enabled us to undertake an objective archival-based account of their work over this period. These research notes cover the period when Edwards, Steptoe and Purdy were working between Oldham and Cambridge, trying to tackle the complex issues and technical challenges involved in converting in-vitro fertilization into live births. In this paper, we describe the primary source material studied in these papers, namely a set of 21 notebooks, plus 571 pages of loose sheets and scraps of paper, which, on cross-referencing, have allowed us to reconstruct the sequence, timing and numbers of the laparoscopic cycles planned, attempted and undertaken between 1969 and 1978, and to identify the numbers of patients involved. This clinical work was undertaken at Oldham District and General Hospital (ODGH) and at the associated Dr Kershaw's Cottage Hospital, but much of the research material was transported for examination to the Physiological Laboratory at Cambridge University (Johnson, 2011).

We also describe the secondary sources and recorded interviews which have provided useful ancillary material for the five papers that follow, each of which focuses on different aspects of the 10-year period:

- the numbers of patient volunteers and treatment cycles involved and their clinical outcomes (Elder and Johnson, 2015a);
- 2. evidence relating to variations attempted in key aspects of the procedures in order to overcome the numerous technical, scientific, practical and logistic challenges faced (Elder and Johnson, 2015b);
- how Edwards and Steptoe tried to address the ethical challenges that their work raised (Johnson and Elder, 2015a);
- 4. a reassessment of the role of Jean Purdy in the research (Johnson and Elder, 2015b);
- 5. evidence relating to the funding of the research, and how this funding was used (Johnson and Elder, 2015c).

Our analysis of the evidence has allowed us (i) to trace the evolution of the clinical and scientific steps that eventually led to the births of Louise Brown and Alastair Montgomery as a result of in-vitro fertilization and embryo transfer, and (ii) to provide a detailed account of some of the organisational, social, ethical and financial issues involved over this significant period of the history of IVF.

The remainder of this paper describes our primary and secondary source materials. We describe this archival material in some detail for two reasons: (i) because it is not yet clear that the material will ever be made available to scholars generally, and (ii) if it is, much of it will be embargoed until 2069 to 2078, as containing identifiable and sensitive patient reproductive information. Those whose primary interest is in the content of the material can move to papers two to six in the series and treat this paper as reference resource where needed.

Materials and methods

Clinical and laboratory data from Oldham

The clinical and scientific data for the papers in this series were abstracted from documents, all of which are now lodged temporarily and securely for the family of Bob and Ruth Edwards in the Churchill Archives Centre at Churchill College, Cambridge. Wherever these papers finally come to be held, if they do become generally available, part of the archive is likely to be embargoed for 100 years, containing as it does identifiable patient reproductive information. The extracted, collated and anonymized data used in these papers will be available with the archive for access by other researchers, and is attached as supplementary material here (Suppl. Table) and to the next paper (Elder and Johnson, 2015a). Two main sources of data have been summarized and analysed, the contents of which are now described. Throughout, all names of patients have been removed, unless they are already in the public domain.

Loose sheets

Boxed loose sheets of notes, initially 479 pages in all, covering the laparoscopy records of 289 patients: these. where dated, were from 1969 to March 1977 (RGE1, 2014; Suppl. Table). They are in a variety of authors' hands, the majority being in an unknown hand, of someone 'transcribing' during the procedure, a few of them having notes added in the hands of Robert Edwards (RGE), Jean Purdy (JP) and Patrick Steptoe (PCS). Two lists compiled by JP contain patient names and dates of laparoscopies, together with dates of last menstrual periods (LMP) and of return to menstruation (RTM), during the periods 9 January to 8 December 1969, and February to September 1972. Six 'scraps' of paper in RGE's writing detail follicle aspirations for six cases between August and September 1969, but, as with many of the records from all these various sources, some have no dates at all, and others only the day/month without a year. Cross-reference to other sources (see below) enabled us to date these scraps of paper as May, July and August 1969.

The first full laparoscopy record amongst these loose notes is dated 8 September 1969, on ODGH paper. Folded scraps of this same notepaper record notes that we have dated by cross-referencing to July, August and September 1969; from 6 October 1969 onwards, customized pages were used with typed headings for name, age, date of laparoscopy, ovarian stimulation, details of follicle aspirations including time and flushing volume, and whether or not heparin or citrate was added to the aspirates. Evidence of pathology, such as endometriosis, adhesions, sclerotic ovaries, etc., is also noted. A few of the earlier cases have notes added in red ink (in JP's hand) regarding cumulus/eggs collected. When compared with data found in the scientific notebooks (see below), it is clear that this collection of notes is incomplete; there are clinical notes for all of the cases recorded in the notebooks during 1969, but the number of records for each year decreases thereafter, so that, in total, approximately half of the cases recorded elsewhere are found in these loose notes. The amount of detail recorded also diminishes steadily after 1973, so that by 1976-1977 increasing numbers of cases are not found, and only surgical notes are recorded, without details of LMP or ovarian stimulation.

Amongst the papers found recently at Edwards' home (RGE2, 1974/78; Suppl. Table), there is a collection of patient instructions, and a set of questionnaires completed in patients' handwriting, for a number of patients treated during 1978, with details of address, date of birth, LMP and previous history. Three handwritten sheets of paper entitled 'All patients ever admitted to Dr Kershaw's for oocytes' contain an alphabetical list of 89 patient names, with name, address, hospital number, and number of times hospitalized (total = 130 cycles). This list is undated, but by cross-referencing to other sources, was probably compiled during 1974. From this list, only one name cannot be found elsewhere in the records, and this patient is not considered further. An envelope contains typed address/LMP details for 16 patients, 14 of whom (by cross-referencing) were treated during 1975–1976. The two additional patients apparently had preliminary laparoscopic investigations, but no records of further treatment were found, and so they are not considered further.

Notebooks

A collection of 21 hard-backed scientific notebooks containing data obtained in Oldham was found, some at Edwards' home and others in the store at Bourn Hall Clinic (RGE3, 2014). Most of the data in these notebooks are in the hand of JP, only a few records being made by RGE himself.

The primary data set comes from a set of 18 notebooks labelled either LO-L9 (for laparoscopy, 10 notebooks; L0 is unlabelled, the notation L0 being ascribed by us), or H0-H9 (for hormones; 8 notebooks, as H5 and 6 do not exist - see below). Between 1969 and 1976 the L and H notebooks have separate numbering systems for each prospective cycle of treatment, and cases being prepared for laparoscopy were allocated two different numbers, an H- and an L-number. The H-numbers are not consecutive, but comprise 'even' numbers only, i.e. H2, H4, H6, up to H564. Some H cycles do not have L-numbers, and a few cycles have neither number. Additionally, some patients with L-numbers do not proceed to laparoscopy. A final complication is that some patients have more than one L- or H-number. A common numbering system was adopted during 1976, as a result of which the L-numbers recorded in notebook L6 skip from L502 on 3 July 1976 to L600 for the next case, 2 September 1976. The corresponding H-numbers for these cases/dates skip from H564 (22 June 1976) in notebook H4 to H600 (2 September 1976) in notebook H7; no notebooks labelled H5 and H6 were found and probably never existed. From September 1976 to July 1978 each case is recorded with the same L- or H-number in corresponding L7, 8, 9/H7, 8, 9 books, (L/H 600 to 747).

The 10 notebooks labelled L0 to L9 contain details of prospective laparoscopic oocyte retrievals (LOR) and their outcomes, from 9 January 1969 to 1 August 1 1978. Hormone assays (TE and PD) were initially recorded in L0, and from 23 October 1969, coinciding with the first use of the customized loose record sheets with typed headings (see earlier), the hormone assays are separately recorded in 'H' notebooks H0 to H4, and then H7, H8, H9. Notebooks H3 and H4 contain endocrine records of cycles that were initiated between 5 April 1973 (H268) and 22 June 1976 (H564). These two notebooks contain endocrine monitoring data for a number of patients whose cycles were tracked during natural or stimulated cycles on several occasions, some (but not all) of which led to LOR procedures, tubal insemination or timed intercourse.

The last section of notebook L0 contains analyses of the laparoscopy results according to all of the different parameters recorded: stimulation dose/interval, day of HCG, interval between HCG and lap, follicles seen/aspirated, oocytes, size of follicles versus oocyte stage, follicle size versus fluid bloodiness and stage of meiosis. Detailed comparisons are reported in Elder and Johnson (2015b). In addition, the names and addresses of 41 women/couples from around the world (23 from southern England, 4 from North America, 3 from Australasia, 2 each from Wales and Germany, and 1 each from India, Switzerland, Greece, Italy, France, Scotland and South Africa) are recorded under a page heading in pencil saying 'Standard letter 2'. Carbon copies of the letters to these women/couples explaining why they could not yet be accepted on the programme were

found in the Edwards papers (RGE2, 1974/78; Johnson and Elder, 2015a).

Together, these 18 'L' and 'H' notebooks contain the richest data sets. A further notebook is labelled T/D (for Tables/Data) and summarizes data collated by patient response to stimulation using laparoscopy (L) or hormone (H) number as identifier, but undated. Dates of procedures in this notebook can be deduced by cross-referencing the L and H numbers recorded in the other data sources. Other sections of this notebook are annotated (incompletely) to record oocyte retrieval (OCR) and embryo transfer (ET) procedures, as well as cancelled laparoscopies and conversions of cycles to clomid + timed intercourse (CTI) or intra-tubal insemination (ITI). The last section of the notebook lists details of 79 OCR procedures carried out in natural cycles with LH monitoring using the Hi-Gonavis assay for LH, and the details correspond very closely to the data published in Steptoe et al. (1980).

A second notebook labelled FF (follicular fluids) contains lists of patients from whom serum (culture blood, CB), follicular fluid and cells for culture were collected between 1969 and 1978. Results for serum and follicular fluid assays are recorded under the patient's L-number for that cycle. The last notebook is labelled F1 (Freezing) and contains records of early attempts at oocyte and embryo freezing in June/July 1977. Since we were drawing on different elements of the same data from the multiple sources listed above to produce our final data tables, we have attempted to disentangle the various complications in the five papers that follow by composing tables of data that reflect the different analytical perspectives. Examples of the materials we were working with are shown in Figure 1.

Travel and expenses data

The back pages of notebooks L1-4, 6 and 7 record, in the hand of JP, records of dates of travel to and from Oldham by RGE and JP, plus records of accommodation used and meals taken. These data formed the basis for expenses claimed from Mr Holmes of the University of Cambridge Financial Board, some of which claims are recorded and priced (see Johnson and Elder, 2015b,c). The form taken by these records varies with time, although all record the dates by year, month and day. Initially (1969–1971; books L1 and 2) the data show simply the numbers of trips and the total number of days for each person. However, in 1972, summary data for total numbers of 'suppers, coffees, lunches, teas and coffees' are also recorded (book L2). Data for 1973 between 1 January and 20 July are missing. Between July 1973 and the end of September 1975 (books L4 and 6), individual 'coffees, lunches, teas, suppers and accommodations' are recorded by date for each person (but not total days), and from December 1975 to 14 June 1976 (Book L7), 'breakfasts' are added to these details. For these dates we have estimated days and trip numbers for both RGE and JP from the patterns of meals/accommodation recorded. However, from 15 June 1976 onwards (Book L7) records are far less detailed, with just one or two 'ticks' per day, for most of which it is possible to deduce which tick is for JP and which for RGE. Records cease after 26 February 1977 and so we lack detailed data for the rest of 1977 and all of 1978.



Figure 1 (a) Pages from notebook H3, when several different cycles were being recorded for the same patient; this page shows five different cycles, two with laparoscopy (Lap) numbers. (b) RGE's 'scraps', unfolded, from 1969.

However, a card in JP's hand found amongst the loose papers records data for Saturdays, Sundays and Bank Holidays in 1978 that may represent days for which JP claimed. Additionally, from January to June 1974 two additional sets of initials appear in the expenses records, namely JS and IF. JS is identified as 'Joe' and IF as 'Ian'.

Archival research

Various scientific papers and the volume *A Matter of Life* (Edwards and Steptoe, 1980) have been consulted. The latter book conveys the atmosphere of events from 1968 to 1978, but was written in part from notes dictated to Dannie Abse, and contains several internal contradictions and inaccuracies, some of which are corrected in the revised 2013 edition (Edwards and Steptoe, 2013). However, where references to this source are made they are usually suitably qualified with cautions and/or corroborative evidence. The Churchill Archives Centre, Churchill College, Cambridge (CAC), Cambridgeshire County Library Archive (CCLA), the

British Medical Association archive (BMA), Cambridge University Archive (CUA) and the National Archive (NA) were also consulted. Archival references in the text are indicated by the archive's initials followed by a reference number and date, and the details for each reference are recorded in the reference list. In addition, some 115 boxes of papers found among the possessions of the late Edwards and his late wife, Ruth Fowler Edwards, which are currently being held for the family by the Churchill Archives Centre, have been kindly made available to us by their family. Items cited in this archive are referenced in the text with the prefix RGE1, 2, 3 etc. followed by a date, and in the reference list their location is described according to the classification system used by the family.

Interviews

Grace MacDonald (GM), John Webster (JW) and Noni Fallows (NF) were interviewed in person, and Sandra Corbett [SC2] was interviewed by telephone, and the interviews recorded and transcribed. Edited transcripts of these interviews are attached as Supplementary materials to the papers where they are first referenced. Where reference is identified by the initials of the interviews, each reference is identified by the initials of the interviewee(s) and the page number(s) within the transcript. In addition, Rosemary Carter [RC] was interviewed in person, and Andrew Steptoe (AS), Alan Dexter (AD), Dr Joe Schulman (JS), John Fallows (JF), Barbara Rankin (BR), Carol Readhead (CR), Virginia Papaioannou (VP), John Fallows (JF) and Caroline Blackwell (CB2) were interviewed by email and/or in person.

Abbreviations used in the Symposium

AD = Alan Dexter; AIH = artificial insemination by husband; AS = Andrew Steptoe; BR = Barbara Rankin; CB = culture blood, used to prepare serum for embryo culture; CB2 = Caroline Blackwell; CR = Carol Readhead; CTI = Clomid + timed intercourse; ERPOC = evacuation of retained products of conception; ET = embryo transfer; FF = follicular fluids; GM = Grace MacDonald; HCG = human chorionic gonadotropin; ITI = intra-tubal insemination; JF = John Fallows; JP = Jean Purdy; JS = Joe Schulman; JW = John Webster; LH = luteinizing hormone; NC = natural cycle; Lap = laparoscopy; LMP = last menstrual period; LOR = laparoscopic oocyte retrieval; NF = Noni Fallows; OCR = oocyte retrieval; ODGH =Oldham District and General Hospital; PCS = Patrick Steptoe; RC = Rosemary Carter; PD = pregnandiol; RGE = Robert Edwards; RTM = return to menstruation; SC = stimulated cycle; SC2 = Sandra Corbett; TE = total estrogens; VP = Virginia Papaioannou.

Discussion

The notebooks and loose sheets were discovered over a period of some five years, the last notebook surfacing in January 2014, and the last set of loose notes in March 2014. We have some evidence that some of the retained paperwork seen by MHJ in 2010 did not survive a programme of sorting begun by Edwards in 2009. However, we are confident from our detailed cross-referencing that we now

have as complete a set of clinical data from the period as is available from these sources, although we do lack some travel and accommodation details. Attempts to locate corroboratory records from clinical notes in Oldham have been unsuccessful. Indeed a letter to RGE from anaesthetist Dr Finlay Campbell dated 16 October 1978 states that 'Alas, the ones [records] at Kershaw's have disappeared' (RGE4, 1978), suggesting their early removal/loss from the site. It is unclear whether or why they were removed or by whom. If any clinical notes were retained from that period, they were evidently destroyed subsequent to the introduction of the Data Protection Act 1998 (see Johnson and Elder, 2015a). Notwithstanding, the existing data set provides a rich source for the analyses that follow.

Finally, we wish to thank, personally and on behalf of the wider community, Bob and Ruth Edwards and latterly their family, as well as Mike Macnamee of Bourn Hall, for their generosity in allowing us relatively unfettered access to this remarkable archive collection.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.rbms.2015.04.001.

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