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I Walk the Line: Between Basic Science and Paediatric Surgery☆

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ABSTRACT

The role of a basic scientist working with paediatric surgeons is not an obvious one. However, there are several levels at which science can contribute to the speciality, and also ways that scientists can learn useful lessons from paediatric surgery. As most conditions treated by paediatric surgeons have low case numbers, we need to find ways of defining optimal treatment and developing novel therapies within a challenging number of patients.

As in any surgical specialty, paediatric surgery can be considered as an art or a craft. This might seem even more true for paediatric surgery, in which surgeons perform a wide variety of operations in relatively small numbers, compared to other specialties in which much higher volumes of a specific operation enable standardization and incremental honing of technique by individual surgeons. One might therefore question the role of a basic scientist, with no medical or surgical training, in paediatric surgery. It is my aim in this article to explain how a basic scientist like myself has spent nearly half of my life in a paediatric surgery unit, and to persuade the reader that the nature of paediatric surgery necessitates a scientific approach to improve outcomes. My bachelor's degree was in Biology, so my knowledge of anatomy and dissection is based on worms, frogs, and plants, and the whole degree was very distant from clinical medicine. Following my BSc, I then commenced a PhD in Biochemistry, at the University of Newcastle. Although my own research was in fatty acid breakdown in rat liver and muscle mitochondria, I also did some work on inborn errors of metabolism and was based in the Department of Child Health. All around me were clinicians collaborating with scientists. I worked closely with paediatricians and neurologists who were focused on mitochondrial disease and inherited disorders of fatty acid oxidation. As biochemists, we thought we knew all the enzymes and pathways, but then my colleagues started diagnosing patients with combined defects that did not fit with our preconceptions. Specifically, rather than activity of a single enzyme being deficient, there were combined defects of three enzymes [1]. The reason for this became clear when biochemists working in rat liver found that there was a single protein with three different functions [2]. This persuaded me of the power of combining basic science and clinical medicine – not only can basic science inform medicine, but medicine (and surgery) can inform basic science.

Following several happy years in Newcastle, I then decided to move to London, to what is now UCL Great Ormond Street Institute of Child Health, and obtained a fellowship to work on an area of biochemistry called metabolic control analysis. My supervisor for this work happened to be based in the Unit of Paediatric Surgery, so whilst applying for the fellowship I met Professor Lewis Spitz (who, as Head of Department, signed my fellowship application) and Professor Agostino Pierro. Little could I have imagined at that time the huge influence that both would have on me.

1. First steps in a paediatric surgery unit

Before I moved to London, I was invited to give a seminar on my PhD work and my fellowship. Agostino Pierro asked me a question which was very valid, but a difficult one for me to answer: what is the relevance of this to paediatric surgery? The honest answer would have been that actually, I did not have any real idea about paediatric surgery, let alone how my proposed fellowship was relevant. I suppose that I probably imagined that paediatric surgery was paediatric cardiac surgery, as I hadn't interacted any variety of paediatric surgeon in Newcastle. After returning to Newcastle to lick my wounds following my seminar, I thought that I should take a look at the *Journal of Pediatric Surgery*. I still remember opening a silver-covered issue in the University medical library, only to be completely confused by a whole new lexicon that I was thoroughly clueless about – orchidopexy, Hirschsprung's, tracheo-oesophageal fistula, and so on. Luckily, my heart was already set on moving to

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London and so I arrived in the Paediatric Surgery Unit in February 1997 to start my fellowship. In the laboratory at the time were four junior paediatric surgeons: Carmelo Romeo, Michele Markley, Marcello Zamparelli and Kalpana Patil, all working on septic damage to hepatocytes, all jointly supervised by Agostino and the same basic scientist that was supervising my fellowship. By that time, I had nearly 10 years of lab experience under my belt, so I was able to help the surgeons in laboratory work. I also had my first involvement in clinical research in paediatric surgery, a study on free radical production in infants on parenteral nutrition, in which I helped Raj Basu undertake free radical analyses, resulting in my first publication in *Journal of Pediatric Surgery* [3] followed swiftly by papers with Carmelo Romeo [4] and Marcello Zamparelli [5]. By this time my basic science supervisor had left the Paediatric Surgery Unit, but I had decided to stay, thanks to the support of Lewis Spitz and Agostino Pierro, together with other basic scientists in the Institute of Child Health. Agostino Pierro always had a focus on potential clinical interventions, so we also embarked on a series of preclinical experiments on glutamine in sepsis, resulting in a paper with Michele Markley [6]. However, Agostino and myself soon realized that the available preclinical models were not really representative of surgical infants, so it was time to enter the world of randomized controlled trials.

2. Randomized controlled trials and their Tribulations

Following the promising glutamine experiments, the next step was to undertake a randomized controlled trial (RCT) of glutamine supplementation of parenteral nutrition in surgical infants – the SIGN trial, co-ordinated by Peng Ong [7]. In retrospect, this was a pretty ambitious first RCT to undertake– a multicentre trial of a pharmacological intervention. As if one multicentre RCT was not enough, we also initiated another: drain vs. laparotomy in neonatal bowel perforation, the NET trial, coordinated by Clare Rees [8]. For a while, we fell foul of Maslow's axiom that "*I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail*" [9], and everything became a potential RCT. Probably luckily, most of these ideas didn't make it past the ward round or departmental meeting but it was a fun time. The combination of trying to do difficult trials and thinking deeply about potentially impossible trials was a great experience, shared with Agostino and with Nigel Hall, who was by then doing a PhD with us. I also learned a huge amount about paediatric surgery during this process – in order to design a surgical trial it is necessary to really understand all the potential confounders that might come from pre-operative differences, subtleties of an operation, and factors in post-operative care – and I apologise to Agostino, Ed Kiely, Nigel, Clare, Peng and all the other research fellows for the naïve questions that I asked. A lot of lessons were learned during this period of thinking about and doing trials, with one of the foremost being the problems we face by having lots of different conditions with relatively low frequency. Other than hernia repair, pyloromyotomy, appendicectomy and gastrostomy insertion, there are not many paediatric surgical conditions with volumes amenable to appropriately powered RCTs with meaningful primary endpoints. If RCTs were designed to answer the controversial issues from ERNICA consensus conferences on oesophageal atresia [10–12], with a very optimistic 20 patients in each arm, with a clear and appropriate primary endpoint, one would need to recruit 840 oesophageal atresia/tracheo-oesophageal fistula patients, and 640 long-gap oesophageal atresia patients. This is clearly impossible. It can be tempting to try to power a study on a composite primary endpoint, but are we really advancing paediatric surgery and helping patients if we end up doing a trial that is difficult to translate into clinical practice because the endpoint doesn't directly mean anything? An example here is the contortions that have been necessary to design primary endpoints in appropriately powered RCTs of non-operative management of acute uncomplicated appendicitis: if one designed a conventional superiority trial of non-operative management vs. appendicectomy, based on the data from Jan Svensson's pilot RCT [13] of 100 % success in the appendicectomy arm and 62 % success (no recurrence in one year) in the non-operative arm, 26 patients in total would be required to show that appendicectomy is superior to non-operative management (80 % power, alpha = 0.05). This wouldn't really be a useful study as it is a rather obvious conclusion-removing the appendix is always going to result in a lower recurrence rate than not removing the appendix. The APPY Trial [14] and CONTRACT2 in the UK [15] have used complex non-inferiority primary outcomes (including a penalty for negative appendicectomy) for RCTs to satisfy funder's requirements, where really the actual outcome of interest for surgeons, young people and their parents is the recurrence rate in those treated non-operatively. Another aspect of RCTs that needs more careful thought is the interpretation and dissemination of the results. For example, in the NET trial, 74 % patients that had a drain inserted as a primary procedure subsequently had a laparotomy, and only 4 patients receiving a drain survived without having a laparotomy [8]. Does this mean that there is no role for a drain insertion in NEC? No, it means that a drain is not effective as a *definitive* procedure, but there may be a role for drain insertion in stabilizing and/or transfer, although surgeons should anticipate a laparotomy if a drain is inserted. Of course, in theory one could or should do follow-on trials of drain insertion for stabilization in NEC but seeing how difficult these trials are to do, I am not sure whether this will ever be achieved. So, given the problems of performing adequately powered RCTs in paediatric surgery with meaningful primary outcomes, how should we improve the evidence?

3. Beyond trials

In order to improve the quality of care and the outcomes for paediatric surgical patients, we need to use available data more wisely, with less inherent bias, and focus on what matters to patients and caregivers. This is true whether the data comes from retrospective studies, prospective studies, meta-analyses, registries, or other types of study. Key to this is an understanding of what matters to patients, caregivers and other stakeholders. Initiatives such as development of core outcome sets such as those developed for gastroschisis [16], Hirschsprung's disease [17] and uncomplicated acute appendicitis [18] condition-specific quality of life measures such as those developed for children and adolescents [19] and for adults [20] with oesophageal atresia can help to guide us past the surgeon's eye view of outcomes by involving patients and their caregivers. With oesophageal atresia can help to guide us past the surgeon's eye view of outcomes by involving patients and their caregivers. Although I am a quantitative scientist through and through, I would like to emphasise here the importance of qualitative research, often dismissed as unscientific. Qualitative research, using appropriate methodology, can enrich and inform quantitative research. For example, a qualitative study embedded within the CONTRACT trial (CONservative TReatment of Appendicitis in Children a randomised controlled Trial) identified barriers to recruitment, and facilitated improved trial recruitment following bespoke training based on the qualitative findings [21]. Similarly, a qualitative study of feeding issues in oesophageal atresia has highlighted the fact that some parents find feeding their infant traumatic, scary and isolating [22]. Identification of these issues via qualitative research may be biased, but knowing that they may be present

allows support to be put into place and also allows a more quantitative approach to be followed to determine their prevalence. In addition to ensuring that reported data are those important to patients as well as surgeons, we must endeavour to improve reporting of surgical data. For example, how complications are reported in paediatric surgical studies is extremely variable. Complications have often been grouped into major or minor complications, but this division can be somewhat arbitrary. In adult surgical studies, the Clavien-Dindo classification [23] is often used; indeed in the absence of a validated paediatric surgical complication score, the Clavien-Dindo grading has often been used [24]. Recently, a paediatric version of Clavien-Dindo, named the Clavien-Madadi classification, has been developed and validated [25]. Interestingly, the new classification includes organizational and management errors in addition to surgical complications, so is better termed a classification of unexpected events. With tools such as the Clavien-Madadi classification, and knowledge of which outcomes matter, the paediatric surgical community is better equipped to undertake meaningful prospective observational studies where trials are not feasible. Registries can also be powerful tools, but require careful planning and, in order to be meaningful, include a commitment from the centres and surgeons involved to enter data on all their cases, not just those with the good outcomes. Core indicator sets for registries are similar in concept to a core outcome set for research studies, and are also developed with input from multiple stakeholder groups. An example is that recently developed for oesophageal atresia (Teunissen et al., in press) [26] within the European Pediatric Surgery Audit (EPSA), the registry for ERNICA (the European Reference Network for Inherited Congenital Anomalies). Data entry into registries is, however, a burden, and one dream for the future would be a way of automatically linking hospital Electronic Patient Record systems with registries to minimize this, although the barriers to implementing this kind of system may be at least as much bureaucratic as technological. In RCTs, we try to design the trials in a way that minimizes bias. Avoiding bias in prospective observational studies, or analysis of registries, is more difficult and relies on avoidance of both conscious and unconscious bias in entering and analysing data and drawing reasonable and fair conclusions from those data. This is one area where a basic scientist has a perverse advantage – although I might not understand the data in the same way that a surgeon would, the very fact that I am not invested in one technique/treatment pathway over another may at least allow me to analyse data more objectively. If one reads a paper, or a meta-analysis, where the stated aim is "*to show the benefit of minimally invasive surgery for ….* ", then can we really expect the comparisons to be unbiased? Thus, basic scientists embedded

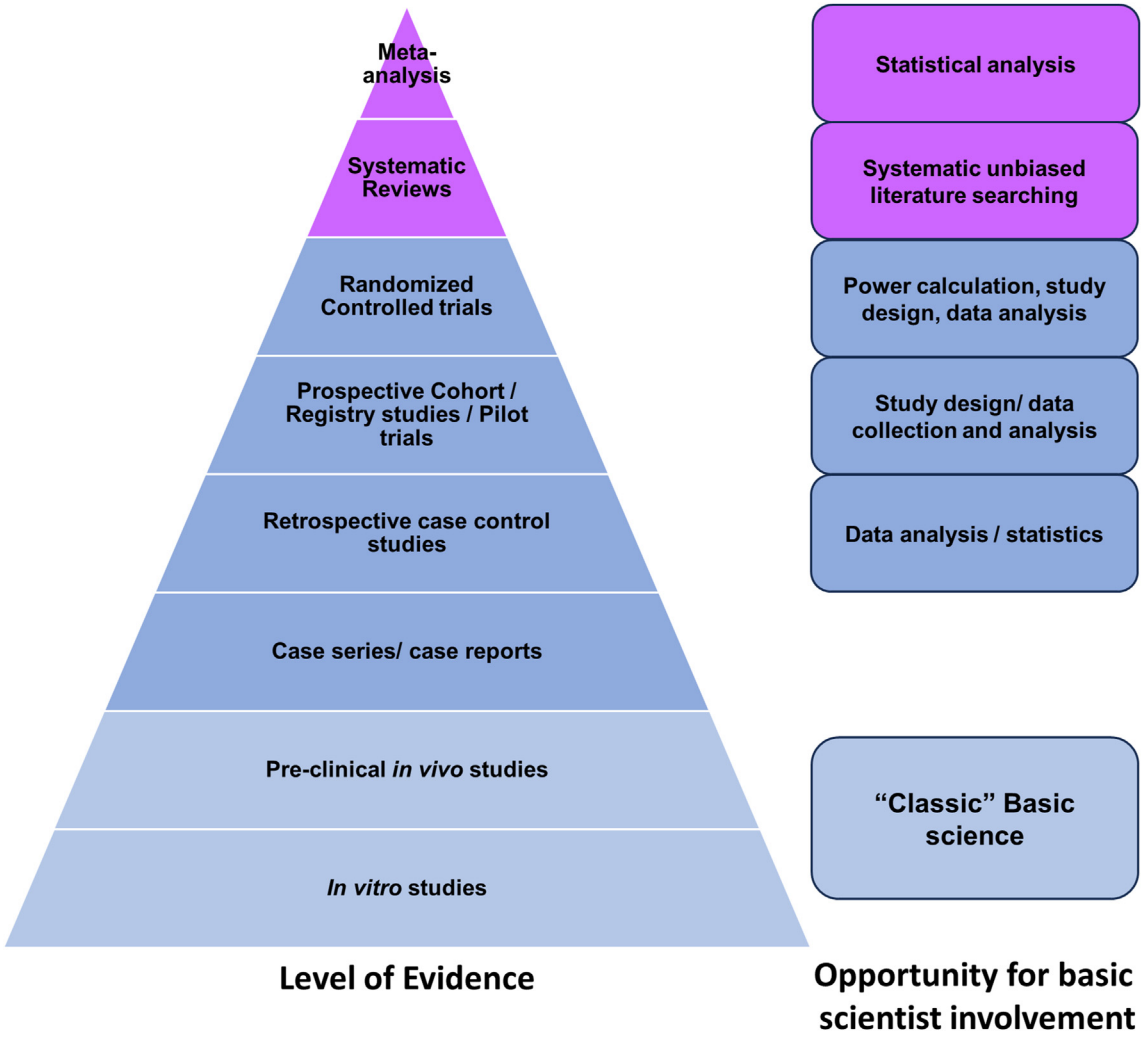

Fig. 1. Modified Oxford Levels of Evidence schema indicating areas in which interaction between surgeons and scientists is useful.

within paediatric surgery departments can usefully contribute at several stages of the evidence-based medicine pyramid (Fig. 1).

4. Innovation, translation and responsibility

The role of a basic scientist in a clinical discipline necessarily involves steps of translation. Firstly, there must be translation from surgeons to scientists about what a condition or its treatment actually involves. This should not be underestimated – although the concept of oesophageal atresia is fairly simple, there are layers of complexity in diagnosis, anatomical variants, treatment (e.g. options for long-gap oesophageal atresia) and sequelae, that scientists may need to understand in order to usefully contribute. For instance, although I understand the principles of surgery for Hirschsprung's disease, I am not sure that I will ever completely understand the differences between Soave, Swenson and Duhamel. Early on in my experience in the surgery unit, I soaked up this information from ward rounds, surgical meetings and conferences, and discussions with surgical colleagues. I strongly recommend this to any non-clinical scientist who really wants to grasp at least some meaningful understanding on the conditions considered. Secondly, the scientist must be able to translate the research methods that are being used so that the surgeon understands the strengths and limitations of the methodology used, whether molecular biological, statistical or any other methodology not familiar to the surgeon. What we usually refer to as translational medicine is the transfer of therapeutical or diagnostic innovations to the patient, but the effectiveness of this translational stage depends on the effectiveness of the earlier surgeon to scientist and scientist to surgeon "linguistic" stages where a common language is established. Over the years, paediatric surgeons have proven themselves to be capable of making both significant contributions to basic science (e.g. Judah Folkman and angiogenesis) and biotechnological innovations in surgical care. However, it is important to recognize that the translational aspects of basic science and paediatric surgery carry great responsibility, that of honesty and integrity. Paediatric surgeons treat their patients with individualized care and compassion, and as a community we should treat the data from those patients with a similar degree of care. If a patient has experienced a complication, then the duty of care to that patient should extend not only to treating that complication, but also a moral and ethical responsibility to reporting that complication honestly if that patient is included in a retrospective review, in a registry, an audit or a randomized controlled trial, and to analysing data from those studies in a statistically honest and robust way. This principle is especially important where translational or innovative treatments are being trialed. Regenerative medicine, for example, has great potential in paediatric surgery, but in addition to the initial report of successful use of a tissue engineered trachea in a child [27], follow-up of the same child [28] and failure in another child [29], the allure of regenerative medicine has been considerably tarnished by the dishonesty displayed by Paolo Macchiarini both in clinical use on reporting of tracheal implants [30], and also basic science of tissue engineered oesophagus ([31], now retracted). We all have to behave responsibly in describing, reporting and communicating our work, particularly in a world where everything is reduced down to short headlines in social media.

5. Conclusion

As a basic scientist it has been a privilege to work with paediatric surgeons dedicated to the care of their patients, and to be welcomed into a rather small specialty. It is also a great honour to have been asked to give the 2023 JPS Lecture at BAPS, to review for the journal and act as an Assistant Editor, something that I could not have imagined in 1996 when I first looked bemusedly at the article titles in an issue of JPS. I can I only hope that I can continue to help the future paediatric surgeon-scientists to continue to innovate.

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