BOOK REVIEW

REPRODUCTION REBORN: HOW SCIENCE, ETHICS, AND LAW SHAPE MITOCHONDRIAL REPLACEMENT THERAPIES

Diana M. Bowman, Karinne Ludlow, and Walter G. Johnson eds.
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Mitochondrial diseases are a complex assortment of severe genetic disorders caused by dysfunctions in the mitochondria.[1] Mitochondria reside in each cell's cytoplasm, surrounding the cell's nucleus.[2] Mitochondria convert food and oxygen into energy that the cell needs to function and grow.[3] The mitochondria communicate with the nucleus to regulate cellular functions.[4] Human mitochondrial DNA (mtDNA) consists of about 16,500 base pairs, encoding just 37 genes, compared to nuclear DNA (nDNA) which has over 3 billion base pairs and around 20,000–25,000 genes.[5] Though mtDNA represents a very small proportion of genetic material in a person's genome, it does a lot of work and, when things go awry, it can do a great deal of harm.[6]

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1. Cathy Herbrand, *Reproductive Decisions and Mitochondrial Disease: Disruption Risk, and Uncertainty*, *in* REPRODUCTION REBORN: HOW SCIENCE, ETHICS, AND LAW SHAPE MITOCHONDRIAL REPLACEMENT THERAPIES 62, 62 (Diana M. Bowman, Karinne Ludlow, & Walter G. Johnson eds., 2023) [hereinafter REPRODUCTION REBORN].

2. *See* Jeffrey R. Mann et al., *Development of Mitochondrial Replacement Theories*, *in* REPRODUCTION REBORN, *supra* note 1, at 17, 17.

3. *Id.*

4. *See id.*; Lydia W.S. Finley & Marcia C. Haigis, *The Coordination of Nuclear and Mitochondrial Communication During Aging and Calorie Restriction*, AGEING RSCH. REVS. 173, 173 (2009).

5. Mann et al., *supra* note 2, at 17; *Beth Heuer, Mitochondrial DNA: Unraveling the "Other" Genome*, 33 J. AM. ASS'N NURSE PRAC. 673, 673 (2021).

6. *See* Mann et al., *supra* note 2, at 17–18.

In reproduction, because egg cells (not sperm) provide the cytoplasm and mitochondria, only the mother's mtDNA is passed on to the next generation.[7] Because of their different mechanisms for replication and repair, mtDNA has a higher mutation rate than nDNA.[8]

Mutations in mtDNA affect cell function directly.[9] The resulting mitochondrial diseases can lead to debilitating and often life-threatening conditions, producing a wide variety of symptoms such as muscle weakness, neurological problems, stroke-like episodes, hearing loss, blindness, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, and increased risk of infection.[10] Because there are no cures yet, only symptom management strategies are available to someone afflicted with mitochondrial disease.[11]

Patients with mitochondrial disease understandably would like to prevent their offspring from inheriting the mother's disease, while still having a genetically related child.[12] The workaround that achieves that goal—mitochondrial replacement therapies (MRT)—is the most recent advance in assisted reproductive technologies and the focus of the book under review.[13]

MRT is accomplished with the DNA of three different persons, and so three adults are the biological parents of the resulting child.[14] Eggs are collected from both the mother (who has faulty mitochondria) and a third-party donor (who has healthy mitochondria).[15] The nucleus is removed from the donor's egg, leaving only her healthy mitochondria.[16] Inserted in its place is the nucleus from the mother's egg.[17] This creates an egg with the mother's nDNA along with the donor's mtDNA.[18] The reconstituted egg is then fertilized with the father's sperm and implanted into the uterus of the mother (or a surrogate).[19]

Until future research discovers how to prevent or treat mitochondrial diseases, MRT is the best solution available for producing biologically related children who are spared their mother's condition.[20] Like all previous assisted reproductive technologies, starting with the birth of the first "'test tube' baby" in 1978,[21] this one has also been accompanied by medical, ethical, societal, and

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7. Robert Sparrow et al., *Mitochondrial Replacement Techniques*, *in* REPRODUCTION REBORN, *supra* note 1, at 32, 32; Mann et al., *supra* note 2, at 18.

8. Mann et al., *supra* note 2, at 18.

9. *See id.*

10. Sparrow et al., *supra* note 7, at 32.

11. *See* Rebecca Dimond & Neil Stephens, *Legalising MRT in the United Kingdom*, *in* REPRODUCTION REBORN, *supra* note 1, at 87, 88.

12. Herbrand, *supra* note 1, at 75.

13. Diane M. Bowman et al., *Introduction*, *in* REPRODUCTION REBORN, *supra* note 1, at 1, 1.

14. Sparrow et. al., *supra* note 7, at 38.

15. *Id.*

16. Mann et al., *supra* note 2, at 19.

17. *Id.*

18. *See id.*

19. *See id.* at 20; *see also* Sparrow et. al., *supra* note 7, at 42 (discussing how "gestational surrogacy" in MRT can complicate parenthood determinations).

20. *See* Herbrand, *supra* note 1, at 63.

21. Dimond & Stephens, *supra* note 11, at 89.

legal controversy, which in turn shapes whether and how MRT can be offered clinically.[22]

Reproduction Reborn, the book under review, is an exceptional source for up-to-date information about those multidimensional issues. Its editors have well-established backgrounds in the governance of emerging biotechnologies in addition to MRT. Diana Bowman is based in the United States, at Arizona State University's College of Law and College of Global Futures. Her past work has dealt with legal and policy issues associated with emerging technologies and public health. The other two editors are based in Australia. Karinne Ludlow, on the law faculty at Monash University, has focused on regulation of, and legal challenges to, innovative technologies, especially biotechnology. Walter Johnson, whose training in law as well as science and technology policy was acquired in the United States, is now a Ph.D. scholar studying regulation and global governance at the Australian National University. The editors assembled leading experts on varied aspects of MRT, from the fields of medicine, genetics, ethics, sociology, law, and policy, united by their interest in emerging reproductive and other biotechnologies.[23]

The book is structured into three Parts. Part I contains chapters that explain the foundational research and development of MRT (Jeffrey Mann, Mary Herbert, Deirdre Zander-Fox, Deepak Adhikari, and John Carroll),[24] provide a critical review of the ethical issues (Robert Sparrow, Julian Koplin, and Catherine Mills),[25] and offer the viewpoint of women affected by mitochondrial disorders who are making reproductive decisions, in some cases after losing children to the disease (Cathy Herbrand).[26] Part II examines differing legal approaches to regulating MRT which have arisen in different parts of the world (to be discussed further in a moment).[27] Part III concludes and looks forward to what is likely to come.[28] One chapter describes three new technologies (genome engineering, gametogenesis, and artificial wombs), the potential ethical issues raised by each, and how their use might be regulated (Kevin Doxzen).[29] The human reproductive landscape of the future, as envisioned in that chapter, appears quite different from that of the present. In the final chapter (Ludlow, Johnson, and Bowman),[30] drawing on all of the pieces that preceded it, the editors place MRT within the advancing and evolving techno-legal world of reproductive technologies, in part to better understand where the regulation of MRT is and is going, and to some extent offering a peek at the future of the broader regulatory context of reproduction.

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22. Bowman et al., *supra* note 13, at 1–2.
23. *Id.* at 2.
24. Mann et al., *supra* note 2.
25. Sparrow et al., *supra* note 7.
26. Herbrand, *supra* note 1.
27. Bowman et al., *supra* note 13, at 7.
28. *Id.* at 11.
29. Kevin Doxzen, *Future Technological Advancements*, *in* REPRODUCTION REBORN, *supra* note 1, at 215.
30. Karinne Ludlow et al., *Placing MRT in the Evolution of Reproduction*, *in* REPRODUCTION REBORN, *supra* note 1, at 243.

Let's take a somewhat closer look at the large middle Part of *Reproduction Reborn*, which explores variations in regulatory frameworks transnationally. Interestingly—and importantly—many of the book's chapters' authors were recruited from various parts of the world to write about the differing legal and policy approaches with which they are especially knowledgeable. These chapters look at the United Kingdom,[31] Australia,[32] United States,[33] Mexico,[34] European Union,[35] and Asia.[36] Each region's unique approach to MRT regulation highlights the complex interplay of ethical, cultural, and legal factors influencing assisted reproductive technologies. In analyzing comparative MRT law, they unroll a story not only of regulatory diversity, but also describe the evolution of regulation of MRT (or its nonregulation or prohibition).

One chapter analyzes the path to legalization in the United Kingdom (Rebecca Dimond and Neil Stephens).[37] That road seems to have been paved somewhat by U.K. scientists having taken the lead in *in vitro* fertilization advances in the 1970s, with the United Kingdom establishing one of the earliest regulatory regimes for embryo research.[38] In 2012, the United Kingdom authorized an expert group to study the social, ethical, and legal issues surrounding MRT.[39] Despite contentious public and parliamentary debates, in 2015 the United Kingdom passed the world's first legislation for MRT: the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations.[40] The United Kingdom's strict regulations permit licensed clinics to provide MRT for the purpose of preventing mitochondrial diseases.[41]

The chapter on Australia's MRT law (Ludlow) traces a more circuitous path.[42] A committee of the Australian Senate recommended legalizing MRT in June 2018, at a time when state laws generally prohibited the use of MRT in clinical settings.[43] Eventually, in 2022, Maeve's Law was passed, legalizing MRT under specified conditions for research, training, and clinical applications.[44]

The law of MRT in the United States has been especially complex (I. Glenn Cohen, Priyanka Menon, and Eli Adashi), but in the end amounts to a prohibi-

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31. Dimond & Stephens, *supra* note 11.

32. Karinne Ludlow, *MRT in Australia*, *in* REPRODUCTION REBORN, *supra* note 1, at 108.

33. I. Glenn Cohen et al., *MRT in the United States*, *in* REPRODUCTION REBORN, *supra* note 1, at 129.

34. Sandra González-Santos & Abril Saldaña-Tejeda, *Contesting the 'No Rules' Label: ARTs in Mexico Before and After the First MRT Baby*, *in* REPRODUCTION REBORN, *supra* note 1, at 143.

35. Walter G. Johnson & Diana M. Bowman, *Medical Tourism and Multilevel Regulation for MRT in the European Union*, *in* REPRODUCTION REBORN, *supra* note 1, at 171.

36. Tetsuya Ishii, *Asia*, *in* REPRODUCTION REBORN, *supra* note 1, at 189.

37. Dimond & Stephens, *supra* note 11.

38. *See id.* at 88–89.

39. *Id.* at 89.

40. *Id.* at 87, 99.

41. *See id.* at 99.

42. Ludlow, *supra* note 32.

43. *Id.* at 115; SENATE CMTY. AFFS. REFERENCES COMM., PARLIAMENT OF AUSTL., SCIENCE OF MITOCHONDRIAL DONATION AND RELATED MATTERS (2018).

44. Ludlow, *supra* note 32, at 108.

tion.[45] The regulation of much reproductive technology has been in the hands of individual states.[46] Because MRT was framed as a therapeutic product, however, it fell under the governance of the Food and Drug Administration (FDA).[47] While the FDA was analyzing a regulatory path forward for MRT, in 2016 Congress passed a bill containing a rider which prohibited the FDA from acting on proposals involving the implantation of modified embryos.[48] Until the law is changed, that prevents the approval of any clinical uses of MRT.[49]

In 2016, Mexico was home to the world's first live birth of a child conceived using MRT (Sandra González-Santos and Abril Saldaña-Tejeda).[50] The chapter describes the nature and context of Mexico's evolving reproductive technologies, including the research and market conditions, the impact of science and religion, and the complex role of regulation by government at multiple levels as well as by professional associations.

The E.U. chapter (Johnson and Bowman) analyzes an inherently complex situation, since each member nation regulates its own healthcare system.[51] This allows for a spectrum of regulation of assisted reproductive technologies, leading to fragmentation, but also to easy movement of citizens within and beyond the block to obtain the healthcare they want but cannot find at home, including MRT.[52] The result is that advanced reproductive services flourish within the European Union.[53]

Finally, the chapter focused on Asia (Tetsuya Ishii) describes the evolution of reproductive technological experimentation, including MRT, in China, Japan, Singapore, and Taiwan.[54] Those histories depict different paces of development, different clinical activities, and different public responses. The regulatory frameworks that have developed differ markedly not only from those of the United Kingdom and Australia, for example, but also from each other.[55]

If, as has often been said, the states of the United States serve as legal laboratories—in which different laws can be adopted in different states, thereby assisting other states in evaluating which approaches work well and consequently deserve to be replicated—the same is true of the laws of different nations or regions of the world.

Numerous influences feed the roots of different regulatory regimes—economic, religious, cultural, public opinion about particular technologies and the needs they serve (e.g., sympathy toward the plight of victims of MRT), grassroots and professional organizations, and so on.[56] Perhaps the most fundamental,

45. Cohen et al., *supra* note 33.
46. *Id.* at 130.
47. *See id.* at 132.
48. *Id.* at 134.
49. *Id.* at 135.
50. González-Santos & Saldaña-Tejeda, *supra* note 34.
51. Johnson & Bowman, *supra* note 35.
52. *Id.* at 173–74.
53. *Id.* at 182.
54. Ishii, *supra* note 36.
55. *Id.* at 208.
56. Ludlow et al., *supra* note 30, at 249–54.

embracing all the others, are ethical concerns that surround MRT. This is where technological capability, on the one hand, and moral and prudential choice, on the other, can clash: just because a technology like MRT is possible, should it be pursued?

Though ethical and other philosophical issues arise in various chapters, they are explored most systematically in the chapter by Sparrow and his coauthors.[57] Among the issues are the following:

> • How does the framing of MRT—as a therapeutic intervention against disease or as a technique for securing genetic relatedness of a child to a parent—affect the case for regulating it (or prohibiting it)? Which framing is better justified?
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> • What are the implications of MRT for the identity of a child and its relation to a family, given that the child is the product of genetic material from three adults (three biological parents)?
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> • Will the child be subject to some kind of genetic discrimination because of its unusual biological parentage?
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> • Does the child have a right to learn who the mtDNA donor is?
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> • Does the idea of a right to reproductive liberty make it wrong for the state to limit access to MRT?
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> • Does the implementation of MRT allocate resources in an undesirable way? The problem, if there is one, is not financial—investment in MRT prevents far greater lifelong care expenses for those born with mitochondrial disease—so much as it concerns the best use of scarce oocytes that could be used for other kinds of assisted reproduction.
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> • What risks does MRT present to parents, to the ova donor, to the newly created child (both physical and mental), and to future generations?
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> • What social impacts will the adoption of MRT create? One suggestion is that the embrace of MRT could be one step on a slippery slope that would alter public and policy-makers' attitudes toward germline genetic modification of humans, particularly human heritable genome editing (which heretofore has been received with considerable opposition).
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> • On the other side of that coin, does it make sense (biologically or ethically) to categorize MRT with other controversial technologies, like cloning or gene editing, as some have been doing? MRT can be viewed as similar to those other technologies in that, for example, they involve *in vitro* fertilization and other procedures to manipulate eggs and embryos outside the body, that manipulation of genetic material occurs at a cellular level, and the newborn's genome can be passed down to subsequent generations. In some sense, however, cloning and MRT move in opposite directions. While cloning aims to create a genetically identical copy of an organism, MRT creates an individual whose DNA draws more broadly from the gene pool than normal reproduction does. As to gene editing, the manipulation of components of the parent and donor eggs is at a much higher level of aggregation in MRT than the editing of genes on strands of DNA.

57. Sparrow et. al., *supra* note 7.

Reproduction Reborn provides an excellent analysis and summary of the issues presented by this newest form of assisted reproductive technology, and how different societies have chosen, thus far, to regulate its use. Being an early form of genetic modification, MRT and the debates and diverse regulations that surround it, preview the issues and responses that will arise with greater intensity when interventions involving more advanced technologies, presenting more significant ethical challenges, come into being. This might be the longer-term value of *Reproduction Reborn* that will serve interested scholars, scientists, lawmakers and the public into the future.