Navigating Brave New Worlds: A Close Analysis of Anne McLaren’s Laboratory Notebook

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Introduction

Dr Anne McLaren (1927–2007) was a leading developmental biologist with a decorated career that spanned more than fifty years. As McLaren herself often put it, she was interested in ‘everything involved in getting from one generation to the next’, and in particular, she emphasized the ways in which an individual is always connected to, and a part of, its many environments. This interest led McLaren to the study of mammalian development and genetics, where her work famously advanced the development of in vitro fertilization (IVF). Far from staying within the confines of the laboratory, however, McLaren worked equally hard to uphold what she saw as the duty of the scientist, that is, the imperative to share research widely and to work with the public in ensuring that science progresses ethically. McLaren therefore coupled her academic research with publicly engaged efforts, which led to her serving on the Warnock Committee from 1982 to 1984 and contributing to the report that would result in the UK’s Human Fertilisation and Embryology Act 1990. After the establishment of the Act, she served on the Human Fertilisation and Embryology Authority for a decade. In 1991, she became the first female officer of the Royal Society – 331 years after the Royal Society was founded in 1660. Across her career, she would continue to receive many accolades and awards, including as a joint recipient of the Japan Prize in 2002, all of which attests to the depth of influence McLaren has had and continues to have both socially and scientifically.

The British Library holds an extensive collection of McLaren’s papers (Add. MSS. 83830-83981 and Add. MS. 89202) that provide insight into her research and professional life. These papers include correspondence, such as that between McLaren and her advisor Dr Peter Medawar (1915–1987) during her early years of study, annotated papers and articles, and several laboratory notebooks. From this rich archive, my article focuses on one laboratory notebook in particular, Add. MS. 83844, in order to showcase the value of considering the painstaking daily tasks on which scientific advancements rely and to unpack some of the many insights the notebook provides into McLaren’s working environments as she approached the IVF breakthrough.

What’s in a Notebook?

Although documents such as correspondence, drafts of papers, and photographs are widely consulted by researchers in archives, laboratory notebooks are a historically underutilized...
resource, if indeed they are even archived in the first place. As Clark A. Elliott notes in his 1974 article, many researchers and archivists alike believed that published scientific papers were sufficient as a record of the underlying research, which limited engagement with notebooks and similar ephemera; however, this condensed data does not show ‘fully the nature of important experimental work – how it was carried out, what the results were, and how successive experiments approximated the theoretical expectations.’\footnote{Clark A. Elliott, ‘Experimental Data as a Source the History of Science,’ *The American Archivist*, xxxvii (1974), p. 30.} For this type of detailed analysis, Elliott argues for the value of laboratory notebooks, which he situates as being ‘at the base of experimental science documentation’, while all other records, including published papers, ‘are summaries at different levels or in different contexts’.\footnote{Ibid, p. 28.} Sixteen years later, Frederic L. Holmes put forward a similar argument to Elliott’s, stating that unless researchers ‘include analyses of scientific activity at the fine level of resolution’ provided by documents like laboratory notebooks, ‘the large claims currently being made that we understand the nature of scientific practice, the processes of discovery, and the construction of scientific knowledge, will not rest on solid foundations.’\footnote{Frederic L. Holmes, ‘Laboratory Notebooks: Can the Daily Record Illuminate the Broader Picture?’, *Proceedings of the American Philosophical Society*, cxxiv (1990), p. 366.} Other papers, including a 2007 letter to *Nature* by Sydney Brenner and Robert J. Roberts\footnote{Sydney Brenner and Robert J. Roberts, ‘Save Your Notes, Drafts, and Printouts: Today’s Work Is Tomorrow’s History,’ *Nature*, cdxlvi (2007), p. 725.} and a 2017 article in *EMBO reports* by Anne-Flore Laloë\footnote{Anne-Flore Laloë, ‘Archives of and for Science: Archives for Molecular Biology Preserve the Heritage of Science Beyond the Published Record for Future Scholars’, *EMBO rep.*, xviii (2017), pp. 1273–78 <https://doi.org/10.15252/embr.201744733> .} continue to argue that crucial pieces in the history of science are lost when the ephemera of laboratory work is not archived and consulted. The increasingly digital nature of scientific research in recent years also raises new questions about where and how to access the ephemera of science research as electronic devices and various programs are being used in the place of laboratory notebooks.\footnote{See, for example, Santiago Guerrero et al., ‘Analysis and Implementation of an Electronic Laboratory Notebook in a Biomedical Research Institute’, *PLOS ONE*, xi (2016), pp. 1–11 <https://doi.org/DOI:10.1371/journal.pone.0160428> and Samantha Kanza et al., ‘Electronic Lab Notebooks: Can They Replace Paper?’, *Journal of Cheminformatics*, ix (2017), pp. 1–15 <https://doi.org/10.1186/s13321-017-0221-3> .} Whether in paper or digital form, then, laboratory notebooks comprise a crucial piece of the history of science and demand more critical attention.

McLaren’s experimental notebooks, including Add. MS. 83844, are a testament to the rich data that can be accessed through engagement with primary scientific records. This particular notebook covers the time periods of March 1955 to September 1957 and January 1958 to March 1959 and records data for one of McLaren’s earliest research projects. In an experiment she conceived of with her collaborator Dr Donald Michie (1923–2007), who was also her husband at the time, she became interested in exploring the genetic effects that a mother’s uterus – not just the material contained in the egg – had on the development of an embryo. To study this, she and Michie worked with two strains of mice, one of which was genetically disposed to have 5 lumbar vertebrae (C3H/Bi) and the other to have 6 lumbar vertebrae (C57BL). Together, they developed a technique of transferring fertilized eggs from donors of one strain to surrogates from the other strain in order to test the effects of different uterine environments on the genetic development of the offspring. The notebook records three phases of the experiments: transfers from C3H to C57 females, both mated to C57...
males, running from 4 March 1955 to 14 September 1958; transfers from C57 pairs to C3H females, running from 19 January 1958 to 22 April 1958; and transfers between C57 pairs and C3H pairs running from 17 April 1958 to 20 March 1959.

McLaren and Michie focused their analysis on female progeny to rule out any potential effect of sex-linked genes and determined in each of these experiments that the transferred babies (or ‘aliens’, as McLaren and Michie referred to them) unambiguously took after their surrogate mother in number of lumbar vertebrae, thus proving a uterine effect. Although the egg transfer experiments played a significant part in launching McLaren’s early career, it is interesting to note that neither she nor Michie were able to explain the genetic influence that their experiments proved. As McLaren would later state in a letter written to Dr. Robb Krumlauf in 1990:

[T]he effect seemed totally mysterious. Lumbar vertebrae number was not related to number in the litter or to fetal weight, and the body temperature of the two strains was not significantly different. Number of lumbar vertebrae was likely to be determined during the 7½–9½ dpc period, which in the 1950s was even more of a black box than it is today, so I decided to leave the problem alone until it became more accessible.  

She would indeed return briefly to the problem around the time of this letter in order to test whether or not differences in retinoic acid levels between the two strains could have genetic effects, but her results proved unsatisfactory. In fact, even today, the mechanisms of uterine effects are opaque. Nonetheless, the results of these egg transfer experiments remain valid and the techniques that McLaren and Michie developed over the course of these experiments have proven to be critical, both to McLaren’s career and to twentieth-century developmental biology, as the second section of this article will work to discuss more fully. The data contained within Add. MS. 83844 therefore has much to offer in understanding how these fascinating experiments were conducted.

Add. MS. 83844 shows the careful work that McLaren and Michie had to carry out in order to amass adequate proof to support the genetic effect that they hypothesized. Just flipping through the many pages of experimental data contained within the notebook makes clear the demanding and even tedious nature of the work required by this experiment over several years. This tediousness was exacerbated by the naturally low birth rates of the two strains of mice that McLaren and Michie worked with and by their limited ability to control whether or not transplanted offspring would be present in a litter. Collectively, these factors meant that, in order to amass a robust enough sample size, McLaren and Michie performed 197 transfer operations that resulted in 30 female mice born from transferred eggs – a figure which does not take into account the labour expended on mice not viable for the transfer operations or those kept as control mice.

In addition to showing the volume of data produced and the labour required in the laboratory, analysis of the notebook also reveals how the structure of the book itself was deployed as a tool to help organize the information collected. On first glance, the notebook can be quite daunting, given the various notations, different coloured inks, and small charts that cover the pages. However, the structured nature of the data quickly reveals itself, as I will demonstrate using page 28 and its facing page as a guide (fig.1).

10 Anne McLaren, ‘Letter to Dr. Robb Krumlauf,’ 6 Nov. 1990, uncatalogued, BL.
Fig. 1. Add. MS. 83844, p. 28 showing egg transfer experiments conducted by McLaren and Michie in November 1958.

As Figure 1 shows, right-facing pages in the notebook are used to record egg transfer procedures. The 5-vertebrae C3H mice are identified with an ‘M’ and the 6-vertebrae C57 mice with a ‘C’, while the mouse’s status as either a donor or recipient is recorded and uniquely numbered along the right side of the page (e.g. D61 and R82 in figure 2). For each transfer operation, the notebook contains annotations that describe the condition and location (e.g. right ovary) of any eggs found in the donor mouse. Similarly detailed notes are provided for the transfer operation performed on the recipient mouse. McLaren’s operation notes also often include initials (e.g. [AM] in figure 2) to indicate whether she or Michie performed the transfer, thereby offering insight into the division of labour within their collaboration. Certainly, this type of detailed observation about each mouse and each procedure does not appear in the published record of this research and so represents a unique data site.

Fig. 2. Detail from Add. MS. 83844, p. 28.
Throughout the notebook, some mice are marked as ‘Unoperated’, indicating those that were used as control mice. McLaren and Michie collected control mice across the duration of the experiment to ensure any effects that might influence the strains over time would be captured in the control mice as well as in the experimental mice. If suitable eggs were not found in the donors, intended recipients were also kept as unoperated controls and this is noted in the operation pages of the notebook.

Left-facing pages in the notebook record the outcomes of the embryo transfers throughout the pregnancy and deliveries, with an arrow indicating to which transfer operation the results refer (e.g. arrowing pointing to R83 in figure 3). Interestingly, while the right-facing pages are written almost uniformly in McLaren’s hand, the left-facing pages show several hands, as lab assistants were able to help McLaren and Michie keep track of the offspring in a way that they could not help during the more experimental and technically demanding transfer operations. Nonetheless, these result pages show the same standards of detailed reporting as the operation pages.

Recipient mice that did not become pregnant as a result of the operations are listed as either having been killed and autopsied to deduce possible complications or retained as unoperated controls. For mice that become pregnant, the date of confirmed pregnancy, as well as either the date of delivery or of a confirmed failed pregnancy, are recorded. In the cases of successful pregnancies, the genders of the offspring are recorded, they are weighed, and they are given letters (e.g. 3a, 3b, etc. in figure 3) to distinguish them in the notebook. The offspring are also annotated with either an ‘a’ to indicate native offspring or with an ‘A’ or ‘A+’ to indicate alien offspring, which was a categorization readily apparent upon birth, as the two strains had different coat colours. Lumbar vertebrae counts are recorded in pink ink, making them highly visible on the page. These counts appear as ‘5’, ‘6’, ‘6/5’, or ‘5/6’, with the latter two counts indicating offspring that had an unequal number of lumbar vertebrae on each side. Occasionally a chart is also included to indicate that the feet of the offspring had been marked to distinguish them physically (e.g. an ‘x’ under Back R indicating back right foot in figure 3). Other annotations on these left-facing pages provide some insight into the fate of the mothers and the offspring. For example, ‘D’ indicates dead, ‘K’ indicates killed, and ‘G’ indicates gone; however, some notes are more detailed, such as one on page 7 that reports a male offspring as ‘Escaped, prob. lost’ (fig. 4).

In addition to the experimental data, the physical presence of the notebooks themselves has an impact on the researcher as reader. Marks, spills, and stains on the notebook’s pages help attest to the unpredictable and often messy realities of working in a laboratory, while the handwritten nature of the notebooks helps remind the reader of the humanity of the individuals behind the research. Published papers sweep away these material traces and so can foster an image of scientific research as cut and dry, when the lived reality is anything
but. Whether providing detailed laboratory results that inform the summarized versions presented in papers or providing insight into the very human processes of scientific discovery, then, this notebook readily asserts its presence as a valuable asset to anyone interested in McLaren or her work.

**Influencing Environments: Reading the Notebook in Context**

I have already argued that Add. MS. 83844 is valuable in and of itself not only for the raw data that it contains but also for the insights that it provides into the research methodologies and data collection processes used during the egg transfer experiments. However, I argue that situating this notebook within the broader environments of McLaren’s work compounds its value even further. This is because the notebook represents only one of many experiments that McLaren undertook in the 1950s and placing it in conversation with these other activities allows it to demonstrate the interconnected nature of scientific research and the social structures that can either help or hinder that research. Moreover, within this network of research, I argue that this notebook shares a direct connection with the IVF breakthrough for which McLaren is perhaps best known. As such, it is only by approaching the notebook within its broader contexts that its full value and impact can be revealed.

The data in Add. MS. 83844 begins when McLaren and Michie were working at University College in Medawar’s department. However, they soon ran out of space for their mice, which necessitated a move in 1955 to the Royal Veterinary College in London. Page 24 of the notebook records 17 October 1955 as the date on which their mouse populations had been fully relocated and settled, allowing for the egg transfer experiments to begin again (fig. 5). McLaren and Michie would remain at the Vet College until 1959 (at which point McLaren and Michie divorced and both moved to Edinburgh to continue their careers). Reflecting back on the move to the Vet College, McLaren stated that it proved a fortuitous situation for her and Michie not only because they had more physical space but also because they were able to conduct their research apart from any particular department, which gave them a great amount of freedom.12

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12 ‘Professor Dame Anne McLaren interviewed by Martin Johnson and Sarah Franklin,’ Audio Recording, 2007, BL.
As a result of these expansions in both facilities and freedom, Michie and McLaren had ample room to explore multiple questions in their research, as evidenced by the productivity that they were able to maintain during these years. In addition to the egg transfer experiments recorded in Add. MS. 83844, McLaren and Michie also continued earlier experiments with superovulation and superpregnancy by means of treatment with gonadotropic hormones, or, in other words, hormonally triggered ovulation cycles and artificially increased litter sizes respectively. These experiments allowed them to consider, for example, what factors might hinder an embryo’s chance of survival, such as uterine crowding, and to assess the limits for how large a litter size could be physically supported by the mice they studied.\(^{13}\)

Being in the new laboratory space also meant that McLaren and Michie were put in contact with new colleagues, including most crucially Dr John Biggers (1924–2001). The research interests of the three scientists overlapped and, with Biggers, McLaren and Michie undertook even more parallel experiments. One such experiment considered the effect of ambient temperature on population variance, which was inspired in part because they had access to three different temperature rooms at the Vet College. The results of this experiment are recorded in notebooks Add. MS. 83846, Add. MS. 83847, and Add. MS. 83848. Biggers, McLaren, and Michie also briefly considered the relationship between the length of a mouse’s tail – a major site of heat loss – and its ability to regulate temperature,\(^ {14}\) although Biggers reports that they never fully explored that project.\(^ {15}\)

This rich, collaborative, and multi-tasked environment can be likened to a Darwinian tree of research ideas with many offshoots, including highly productive branches, such as the egg transfer experiments, and curtailed experiments, such as the tail-length data. The questions asked in one project prompted insights in the other projects, thus producing a rich network of ideas that cannot be neatly separated from one another. Perhaps nothing illustrates this point as clearly as a seemingly small experiment that occurred in 1958 as a product of this environment. Biggers recounts reading an article by Dr Wesley Whitten in the Senior Common Room of the Vet College with McLaren and Michie that reported on the ‘successful culture of eight cell mouse embryos to the blastocyst stage’.\(^ {16}\) He says that he and McLaren quickly realized that between McLaren’s expertise on preimplantation egg transfers, Biggers’s own work on ‘designing chemically defined media for organ culture’, and the facilities at their disposal, they could take this research to the next logical step, namely, to prove that these \textit{in vitro} blastocysts could ‘give rise to normal mice after being allowed to develop in the uterus of a surrogate mother’.\(^ {17}\) That summer, McLaren and Biggers first cultured 249 fertilized embryos for forty-eight hours \textit{in vitro} before transplanting them into eight female mice.\(^ {18}\) Nineteen days later, these transplants resulted in the live birth of two mice, or as McLaren called them, ‘bottled babies’, which were the first mammals ever cultured outside of a uterine environment pre-implantation.\(^ {19}\) Only twenty years later, in 1978, Louise Brown would become the first human to be born as a result of IVF treatment.

Strikingly, Add. MS. 83844 makes no mention either of its relationship to this landmark discovery or the birth of what the press soon dubbed the ‘brave new mice’ (fig. 6),\(^ {20}\) despite

\(^{13}\) Add. MS. 83830 (1953–1964).
\(^{16}\) Ibid, 472.
\(^{17}\) Ibid, 472.
\(^{19}\) Biggers, op. cit., p. 472.
the fact that this notebook covers the exact dates during which the IVF experiments took place. Whether stated or not, however, this notebook remains entangled with the history of IVF, because, without the years of egg transfer work that it documents, the brave new mice would not have come about in the way that they did. In fact, this notebook may be the closest thing to a primary document attesting to the processes that McLaren used during the IVF experiments, because, as of the writing of this article, there are no known laboratory notebooks or similar ephemera surviving from the 1958 IVF experiments.

Fig. 6. Brave New Mice.

While the IVF experiments taken on their own might seem to burst onto the scientific scene, then, taking hardly two months from the breakroom discussions described by Biggers to the birth of the bottled babies, Add. MS. 83844 and the other documents archived by the British Library in the Anne McLaren Papers resist such an illusion. Instead, they demand that attention be paid to the detailed work that McLaren and Michie undertook to develop the expertise that enabled McLaren to so swiftly carry out her role in the IVF experiments. Moreover, the IVF experiment itself was a single offshoot in a much larger network of experiments in which IVF as such was not specifically McLaren’s focus. As McLaren’s later work shows, she continued to develop the processes used during the egg transplant and IVF experiments for other means, including in her well-known experiments with chimeras, or mice made from mixing two different eight-cell eggs before implantation, which led to the publication of her influential book *Mammalian Chimeras* in 1976.

**Conclusion**

Throughout her life, McLaren’s research repeatedly showed how interconnected all living things are with their environments, whether these environments are large and encompassing, such as the effect of climate, or as small as the environment of a cell. It is therefore unsurprising that her own practices and working methods show an acute awareness for how this interconnectivity proves equally true for science itself. She knew that science needed diverse perspectives to grow, and so she actively fostered collaborative working environments, as a colleague, teacher, and mentor, while remaining highly attuned to socio-political issues, including the changing interests of funding bodies, structural gaps, like the lack of accessible childcare, that limit the participation of women in science, and the rise of new social concerns, including those surrounding ‘designer babies’ as embryonic research progressed. As my preceding discussion shows, Add. MS. 83844 becomes a rich point of contact within this complex scientific environment for many strands of research that shaped McLaren’s early work, not least of all the IVF work that features so prominently in her legacy. Moreover, when placed into the context of the collaborative environment that McLaren, Michie, and Biggers fostered for their work at the Vet College, Add. MS. 83844 becomes a piece of a larger puzzle that attests to the ways in which McLaren used the environments, people, and resources around her to their fullest potential, asking as much as she could from them while also giving back to and through them.