Chapter 1

Introduction

Fighting against Murphy's Law in ART

"If something can go wrong, it will. . .": Murphy's Law has belonged to popular wisdom for many years. The modern version of the law has its roots in 1949 US Air Force studies on the effects of rapid deceleration on pilots: volunteers were strapped on to a rocket-propelled sled, and their condition monitored via electrodes fitted to a harness as the sled was brought to an abrupt halt. The monitoring harness was designed by Captain Edward A. Murphy, and technicians were puzzled by the fact that it failed to record any data. Murphy discovered that all of the electrodes had been wired incorrectly, prompting him to declare:

> *"If there are two or more ways of doing something, and one of them can lead to catastrophe, then someone will do it."*

Project engineers presented Murphy's observation as an excellent working assumption in safety-critical engineering, but to Murphy's chagrin, his principle was transformed into an apparently flippant statement about the cussedness of everyday events. Ironically, by losing control over his original meaning, Murphy thus became the first victim of his eponymous law. Murphy was perhaps unaware that the essential idea behind his law had been observed by the Scottish poet Robert Burns in 1786:

> *"The best laid schemes o' Mice an' Men Gang aft agley (often go awry)."*

Another famous example of Murphy's law was described in 1884 by the Victorian satirist James Payne:

> *"I never had a piece of toast*
> *Particularly long and wide*
> *But fell upon the sanded floor*
> *And always on the buttered side."*

Many scientists will consider Murphy's law as part of a vast body of folklore, considered both humorous – and a source of truth about human nature. Robert Matthews, in a scientific study of the Tumbling Toast phenomenon (1996) stated that the awful truth is that the universe is against us. He used a wide range of mathematics and science, from probability theory to rigid-body dynamics and found that Murphy's law finds its explanation in cosmic constants, combinatoric analysis, etc.

Perhaps Murphy's true legacy is the concept that *apparently trivial phenomena often have explanations that are far from trivial.* This brings us back to a basic premise: *Life is difficult!* and to the first of Buddha's Four Noble Truths, which states: *"Life is suffering."* The embryologist may add to this: "*ART is more suffering."* Applying M. Scott Peck's vision (1978) we may state:

> "Once we truly know that ART is difficult – once we truly understand and accept it – then ART is no longer difficult, because once the principle is accepted, the fact that it is difficult no longer matters."

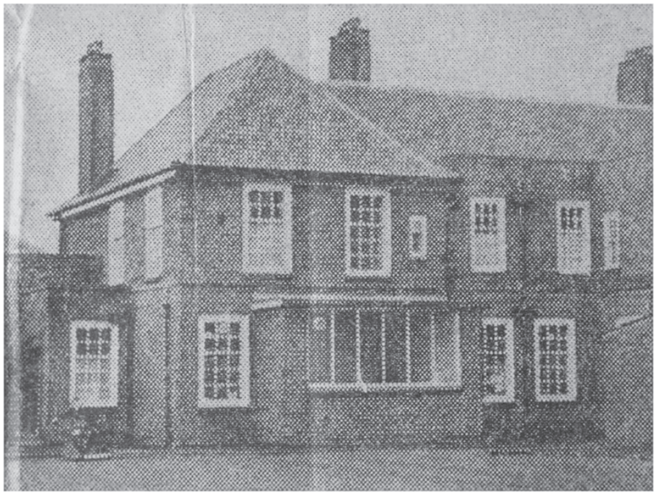
Peck explains that problems cause uncomfortable feelings such as frustration, grief, guilt, anger, fear, and anxiety. Nevertheless, problems are also the

> "cutting edge that distinguishes between success and failure. Problems call forth our courage and our wisdom: indeed, they create our courage and our wisdom."

The field of human ART evolved over a "gestation period" of nearly 10 years, in Oldham, a small town in the north of England, near Manchester. After starting their laboratory work in a laundry room adjacent to the operating theatre at Oldham and District General Hospital, a small room in nearby Dr. Kershaw's Cottage Hospital (Fig. 1.1) was converted into a makeshift laboratory where Bob Edwards and his assistant Jean Purdy developed the methods that were to lead eventually to successful IVF. The arduous journey undertaken by Robert Edwards, Patrick Steptoe, and Jean Purdy that led to the birth of Louise Brown in 1978 (Fig. 1.2) was beset with problems from every possible perspective: clinical, laboratory, logistic – as well as controversy and criticism from numerous aspects of the outside world. There is no doubt that their eventual success certainly required exceptional – and extraordinary – courage and wisdom (Edwards & Steptoe, 1975; Elder & Johnson, 2015a, b, c; Johnson & Elder, 2015a, b, c), and a study of their journey through numerous challenges and problems represents a classical approach to troubleshooting. Their empirical approach to treatment variation was based on several previous decades of background research and experience, so that they were able to derive a rational approach to the many problems encountered. Without recourse to any of the sophisticated technology that subsequently became available, this crucial background of accumulated wisdom allowed each problem encountered to be addressed scientifically, using methods that were solidly based on informed reading of the contemporary literature available at the time.

Despite nearly four decades of progress in reproductive medicine and technology, problems continue to be inevitable; our tools have increased in complexity, and complex systems bring problems that can only be tackled with an in-depth knowledge of the associated scientific principles. Computer-controlled data acquisition and continuous monitoring systems can provide records from multiple instrument inputs, but the data must be checked and analyzed by well-trained, educated, and experienced scientists who are able to appreciate that *apparently trivial phenomena often have explanations that are far from trivial.* This is especially true in ART, where small details that might be perceived as insignificant can collectively contribute to successful healthy embryo development. Problem-solving to dissect and discover the root and cause, whether or not it may be "far from trivial," requires an understanding of the many background layers that make up the sophisticated physico-chemical and physiological foundation of IVF systems.

(a)



(b)

Fig. 1.1 Dr. Kershaw's Cottage Hospital, near Oldham, Manchester.

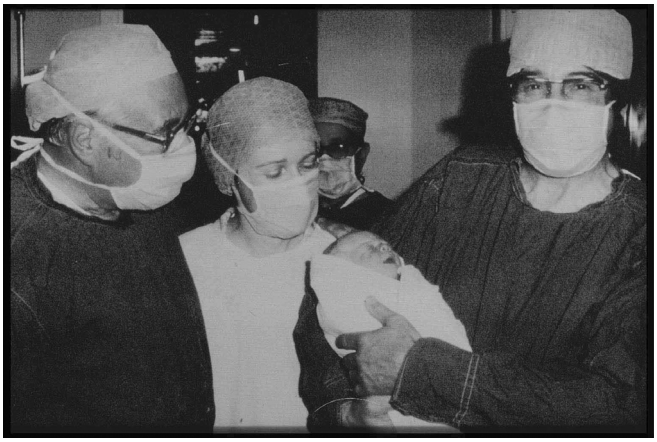


Fig.1.2 The birth of Louise Brown at Oldham and District General Hospital, July 25th 1978; Patrick Steptoe, Jean Purdy (center) and Robert Edwards holding the baby.

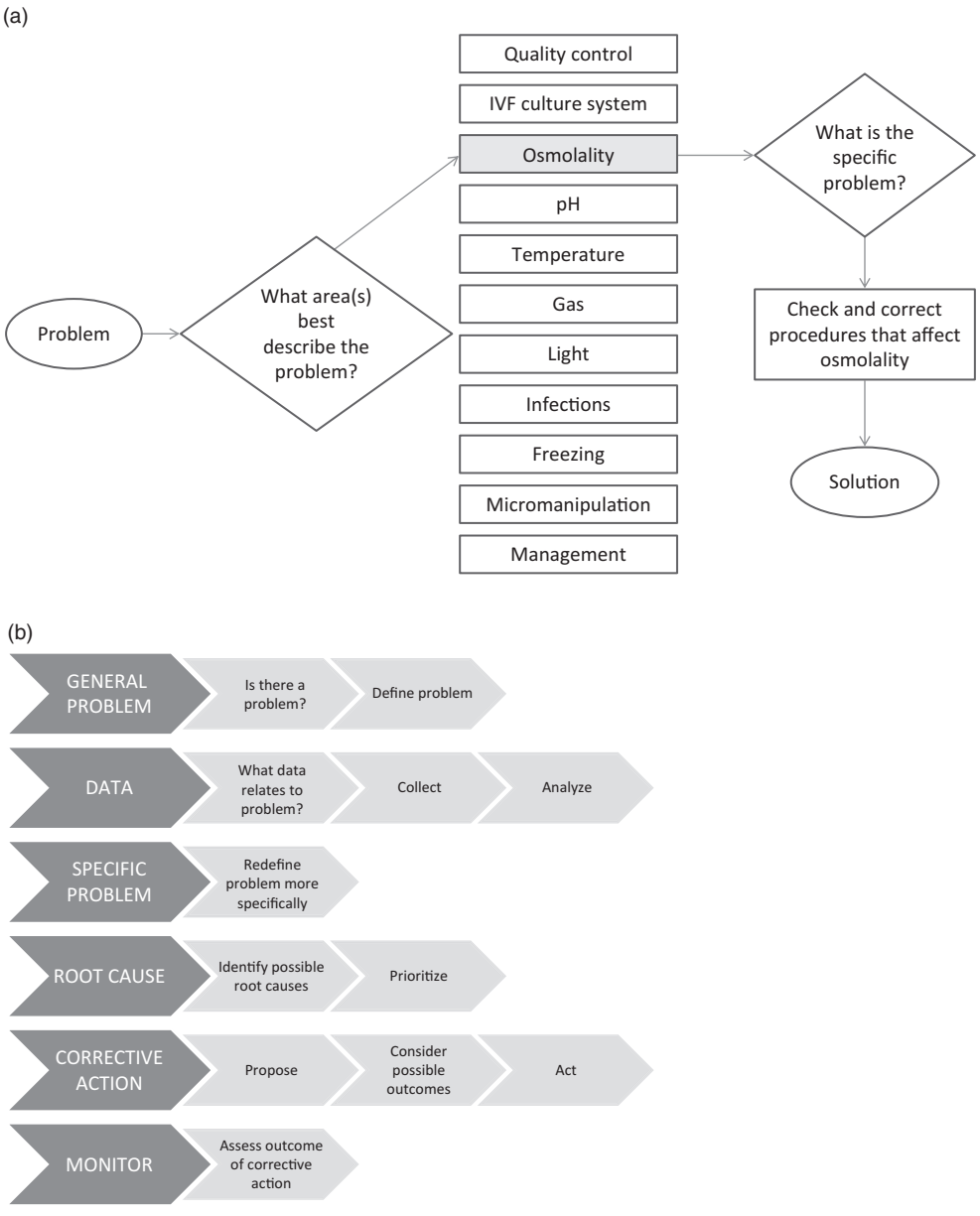


Fig. 1.3 (a) General troubleshooting process map. (b) Troubleshooting guide.

Hoping that ART will be a "bed of roses" is setting ourselves up for failure, as every rose has its thorn. A carefully controlled scientific approach to every detail of the complex procedures involved in ART can help to reduce the impact of Murphy's law on the final outcome of the program: the live birth of healthy children.

"Troubleshooting" is defined as a form of problem-solving, applied to repair failed products or processes. It is a logical, systematic search for the source of a problem in order

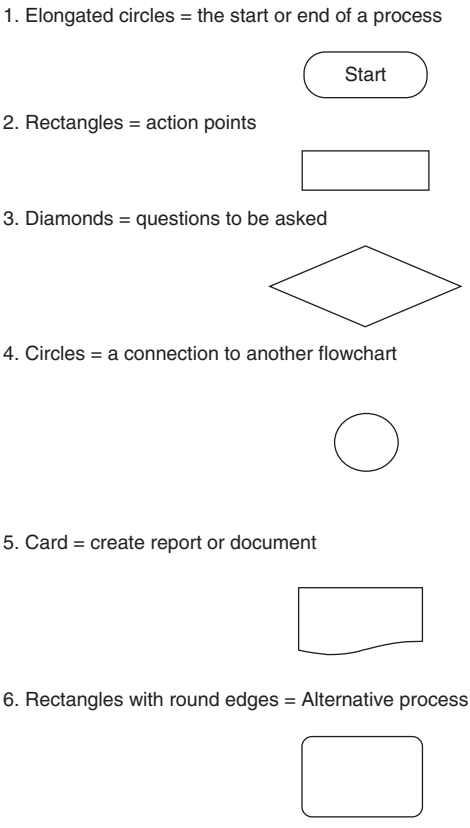


Fig. 1.4 Flowchart symbols: each symbol can be accompanied by a very brief summary that indicates the start or end of the process, the action to be taken, and the decision to be made.

to find a solution that will make the product or process successfully functional again. The ART laboratory represents the synthesis of multiple complex systems, and the symptoms of a problem can have many possible causes. Attention must be paid to any element in the culture system that might cause physiological stress to embryos, reducing their potential viability. Effective maintenance of any ART laboratory requires an ongoing process that will support troubleshooting.

It is often tempting to blame external supplies for any downturn in results, when the real problem may be something quite different. In order to make a valid assessment of a potential problem, it is essential to keep consistent and reliable records at all times, so that parameters can be compared during different time periods. Rates of fertilization, cleavage, blastocyst development, implantation, biochemical and clinical pregnancy should form a baseline for comparison. Any changes in patient demographics, including age, fertility diagnoses, stimulation protocols, drug batches and doses, response to stimulation, sperm characteristics, and oocyte quality for embryos cultured can have downstream effects on results, as well as any changes in culture conditions: incubator(s), measured temperature and pH, gases, dishes, and the culture media (basic constituents and supplemented protein).

IVF systems as a whole are made up of several interrelated and overlapping complex systems, each with an impact on other factors within the system. Gamete quality is affected by the patient's environment and lifestyle, as well as by clinical features during ovarian

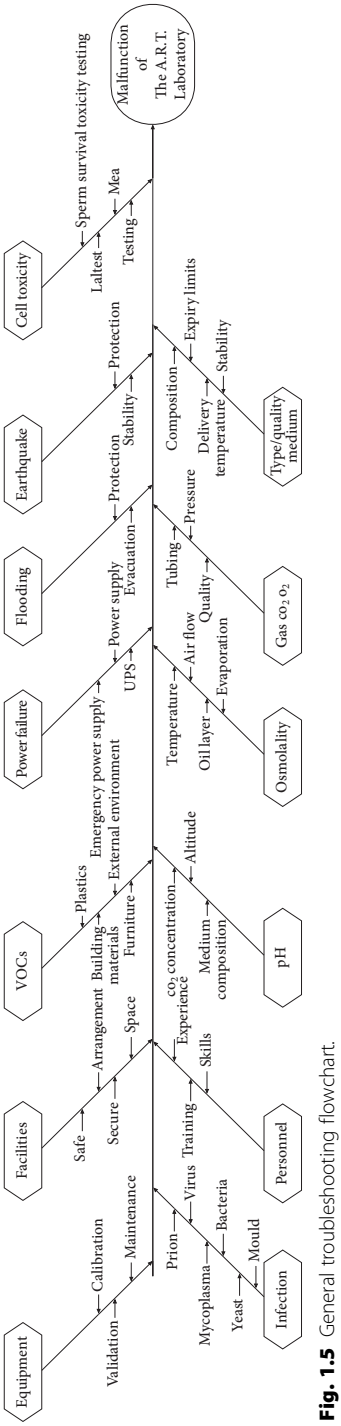


Fig. 1.5 General troubleshooting flowchart.

stimulation, monitoring, and oocyte retrieval. Within this perspective, providing the gametes and embryos with optimal and stable conditions within the laboratory culture system represents further interrelated and overlapping parameters that can easily go wrong. When problems arise, it can be very difficult to know where to begin. The process of troubleshooting can be rationalized/simplified by a summary of steps, using flowcharts to provide guidance and direction to potential problems. Concentrating on basic individual steps allows more precise focus, lessening the overwhelming impact of the general problem within the big picture:

1. Define the problem
2. Produce a step-by-step process for analysis
3. Re-define the problem, find the root cause, and suggest solutions to the problem (Fig. 1.3).

Flowcharts that are easy to follow can be built using symbols that are linked by arrows to show the direction of flow (Fig. 1.4).

Examples of suggested troubleshooting process maps and flowcharts are provided at the end of each chapter in this book.

Clinical embryologists who handle human embryos do not "create" life, but instead have the responsibility of "nurturing" life by protecting the vulnerable preimplantation embryo from physiological and biochemical stress factors associated with *in vitro* culture. All technical procedures must be handled in a manner that respects and supports the physiology, biochemistry, chemistry, and physics that allow components of the culture system to interact harmoniously. We hope that the following chapters will provide guidance towards maintaining a homeostatic culture environment that will nurture the potential viability of each precious human embryo entrusted to our care (Fig. 1.5).

Further reading

Go KJ, Patel JC, Dietz R (2012). Troubleshooting in the clinical embryology laboratory: the art of problem-solving in ART. In: *Practical Manual* of In Vitro *Fertilization, Advanced Methods and Novel Devices*, P Nagy, AC Varghese, & A Agarwal (eds.) Springer NY, p.631–7.

Mortimer D, Mortimer ST (2007). *Quality and Risk Management in the IVF Laboratory*. Cambridge University Press.

References

Edwards RG, Steptoe PC (1975). Induction of follicular growth, ovulation and luteinization in the human ovary. *J Reprod Fertil (Suppl)* **22**, 121–63.

Elder K, Johnson MH (2015). The Oldham Notebooks: an analysis of the development of IVF 1969–1978. *Reprod Biomed and Society, in press.*

Johnson MH, Elder K (2015). The Oldham Notebooks: an analysis of the development of IVF 1969–1978. *Reprod Biomed and Society, in press.*

Mathews RAJ (1995). Tumbling toast, Murphy's Law and the fundamental constants. *Eur J Phys* **16**, 172–8.

Peck MS (1978). *The Road Less Travelled*, Simon & Schuster, NY.

Chapter 2

Quality control, certification, and accreditation

Introduction: guidelines and good practice

Careful Quality Control (QC) in the IVF laboratory has always been recognized as essential for success. Controversy surrounding the birth of Louise Brown in July 1978, together with lack of funding, brought the work of Steptoe and Edwards to an abrupt halt in 1978 (Johnson *et al.*, 2010), to be resumed only after Bourn Hall opened its doors to patients in September 1980. The patients were prepared for natural cycle IVF, using the same methods developed in Oldham (Elder & Johnson 2015a, b, c), and the first laparoscopic oocyte retrieval was carried out in October 1980. Over the following 2-week period, two out of nine embryo transfers led to pregnancies and subsequent healthy live births: a remarkable success, which could only have been achieved by meticulous attention to detail: "Quality Control" – at every step. The first international IVF meeting took place at Bourn Hall, Cambridge, UK, in 1981 (Fig. 2.1), with proceedings of the meeting published in 1982 (Edwards & Purdy, 1982). A chapter authored by Jean Purdy describes some of the difficulties that the Oldham team had encountered in various stages of the procedure between 1969–1978, and clearly states (Purdy, 1982; p.135):

"It is essential to maintain a careful and rigorous control over the methods used throughout each stage, the purchasing and testing of equipment, methods used in making and testing media, preparing spermatozoa, and achieving fertilization and embryo culture in vitro."

Successful ART continues to be crucially dependent on carefully controlled conditions in every aspect of the IVF laboratory routine, and a comprehensive total Quality Management System (QMS) is mandatory. An accredited/certified laboratory is obliged to provide evidence that all aspects of facilities, treatment, and personnel meet the standards required by specific regulatory bodies. Organizations such as the Human Fertilization and Embryology Authority (HFEA) in the UK, the College of American Pathologists (CAP) in the USA, and Joint Commission International (JCI) require documented evidence of a QMS. In Europe, all EU States have been asked to incorporate the European Union Tissues and Cells Directive 2004/23/EC into their country's regulation for IVF. This Directive, issued in 2004, sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells. The International Organization for Standardization (ISO: www.iso.org) provides sets of standards, which include:

- ISO 9000:2000. Quality Management Systems: Fundamentals and vocabulary
- ISO 9001:2008. Quality Management Systems: Requirements
- ISO 15189:2012. Medical laboratories: Requirements for quality and competence.

Fig. 2.1 Group photograph of the First IVF meeting, held at Bourn Hall Sept 5th – 8th 1981; front row: Bob Edwards, Jean Purdy, Patrick Steptoe, John Webster, Simon Fishel.

The ISO also produces standards in collaboration with the International Electrotechnical Commission (IEC), which includes ISO/IEC 17025:2005: an innovative standard for laboratory quality systems. ISO standards are endorsed by the European Committee for Standardization (CEN: www.cen.eu) which describes Quality Assurance systems.

Elements of a quality management system

Accurate and comprehensive records are the basic foundation for troubleshooting, the essential first step that allows any potential hazard that may have been introduced to be detected. Components of a good QMS will cover not only a basic audit of implantation and pregnancy rates, but also reflect the accuracy and reproducibility of results, as well as confirming appropriate standards for the largest possible range of items related to laboratory practice. Systematic and periodical surveys assess:

- Optimum function of all equipment and instruments in use
- Quality of all consumables and media in use
- Critical periodic analysis of individual performance within the team.

Essential elements of a QMS include:

1. Process flowchart
2. Standard Operating Procedures (SOPs)

3. Job descriptions for all members of staff and an organizational chart
4. Forms: for information, records of procedures, instructions, etc.
5. Consent forms
6. Key Performance Indicators (KPIs).

Standard Operating Procedures (SOPs), written in a consistent format, describe protocols for all procedures carried out in the laboratory; other areas, e.g. nursing, clinicians, administration, etc. will also have their own SOPs. SOPs undergo a system of scheduled review, ensuring that personnel are familiar with the SOPs for all routinely performed procedures, as well as with updates following each review. The accepted SOP format includes:

- The goal of the procedure
- Personnel allowed to use and apply the procedure
- Products and equipment used in the procedure
- How to perform the procedure
- Validation for the procedure
- Any other SOPs and forms related to the described procedure.

Equipment specifications

A user's manual is essential for every piece of equipment, together with traceable validation, e.g:

- Installation Qualification (IQ) – documented proof that the equipment has been delivered and installed in accordance with the requirements and statutory safety regulations stipulated in the design qualification. IQ documentation includes a test plan and a report.
- Operation Qualification (OQ) – documented proof of a test process that evaluates whether the equipment functions correctly. All items specified in the test plan are processed and documented in writing, to ensure that the system functions in accordance with specifications. OQ documentation includes a test plan and a report.
- Performance Qualification (PQ) – documented proof that verifies reproducible equipment function across the entire specified working range and limits.

All maintenance records are dated and kept in a QC register, including annual service (or less or more frequently, as required). Documented records of the working parameters are kept, e.g. logs of incubator temperature and gas composition, logs that document the first used of each batch of new items and supplies, as well as usage logs for new or repaired equipment.

Monitoring laboratory equipment

The chance of equipment failure or suboptimal operation can be minimized by establishing service contracts with reliable companies. ISO norms require that companies are able to provide calibration certificates, including a description of the method used for calibration and the tools used in servicing and calibrating the equipment. Metrological traceability of the calibration standard for each item of equipment is required, and any correction factors need to be accounted for in future use. The calibration status and recommended re-calibration date should be clearly recorded. Equipment manuals for all equipment should