Transforming Mice: Technique and communication in the making of transgenic animals, 1974–1988

Dmitriy Myelnikov
Department of History and Philosophy of Science
Emmanuel College
University of Cambridge

September 2014

Corrected version, May 2015

This dissertation is submitted for the degree of Doctor of Philosophy

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text. No parts of this dissertation have been submitted for other qualifications. It does not exceed 80,000 words.

Dmitriy Myelnikov

Table of Contents

Acknowledgements

First and foremost, enormous thanks go to my supervisor, Nick Hopwood, whose insight, rigour and dedication to his students are unparalleled. I am very grateful to Martin Johnson for advising on the thesis, directing me through the scientific issues and sharing his own memories of the mammalian development community. Jim Secord has given me invaluable guidance and delivered insightful suggestions with life-affirming encouragement. I tried to take in as much advice as I could, but of course, all faults of this work are my responsibility. I am extremely grateful to the Wellcome Trust who made this work possible through a generous doctoral studentship; the Raymond and Edith Williamson Fund at the University of Cambridge for contributing to the cost of overseas fees; and Emmanuel College, for being a second home for such a long time and for helping out with travel funds.

I would like to thank all those who spared their time to participate in the oral history interviews and email surveys for their generosity. I was deeply saddened when Frank Ruddle passed away in 2013. He was the first scientist I interviewed, and I could see why his students and colleagues spoke of him with such admiration. Archivists and librarians have been tremendously helpful – I would particularly like to thank Ashley Augustyniak, Clare Button, Clare Clark, Lee Hiltzik, Bill Kimok, Douglas Macbeth and Nancy Miller. Rob Perks and Graham Smith offered excellent training at the 2011 Wellcome Trust Oral History of Medicine course at Royal Holloway. I would also like to thank B. M. for a fascinating extended tour around modern-day transgenic facilities and showing me how to make a transgenic mouse.

Many ideas were born and made in exciting conversations with other scholars. I am especially grateful to Jenny Bangham, Christina Brandt, Nathan Crowe, Helen Curry, Sarah Franklin, Rob Kirk, Susan Lindee, Mikey McGovern, Jesse Olszynko-Gryn, Joanna Radin, Robin Scheffler and Kathryn Schoefert for inspiring conversations and comments on my work. I appreciate how lucky I am to have spent my PhD years in the History and Philosophy of Science department at the University of Cambridge. It has been an incredible work environment with a superb sense of community, and I have benefitted tremendously from the mad number of events it holds. Tamara Hug,

Anna Jones, Aga Lanucha, Dawn Moutrey, Louisa Russell, and David Thompson run a tight ship, which has been much appreciated.

I would like to thank Maggie Jack, Viktoria Korman and Rob Mullalay, Patrick Orson, Joanna Radin and Matthew Grant, as well as Etienne Stockland for their hospitality during my research trips. Similar gratitude extends to the History and Sociology of Science department, University of Pennsylvania, for cordially allowing me to loiter in their space and attend events on my extended visit to the East Coast. I am very happy to have been able to see my wonderful cousin Yulia Georgieva, her husband Goran and little Sasha in San Diego, although the time we spent together was nowhere near long enough.

To those I have not yet named, but who made these years bearable, exciting and worthwhile – I am so grateful, Leah Astbury, Shahar Avin, Beatrice Balfour, Katy Barrett, Riana Betzler, Toby Bryant, Andrew Buskell, Maria Campbell, Riley Doyle, Rachel Epstein, Hannah Fair, Annabelle and Abby Guillermo, James Hall, Joseph Keslar, Evgeniya Petrova, Ruth Rand, Sophie Waring, Michelle Wallis and Caitlin Wylie. Infinite thanks go to my parents, who have been supportive in more ways than they can imagine. I wish to dedicate this thesis to the memory of my aunt and uncle, Margarita Myelnikova and Vasiliy Deryabin, who nurtured my fascination with biology and scholarship from an early age.

Abbreviations

ARC	Agriculture Research Council (UK)
DHEW	US Department of Health, Education and Welfare
EMBL	European Molecular Biology Laboratory, Heidelberg, Federal Republic of Germany
GEIS	*General Embryological Information Service* (newsletter)
HAT	Hypoxanthine-aminopterin-thymidine culture medium
HRPT	Hypoxanthine-guanine phosphoribosyltransferase
HSV tk	Herpes simplex virus thymidine kinase
LMB	MRC Laboratory of Molecular Biology, Cambridge, UK
MMTV	Mouse mammary tumour virus
M-MuLV	Moloney murine leukaemia virus
MRC	Medical Research Council (UK)
NAS	National Academy of Sciences (USA)
NIH	National Institutes of Health (USA)
NIMR	National Institute for Medical Research, Mill Hill, London
NSF	National Science Foundation (USA)
OTA	Office of Technology Assessment, United States Congress
PNAS	*Proceedings of the National Academy of Sciences of the United States of America*
pMT1	metallothionein promoter 1
RAC	Recombinant DNA Advisory Committee (USA)
SDS	Sodium dodecyl sulfate
SV40	Simian virus 40
TIBS	*Trends in Biochemical Sciences*
UCL	University College, London
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
USPTO	United States Patent and Trademarks Office

Introduction

Today, genetically modified animals are a routine biomedical technology, used as research models and test subjects in drug development. The vast majority of such experiments relies on transgenic mice that carry experimentally introduced foreign genes. Overwhelmingly, they are produced by direct injection of isolated DNA into a one-cell embryo through a minute glass needle. In 1980–81, six laboratories reported the successful use of the procedure, called pronuclear injection, although researchers had tried to insert new genes into mice in various ways since the 1960s. Despite the gradual decrease in animal research in American and European laboratories since the passage of updated laboratory animal legislation between the mid-60s and the mid-80s, these modified rodents have shown consistent growth (Fig. i). Today, the production of transgenic mice has been outsourced to quasi-commercial academic 'core facilities' and for-profit providers, with a sizeable industry around them. Throughout the 1980s, however, these mice were made in a few hundred laboratories that combined the necessary funding, equipment and expertise.

Transgenic mice were invented during dramatic shifts in the organisation, funding and communication of biomedical research. This thesis is the first extended history of their invention and early adoption, leading up to the 1988 US patent on the 'Harvard mouse' or OncoMouse, a transgenic animal modified to carry cancer-causing oncogenes and the first animal – though not the first organism – to be patented.[1] I place these animals within the changes in biology, transformations in science funding and the altered vectors of scientific communication. I consider the diverse audiences to which transgenic mice were communicated, the modes of production and exchange of molecules, modified embryos and mice, as well as how this invention has been remembered. Rather than follow one theme or approach, I bring multiple perspectives and literatures to bear on the history of these animals. This introduction will consider existing histories of transgenic animals and their place in the biotechnology story; histories of animals in science and beyond; perspectives on innovation and invention; the role of media in science and changes in sci-

[1] I allude to, but do not cover subsequent developments, most notably knockout mice, available since 1989, in which specific genes could be removed through stem cell manipulation. These were the subject of the 2007 Nobel Prize.

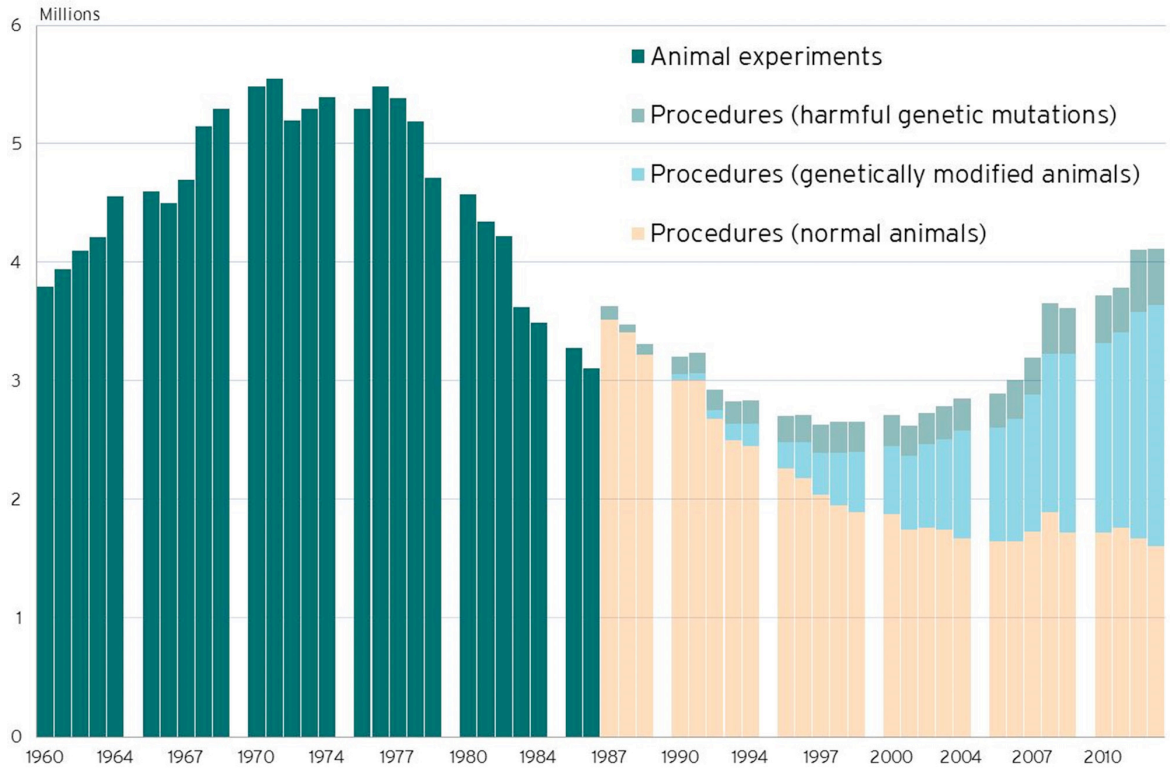


Fig. i. Use of animals in scientific experiments in the UK, 1960–2012**.** The vast majority of genetic modification experiments was carried out with mice, and the species represents 75% of all procedures carried out in recent years. 'Harmful genetic mutations' refers to breeding animals with serious pathologies through conventional means. The Home Office statistics includes only vertebrates.

Source: Understanding Animal research, www.understandinganimalresearch.org.uk/resources/image-library/1674/times-series-data-of-procedures-1960-2013, accessed on 28 August 2014. Latest official statistics from the Home Office can be found at www.gov.uk/government/collections/statistics-of-scientific-procedures-on-living-animals.

ence journalism in the period covered; studies of knowledge and materials and transit; and finally, moral economies of science.

With multiple actors involved in the early events, the scientists' reviews and memories, while emphasising different research trajectories as key, all graciously acknowledge the multiple invention of transgenesis and highlight the diversity of agendas at stake.[2] Science and technology studies (STS) scholars, lawyers and historians, by contrast, have concentrated on the OncoMouse. These studies have tended to focus on the embodiment of novel forms of biocapitalism, on changes in intellectual property law within 'knowledge economy' discourses and on how transgenic mice undermine boundaries between the natural and the artificial.[3] Yet in many ways, On-

[2] Gordon 1983, Palmiter & Brinster 1985, Wagner 1990, Papaioannou 1998, Brinster & Arechaga 1998, Graham 2000, Hanahan, et al. 2007.

[3] Moga 1994, Haraway 1997, Knorr Cetina 1999, Fuller 2008, Robins 2008, Murray 2010.

coMouse was a commercial failure, though its multiple versions and strains are still in use.[4] As Fiona Murray has shown, the restrictive licensing policy that conflicted with the common modes of exchanging experimental animals was partly to blame.[5] While her account conflates the diverse and emergent disciplinary communities around these animals into 'mouse geneticists', she usefully highlights the resistances to patenting among scientists and its effects on adoption and use. Despite the initial excitement, Harvard and DuPont misjudged the potential market for cancer models; in the late 1980s and early 90s, inbred mouse strains were seen as good enough and more reliable. The history of the invention of transgenic mice and their resulting production, still concentrated in academic labs, goes some way towards explaining how these animals came to be seen as a commercially promising path for the biotech industry and how their production and established uses of transgenic mice impeded commercialisation.

As an important yet not straightforwardly profitable innovation, transgenic mice are a peculiar case in the history of biotechnology. Invented in academic institutions when universities were actively encouraged to secure intellectual property, they highlight the changing purposes of university science and the increasing permeability between academic and industrial biomedicine. Beyond extended work on regulation, scholars have surveyed the longue durée history of biotechnology and established the importance of industrial interests in biology throughout the twentieth century.[6] But the 1970s transformed molecular biology in dramatic ways and on a large scale. As I show, these changes were not limited to what came to be defined as recombinant DNA techniques, but built on multiple research programmes and institutional changes. In the USA, the role of state and federal government in supposedly "private science" went beyond regulation and deregulation in response to the dramatic controversies over recombinant DNA. The Carter and especially the Reagan administrations sought to create a favourable climate for biotechnology by

[4] Löwy 2000.

[5] Murray 2010.

[6] On regulating biotechnology, see Krimsky 1984, Wright 1994, Gottweis 1998. On placing biotechnology within longer history of industrialising biology, see Bud 1993, 2010. For a historiographical review of continuities and changes in biotechnology, see Gaudillière 2009. On the historical importance of industry to biomedical research, see the essays in Löwy & Gaudillière 1998b.

changing patent law and practice, brokering international agreements and offering generous seed funding – strategies that were to some extent emulated in Britain.[7]

Beyond patenting, the increased entanglement between academic laboratories, emergent biotech and its big pharmaceutical and chemical backers also affected practices of sharing and communicating research. The dramatic controversy over the first uses of what came to be know as "recombinant DNA" was key to this environment. Safety issues culminated in the Asilomar conference of 1975 and subsequent NIH guidelines that required containment and extensive regulation of experiments with genetically modified bacteria.[8] In response, scientists and industry representatives became much more engaged in communicating their work and trying to direct the response."Cloning by press conference" – a phrase coined to criticise the aggressive PR of new biotech ventures – became increasingly common in respectable academic institutions, expanding the scope of acceptable media through which scientists could successfully promote their work, as well as the general interest in scientific news.[9] As I will show, these strategies created an environment where transgenic mice could be seen as safe animals that could be used to discuss the future of genetic engineering and its application to humans.

Histories of human-animal relationships have emphasised the importance of other animals in analysing human culture.[10] More recently, some scholars under the loose rubric of animal studies have sought to restore the agency of animals in the stories we tell about them. The projects to reconstruct animal agency, while fascinating, are troubled by their reliance on human sources that survive, or have to build on too many assumptions about animal psychology.[11] So like much historical work that deals with animals, this thesis is primarily a story about people who worked with mice. Laboratory organisms are now a standard topic in history of biology, thanks especially

---

[7] Sell 2003, Parry 2004, Cooper 2008. On the British story, see de Chadarevian 2011.

[8] Krimsky 1984, Wright 1994.

[9] Andreopoulos 1980, Anon. 1980b, Nelkin 1995, Yi 2011, Hughes 2011.

[10] See e.g. Ritvo 1989, Robbins 2002. On the mouse, see Rader 2007.

[11] Fudge 2002, Daston & Mitman 2005. For attempts to theorise animal agency, see Haraway 2007, essays in Freeman, et al. 2011: Part III.

to Robert Kohler's *Lords of the Fly,* a study of early *Drosophila* genetics.[12] Kohler showed how a common fruit fly colonised genetics laboratories in the 1910s and became a tool, a "breeder reactor" generating multiple mutants for T. H. Morgan's genetic work, and how the laboratory in turn became its ecological niche. Focusing on the material world of fly genetics, Kohler argues that the practical and mundane problems of record-keeping and the need to update neo-Mendelian nomenclature and formulas shaped Morgan's celebrated chromosomal mapping project.[13]

Histories of other key genetic species have also tended to focus on their contingent domestication and genetic standardisation as a way to make reliable knowledge that could generate new practices and infrastructures.[14] These animals are now routinely referred to as 'model organisms' – although this term was rarely used before the genome projects that started in the late 1980s – and there is a lively scientific debate as to the advantages and disadvantages of limiting research to a handful of well-studied organisms, especially with the rise of evo-devo.[15] More recent historical work has highlighted alternative ways to standardise laboratory animals, and how debates about standardisation strategies could help generate new communities and fields.[16] Similarly, and by contrast with histories of domestication, this thesis considers how a well-established laboratory animal was modified to move into new fields of inquiry and modes of production.

Geneticists first domesticated mice at Harvard's Bussey Institution for Applied Biology at the turn of the twentieth century as they relied on the supply of exotic strains of mice as 'fancy animals'.[17] Finding a new home at the Jackson Laboratory in Bar Harbor, Maine, inbred strains of mice were shipped globally though quasi-commercial networks of exchange. In the atomic age after World War II, mice became central to the study of mutation and the biological effects of radiation, with large-scale colonies built in new sites of atomic science next to experimental nuclear reactors,

---

[12] Kohler 1994.

[13] Ibid.: 53–90.

[14] On 'model organisms', see Ankeny 2001 Ankeny & Leonelli 2011. On other species, see Clause 1993, Rader 2004, Gurdon & Hopwood 2000, de Chadarevian 1998, Ankeny 2000, Leonelli 2007.

[15] See e.g. Gilbert 2009, Hopwood 2011.

[16] Leonelli, et al. Forthcoming, 2014, Kirk 2008, 2010, 2012.

[17] Rader 1998, 2004.

such as at Oak Ridge, Tennessee and Harwell in the UK.[18] In other areas, however, the mouse remained marginal, notably in embryology. It was not until the 1950s that embryologists did serious mouse work – a transition aided by their interest in appropriating genetic knowledge and tools. This adoption was made possible by the newly available culture media that allowed *in vitro* manipulation of embryos, but as I show, the development of these techniques was driven by the low cost of mice, widespread breeding infrastructure and a growing interest in the role of developmental factors to explain significant physiological variation within genetically standardised mouse lines. The importance of molecular explanations in the 1960s and 1970s extended to work with embryos. The mouse became the key mammal, and one of the handful of species, both novel and familiar – *Drosophila,* the frog *Xenopus,* the nematode *Caenorhabditis elegans* – featured in productive discussions about using molecular approaches.

In the 1970s, mouse embryologists and molecular biologists connected at the bench, too. These new alliances overwhelmingly relied on interdisciplinary collaboration and various strategies of combining embryological and molecular expertise. Disciplinary identities played out in diverse ways depending on the audiences: thus, scientists routinely referred to themselves as 'embryologists' at the bench, while the more cumbersome yet modern-sounding 'developmental biology' drove the agenda for meetings, textbooks and funding bodies.[19] The first project to introduce genes into mouse embryos came from a variety of disciplinary agendas. Following the adoption of transgenic technology, a new generation of researchers had been trained in both embryological and molecular techniques through a lively set of courses, personal contact and independent tinkering, and technical expertise was much more defining in career path and the kind of experimental labour a scientist could do.

Like many histories of biomedical technologies, this thesis is about innovation and its early adoption. David Edgerton has forcefully argued that our view of technology relies too heavily on invention and that following use is more illuminating when it comes to explaining technological

---

[18] de Chadarevian 2006, Rader 2004**,** Gaudillière 2004. On the influence of the atomic age on biology, see also Lindee 1994, Creager 2013.

[19] On developmental biology, see Oppenheimer 1966, Gilbert 1996, Keller 1995, 2000, Crowe, et al. Under review.

change.[20] Yet Edgerton's call is not to abandon studies of innovation, but to rethink approaches alongside accounts of use.[21] My take on the invention of transgenic mice stresses the ambiguity of assigning priority, investigates how communication around distributing credit contributed to making transgenic mice a new experimental tool, and shows that priority has been fluid and open for re-interpretation. In the community of scientists involved in transgenic research, the multiple invention narrative remains recognised by all parties, but different contributions are highlighted and others omitted, depending on whom one asks. The very identity of the technology was made and remade, as a novel experimental procedure was recast into a powerful instrument to raise and answer pertinent biological questions.

In examining the invention of transgenic mice, I revisit Robert Merton's call to study multiple discoveries and his argument that 'singleton' inventions are the exception to the rule in modern science.[22] The question has been largely ignored in history of science with the decline of Merton's normative approach.[23] I approach multiple invention with a practice-oriented set of tools, showing how context-specific experimental work, communication and distribution of credit resulted in transgenic mice being made in different places within a year and subsequently accepted as a multiple invention. I argue that the diverse interests, technological backgrounds and organisation of the pioneer groups contributed to the rapid enthusiasm about transgenic mice and their adoption by a considerable range of institutions. This mix of stakeholders created an environment where a new technology could succeed.

This thesis is about the circulation of materials, the knowledge that travels with them, and the claims about new animals and methods used to produce them. After the 'turn to practice' in late 1980s history of science and the explosion of laboratory ethnographies, we have multiple accounts of local knowledge production and adoption. However, communication and circulation need further attention if we are to combine accounts of local practices that move beyond specific

---

[20] Edgerton 2007, 2010. On the role of users in technology, see also Oudshoorn & Pinch 2003.

[21] Edgerton 2010: 685.

[22] Merton 1973.

[23] But see Cozzens 1989.

sites and may scale up and down again through their histories. Rather than selecting specific laboratories to follow, my analysis considers the multiple actors involved in the making of transgenic technology. This account focuses on the USA and Britain – the key locations where transgenic mice were invented and produced. I take seriously the call to look at knowledge-in-transit, how and where it travels, and crucially, how it changes in the process, and to pay careful attention to communication as an inherent attribute of making knowledge.[24]

The work of Ludwik Fleck, a bacteriologist and philosopher of medicine is a helpful starting point, especially his emphasis on how knowledge acquires credibility and gravitas as it moves between 'esoteric' and 'exoteric' circles.[25] Without embracing the division as a dichotomy – it was not clear-cut for Fleck, in any case – the audiences considered in this thesis ranged from fellow bench-workers, experts in different disciplines and interested biologists to university administrators, patent lawyers, congresspeople, activists, readers of glossy magazines and tabloids and watchers of the evening news. I do not view this list of the actors as the gradient between "science" and "society", that is still occasionally implicit in discussions of "popularisation" despite the now-commonplace critiques of diffusion models in the field.[26] While a distinction between scientific and popular communication existed as an actors' category, it blurred for some scientists in the 1980s and they actively recognised the utility of broad communication. Bruce Lewenstein's metaphor of the "sphere of communication", proposed in his influential study of cold fusion, interrupts this implicit gradient of popularisation and shows how knowledge claims travel through unexpected routes and in many directions, generating competing narratives that may succeed or fail.[27] In an age of strongly organised science, driven by the commercial promises of biotechnology, appealing to diverse audiences was not dangerous or disreputable but advantageous. A number of sociologists labelled this trend the 'medialisation' of science.[28] Even between 1945 and 1970, a period of unprecedented authority for university science and rapidly expanding funding, re-

[24] Secord 2004.

[25] Fleck 1935/1981, esp. 93–106.

[26] On critiques of the 'diffusion model', see Hilgartner 1990, Bucchi 1998, Secord 2004.

[27] Lewenstein 1995.

[28] Franzen, et al. 2012, Hilgartner 2012.

cruiting new audiences remained useful, and while there are stories of reputations destroyed by publicity-seeking, thorough studies tend to find different explanations.[29] What changed in the age of genetic engineering was the willingness of scientists to announce innovations to the media in parallel with communicating them to their peers, as well as the growing interest of journalists in covering basic science. The attention to genetic engineering in the late 1970s coincided with the expansion of science journalism.

While science writing had been expanding and professionalising since World War II, publishers were increasingly willing to venture into popular science.[30] Debates around recombinant DNA generated dramatic interest in biological research, and growing ambivalence about science helped create a new market. With dwindling profits for print media as audiences drifted to television and radio,[31] science and technology became a promising direction, especially in the United States where, as one editor put it, "the Sputnik generation [was] now of the magazine buying age."[32] In 1978, a dedicated science section appeared in the *New York Times,* in parallel with a flurry of new upmarket popular science magazines.[33] Newspaper and magazine editors and science writers publicly criticised slow journal publication cycles and defended their right to report new discoveries in advance of peer-reviewed publication.

Traditional modes of publishing science, with added loopholes and shortcuts, were thus supplemented with unexpected connections, contingent and seldom well-orchestrated – a press conference given by two bemused postdocs, a mid-western university president who knew the president of the National Academy of Science, a celebrated television comedian responding to a fresh science story.[34] As a result, multiple communication efforts came together to affect the responses to a

---

[29] For recent studies of science-media relations in twentieth-century biology and medicine, see Nelkin 1995, Turney 1998, Nathoo 2009, Hansen 2009, Kirby 2011, Wilson 2011.

[30] Lewenstein 1989.

[31] Emery, et al. 2000.

[32] Edward Edelson, quoted in Anon. 1980b: 48.

[33] Asimov 1980, Nisbet & Lewenstein 2002, Bauer 2012.

[34] To borrow Steven Hilgartner's metaphor of public science as a theatre of credibility, improvisation was an important part of communicating even before university PR departments were firmly institutionalised. See Hilgartner 2012.

new kind of mouse, whose properties and promises were made in the process, in journal articles and television interviews alike.

In reconstructing how an invention was made almost simultaneously in different places that were not directly in contact, circulation of knowledge is key. Knowledge about progress, experiments and techniques travelled between multiple laboratories. Some ended up making transgenic mice and some did not. The circulation metaphor invokes location and brings up questions of proximity and distance. For some scientists, being in the right place at the right time was crucial. Thus, Rudolph Jaenisch, a molecular virologist interested in expanding his work to mammals, benefited from commuting between Princeton, where he held a postdoctoral fellowship, and Fox Chase Institute for Cancer Research outside Philadelphia, where Beatrice Mintz taught him to manipulate mouse embryos. His subsequent position at the Salk institute in San Diego brought him in touch with the leading genetic engineers and allowed him to learn unpublished techniques.

On the other hand, distance – geographic or conceptual – was not always an obstacle to be overcome, but a key and sometimes productive property of circulation. Mario Biagioli's study of the discovery of the Medicean stars shows how partial ignorance, lack of familiarity and need to make conclusions based on speculative reputation contributed to Galileo's success despite problems that appeared insurmountable closer to home.[35] The distance and very limited communication between the laboratories involved in trying to transfer genes into mouse embryos suggested the pursuit was an attractive goal for which credit had yet to be taken, even if it came hand-in-hand with skepticism about the possibility of success. Distance could also play a role in sustaining efficient divisions of labour between molecular biological and embryological work, with animals, their organs and data about them travelling between sites. One of the most successful and prolific collaborations in early transgenic research, between Ralph Brinster at the University of Pennsylvania and Richard Palmiter at the University of Washington in Seattle, happened through courier services and weekly phone calls for over a decade. Keeping molecular and embryological expertise separate allowed the two labs to play to their strengths and avoid internal tensions.

[35] Biagioli 2006. See also Howlett & Morgan 2011, and essays on 'agnotology' in Proctor & Schiebinger 2008 – although these mostly focus on the construction of ignorance among lay audiences.

Material objects moved hand-in-hand with knowledge. Animals, cells, DNA molecules and culture media moved via the postal system, cars and scientists' suitcases, despite alarm about the biohazards of genetically modified molecules and organisms. Sharing materials and techniques had a long tradition in biological research, particularly within emerging fields such as experimental organism communities or phage genetics.[36] Through liberal exchange, plasmids – bacterial molecules into which genes could be inserted and the resulting products then transferred into cells – travelled widely, often following the contingent relocations of highly mobile postdocs, and reached far and wide beyond the key sites of recombinant DNA research. Knowledge, techniques and expertise required to deal with these molecules had to be cultivated or recruited for successful experiments.[37]

Kohler's *Lords of the Fly* is again pertinent here, for the way it turned the attention of historians of science to a 'moral economy', describing the unspoken rules that governed the behaviours of drosophilists and helped forge a powerful community.[38] The major success of *Drosophila*, Kohler argues, lay both in the ability to generate a great number of new mutants and in Morgan's Fly Room at Columbia as a centre for circulating strains. Kohler suggests that these exchanges were governed by three rules: reciprocity, disclosure and the communal sharing of tools and techniques. At the same time, recognition and proper ways of attribution were developed. Trying to account for the way these rules work, Lorraine Daston links moral economy with individual values that stand in a defined relationship to one another, and draws on theories of affect to link the social order of science with its routine practices that are "more about self-discipline than coercion".[39] By contrast with Mertonian norms, moral economies place scientists' conduct historically and recognise its mutability.

---

[36] Kohler 1994, Rader 2004, Kelty 2012b, Kay 1993.

[37] On knowledge and expertise traveling with material objects, see Latour 1999, Hopwood 2000, Santesmases 2009, Creager 2013.

[38] Kohler 1994. See especially Chapter 5. 'Moral economy' is borrowed from E. P. Thomspon's classic study of eighteenth-century bread riots, Thompson 1971.

[39] Daston 1995. For a case study contemporary to my account that explores the moral economies of cataloguing gene and protein sequences, see Strasser 2011.

Recombinant DNA molecules were exchanged between molecular biologists in the context of heavy regulation and anxiety about containment, but reached unexpected addressees, including developmental biologists and geneticists, usually within collaborations. The NIH regulations, while falling short of federal legislation that most scientists were eager to avoid, ended up limiting the exchanges to facilities with sufficient funding and commitment to adhering to the containment requirements. Yet unlike the earlier case studies, no single centre existed for exchange of plasmids. Despite attempts to limit sharing and create central repositories and supply centres, the enormous interest they generated and the sheer scale of molecular biological work in the 1970s made these molecules remarkably mobile.

Once transgenic mice were produced, they came to be a resource-intensive and limited venture. The main interest in making them revolved around studying specific genes, so most were produced from scratch for a particular experiment. Courses, conferences and personal contacts were established to meet the demand for new techniques, continuous with the older traditions of molecular biology – it is no coincidence that Cold Spring Harbor became the key site of such training, as it had been for phage genetics and the recombinant DNA methods. However, while owing their birth to the great mobility of molecules, the mice themselves were rarely exchanged outside committed collaborations. The difficulties of production and the limited utility of already-published strains kept the circulation low and it was not until the 1990s that established mouse providers supplied transgenic strains.

By that point, these mice were subject to a series of patent restrictions and unusual limitations on breeding and further commercial exploration, in a hybrid economy that encouraged spin-offs from publicly funded research. As Angela Creager's work on radioisotopes shows, from a model of generous exchange from a cyclotron at Berkeley, these chemicals came to be produced in government-run nuclear facilities and were subjects of diplomatic negotiations, poster children for the Atoms for Peace policies and drivers for privatising nuclear industries.[40] Similarly, through extensive media exposure and the debates surrounding the patenting of OncoMouse, transgenic mice became icons of genetic engineering and biotechnology in the 1980s, even if their

[40] Creager 2013

role and production remained expensive and modest by comparison to other tools, and their commercial success proved limited.

This thesis is organised chronologically. Chapter 1 considers the emergence of the mouse embryo as a subject of experimental manipulation after World War II and focuses on the species politics of embryology and the scientific and communicative work that enabled the mouse to become an important embryo for developmental biology. Chapter 2 revisits the rise of recombinant DNA in the 1970s and shows how genetic engineering was pursued and adopted by communities working with multicellular organisms. By focusing on the collaboration between Beatrice Mintz and Rudolf Jaenisch, who inserted viral DNA into a mouse embryo before the 'cut-and-paste' recombinant techniques were available, it offers alternative genealogies to genetic engineering and explores the moral economy of molecular biology in the 1970s.

Chapter 3 then discusses the simultaneous inventions of transgenic mice in 1979–81 that relied on using isolated genes. I argue that the diverse goals and partial knowledge about competitors were productive for developing a new biological entity, and highlight the diversity of approaches and imagined uses for putting genes into mice. Chapter 4 then examines the initial communication of transgenic mice to a variety of audiences, largely lauded as a medical breakthrough. Journals may have been the key medium to claim priority, but other avenues of communication were important: newspapers, television programmes and patent applications all carried new claims about an as-yet uncertain set of experiments.

Finally, in Chapter 5 I focus on the adoption of transgenesis in the 1980s. Publicity that surrounded these animals, most prominently the giant 'supermice' made in 1982, played a significant role in attracting scientists and funders to the new technology. Commercial promises created new spaces and alternative networks, often geared to agricultural applications, even though most work still took place in academic labs, some with industrial money. Despite the lively interest in these mice, however, they remained at odds with the logic of large-scale genetics, and their production, concentrated in molecular and developmental laboratories, became a boutique operation.

Note on sources

Historians of the late twentieth century are faced with a maddening range of materials, but also gaps on the record that are hard to map. I undertook a series of oral history interviews with the key actors, mostly scientists, but also journalists and biotechnology entrepreneurs. Their stories have been extremely helpful alongside textual traces in directing my work and helping me reconstruct practice and laboratory life. Two of the key primary investigators in this story – Beatrice Mintz and Ralph Brinster – declined to participate in the oral history project. Dr Brinster referred me to an extensive published interview and his reviews,[41] while Dr Mintz explained her doubts about this project over a fascinating two-hour phone call. I have been able to interview their colleagues and postdocs, however.

I was offered a variety of perspectives on the events, and the oral history side of my project made me reflect more on the partiality of communication and the instability of innovation narratives that Chapters 3 and 4 elaborate on. In addition, I have recruited memories from subscribers of transgenic-list, an email newsletter for transgenic mouse practitioners where they have been sharing tips, news and job ads since 1996. My brief questionnaire was met with a very enthusiastic response. I have already acknowledged those who were willing to spare their time and talk to me, but would like to reiterate my gratitude here. I tried to remain critical and treat oral history as yet another source, heavily based on memories, and my interviewees were aware that their memories of specific events were not always reliable.

I am extremely glad to have had the privilege to collect memories from living actors that could be otherwise lost. With this in mind, published materials proved most useful, and I tried to read them in multiple ways to reconstruct networks and think of them as artefacts of material communication as well as texts. Handbooks, textbooks, conference proceedings, newspaper and magazine articles, newsletters and directories, institutional reports and promotional magazines came together to inform this account. While no central archives or laboratory notebooks are available for the key part of this story, I have benefited from the scattered archival evidence listed

[41] Palmiter & Brinster 1985, Brinster & Arechaga 1998

in the reference section. While triangulating my sources, I tried to keep remaining uncertainties on the surface. I am of course fully aware that as further documents may come to light and considerably alter some of the details. However, as much communication happened in person and over the telephone, and as scientists routinely throw away their papers, it is not clear to me that such evidence might become available.

Chapter 1. The rise of the mouse embryo, 1941–1970

Despite their molecular and genetic connotations and uses, transgenic animals were made possible by the experimental tradition of embryo manipulation. Yet, while routinely used by geneticists and cancer researchers since the 1920s, the mouse was marginal among embryologists until the 1960s, when its importance in developmental research surged .[1] Even among other mammals, the mouse had been seen as a difficult embryological subject, and rabbit, pig and human embryos were much more popular before the war. Existing histories of mammalian embryology focus on the mammalian embryo as a monolithic experimental subject, justifiably as cross-species comparisons were readily made.[2] However, explaining the rise of the *mouse* embryo as the dominant experimental subject is essential to understanding the origins of genetically modified animals.

As historians of laboratory animals have argued, such organisms are domesticated and adapted to new environments in multiple ways. Their bodies and heredity are changed dramatically to fit experimental purposes.[3] They become subjects of extensive standardisation and of negotiations to make them mobile and comparable across widely distributed sites.[4] In tracing the domestication of the laboratory mouse and the early history of the Jackson Lab, Karen Rader suggested that the mouse came to embody the genetic approach to medical research, rising to dominance as the gene became increasingly valued in American science and culture. Her work explores standardisation as a resource for community building. Referring to an older meaning of "standard" – a military banner marking a rallying point – Rader argued that the new community of "mousers" and their mascot animal marched across disciplines, with the gene as their weapon. The mouse offered a way of asking genetic questions through an established and expanding set of practices. Moreover, as a mammal it offered evolutionary kinship with humans.[5]

---

[1] On mouse in genetics and cancer research, see Rader 2004, Löwy & Gaudillière 1998a, Gaudillière 1998b, Gaudillière 2001, Gaudillière & Löwy 2003b, Gaudillière 2004. On mice in developmental biology, see Davies 2007.

[2] Clarke 1998, Graham 2000, Alexandre 2001, Franklin 2013: 102–49.

[3] Lynch 1988, Kohler 1994, Birke 2012, Kirk 2010, 2012

[4] Clause 1993, Rader 2004, Kirk 2008, Ankeny & Leonelli 2011, Leonelli, Ramsden, Nelson & Ankeny Forthcoming, 2014

[5] Rader 2004

Standardisation, while a key resource enabling communication and exchange, could also be challenged, and in the process new research questions and experimental subjects promoted. In the 1950s, several scientists interested in mouse development, husbandry and physiology questioned the claim that inbred mouse lines were the best tool for any experiment.[6] A number of agencies and researchers also recruited the reinterpretation of genetic purity to advocate for laboratory animal science as an autonomous field.[7] As I will show here, a similar strategy enabled genetically-oriented physiologists to elaborate programmes for the study of the effects of the maternal environment on developing mice and through this process, to turn the mouse embryo into a viable experimental object.

Finally, addressing the quality of versatility, I will examine the expansion of molecular thinking about development into the mouse. I will argue that the rise and institutionalisation of 'developmental biology' as a new way of working with embryos in the 1950s provided a communicative space that allowed molecular biologists to enter the conversation, and embryologists to embrace molecular instruments and discourse. Transition to the agendas of developmental biology, and the growing importance of combining embryology with molecular biolow gy and genetics, went hand-in-hand with changing uses of laboratory organisms. Jamie Davies's survey of papers published in developmental biology journals since 1965 (Fig. 1-1) shows the dramatic surge of work done with the mouse and *Drosophila*, both paragon genetic animals, and a steady decline of the chick favoured by classical embryology.[8] The mouse could become a viable choice for some of these scientists because several mammalian embryologists – at the time emerging as a new identity – had actively promoted it, and because new experimental systems applied the petri-dish practices of molecular biology to the complexities of eukaryotic life.

---

[6] Gaudillière & Löwy 2003a, Löwy & Gaudillière 1998a.

[7] Kirk 2010.

[8] Davies 2007

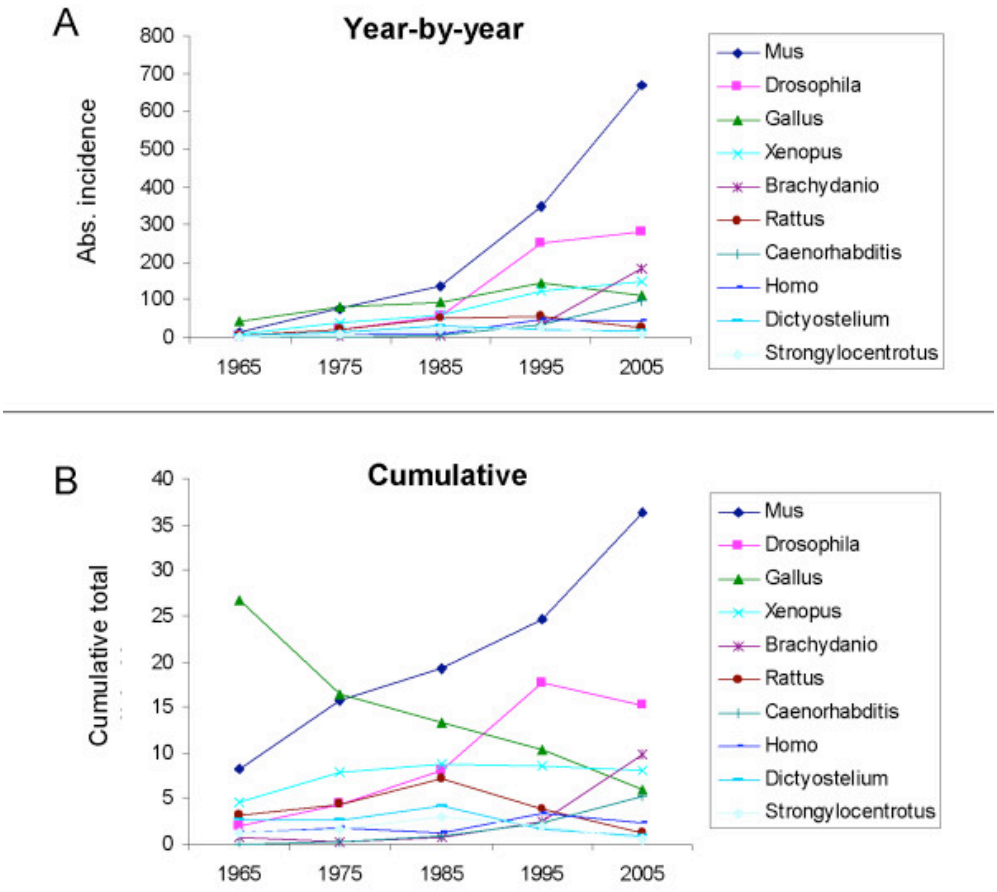


Fig. 1-1. Year-by-year (A) and cumulative (B) number of publications in developmental biology for the top ten organisms used today.

From Davies 2007.

§1. The genetic mammal

In 1941, the Jackson Laboratory in Bar Harbor, Maine, published a sizeable book, *Biology of the Laboratory Mouse*.[9] Founded in 1929 by C. C. Little, the Jackson Lab had become the centre of mouse genetics in the United States and a key supplier of inbred strains. The handbook, edited by George Snell, was its first major publication. It reviewed the achievements of mouse genetics, catalogued known genes and traits and featured practical advice on husbandry, breeding and record-keeping. Unusually, it was organised "vertically" around the central organism, rather than offering a multi-species discipline-centred textbook account. Indeed, the introduction stated that the intention was to help researchers cross disciplinary boundaries, carrying mice with them as they did so:

[9] Snell 1941

> At the present time there are, for example, increasingly well beaten paths between genetics and embryology, between endocrinology and cancer research, between cancer research and bacteriology, between bacteriology and genetics. It is a major purpose of this book, by gathering together the fundamental knowledge about the mouse from several fields of study, to make it easier for the research worker using mice as his experimental material to traverse these interconnected paths of science.[10]

The handbook established the authority of the Jackson Lab over the mouse, and defended mouse genetics as the prime subject for future investigations. Offering a comprehensive overview of the animal, its focus was overwhelmingly on genetics, but it was also to serve as a guide for setting up mouse colonies elsewhere. It was also designed to synthesise the papers that appeared in a staggering variety of journals (and languages), not straightforwardly found in smaller libraries.

The volume started at conception, with the first chapter dedicated to the early embryology. Snell, who authored the chapter, claimed to have undertaken "a complete reinvestigation of the whole field."[11] While the claim dramatised the novelty of Jackson's contribution, it was not far off. Among embryologists, mice had long been marginal animals. The most consistent account of its early development approaching a normal table was a series of turn-of-the-century articles by the German anatomist Johannes Sobotta, scattered through the *Archiv für mikroskopische Anatomie*.[12] A truncated description of early mouse development was also available from the Carnegie Institution of Washington Department of Embryology, a centre for human embryo collection and standardisation, where Warren Lewis and Elsie Wright had published multiple images of normal and abnormal mouse development in 1935, using the latest techniques of tissue culture and microcinematography that they had successfully employed to describe early rabbit development in 1929.[13] Still, by comparison with the lower vertebrates, the mammalian embryo was inaccessible and opaque as it developed inside the body, concealed further by the zona pellucida, a thick membrane surrounding the early embryo before implantation, and later the placenta. Experimental embryolo-

---

[10] Ibid.: viii.

[11] Ibid.: 1.

[12] E.g. Sobotta 1895, Sobotta 1902, Sobotta 1911. A normal table is a standard depiction of embryonic development for a species, used as a reference – see Hopwood 2007.

[13] Lewis & Wright 1935. See Landecker 2004. On the Carnegie Department of Embryology, see other essays in Maienschein, et al. 2004, Morgan 2009.

gists strategically focused on lower vertebrates, while medical schools favoured the pig and the increasingly available human embryos for morphological work.

After the First World War, mammalian eggs and early embryos attracted the attention of a different group of scientists drawn to questions of reproductive physiology in farm animals and humans.[14] In these studies, however, the mammal in general was of interest, and species were interchangeable. A major early account synthesising this research and setting further questions was *The Eggs of Mammals* (1936) by Gregory Pincus, the future co-inventor of the pill then based at Harvard.[15] Following other scientists interested in reproduction, he promoted the rabbit as a robust species best suited for embryological investigation:

> Among the laboratory mammals the rabbit is by far superior, and for one very simple reason, namely, rabbit ova seem to withstand the process of handling better than other ova. Mouse, rat and guinea pig ova, for example, begin to fragment very soon after removal from the tubes...[16]

The structure of the book and the liberal use of citations brought together experiments performed on a variety of mammals – mice, rats, guinea pigs, dogs, cats, even ferrets. Moreover, the serial plates that showed egg maturation featured several species to establish a continuous 'mammalian' development.

Snell's chapter on the early embryology thus offered a convenient reevaluation. Yet its potential utility went beyond offering a complete biological view of the organism or showcasing the work that he carried out with his embryologically-adept technicians. It spoke directly to the burgeoning interest in using mouse embryos to extend genetic knowledge, when the study of developmental mutations was drawing interest among American and British geneticists. Developmental or physiological genetics had been pursued in Germany throughout the early twentieth century alongside 'transmission genetics' with its focus on mapping, which was favoured in the USA and most closely associated with T. H. Morgan, an embryologist-turned-geneticist who built and ran

---

[14] Clarke 1998, Clarke 2007. See also Oudshoorn 1994.

[15] Pincus 1936. On Pincus, see Marks 2001, Speroff 2009, Franklin 2013: 131–43.

[16] Pincus 1936: 62.

the Columbia Fly Room.[17] With the elaboration of Morgan's mapping, the emphasis on development – a prominent feature of early genetics, asking how phenotypes arise from genotypes – was receiving new attention.

Alongside *Drosophila*, the mouse was useful for developmental genetics.[18] In the 1930s, mutants that could be studied before birth were travelling across the Atlantic via a series of biologists. The most prominent and mystifying series of tailless and lethal mutations, subsequently mapped to the '*T* complex', were first described by Nadezhda Dobrovolskaya-Zavadskaya, a Russian emigré geneticist at the Institut Pasteur. In 1930, while lecturing in New York, she met Lesley Dunn at Columbia University and told him about the odd mutations, sending mice soon afterwards.[19] Dunn had been Little's peer at Harvard's Bussey Institution, where the mouse was first used for genetic studies, and while his peers subsequently embraced a wide variety of organisms, he remained a "mouser". In 1928, he inherited Morgan's position at Columbia, making mouse genetics a new staple of the institution renowned for its fly work. With another emigré, Salome Gluecksohn,[20] Dunn undertook a series of studies that tried to tie the lethality of *T* genes at embryonic stages. Gluecksohn, a German Jewish woman, had trained with the eminent embryologist Hans Spemann at the University of Freiburg and fled Nazi Germany in 1933. With Dunn, she proposed to answer the pertinent embryological question – that of induction – with the very genetic tools that Spemann had dismissed. In 1938, she published her first paper on the *T* mutations in *Genetics*. Even though it was not the first publication to deal with the genetics of the *T* locus, nor the first to show their embryonic effect, it explicitly addressed disciplinary concerns and heralded an integrated approach to mouse development.

Mouse developmental work attracted a few more geneticists in the 1940s, among them another German Jew fleeing National Socialism, Hans Grüneberg, who had found refuge at University College, London (UCL). His choice of the organism was also accidental – Grüneberg had trained as a

---

[17] Kohler 1994

[18] On the early history of *Drosophila* development genetics, see Ibid.: 208–33

[19] Löwy & Gaudillière 1998a, Gaudillière & Löwy 2003b, Gaudillière 2001, Gaudillière 2004.

[20] Her full name was Salome Gluecksohn–Schoenheimer at the time, but she is now better known as Salome Gluecksohn-Waelsch, a surname she adopted after her second marriage. See Zuckerman, et al. 1991, Silver 2008, Gilbert 2005, Gilbert & Rader 2001.

Drosophila geneticist but switched organisms on his move to London, on J. B. S. Haldane's suggestion. In the war years, despite paper shortages, Grüneberg published a major monograph, *The Genetics of the Mouse*, devoting space to developmental genetic and the *T* mutations in particular.[21] The book, negotiated with Snell to avoid extensive overlaps with the Jackson handbook, was an important contribution to the field, but even before it was published Grüneberg was already in the middle of the transatlantic mouse genetics network, having been elected to the international mouse Nomenclature Committee alongside Dunn and Snell.[22]

Grüneberg, Snell and Dunn all had reservations about mouse research becoming exclusively about cancer, and stressed that the revived *Mouse Newsletter* should to incorporate broader genetic projects.[23] Dunn and Gluecksohn were also heavily involved in remodelling this publication. Founded by Little at Cold Spring Harbor in the 1920s, it was revived by Snell as *Mouse Genetic News,* a way to summarise available strains and mutations, but only two issues appeared in 1941 and 1945. Based heavily on the *Drosophila Information Service,* and responding to the demand expressed by mouse geneticists, Dunn and Gluecksohn turned it into a regular circular that encouraged the exchange of strains and techniques, and reified the dominance of Jackson as the place where all strains were held.[24] As Christopher Kelty argues, organism newsletters did more than encourage circulation – they also defined the new collective knowledge and lines of inquiry. These periodicals, aimed widely at the newly defined community, helped build disciplinary identities and open up informal exchanges beyond letter-writing. At the same time, they established new boundaries by excluding outsiders – both lay and scientific – from the network, and defined the notions of "property and propriety" when it came to speedy circulation of facts and advice, giving credit for the information submitted but also claiming communal property over the knowledge, unlike conventional publications.[25]

---

[21]Grüneberg 1943.

[22] Lyon 1990.

[23] Salome Gluecksohn-Shoenheimer (Waelsch) to Grüneberg, 16 September & 22 October 1948; PP/GRU/85/1, Hans Grüneberg Papers, The Wellcome Library, London.

[24]Rader 2004: 170.

[25] Kelty 2012a.

By 1950, interest in studying mutations in mouse embryos as well as adult animals had been firmly established among geneticists, and some of the key proponents of this research occupied strategic locations in transatlantic mouse networks. Moreover, with the expansive use of mice in studying the effects of radiation after World War II, they became widely available and attracted significant research funding. Major mouse colonies were established in biological institutions attached to experimental nuclear reactors, at Oak Ridge Laboratory in Tennessee and at the University of Edinburgh in collaboration with the MRC Radiobiology Unit in Harwell, Oxfordshire, where the project eventually moved.[26] With this expansion of mouse work, and the growing importance of genetics across the biological sciences, mouse embryology received broader attention. In the 1950s and early 1960s, this interest crystallised new questions about mouse development and encouraged work on new techniques of embryo culture and manipulation.

§2. Standards and embryos

Inbred mice produced in Jackson are a paragon of mid-twentieth-century biological standardisation, and were promoted and marketed as such. The language and practices of standardisation were convincing enough to enabled productive communication, while the uncertainty and local differences were exploited to adapt mice to new institutions and questions.[27] However, the standards of genetic purity in mouse research were never completely settled. They were renegotiated and challenged throughout the twentieth century, often by new collectives seeking to adapt existing experimental systems to new uses.[28] As this section will show, in the 1950s, opening up accepted standards of genetic purity allowed for productive exchanges among a new group of biologists whose work centred around the mouse embryo.

Despite the practices of genetic purity for which the Jackson Lab had become famous, Snell's studies of the mouse embryo relied on outbred animals – he claimed their 'hybrid vigour' made these

---

[26] On Oak Ridge, see Rader 2004: 230–49. On Harwell, see de Chadarevian 2006. The MRC Mammalain Genetics Unit at Harwell became a major site of mouse genetics and supply in the UK, and a co-publisher of the *Mouse Newsletter* with JAX. On the Edinburgh group, see also Falconer 1993.

[27] Rader 2004.

[28] Löwy & Gaudillière 1998a.

embryos more robust to the sectioning and preparation techniques. The idea of hybrid vigour – that organisms bred from distant strains were healthier and better adapted – has a long history in breeding and the study of heredity, but as the focus on standardising animals for disease research overtook hybridisation agendas, pure lines became the dominant instrument of mammalian genetics.[29] However, further explorations of this phenomenon, also known as heterosis, continued, notably by Snell, who published a review of human heterosis in 1951, using the mixed ancestry of American luminaries to make his case.[30]

The hybrid vigour of the recalcitrant mouse embryos challenged the standardisation practices of mouse genetics. However, in the 1950s a loose group of researchers, most of them British, emphasised the importance of maternal effects on the phenotype to raise the profile of developmental genetics and propose alternative means of controlling variation.[31] In the 1950s, Hans Grüneberg conducted an extended series of genetic experiments on skeletal development. His results suggested that the supposedly 'pure' inbred mice showed striking variation in number of vertebrae and when these formed during development. Grüneberg's vocal argument and his position in genetic networks – British and global – was recruited by the MRC Laboratory Animal Bureau to make a case for establishing laboratory animal science as an international discipline. If the mice supplied to researchers in great numbers were not uniform, and the problems did not reside entirely with husbandry and disease management, a new kind of expertise was required.[32]

The issue was followed up by several younger biologists: Anne McLaren, her husband Donald Michie (Fig. 1-2), and John Biggers. In 1954, *Nature* published a number of their letters and brief papers that questioned the physiological homogeneity of inbred lines.[33] Backed by Grüneberg's more extensive article in the journal, these pieces claimed an extensive variation within inbred

---

[29] Müller-Wille 2007, Müller-Wille & Rheinberger 2012: 127–60, Bonneuil 2008.

[30] The work on heterosis received high profile shortly after the war and coincided with international critiques of scientific racism, epitomised in the 1951 UNESCO statement on race – see Brattain 2007, Bangham 2013: Chapter 6. The cultural and political dimensions of the work discussed in this section require further investigation.

[31] On different strategies of dealing with variation in the laboratory, see Geison & Laubichler 2001, Leonelli, Ramsden, Nelson & Ankeny Forthcoming, 2014.

[32] Kirk 2010

[33] McLaren & Michie 1954, Grüneberg 1954, Biggers & Claringbold 1954

Fig. 1-2. Anne McLaren and Donald Michie, on a laboratory visit in Prague, 1956.

Courtesy of Jonathan Michie.

strains in a number of physiological traits beyond skeletal development, for instance in their reaction to anaesthetics. Hybrid mice produced by crossing two inbred strains were offered as a possible solution and a better experimental tool for physiological work. This was not equivalent to using outbred animals – the first generation or F_1 hybrids were valued in particular, while subsequent generations of hybrids showed more variation.[34] This solution did not challenge the possibility of genetic standardisation per se, but rather sought to improve the existing practices for different kinds of experiments, providing ways to control variation for different experimental designs.

McLaren had trained in Zoology at Oxford and went on to complete her PhD with Peter Medawar at UCL, working on rabbit genetics and murine viruses. Michie had had a fascinating career as a coder at Bletchley Park during the war, and afterwards moved on to study mammalian genetics at Oxford, before returning to artificial intelligence research in Edinburgh later in his career. Biggers, a British-born physiologist, had worked on sex hormones in Sydney, and was introduced to

[34] Snell 1951: 333, McLaren & Michie 1955

McLaren and Michie by Grüneberg at his UCL office shortly after the articles appeared. By that point, the couple had moved from UCL to the Royal Veterinary College in Camden Town, London, where more space was available for their mouse colonies in the 'canine block'. On his visit, Biggers was invited to take up a position there, which he accepted. They would work next to each other, to open up the early mouse embryo for culture.[35]

The problem with embryo culture largely lay with the use of media that had been borrowed from tissue culture studies. Rabbit embryos, surrounded by a mucous membrane unlike most mammals, had been cultured successfully starting with Walter Heape's 1890–91 experiments in Cambridge.[36] In mice, several attempts were performed at Jackson, embedded in genetic studies. Elizabeth Fekete, who had helped Snell with the embryology chapter of the Jackson handbook, worked with C. C. Little on transplanting mouse embryos in the 1940s. Using Locke's solution, a physiological medium containing salts and glucose, Fekete moved early mouse embryos between the more and less cancer-prone strains to study maternal effects on tumour incidence.[37]

Subsequently, as her career blossomed, McLaren often fashioned herself as a geneticist who became fascinated by the environmental effects that the mammalian embryo faced in the uterus, and she worked extensively with Biggers on embryo culture and observing the variation within genetically bred mice. While the experiments were largely on the early embryos, the importance of genetic questions allowed her to defend the mouse, an organism in which she had consistently invested as the right tool for the job. McLaren, Michie and Biggers relied on a new medium published in 1956 by Wesley Whitten at the Australian National University in Canberra, who had attempted to culture mouse embryos *in vitro*. Replacing the egg elements with bovine serum albumin, a protein readily available from the meatpacking industry, Whitten cultured an 8-cell embryo to blastocyst, and a year later, by replacing calcium chloride with lactate, reported that an even earlier 2-cell embryo could be cultured to the blastocyst stage.[38] McLaren and Biggers used

[35] Biggers 2001.

[36] Franklin 2013: 126–9.

[37] Fekete & Little 1942, Fekete 1947.

[38] Whitten 1956, 1957. For a comprehensive review of mammalian egg culture attempts before 1960, see Austin 1961:109–48.

this medium to culture 8-cell embryos to blastocyst and implant them into a surrogate mother of a different strain, resulting in the birth of live mice.

These claims to embryo transfer were not entirely new. Beyond Walter Heape's 1891 paper, multiple attempts had been publicised, most notably Pincus's work with the rabbit, claiming *in vitro* fertilisation, embryo transfer and artificial parthenogenesis – initiation of development without fertilisation. As multiple claims co-existed and were met with publicity, doubt and failures to replicate the experiments, a set of criteria was being articulated in response.[39] Moreover, claims for the mouse embryo transfer had been made by Fekete, and the geneticist Alan Beatty in Edinburgh even produced a film demonstrating eggs could be transplanted through the cervix and mice born as a result of the procedure.[40] Culturing embryos was a key claim for McLaren and Biggers, as was showing that the medium did not interfere with development so live mice could be born. To rule out the pups coming from the surrogate mother, McLaren and Biggers used a genetic marker as they relied on the coat colour of newborn mice.

The new experiments attracted some media attention. On 6 October 1958, just over a week after a brief letter in *Nature* announced the results, a column in *The Daily Telegraph* described the new animals as 'Brave New Mice'.[41]As Biggers recalled, the publicity raised some academic eyebrows, but also enabled the scientists to promote their work and delineate its implications though more legitimate means. However, it was by no means the first time they had appealed to broader audiences. With McLaren, Biggers contributed a chapter to a volume in Penguin's *New Biology* series, highlighting the work on hybridisation for physiological research.[42] Michie was also a contributor to a fancy animal publication and penned articles for boys on how to keep fancy mice.[43]

---

[39] Franklin 2013: 136–43.

[40] Fekete & Little 1942. Alan Beatty's video was called *Inovulation*. See Edwards & Steptoe 1980:20–1, Franklin 2013: 145.

[41] Smith 1958, reproduced in Biggers 2001.

[42] McLaren & Michie 1955

[43] The 1961 articles on "Keeping Mice" in *The Daily Worker* are reprinted in Srinivasan 2009.

McLaren and Biggers were approached by the editor of *Discovery*, a London popular science periodical, to write about their work.[44] Their piece described the development of the early mammalian embryos and the experiments, and discussed the implications. Biggers and McLaren engaged with the newspaper coverage by finishing their article with a provocative subheading, 'Brave New World', where they distanced their work from any human extensions reminiscent of Aldous Huxley's novel – a long-standing cultural reference that had also followed Pincus.[45] Instead, they emphasised the utility of culturing mouse embryos to foster exchange of laboratory animals and possible agricultural uses. McLaren was funded by the Agricultural Research Council, so she was eager to argue for the relevance of her mouse work and showcase the utility of Whitten's medium. The scientists suggested embryos could be stored and exchanged in lightly-refrigerated culture media, and cited their successful posting of embryos to the Cambridge School of Agriculture.[46] The mobility of embryos, fragile and recalcitrant to culture, was a desired feature that could build on the extensive exchanges of mouse strains among geneticists.

The interest in circulating embryos reflected a commitment to reinforcing the new network of researchers exploring mammalian embryos, and McLaren, Biggers and to a lesser extent Grüneberg participated in interdisciplinary conversations in Britain and the USA. Other biologists in Britain, most of them with a strong genetic background, were moving to work with mouse embryos. Thus, the human IVF pioneer Robert Edwards started his career as a mouse geneticist at the Institute for Animal Genetics at the University of Edinburgh, working on inducing ovulation with hormones – as he later claimed, to adapt the animals to his own social timetable and not have to wait for them to breed at night.[47]

Moreover, discussions on the role of maternal effects in development were happening in the USA, with the Jackson Lab playing a central role and expanding collaborations with embryologists, even though funders who wanted to push the Lab into providing mice for large-scale cancer re-

---

[44] Biggers & McLaren 1958

[45] Turney 1998, Franklin 2013: 142.

[46] On the connections between reproductive studies and agriculture, see Clarke 2007, .

[47] Edwards & Steptoe 1980: 28.

search dismissed this line of investigation.[48] One of the converts to the mouse, attracted by the genetic knowledge it could offer, was Beatrice Mintz. Like Gluecksohn, Mintz was a classically trained embryologist who shifted her focus to mice in the 1950s. She trained at the University of Iowa with Emil Witschi, a German emigre amphibian embryologist with an interest in germ cell differentiation. In 1946, Mintz accepted an assistant professorship at the University of Chicago, where she worked with frogs, salamanders, leghorn fowl and chicks. In the early 1950s, her move to mice was cemented when she started a collaboration with Elizabeth 'Tibby' Russell at the Jackson, aiming to trace the origin of germ cells by genetic tools. Their work, first presented in 1955 and published in full in 1957, showed a new kind of union between embryological and genetic approaches in the mouse. If the tradition of developmental genetics tended to use mouse embryos to answer questions about genes and their effects, the Russell-Mintz paper also used the alleles in the *W* (white-spotted) locus to trace the fate of germ cells.[49]

This work relied on painstaking serial sections and staining of the embryos, with the assistance of two technicians. However, with the availability of culture media, Mintz moved her focus onto the living mouse embryo. In 1960, she was offered a position at the Institute for Cancer Research in Fox Chase, a suburb of Philadelphia, where she gladly moved to avoid undergraduate teaching.[50] The institution was a prime place where investigations into embryology were believed to complement cancer research.[51] In charge of a small laboratory, Mintz worked on culturing the early embryo and removing the zona pellucida, a thick membrane surrounding the embryo and keeping cells together until blastulation.

The considerable number of high-profile women in twentieth-century embryology has been noted, and the mouse tended to be the organism most of them studied.[52] Gluecksohn, McLaren

---

[48] Gaudillière 2004: 173.

[49] Mintz & Russell 1957.

[50] Mintz to Grüneberg, 28 December 1959; Grüneberg to Mintz, 4 January 1960 ("It is wonderful news that you are leaving this horrible place for a laboratory in which you can do really useful work instead of having to devote most of your time to dull routine teaching."). PP/GRU/54, Hans Grüneberg papers, Wellcome Library.

[51] On the history of the Fox Chase Institute for Cancer Research, see Crowe 2014 and the official website timeline, https://www.fccc.edu/whyChoose/centuryExcellence/Timeline/

[52] Keller 1995, Gilbert & Rader 2001.

and Mintz, and to a lesser extent Fekete, represented an early generation of eminent scholars and leaders in the field they were creating. It is possible, though debated, that these pioneering women attracted more female scholars in the 1960s and 70s.[53] Mammalian embryology, associated with a woman's body but without the controversial aspects of men-dominated reproductive sciences, may have been viewed as an appropriate trajectory for a middle-class woman.[54] The laborious, protracted and unpredictable practice of embryology made it a less attractive subject unlikely to bring immediate reputational gains. The disciplinary marginality of mouse work is thus a more plausible explanation, as many women found work in new and obscure fields earlier in the twentieth century, for instance plant and fly genetics.[55]

By 1960, the mouse embryo had moved from a marginal curiosity to one of the promising objects of investigation. The development of culture techniques and the new promise of manipulation that they offered played a significant part in this transition. However, similar high-profile experiments were made with other mammalian species, notably the rabbit. In 1959, Min Chueh Chang, a former colleague of Pincus, published an account of *in vitro* fertilisation in rabbit egg, his account gaining more traction than Pincus' original 1935 claim that had not been replicated. What placed the mouse in an advantageous position was its status as a genetic animal and mammal, and an ability to bring researchers across disciplinary boundaries. If the rabbit was firmly a reproductive animal, the mouse had an established place in genetics, teratology and cancer research. Despite the investment into rabbits, their embryos proved much more resilient to the kind of manipulations that new culture media allowed in the 1960s, pushing the mouse further towards being the mammal of choice for experimental embryology. Finally, with the expansion of large-scale work on the effects of radiation, these rodents were widely available and cheap, with most major biomedical research institutions eager to invest into a mouse facility.

Through engagement with environmental effects on the organism and exploration of culture media, a group of embryologists and reproductive physiologists emphasised the interest mouse em-

---

[53] Papaioannou 1999. But see Zuckerman, Cole & Bruer 1991.

[54] Gilbert & Rader 2001

[55] Richmond 2001, Stamhuis & Monsen 2007, Dietrich & Tambasco 2007.

bryo could pose to geneticists and reproductive physiologists. Challenges to standardisation narratives of the large-scale screening genetics enabled this group to develop a strong published voice that also spread beyond the professional periodicals into the press. Similarly, using genetics to approach development by moving beyond treating the mouse embryos as phenotypes of specific mutations and promising manipulation techniques enabled this group to raise the status of their animal among embryologists. Furthermore, in the 1960s new dynamic networks of researchers working with mouse embryos were established. These incorporated reproductive physiologists, embryologists and some curious geneticists, and as I will argue below, they were successful at incorporating the mouse as a key mammal under the ultra-disciplinary banner of developmental biology.

§3. Manipulating development

As Mintz was beginning her collaboration with Elizabeth Russell, she edited a short volume dedicated to the *Environmental Influences on Prenatal Development*, a summary of papers and conversations at a Jackson Lab conference.[56] This was one of numerous meetings on 'developmental biology' in the summer of 1956. The more extensive and generalist first International Congress on Developmental Biology was held at Brown University, and the Jackson Lab hosted another meeting, 'Immunology and Development'. These were sponsored by the US National Science Foundation (NSF) and represented a new disciplinary alignment in the funding of biomedical sciences in the USA, and the study of embryos in particular. As some projects of embryology – in particular, the organiser as a source of induction – were seen to be in decline or replaced by biochemical investigations, 'developmental biology' came to represent a new direction of research, and a disciplinary identity that researchers chose to adopt depending on context and audience.[57]

Jane Oppenheimer's lecture at the 1966 meeting of the Society for Developmental Biology (which had only just changed its name from Society for the Study of Growth and Development) placed the origins of this field in the Society's symposia that began in 1939. These became an important space

[56] Mintz 1958.

[57] Hopwood 2009, Maienschein 2014: 107–9, Crowe, Dietrich, Alomepe, Antrim, ByrneSim & He Under review.

for interdisciplinary communication where embryological agendas were expanded to include methods and questions from genetics, evolution, biochemistry, endocrinology and general physiology.[58] However, while there was considerable talk of development and differentiation in these meetings, the category of 'developmental biology' was not in wide use until the 1960s; no textbooks and handbooks treated the subject, and among the few relevant journals, *Growth* changed its name to *Developmental Biology* in 1959. Wider recognition came even later: the first graduate course to use the label was offered in 1972.[59]

At the level of practice, the story is more complex. Thus, for Donald Brown, one of the key players of molecular studies of development, the field "came of age" only in 1990s with the molecular techniques and interpretations, of which transgenic mice were a significant example.[60] While "coming of age" narratives are a common trope in negotiating disciplinary histories, Brown's lecture offers an interesting counterpoint to more self-congratulatory accounts. Stating that "[d]evelopmental biology is above all a set of questions. It is not a discipline", Brown argued that "from the 1930s into the 1960s developmental biology was isolated, with its own theories, methods, and even experimental animals… a third-world scientific community, blissfully doing our thing in isolation."[61]

However, long before textbooks on the subject were published and societies updated their names, developmental biology became a category that defined science funding in the USA. The NSF, established in 1950 as the American federal government decided to invest heavily into the life sciences after the war, listed 'Developmental Biology' as one of its major funding categories. It incorporated "growth and differentiation, reproduction, fertilization, growth and reproduction of subcellular units and of cells, morphogenesis, regeneration, senescence", and was to correspond with the traditional disciplines of "embryology, experimental morphology, gerontology, oncology".[62] This vision of 'developmental biology' came from Paul Weiss, a co-founder of the Society for De-

[58] Oppenheimer 1966.

[59] Keller 1995.

[60] Brown 1993.

[61] Ibid.: 1–2.

[62] Consolazio & Green 1956: 523.

velopment and Growth and editor of *Growth,* who proposed revising funding areas so as to emphasise the unity of biology, arguing that the old categories entrenched irrelevant boundaries between plants, animals and microorganisms and were no longer helpful.[63] As Toby Appel shows, this bold 'one biology' agenda impressed the NSF management and allowed them to separate their scope from the overlapping domains of the NIH.[64]

Beyond US funding arrangements and a new label, globally, the research under the rubric of developmental biology expanded and diversified in the late 1950s.[65] By bringing together a diverse group of biologists working with a variety of experimental systems, from mathematical modelling and viruses to humans, these changes in the networks of research represented new opportunities in the species politics of embryology. Even at the first Symposium on Development and Growth, the fly geneticist Curt Stern juxtaposed his animal of choice to the amphibian embryo:

> There have been many who complained, "If only the amphibians, ideal for developmental studies, were more easily accessible from the genetic angle!" and who added, "if only *Drosophila*, revealer of genetic secrets, could be treated in the embryologists' fashion".[66]

Ambitiously, Stern argued that those voices had finally been silenced, showing how his work on mosaicism in the fly could combine embryological and genetic tools. The emphasis on integrating the different approaches in one species persisted as developmental biology created a space where disciplinary crossings were becoming more straightforward. The mouse had an established genetic status, which set it aside from other mammals. With the more straightforward culture media and a growing interest from embryologists, manipulation took centre stage in the 1960s.

In Britain, funding models were not at stake for these changes, but similar discussions were taking place, driven in part by significant transatlantic communication as well as stronger links with continental institutions. The informal London Embryologists' Club founded in 1948 had explored

---

[63] The other categories of biological funding included molecular, genetic, regulatory, structural, environmental and systematic biologies, as well as psychobiology.

[64] Appel 2000: 63–67.

[65] This is reflected in the statistical analysis of projects listed in *GEIS* and categories used to classify them, with particular focus on 1959–1961, in Crowe et al. Under review.

[66] Stern 1940: 19.

the possibility of experimental embryology in organisms beyond the amphibians.[67] From its early days, it built links with the private Hubrecht Laboratory in the Netherlands associated with Institut Internationale d'Embryologie, publisher of *GEIS*. With theoretically-inclined embryologists such as Joseph Needham and C. H. Waddington, the Club was engaging with diverse topics, including a meeting on "Development and DNA" in 1960. In 1964, the body went national, becoming the Society for Developmental Biology, adding British to the title after the U.S. based Society for the Study of Growth and Development took the same name in 1965.[68]

McLaren was an active member of the London Club. In 1959, after failing to secure funding for an ARC research unit on reproduction at the Royal Veterinary College, McLaren moved to C. H. Waddington's Institute for Animal Genetics in Edinburgh, while Biggers secured a position at the Wistar Institute and a parallel professorship in reproductive sciences at the University of Pennsylvania. There, he focused on making robust standard media that could be easily made in any laboratory. One of his first graduate students was Ralph Brinster who had trained as a veterinary physician at Penn. His project involved defining a medium chemically, following Whitten, by avoiding biologically-derived reagents such as blood serum or egg yolk. Brinster's choice of mice was not self-evident, but his experiments required large quantities, and mice by that point were cheaper and widely available, and Biggers had expertise in using them. In discussing the properties of the early rabbit embryo, Brinster highlighted how the thick mucinous coat that surrounds the egg, while probably responsible for the robustness of the rabbit embryos in culture, made it less analogous to humans and domestic animals, whose embryos had a thin clear coat like mice.[69]

The group published the new medium in 1962 and 1963, with the chemical definition as its key selling point. A standard medium would enable embryo culture to become predictable and attract new researchers to work on mice. Brinster argued that although mammalian embryos had been cultured for decades, the new standard could remove the uncertainties and local variation involved in embryo work. As a testament to the efficiency of his technique, Brinster could demon-

---

[67] The second meeting was dedicated to "The limitations of amphibian material in experimental embryology", and its first president, J. P. Hill, was a mammalian embryologist.

[68] Slack 2000.

[69] Brinster 1964: 3. See also Brinster & Arechaga 1998.

strate an embryo developing from the two-cell stage to the blastocyst, achieving the notoriously difficult early divisions *in vitro*. Moreover, the chemically defined medium allowed an in-depth biochemical study of the needs of developing embryos, which Brinster pursued in the years following his PhD.

Yet even before the wide spread of Brinster's medium, as it was called, the approaches to culture resulted in a new kind of manipulation to make genetically mosaic mice. In 1961, a Polish embryologist, Andrzej Krzysztof Tarkowski,[70] reported that early mouse embryos could be combined once the zona pellucida – the membrane that holds the early embryo together – had been removed. Relying on a scientific exchange grant from the Rockefeller Foundation that sought to strengthen scientific connections across the Iron Curtain, Tarkowski did most of this work at the University College of North Wales (now Bangor University). Despite his permanent position in Warsaw, Tarkowski came to Britain often and was well placed in the country's community of embryologists and reproductive physiologists.[71]

Tarkowski relied on squeezing the embryo though a carefully sized pipette to remove the zona pellucida. Unbeknownst to Tarkowski, Mintz was also working on culturing the early mouse embryo and removing the zona at Fox Chase. Her method, however, relied on the enzyme mixture pronase rather than mechanical manipulation, and where Tarkowski could report only foetuses with clear mosaicism, Mintz had adult mice with the characteristic blotchy coat-colour pattern to show (Fig. 1-3). Both announced the results at the 1962 meeting of the American Society of Zoologists. Like McLaren and Biggers, Mintz and Tarkowski both recruited the rhetoric of manipulation as something that had been lacking but could then open mammals up to proper embryology. Their parallel discovery is well recorded and accepted, yet Mintz's more adaptable pronase method was more widely used as the production of fused embryos continued. The naming patterns, however, reflect some of the tendencies in credit allocation. For Mintz, these embryos were genetic mosaics and she used the term *allophenic* to stress the different cellular phenotypes that could be linked to genotypes. Tarkowski, by contrast, called the mice *chimaeric*, building on a rec-

[70] Tarkowski was known as Krzysztof to his colleagues abroad, but is usually referred to by his first name in historical accounts.

[71] Tarkowski 1961; Tarkowski 1998, Maleszewski & Tarkowski 2008, Graham 2008, Brandt 2012.

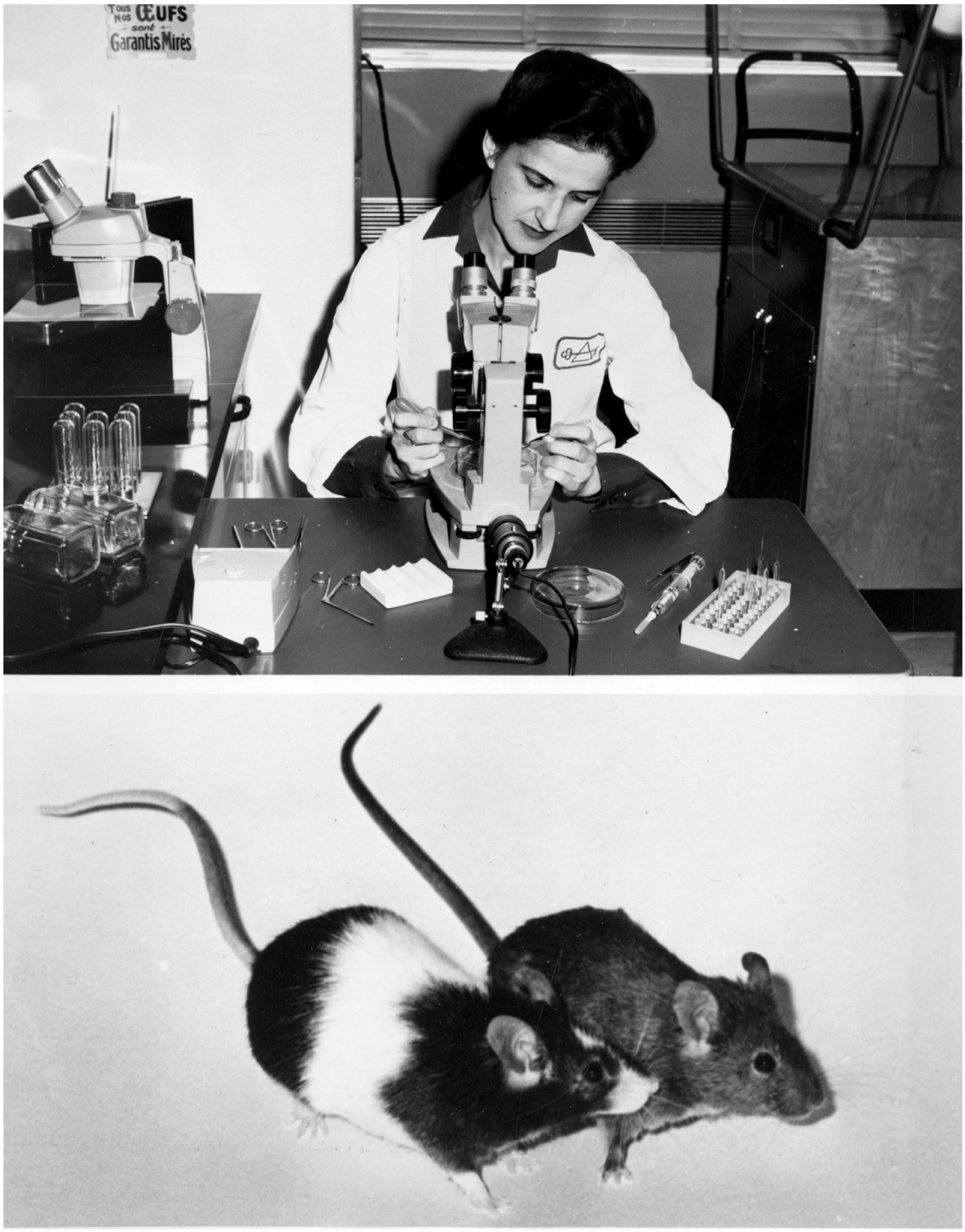


Fig. 1-3. Above, Beatrice Mintz at a dissection microscope at the Institute for Cancer Research, Fox Chase. The poster at the back reads, in French, "All our eggs are guaranteed to have been candled [i.e. inspected for embryonic viability]". Below, an allophenic or chimaeric mouse with patches of black and white fur from different genetic lineages, next to a control animal. No date, likely c. 1965.

ognised use in hybrid studies that referred to the Greek monster – a term Mintz detested. In fact, in a 1974 review of the field, she argued 'chimaera' was a "metaphor inapt for harmoniously integrated, nonfictional, genotypic mosaics. According to the ancient Greeks, Bellerophon overcame and slew the chimera; may it rest in peace."[72] However, *chimaera* stuck despite Mintz's insistence on using *allophenic* – for convenience, as well as because of Tarkowski's stronger links with mouse embryologists, still concentrated in Britain.

The new kinds of experiment performed on mouse embryos in the early 1960s were localised in a few laboratories in Britain and the USA, but the disciplinary identities of the players were fluid. McLaren referred to herself as a geneticist who became a reproductive physiologist through an interest in the effects of maternal environment on the developing embryo. Mintz was an experimental embryologist with a keen interest in using genes as instruments for understanding the mechanics of developmental events. On his move to Philadelphia, Biggers was appointed Professor of Reproduction, and Brinster was a reproductive physiologist who maintained his veterinary roots. Between 1955 and 1965, most papers appeared in journals with general scope: the British *Nature,* as well as occasional papers in *Science;* the *Journal of Reproduction and Fertility* carried a number of articles from Biggers and McLaren, but the *Journal of Experimental Zoology* was by far the dominant specialist publication.

Conferences at which these scientists presented can give a better idea of the work that went into building productive communication, drawing from the dramatic interest in the problems of overpopulation and fertility. The first meeting to attract an illustrious set of speakers working explicitly on early mammalian development took place in London in 1963. Titled 'Preimplantation Stages of Pregnancy', it was envisioned and seen through by Biggers and McLaren on her visit to Philadelphia. By aligning mammalian embryology with problems of human fertility, and couching the meeting in terms of pregnancy, McLaren secured funding from the Ciba Foundation, the charity arm of the Swiss pharmaceutical company that had an office in London and funded small conferences. While some physicians who reviewed the published proceedings commented on the lack of immediate clinical relevance, they and the more laboratory-minded reviewers deemed the

[72] Mintz 1974: 411.

event and its published proceedings a success. The meeting has also been lauded as a landmark in actors' histories.[73] C. H. Waddington chaired, and as he observed, McLaren and Biggers had "brought together quite an army of gladiators."[74] Gregory Pincus and Colin "Bunny" Austin from Cambridge were also present, alongside Brinster, Tarkowski and Mintz.[75]

The Ciba conference brought together diverse perspectives on the mammalian embryo. Already, most of the work presented was on mice. Of 16 talks, nine were on the mouse; two on the rabbit; one on the rat; one talk juxtaposed mice and rats, while three more were comparative studies of several mammalian species. Mintz and Tarkowski announced their early results with chimeras. Brinster, as well as Mintz in her second paper, also reported the progress in defining the biochemical requirements for the early embryo and stages of nucleic acid production after fertilisation. While the general discussion touched on the need to improve culture methods for other species, including admissions of failure to make hamster and rat embryos develop in culture, the mouse took centre stage. The major issue was the challenge of culturing embryos at the earliest stages through the first division of a fertilised egg. In existing media, it would undergo the first cleavage, but then slowly deteriorate, even if a two-cell embryo could develop to blastocyst. The process, eventually labelled 'two-cell block', represented a gap in the desired ability to culture the early embryo from fertilisation to implantation.

As Sarah Franklin has argued, the ethos of experimental embryology lies with manipulation and control over living objects through tools, and an embryologist explores and expands the frontier as a toolmaker.[76] New methods were consistently developed and updated, but were often difficult to replicate. Local instruments were improvised at the bench, new media prepared and tested. Yet with increased communication around the mouse embryo, existing techniques and instrument designs were being exchanged as new ones were constantly designed. Thus, Mintz's pronase method was adopted by several researchers, notably in Bigger's laboratory at the University of

[73] Biggers 2001, McLaren 1996.

[74] Wolstenholme & O'Connor 1965: 1.

[75] Whitten was also invited, but could not attend due to the lack of funds to pay for his travels from Australia. Biggers 2001.

[76] Franklin 2013: 103–11.

Pennsylvania, and there were several fraught attempts to extend its use to other organisms. Both Mintz and Tarkowski relied on local versions of the Whitten medium with ovalbumin, and Mintz also used a biological medium with foetal calf serum for some of her work. While 'chemical definition' made preparation more straightforward, it did not do away with local difficulties of embryo culture. Not every batch seemed to work, or work in the same way, and various explanations were employed to deal with the recalcitrance of the embryo. Thus, the source of water was commonly invoked, and Bar Harbor and Oxford water seemed particularly favourable.[77] Through his career, Tarkowski would request portions of BMOC (one of Brinster's media), alongside a great number of biochemicals, from Oxford colleagues for his underfunded Warsaw laboratory.[78]

With a growing range of questions, new methods to make chimeric mice were being attempted. Thus, in 1968, Richard Gardner's group in Oxford published a method to make chimeras at the later blastocyst stage (see Fig. i, p. vii), by replacing the inner cell mass through a micropipette. Other forms of micromanipulation were devised. Teh Ping Lin used micropipettes to inject inert substances into the mouse egg in the anatomy department of the University of California, San Francisco. Reporting this work in 1966, Lin suggested that the ability to inject fertilised mouse eggs brought the animal closer to the investigations possible in amphibia, with the added advantage of having standard genetic lines.[79]

As techniques were accumulated and adopted by scientists working on mammalian development, they began to be codified in handbooks. The first manual of experimental technique under the explicit *developmental biology* label was the 1967 *Methods in Developmental Biology*.[80] The book was in two parts, the first outlining the practicalities of maintaining specific experimental animals, and the second describing techniques. The mouse was listed first and was the only mammal. A technique chapter dedicated to manipulation of mammalian eggs was written by Mintz, and she made clear that for her 'mammalian' meant 'murine':

---

[77] Jaenisch interview; T. Wagner interview.

[78] Graham 2008; Richard Gardner, talk at the IVF Histories and Cultures workshop, 23 June 2014, Cambridge, UK.

[79] Lin 1966. A more detailed discussion of the history of micromanipulation is offered in Chapter 3 §3.

[80] Wilt & Wessels 1967.

> And, while interesting mutations are increasingly coming to light in a number of vertebrate species, the mouse at present far outranks all other vertebrates in the total potentialities which it offers for genetic analysis...
>
> Among laboratory mammals, the mouse combines the largest number of advantages for the study of development. It is, as already indicated, excellent material from a genetic point of view; it is easily maintained and bred; and its embryos can now be grown *in vitro* from two-cell stage to blastocyst, and during part of the postimplantation period.[81]

The chapter covered culture techniques, biochemical requirements of the embryo, ways of making mosaic mice and the recent experiments by Lin. Overall, the emphasis on the mouse embedded its status as the most promising mammal with which to ask developmental questions. While much reproductive work continued on the rabbit, manipulation proved difficult. The early rabbit embryo was easier to culture and grew much larger than the mouse, reaching 3mm at the blastocyst stage, but chimeric embryos failed to develop, which was subsequently explained by the rapid expansion of the blastocyst and inability for the rabbit embryo to implant without the zona.[82] With mice increasingly available for large-scale genetic tests, complete with extensive husbandry know-how, their use was also more economical.

In the early 1960s, the scope and focus of embryology were in transition and as new scientists were entering the field, the choice of organism was open for renegotiation. While other vertebrate species still dominated the field, the genetic status of mice, their availability and the new techniques for culture and manipulation made them an attractive option for new work, especially among mammals. In the late 1960s, with the growing engagement of molecular biologists in discussions about development, mice received a further boost.

§4. Molecular promises

As embryology was increasingly labelled developmental biology, more and more molecular biologists participated in debates concerning higher organisms. While the field diversified and ex-

[81] Mintz 1967: 379.

[82] Chimeric rabbits made by blastocyst microinjection were reported in 1974. See Gardner & Munro 1974, McLaren 1976: 15, Papaioannou & Dieterlen-Lièvre 1984.

panded before significant molecularisation had taken place, the growing dominance of molecular approaches helped give developmental biology a coherent identity.[83] In the process, the range of species used to study development shifted. New organisms such as the nematode worm *Caenorhabditis elegans* entered laboratories, while others like the chick or the rabbit were becoming less relevant. The sustained interest of mouse embryologists and the new availability of cell lines gave the mouse the potential to combine not only genetic, but also molecular analysis with answering questions about mammalian – and therefore human – development. While several laboratories adopted mice – most famously François Jacob at the Institut Pasteur – in the late 1960s, molecular thinking about mouse embryos mostly happened at cross-disciplinary conferences and in speculative publications: lectures, reviews and introductions to new journals. However, it was by no means limited to them. Discussions about cloning, the future of human genetics and engineering the germline spread widely beyond scientific audiences.[84]

As several historians have argued, the discovery of the DNA structure in 1953 was less significant to 1950s biology than retrospective accounts would have it, notably James Watson's *The Double Helix*.[85] It was the expansive research on the genetic code – how the DNA sequence corresponds to proteins – that pushed DNA centre-stage in the 1960s. The focus on the regulation of genes was a dominant feature of high-profile research, with the '*lac* operon' elaborated by Jacob and Jacques Monod showing how bacterial genes respond to changes in the level of the protein for which they code.[86] Having 'solved' the regulation of phage genes and the *lac* operon of *E. coli*, some molecular biologists argued that the time was ripe for expanding their focus to higher organisms.[87] A crucial difference was multicellularity and the mechanisms that regulate the growth of an embryo from a cell to an organism – the question of development.

---

[83] Burian & Thieffry 2000, de Chadarevian 2000, Morange 2000. The argument that diversification of developmental biology predated wide spread of molecular techniques is made in Crowe, et al. Under review.

[84] Kevles 1985: 251–68, Bud 1993: 163–88, Nelkin & Lindee 1995: 19–37, Haran, et al. 2007, Brandt 2013.

[85] Abir-Am 1985, de Chadarevian 2002: 164–98, de Chadarevian 2003.

[86] Kay 2000: 193–234.

[87] Morange 1997b.

Long before actively pursuing higher organism research at the bench, molecular biologists entered the conversation about the role of genes and gene expression in regulating differentiation. The Symposia on Development and Growth had offered some space for biochemical interpretations of differentiation, and debates about the roles of enzymes in the cytoplasm and genes in the nucleus reprised older discussions in embryology and genetics. Both biochemists working with microorganisms such as Sol Spiegelman and theoretically minded embryologists such as C. H. Waddington readily embraced the new ways of discussing problems in terms of enzymes.[88] Furthermore, with the experimentally-supported consensus that genes do not change between cells and therefore their activity must be regulated during development, the language of genetic programmes, building on the earlier ideas of 'gene action' replaced the search for the chemical nature of the organiser as a key priority. With the elaboration of the mechanisms and principles of gene regulation in bacteria and viruses, and theoretical constructs inspired by information science – if not straightforwardly derived from it, – similar frameworks were often fitted onto the higher animals.

Thus, as Lily Kay shows, Marshall Nirenberg had in mind grand questions of fertilisation, differentiation and the role of genes in development as he was working on unravelling the genetic code in *E. coli*.[89] Similar questions drove the new stars of molecular biology at the Institut Pasteur, where the iconic *lac* operon model was elaborated in the late 1950s. The *lac* operon referred to a series of genes controlled by a repressor, a DNA-binding protein that blocked transcription of enzyme genes when the substrate (lactose) was unavailable.[90] At the 1961 Cold Spring Harbor Symposium on gene expression, Francois Jacob, Monod and André Lwoff delivered a series of influential papers on messenger RNA, gene expression and possible models of control of differentiation in higher organisms, interpolating from bacterial work. These speculative ventures into multicellular organisms were welcomed by some conference organisers who often invited a token molecular biologist to illuminate discussion on development. Thus, Jacob and Monod attended the meeting of the Society for Differentiation and Growth in 1963. In 1964, a conference on The Role of

[88] Gilbert 1996.

[89] Kay 2000.

[90] On Jacob, Monod and the *lac* operon, see e.g. Morange 1998: 150–63; 2005.

Genes in Development in New York featured wide-ranging discussions that incorporated the new knowledge of DNA, RNA and proteins, as well as the informatic metaphor. The meeting was sponsored by the New York Heart Foundation – a surprising patron – but as its president noted in the proceedings published in the *Journal of Experimental Zoology*, the topic's tenuous relevance to heart disease "has been of little concern to the New York Heart Association. It is our conviction that the most important advances in biological and medical science will come from investigations which are not too narrowly conceived in terms of current notions as to the nature of disease."[91]

Mintz was present at the meeting alongside two other developmental biologists, Clement Markert and Donald Brown. Advocating wider use of the mammalian embryo, she drew on recent work to make her case:

> The mammalian embryo, though it is an object of considerable potential interest, has remained largely at the periphery of experimental investigation into problems of early development. Many practical difficulties concerning availability of material and its handling outside the maternal organism have continued to deter inquiry. Recent attempts to surmount these obstacles have begun to yield information and to disclose possibilities for further exploration.[92]

Citing accumulating evidence on DNA, RNA and protein synthesis in the early mouse embryos, Mintz placed her work on allophenic mice within the theoretical concepts of gradients and determination of cell fate.

Mintz was one of the few voices to promote the mouse from within the embryological community in the USA. However, other biologists were being convinced. When *Current Topics in Developmental Biology* was launched in 1966, to aid interdisciplinary communication among biologists,[93] the editors invited Joshua Lederberg to open the first issue. The eminent *E.coli* geneticist and recipient of the 1958 Nobel Prize claimed that:

> Right now is a particularly awkward time to frame any useful commentary on developmental biology. The field has had enough fancy; more recently its methodology has been

[91] Chasis 1964: vii.

[92] Mintz 1964: 85.

[93] Suárez-Díaz & García-Deister 2015

> under enormous pressure to accommodate the inspirations of molecular biology and the models of development that can be read into microbial genetic systems.[94]

Lederberg may have underplayed his expertise in the field by claiming his invitation stemmed from an unguarded remark that "embryology should be studied with embryos" – as opposed to elaborate quasi-developing bacterial systems. Yet he presented a bold vision for a new way of approaching the embryo, emphasising the theoretical ambiguities in classical approaches and suggesting that molecular frameworks could bring clarity:

> Despite the mechanistic flavor of the now classic work on tissue induction, embryology has historically had more than its share of mysticism, with some mysterious property of "organization" always in the background to inhibit bold experiments... For the most part, organization seems to be turning out to be quite comprehensible, even to the unaided human mind, as one more level of macromolecular chemistry.[95]

This phrase echoed another molecular biologist, Sol Spiegelman, and his frustration with the mystique of development voiced in 1958 when he had an imaginary collective embryologist exclaim, "My God, this [problem of morphogenesis] is wonderful, it is so complicated that we will never understand it."[96] For him, the solution lay not only in changing the metaphors, but also in the choice of organism. Spiegelman's proposal was thus to direct the collective effort at one organism, be it a yeast or a sea urchin.[97] Lederberg was keener to emphasise the mammals:

> If any single experimental system in developmental biology had a fraction of the convergent attention that was given the T phages, we might be more optimistic about the pace of further work, but embryology suffers from being a traditional field, and seems to need the impulse of more novelty than frog gastrulae would now offer... I have little doubt in my own mind that the mouse should be that central material, but this is a prejudice possibly based on expectations of utility from and for genetics, biochemistry, cytology, immunology, psychology, oncology, and medicine rather than on any significant personal experience. At the other pole, some very simple system like a rotifer or a nematode needs to be conventionalized...[98]

---

[94] Lederberg 1966: ix.

[95] Ibid.: ix–x.

[96] Quoted in Gilbert 1996: 115.

[97] Brown 1993.

[98] Lederberg 1966: xii.

The possible contribution of the mouse to understanding development in molecular terms was being increasingly tied to the possibility of molecular intervention. The promise of inserting genes into animals, including humans, flourished in speculative reviews, essays and speeches – a genre into which prominent scientists with established reputations could afford to venture.[99] One prominent example is Edward Tatum's 1958 Nobel lecture – he shared the prize with Lederberg – which went as far as suggesting the possible means of introducing the molecules into the genome:

> Perhaps within the lifetime of some of us here, the code of life processes tied up in the molecular structure of proteins and nucleic acids will be broken. This may permit the improvement of all living organisms by processes which we might call biological engineering.
>
> This might proceed in stages from the *in vitro* biosynthesis of better and more efficient enzymes, to the biosynthesis of the corresponding nucleic acid molecules, and to the introduction of these molecules into the genome of organisms, whether via injection, viral introduction into germ cells, or via a process analogous to transformation.[100]

Through the 1960s, the idea was promoted by Tatum and other prominent biologists, including Lederberg. Others were not as enthusiastic, however. Around 1968, a strong sense of a new "biological revolution" was gaining ground, and the future uses of envisioned technologies questioned, in the context of the strong opposition to the Vietnam War and student protest in Europe. Salvador Luria, one of the founding figures of molecular biology and an outspoken anti-war activist, published an article expressing concern about the new biology in the left-wing *The Nation* in 1969, the same year he was awarded the Nobel Prize. In the article, he called modern biology a "terrifying power", and argued for a social policy that would direct the potential application of the growing control over human heredity. As an epitome of these technologies, Luria envisioned genetic engineering of humans and other animals.

Concerns about the potential of biology – especially on the molecular and reproductive frontiers – were also expressed by science writers addressing much broader audiences. In 1968, Gordon Rat-

---

[99] For a good account of these debates, see Bud 1993.

[100] Tatum 1958. Here, t*ransformation,* a bacterial genetic term, refers to a change of a cell's phenotype by absorption of extraneous genetic material.

tray Taylor's *The Biological Time Bomb* was published in London.[101] As the title implies, the book offered an uneasy mix of hopes and fears about the biological future – from medical applications and genetic improvements to more putative discussions of mind control. Taylor was no sensationalist hack. He was educated in natural sciences and the editor of BBC science documentaries, and the book was reviewed by the likes of Robert Edwards and Waddington.[102] Published in the US next year, it was widely read on both sides of the Atlantic.[103]

In the *Biological Time Bomb,* Taylor picked up on some obscure work including experiments by Sergey Gershenzon in Soviet Ukraine, who induced mutations in *Drosophila* by bathing them in calf DNA as early as 1939. Another example was Teh Pin Lin's 1966 *Science* article on using microscopic needles to inject inert substances into mouse oocytes.[104] Lin's elaborate work received little attention and was barely cited until well into the 1970s, but Taylor saw a potential there:

> Dr Teh [sic] chose globulin as being a harmless substance... But obviously the technique, once established, will be used to introduce many other agents, in order to explore their influence on development and thus help unravel the problems of embryology. Such agents will no doubt include hormones, and substances known to have a specific effect on development, such as thalidomide, and they will undoubtedly include DNA.[105]

As molecular biologists were contemplating mouse work, the idea of inserting DNA into mammals was thus in circulation, as were visions of gene therapy or a new eugenics. They implied a connection between the new embryology and the new molecular biology, with practitioners from both fields increasingly interacting in the spaces created under the aegis of developmental biology. Yet despite the growing influence of molecular ideas on embryologists, and the ventures of molecular biologists into higher organisms, by 1970 few connections had been made at the level of practice. John Gurdon and Donald Brown's work on nucleic acids in *Xenopus* ococytes, Eric David-

---

[101] Taylor 1968.

[102] Edwards 1968, Waddington 1969a.

[103] Bud 1993: 172–3.

[104] Lin 1966.

[105] Taylor 1968.

son's interest in sea urchin DNA and Sydney Brenner's *C. elegans* project are the few examples of practical work that emerged in the late '60s.

Many of these experiments responded to doubts as to the applicability of Jacob and Monod's bacterial models of gene expression to higher organisms.[106] By the 1970s, the assumption that eukaryotic genes were regulated by repressor mechanisms similar to the *lac* operon model – summarised by that often-quoted assertion of Monod's, "anything found to be true of *E. coli* must also be true of Elephants"[107] – had come under pressure. Growing attention to eukaryotic cells and especially their RNA produced new models of gene actions in development, most famously those elaborated by Davidson and the molecular biologist Roy Britten, first published in Davidson's 1968 *Gene Activity in Early Development*.[108] Responding to observation of large-scale RNA production in embryos, it suggested a much higher level of genomic organisation in eukaryotes, with "batteries" of non-contiguous genes, on a much greater scale than an operon, activated by a signal event or external signal, with whole families of regulatory genes controlling these cascades. Such new molecular explanations, embedded in the peculiarities of eukaryotic cells and genomes, were more palatable to developmental biologists. Thus, in response to Britten and Davidson, Waddington wrote that theirs was "the first speculation about the molecular mechanisms that control epigenesis of higher forms that begins to make sense to an embryologist who has been thinking along those lines for 30 years or more."[109] Jacob and Monod themselves lost faith in the universality of their bacterial models by 1970s. In pursuit of new regulatory explanations, Jacob converted to a higher organisms, picking the mouse as his animal of choice.

Jacob recalls deciding to settle on a new multicellular organism around 1967. According to his memoirs, unable to choose between the usual animals of embryology, he wrote down the list of features for his perfect animal, only to find it did not exist.After flirtations with the flatworm *Planaria*, *Drosophila* and Brenner's nematode, Jacob settled on mice. He reconstructs two reasons for

---

[106] Morange 1997b, Suárez-Díaz & García-Deister 2015.

[107] Monod & Jacob 1961: 393. See also Friedmann 2004.

[108] Davidson 1968, Britten & Davidson 1969. See also Suárez-Díaz & García-Deister 2015, Morange 2009, García-Deister 2011.

[109] Waddington 1969b: 639.

this. First, the mouse had close scientific and rhetorical connections with humans and was used across a range of disciplines, and it was the smallest mammal with a short reproductive cycle. Second, Jacob claimed to have been adamant about staying at the Institute Pasteur, and adapting his laboratory to work on the mouse made the most sense, both because there was other work on the organism carried out there, and because it was relevant to the Institute Pasteur's ultimate focus on human pathology. With the institution's expansion of the animal facilities in the early 1970s, Jacob had to fight to make the mouse a species of choice, using the promise of genetic analysis and his position to convince local immunologists to shift their attention from rabbits. However, a key factor in Jacob's mouse project was a new technician who could help him through the species transition.[110] This was Hedwig Jakob, who had built expertise in mouse cell culture in Gif-sur-Yvette, working with Boris Ephrussi, most famous as a *Drosophila* developmental geneticist.[111]

The cells that Jacob settled on were teratocarcinoma cells, derived by Leroy Stevens at the Jackson Lab from a bizarre mouse tumour that seemed to resemble embryonic cells. A geneticist working on carcinogenesis, Stevens bred the "129 strain" that developed a specific cancer, teratoma, with high frequency. Teratomas manifested as highly unusual encapsulated tumours, containing a variety of anatomically normal cells of tissue types that were not expected in the testes, such as hair follicles, teeth, and even eye or limb cells. These tumours also contained undifferentiated cells that gave rise to those tissues, which closely resembled the inner cell mass of the blastocyst. The parallels between the tumour and embryonic cells led Stevens to speculate that these were derived from embryonic tissues that failed to differentiate. For Jacob, these cells offered an intermediate system that could combine a study of differentiating mammalian cells with culture techniques familiar to a molecular biologist working with bacteria.[112]

---

[110] Jacob 1998, Morange 2000.

[111] On Ephrussi, see Zallen & Burian 1992,

[112] Jacob 1998, Morange 2000, Lewis 2001: 127–38. In 1970, Stevens reported that early embryos transplanted into mice could give rise to similar tumours, further cementing the link between teratomas and embryonic cells and attracting more researchers – Stevens 1970.

In the 1970s, Jacob's lab pursued the study of the *T* complex, that central enigma of mouse developmental genetics, building alliances with the Cornell mouse geneticist Dorothea Bennet, whose student Karen Artzt was hired by Jacob in 1972.[113] With the expansion of molecular discussion around the mouse, present in speculative commentary and embedded in concerns about the future of biology, Jacob's transition is informative at the level of practice. While the mouse was increasingly seen as a useful system for asking developmental questions with a molecular twist, much more mundane challenges had to be met. Infrastructure and technical expertise continued to be crucial factors in changing species, as was being able to afford the time and costs such a change of direction would incur. As the next chapter will show, it took the circulation of postdocs with diverse scientific backgrounds and increasingly mobile careers, as well as the emergence and institutionalisation of easily mobile tools to make molecular intervention in mouse embryos viable in the 1970s.

Conclusion

In 1970, Keen Rafferty's *Methods in Experimental Mouse Embryology* was published. It was the first handbook to deal exclusively with mouse embryology.[114] Extensively illustrated with line drawings, it targeted biology and medical students and was based on a course for first-year medical students Rafferty had organised at Johns Hopkins. While some reviewers found the volume too challenging and impractical for undergraduate students, it was well received and recommended for graduate courses and even experienced researchers.[115] With considerable coverage of mouse husbandry, equipment and culture media, as well as very recent embryological techniques, Rafferty's volume announced that the mouse embryo had become so prominent that it could be included in routine university teaching. The preface presented the case: "Among mammals, the mouse has been singled out for exclusive attention for the related reasons that the animal is easily

[113] Morange 2000. Before moving to Cornell in 1962, Bennett had completed her doctoral studies at Columbia and then had worked in L. C. Dunn's lab there.

[114] Rafferty 1970.

[115] Billington 1971.

the most economical and has been the object of far more attention than any other mammal."[116] Only a decade earlier, such a statement would have lacked any credibility. During the 1960s, the mouse took centre stage in the study of mammalian development. In 1972, a detailed atlas of mouse development appeared in print, accompanied by black-and-white photographs. Authored by Karl Theiler, an embryologist at the University of Zurich, and it standardised the events in mouse developments as specific normal stages.[117]

The extensive standardisation of the mouse, both genetic and physiological, was a resource that made the species widely appealing, but also offered an opportunity in that it was open for challenge. A few biologists, McLaren, Biggers and to a lesser extent Grüneberg, made their careers by investigating the alternatives to the pure lines espoused by Jackson Lab. In the process, the mouse embryo became a viable and promising object for laboratory culture and intervention, bringing together expertise in genetics, reproductive physiology, embryology and biochemistry. With the rise of developmental biology, the species landscape had become unstable and open for renegotiation. With the new manipulation techniques and rhetoric, the mouse was taking a place alongside the other key embryos, and the wide range of the networks that the mouse held together made it a promising choice for the jobs that were often yet to be articulated.

While other species had had more sway in reproductive and embryological research, the mouse became attractive because of its position at the boundaries of multiple research agendas. The mouse embryo was made into a particularly successful boundary object, better than its more 'robust' analogues. The wide-ranging availability of techniques, husbandry know-how, genetic knowledge and pre-existing fora for exchanging facts and materials also made it into an exemplary laboratory species. Yet the boundary crossing that is significant to this story – that between embryologists and molecular biologists – was not yet realised as practical collaborations or straightforward exchanges of techniques. These transitions took place in the 1970s, and coincided with the rise of recombinant DNA techniques.

---

[116] Rafferty 1970: viii.

[117] Theiler 1972.

Chapter 2. Recombinant networks: The moral economy of genetic engineering in the 1970s

Many accounts treat transgenic mice as one application of new molecular methods under the label of 'recombinant DNA'.[1] These techniques, invented in 1973, allowed researchers to isolate, splice and insert genetic material from any species into a circular bacterial DNA molecule known as a *plasmid* that could then be taken up by cultured cells – usually bacteria. On surface, the statement is not inaccurate – all the groups that reported gene transfer into mice animals in 1980–81 relied on these methods. Yet treating transgenic mice as a case of such straightforward molecularisation is misleading for two reasons. First, the earliest experiments to introduce genetic material into mouse cells and embryos predated these methods, and stemmed from alternative experimental programmes. Second, the genealogy and coherence of recombinant DNA is anything but straightforward, and more recent histories of biotechnology explored continuities with older research programmes and alternative genealogies for the methods. As I will argue here and in the following chapter, means of inserting genes into mice predated recombinant DNA. These new methods did, however, make an essential contribution as they streamlined existing experimental practices, scaled up the work on gene transfer and generated new scientific networks through which techniques and molecules circulated.

Existing histories of recombinant DNA and the biotechnology industry focus on *E. coli*, the powerhouse bacterium of molecular biology that became at the centre both the dramatic safety debates and the spectacular early industrial applications.[2] The possibility that modified *E. coli* might escape into the environment drove extremely public controversy, with scientists on both sides,

---

[1] Papaioannou 1998, Fujimura 1996, Murray 2010: 354–6.

[2] For the first wave of recombinant DNA histories with the focus on regulation and safety debates, see Wade 1977, Goodfield 1981, Watson & Tooze 1981, Krimsky 1984, Wright 1986, 1994. There are multiple scientist's accounts, e.g. Watson & Tooze 1981, Friedrickson 2001, Berg & Mertz 2010. For more recent historical work see, Fujimura 1996, Vettel 2006, Bud 2009, Yi 2008b, 2011. An excellent collection of historical scholarship on biotechnology from a range of perspectives was published as Thackray 1998. Bud 1993 places both the industrial practices of biotechnology and the 1970s debates about genetic engineering in the longer history of the fermentation industry and critiques of the New Biology and science in general. For the rise of the US biotech industry, see Kenney 1986, Bud 1993, Hughes 2011, Kenney 1986, Rabinow 1996, Thackray 1998. For the British perspective, see de Chadarevian 2011. For an overview of the historiographic debates on continuity vs. change when it comes to recombinant DNA, see Gaudillière 2009.

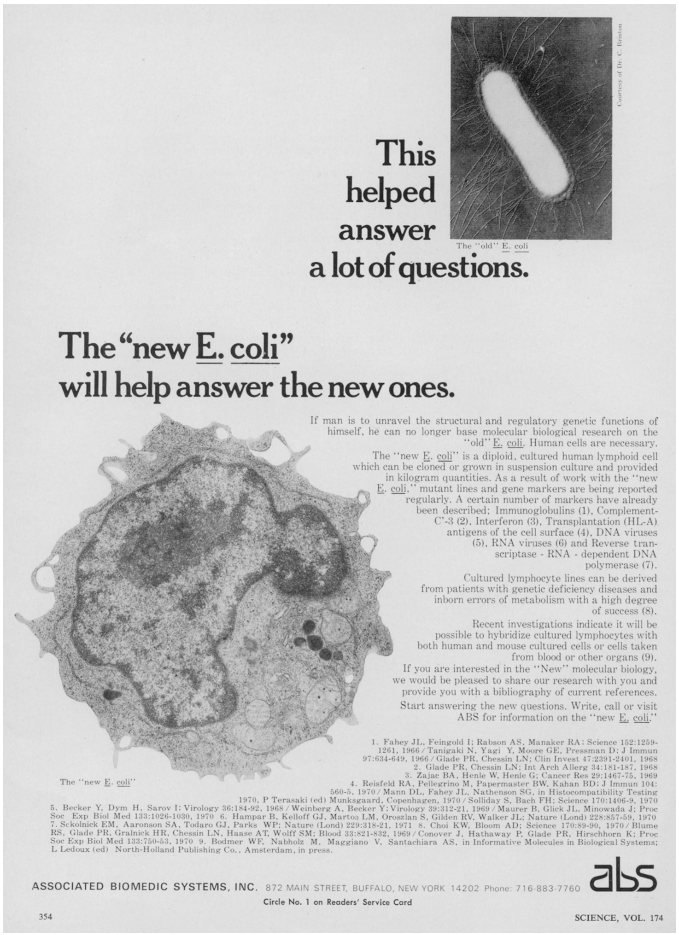


Fig. 2-1: The "New *E.coli*", an advertisement for human lymphoid cells from Associated Biomedic Systems, Ltd. The extensive detail visible on the cell micrograph compared to the *E. coli* image makes the additional visual argument for tackling cellular complexity.

Science 174(4007), 1971.

that culminated at the 1975 Asilomar conference, with subsequent guidelines published by the NIH that required stringent containment from any grant receiver, with requirements gradually relaxed by 1980. First success stories of the biotech start-ups – synthesis of somatostatin, human growth hormone and insulin – were also performed in bacteria. Yet despite the focus on application in bacteria, the study of eukaryotic cells and genes were important for the adoption of recombinant techniques.[3] New experimental systems were explored with cultured cells of humans, mice, hamsters and monkeys were the key mammalian species (see Fig. 2-1).

This chapter revises the history of recombinant DNA research in two ways. First, I examine alternative genealogies of moving genes between species, in particular gene transfer work with cultured cells, somatic cell genetics and animal virus research. One of these experiments, a collaboration between a molecular virologist Rudolf Jaenisch with Beatrice Mintz that was reported in 1974, revolved around inserting viral DNA into mouse embryos. Second, I focus on the circulation

[3] Yi 2008a.

of techniques and plasmids between institutions that attracted unexpected users beyond the core molecular biology community. Unusually, these networks were highly decentralised and had to function in a difficult regulatory environment. One inadvertent outcome of the post-Asilomar NIH guidelines was the exclusion of certain institutions from the networks of exchange due to financial constrains that prevented them from building proper containment facilities and were influenced by the local regulation context. Still, through contingent moves of individuals, recombinant molecules could often make it to unexpected sites. The exchange patterns thus concentrated the transitions of recombinant DNA across disciplines to elite institutions, but also allowed and set the stage for unexpected collaborations.

I will first discuss the state of gene transfer in higher organisms circa 1970, and move on to focus on the Jaenisch-Mintz collaboration in section 2. Section 3 examines the circulation patterns in the light of recombinant DNA guidelines, and the role of sharing and credit in the moral economy of this expanding enterprise. Finally, section 4 will discuss the articulation of gene transfer into mammalian cells as a coherent programme with its own set of conferences, tools and expectations.

§1. Gene transfer and somatic cell genetics

The success of research on the molecular biology of viruses and bacteria in the 1960s seeded several research programmes that focused on investigating the effects of DNA on multicellular organisms. In the late 1940s and early 50s, the use of bacteriophages (viruses infecting bacteria), labelled with the newly available radioisotopes, was key in several experiments that established the nucleic acid component as the carrier of genetic information.[4] The phrase "gene transfer" originated from bacterial genetics around the same time, to describe the exchange of genes between bacterial cells, often from diverse strains. This phenomenon was cited widely in the debates about recombinant DNA in the 1970s to normalise the experimental insertion of foreign genes into *E. coli* as an extension of a natural process. However, before the controversy broke,

[4] Creager 2013: 239–53.

gene transfer was discussed in relation to mammalian cells and experimental interventions took place in the 1960s and the early 1970s.

As early as 1962, a paper by the microbiologist Wacław Szybalski and his wife Elizabeth Hunter Szybalska in the *Proceedings of the National Academy of Sciences of the USA (PNAS)* claimed a successful incorporation of whole genomic DNA from one human cell line into another characterised by its lack of a specific enzyme, HPRT. Crucial to the work, done at the McArdle Laboratory at the University of Wisconsin, Madison, was the ability to select the cells that had taken up foreign DNA. To achieve this, the Szybalskis developed a tissue culture medium they named HAT after its components (hypoxanthine, aminopterin and thymidine). Only the cells that had taken up the normal HPRT gene could grow in HAT. This was one of several similar studies published around the time. At Allen Fox's laboratory, also at Madison, scientists treated *Drosophila* embryos with DNA extracts from different strains seeking to observe phenotypic effects.[5] Again, while there was some evidence that DNA could change phenotype, it appeared to be merely associated with the fly genome without integration – reversal of the effect was frequent.[6] Such work was t was not received with much enthusiasm. The majority of molecular biology was done in bacteria and the λ phage, with the genetic code being a major publicised problem at the time. The Szybalskis followed the trend and returned to *E. coli*.[7]

This return to bacterial cells was understandable given the availability of instruments, techniques and communication networks to support such work, but a small community of biologists working on transfer of DNA into eukaryotes did persist on the margins. Thus, Lucien Ledoux, based in Mol, Belgium, claimed transformation of plants with bacterial DNA as early as 1966.[8] In his experiments with tomatoes, barley and *Arabidopsis*, Ledoux treated seeds from the strains deficient for the synthesis of thymidine (one of the four DNA components) with radioactively-labelled bacterial DNA. By separating the plant DNA on caesium chloride gradient – a laborious process in-

[5] E.g. Fox, et al. 1970, Fox, et al. 1971.

[6] Willison 1980.

[7] See Wolff & Lederberg 1994, 472–73.

[8] Stroun, et al. 1966.

vented by Meshelsohn and Stahl for their experiments that demonstrated the semi-conservative replication of DNA[9] – Ledoux detected peaks that indicated that the modified plants not only took up the bacterial DNA and broke it up it to make their own, but could also eventually produce unlabelled nucleotides, suggesting gene transfer from bacteria. Yet this work could not be straightforwardly replicated and remained a citation oddity.[10]

Some of the efforts were collated at a 1970 NATO-sponsored conference on Informative [*sic*] Molecules in Biological Systems in Mol, organised by Ledoux.[11] The conference brought together bacterial, plant and mammalian workers, and presented many claims for transformation of mammals. The introduction acknowledged the lack of solid knowledge about the behaviour of DNA in mammalian cells, while expressing cautious enthusiasm. The concluding remarks were also ambivalent. Written by Hubert Chantrenne, a Belgian molecular biology pioneer based in Brussels, they divided the experimental work into two categories: classical and emergent. The latter included experiments with higher organisms, which were rather backhandedly likened to "black magic": "controls were inadequate… It took a lot of courage and faith to continue to work along such disreputable lines".[12] By contrast, the work on animal viruses and on the genetics of somatic cells were elevated as worthwhile pursuits due to their practicality.

The reviews of the published proceedings were also mixed, often treating the results in eukaryotic cells as suspect. As one reviewer noted, the interesting questions – whether the foreign genes were expressed and integrated into the host genome – were rarely answered in these studies.[13] Moreover, as some of the convenors agreed, the results were not certain and artefact could not be ruled out, for instance contamination. The black magic metaphor persisted around gene transfer into mammalian cells even as it became acceptable. While viral and somatic cell genetic work drew on older traditions and had some eminent names attached to it, the injection of naked DNA

---

[9] I.e. that a replicated DNA molecule consisted of one strand from the parent molecule, and the complimentary strand synthesised *de novo*. See Holmes 2001, esp. pp. 168–79 on the caesium chloride gradient.

[10] On Ledoux, see Lurquin 2001: 5–31.

[11] Ledoux 1971.

[12]

[13] Ward 1972.

remained disreputable, and results uncertain. Its status is a reminder that while multiple claims about scientific works were routinely made their survival relied on instruments of credibility, best conferred by nurturing further work that could then also function as evidence of replication.

Unlike the work on using isolated genomic DNA to modify tissues *in vitro*, cell hybridisation and viral experiments were part of established and well-funded research programmes. Since the late 1950s, several geneticists looked to mammalian – and especially human – cell culture to map genes onto specific parts of chromosomes. The field, labelled 'somatic cell genetics', sought to override the limitations of tracing human genes through family trees and the goal of these experiments was to make animal cells more like bacteria, by focusing on cells that could be easily cultured, controlled and manipulated. Envisioned and developed in the early 1960s in the laboratories of Boris Ephrussi (Gif-sur-Yvette), Guido Pontecorvo (University of Glasgow) and Henry Harris (Oxford University), among others, techniques to make cell hybrids between different strains and species allowed gene mapping based on the few markers, mostly associated with the ability to grow in different media. As these hybrids were genetically unstable and lost chromosomes in the process of cell division, the correlation between the remaining chromosomes and their parts and the cells' new phenotype could suggest the position of specific genes.[14]

The early experiments on somatic cell fusion were received with much controversy. When Henry Harris first reported his human-mouse cell hybrids in 1965, dramatic reactions followed from the British and American press. The press seized upon the experiments as another manifestation of the biological revolution and a new frontier that could one day lead to human-animal chimeras. Harris's reaction courted controversy, even as he attempted to distance himself from the press. The choice of human and mouse cells in the experiment was deliberate to make a more dramatic impression on his colleagues, and when confronted by interviewers, Harris would not dismiss future applications to humans and even went as far as entertaining the possibility of a human-ape hybrid (a 'mape') on television. The late 1960s were a time of dramatic concern over the new biological research, with bold statements from scientists that would become extremely rare post-Asilomar. Harris's insistence on framing his work in terms of species did much to shape the re-

[14] On somatic cell genetics and its pioneers, see Zallen & Burian 1992, Harris 1995, Cohen 2000, Ruddle 2001, Siddiqi 2002, Landecker 2007: 180–218, Wilson 2011.

sponse, even as he subsequently tried to minimise the fallout by pointing out that cells were not whole organisms. His work featured in *The Biological Time Bomb* alongside many others, as part of the "new eugenics" narrative in Rattray Taylor's pessimistic account.[15]

Work on gene transfer into mammalian cells was becoming visible in scientific publications, and several reviews appeared in the news section of journals and science magazines. In 1971, a *Science* article reviewed Harris' latest cell-fusion research, alongside work on using a virus to modify mouse cells. Noting that the ability to insert foreign DNA, either through viruses or in cell hybrids, was going to help with mapping efforts and understanding gene expression, it concluded by addressing concerns about genetic engineering and argued that the tools were coming together to deliver gene therapy before society was ready. A 1972 piece in *New Scientist,* the British popular science journal with a balanced approach to the new biology, offered another opinion.[16] It was authored by Benjamin Lewin, a former editor of *Nature New Biology*[17] and NIH cancer researcher. The opening sentence claimed, "'Genetic engineering' is already a cliché whose very existence obscures reality. Claims to have cured genetic defects in cells by the addition of foreign genetic information are as controversial as the arguments about the morality of applying genetic therapy to man."[18] Framed as a critical survey, the article covered cell hybridisation, using viruses as vectors, "which ha[d] been in the minds of molecular biologists for some time", and "just adding DNA". Lewin concluded that genetic engineering was too premature to warrant ethical guidelines that would inevitably become outdated, a rhetorical strategy that became common as dramatic new experiments were being published. But he also articulated criteria for successful genetic modification: stable integration of the gene, use of clear selectable markers and genetic analyses to confirm gene transfer, and the presence of the new genetic material in the germ line and therefore subsequent generations, where whole organisms were concerned.

---

[15] Ibid.: 70–81.

[16] Lewin 1972.

[17] This journal was part of *Nature's* short-lived experiment in dividing its content into three thematic parts.

[18] Ibid.: 122.

Published over a year before the start of the recombinant DNA controversy, these pieces highlight continuities in the debates over genetic engineering. They also indicate a divided biological opinion that the controversy would expose. However, by the early 1970s, media interest in cell fusion faded as embryo culture and artificial fertilisation became icons of the new biology, while somatic genetic research was in full swing.[19] In pursuit of a higher resolution of mapping, specific chromosomes were being isolated. In 1973, a paper by Wesley McBride and Harvey Ozer at the National Cancer Institute in Bethesda detailed a new means of allocating genes by what they called "chromosome-mediated gene transfer".[20]The technique was a means of making cross-species hybrids by incubating cells with chromosomes purified by centrifugation, and observing the changes that took place in the cells.

In order for these experiments to be meaningful, a series of cell lines, markers and mutations had to be developed. The few known mutants relied on metabolic characteristics, such as the ability of cells to grow in specific media such as Szybalskis' HAT. This remained the simplest system, and lack of enzymes such as thymidine kinase (tk) and HRPT could be detected. In the 1960s and 1970s, the standard biochemical technique of gel electrophoresis was adapted to expand the repertoire of phenotypes, as different forms of enzymes would migrate differently on a two-dimensional gel.[21] Moreover, by the 1960s animal cells were widely standardised and accessible though centralised facilities. In 1964, the American Type Culture Collection, established for storage of microbial samples, began accepting animal cells that could be frozen in liquid nitrogen and samples then sent to researchers.[22] In the 1970s, these activities expanded and new cell banks emerged. One at the MIT was sponsored by the National Science Foundation, while a human cell culture bank was established in Camden, New Jersey in 1972.

One geneticist was heavily involved with the expansion of somatic cell genetics in the USA was Frank Ruddle, a former postdoc of Pontecorvo. Chairman of the Department of Biology at Yale,

---

[19] Wilson 2011: 80.

[20] McBride & Ozer 1973.

[21] Kay 1988.

[22] On ATCC, see Brauckmann 2006.

Ruddle managed to secure an uncharacteristically long-term grant for his laboratory from the newly established National Institute for the General Medical Sciences (NIGMS) for his research into the "genetics of somatic cells".[23] At Yale, Ruddle established multiple networks of collaborations within and outside the institution, overseeing and working on several projects associated with murine cell genetics, as well as human population genetics. He was also involved in building genetic networks. Thus, Ruddle helped the Camden tissue bank secure NIGMS contracts and actively encouraged his colleagues to contribute cells to the bank, offering them to put a "hold" on the material for up to a year so that it could be exploited further before sharing.[24] With Victor McKusick, he initiated the series of Human Gene Mapping Workshops in 1973, which became the major vehicle for communication within the human genetics community. Subsequent meetings standardised the nomenclature of human genes and established communication and logistical networks that were important in initiating the Human Genome Project.

Ruddle actively promoted somatic cell genetics, for instance by introducing the approach as a way to study development. In 1972, he chaired the annual Symposium of the Society for Developmental Biology dedicated to the Genetic Mechanisms of Development at the Wesleyan University, Connecticut. The meeting brought together topics seemingly distant from embryology. Its first third was devoted to bacteria and viruses, envisioned as "as paradigms for the genetic analysis of differentiation and morphogenesis in the complex eukaryotes."[25] Another panel was devoted to using Mendelian analysis for interpreting development, with the usual animal suspects – *Drosophila*, *Xenopus* and the mouse – and the third part discussing how somatic cells could be "a new tool for the developmental biologist". According to Ruddle,

> In these experimental systems, parasexuality in somatic cell populations is used to extract genetic information pertinent to developmental control mechanisms. In a sense, this approach permits the concepts and methodologies inherent in microbial genetics to

[23] McKusick 1984.

[24] Frank Ruddle to Malcolm Ferguson-Smith, 24 November 1975, UGC 188/3/3/18/12, Glasgow University Archive.

[25] Ruddle 1973: xi.

> be applied directly to the study of differentiated soma of higher eukaryotes explanted *in vitro*.[26]

Another unusual aspect of the symposium was a public launch of a film about the impact of scientific research on social problems. Responding to the recent debates, its topic was genetic engineering. Some argued for oversight from the scientific community, including new committees on ethics and safety. These approaches echoed the sentiment of the 1973 Gordon research conference that is usually taken as the starting point of the recombinant DNA controversies, where the concerned scientists voiced public health concerns through open letters to the scientific community.[27] While these debates ultimately focused on the containment of *E. coli*, a potential human pathogen, it was the inserted DNA that caused most concern. In the original experiments from the Berg laboratory at Stanford, these genes came from the tumour virus SV40. Virus research had played a key role in developing techniques to insert foreign DNA into cells – an approach developed in mammalian cells.

§2. Viruses and embryos: The Jaenisch-Mintz collaboration

As Chapter 1 showed, in the 1960s molecular biologists were eager to expand into higher organisms, and embryologists were increasingly attracted to molecular tools and questions. Several candidate species attracted big names, the mouse among them. For Sydney Brenner and Francois Jacob, working with *C. elegans* and mouse teratocarcinoma cells, there was no sharp transition between molecular and developmental practices – the techniques and instruments were a part of locally-elaborated sets of questions.[28] Yet such synthesis was not the rule. Success stories in molecularising the mouse embryo typically relied on collaboration between molecular biologists and embryologists, often carried out through the extensive circulation of young postdoctoral fellows between institutions. Divisions between expertise were significant and parts of the projects were often performed in different locations best suited for specific techniques. Here, I discuss one of

---

[26] Ibid.

[27] Krimsky 1984, Wright 1994.

[28] de Chadarevian 2000, Morange 2000.

the earliest collaborations that resulted in the first announcement of inserting foreign genetic material – a virus – into the mouse embryo.

In 1971, the Princeton molecular virologist Rudolf Jaenisch approached Beatrice Mintz with an ambitious project – to insert a virus into the mouse embryo. Jaenisch had just moved to Arnold Levine's Princeton laboratory from the University of Munich, where he had completed a medical degree combined with a PhD in the molecular biology of bacteriophages. Levine had secured his assistant professorship at Princeton in 1968, having studied the replication and control of host metabolism by bacteriophage ΦX174 and SV40. The latter virus was to become a major project for his laboratory in the early 1970s, and Jaenisch was one of his first postdocs who helped establish the system.[29]

Study of tumour viruses had flourished since the 1960s, when they were successfully promoted as a major experimental system to study cancer causation. In the USA, funding for tumour virus studies ranked second in National Cancer Institute expenses, topped only by chemotherapy.[30] The role of viruses as causative agents of all cancers remained controversial, but arguments had been made for their use as an experimental system. Before the war, work in fowl and mice showed some tumours could be induced by viral particles, even though these kinds of infectious hereditary causes went in and out of fashion.[31] In postwar America, the complex "policy-making community" encompassing politicians, cancer charities, pharmaceutical companies and healthcare bureaucracies was compelled to invest major funds into the study of tumour viruses.[32] This was in response to the political agendas of the war on cancer, the widespread use of molecular biological approaches and instruments such as ultracentrifuges to purify viruses, and the major success of polio research that led to the unveiling of the Salk vaccine in 1955.

Leukemia viruses received much initial funding, but other tumour viruses soon became key research objects. Building on the success of mapping bacteriophages, prominent molecular biolo-

---

[29] Jaenisch interview.

[30] Gaudillière 1998a, Fujimura 1996.

[31] Gaudillière 1998a, 2001, Gaudillière & Löwy 2003a, Löwy & Gaudillière 1998a.

[32] Gaudillière 1998a: 150–8.

gists and virologists turned to new systems such as the polyoma virus and SV40.[33] Jaenisch was one of many participants in this migration. In 1971, Levine took sabbatical leave to Europe, and Jaenisch was effectively in charge of the lab. As a recent convert to animal viruses, Jaenisch was eager to explore the more ambitious questions of tumour causation that went beyond the monkey cell system in which SV40 was cultured. He was attracted to the problem of tissue specificity, or viral tropism. Why did SV40 give rise to skin cancer but did not affect the liver? Was it unable to infect the liver cells, or unable to make them grow uncontrollably, that is, to *transform* them?[34] He had come across Mintz' work on allophenic mice and was attracted by her use of genetics to answer developmental questions. If a virus could infect the early embryo, the expectation was that its DNA would infect the majority of cells and tissues. Jaenisch called Mintz to tell her about his ideas, and she invited him to visit her lab – a short drive from Princeton. Jaenisch recalls her as polite, but skeptical, to the extent that he began reaching out to other mouse labs. However, after some time Mintz called him back and suggested they work together.

The collaboration was negotiated with the absent Levine, and relied on Jaenisch driving between Princeton and Fox Chase. In Mintz's lab, he would learn to deal with mouse embryos – a prime location for the task. At Levine's lab, he would purify SV40 DNA after growing it in monkey cells by isolation in alkaline sucrose gradient and further purification. Jaenisch would then take the isolated viral DNA to Fox Chase, where he would attempt to inject the isolated viral DNA into the blastocyst, following Mintz's guidance. This technique was based on Teh-Ping Lin's microinjection method and Richard Gardner's work on microinjecting inner cell mass into the blastocyst, with which Mintz was familiar.

Mintz may have thought Jaenisch's project risky, but several other laboratories were pursuing similar research. Lin's was one: as Jaenisch recalls, he went for a brief visit to UCSF that he did not find particularly helpful, and he was perplexed by Lin's attempts to inject ribosomal RNA into mouse eggs that remained unpublished. At the Rockefeller University in New York, Elaine Diacumakos, a student of Edward Tatum and an expert in microinjection of somatic cells, was trying to

---

[33] See Kevles 1993, Yi 2008a.

[34] Note the dual meaning of transformation in this context: cancer cells that undergo uncontrolled division are labelled as 'transformed', as are cells that had been genetically modified.

work with mouse eggs slightly later, in 1973–1974, again with little success.[35] In the UK, Anne McLaren was experimenting with the effects of nucleotides on the developing mouse embryo, by culturing them in a solution of DNA.[36] McLaren's interest in rodent DNA can be traced to her late 1960s experiments on repetitive sequences in mice and rats, studies that generated some interest among the molecular biologist experts on the issue.[37] In 1973, McLaren co-authored a paper on the effect of DNA on the growth on the mouse embryo with her student Michael Snow. Snow and McLaren's report showed little effect of external DNA on the embryo – it suggested that freshly-prepared DNA enhanced growth, while if it had been stored for a while, the effect was deleterious. There was, however, no evidence of genetic modification.

The early experiments on gene transfer mostly relied on phenotypic markers to detect genetic modification. While Snow and McLaren used radioactively-labelled nucleotides to follow them into the embryo, their conclusions also relied on the lack of phenotypic change. Jaenisch hoped to see phenotypic effects – tumours in adult mice, but he was also interested in the fate of the virus in tissues where it was suppressed. For this, he was seeking a tool to detect the viral DNA regardless of its function, a nontrivial task. Specific DNA could be detected by measuring rates of hybridisation of radioactively-labelled molecules. A DNA solution was heated to just below boiling point, and the double strands would unzip and separate. As the temperature was lowered, the single strands hybridised again into double-stranded molecules, and the rate of the process could be measured through radiation detectors. The hybridisation rate was assumed to be proportional to the sequence similarity between the molecules – if it was rapid, it could be assumed many identical sequences were present in solution. The measurements were inscribed as C_0t curves (or "cot curves"), and were a means of confirming presence of specific DNA as well as being useful in early studies of genome complexity and repetitive DNA (Fig. 2-2).

---

[35] "Microsurgery" notebooks, Elaine Diacumakos papers, RU405, Rockefeller Archives, Tarrytown, NY.

[36] Snow & McLaren 1974

[37] Letter from Roy Britten to Joshua Lederberg, 1 November 1968, The Joshua Lederberg Papers, National Library of Medicine, Bethesda, MA. Available at http://profiles.nlm.nih.gov/ps/access/BBGDSV.pdf, accessed on 1 July 2013.

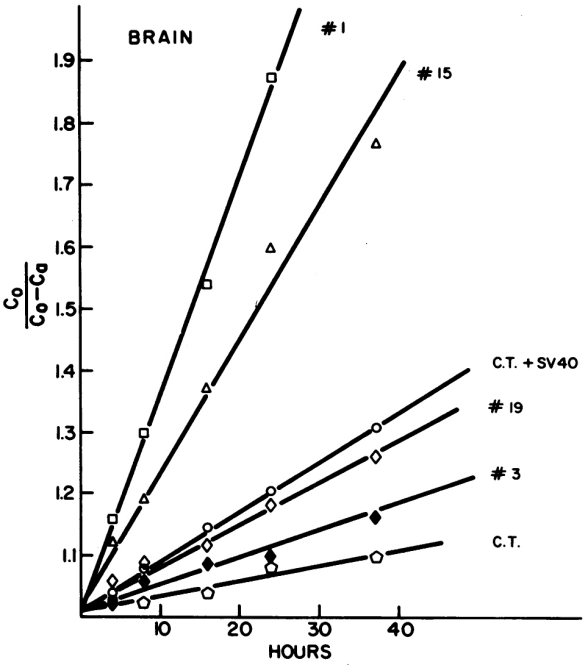


Fig. 2-2: A C_0t curve from Jaenisch and Mintz's 1974 paper, showing extracts from the brain tissue in several mice (numbered). The relative rate of reannealment between single stranded DNA molecules $[c_0/(c_0 - c_a)]$ is plotted against incubation time. The high rate for mice #1 and #15 indicates presence of SV40 sequences. C.T. stands for calf thymus DNA, used as a control on its own and with a sample of SV40 DNA ("C.T. + SV40") to rule out contamination.

For Jaenisch's experiment to work, the SV40 probe had to be identifiable in the mix of mouse DNA that had been sheared with a non-specific restriction enzyme. He achieved this by preparing a highly radioactive ("hot") probe from the purified SV40 DNA, a solution that presented itself in 1973, when, having completed his postdoc at Princeton, Jaenisch moved to the Salk Institute. Located in La Jolla, San Diego, the Salk had been pioneering small laboratories for new faculty.[38] It was also attracting prominent molecular biologists as non-resident fellows. Among them was Paul Berg, who joined the institute just as the recombinant controversy began to unfold. With a British postdoc Peter Rigby, Berg was developing "nick translation", a method to make specific DNA molecules highly radioactive.[39]

At the Salk, Berg passed the protocol for the technique to Jaenisch as early as 1973, though it remained unpublished until 1977. Such circulation of methods was not uncommon among molecular biologists, given long delays in publication, but Jaenisch certainly benefited from access to Berg that his position at Salk allowed. Another crucial technique for DNA detection that superseded cot curves, Southern blotting, was developed in 1973 at the University of Edinburgh by Edwin Southern, but was only published in 1975. In Southern's case, the *Journal of Molecular Biology*

[38] Bourgeois 2013

[39] Rigby, et al. 1977. The technique relied on a cell-free system with a bacterial polymerase to replace some base pairs with their radioactive equivalents from the solution.

rejected his "methods" manuscript until a significant biological application could be included, in line with its policy. However, Southern liberally shared his protocols with fellow biologists, and they soon spread to the USA via his transatlantic visits.[40] Berg went even further, allowing Jaenisch to announce and briefly describe nick translation in the paper with Mintz. This generosity was not restricted to Jaenisch – Berg's 1977 method paper on nick translation lists nine further publications that had relied on the technique in 1973–77, most of them from Stanford. Berg was duly acknowledged as a donor of the technique, and its emerging use enabled him to garner evidence for future publications and demonstrate a clear biological significance of his method.

Jaenisch and Mintz published their results in the *Proceedings of the National Academy of Sciences (PNAS)* in 1974. Mintz had been elected to the Academy in 1973, which made it easy for her to submit papers without looking for another fellow to "communicate" the manuscript, and the publication was fast. Their data strongly suggested that SV40 DNA was present in the tissues of the embryo, in various concentrations, and they speculated that the virus had probably integrated into the mouse genome, even though alternative possibilities could not be entirely dismissed. Otherwise, the framing of the paper was in terms of tumour virus biology – tissue specificity, the effect of the embryo on viral activity and tumour formation. Remarkably, the experiment was not positioned as an attempt at genetic intervention, nor was the possibility suggested in the rather focused language of the paper. It is unlikely that it had not been entertained, but perhaps the authors felt it was too fanciful – and potentially controversial – to express in print. While the experiment did not use recombinant DNA, SV40 was a source of anxiety that fuelled the recombinant controversy in the first place. While the 1974 paper suggested that viral DNA might integrate into an embryo, this was not entirely unexpected, since this is what viral DNA is supposed to do. Whatever the reason for refraining from genetic speculation, the Jaenisch-Mintz SV40 work went unnoticed beyond the expert community, although it was well-received within. In the following years, Mintz shifted her agenda to work on teratocarcinoma cells, but Jaenisch continued viral work with mouse embryos.

[40] Gitschier 2013, Southern 1975. See also Tofano, et al. 2006

§3. Recombinant exchanges

Methods to isolate DNA and analyse it predated 1970s and, while laborious and sometimes yielding ambiguous data, as in the case of Ledoux, they could be used successfully and to much acclaim. However, with the ability to cut and paste DNA using restriction enzymes and DNA ligase, insert it into a circular bacterial molecule called a plasmid that could then be taken up by other cells, and then detect and map fragments through radiolabelling methods. These techniques, coming together in 1974, rapidly expanded the scope and scale of research with DNA. In a complex political climax in the USA, with severe concern over the safety of such experiments, new networks formed through which plasmids travelled. This section will examine the circulation of recombinant DNA in the second half of the 1970s, stressing the concerns about access, sharing and communication that were part of the moral economy of recombinant DNA research. This context is crucial to place the subsequent invention and communication of transgenic animals, as the laboratories that made these mice partially adopted the new style of doing molecular biology with the plasmids and tools that they received from these networks.

For Jaenisch, SV40 was convenient because he had much expertise in handling it, and it was available in Levine's Princeton lab. It was also a major instrument of molecular virology, and the timing of the *PNAS* publication was opportune. In 1973, John Tooze authored the first textbook on the subject.[41] Moreover, shortly after the paper appeared in the April 1974 issue of *PNAS*, the Cold Spring Harbor Symposium on Quantitative Biology, an eminent annual meeting at the core of molecular biology in the USA and globally, was dedicated to tumour viruses (Fig. 2-3). The topic was chosen by James Watson, still combining his position at Harvard with directorship of Cold Spring Harbor, and it brought together leading researchers. Jaenisch's paper was received as further evidence for the transforming activity of SV40 and its ability to integrate into embryonic cells and it was mentioned in David Baltimore's symposium summary.[42]

Back at the Salk, Jaenisch's attempts to detect tumours in injected mice, or at least SV40 proteins in the embryo (which would indicate gene expression) were not successful. Nor would the mouse

[41] Tooze 1973.

[42] Baltimore 1974.

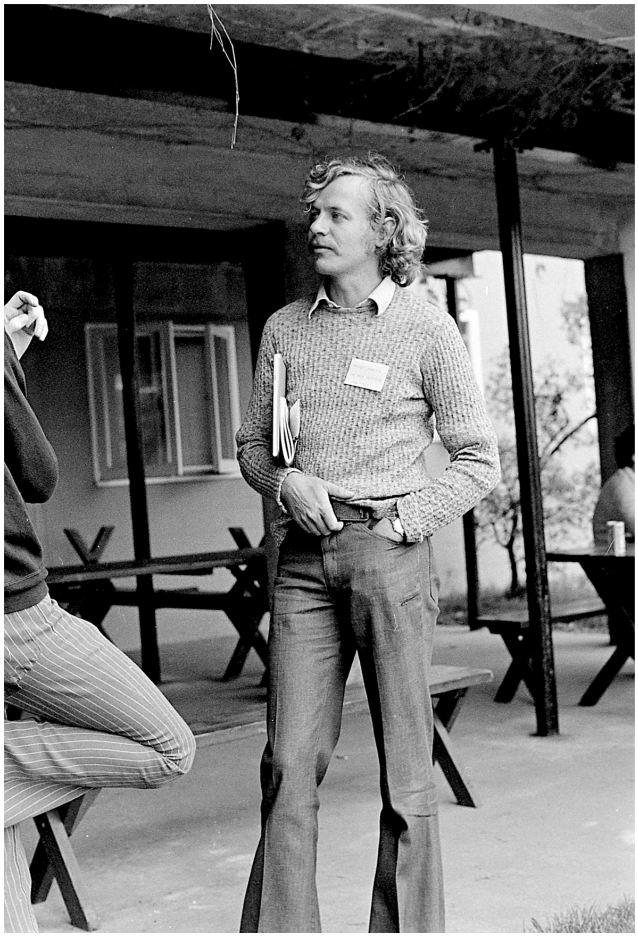


Fig. 2-3: Rudolf Jaenisch at the June 1974 Cold Spring Harbor Symposium on Quantitative Biology.

lines established from the manipulated embryos germline transmission. The embryos appeared extremely mosaic and the germ tissues did not appear to have taken up SV40. While Jaenisch kept breeding the SV40 mice, he was also looking for other systems that might have at least some of the molecular knowledge offered by SV40. Luckily, in the dynamic environment of the Salk Institute, such a system came with new postdocs in 1975. Arriving from David Balimore's MIT laboratory, they brought Moloney murine leukemia virus (M-MuLV) with them, another virus that had been used extensively in mouse cancer research.[43]

Postdoctoral fellowships were established in the interwar USA, as research was becoming an increasingly important part of academic work but universities remained reluctant to hire full-time research staff. The funding came from philanthropic foundations such as the Rockefeller and was intended to encourage transatlantic exchange as European research institutions were blossoming.[44] With the major expansion of American biomedical funding after World War II, the

[43] Gaudillière 1998a

[44] Assmus 1993. On the Rockefeller Foundation and the making of molecular biology, see Kay 1993.

trajectory frequently turned the other way as many European scientists, especially molecular biologists, went to the USA for brief periods.[45] As funding for biomedical research grew steadily through the 1950s and 1960s, postdoctoral positions became increasingly common, with the expectation that young scientists who had just completed their graduate studies would spend between 9 months and 3 years in several laboratories before getting a permanent position and, if successful, starting their own group. Perhaps the most famous postdoc, James Watson, spent several years in Copenhagen and Cambridge, before returning to the USA and taking up a position at Harvard.

The senior scientists running the labs – the principal investigators, or PIs – performed increasingly managerial duties. In universities, they were hiring, teaching and sitting on university boards as well as running their laboratories. However, even in research institutions like the Salk, PIs had to submit multiple grant applications to attract funds and prestige to their laboratory; they would travel the conference circuit, presenting their results and help articulate the 'state of the art' in their field. Some continued to do bench work – this was often important to their reputation as good scientists uninterested in institutional 'politics' – but running a successful laboratory was usually very time-consuming. Thus, while the circulation of postdocs was supposed to expose young scientists to diverse techniques and let them publish as many experiments as possible to be in position to start their own group, postdocs and graduate students also performed the vast majority of experimental labour.

Moreover, they served as immediate vehicles of disciplinary exchanges and cross-fertilisations of techniques, ideas and experimental systems. While Jaenisch was not a formal postdoc in Mintz's laboratory, the combination of expertise and access to resources between Princeton and Fox Chase were crucial to their experiments. Many stories of resource circulation feature DNA samples, enzymes and cells that postdocs brought with them. Thus, the celebrated Cohen-Boyer-Berg collaboration used *Xenopus* DNA that Berg's postdoc John Morrow brought from Don Brown's lab at the Carnegie Institution, and plasmids were then ferried between UCSF and Stanford by a re-

[45] Gaudillière 2002.

search assistant in a Volkswagen Beetle.[46] Similarly, restriction enzymes required for these experiments arrived in a thermos flask from Holland with Boyer's postdoc. As Sally Smith Hughes points out, "these enzymes were not then available commercially and had to be begged for or borrowed through a network of material exchange or tediously synthesized and purified from scratch."[47]

The free exchange of materials was the basic premise in the moral economy of molecular biology, and it thrived through the 1970s. However, it was perceived to be under attack by the attempts to regulate and to commercialise recombinant DNA. Even the earliest attempts to control the use of the plasmids that Cohen, Boyer and Berg shared met resistance. The requests as innocuous as not inserting tumour virus DNA onto plasmids for safety reasons could be resisted, and the insistence on not sharing the DNA further was met with suspicion. In 1971, Andrew Lewis, a young virologist at the National Institute of Allergy and Infectious Diseases developed a hybrid between SV40 and a common cold adenovirus, he drew up a memorandum of understanding that asked recipients of the new construct to take safety precautions and not to share it further unless they could receive similar assurance. Heads of major molecular labs, including Paul Berg, James Watson and Daniel Nathans (Johns Hopkins), refused to sign. Lewis was breaking the code of sharing and his implicit doubts about the competence of senior molecular biologists were a major faux pas.[48]

Later in the 1970s, when limitations on recombinant research were grudgingly accepted by some biologists (and eagerly promoted by others), the problem of sharing did not diminish. Despite the culture of sharing resources, credit had to be allocated properly and it was expected that the inventor would 'capitalise' on his or her technique. The field was highly competitive, between individuals and institutions. The moratorium on this research, as well as the further NIH guidelines and public hearings had real effects on some careers, and several scientists concerned about their future went as far as moving institutions. Thus, after public debates in Cambridge, MA led to a brief local moratorium on recombinant research, Tom Maniatis moved to Cold Spring Harbor.

---

[46] Hughes 2011:13–20

[47] Ibid.: 51.

[48] Wade 1977: 32

Maniatis had just received an assistant professorship at Harvard and was working on techniques for cloning DNA using mRNA molecules as templates (complementary DNA or 'cDNA'). The lab that was being built for recombinant work at Harvard, which would include the Maniatis group, was one of the focal points of the criticism. Through an encounter with James Watson, he was offered to move to the more peaceful environment at Cold Spring Harbor, and subsequently settled at the California Institute of Technology (CalTech) in Pasadena, where he moved on to work on inserting cDNA fragments into mammalian cells.[49]

Maniatis was recruited to CalTech by Robert Sinsheimer, one of the most vocal opponents of recombinant DNA research in scientific circles. Despite his political commitments, he believed that it was his responsibility as chair of the biology division to attract the best talent at the cutting edge of research. Less prominent and endowed departments, by contrast, were less likely to invest in required facilities. Thus, Richard Palmiter, a biochemist at the University of Washington in Seattle who was then working on chicken ovalbumin gene spent much time in Pierre Chambon's laboratory in Paris after his home institution was reluctant to build containment facilities.[50]

My goal here is not to criticise the NIH guidelines, which were a result of complex negotiations with great scientific input and in many ways a success story of the scientific lobby that avoided federal regulation. It is rather to note the effect they had on the dynamics of circulation and experimental work and access to novel techniques before their standardisation. Despite the constraints that the guidelines imposed on research, recombinant molecules could circulate with relative ease. Even though it was recognised that molecular biologists had limited awareness of how to work with potential pathogens, the exchange of reagents was defended. At Asilomar, a group of delegates voiced concerns about the effects regulation could have on sharing, and argued that the dangers were limited to the primary stage of inventing new recombinants and were best

[49] Maniatis 2012

[50] Palmiter interview. The cost of the higher-level P3 containment suitable for most recombinant experiments except those involving dangerous pathogens – was estimated at $50,000 (Wade 1977) – abpout $200,000 in today's prices and roughly the cost of a large ultracentrifuge. This was expensive, but affordable for most research universities. The political costs of allowing controversial research were perhaps more significant.

left to 'quality' labs.[51] Isolated DNA could be posted through courier services within a secondary container in case of spillage.[52] The space in the large dry ice boxes used to ship samples could even be optimised by packing in some ice-cream and occasionally lobsters.[53] It was the escape of modified organisms that was most strongly policed, even though these could also be shipped with proper requirements.

Circulation of molecules and information were also important concerns in the patenting debates surrounding the basic "cut and paste" methods. As Boyer and Cohen published their work on inserting a *Xenopus* gene into *E.coli* in 1974, Stanford's patenting officer learned about it from the front page of the *New York Times* and set off to file a patent application within the remits of the university's institutional patent agreement with the US Department of Health, Education and Welfare (DHEW). The move caused severe debates both within Stanford and in the scientific community at large.[54] In these early discussions, Cohen and Boyer agreed that their experiments were made possible by multiple existing tools and innovations. The challenge to the distribution of credit within the moral economy of recombinant research was negotiated through the late 1970s, partly by making the case for patents being in public interest, and by the great interest of the US government in biotechnology as the industry to reinvigorate flailing US economy.[55]

In 1976, under the leadership of NIH director Donald Fredrickson, DHEW consulted scientists, scientific associations, industry representatives, patent lawyers and a few consumer organisations on patenting recombinant methods.[56] University scientists' responses were diverse, ranging

---

[51] "The power of these techniques is such that many others will be tempted to follow on immediately, perhaps with less experience and poorer facilities. I only hope that Rougeon, Rabbitts, Maniatis, Salser and their co-workers and followers will make their recombinants freely available. In this field, the way we start will determine whether others will act responsibly later." Williamson 1976

[52] USA Department of Health 1979: 173–180.

[53] Around 1975, Jim Dahlberg would send ice cream from Madison to David Baltimore at MIT alongside virus and RNA samples for their collaboration that focused on reverse transcriptase. In return, he would occasionally get a few lobsters. "Jim Dahlberg on 1974 Cold Spring Harbor Symposium on Tumor Viruses: Collaboration with David Baltimore," Jim Dahlberg oral history interview, Cold Spring Harbor Oral History Colleciton, available at library.cshl.edu/oralhistory/interview/cshl/symposia/dahlberg-1974-cold-spring-harbor-symposia, accessed on 12 September 2014

[54] Hughes 2001, Yi 2011, Berg & Mertz 2010

[55] Yi 2011, Wright 1994, Kenney 1986

[56] US DHEW 1978. See also Fredrickson 2001: 92–104

from reluctance to comment to outright opposition. Some, like Szybalski, assumed commercialisation was inevitable and resigned to it. Others were more positive about industrial applications, but felt recombinant DNA was too controversial a field, both in public arena and in terms of distributing credit among the inventors. However, while scientists were uncomfortable with secrecy, administrators and patent lawyers believed that patents would not delay communication. Even though both academic and industrial correspondents were worried about trade secrets (companies wanted to be able to keep them, scientists were concerned they would arrest the progress in the field), the feeling was that publications were too important for academic researchers, especially in such a dominant and novel area, to be significantly delayed by patent concerns, and peer review and journal back-logs would likely be a much more significant obstacle to speedy circulation of data.[57]

The exchange of information was thus another key concern. It occurred through specialised publications, conferences and the scientific grapevine. New journals appeared continuously in the 1970s, despite the steady growth in price and the declining resources of scientific libraries. Some of them were responding to the growing publication lags between submission and appearing in print – something that could take between 6 and nine months, according to a *Nature* comment in 1972. *Cell,* a new journal of "exciting biology" as claimed in its first editorial, was founded in 1974 by Benjamin Lewin and promised a rapid publication of comprehensively research and argued papers using an international board of editors who could deal with manuscripts on a more local basis. In the same year, *Nucleic Acid Research* was founded, also promising rapid publication. Journals more specific to recombinant research appeared in the late 1970s. *Gene,* dedicated largely to gene mapping with restriction enzyme but in practice publishing an array of recombinant research, was founded in 1977, and was flooded with manuscripts. It was edited by Szybalski who used his journal's editorials as a platform to comment on the current state of knowledge and regulation.

[57] There was some flexibility with journal publication in the USA, as patent applications need to be filed within a year of public disclosure to qualify for US Patent and Trademark Office. This would, however, disable most international patent protection at the time.

Despite the emphasis on speeding up publication, they were never fast enough for the key sites of molecular research, and much personal exchange of information occurred before publication. Preprints of papers and conference talks circulated between collaborators without the pressure of formal publication. Conversations and personal correspondence often involved data and images sent as courtesy. Again, expectations on sharing existed, even though they had to be counterbalanced by interest in securing priority and developing one's own work. James Watson's essay in the 1973 Cold Spring Harbor annual report summarised this paradoxical situation. It emphasised the importance of priority as not a mere matter of pride, but a career requirement for securing positions and research funds ("There is little enthusiasm for those who always come in second").[58] How one learned about a competitor's results was an important consideration in adopting someone else's method or experimental system: if there had been a publication, the problem was "up for grabs", but if one learned about it informally, an expectation existed that one should let the author publish. Publications lags were thus not only frustrating to the author, but to those waiting to reap the benefits of the paper. However, most manuscripts circulated as preprints, given to students, collaborators and selected colleagues – the writing up moment, Watson argued, was the more useful timing of discovery. While the author may have requested that a colleague refrain from sharing the data, news and secrets were impossible to keep once they began circulating beyond the author. Watson concluded with a call to persevere with science, to the best of one's ability, despite the inevitable "the rat-race aspects of much of the high-power science" that was not going to disappear.[59]

With the rapid pace of recombinant DNA research and political uncertainties around it, its scale expanded dramatically. Unlike earlier stories of animals or isotopes, there were many hubs of sharing DNA. While they were attempt to centralise plasmid supply and catalogue isolated genes – most notably by GenBank, but it collected sequence data[60] – plasmids moved contingently before

---

[58] Reprinted as Watson 2000. Quote on p.103. Watson, himself notoriously benefitting from being shown Rosalind Franklin's unpublished DNA X-ray crystallography images without her knowledge – an episode that *The Double Helix* recounts in vivid and nonchalant detail – had a case to make.

[59] Ibid.:103. Latour and Woolgar's influential *Laboratory Life* reflects a similar take on publications and credibility. While they may have presented their book as a study of contemporary science in general, it is no accident that their fieldwork was conducted in a high-profile molecular biology lab. Latour & Woolgar 1986: 187–233.

[60] Strasser 2011, Stevens 2013: 137–62.

the courses and handbooks on recombinant DNA techniques were available. In these years, jumping on the "molecular bandwagon" relied on alliances that were likelier to succeed at prestigious and well-funded institutions. With the growing interest in eukaryotic genes that were now mobile and subject to analysis, scientists working with animal cells and even embryos were increasingly securing access to these networks.

§4. "DNA-mediated gene transfer": Expanding the networks

While Jaenisch benefited greatly from his position at the Salk, his work remained within the bounds of animal virus research. With M-MuLV, Jaenisch was able to trace the virus through the cell and subsequent generations of mice, establishing Mendelian transmission of the virus. He had developed a more straightforward method to detect specific DNA, using viral cDNA after the methods pioneered by Tom Maniatis spread through the elite networks of molecular research. Moreover, he found that embryos could be infected with M-MuLV at 4–8 cell stages, avoiding the need for microinjection that made the procedure much easier to perform.[61] There were no suggestions in the papers that viruses could be used to introduce new genes via recombinant experiments. Given the central role of tumour viruses in inspiring such work, it is hardly the case that the idea hadn't occurred to him or his readers. However, such an emphasis allowed Jaenisch to avoid participating in unsavoury debates and to focus on the important questions of cancer origins and the regulation of viral DNA. However, other labs were increasingly looking to use plasmids to answer questions about mammalian gene expression. The success of this programme drew on aligning research from somatic cell genetics, tumour virus work and recombinant experiments to articulate a new agenda for genetic modification of mammalian cells.

In 1976, gene splicing delivered on the promise of isolating eukaryotic genes; the first plasmids carrying interesting genes were reported and shared. Genes for various globins and immunoglobulins were isolated among others. Combined with the array of other techniques mentioned above, but not yet in wide use, the researchers working on eukaryotic DNA were in optimistic

[61] Jaenisch 1976, 1977.

mood. The new work was brought together in the 1977 Cold Spring Harbor symposium on 'Chromatin', the structural element of eukaryotic chromosomes that combines DNA and proteins. The symposium on 'Chromosome Structure and Function' had been held as recently as 1973, so the return to the topic – and the subsequent 1978 symposium on DNA replication – signalled enthusiasm about eukaryotic genomes. In his forward to the published proceedings of the Chromatin symposium, James Watson noted that "at the end we were both overwhelmed and dazzled, and many participants left feeling they had been part of an historic occasion".[62] Pierre Chambon's summary reviewed recent research on eukaryotic cells to claim that the previously 'dirty' field that had looked up to bacterial genetics for its clarity and elegance was now more than capable of being understood in similar terms. It also brought together the molecular techniques of gene splicing and nascent DNA sequencing with the more nuanced appreciation of eukaryotic genes in cellular context. All the advances, Chambon suggested, "marked the beginning of a new phase where we can foresee the day when eukaryotic developmental problems will be elucidated at the molecular level."[63]

While gene transfer in mammalian cells was still seen as 'black magic',[64] experiments that aimed to adapt bacterial transformation protocols to tissue culture were gaining traction. In 1973, the Canadian microbiologist Frank Graham had published a paper with Alex van der Eb, whose lab in Leiden he was visiting, in which they developed a method of transferring purified herpes simplex virus (HSV) DNA using calcium phosphate and salmon sperm DNA. In April 1977, Graham published further work on inserting isolated fragments of the herpes virus with the thymidine kinase (*tk*) gene into human cells in *PNAS*.[65] A month later, a similar paper from Richard Axel's group at Columbia University appeared in *Cell*, refining the method somewhat.[66] As a brief review in *Na-*

[62] Watson 1978: xv.

[63] Chambon 1978: 1209.

[64] Angier 1988: 56–9.

[65] Graham & van der Eb 1973.

[66] Wigler, et al. 1977.

ture suggested in 1977, "it may eventually become feasible to use the HSV model for DNA-mediated gene transfer."[67] In the late 1970s plasmid carrying the *tk* gene became a vector of choice.

The use of HSV *tk* relied on the older work on gene transfer from the early 1970s, as it was one of the first genes whose phenotype could be easily detected in cell culture by the ability to grow on specific media such as HAT. The transition of HSV tk from a sign of viral infection was representative of a broader instrumental shift towards using plasmids made with restriction enzymes to ask questions previously addressed by infection research. Similarly, SV40 DNA was being routinely isolated and inserted into plasmids, as one of the first materials of interest to recombinant researchers. New means of detecting and assaying for the *tk* gene were being developed,[68] and it was shared widely. Moreover, as purified DNA was increasingly accessible, a new network of discussions was constructed around its use in higher organisms.

Designed to foster communication between different fields, conferences on gene transfer helped elaborate new questions, and their proceedings, increasingly published through rapid photoprinting, document the attempts to give some coherence to the 'cutting edge'. A major meeting dedicated to 'Genetic interaction and gene transfer' took place in 1977 at the Brookhaven National Laboratory. Its convenors claimed the objective was to "collect information, scattered in different disciplines in biology, pertaining to how functional genetic material could be efficiently transferred to a eukaryotic cell, maintained in a stable state and expressed in a regular manner."[69] The audience was diverse: Beatrice Mintz talked about using teratocarcinoma cells as vehicles for foreign genes; Frank Ruddle about chromosome-mediated gene transfer; John Gurdon about nuclear transfer as a way of introducing new genes into frogs. Plasmids, viruses, gene expression of eukaryotic genes in bacteria and bacterial genes in cultured mammalian cells were all discussed.

The diversity of agendas was not easy to organise. The final talk by the respondent, Charles Thomas from Harvard, was instead devoted to the public discussion of genetic engineering.[70] Titled

---

[67] Portugal 1977.

[68]Summers & Summers 1977.

[69] Anderson 1978, Introduction.

[70] Thomas 1978.

'The fanciful future of gene transfer experiments', it attacked the confused discussion of 'genetic engineering' in the press, claiming its perceived hazards were "totally conjectural". In practice, however, Thomas' piece engaged heavily with the scientist-critics of genetic engineering such as Salvador Luria or Robert Sinsheimer, as well as some science journalists. The message was to avoid exciting public distrust through conjectures and science fiction and focus on pressing concerns. Thomas believed gene therapy, a major theme in these earlier debates, was not feasible for the majority of hereditary disease. Instead, he emphasised the practical concerns of economic advance and the growth of knowledge: producing useful proteins in cells and understanding the developing organism, and by extension cancer that he argued was a developmental programme gone awry.

Even though the scientists involved had expressed diverse views about regulating recombinant molecules, the pressures of compliance and a sense of urgency contributed to constructing a community that was often made up from diverse research programmes. The emphasis on communication was repeatedly used to create new spaces for exchange. In 1977, a Gordon research conference on 'Introducing macromolecules into eukaryotic cells' was proposed, with the first meeting held in 1980.[71] The Gordon Research Conferences were a series of elite scientific meetings in New Hampshire started in 1932 by the chemist Neil Gordon under the aegis of the American Association for the Advancement of Science. By 1970, they had turned into a wide web of specialised events spanning the academic summer. These meetings became prestigious, a networking space where the trends in biology could be discussed and created.[72] Each conference was limited to about 100 delegates, no records were published and note-taking was discouraged.[73] Prominent scientists, including Berg and Ruddle, backed the proposal to have a dedicated meeting on introducing macromolecules into eukaryotic cells. Its author, Martin Rechsteiner, associate professor of biology at the University of Utah, stressed the need for wider communication and argued that "the conference [would] draw individuals from the diverse disciplines of lipid biochemistry,

[71] Gordon Conference Archive, Othmer Library, Chemical Heritage Foundation, Philadelphia.

[72] The recombinant DNA controversy began at a 1973 Gordon conference, when proposed experiments from Berg's lab raised major concern.

[73] Gordon Research Conference Records Finding Aid. Othmer Library, Chemical Heritage Foundation, Philadelphia. Available at http://othmerlib.chemheritage.org/articles/1043271.6959/1.PDF, accessed on 14 March 2013.

genetics, cell biology, and nucleic acid chemistry. At present, there is simply no forum in which these individuals can meet and exchange ideas."[74]

In May 1979, a major Wistar Institute workshop on 'Introducing Macromolecules into Viable Mammalian Cells' took place in Philadelphia, a few months after the NIH significantly relaxed its recombinant DNA guidelines. Representing the state of the art, the focus was on the new approaches to gene transfer in mammals, especially recombinant techniques. The papers encompassed several approaches. The established calcium phosphate method was presented by its inventor Frank Graham. Microinjection of molecules was discussed by several scientists whose laboratories were experimenting with the technique. Attempts to use membrane components to deliver DNA were also communicated.

Despite the concerns expressed in the Gordon conference application, the extent of existing collaboration between researchers at the cutting edge was evident in the Wistar papers. Cell lines, virus fragments and increasingly plasmids were being shared and acknowledged in publications. Richard Axel, Saul Silverstein and Michael Wigler were especially generous with their material, sharing the herpes virus fragments with the *tk* gene and the cells widely among the Wistar presenters. Moreover, with Tom Maniatis, Axel's group was advertising a new means of introducing any gene into mammalian cells, based on the *tk* selection. If a plasmid could be made that carried the gene of interest *and* HSV *tk*, the transformed cells could be selected straightforwardly on HAT medium or with drugs that specifically targeted the viral protein.[75]

Alongside this wide sharing, Columbia was also filing a patent on the co-transformation technique developed by Axel's group. The Columbia patent proved to be extremely lucrative, bringing around $790 million in over through its lifetime.[76] The first of what came to be known as the 'Axel patents' were filed on the cusp of a major transformation in the debates on patenting federally-funded research, just after the Bayh-Dole Act was passed in 1980 but before it came into force in

---

[74] Rechsteiner, letter and application to Alexander M. Cruickshank, 21 November 1977. Directors' files: Alexander M. Cruickshank – correspondence, Series III, Gordon Research Conference records, Othmer Library, Chemical Heritage Foundation, Philadelphia.

[75] Wigler, et al. 1979

[76] Colaianni & Cook-Deegan 2009

1981. The Bayh-Dole Act, initiated during Jimmy Carter's administration but seen to effect by Reagan's, was a product of the US government's anxieties about the future of US economy and the decline in traditional manufacturing. It was hoped that it would encourage the rise of a knowledge-intensive economy and so reinforce the US position in the global marketplace – a hope for which the nascent biotech industry was a poster-child.[77]

The wide sharing and promotion of the cotransformation technique in the academic community was not in immediate conflict with the patenting attempts and indeed was generating a market for them. Even if the application was controversial in some circles, it was much less so than the Cohen-Boyer application, and the commercial viability was uncertain, at least according to the scientists' recollections. In fact, by the time the patent was granted in 1983, the technique was widely used both in industry and university research, which enabled Columbia to charge royalties retroactively. This ability to use mammalian cells brought recombinant methods further in line with the growing interest in eukaryotic genes and their products, including potential drugs like insulin and interferon, as well as molecules implicated in genetic disease, most notably haemoglobin.

With the expansion of recombinant DNA techniques to mammalian cells, the amount of researchers who could benefit from the rapid techniques and circulating genes moved beyond the expanded laboratories. New experiments could be envisioned, and several high-profile reports of modifying mouse and human somatic cells were made in 1980. As the next section will demonstrate, this expanded circulation and communication also included scientists who were considering transferring genes into mouse embryos. While Jaenisch and Mintz's work had shown that molecular intervention into the mouse embryo was feasible, it was the growing circulation of plasmids, easier methods for detecting foreign DNA and assaying expression, success with somatic cells and new communication arenas that encouraged several groups to attempt genetic engineering in the mouse.

[77] Ibid., Mowery, et al. 2004, Kenney 1986, Cooper 2008

Conclusion

The story of "genetic engineering" in the 1970s – both as a controversy and as a loose set of scientific research programmes – goes far beyond the now 'classic' experiments in bacteria or debates over public safety and regulation. Activities at the margins drew many high-profile followers, and integrated older research traditions with new techniques. Thus, the work of Beatrice Mintz and Rudolf Jaenisch that would become a common reference point for the actors' histories and citation pattern on transgenic mice, predated recombinant technology. However, such research projects benefited greatly from the emergence of simpler, adaptable and dramatically mobile techniques that allowed the experiments to become more efficient.

One of the crucial effects of recombinant research was the making of exchange networks and the expanded communication between institutions. Access to these networks was not necessarily exclusive – the likes of Berg or Axel shared with colleagues from unestablished laboratories. Yet it was limited by both the proximity to the key sites where recombinant work was done, and by the economic and political costs of proceeding with such experiments in a safe manner. As Rudolf Jaenisch's 1970s career shows, a location at the crossroads of people, techniques and information could be extremely productive for someone eager to engage with cutting-edge methods and perform experiments that aimed to answer ambitious questions.

In the emergent field of recombinant research, sharing was a paramount impetus that allowed specific methods to disseminate widely, and their inventor to receive credit. However, these exchanges happened in a competitive field and an extremely unstable climate for experimentation. The possibility of federal regulation was successfully avoided by the scientific lobby, and was in many ways transitory. Other longer-term changes were more pertinent to the practices of circulation. First, the standards of what counted as a legitimate means of circulating knowledge were relaxed somewhat, as experimental results were discussed widely before formal publication (see alsoChapter 4), and journalists became heavily engaged with recombinant debates and received easy access to most regulatory and scientific meetings. Second, the rise of the commercial promise of genetic engineering introduced a new form of distributing credit: the patent application.

While patenting university research had not been unheard of before the 1970s, it was largely absent from molecular biology. With the slow growth of federal funding in the 1970s, coupled with institutional and government impetus to secure private patronage for biomedicine, intellectual property was being firmly introduced on campus.

As I have shown, intellectual property concerns did not necessarily affect the circulation of materials between academic sites in the early days, but they did introduce a whole other series of considerations when conducting research, as well as opening up new opportunities for molecular biologists. In this context, ideas and methods for gene transfer into eukaryotic cells were becoming articulated more readily, and new alliances were being made across disciplines and subdisciplines, increasingly defined in terms of experimental methods and held together by distinct sharing networks. Such alliances enabled ambitious the experiments that ultimately yielded transgenic mice.

Chapter 3. Putting genes into mice: Promises, experimental trajectories and expertise

Between 1980 and 1981, six groups published articles claiming that foreign DNA could be injected into a mouse embryo and persist through development. The papers relied on similar methods: direct microinjection of DNA solution into a fertilised mouse egg at the one-cell stage. However, as all participants have agreed, the results were achieved independently, with one exception in which techniques were learned directly from another group. These mice were thus a multiple invention – something Robert Merton believed to be routine in scientific research and a prime site for investigating the functioning of scientific norms.[1] With the decline of the Mertonian norm-centred programme of sociology and the constructionist and practical "turns" in history of science, multiple discoveries have mostly slipped out of focus. The social mechanisms behind settling priority received some attention in the 1980s,[2] and I will address the assignment of credit in Chapter 4. Here, I am interested in the practical worlds of the multiple laboratories that worked on introducing DNA into mouse embryos, their traditions and diverse experimental expertise. While multiple inventions are assigned as such retrospectively, the question remains: how did very similar scientific programmes come to be pursued at multiple locations? What explains the scientific *Zeitgeist*?

As late as 1979 it was not at all clear that introducing DNA into a mouse would work in the near future, or indeed that it was necessarily a productive avenue to pursue. While the idea of a genetically modified mammal – or rather, various ideas – were floated in keynote lectures and discussions, other ways of combining mammalian development with the techniques of molecular biology received more attention. Despite the apparent homogeneity of methods and goals in the dry published accounts, the successful laboratories represented a diverse set of research traditions and experimental programmes.

To some extent, the locations and timings of these experimental results were historical accidents. Yet there were certain ways of organising research and DNA exchange that were essential for

---

[1] Merton 1973, Murray 2010.

[2] Brannigan 1981, Cozzens 1989.

gene transfer into mice to work. Others pursued similar lines of research but did not generate comparable results – a useful point of comparison for conditions that made collaborations successful. For the work to succeed, considerable expertise in working with mice and their embryos was essential. Some groups fulfilled these criteria by complementing their laboratory expertise by hiring postdocs; others managed to establish productive collaborations through well-managed divisions of labour. Moreover, plasmid exchanges and growing access to molecular tools made risky experiments with mouse embryos a possibility for those laboratories that could afford speculative research.

In addition, I will argue that a system of partial communication of unpublished results and speculation about what was happening in other laboratories promised high rewards due to a sense of competition and the lack of a clear leader. Distance between sites played a doubly productive role. Rumours that others were attempting this kind of experiment pulled the cutting-edge project into the realm of the possible and made it an attractive avenue. At the same time, limited and unconfirmed knowledge about whether competitor laboratories had been successful meant that credit for modifying a mouse was up for grabs.

I begin by examining the discussions about making a genetically modified animal in the late 1970s, which shared little consensus as to the right experiments to pursue. I will then examine the research programmes in laboratories that ended up reporting gene transfer into mouse eggs. In the second half of the chapter, I will focus on the experimental work that was done in these laboratories, especially microinjection and the interaction between embryological and molecular work at the bench.

§1. "Possibilities and realities"

> The interest in... monsters is that they show how a culture handles the possible and marks its limits.[3]
>
> *François Jacob*

A discussion of monsters and their role in delineating the future opened François Jacob's lecture at the University of California, Berkeley in 1977. In a sweeping overview of recent biological sciences Jacob touched on the different modes of inquiry and explanation, from magic to science; the hierarchy of scientific objects and therefore disciplines, from 'hard' physics to 'complex' social sciences; and the metaphors of evolution, at the heart of his argument that one best think about natural change as "tinkering" rather than design. At no point was genetic engineering mentioned, but the omission was rhetorical: the subject was constantly alluded to and flirted with, from the introduction devoted to monsters to a section on 'molecular tinkering'. This lecture fit well within Jacob's writing, known for its elegance and philosophical ambition, but it also resonated with the wider contemporary narratives of naturalising gene splicing, giving these experiments a long genealogy rooted not only in established human activities such as breeding, but also in the way nature itself worked. For Jacob, naturalising genetic tinkering meant that the scientific approach – which he couched as a mode of human understanding – was the best way of delineating the possible.

The idea of introducing genetic changes into animals (including humans) had been at the forefront of 'new biology' discussions in the 1960s. Despite the focus on bacteria in the recombinant DNA controversy of the 1970s, the interest in using the new methods to manipulate animals and plants was strong. As I have shown in Chapter 2, in the 1970s the ability to manipulate eukaryotic genes in bacteria and eukaryotic cells attracted many scientists to recombinant DNA. The molecular promise also captivated a number of laboratories that sought to apply the power of genetics to differentiating embryos. These latter programmes often predated the expansion of recombinant DNA and relied on the burgeoning research into animal viruses, somatic cell genetics and the biochemistry of proteins and nucleic acid.

---

[3] Jacob 1977: 1161.

Given the political difficulties around genetic engineering, suggestions for potentially controversial future research tended to no longer be aired in public. Scientific papers were rarely a place for speculation. However, writing that addressed expert audiences without a firm commitment to presenting experimental results – review articles, "trends" pieces, lectures and talks – did and discuss future experiments. These sources hint at multiple plans to harness recombinant DNA to modify animals in the late 1970s, even though the most promising routes were by no means settled. By adopting the rhetoric of future directions, senior scientists shared their awareness of experimental work that was being pursued before publication, highlighted what they saw as worthwhile projects and made links between the possible and the real.

With the new techniques of somatic cell genetics and recombinant DNA, genes themselves became instruments as well as subjects of molecular analysis. Early attempts to introduce nucleic acids into embryos, such as the Jaenisch-Mintz experiment, focused on viruses as a subject of investigation. Concurrently, John Gurdon was turning another kind of germ cell, the frog oocyte, into a powerhouse of molecular analysis. Celebrated for cloning *Xenopus* by transferring a nucleus from a tadpole cell into an enucleated egg in 1958, Gurdon articulated the need to understand gene regulation to decipher the mechanics of development.[4] In the early 1970s, his Oxford group collaborated with Donald Brown at the Carnegie Department of Embryology to inject RNA molecules into oocytes – large egg cell precursors, around 1 mm in diameter, that could be easily cultured. In 1971, Gurdon moved to the Laboratory of Molecular Biology (LMB) in Cambridge, where he extended his system to analyse DNA.

With a strong emphasis on molecular thinking as a way to understand eukaryotic biology, Gurdon and his followers were representing the *Xenopus* oocyte as a simple system that resembled *E.coli* and could become attractive to molecular workers. Moving away from the discussions of embryonic complexity and determination common in developmental discourses, Gurdon repeatedly employed the metaphor of a test-tube to describe the oocyte (Fig. 3-1). In reviews and forward-looking pieces, such as a 1977 "Future Trends" article in *Trends in Biochemical Sciences*, Gurdon and colleagues argued for the advantages that oocytes offered over cell-free systems and bacteria,

[4] Gurdon, et al. 1958. For Gurdon's microinjection work, see Lane, et al. 1971, Mertz & Gurdon 1977, Gurdon & Melton 1981. Gurdon's lectures on gene expression in development were published as Gurdon 1974a.

claiming that the "crudest" system such as the living eukaryotic cell might also be best for detailed biochemical analyses.[5] With the spread of DNA cloning, *Xenopus* oocytes were envisioned as a promising system to track the elusive promoters – DNA sequences upstream of a gene that control its expression: "One way of overcoming these problems [lack of promoter mutations and adequate transcription assays] would be to combine methods of DNA cloning with the injection of DNA into oocyte nuclei.... The injection of these DNAs into oocytes should make it possible to identify which segment contains the promoter."[6]

Frog oocytes offered a well-established system with large cells. By contrast, mammalian embryos had been notorious for their relative scarcity and small size that made detection of minute concentrations of molecules a challenge. Several mammalian embryologists with an interest in molecular questions, such as Mintz, Brinster and Gardner, experimented with teratocarcinoma cells, an alternative system that combined elements of cell culture and embryo-like behaviour.[7] They were incorporated into existing practices of manipulating mouse embryos. In 1974, Ralph Brinster announced successful microinjection and subsequent incorporation of such cells into a mouse embryo, which he recently called the hardest experiment he had ever done.[8] In 1975, Mintz's and Gardner's groups also reported incorporation of teratocarcinomas into a developing blastocyst and showed their contribution to adult tissues and reversal from a cancer-inducing phenotype.[9] The younger scientists who were involved with these experiments went on to become key names in mammalian development: Mintz's postdoc Karl Illmensee, Gardner's student Virginia Papaioannou as well as Martin Evans and Gail Martin, then at UCL, who went on to culture embryonic stem cells in 1981. Between 1975 and 1981, teratocarcinomas were promoted as a means of integrating cellular approaches (such as somatic cell genetics) with embryology, by nobody as strongly as Mintz.

---

[5] De Robertis, et al. 1977. See also Gurdon 1974b.

[6] De Robertis, Laskey & Gurdon 1977.

[7] There is a technical distinction between teratocarcinoma cells and embryonal carcinoma cells (ECCs) – the latter are the stem cells from which teratocarcinomas differentiate into all the diverse tissue. ECCs can be isolated when teratocarcinoma cells are cultured in suspension and form cyst-like 'embryoid bodies'. However, because scientists routinely used these terms interchangeably, I use "teratocarcinoma cells" for the sake of clarity.

[8] Brinster 2013.

[9] Mintz & Illmensee 1975, Papaioannou, et al. 1975.

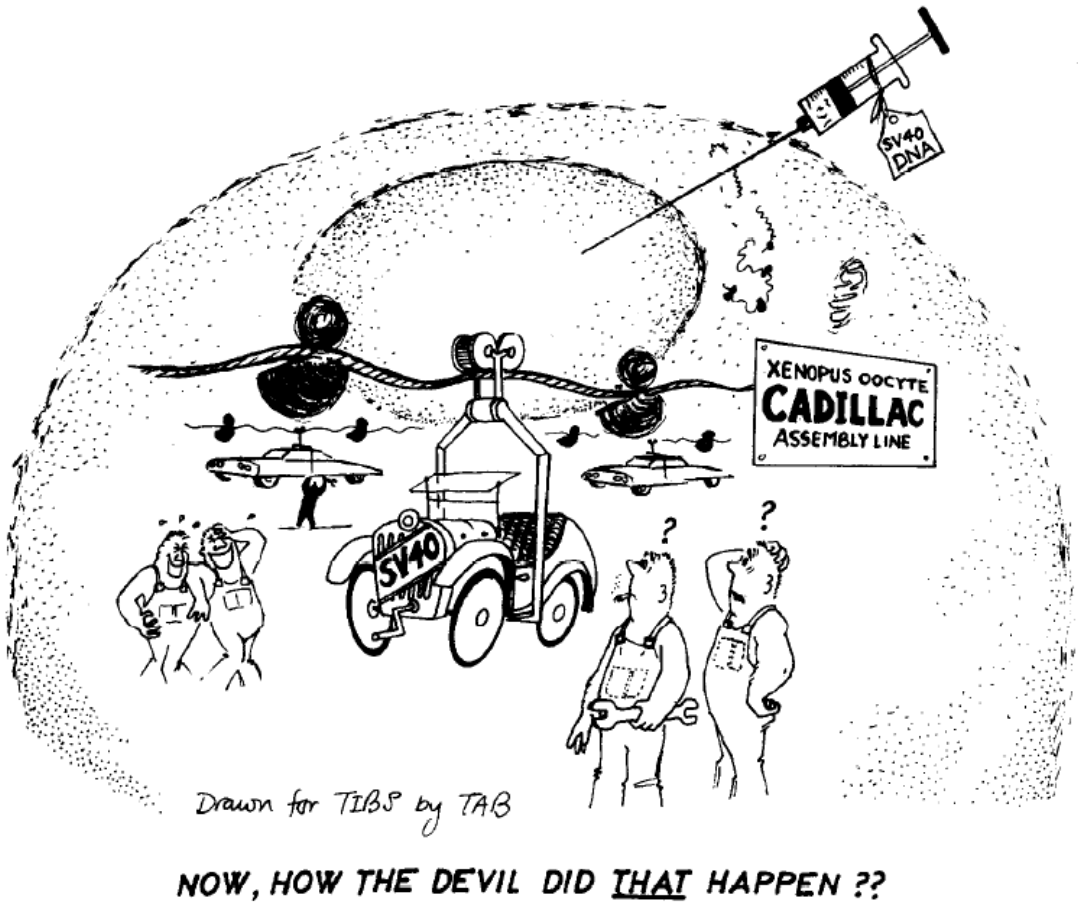


Fig. 3-1. "*Xenopus* oocyte Cadillac assembly line" – a drawing from Gurdon's programmatic review in *Trends in Biochemistry*.

De Robertis et al 1977

Mintz was receiving wider recognition in American biology, having been elected to the National Academy of Sciences in 1973. Her work on mosaic mouse embryos had been occasionally reported in the *New York Times* since the mid-1960s, and in 1976 it was included in a magnificently-illustrated three-part feature on the 'New Biology' by the *National Geographic*.[10] Like the other prominent scientists, however, Mintz balanced speculation with reality checks in her public appearances. She delivered a series of high-profile lectures in the late 1970s, many of them devoted to the problems of cancer, development and genetics. Thus, in 1976 she was among the Harvey lecturers at the New York Academy of Science and argued for the need to "seek ways of analyzing some of the most complex, and least understood, aspects of [cancer and differentiation] where

[10] Gore 1976.

they actually occur: *in vivo*."[11] She suggested two wide ranging experimental programmes. One was to focus on the problem of malignancy, which she approached in decidedly developmental terms – whether tumours arose from one cell or many, which factors affect their growth and differentiation, and whether the key changes were genetic. The other approach sought to interrogate differentiation more generally by looking for new informative mutations:

> Through mutagenesis and selection *in vitro*, followed by differentiation *in vivo*, experimentally useful genes could be introduced into mice. There, the full developmental consequences of specific gene mutations coding for biochemically identified changes could be brought to light.[12]

A year later, when addressing a specialist audience at the 1977 Brookhaven meeting on gene transfer, Mintz made the point even more strongly: she referred to teratocarcinomas as "surrogate eggs", cells that could integrate the whole-organism approach of classical genetics with the selection advantages offered by somatic cell genetics. She specifically discouraged the use of mouse eggs as they were too few in number and impossible to select in culture, while other kinds of somatic cells could not contribute to the embryo since they were already differentiated and their genetic status was "usually uncertain".[13] By contrast, teratocarcinoma cells had the potential to fulfil these criteria, even though their genetic status, as cancerous cells that accumulated mutations, was not exactly certain. Mintz's talk at the Brookhaven meeting provoked many questions, including from Ruddle, and in the following years her lab focused on developing a teratocarcinoma line that would be seen as genetically stable and could contribute to the germline in allophenic mice.

Beyond these important meetings, Mintz's growing clout exposed her to new audiences. In 1978, she was a go-to source for scientific comment in the affair that unravelled around David Rorvik's book *In His Image* that claimed a Californian millionaire had himself cloned in a remote jungle clinic on a South American island. Rorvik's established medical publisher, J. B. Lippincott, marketed the book as non-fiction based on Rorvik's word and his supposed role as negotiator in the

---

[11] Mintz 1978a: 238.

[12] Ibid.

[13] Mintz 1978b.

murky process. The book was dismissed as a hoax by the scientific community, but it stirred a heated media debate about the possibility and ethics of human cloning.[14] Mintz, alongside Clement Markert, Peter Hoppe and Derek Bromhall, was quoted in multiple sources commenting on inconsistencies in book and the state of the art in mammalian development, delivering some choice quotations to journalists, for instance when she described Rorvik as "a fraud and a jackass".[15] In May 1978 congressional hearings before the Subcommittee for Health and Environment of the US House of Representatives ensued. Designed to interrogate Rorvik, who failed to show up, they ended up focusing on the state of research and funding in cell biology. Testifying alongside such scientists as Markert, cloning pioneers and Fox Chase colleagues Thomas King and Robert Briggs, NIH officials and the omnipresent lobbyist and genetic engineering opponent Jeremy Rifkin, Mintz used the hearings as an opportunity to outline her work and to express anxiety about effects of unsavoury public exposure on future funding.[16]

Several conferences with ambitious titles encouraged their speakers to go beyond presenting the latest experiments. The 1978 Ciba Foundation London symposium on "Genetics and Human Biology: Possibilities and Realities" was one such event. Sydney Brenner's introductory remarks picked up Jacob's 1977 lecture on monsters and tinkering. Referring to contemporary debates, Brenner argued that genetic engineering in the sense of designing an organism had not been developed. "All we can do is a little 'tinkering', but that, as François Jacob… has pointed out is nature's way and not ours."[17] Jacob was in the audience, alongside other luminaries of molecular biology, developmental biology and genetics, including Walter Bodmer, Francis Crick, Richard Gardner, John Gurdon, Henry Harris, Hilary Koprowski, James Neel, Guido Pontecorvo and Ruddle (Fig. 3-2). In the speculative atmosphere of the symposium, participants discussed papers on recent advances and possible futures in genetics, from cultural evolution to cancer. The symposium was dedicated to the retirement of Sir Gordon Wolstenholme, the Ciba Foundation's director and chairman of the Genetic Manipulation Advisory Group (the British equivalent of RAC), which

[14] Rorvik 1978. On the Rorvik affair, see Goodfield 1981: 51–67, Kolata 1998: 80–102.

[15] Quoted in Gwynne, et al. 1978.

[16] USA House of Representatives Committee on Interstate and Foreign Commerce 1978.

[17] Brenner 1979: 2.

explains its ambitious scope. Given the Ciba Foundation's policy of publishing edited discussions as well as presented papers, the proceedings offer a rare glimpse into the informal process of delineating future possibilities by some of the biggest names in the field.[18]

Charles Weissmann, a molecular biologist at the University of Zurich, presented a programme of what he called "reversed genetics", a new way of asking questions by manipulating the DNA molecules to introduce mutations and assess their effects. The phrase was novel, even though discussions about doing 'genetics in reverse' had been already aired.[19] With the expanding availability of eukaryotic genes, ways to induce specific DNA mutations, DNA synthesis and new sequencing techniques, "reversed genetics" offered an alternative to the workflow of classical genetics, which started from a mutation phenotype and then mapped the relevant genes. A lively discussion arose as to which experimental systems would be best suited for such an approach, as the attendees worked on a diverse group of laboratory species and cell-free systems. It is helpful to quote at length:

> *Gurdon:* Professor Pontecorvo, do you prefer the use of a true *in vitro* system (test tubes) to the alternative *in vivo* cells (injected living cells)?
>
> *Pontecorvo:* Yes. It is a lot simpler.
>
> *Crick:* He is a reductionist! The thing is surely clear: one tries the simplest system first; it may be slightly artifactual so one checks it against different stages of *in vivo* or i*n vitro* systems. There is no real conflict here.
>
> *Brenner:* This is simple molecular biology, but there is also the problem of assessing the value of genes that may have to work in entire organisms to produce their effects. Could you comment on the very long-term idea of putting genes back into organisms?
>
> *Weissmann:* I think that John Gurdon's [oocyte and egg injection] system will eventually lend itself to this approach. It should be possible to do the injections in such a way that one ultimately gets development of the embryo and takes the inserted DNA through the complete cycle.[20]

---

[18] Porter & O'Connor 1979.

[19] For instance, there is a reference in the Gurdon group's essay discussed above, De Robertis, Laskey & Gurdon 1977.

[20] Porter & O'Connor 1979: 60.

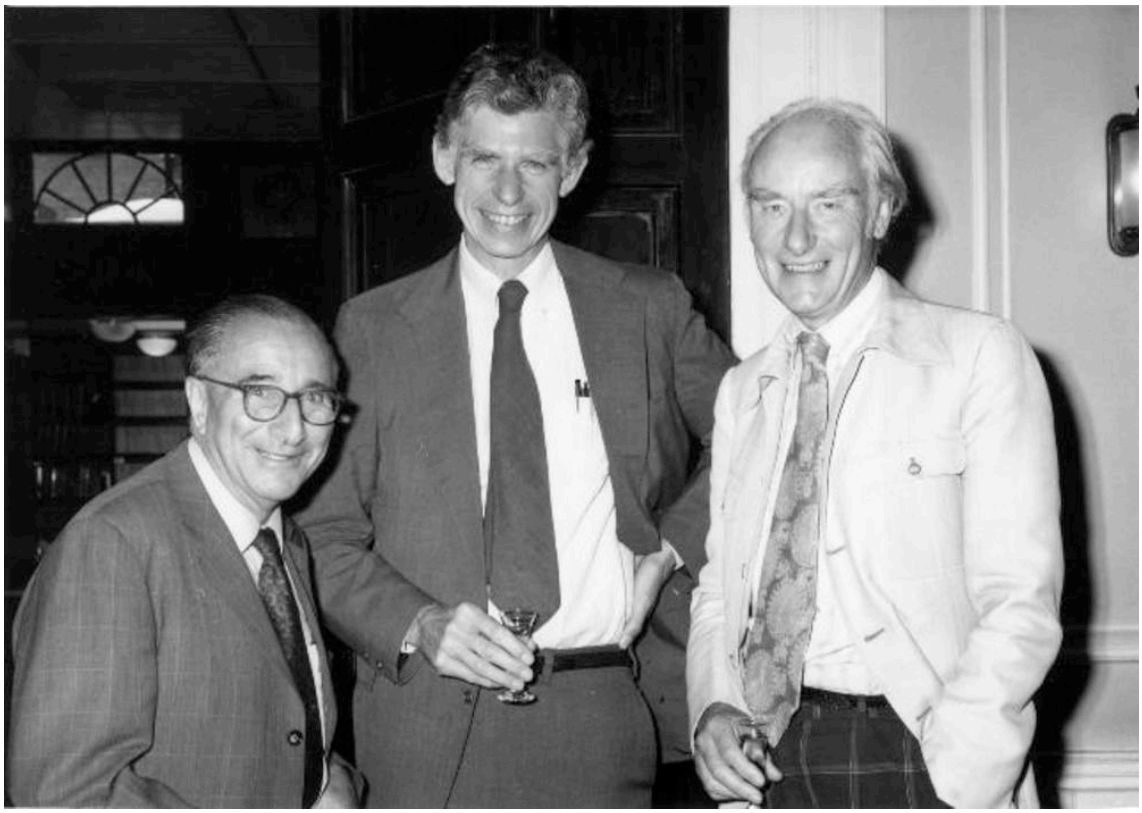


Fig. 3-2. Frank Ruddle (centre) with Guido Pontecorvo (left) and Francis Crick (right) at the 1978 Ciba symposium on Genetics and Human Biology.

Guido Pontecorvo Archives, Glasgow University. Available through the Wellcome Library *Codebreakers* website.

Brenner described the idea of putting a gene into an organism as 'long-term', but Weissmann suggested he was attempting just this kind of work with Hilary Koprowski at the Wistar institute, following the lines of the Jaenisch-Mintz experiment:

> The other approach we are discussing with Dr. Koprowski is the injection of cloned DNA into mouse blastocysts... By introducing appropriate mutations at predetermined sites the functions of control and other regions of the DNA can be explored. It may be possible to get mice which are thymidine kinase-minus, add some selective pressure by dampening the *in vivo* synthesis of thymidine, and give the cells which carry the vector certain advantages. Thus, one might get most of the embryo populated with the DNA hybrid. Those are dreams at present.
>
> *Henry Harris:* I don't really think they are dreams. People have got quite a long way with this kind of thing. David Martin has used mutant teratocarcinomas that are deficient in the gene for [HPRT]. The animal can be populated with the mutant HRPT^{-} cells. It is not

> at all difficult to put a chromosome fragment bearing a good HRPT gene into such cells by cell fusion technique.[21]

The language of dreams and possibilities highlighted the interest in introducing genes into an animal, but stressed the difficulty of this scenario as an experimental programme. The tension between the possible and the existing reflected the perceived pace of change in biology, with hopes placed on new techniques, but also left open the exact way this might be pursued. It was revisited by Frank Ruddle after John Gurdon's talk:

> *Ruddle:* Your experimental system might be well-suited to studying the integration of foreign DNA into chromosomes and the propagation of integrated sequences through the developing organism. There is also the possibility of recovering integrated sequences in the germ plasm. Are you looking into this?
>
> *Gurdon:* We are starting experiments on that but most of these things have technical difficulties.[22]

The experiments with teratocarcinoma cells that Henry Harris referred to were a collaboration between Gail Martin and David Martin at UCSF, and Beatrice Mintz's laboratory.[23] Mintz hoped that once a mouse could be produced from the teratocarcinoma line in the mosaic "the animal would literally be the model of the human disease", but her lab was still having problems making teratocarcinomas contribute to the germline.[24] Mintz was not at the Ciba symposium, and her work came from a different research trajectory. If the questions among the geneticists at Ciba focused on the way to trace a gene through the developing embryo, Mintz was concerned much more with development and cancer, using genes as markers to track differentiation rather than a primary subject of investigation.

While Mintz's lab was a key site of teratocarcinoma research, others pursued this experimental system. Teratocarcinomas as a vehicle for genetic modification were being explored by Karl Illmensee, who moved out of Mintz's lab to work with Carlo Croce at the Wistar and subsequently

---

[21] Ibid.: 60–1.

[22] Gurdon, et al. 1979: 75–6.

[23] Dewey, et al. 1977.

[24] U. S. House of Representatives 1978a: 6.

secured a permanent position at the University of Geneva in 1977. Today, Illmensee is most famous, or notorious, for the allegations of fraud surrounding his claims to have cloned three mice in 1981, but this controversy did not break until 1983.[25] In the late 1970s, he was a rising star in developmental biology, garnering a reputation as a virtuoso experimentalist and a charismatic public speaker.[26] With Croce, Illmensee hybridised teratocarcinoma cells with different somatic lines, hoping to make a hybrid that would contribute to the developing embryo and perhaps introduce novel mutations from somatic cell lines into the whole mouse. Moreover, Illmensee established a collaboration with Peter Hoppe, a mouse embryologist at the Jackson lab, with whom he attempted making parthenogenetic eggs (eggs induced to begin development without fertilisation) and nuclear transfer – a programme of cloning in mammals. After a series of high-profile publications, mostly in *PNAS*, Illmensee was writing programmatic review papers and gave several keynote lectures in 1980.[27] These were devoted to genetic modification of the embryo – yet the methods he proposed were diverse, covering his cell hybrid work, parthenogenesis and nuclear transfer, and differed significantly from those that proved successful.

In these discussions, recombinant DNA was not the primary tool for the job, nor had it always been entertained as relevant, even though it was being used in several locations. The extent of these attempts is hard to assess as few led to publication, but some can be traced. Howard Goodman – famous for a conflict with Genentech over work on the insulin gene – applied to RAC in early 1980 to insert rat insulin DNA into a two-cell mouse embryo, even though no results came out of this project.[28] Illmensee attempted to inject a plasmid containing the mouse beta globin gene into a mouse egg, in an experiment designed to distinguish between the native and foreign versions of the protein. However, such work was seen as a long shot, the protein from the plasmid could not be detected and the work was therefore never published, surviving only as a "personal communication" in a PhD thesis.[29]

---

[25] See Kolata 1998: 103–33.

[26] Jaenisch and E. Wagner interviews.

[27] Illmensee 1980, 1981.

[28] U. S. Department of Health and Human Services 1981: 59. On the Goodman-Genentect conflict, see Hughes 2011: 77–94.

[29] Willison 1980: 160.

Recombinant techniques were still novel and inaccessible to most developmental biologists but were met with interest as a promising new tool. A review in *Developmental Biology* published in 1979 gives a good idea of the more obvious applications. The focus was decidedly on the new information about eukaryotic genomes and on isolating specific genes known to be involved in developmental phenomena. It also thematised gene regulation and its possible role in differentiation – a well-established molecular take on development by then – as well as the two families that were receiving much attention for their roles in disease and immune response: globins and immunoglobulins. Even in its more speculative parts, however, the review did not raise the prospect of using isolated genes to modify an embryo.

The overall focus was on understanding eukaryotic gene regulation in simpler systems: cultured cells or even as isolated molecules *in vitro* – practices much more consistent with the triumphant model of microbial molecular biology. As Tim Stewart, Mintz's postdoc who ended up succeeding at injecting DNA into mouse eggs and then tracing those sequences in an adult mouse, pointed out,

> Most of the DNA... transfectional work going on... was primarily focused on understanding the relationship between gene structure and expression, as opposed to: what is the gene product doing in the context of the whole animal? And so when you think about, if that's your motivation, trying to understand gene expression, it seemed like a hell of a lot of work for pretty modest pay-offs.

Despite conflicting ideas as to what genetic manipulation of the the mammalian embryo might look like, several laboratories simultaneously pursued experiments that involved microinjecting DNA into mouse egg. Discussions of possible uses crystallised around existing laboratory practices and agendas of individual researchers to become biological reality and a new entity. In the following section, I discuss the research programmes of the successful laboratories.

§2. Research agendas

Genetic modification of a whole mouse, while entertained in increasing detail, was not a clearly articulated agenda in 1980, and prominent biologists relegated it into the realm of distant possi-

bilities. However, in 1979–80, at least eight groups worked on introducing various forms of DNA into cultured mouse embryos at the one or two-cell stage, with six of them eventually reporting successful results. As I will show, these were mostly speculative projects pursued by postdocs or graduate students in well-funded laboratories that were integrating new molecular tools into their everyday practice. Most of these had secure funding, a certain level of prestige and access to the exchange networks of plasmids discussed in Chapter 2. These laboratories, mapped on Fig. 3-3, pursued experimental programmes over a considerable disciplinary range. Here, I will review their agendas and focus on what made these local and collaborative enterprises the places where mice would be genetically modified.

The NIH recombinant DNA regulations were relaxed in late 1978 and allowed wide-ranging work with eukaryotic DNA and cells, with even further scope permitted in 1980. Yet while the promise of genetic modification of mammals was being discussed, converting this into a research agenda was not straightforward. Various audiences had to be convinced that these experiments were worthwhile and fundable pursuits – a challenge given their speculative status. These projects therefore tended to be spin-offs from already established grants on the more fundable strands of research– a practice known as 'bootlegging'.[30] Thus, Ralph Brinster at the University of Pennsylvania felt that DNA injections into mouse embryos was 'unfundable', and instead built his successful grant applications to both the NIH and the NSF around replicating John Gurdon's experiments with mRNA in *Xenopus*. These RNA grants then bankrolled the DNA injection work.[31] In Beatrice Mintz's lab, the DNA injection was a sideline in the teratocarcinoma project. At Yale, Frank Ruddle relied on his generous somatic cell genetics grant from the National Institute of General Medical Sciences, and his large laboratory to assign first a graduate student and then a postdoc to the project.[32]

While perfectly aware of the recombinant turn, Rudolf Jaenisch continued to work with viruses. After spending five years at the Salk Institute, he was recruited to head the Tumour Virology de-

[30] Greenberg 1966.

[31] Brinster 2013.

[32] Ruddle interview, McKusick 1984, Anon. 2013.

partment at the Heinrich Pette Institute, University of Hamburg, in 1977. There, he spent several years setting up a mouse facility and continued working on introducing viral DNA into the embryo. Using the Moloney virus, Jaenisch and his students injected it into embryos at various stages: blastocyst, four-cell embryo and eventually a fertilised one-cell egg. Their questions centred on preferential viral gene expression in specific tissues and the effect of an embryonic environment on viral replication and activity. Despite reports from Hilary Koprowski at the Wistar that SV40 and the Moloney virus could be active in the embryo, Jaenisch could not replicate these results. Experimenting with infection at various stages in mouse development, Jaenisch adapted microinjection techniques to work on the newly-fertilised egg.[33] Yet, despite powerful programmes focusing on animal viruses, with the expansion of DNA cloning viruses were becoming less attractive as a means of delivering genetic information into cells.

Not all experiments took place in established mouse labs. John Gurdon's injection work on *Xenopus* continued in Cambridge, and one of his PhD students, Keith Willison, decided to pursue mouse embryos. Willison attempted to inject SV40 DNA into two-cell embryos and into blastocysts, with some results suggesting he could detect injected DNA in adult mice.[34] Expertise in manipulating mouse embryos – not an animal used at the LMB – came from elsewhere: the Cambridge Anatomy and Genetics departments (notably from Martin Johnson and Martin Evans), as well as Willison's relationship with Oxford embryologists. The overall inspiration and guidance came from Gurdon, but Willison obtained SV40 DNA and learned the latest methods of detecting and analysing it from Janet Mertz, who had moved to the LMB from Stanford. Mertz had been a graduate student of Paul Berg – her proposed experiments with SV40 genes had started the recombinant DNA controversy in 1973. When she moved to Cambridge, she brought expertise from the cradle of recombinant research as well as the SV40 molecules that Gurdon's group would use.[35]

Towards the end of his PhD, an institutional contingency severely damaged Willison's research – with no mouse facility at the LMB, he kept his animals at Addenbrooke's Hospital, where the

[33] Jaenisch 1980, Jähner & Jaenisch 1980; Jaenisch interview.

[34] Willison 1980.

[35] Willison, unrecorded interview.

Fig. 3-3. Laboratories that worked on on microinjecting DNA into fertilised mouse eggs in 1979–81.

1. Keith Willison in **John Gurdon's** laboratory, MRC Laboratory of Molecular Biology, Cambridge
2. Karl Illmensee, University of Geneva
3. Axel Ullrich, Genentech
4. Howard Goodman, UCSF

—— collaboration
------ teaching technique

ICR – Institute for Cancer Research
HPI – Heinrich-Pette Institute

whole colony was culled without any warning after a viral infection. Salvaging some results that he had collected and collating them into a thesis, Willison submitted in late 1978, with final corrections approved in December 1979. By then, he had moved on to a postdoc at Cold Spring Harbor to learn the recombinant techniques and had set his mouse work aside.[36] Rudolf Jaenisch cited his thesis in a 1981 paper (misattributing both the submission year and the institution where it was undertaken) but overall it was not easily available and any hints of results would only spread through word of mouth.[37] While the culling of Willison's mice was unpredictable and unfortunate, it highlights the importance of solid infrastructure for speculative work. An institutional commitment to using the mouse as a laboratory organism, combined with local expertise from animal technicians and scientists was common to those laboratories that ended up publishing such experiments.

Gurdon's experiments on nucleic acid injections in *Xenopus* were an inspiration for mouse embryologists beyond his laboratory. Since 1979, Ralph Brinster's laboratory in the University of Pennsylvania Veterinary School in West Philadelphia was abuzz with work on manipulating mouse eggs, including injecting RNA and DNA. In a 1998 interview, Brinster recalled that the ultimate goal was to use purified DNA, readily available with the new gene cloning techniques, but that he started with RNAs as a more fundable project with precedent in other species.[38] Like Mintz, Brinster had adopted microinjection in the early 1970s to inject cells into blastocysts – another side-project that he funded by using his embryo culture grants to purchase microinjection equipment.[39] With postdocs Mary Avarbock, Howard Chen and Myrna Trumbauer, he developed the technique to work with the even smaller mouse eggs.

While Brinster was an experienced embryologist with the capacity for honing micromanipulation techniques in his own laboratory, the purified nucleic acids came mostly from Gurdon's collaborators. Thus, the rabbit beta globin RNA came from Jerry Lingrel, a molecular biologist at the Uni-

---

[36] Keith Willison, unrecorded interview.

[37] Harbers, et al. 1981: 542.

[38] Palmiter interview, Brinster 2013.

[39] Brinster 1974, Brinster 2013.

versity of Cincinnati.[40] The second RNA was for a *Xenopus* 5S gene from another Gurdon collaborator, Donald Brown.[41] The HSV *tk* gene was a gift from Carlo Croce of the Wistar institute down the road. In 1979, after reading Paul Berg's published a paper in *Nature* that described a viral construct with the rabbit beta globin gene, Brinster requested a sample, which was provided in September 1979.[42]

Finally, in autumn 1979, Brinster contacted Richard Palmiter, a biochemist at the University of Washington in Seattle, to secure ovalbumin RNA. This connection resulted in a long-term collaboration, in which Palmiter supplied plasmids for the future gene transfer work.[43] Brinster's connections and institutional position at a major university enabled him to benefit from the networks of exchange with molecular biologists, who had provided samples of nucleic acids that could be expanded into new systems. In January 1980, Brinster published a brief communication in *Nature* showing the successful translation of rabbit beta globin RNA in mouse eggs, while his group was working on injecting DNA and trying to trace its presence in adult mice at the same time.[44]

Only a short train ride from the University of Pennsylvania, in the suburb of Fox Chase, Mintz's group carried on working with teratocarcinoma cells, although not in communication with Brinster. In 1979, Mintz started a collaboration with Richard Axel's laboratory at Columbia.[45] Their work brought together expertise in culturing teratocarcinomas and gene transfer into mammalian cells. Using a teratocarcinoma mutant line that lacked functional thymidine kinase, the researchers inserted a plasmid containing the *HSV tk* gene combined with the human beta globin gene that had been purified by Maniatis, Axel's collaborator and friend. The plasmid remained in Mintz's laboratory and was used in new experiments.

---

[40] Gurdon and Lingrel had published work on injecting the mouse and rabbit beta globin RNA into oocytes, that relied on the latter scientist's novel method for purifying these molecules: Evans & Lingrel 1969, Gurdon, et al. 1973.

[41] The 5S gene encodes an RNA component of the ribosome, where mRNA is translated into protein.

[42] Mulligan, et al. 1979.

[43] Brinster 1998, Palmiter interview.

[44] Brinster, et al. 1980.

[45] Pellicer, et al. 1980.

Quite how much anyone knew about what was going on in Mintz's lab is an open question. Her teratocarcinoma research certainly put Mintz's lab on the radar as a place where a genetically modified animal could soon be born. Her postdocs' recollections refer to multiple conversations about possibilities and research plans.[46] Apart from the sense of expectation from scientists in other labs that they recalled in interviews, this is evidenced by a letter from Paul Berg to the RAC that inquired about whole animals as hosts for recombinant experiments – something that had seemed like a fantastic possibility only a few years earlier. In the letter, Berg stressed the "tremendous scientific and medical importance of such experiments", and wrote:

> As you know the experimental ground work for [introducing recombinant DNA into whole animals] has already been provided by Dr. Beatrice Mintz's experiments. She has shown that teratocarcinoma cells grown in culture can be incorporated into mouse blastocysts which ultimately can yield mice containing a variety of cell types derived from the teratocarcinoma cells. Using appropriate selections it is feasible to introduce exogenous DNAs (be they derived by recombinant techniques or otherwise) into such teratocarcinoma cells and hence into animals.[47]

It was not just developmental biologists who pursued genetic modification of the mouse embryo. Two final research programmes I will discuss came from less expected trjectories. One was Frank Ruddle's lab at Yale with a catholic focus on somatic cell genetics. The other was the result of a partnership between Peter Hoppe – a mouse embryologist at the Jackson Lab and Illmensee's collaborator – and Thomas Wagner, a biochemist at Ohio University.

Ruddle's approach to somatic cell genetics went beyond traditional disciplinary divides that were increasingly irrelevant in the world of biomedicine. He ran a large laboratory of about 30 people and made efforts to connect to diverse communities of practicing biologists. Ruddle's extensive participation in academic networks combined with his secure institutional position allowed him to start multiple collaborations, and his eclectic approach brought many techniques to his lab. Ruddle's laboratory was exploring chromosome-mediated gene transfer, and in pursuit of higher efficiency, he sought new means of incorporating genes into somatic cells. Learning of microin-

---

[46] Stewart and E. Wagner interviews

[47] Paul Berg to William Gartland, 5 February 1979, Paul Berg Papers. Available online though the National Library of Medicine *Profiles in Science*: http://profiles.nlm.nih.gov/ps/access/CDBBGT.pdf. Accessed on 9 August 2013.

jection from Elaine Diacumakos at Rockefeller University, who had worked extensively on honing the technique, Ruddle eagerly adopted the apparatus and introduced a microinjection room in his laboratory, with a NSF instrumentation grant and help from Clement Markert. The first publication from Ruddle's laboratory that relied on the technique appeared in 1979.[48]

Despite multiple scientific commitments and co-authored papers, Ruddle's main focus was on mapping human genes in somatic cells. Experiments with recombinant plasmids that he labelled DNA-mediated gene transfer offered an even higher degree of resolution, as transferred genes could be radioactively detected on specific parts of the chromosomes. The injection of DNA into embryos, on the other hand, was a speculative experiment that Ruddle hoped could be useful for developmental studies. He applied to inject recombinant DNA into mouse embryos to the university's Biohazard Committee and received approval in March 1978.[49] Initially, Ruddle assigned a graduate student to the project, with little success, and then decided to recruit a postdoc.[50] This was Jon Gordon,[51] a medical student in the MD-PhD programme at Yale who had just completed a thesis with Markert that relied on making chimeric mice. With much experience in micromanipulation and dealing with mice, Gordon was assigned to the embryo project and given much autonomy.

The final group that worked with mouse eggs was the collaboration between Thomas Wagner at Ohio University (Fig. 3–4) and Peter Hoppe, a Jackson Lab-based developmental biologist. Wagner was a molecular biologist with a background in the physical chemistry of DNA who had set up Ohio's Department of Molecular and Cell Biology in 1970. Wagner struggled to secure large-scale federal funding for his department, and despite the administration's interest in building up its research programme, the university was at the periphery of molecular research. Wagner's experimental focus was largely structural, but through friendship with Azim Surani, a developmen-

---

[48] Liu, et al. 1979. In his recollections, Mario Capecchi implied that he pointed Ruddle towards microinjection at a 1978 meeting in Portugal (Capecchi 2005). While Capecchi's suggestion and early results in cell culture may have been influential, Ruddle did not recall it in the interview, and as evidenced by Diacumakos' daily planner, he may have been aware of her work as early as 1974. Elaine Diacumakos papers, RU450, Rockefeller Archives, Terrytown, NY.

[49] Corvini 1979.

[50] Ruddle interview.

[51] Not to be confused with John Gurdon.

tal biologist at the Animal Research Station in Cambridge, Wagner became interested in how DNA was regulated during development. In the late 1970s, he worked on mouse sperm DNA, and published a series of papers on its structure. The sperm nucleus is extremely small and it had been recognised that sperm DNA was packaged much more tightly compared to other cells, and that it had a different kind of protein in its chromatin. Through structural calculations and experimental analysis of sperm DNA, Wagner hypothesised that it had to contain breaks to fit the sperm nucleus.

The notion of broken-up sperm DNA was unorthodox, and Wagner published his results in *Archives of Andrology,* an obscure journal unlikely to be read by molecular biologists.[52] However, for Wagner, these results implied that sperm DNA had to undergo a series of repairs after fertilisation. At this point, he suggested it might be possible to introduce foreign DNA into the host genome. Wagner shared his thoughts with Hoppe on a taxi ride to the airport at a conference in Washington, D. C. By then, Hoppe had already been collaborating with Illmensee, and said he could carry out an injection into the male pronucleus. On his return, Wagner sent a rabbit beta globin plasmid that he had obtained from Richard Flavell in London via a postdoc and sent it to Jackson Lab for injection.[53]

Most of the key participants above agree that their work was independent. A few expressed their suspicions about premature familiarity with unpublished data in interviews, but quickly pointed out they had no certain knowledge either way. The exact chronology of these projects thus poses a challenge. While the record of publications is clear, it is by no means a straightforward way to establish the timing of the work (see also Chapter 4). Without access to laboratory notebooks, it can only be extrapolated from ephemeral and circumstantial evidence. Ruddle initiated the experiment after the NIH guidelines were relaxed in December 1978, and commented on the preliminary results to *Yale Daily News* in April 1979, and had his research programme clearly adver-

[52] Wagner, et al. 1978, Wagner & Yun 1979. The DNA break hypothesis has not been accepted, with current consensus stating that the super-tight packaging is achieved by replacing histones – normal chromosomal proteins that neutralise the nucleic acid negative charge and coiled DNA – with smaller protamines. Miller, et al. 2010.

[53] T. Wagner interview.

Fig. 3-4. Thomas Wagner at Ohio University, circa 1985.

Courtesy of Thomas Wagner.

tised in the 1980 issue of *GEIS*.[54] However, not all groups were as open about their research in progress. Recruitment of postdocs who performed the experimental work at Yale and Fox Chase offers another bookend – most of them joined in 1978–79. The sequence of Fox Chase scientific reports shows that Mintz had not listed the egg project as of September 1980, and whether it had been attempted before is unclear. Brinster reported some preliminary success with DNA injection in a note added in proof to one of his RNA papers that appeared in print in January 1981, a few months after Ruddle announced his group's success.[55]

However, it is worth remembering that uncertainty about the exact experiments in progress was a condition that other scientists faced. The idea that such work was happening elsewhere, while the credit was yet to be allocated, was a motivation to go forward and it created a sense of competition. Rumours circulated about what other labs were doing. As Tim Stewart, then Mintz's post-

[54] Corvini 1979. Not all groups contributed to *GEIS* – for instance, Brinster did not – but the publication was then in terminal decline, with the final issue published in 1981.

[55] Brinster, et al. 1981: 398.

doc, noted, "it's always been very hard to keep secrets, people talk about what they're doing, people are excited about what they're doing and they don't want to keep it a secret".[56] On the other hand, no officially published claims had been made and the experiments remained a prize worth pursuing, even if the risk was high for junior scientists. The experimental procedures were time-consuming and uncertain to yield results and therefore publications. The next two sections will focus on the laboratory practices of microinjection and molecular analysis, and how they were brought together and synchronised in these diverse laboratories.

§3. Mastering microinjection

The expansion of developmental biology as a coherent supra-disciplinary identity has been associated with the expansion of communication between embryology and molecular biology in conferences, textbooks and courses. But synthesis of experimental practices was less straightforward. In a few labs, a hybrid way of practicing developmental biology emerged in the 1960s and 1970s. The most famous hybrid practices were devised by molecular biologists moving to work with embryos, such as Sydney Brenner with *C. elegans* or François Jacob and mouse teratocarcinoma cells.[57] John Gurdon, a molecularly inclined zoologist, was another notable example whose move to the LMB further embedded his work in a molecular context. However, such synthetic approaches to what Gurdon called "molecular embryology" were not the rule. In all laboratories that worked on gene transfer into mouse embryos, there was a division of labour between molecular biologists and embryologists, and the latter disciplinary identity was consistently used in interviews rather than the cumbersome "developmental biologist". In this section, I will focus on the key embryological technique that made mouse transformation possible, microinjection of DNA into a fertilised egg, and then in the next section compare it with the techniques of molecular analysis.

Microinjection is a form of microsurgery or 'micrurgy', an instrumental tradition established in biological research since the turn of the twentieth century. First widely employed in bacteriology

[56] Stewart interview.

[57] de Chadarevian 1998, de Chadarevian 2000, Morange 2000.

to isolate single cells, microsurgical procedures relied on micromanipulators – instruments that converted the manipulation of screws, knobs or joy-sticks into minute three-dimensional movements of capillary needles or pipettes.[58] The first commercially available micromanipulators were devised in the 1930s. By the 1960s Leitz models dominated the biological market.[59] Embryologists had been using micromanipulators since their early days, as did cell biologists. If much early microscopic work in experimental embryology, notably in Spemann's laboratory, was done by unaided hand, nuclear transfer experiments relied on careful micromanipulation, as did the new methods of producing mouse chimeras by blastocyst injection.[60] Teh-Ping Lin's work on microinjecting mouse eggs made it into key handbooks, but had little productive use in the 1970s. Scientists at the key sites of making chimeric mice were adept at microinjecting blastocysts: Mintz's, Brinster's and Gardner's laboratories had integrated the technique into their everyday practices.

Beyond the embryological tradition, micromanipulation was used by cell biologists mostly to study the effects of removing specific organelles and even chromosomes. Thus, Elaine Diacumakos at Rockefeller University and Adolf Graessman's group at the Free University in West Berlin pursued the technique with limited communication beyond their immediate colleagues. However, through growing interest in cell manipulation – encouraged by the expansion of somatic cell genetics – these techniques attracted several geneticists. Thus, both Frank Ruddle and the gene therapy pioneer French Anderson approached Diacumakos to learn her methods, and microinjection became a potential tool for gene transfer into eukaryotic cells in the late 1970s.[61]

Microinjection experts emphasised its attractiveness from two angles. On the one hand, they highlighted simplicity and utility for molecular biology, arguing that the procedure could turn a cell into a test-tube. The cell-as-test-tube metaphor was used in reviews from the Gurdon and Graessman groups.[62] At the same time, the virtues of working with "natural" cells, free of arte-

---

[58] Korzh & Strähle 2002.

[59] El-Badry 1963: 22–72.

[60] Hamburger 1988; Gardner 1968.

[61] Burke & Epperson 2003: 198–9; Ruddle interview.

[62] De Robertis, Laskey & Gurdon 1977, Mueller, et al. 1980.

facts, were extolled, with implication that the method could conquer eukaryotic complexity.[63] Thus, when addressing a mixed scientific audience interested in gene transfer, Diacumakos moved away from the test-tube metaphor and suggested instead that:

> Another disadvantage [of microinjection], which is only superficial, is that "quick and dirty experiments" are not doable. The design of experiments using this approach must therefore be defined and clear-cut... This is not the type of activity that someone with no knowledge of cell biology can perform and interpret accurately...
>
> [T]his is an approach that should be considered seriously, for the cell is not merely a test tube, in the hands of a good cell biologist; the cell itself can become a laboratory.[64]

The craft-like nature of micromanipulation was stressed routinely in contemporary accounts and in recollections. Karl Illmensee's remarkable experiments and his growing reputation in developmental circles relied on his perceived "golden hands". In 1979, the eminent geneticist James Crow was quoted saying "Karl Illmensee has the embryological equivalent of a green thumb. He actually does the experiments everyone else talks about."[65]

In the labs that decided to microinject plasmid DNA into mouse eggs in-house, this practical expertise was carried by the postdocs who performed the experiments. The experimental design appeared straightforward enough: DNA was to be injected into a pronucleus, with the egg subsequently implanted into the oviduct of a surrogate mouse. Yet for both Gordon and Stewart, attempting such a speculative project was a career risk. As postdocs without secure prospects, despite being placed in highly-respected laboratories, they required publications of impressive results to secure a permanent position. As Gordon recalls,

> In Frank [Ruddle]'s lab, the atmosphere was that this was more or less a speculative effort. A lot of big-time labs were unable to do it, I mean, Beatrice Mintz, it's a big time lab... so I don't think a lot of people felt that it was very likely I would do it, and I told

---

[63] See e.g. McKinnel 1978: 118: "Certainly, one of the virtues of the [*Xenopus* oocyte] test system is that it is natural. A nucleus is asked how it will perform in a milieu of normal and unmutilated cytoplasm."

[64] Diacumakos 1979: 97–8.

[65] Anon. 1979. On the other hand, Mintz was reportedly rather critical of Illmensee in private conversations once he had left Fox Chase. The golden hands argument later was pivotal to Illmensee's defence in the face of fraud allegations about his nuclear transfer work – Kolata 1998. On micromanipulation and mammalian embryology, see also Franklin 2007a, 2013.

> Frank that, I said 'Hey, look, I need a back-up project. I'm on a postdoc here, what if this isn't possible? Can I map a gene?'[66]

Similarly, Stewart said:

> When I got there I knew that Bea [Mintz] had been writing grants, talking about this. There was a lot of scepticism and I remember talking to one of the postdocs at Fox Chase and I think there might have been scepticism outside the institution. Can you actually do it? – and even if you could, how much value are you *really* going to get out of this? [...] getting [DNA] into an embryo and then having that embryo survive the trauma of this manipulation and to get a whole animal out of it was considered a long shot.[67]

The decision to work with a one-cell fertilised egg was not obvious. The mouse egg had been seen as difficult. Much like the rabbit embryo was once elevated over other mammals as a 'robust' subject of manipulation, stages in egg development were not created equal. Thus, in John Gurdon's *Xenopus* work, the oocyte – precursor of egg – was characterised as the robust cell, whereas the freshly fertilised egg was seen as extremely fragile until it approached its first division.[68] Though Elaine Diacumakos stressed that her work showed the somatic nucleus to be much more robust than previously thought and able to withstand injection, it was a different matter to make the experiments work in another lab and with a different type of cell.[69]

Moreover, for mammalian development, the two-cell block was an important concern: whereas eggs at the two-cell stage could be forced to develop to blastocyst and then implanted into the uterus, eggs extracted just after fertilisation would only divide once *in vitro* and degrade. Methods had been developed to overcome the two-cell block, particularly by Biggers, Whitten and David Whittingham, either by adding oviduct extracts or by changing the culture medium.[70] Still, the phenomenon itself remained somewhat mysterious, with suggestions that it was affected by the strain of mice used. Ways of avoiding the two-cell block had not been routinised, since most em-

---

[66] Gordon interview.

[67] Stewart interview.

[68] "In general, oocytes are very much more tolerant to injection than fertilized eggs, which are best injected at the 2-cell stage", Willison 1980.

[69] Diacumakos, et al. 1970; stressed in Diacumakos 1979.

[70] Whittingham & Biggers 1967, Whitten & Biggers 1968. See also Biggers 1987, Biggers 1998.

bryological experiments did not require complete culture. This concern about the two-cell block led Keith Willison to inject mouse eggs at the two-cell stage, as well as at the blastocyst. Gordon also attempted two-cell injections, with little success.

Existing techniques were being reinvented from scratch, and many avenues led nowhere. Part of the problem was that the criteria of a successful experiment were by no means agreed, because nobody expected that most injected eggs would survive the process and indeed have detectable DNA in the end. Contamination could not be ruled out straightforwardly, even with control experiments. Issues of efficiency were also at stake because selection was not an option, in contrast to cells culture experiments. Thus, multiple eggs had to be injected in one go, which required making the procedure routine and keeping the timeframe of embryo transfer as brief as possible to avoid the two-cell block – a technique Gordon and Stewart both settled on independently. They cultured multiple eggs and injected them in series, sucking each egg with a holding pipette. Willison came up with a technical innovation, adapting a Nylon grid to keep the eggs in order – a method that never spread, probably because his thesis remained largely unread.

Microinjection was thus a fraught procedure that relied on embodied skill. Adapting local instruments, developing ways of focusing the optics and arranging the pipettes to achieve best results, as well as training the eye to tell when a pronucleus was pierced and successfully filled with the DNA solution all took time and effort, and the skill set was not easily portable (Fig. 3-5). It is uncertain how many other labs attempted similar experiments, beyond Illmensee, Lin and Diacumakos. However, success in the enterprise did not rely solely on injection skills or the perseverance of dedicated postdocs working long hours. It was also crucial that experimenters had access to DNA to inject as well as means of tracing it once the embryos were transferred into surrogate mothers. This relied on a synthesis of molecular and developmental practices, for which there were many possible arrangements. In the next section, I will focus on these means of combining embryological and molecular skills.

§4. Recruiting molecular expertise

Many people were thinking about development in molecular terms and envisioning experiments that could help interpret gene expression, but combining molecular and developmental practices was difficult. While some molecular laboratories had embraced a synthesis of both approaches in the late 1960s, there was still a sharp division of labour and identities, even in spaces that encouraged interdisciplinary research. The laboratories that developed microinjection into mouse eggs combined these kinds of expertise in several distinct ways, which were crucial to their success.

First, getting hold of genes that could be injected and detected in the mouse embryo was still not entirely straightforward in 1980. A lab either had to have a recombinant DNA research programme in its vicinity, furnished with appropriate containment facilities, or it had to access the plasmids exchange networks discussed in Chapter 2 (Fig. 3-6). Second, once the DNA was injected, it had to be followed through in the adult embryo and tested for expression. The techniques for these procedures were established and increasingly routine in molecular laboratories, but not yet standardised or widely disseminated beyond the core molecular community. Finally, to be certain of the potential positive results, proper methods of visualising and publishing the data had to be followed.

For Mintz and Ruddle, access to plasmids was straightforward. Both had collaborated with Richard Axel and Saul Silverstein at Columbia – Mintz working on teratocarcinomas and Ruddle on chromosome-mediated gene transfer.[71] Mintz's laboratory used the dual *HSV-tk/beta globin* construct. In Ruddle's laboratory, Diane Plotkin and Jim Barbosa were working on culturing and modifying the Columbia *HSV-tk* plasmid. Moreover, Ruddle's Yale colleague Bill Summers had established tests for the expression of HSV *tk*. The gene had been used widely in selection experiments, while the globin genes were among the first to be cloned for their relevance to heritable blood diseases. These DNA constructs were chosen not for their value in answering developmental questions, but simply because they were available and readily detectable.

[71] Pellicer, et al. 1980, Scangos, et al. 1979.

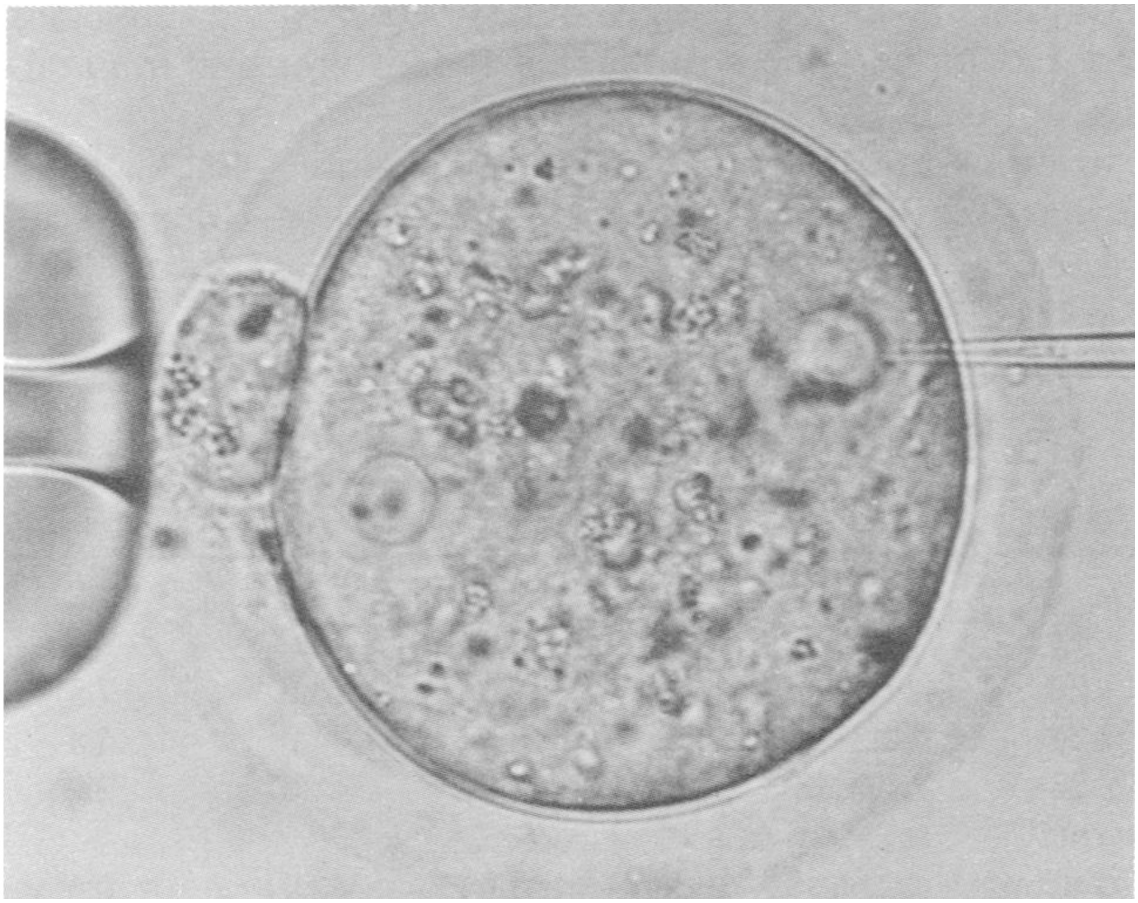


Fig. 3-5. Photomicrograph of an egg being microinjected. The egg is kept in place by a holding pipette on the left, with the smaller micropipette piercing a pronucleus on the right.

T. Wagner et al 1981.

Brinster had been securing DNAs and RNAs from a variety of high-profile American scientists for his experiments, from Donald Brown to Paul Berg. However, as his programme of microinjection was expanding, he first collaborated with Carlo Croce at the Wistar, and eventually settled on a long-term relationship with Richard Palmiter at the University of Washington in Seattle, who had been sending him ovalbumin, metallothionein and HSV *tk* DNA. Even though Palmiter had to go to Strasbourg to perform his first recombinant experiments with ovalbumin, by 1980 the University of Washington established proper containment facilities and Palmiter could produce enough DNA to ship. Thomas Wagner's access to a plasmid was less straightforward. His laboratory was not at the time pursuing gene splicing and plasmids could not be easily obtained on the margins of the East and West Coast exchange networks. Luckily, one of Wagner's students, Christine Schumacher, was moving on to a postdoc with Richard A. Flavell at the National Institute for Medical Re-

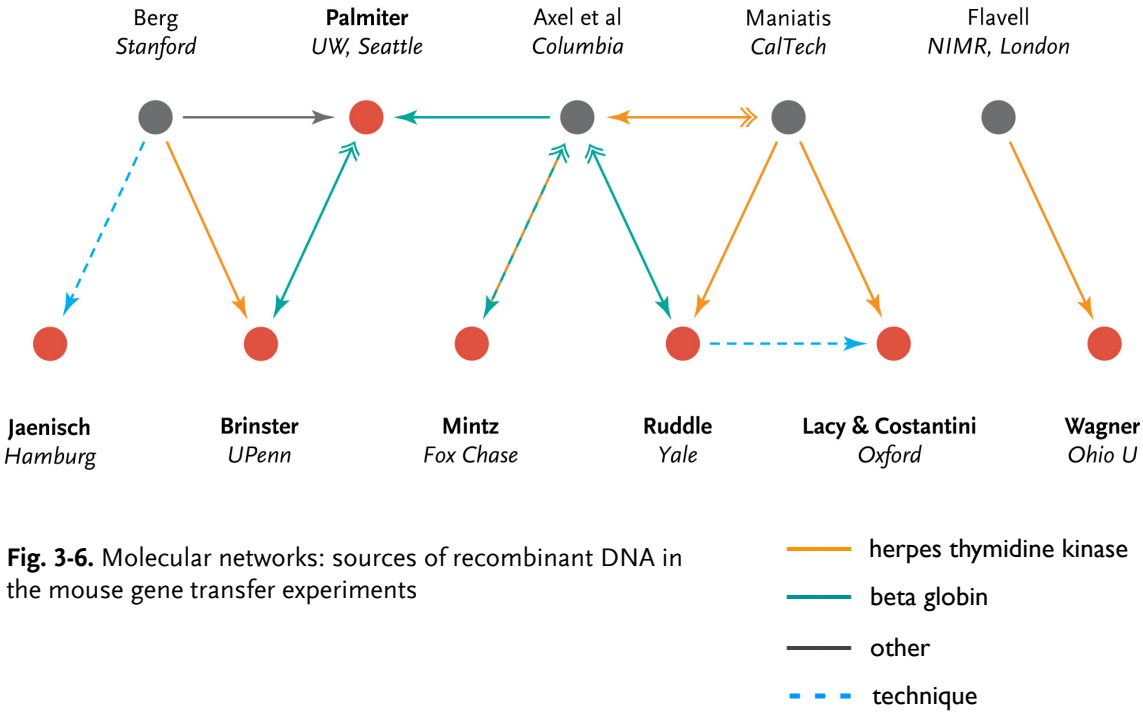


Fig. 3-6. Molecular networks: sources of recombinant DNA in the mouse gene transfer experiments

search in the London suburb of Mill Hill. Flavell was one of the first biologists to clone the rabbit beta globin gene, which circulated alongside the Maniatis construct. On Wagner's request, Christine Schumacher sent the DNA to Ohio in the post, and Wagner started a collaboration with Joseph Jollick, a biochemist at Ohio University with expertise in recombinant methods.

Analysis of the experiments required a more committed interaction. Collaborations that combined expertise of different laboratories were a common strategy, but both Ruddle and Mintz sought to expand on using molecular techniques that fitted their research agendas. As primary investigators in highly regarded laboratories, the most straightforward way to gain practical expertise was to recruit expert associates. In 1979, Ruddle hired George Scangos, a microbiologist trained in *E. coli* genetics at the University of Massachusetts. In Ruddle's lab, Scangos worked on DNA-mediated gene transfer into somatic cells, as well as doing some work on analysing the molecules in experiments. In June 1979, Erwin Wagner (no relation of Thomas Wagner) joined Mintz's lab. A molecular biologist with some experience in researching development, Wagner had been trained in animal virus genetics in Munich. During his doctoral work, he visited Francois Jacob's lab at the Institut Pasteur were he encountered teratocarcinomas. As Wagner recalls, a strict divi-

sion of labour was imposed in Mintz's laboratory, and his collaboration with Stewart's oocyte injections (and learning the associated embryological techniques) had to happen on the side.[72]

By contrast, both Brinster and Thomas Wagner established long-distance collaborations. Wagner worked with Jollick on molecular analyses and immunological tests in attempts to detect rabbit beta globin, using the mice made by Peter Hoppe at the Jackson Lab. Brinster's collaboration was more long-term: Palmiter was attracted by the new project and once the results turned promising, abandoned most of his earlier work on ovalbumin. In 1981, a two-way postal relationship emerged between Seattle and Philadelphia. Brinster would receive the DNA, inject it in his laboratory and send the samples back to Seattle for analysis – an arrangement that persisted throughout the 1980s and was made routine. Coordinating the molecular and developmental aspects of the work was carried out in regular Saturday phone conversations. In fact, Brinster and Palmiter had not met in person until just before the publication of their first paper in November 1981 (Fig. 3-7). Once the relationship was stable, Brinster's lab would conduct the injections, take liver, spleen or tail samples from the resulting mice and send them to Seattle in SDS, a chemical that denatured the tissues for analysis. Palmiter would then post the DNA analysis results back. FedEx thus became an extension of the laboratory.[73]

The first products of these analyses were usually Southern or dot-hybridisation blots (Fig. 3-8). The former allowed to determine the size of cut DNA fragments to further confirm identity, the latter gave a yes-or-no answer to the presence of the tested DNA. Since their early dissemination, Southern blots had become the standard in analysing specific DNA, replacing the cumbersome cot curves, and were becoming a publication standard in molecular biology. These images were also the first indication that microinjection worked and the foreign genes could be detected in the newborn mice. They did not provide any certainty as to whether the genes integrated into the mouse genome or persisted as extra-chromosomal elements. Unlike cot curves, these analyses could also be straightforwardly applied to a large number of samples, in line with overcoming the problems of efficiency in microinjection. Scangos and Gordon analysed 78 newborn mice, born

[72] E. Wagner interview.

[73] Brinster & Arechaga 1998, Brinster 2013, Palmiter interview, Hanahan, Wagner & Palmiter 2007.

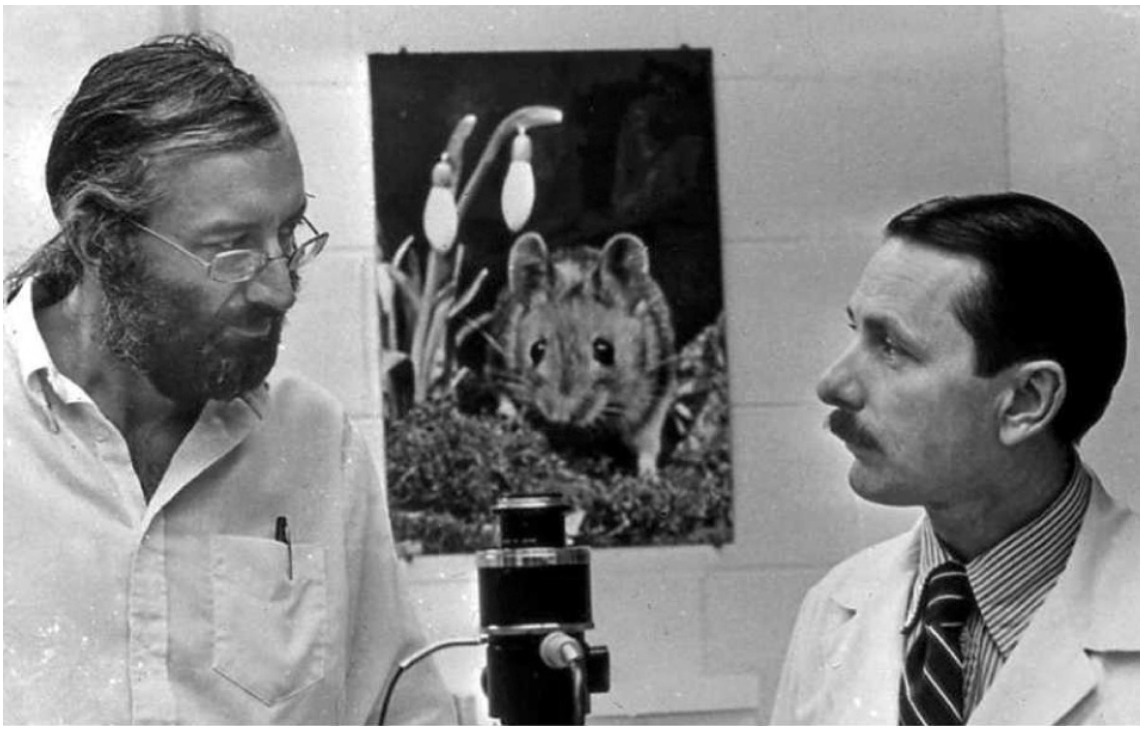


Fig. 3-7. Richard Palmiter (left) and Ralph Brinster, meeting in person for the first time in November 1981.

From Hanahan, Wagner & Palmiter 2007.

after several hundred embryos had been injected and transplanted into surrogate mothers. The newborn mice were killed and homogenised and the resulting blended mix analysed. Of these, only two (no. 48 and 73) showed the foreign HSV *tk* sequences on Southern blots – luckily, since after a beer to celebrate the first positive result, Ruddle sent the pair to look at more blots to see if they could confirm the result. Similarly, Stewart and Erwin Wagner analysed 33 surviving foetuses, of which five responded positively to the test.

In the accounts of the technique and actors' recollections about this work, microinjection received the greatest focus as the difficult technique that had to be figured out. By contrast, molecular methods are often taken for granted and were seen as straightforward. They had been settled to some extent. Southern blotting, DNA cloning and purification were becoming common, but the techniques had not been codified yet. These molecular tools, however, became routine during the 1980s, while microinjection remained a laborious process, and it is likely that these accounts responded to this configuration. Yet much local variation and personal knowledge were involved in

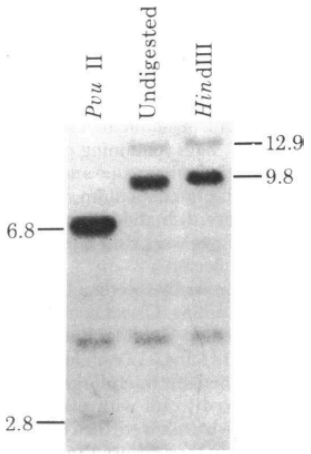


FIG. 3. DNA from mouse no. 48 digested with *Hin*dIII or *Pvu* II, or undigested; probed with pST6. Fragment sizes are indicated in kb.

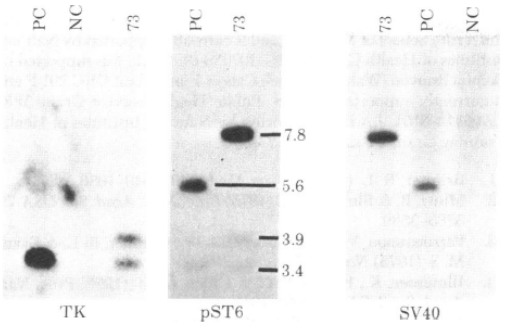


FIG. 4. DNA from mouse no. 73 digested with *Bam*HI and probed with pST6 (*Center*), SV40 DNA (*Right*), or TK fragment (*Left*). Positive control (PC) consists of pST6 added to mouse DNA to a concentration of 10^{-6} by weight. NC denotes the negative control (DNA isolated from uninjected mice).

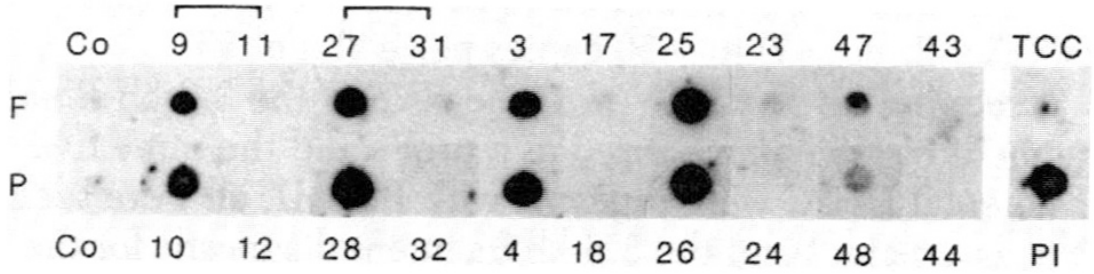


Fig. 3-8: Visualising DNA. Above, Southern blots images from Gordon and Scangos' analyses of two mice that carried the injected DNA after birth. Below, Tim Stewart and Erwin Wagner's dot-blot hybrids for fetuses (F) and placentas (P) (their Southern blots were also published). These images were pasted together from multiple photographs.

From Gordon et al 1980 and E. Wagner, Stewart & Mintz 1981.

making molecular methods work, too.[74] But the emphasis on the difficulty of the embryo remained an important story in the field, one that had to be actively challenged as transgenic mice propagated through courses (see chapter 5). In these experiments, molecules circulated between sites of injection, and molecular representations such as Southern blot photographs were key evidence. With molecular techniques outsourced to either expert postdocs or outside institutions, molecular analysis received a stable image.

[74] Lynch & Jordan 1992.

Conclusion

A genetically modified mouse had been envisioned and discussed for a long time, drawing on both existing experiments such as the Jaenisch-Mintz work and applications of new techniques. Heterogeneous approaches were pursued to integrate foreign genes into an animal, in laboratories on a broad disciplinary spectrum. The early success with microinjection happened in the few laboratories that combined specific molecular and developmental expertise, had the infrastructure to support large-scale mouse work and sufficient financial means to pursue a highly speculative and potentially "unfundable" endeavour. Multiple divisions of labour – between molecular and embryological skills, between PIs and postdocs, occasionally geographically separated – were a common criterion of success.

In the social studies of science, much has been made of the importance of proximity in making experiments travel and be replicated and the need for direct contact to transfer tacit knowledge that comes with experimental practice.[75] However, distance was not necessarily an obstacle to be overcome, but could in itself be a productive resource. As Mario Biagioli points out in his study of Galileo's strategies of securing credit, knowledge at large is "constituted through a range of distance-based partial perceptions".[76] In this case, the limited communication between laboratories, the "grapevine" and speculations about what was going on in competing laboratories sustained an interest in pursuing gene transfer into embryos as a promising and cutting-edge line of research. However, the partiality of communication maintained a diversity of local practices and fostered the attempts to keep trying. The few "failed" experiments that can be gleaned from the records, and the many more that one can only speculate about, never achieved the status of secure knowledge and remained rumours, leaving the horizon of possibility open and not discouraging scientists who also had to worry about advancing their academic positions. Thinking about multiple discoveries therefore needs to involve the productive power of partial perceptions as a means of keeping the field open.

---

[75] Collins 1985, Shapin & Schaffer 1985, Schaffer 1989.

[76] "I do not look at how a knowledge claim travels from A to B, but at how the transactions made possible by the fact that A and B are distant from each other allow for the production at such a knowledge claim." Biagioli 2006: 26. I thank Robin Scheffler for pointing me in this direction.

Moreover, distance was recruited as a way of negotiating the distinct practices of molecular analysis and embryo manipulation. These laboratories avoided the synthetic programmes focusing on compromise experimental objects, for instance the ultimately unproductive teratocarcinoma system in Jacob's lab.[77] By maintaining the division of molecular and embryological labour in the early stages, either within the same laboratory or through postal contact, local problems and minute details involved in manipulation or DNA analysis could be resolved by the expert, whereas material objects were produced at the border with exchange in mind: plasmids, biopsies from resulting mice and molecular inscriptions, whether in the form of Southern blot images or otherwise. Though such arrangements had to be reconfigured to make transgenic mice a technology that could be easily taught and disseminated, at the time of emergence of a new and as-yet untested set of methods the division of labour was a pragmatic way to legitimise these mice among distinct communities, as I will discuss in the next chapter.

[77] Morange 2000.

Chapter 4. Negotiating new mice: News, journals and priority

In 1980, several groups were pursuing similar strategies that relied on microinjection to introduce new genes into mouse embryos, and they announced their successes within a short space of time (Table 4-1). There is still little consensus as to which experiment was first, with different participants and commentators variously emphasising the achievement of one or another team. While none of the participants have publicly contested the succession of events and publications, and the key players I interviewed unanimously confirmed the independence of their work to the best of their knowledge, there is still no clear answer to the apparently innocent question, who invented transgenic mice?

Rudolf Jaenisch had refined the techniques for inserting viral DNA into later-stage mouse embryos at the Salk Institute as early as 1976 and claimed that Moloney Murine Leukemia Virus (M-MuLV) integrated into the mouse germline. His major interest, however, was not in inserting new genes into mice but in studying the activity of animal viruses and the effects of embryonic development on their function. The first announcement of inserting recombinant DNA into mouse embryos came from Frank Ruddle's lab at Yale in 1980, though the results were not immediately embraced by all of his colleagues. Many claims to dramatic biological experiments had been made and unmade before, so one lone announcement, even from a very prestigious group, was not enough to establish animal modification.

Credit for multiple discoveries, or any discovery for that matter, is necessarily allocated after the event. In the historiography of science, the focus on social and retrospective allocation of credit was emphasised by the sociologist Augustine Brannigan in 1981, in line with the Strong Programme in sociology of scientific knowledge.[1] Many studies have followed in that key. Thus, designation of Gregor Mendel as the 'unnoticed father' of genetics has been analysed as a strategy to settle a potential priority dispute between the 'rediscoverers' of genetics in 1900.[2] Similarly, the origin of molecular biology and the famous story of elucidating DNA structure all highlight the

[1] Brannigan 1981.

[2] Olby 1997.

post-factum negotiations and allocation of credit in defining disciplines and making their origin stories, and the variety of publications, images and perspectives that are recruited in the process.[3]

Many discovery accounts that have drawn historical attention were at various points controversial, since controversies can force scientists to articulate tacit assumptions. Two prominent examples around the time when transgenic mice were being made are the discovery of HIV and the controversy over the patenting of monoclonal antibodies in the US.[4] In both cases, there were highly public tensions between two camps with stakes beyond academic credit – the former dealt with a terrible pandemic, the latter pushed painful issues over the changing ways of benefitting from scientific work. The discussion over transgenic mice never reached comparable levels of animosity. None of the dissenting opinions that interviewees expressed 30 years after the events had appeared in print at the time. This was, in fact, a successful resolution of priority that was no resolution at all, leaving fluid allocation between laboratories with different research agendas that were mostly secure in their funding and not in immediate competition in other areas.

Still, work was done to register and communicate the experimental results. Some of this happened through the traditional medium of the peer-reviewed scientific paper, and a citation pattern was established to reflect a consensus genealogy. Discussions of discovery narratives for monoclonal antibodies,[5] citation analysis of the HIV debate or the controversy over lizard sex have focused almost exclusively on scientific papers. While informative, this focus conceals the variety of arenas where a discovery or invention may be negotiated. Case studies from Louis Pasteur's public performances of vaccination to the media frenzy surrounding the first heart transplants all highlight the utility of recruiting broad audiences in building successful careers and registering scientific or medical events as significant.[6]

---

[3] On constructing the discovery of the DNA structure as the origin story of molecular biology, see de Chadarevian 2002: 164–72, 236–259; de Chadarevian 2003. For an in-depth discussion on the history of molecular biology as reconstructed by its high-profile practitioners, see Abir-Am 1985, 1999.

[4] On the French/American HIV tensions, see Epstein 1998: 55–105, Rawling 1994. On the monoclonal scandal, see Keating & Cambrosio 1995: 167–200, de Chadarevian 2002: 351–66, de Chadarevian 2011, Marks forthcoming.

[5] Keating & Cambrosio 1995: 3–44, Rawling 1994, Myers 1990.

[6] Bucchi 1998, Nathoo 2009.

This chapter addresses the making of a new kind of laboratory animal in 1980–81, at a time when science-media relations in biomedical research were unstable and new avenues of communication became increasingly common and acceptable. The first section will focus on the announcement of the Yale experiments and the media adaptations of the story. Rather than treating it as a narrative of genetic monsters, as would have been the case circa 1976, most reporters instead represented these mice as new wonders that carried medical promises. I then move to consider the interests and constraints that scientists had in promoting their work in the media alongside, and often before, journal publication, and what this meant for assigning priority. In the third section, I analyse the different categories that the groups who followed Ruddle elaborated and sought to elevate in journal publications. Finally, in the fourth section I discuss the labelling of these new mice as 'transgenic', and the establishment of a set citation pattern that contained a narrative of the invention, though this could be used flexibly to emphasise some agendas over others. This fluid resolution of priority united the efforts from diverse laboratories that had not been in immediate competition into a new field, but it also excluded or downplayed other projects. The inclusions and exclusions were multi-sited, distributed across multiple locations and media, and frequently improvised by scientists, journalists and university administrators.

Table 4-1. Major papers on gene transfer into mice, 1974–1981.

Authors	Journal	Published	Submitted	Revised	Announced	Major claims
Jaenisch & Mintz (Salk Inst. & Fox Chase)	*PNAS*	April 1974	13 Dec 1973	—	—	SV40 virus injected into mouse embryo at blastocyst stage can be found in several tissues of resulting mice. No *expression* or *germline transmission.*
Jaenisch (Salk Inst.)	PNAS	April 1976	26 Jan 1976	—	—	M-MuLV incubated with blastocysts integrates, *germline transmission.*
Gordon, Ruddle et al. (Yale)	*PNAS*	Dec 1980	23 Sept 1980	—	3 Sept 1980, *New York Times*	HSV *tk* gene detected in 2 microinjected mice out of 79. Integration into the genome unclear.
Harbers, Jähner & Jaenisch (Hamburg)	*Nature*	15 Oct 1981	13 Jul 1981	28 Aug 1981	3 Sept 1980, *New York Times*	M-MuLV integrates and is expressed after microinjection
E. Wagner, Stewart & Mintz (Fox Chase)	*PNAS*	Aug 1981	13 May 1981	—	28 Aug 1980, *Science*	Human β-globin injected as well as HSV *tk*. Integration indicated. *tk* expressed.
T. Wagner, Hoppe et al. (Ohio U and Jackson)	*PNAS*	Oct 1981	1. Feb 1981* 2. 9 Jul 1981	—	8 Sept 1980, *Washington Post* (patent filed 12 Jun 1981)	Rabbit β-globin successfully injected and *expressed*. *Germline transmission*.
Costantini & Lacy (Oxford)	*Nature*	15 Nov 1981	20 Jul 1981	11 Sept 1981	15 Nov 1981, *Nature* comment	*Germline transmission* of rabbit β-globin.
Brinster, Palmiter et al. (U Penn & U Washington)	*Cell*	5 Nov 1981	4 Sept 1981	25 Sept 1981	—	HSV *tk* strongly *expressed* under control of the metallothionein promoter, integration strongly supported.
Gordon & Ruddle (Yale)	*Science*	11 Dec 1981	30 Sept 1981	30 Oct 1981	—	"Transgenic" coined; synthesis of existing papers. *Germline transmission* of HSV *tk* gene and human interferon. Integration strongly indicated.

* Paper returned for extensive revisions after peer review – Marx 1981b, T. Wagner interview.

§1. Breaking the news

When Jon Gordon and George Scangos told Frank Ruddle about the results with mice, Ruddle was on his way to attend the Second International Congress on Cell Biology in West Berlin that ran through the first week of September 1980. He was scheduled to give a plenary lecture on the various methods of gene transfer into cultured animal cells. The congress may have been described by the *New Scientist* as a 'prosaic meeting on cell biology', but was in fact a major event bringing together key scientists working in cytology, molecular biology and development.[7] The sheer number of participants (almost 1800 abstracts were submitted) and the variety of topics covered by presentations and workshops offered a large-scale opportunity to communicate new research and capture cutting-edge work. According to the president's address, such a meeting was "desirable in order to broaden our outlook and make us aware of stimulating and exciting new developments in neighbouring fields." He expressed the hope that "the younger generation will have had their horizons extended, and that the older generation will appreciate that we all benefit far more than we sometimes tend to admit from personal contacts."[8]

Despite the wide scope of the talks, which ranged from chromosome structure to cell membrane components, the plenary lectures were devoted exclusively to molecular genetics and gene manipulation, preempting the focus on 'molecular cell biology' that would become the dominant way of conceptualising the field in the 1980s.[9] Illmensee's presentation focused on genetic manipulation of the embryo via nuclear transfer or artificial parthenogenesis, while others gave talks on expressing eukaryotic genes in bacteria or the organisation of immunoglobulin genes. On 3 September, Ruddle gave his lecture on gene mapping by gene transfer in mammalian cells that mostly addressed the utility of cross-species cell hybrids and gene transfer into cultured mammalian cells. At the end, Ruddle briefly mentioned the new results on gene transfer into fertilised eggs. Yet this was the highlight of the talk, received with both excitement and doubt, as he recalls.[10]

---

[7] Yanchinski 1980

[8] Schweiger 1981, Peter Galliard's foreword.

[9] 'Molecular cell biology' was made a commonplace way of thinking about the cell most dramatically in 1983, when the definitive textbook, *Molecular Biology of the Cell*, was published: Alberts, et al. 1983. See Serpente 2011.

[10] Ruddle interview.

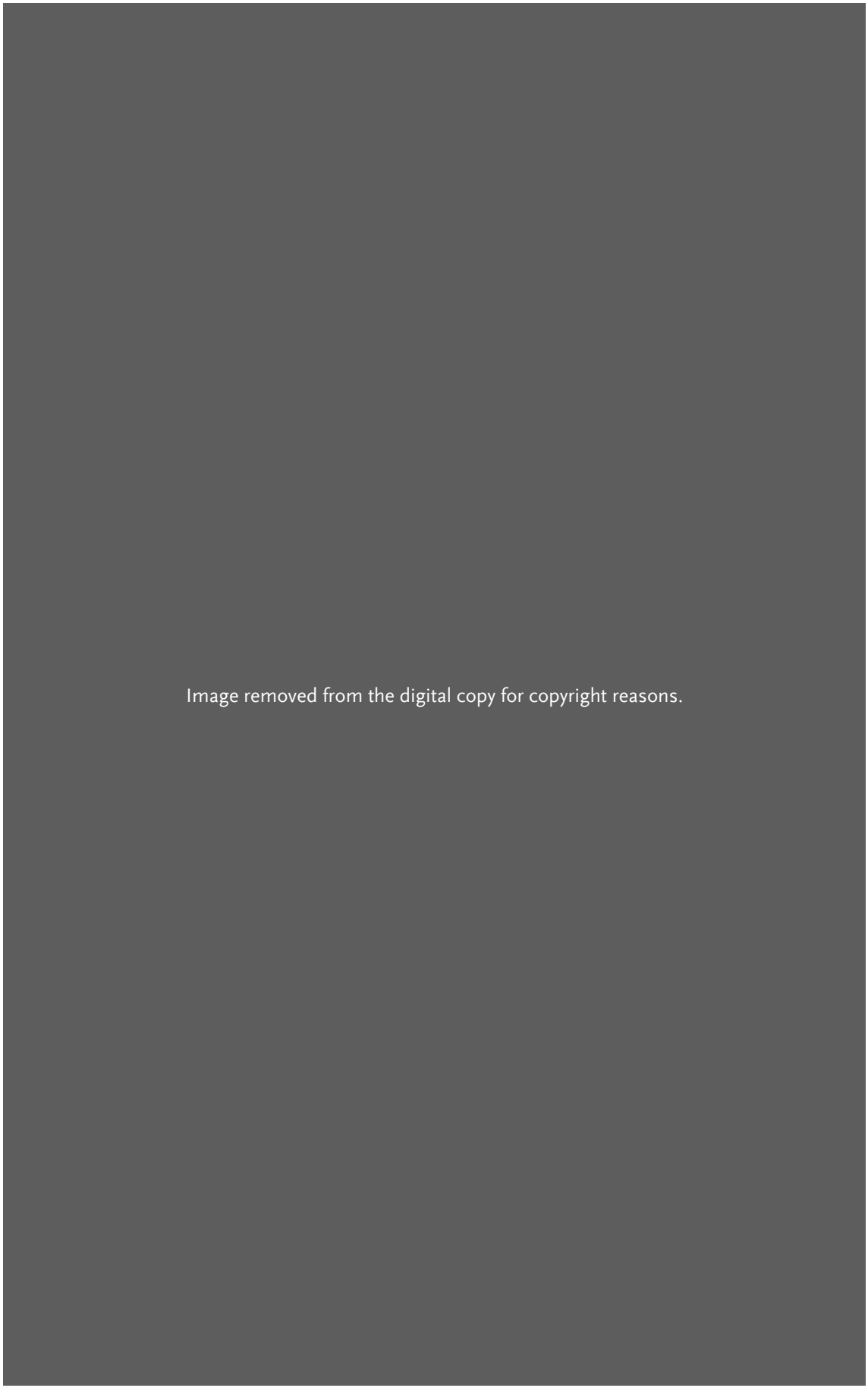


Fig. 4-1. Front page, *New York Times*, 3 September 1980, A1.

Ruddle did not limit his audience to the congress attendees. Before making the announcement, he phoned Harold Schmeck at *The New York Times*, who had covered scientific news for the paper since the 1960s. Ruddle had met Schmeck at the Jackson Lab course on mouse genetics, where journalists had been regularly invited for extended press conference sessions. Schmeck, who had been covering genetic engineering and cloning in the previous years, was eager to pursue the story. On 3 September, the same day Ruddle delivered his lecture in West Berlin, readers of *The New York Times* learned about the experiment from the front page.[11]

The prominent position may be explained by the somewhat slow news day, as it sat next to the settlement of a Polish coal miner strike, an update on the senatorial race and a piece on the new police academy recruits being sworn in (Fig 4-1). In the following week, the news about the Yale experiment was picked up by major newspapers, magazines and science periodicals in the United States. Footage of mice – ordinary lab mice, not the genetically modified ones – appeared on national television alongside interviews with Ruddle and footage of Gordon performing microinjection. While Ruddle was in Berlin, Yale organised a press conference, putting the bemused Gordon and Scangos in a room full of journalists.[12] A report of he press conference, distributed globally by Associated Press, seeded further news stories.

As Gordon recalls in his 2003 book on the ethics of genetic modification and testing,

> When we first introduced genes into the mouse germline in 1980, much of the scientific community, as well as the popular press, were thunderstruck. Major articles announcing this development as a gigantic leap forward appeared on the front pages of leading newspapers and nationally circulated news magazines. Suddenly, as if out of nowhere, we stood at the threshold of a new era in genetics.[13]

By contrast, in her account of early IVF in the United states, the science writer Robin Marantz Henig offers an apparently contradictory view:

---

[11] Schmeck 1980.

[12] Gordon interview; Scangos interview.

[13] Gordon 2003: 190.

> Opponents of gene swapping at the 1975 Asilomar conference had said it might lead to exactly the kind of research that Gordon and Ruddle were doing five years later. Ironically, however, by the time the Yale investigators proved the critics right, nobody seemed to notice. Had their work received wider publicity, there might have been newspaper columns in which career Cassandras warned that cross-species experimentation would lead to the creation of bizarre man-beasts reminiscent of H.G. Wells' *Island of Dr. Moreau*.[14]

In fact, both accounts shed some light on the events that took place. Gordon's recollection is justified – their press conference did result in major coverage. Yet, even though Henig missed these stories, she does have a point in that the response to the Yale results was brief and largely framed as a breakthrough, even though they clearly subverted the often-aired claims that significant applications of recombinant DNA to animals (and therefore humans) were too fantastic and remote to entertain. The harsh debates about genetic engineering, so prominent in the mid-1970s when the tension between opposing viewpoints was often amplified by the press, were almost absent in this case, and certainly did not come anywhere near the contemporaneous discussions surrounding IVF, gene therapy or cloning. Nor did they recreate the earlier dramatic controversy about cross-species hybrids that followed Harris's work on somatic cells. How, then, did media outlets report gene transfer into mice, and why was the reaction so mild? As the remainder of the chapter will argue, it was a combination of fortuitous timing, with a change in the way journalists were approaching genetic engineering stories, engagement with the press on the scientists' part, and the apparent lack of other dubious elements such as commercial interests to fuel the story.

§2. "A one-way trip to the Brave New World"?

In 1978, *The New York Times* established a pioneering dedicated *Science Times* section that coincided with the foundation of new glossy popular science magazines across the country.[15] Partly driven by publishers' increased interest in dramatic scientific stories as a potential source of revenue, and partly, as one editor put it, by "the Sputnik generation [being] now of magazine-buying age".[16]

---

[14] Henig 2004: 258.

[15] See Bennet 1979, Asimov 1980, Anon. 1980b, Garfield 1986.

[16] Bauer 2012.

Schmeck had worked as the paper's science writer since 1957, and wrote extensively on medical and biological research, including the recombinant DNA controversy.[17] While he had mostly maintained the neutral tone characteristic of the paper's editorial policy, there had been critical articles. Thus, in 1979, Schmeck voiced concern about the rushed and hyped-up clinical trials of interferon, without solid clinical evidence for its efficiency, and then faced criticism from some scientists and new biotech entrepreneurs who accused him of misleading the public and standing in the way of progress.[18]

Despite this, Schmeck took a rather positive view of the Yale news. He described the work as "experiments with profound implications for genetic research", distinguished by their "success at altering an animal's fundamental genetic composition". The article hinted at the possible implications of the technique of transplanting genes: creating animals with new characteristics, and curing genetic disease. At the same time, while noting that genetic engineering was controversial and opposed by some groups, it firmly placed Ruddle group's research within the realm of basic science. Mapping mouse genes was stressed as the main purpose, and the article emphasised the uncertainty as to whether the foreign genes could have an effect on the mouse, and whether they could be transmitted to offspring. The balance between enthusiasm and caution was expressed in the two concluding quotations from Gordon and Ruddle. Ruddle said, "This is just the first step in a long-term project," while Gordon emphasised, "The possibilities that this opens are so broad that it is hard to know where to begin".

Other broadsheets and 'quality' news magazines largely followed Schmeck's template. By the end of the following week, the Yale experiments had made it to the Medicine section of *TIME* magazine, with the headline "Moving Towards Designer Genes."[19] The article also associated the developments with treating human genetic disease, and while voicing Ruddle's reservations about the scientific potential of the technique, focused on potential extensions to humans, and the likely rekindling of the recombinant DNA controversy. *Newsweek* was the only news periodical to give

[17] Yardley 2013.

[18] Nelkin 1995: 156.

[19] Toufexis 1980.

voice to dissenting comments, quoting Jeremy Rifkin, head of the Peoples [sic] Business Commission[20] an activist on a long crusade against genetic engineering, "It's a one-way trip to the Brave New World".[21] Despite this soundbite – not exactly an invitation to debate – the overall coverage was favourable. *The Los Angeles Times* placed the story in the context of a recent breach of NIH guidelines elsewhere and went so far as to suggest that "[t]he scientists' caution about the implications of DNA work may be spurred in part by a desire to allay public concerns about danger from the research."[22]

These very concerns likely encouraged Ruddle to engage with the press and attempt to set the tone for the news stories. The media frenzy that had accompanied discussions of recombinant DNA since Asilomar, and the risk of federal regulation beyond the NIH guidelines made scientists appreciate the risks to their day-to-day work more, and take public relations seriously. While Ruddle's laboratory was not immediately involved with recombinant DNA research and only started using the methods routinely in 1978–79, as head of the Biology Department and its Biohazards Committee, he had overseen the local implementation of the guidelines and had been involved in campus debates on genetic engineering at Yale.[23]

Similarly, the major periodicals that had been perceived to matter, as evidenced by being selected by the Yale news-clipping service, were convinced that inserting genes into mice would not make monsters.[24] Indeed, while Ruddle, Gordon and Scangos were careful to stress the uncertainty of any medical applications, the references to gene therapy were prominent. Much like the other aspects of 'new genetics', gene therapy was moving from the domain of science fiction into tangible experiments and proposed trials.[25] The language used in most publications about the Yale experiments was strongly evocative of medical terms, perhaps echoing 'microsurgery' as a common

---

[20] Soon renamed to Foundation of Economic Trends, famous for its lobbying and multiple lawsuits against genetic engineering experiments in the 1980s.

[21] Begley & Carey 1980.

[22] Dembart 1980.

[23] Paulson 1976a, Paulson 1976b, Krumholz 1979.

[24] Box 3, Accession 1986-A-078, News clippings and articles about Yale University, RU 64, Manuscripts and Archives, Yale University Library, New Haven, CT.

[25] Martin 1999; Wolff & Lederberg 1994.

way to describe embryo manipulation. The genes were "transplanted" into mice, the process was "gene surgery" and an "operation" and Gordon was compared to a skilful surgeon and television footage spotlighted him at his microscope. Reporting medical news was a priority for newspapers, as it carried the human interest, and such use of language helped make the scientific narrative appealing to broad readership.[26]

It would be misleading , of course, to limit the analysis to elite periodicals like *The New York Times*. The *New York Daily News,* an established tabloid whose circulation at the time was only slightly below the *Times,*[27] took a different view. On 7 September, it ran an opinion piece from its science editor, headlined "Gene-Splicing: Will it Create a Monster?".[28] The article echoed the concerns about genetic engineering that were prominent in the mid-1970s, discussing the regulation of genetic engineering by drawing analogies with nuclear energy. The concern had been expected by the Yale scientists, and Gordon and Scangos addressed it in their press conference. A local Connecticut paper, *The Hour,* quoted Gordon as saying "I feel that we will always operate at a level below creating a genetic monster".[29]

However, television evening news reports, reaching much wider audiences, took their cue from *The New York Times*. On 4 September, the day after the announcement, the NBC correspondent, Robert Bazell, stressed that it was not clear whether these experiments would lead to new forms of life, but hailed them as a "big step" in genetics. The report featured a brief interview with Ruddle, who said, "My own feeling is that knowledge is neither good nor evil", implying that how this invention would be used was not a relevant question when pursuing basic research.[30] A week later, ABC News featured the Yale experiment in their final instalment of an investigative report on genetic engineering. Setting the meaning of this work against the concerns about creating new

---

[26] Gutteling, et al. 2002.

[27] The circulation of *Daily News* was over 2.6 million on Sundays and around 1.8 million on weekdays, making it the fourth-highest-circulation newspaper in the United States according to the Ullrich Periodicals Directory, with *The New York Times, Washington Post* and *USA Today* being third, second and first, respectively.

[28] Edelsen 1980.

[29] Dupuis 1980. The sampling of local and tabloid press here is necessarily incomplete and is limited by the available indeces and digital resources. It is however unlikely that there was significant coverage – in any case, it did not feed back into the broadsheet press or television news.

[30] Evening news, NBC, 4 September 1980.

life, the piece ends with the position of the scientists who claimed it would bring new knowledge about human genes in an animal – using the mouse as a test-tube, as Ruddle put it.[31]

The news seemed to make little impact in Europe. In the UK, it was picked up only by the *New Scientist,* where science writer Stephanie Yanchinski argued that the Yale mice were anything but mundane, in a piece provocatively titled 'Opening the Pandora's Box of Biology' – another common metaphor in genetic engineering writing.[32] The opening sentence did not disappoint: "Three Yale scientists have teased open the lid of the Pandora's box of assembly-line human beings." However, in what followed Yanchinski offered an eloquent account that described the experiment in a lot more detail than other publications had done, particularly emphasising Gordon's virtuoso skills as a microsurgical manipulator. The rest of the article speculated about potential uses of microinjection in human gene therapy. Yanchinski placed it alongside the iconic IVF advance of Robert Edwards and Patrick Steptoe, and the article was, in fact, illustrated with a photo of Louise Brown, the first 'test-tube baby' born in July 1978. In the conclusion, Yanchinski argued that combining the two techniques could "fundamentally alter human genetics", and that both experiments might be "the start of something big".

In contrast to the journalism in science periodicals, editorial opinion often aimed to preserve the authority of scientific institutions. A *Nature* editorial by John Maddox took the opportunity to attack outspoken critics of science:

> One of the hopes, perhaps unrealistic, of this new decade was that the arguments about the hazards of this or that new scientific development would be couched in more moderate language than used to be the fashion in the 1970s... Messrs Jeremy Rifkin and Dan Smith, described as directors of the [Peoples Business] commission, say that the development represents "the greatest potential technological threat to the sanctity of life since the beginning of human history"...[33]

Maddox went on to dismiss Rifkin as a "diligent reader of *The New York Times*" unfamiliar with the scientific literature, and suggested that everyone wait for a publication. Around 1980, the moder-

---

[31] Evening news, NBC, 11 September 1980.

[32] Yanchinski 1980.

[33] Anon. 1980a.

ate language that Maddox urged was becoming commonplace for genetic engineering. Since the late 1970s, coverage of biotechnology was increasingly couched in the language of progress and promise at a time of political and economic uncertainty. This trend was recognised at the time and has been documented in retrospective analyses of the US press.[34] In her award-winning 1980 article, 'The Gene Craze', the science studies scholar Rae Goodell observed the shift from debates about the possible health risks of recombinant DNA and the moral implications of genetic engineering to a celebration of a new form of enterprise.[35] She argued that scientists and the emerging biotech industry were strongly behind this change, with eminent scientists and bodies including the National Academy of Sciences lobbying Congress to prevent federal regulation. Moreover, the industry, convinced that there was a new market to explore after announcements about successful synthesis of human somatostatin and insulin in bacteria, brought expertise in public relations into the mix.

Echoing Maddox, Goodell also argued that science writers were exhausted with the polarised debate framework:

> Tired of the fading, repetitive congressional battle, and plagued by the Three Mile Island, test tube babies, and a number of the other complex controversies, science writers were ready for a good, clean science story, and industrial announcement of new DNA discoveries provided it.[36]

As the controversy over the regulation of recombinant DNA was reported as solved, and the voluntary moratorium praised as an unprecedented act of social responsibility, the dissenting opinions were disappearing from news reports, with even left-wing American periodicals such as *Mother Jones, The Progressive* and *New Times* ignoring press releases from the Peoples Business Commission. That the change affected most general periodicals can be explained by Sharon Dunwoody's concept of an 'inner club' of science journalism. Dunwoody argued that most science writers routinely discussed topics among themselves and relied on mutual exchange of expertise,

---

[34]Nisbet & Lewenstein 2002,Gutteling, et al. 2002.

[35] Goodell 1980. See also Goodell 1986, Wright 1994: 256–280. Rae Goodell was herself an early participant in the recombinant DNA debates, initiating the oral history programme and archive dedicated to the controversy at the MIT's Programme for Science, Technology and Society with Charles Weiner, advertised to scholars as early as 1979 – see Weiner 1979.

[36] Goodell 1980: 45.

leading to a rather uniform landscape of reporting. Scientists formed the vast majority of sources, and were rarely criticised or undermined.[37]

While Goodell's account seems to pinpoint the key changes in the late 1970s, it is worth noting that the landscape was more diverse. First, many senior science journalists were increasingly uncomfortable with what they viewed as excessively sensational coverage of the recombinant DNA controversy. This sentiment was expressed at a recorded roundtable organised and published by MIT's *Technology Review* in March 1980.[38] The framing of the conversation suggested that science writers had lost the 'age of innocence' that supposedly existed in the 1960s, and now had to seek balance in a world where science inspired both dramatic interest and strong opposition. 'Breakthrough' was a dirty word, even if editors liked it, and writers knew that many promising reports had failed to deliver in the long run, especially when it came to pharmaceuticals. At the same time, most participants refused to see themselves as advocacy journalists and strongly contested *Mother Jones'*s Mark Dowie suggestion that more were needed in science writing. On recombinant DNA, the feeling was that the press had emphasised the "public's right to know" and that the resolution was satisfactory. The *San Francisco Chronicle's* David Perlman suggested that the opposition between scientific viewpoints had developed to such a passionate degree where "the objective realities that can be discerned in the laboratory have been forgotten," but that at the end "participants and spectators finally reached a more rational level of compassion, so to speak."[39]

Perhaps ironically, journalists writing for the news sections of scientific periodicals, particularly *Science* and *Nature,* were likelier to be critical of specific developments, as Yanchinski's *New Scientist* piece shows. For instance, Nicholas Wade, the news editor for *Science*, had maintained a critical balance over recombinant DNA. With William Broad, he co-authored *Betrayers of the Truth*, a book that unapologetically tackled the uncomfortable subject of scientific fraud when a series of high-profile whistle-blowing cases threw this into the limelight in the early 1980s.[40] However, by

[37] Dunwoody 1986, Nelkin 1995.

[38] Anon. 1980b.

[39] Ibid.: 56.

[40] Broad & Wade 1982. See also Kevles 1998.

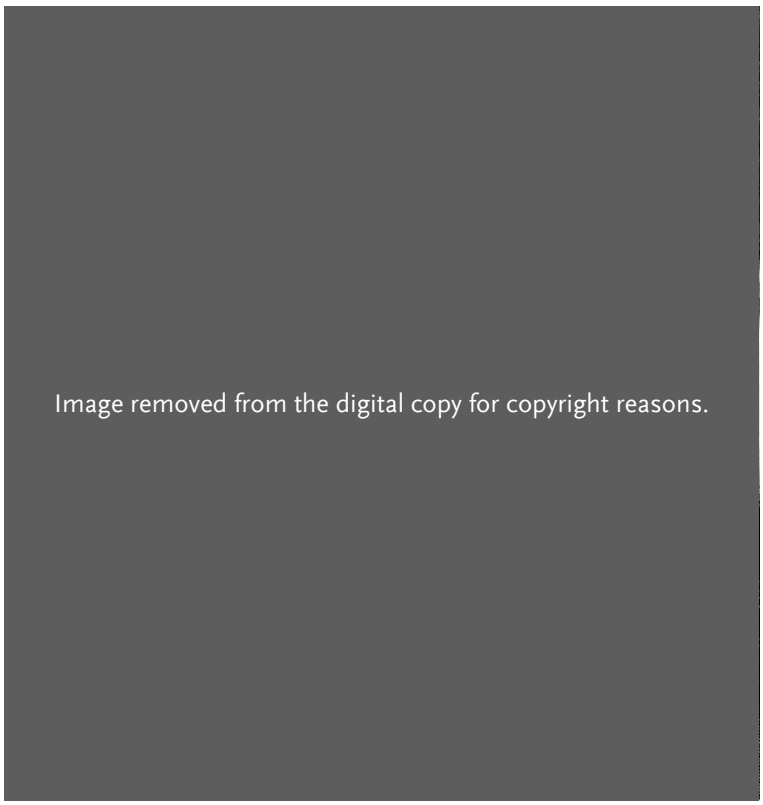


Fig. 4-2. "Gordon with subject"

Newsweek, 22 September 1980.
Photograph by Maggie Steber.

1980 other kinds of stories were drawing the critical attention: the seminal Supreme Court decision in *Diamond v. Chakrabarty* that allowed patenting of bacteria in June 1980; breaches of NIH guidelines; plans for direct involvement of universities such as Harvard in biotech business. A striking example was the backlash against Martin Cline's attempts to extend his experiments with mouse somatic cells when he inserted recombinant globin genes into human blood marrow cells that were then transplanted to two patients suffering from beta-thalassaemia in Italy and Israel, only a month after Ruddle's announcement.[41] By contrast, the Yale experiments were framed as an academic advance with clear medical benefits, the mice predominantly described as genetic wonders rather than monsters. It is also worth remembering that the story, while receiving a remarkable amount of coverage for a scientific experiment, lasted for only two weeks.

Finally, the mice themselves were largely absent from view. Aside from the footage of laboratory mice in newsreels, only one image of a mouse featured in printed sources. *Newsweek* ran a story illustrated with a photograph featuring a cropped profile of Gordon at a microscope with micromanipulators, and in the centre, a white laboratory mouse (Fig. 4-2).[42] This mouse, in the staged

[41] Jacobs 1980.

[42] Begley & Carey 1980.

photograph that was a product of discussion between the photographer, Maggie Steber, and Gordon, who wanted to make the mouse a 'hero' of the image,[43] is atypical. The first batch of transgenic mice was homogenised, their DNA extracted and represented as bands on agarose gels. And while *Newsweek* and NBC featured footage of mice in the laboratory, these were not the specific 'heroes' of the experiment but ordinary lab animals in fleeting shots. Instead, the attention was focused on the elaborate technique and images of microinjection that appeared on the blurry screen attached to the dissecting microscope. This displayed the mysterious process of embryo manipulation while hiding the gruesome fate of the animal subjects from public view.

In December 1981, a *New York Times* piece by Schmeck suggested that "Biotechnology no longer provide[d] intense concern."[44] This observation may have been a reasonable reflection on the coverage in major US newspapers, but according to NSF statistics public support for regulating genetic engineering research remained high. In the 1981 poll, 50% of the respondents 'attentive' to scientific issues suggested some limits should be imposed on research into "creating new life forms", only a 1% drop from 1979 figures. The same indicator among "potential attentives" in 1981 was as high as 67%.[45] The changes in reporting new experiments, including gene transfer into mice, were not following 'public opinion'. To a large extent, they were a product of the changing relationship between science journalists and their sources, and the internal trends in mediating a controversy.

§3. Journals and the politics of priority

Ruddle's engagement with the press allowed him to keep some control over the coverage. While I do not suggest that he controlled publicity religiously – after all, he trusted two inexperienced postdocs to handle the media – by being seen as open and ready to comment, his group became the sole expert voice in the story. Aware of the work going on in Mintz's and Brinster's laboratories, Ruddle understandably wanted to secure priority:

---

[43] Maggie Steber, Facebook message, 10 June 2011.

[44] Schmeck 1981a.

[45] National Science Foundation 1983: 150.

> Well those people who were doing mouse work... it was a very big deal for them and, you know, we were talking about... Mintz and Brinster, and others. They had put a lot of work into doing transformation studies on the mouse and I think it was hard on them, because they had made such a big investment and to have someone like myself come from out of the blue, not having the same kind of experiences that they've had in the kind of work they were doing, I think... it was really difficult for them, but that's science. And I've been in situations where I've been scooped and it's been hard for me.[46]

The press conference at Yale not only addressed the possible implications of inserting genes into mice, it also stressed that the group was at the cutting edge – as Gordon put it, "We're quite a bit ahead of other labs working in this area."[47] Having considered the coverage of the Yale experiment, let us return to the circumstances of the announcement. What did it mean for a scientist to talk to the press about an unpublished scientific result in 1980?

It might appear that in the middle of the twentieth century it was increasingly problematic for researchers to engage with the press and address the public directly. However, the sentiment is rather mythological, as recent studies show.[48] Some respectable activities were beneficial for a senior scientist. Thus, Ruddle wrote detailed articles for *Scientific American* reviewing new fields of research for an educated readership interested in science.[49] Established researchers often acted as experts on controversial matters and advocates of the scientific community, but those roles almost required rhetorical distancing from the 'sensational' press. This happened with Rorvik's *In His Image*, discussed in Chapter 3. Derek Bromhall, an Oxford embryologist whose nuclear transfer work had been mentioned in the book's introduction, went as far as suing for libel.[50] At the same time, Bromhall was happy to consult for *The Boys from Brazil*, a 1978 Hollywood film based on Ira Levin's 1976 novel – a story remarkably similar to Rorvik's, except it was about Joseph Mengele cloning Hitler in a jungle laboratory. Finally, advocates of recombinant DNA research were a ma-

---

[46] Ruddle interview.

[47] Weiss & Oder 1980.

[48] Nathoo 2009, Wilson 2011.

[49] Ledley & Ruddle 1966, Ruddle & Kucherlapati 1974.

[50] Kirby 2003.

jor influence, and that controversy alerted an increasing number of scientists to the importance of engaging with the media.

This, however, was different for new work. At the time, announcing scientific results to the press before publication could be questionable, and publicity-seeking was being associated with the new commercial context of biotechnology and the competition between companies to establish priority claims in a potential intellectual property dispute. It also appeared to challenge the established system of peer review. Thus, an influential opinion piece in the *New England Journal of Medicine* titled "Gene Cloning by Press Conference", was published only a few months before the Yale press conference. The author, Spyros Andreopoulos of the Stanford Medical Centre's news bureau, highlighted the trend among the new biotech companies to announce the isolation of an important and commercially promising gene such as interferon before academic publishing, and lamented the circumvention of the traditional peer-review that "[did] not contribute to either good science, or good science reporting."[51]

Scientific journals deemed themselves the only place where important new science should be announced, and were eager to discipline their authors and science journalists. Since the 1960s, the practice of 'embargoes' was established, whereby journals allowed writers early access to papers on condition that no coverage appeared before the journal article. Journal editors argued that this allowed journalists more time to write quality articles and at the same time enabled experts to consult the 'proper' publication as soon as the story broke in the news.[52] Alternative communicative trajectories were frowned upon. The 1976 guidelines for journal editors, compiled by some of the major figures in science publishing, left accepting papers based on experiments that had been previously announced elsewhere to the discretion of the editor, but advised against approval if "the circumstances suggest that the prior publication in a news medium was actively promoted by the author". For the authors of the guidelines, "premature publications in the scientific or lay

[51] Andreopoulos 1980.

[52] Marshall 1998, Kiernan 2006: 44–81.

news media of research findings that may not be scientifically valid… may therefore mislead and be harmful to society."[53]

The reluctance to allow double publication was commonly known as the 'Ingelfinger rule', after Franz J. Ingelfinger, the editor of the *New England Journal of Medicine* who had imposed it in 1969 mainly to avoid double publication of the same findings in multiple journals.[54] The rule was extended to press coverage in the late 1970s, but its application was never straightforward. As Vincent Kiernan suggests, in the 1970s announcement at a conference was usually sufficient to confirm that the scientific community had learned about an experiment first.[55] A February 1979 editorial in *OMNI*, a lavishly printed new popular science and science fiction periodical co-founded by the publisher of *Penthouse* magazine, lambasted scientific journals' presumed monopoly on disclosure.[56] Referring to the allegations by the *New York Post* that the first IVF baby Louise Brown was a hoax, based on the fact that Patrick Steptoe announced the results to *National Enquirer* rather than a journal, *OMNI*'s Frank Kendig argued that journals were too slow and too specialised to announce new work, and while their caution with what they published was justified, they should not monopolise technical information.[57] Similar opinions were voiced in a 1982 report on press coverage of science by the journal *BioScience*. It cited French Anderson, a public health authority and the head of communications for the American Association for the Advancement of Science, who all claimed that "the public's right to know" trumped the danger of reporting shoddy or overblown research – a sentiment that made sense after Asilomar and with the growth in popular science publishing.

Another dissenting view came from Eugene Garfield, the founder of the Institute of Scientific Information and publisher of *Current Contents*, a lucrative abstracting and reprint-order service. In 1973, he incorporated a *Press Digest* into *Current Contents*, which traced news stories in "popular magazines and newspapers that scientists should know about". He viewed it as part of a "basic-

---

[53] DeBakey 1976: 37.

[54] Marshall 1998.

[55] Kiernan 2006.

[56] On *OMNI* as a science fiction magazine, see Ashley 2007: 367–78.

[57] Kendig 1979.

science lobby" that would reverse the major funding cutbacks and sell academic science to the lay audience more efficiently. The editorial that launched the *Digest* was to the point: "Too many scientists feel that 'public relations' is not only a waste of time, but also a kind of blasphemous malpractice alien to professionalism. Nothing could be further from the truth."[58] While Garfield may not have been the most popular figure in the scientific mainstream and his promotion of bibliometrics to assess scientific output disturbed many critics, his influence was considerable.[59] His invitation to take the general press seriously in 1973 was vindicated by the recombinant DNA debate that followed. In the light of critical interest directed at molecular biology in the mid-1970s, his suggestion at a 1976 conference on plasmids that newspapers were a legitimate way of enhancing science communication made more sense than even five years before: "While we would hope that journals like *Science* and *Nature*, and others of a weekly frequency, would make certain to report [new scientific] information promptly, there can be no doubt that, at the present time, the only prompt outlet for such information of necessity is the *New York Time*s and comparable publications elsewhere."[60] While the bold statement appeared at a relatively obscure meeting in Czechoslovakia where Garfield was advertising his products, he was backed by Esther Lederberg, Joshua Lederberg's wife and collaborator who was promoting a plasmid repository she established at Stanford.

Ruddle's decision to communicate in advance of journal publication might have raised eyebrows, but it was not necessarily against the grain in an increasingly public world of biomedical research. It could have been dangerous for a younger, less established scientist, but someone of Ruddle's stature and reputation was unlikely to face problems, and a brief announcement at a major conference sufficed. Moreover, 'cloning by press conference' was not limited to biotech firms, and work with promises for gene therapy was especially public at that time. Thus, before controversy broke over Cline's clandestine human trials, his results with mice were well-promoted by UCLA – something Nicholas Wade and Gina Kolata retrospectively critiqued in *Science* once the

[58] Garfield 1973

[59] See e.g. Broad 1978

[60] Garfield & Lederberg 1977

trial story broke.[61] Moreover, similar publicity surrounded French Anderson's work with Diacumakos on inserting the HSV *tk* gene into somatic mouse cells. The news broke after an announcement at a conference in October 1979, before the paper was published in *PNAS* in September 1980, despite Anderson's professed reluctance to speak to journalists on a deadline after his earlier thalassaemia research had been blown out of proportion in the early 1970s.[62]

Priority was another major part of the De Bakey journal guidelines. Concerns about priority and credit have a long history, and various practices had been used to resolve possible disputes. Scientific societies were often responsible for distributing credit: thus, the French Académie des Sciences had encouraged sending discovery accounts in sealed envelopes that could be opened in case of dispute. The invention of the telephone is perhaps the most dramatic example, as Alexander Graham Bell and Elisha Gray filed a patent for very similar devices on the same day, 14 February 1876.[63] By the twentieth century, the journals had taken over in that role for university research. The complexities of priority assignment were elaborated in a chapter from the same 1976 guidelines that considered what dates were appropriate markers to serve "as an index of priority".[64] The chapter listed 14 options, ranging from the date of the original idea to the day when the journal issue reached its subscribers, via dates of a preprint being sent out, on the letter of submission, on the postmark, of firm acceptance, and others. Dates that could be firmly established – of receipt of the manuscript, acceptance, receipt of revised version, actual publication – were preferred as easy to confirm and safeguarding the editor from getting involved in a dispute.

To safeguard their claim, the Yale group decided to publish the paper as soon as possible in *PNAS*. This was a reputable journal that required a member of the Academy to submit or "communicate" a paper, and there are indications that this means of assessing credibility meant the review process could be more lax, and publication quicker – not a trivial consideration as waiting times were

---

[61] Wade & Kolata 1980

[62] Burke & Epperson 2003: 202, Schmeck 1979. The paper appeared as Anderson, et al. 1980. Anderson expressed his supposed reluctance to talk to the press to *BioScience* in 1982: "I will always participate in serious scientific analysis pieces because I think that is my obligation, but I do not speak to news reporters who are trying to make the evening deadline, primarily because they are trying to emphasize the most *newsworthy* issue rather than the *real* issue", Boddé 1982: 173–4.

[63] The implications of these patents in the telephone story are, predictably, ambivalent – see Finn 2009.

[64] DeBakey 1976, chapter 10.

growing, to universal discontent. As an active member of the Academy, Ruddle could submit the paper himself and negotiate speedy publication, so that it appeared in December.[65] This timing was especially important, since Ruddle's group was eager for the paper to appear before the end of the calendar year, so that the reference in subsequent papers would be "Gordon et al. 1980", not 1981.[66] The decision was still equivocal among the authors – Diane Plotkin, named as a co-author for providing the DNA, was not convinced the results were sufficiently solid to publish, and felt more work could be done. Gordon, on the other hand, was pressing to publish as soon as possible and establish priority.[67]

An experienced network-builder, Ruddle was promoting the interests of his laboratory and took care to distribute the credit and recognition within his laboratory, allowing the postdocs who performed the experiments to take centre stage. It might be tempting to dismiss Ruddle's media work as an odd episode, and it was indeed the most high-profile in his distinguished career. However, with the next two papers on gene transfer into mouse embryos – from Mintz' lab at the Fox Chase Institute for Cancer Research and Thomas Wagner's at Ohio University – newspapers again acted as an alternative means of scientific communication.

The Mintz paper was the second published claim to support the possibility of gene transfer into mice through microinjection, and from another reputable – if very differently organised – laboratory. It also took the experiments further, showing that the foreign herpes virus *tk* gene was expressed and made viral protein, and indicating that the other injected gene – human beta globin – could have been making RNA. However, before it appeared in print, another manuscript that claimed expression of microinjected beta globin gene, this time from rabbit, had been submitted to *PNAS*. It came from the collaboration between Thomas Wagner's lab at Ohio University and Peter Hoppe at the Jackson Lab. The manuscript had been sent to *PNAS* by the celebrated mouse ge-

---

[65] Gordon, et al. 1980.

[66] From the Ruddle interview: "*Myelnikov*: So why did you choose to go for PNAS, was there any reason? *Ruddle:* Well I was a member of the [National Academy of Sciences] and we wrote the paper and submitted it and then asked them that we'd like to have it published, for priority reasons, in 1980." The tendency to secure publication year to stake a potential priority claim is also dicussed in Jim Watson's Cold Spring Harbor Laboratory report editorial from 1973, reprinted as Watson 2000.

[67] Ruddle interview.

neticist and National Academy member Elizabeth Russell at the Jackson, a former collaborator of Mintz.

The submission date printed on the Ohio/Jackson paper is 9 July 1981. However, at this point one might wish to remember the 14 kinds of dates that could be used for establishing priority that the informal guidelines for science journal editors mentioned. According to Wagner's recollections, contemporary releases from Ohio University's news service and a more recent book about its then-president, Charles Ping, the publication of Thomas Wagner's paper was anything but straightforward. It was submitted to *PNAS* in February 1981, but delayed by a referee who, not uncommonly, insisted further experiments be performed.[68] The Ohio sources claim that the paper was scheduled to be published in September 1981, but once the editors learned that another "better-known lab"[69] (i.e. Fox Chase) was about to publish, they decided to bump the Ohio paper to the October issue. However, the Mintz paper was published in August 1981, not September, and had been submitted to the journal in May.[70]

During the delay, Wagner learned that *The New York Times* was about to run an article that featured the Fox Chase results. This piece, again by Schmeck, appeared on 8 September and tried to integrate recent publications about gene transfer in embryos and somatic cells as a next step in the development of gene therapy, and involved a large image of microinjection acquired from Ruddle's lab (Fig. 4-3).[71] Thomas Wagner had been delaying communicating with the media until his paper was published, in line with the standard embargo practices. Crucially, however, Ohio University filed a patent application on 12 June that claimed priority over microinjection with predictable gene expression.[72]

The Ohio team was then partially funded by Genetic Engineering, Inc., a biotech start-up based in Denver, which would be the exclusive licensee. Patents on basic techniques such as pronuclear

---

[68] Marx 1981. In the interview, Thomas Wagner suggested that the paper may have sat without any response even longer than that. It has not been possible to identify the reviewer.

[69] Ibid.: 137.

[70] T. Wagner interview; Riffe 2004.

[71] Schmeck 1981b.

[72] US Patent 4,873,191.

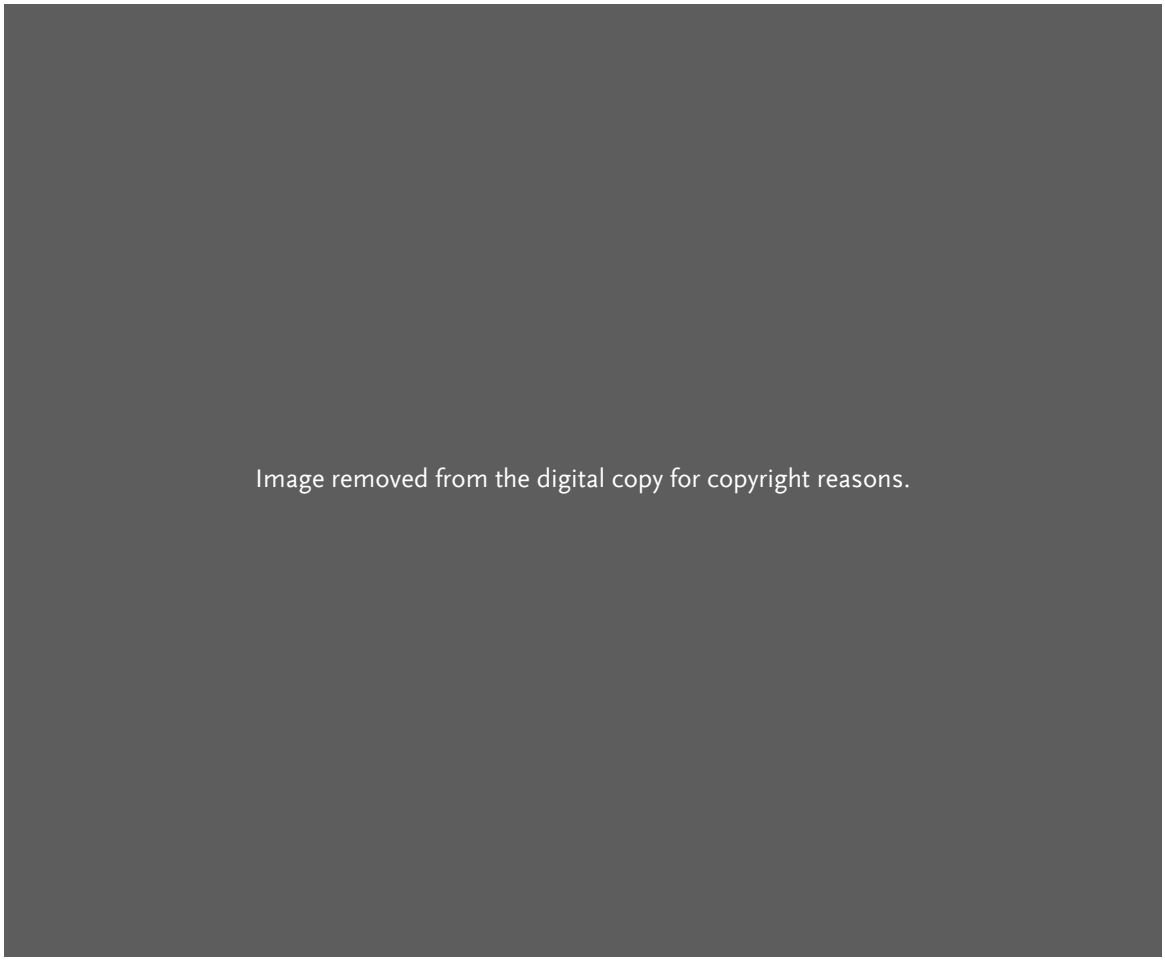


Fig. 4-3. Microinjection in *The New York Times*.

From Schmeck 1981b

microinjection were problematic, as epitomised by the much more controversial patent on making recombinant DNA that was awarded to Stanley Cohen and Herbert Boyer in 1980, and caused much academic discontent.[73] It also went to the core of what David Dickson, a *Nature* correspondent, would call "the new politics of science",[74] as epitomised by the US Bayh-Dole Act passed in 1980 to allow universities to patent the products of federally-funded research. While select universities had used multiple strategies to secure intellectual property since the early twentieth century, it normalised and disseminated these practices.[75]

[73] Hughes 2001, Yi 2011.

[74] Dickson 1988.

[75] For some relevant pieces on patenting in the history of twentieth century biomedicine, see Mowery, et al. 2004, Kevles 2007, Colaianni & Cook-Deegan 2009, Hughes 2001, de Chadarevian 2011, Yi 2011.

On learning about the *PNAS* delay, Wagner appealed to Charles Ping, the president of Ohio University who had recruited him to set up the molecular biology department in 1969, in the hope of placing his institution on the international map of cutting-edge research. Ping contacted his old acquaintance (and former landlord) Philip Handler, then president of the National Academy of Science. As head of the academy, Handler had been a major administrative figure and advocate in the world of research.[76] Handler did not affect the publication date, but he did get in touch with *The Washington Post*'s veteran science writer, Victor Cohn.[77] Probably in a competitive race with Schmeck, the *Post* published the piece on Wagner's work on the same day as the *New York Times*' Mintz-Ruddle story, 8 September 1981, that was followed by a major press conference in Athens, Ohio and follow-up stories in the US dailies (Fig. 4-4).[78]

Cohn's article liberally quoted Wagner, who stressed the potential for agricultural applications of the technique to breed farm animals – cattle as well as "goats or sheep or buffalo" – that would require less feed and be productive on lower diets. The focus was more in line with Genetic Engineering Inc.'s commercial aspirations than Wagner's scientific ambition, but it defined his research through the 1980s. He also suggested that medical applications might be "further away", and reiterated the value for "knowledge". As Cohn paraphrased, "Work like this will give biologists a tool to look into one of nature's greatest mysteries: how genes act or 'express themselves' inside cells, and how and when they are 'turned on' during an embryo's wondrous development." Beside the discussion of future applications, the article stressed the novelty of the work: "The first successful transfer of a gene from one animal species to another – from rabbits to mice and then to their offspring – has been achieved by biologists."[79] Cohn's article mentioned the research done in Mintz's lab, but stressed that their team only managed to insert the viral thymidine kinase gene

---

[76] For instance, he advocated the scientific community's ability to deal with fraud internally in front of Al Gore's committee on science and technology. Well-publicised cases of fraud made the reliability of published data and the moral integrity of the scientific profession an increasingly pressing issue in the early 1980s. For contemporary analysis, see Broad & Wade 1982. See also Kevles 1998.

[77] T. Wagner interview; Riffe 2004: 137.

[78] Cohn 1981.

[79] Ibid., A12.

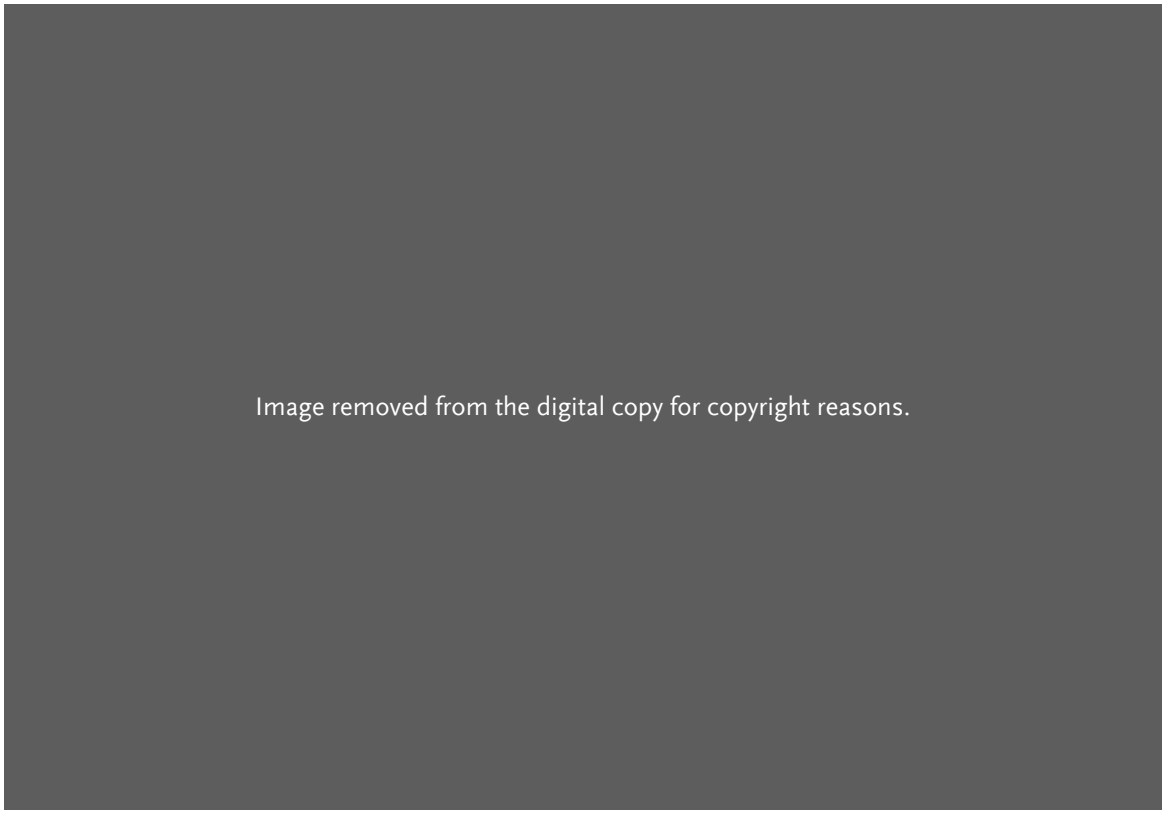


Fig. 4-4. Rabbit genes.

Ohio University Archives; *Chicago Tribune*, 1981.

"at least into the fertilized egg of a female mouse."[80] Wagner's results were presented as the "first" and "quite important", according to Elizabeth Russell.

It can be seen that the politics of priority, brushed over in scientific journal publications, was being played out on the pages of important news sources, and that decisions about press releases and access to journalists were becoming an integral part of making discoveries public. This was especially important for the patent application. But for someone relatively unknown, it was also a risky strategy. Peter Hoppe would have nothing to do with his collaborator's media outreach, and requested that the Jackson Lab public relations department ensure that his name was not mentioned before journal publication.[81]

---

[80] Ibid.

[81] "During the last reporting period, the [press] office also handled media exposure which the [Jackson] Laboratory did not solicit. Responding to inquiries regarding problems with mice shipments resulting from the air traffic controllers strike and, at his request, maintaining a low profile for Dr. Peter Hoppe and the Laboratory during the media focus on Dr. Hoppe's collaboration with Ohio University investigators on successful gene transfer experiments are two examples." Barbara Sanford, "Periodic Summary" to the trustees, 9 November 1981. Folder 17, Box 37, Papers of Barbara Sanford, Head of JAX, 1981–87, The Jackson Laboratory archive, Bar Harbor, ME.

This episode demonstrates the diversity of media that could be recruited to establish priority, and shows that scientists could rely on newspapers to advance their causes. Moreover, it highlights the interest of science writers in publishing stories and claiming greater authority in the dissemination of scientific news, tied to the growing interest and opportunities in popular science publishing. It also indicates the roles played by university administrative offices dealing with the press and intellectual property played that can only be glimpsed in the available sources.

§4. Criteria of success

Despite the great interest and competitive spirit that surrounded the announcement of the Yale gene transfer, there were many uncertainties in the published paper. It was not clear whether the experiments could be replicated, or were even, simply, an artefact. Moreover, their utility to developmental research and gene mapping was not clear, and many alternative approaches were envisioned. This is exemplified by a news article in the December 1980 issue of *Science,* in which the journal's reporter Jean Marx placed Ruddle's work as a curious advance alongside many other manifestations of gene transfer, a field she had been following for several years. Similarly, French Anderson and Elaine Diacumakos placed much more emphasis on gene transfer into cultured somatic cells – their own pursuit – in their *Scientific American* article in the summer of 1981.[82]

Yet with the competition and independent experimental work, the pressure to generate new results beyond what had been published was growing. When Mintz' two postdocs – Tim Stewart and Erwin Wagner – arrived at their results, they pursued further experiments, partly to answer specific questions that were interesting to them, and partly to produce more evidence to justify a publication after Ruddle. By spring 1981, they had a stable means of injecting DNA into pronuclei, and managed to show that the HSV *tk* gene, which was on the same plasmid as the human beta globin, was expressed, and as both RNA and protein. Since Mintz was also a member of the National Academy of Sciences, she submitted the paper to *PNAS* in May 1981. As in Ruddle's case, access to this publication enabled speedy review and the paper was published in August.[83] It set up

[82] Marx 1980, Anderson & Diacumakos 1981.

[83] Wagner, et al. 1981.

the experiment as a successful part of a larger programme of inserting genes into mice, although the modification of teratocarcinoma cells remained her major ambition.

The authors acknowledged the Yale's group recent success in transferring a foreign gene into a whole mouse, the first formal legitimation of this work in the journal circuit as a replication of sorts. However, other citation choices also stressed the existing expertise of the group and a long-running commitment to inserting genes into embryos, starting with the 1974 Jaenisch & Mintz paper, and referencing Teh-Ping Lin as the source of the microinjection technique. Finally, the discussion section stressed their demonstration of the *tk* gene *expression*, implying that this made the technique meaningful:

> Inasmuch as the ultimate objective of *in vivo* gene transfer is the study of gene regulation during development, it was important to learn whether the foreign genetic material in our developing mice could function in its new environment...
>
> The existence of the alpha-thalassemic mutation in mice presents a unique opportunity to extend this experimental system, with alpha-globin gene transfer, for the further analysis *in vivo* of tissue-specific gene function in a hereditary disease.[84]

Yet despite clear progress in establishing gene expression, the criteria that many, including Ruddle, had raised as key to a useful mouse system remained to be met in full. These were the production of proteins from the foreign genes and germline transmission – that is, the inheritance of the genes by the following generations.[85] Wagner's paper claimed both and featured a variety of data indicating the expression of the rabbit globin gene, but his results were treated with suspicion, especially as the other major labs could not demonstrate the presence of the globin protein. While a relationship with the press or commercial ties may have played a role, such treatment was more to do with the lack of an established reputation.

Another important concern in the early days of microinjection was the fate of the injected DNA. Gordon and Ruddle's paper suggested that the DNA integrated into the mouse genome, yet their evidence was ambiguous. Some of the injected DNA was heavily rearranged and appeared to have

---

[84] Ibid.: 5020.

[85] See e.g. Mintz 1978a, Mintz 1978b.

multiplied; this would become a commonly observed phenomenon. The existence of foreign DNA as a separate non-integrated molecule that propagated autonomously, or even contamination of samples with the plasmid, remained a possibility. Such concern was expressed explicitly in a paper from Jaenisch's group.

When Jaenisch secured a tenured position in Hamburg, his laboratory continued working on inserting viral DNA into embryos, and he adapted the microinjection techniques used for blastocysts to fertilised mouse eggs. His results on injecting the Moloney virus were published shortly after Mintz' and Thomas Wagner's reports, in the October 15, 1981 issue of *Nature*.[86] The paper indicated the presence of the viral DNA and suggested its integration into the genome, but expressed caution as to the meaning of the results:

> The data, however, were difficult to interpret with respect to the structure and origin of the recombinant DNA found in the newborns. We find a general problem in such experiments – the possibility of plasmid contamination.[87]

While gene expression was presented by both the scientists and the press as a crucial means of demonstrating that gene transfer into whole animals was an efficient and promising technique, germline transmission – the presence of the gene in subsequent generations – was a major desideratum. Establishing strains in the lab that could be bred and exchanged was crucial to make possible all the applications mentioned in the papers, and would enable the novel animals to colonise further laboratories and recruit more researchers. Moreover, it had been established as an important failure in much previous work. Jaenisch and Mintz' mice born in 1974 did not transmit the SV40 virus to the offspring, nor did the chimeras made from teratocarcinoma cells. Mintz's work on developing a cell line that would contribute to the germline was the group's parallel project, and the laboratory claimed such a line in 1981.[88] However, the results could not be replicated and the original cells were lost.

---

[86] Harbers, Jähner & Jaenisch 1981.

[87] Ibid.: 542.

[88] Mintz & Cronmiller 1981, Stewart & Mintz 1981.

The concern over the actual integration of foreign DNA in the process was also expressed more privately throughout the early days of gene transfer, among both the participating scientists and interested observers.[89] Looking at conference ephemera shows some doubts about the categories firmly postulated in publications. For instance, following their initial announcement, Ruddle and Gordon presented at the 9th Congress of the International Society of Developmental Biologists in Basel, Switzerland, on 29 August–1 September 1981. Among many established developmental biologists, the congress was attended by Anne McLaren. Her notes in the margins suggest a less than wholehearted reception. Thus, in quotation marks there is a weaker claim that most likely came from the presenters: "[the plasmid] has at least interacted w[ith] mouse DNA". But the notes conclude with what appears to be her reflection on the presentation, "Prob[abl]y not integr[ate]d. How can non-integr[ate]d material be maintained this long?"[90]

Integration thus became an important issue that was resolved when germline transmission could be demonstrated. Again, while Thomas Wagner's paper had claimed germline integration, it was a relatively minor point and it was not supported with Southern blot photographs that had become the standard method of visualising specific bits of DNA. By contrast, a paper published in *Nature* just over a month later, on 15 November 1981, revolved around the demonstration of germline integration, and recruited several modes of evidence.[91] It was published by two postdoctoral researchers at Oxford, Frank Costantini and Elizabeth Lacy.

The couple had moved to Oxford from CalTech, where both were exposed to innovative work in molecular biology. Lacy had been a PhD student of Tom Maniatis and moved to CalTech with him. There, Costantini was working with Eric Davidson, an eminent developmental biologist who was elaborating molecular models of sea urchin development. After both completed their graduate studies, they were eager to move into developmental biology, and managed to secure a double postdoc at Chris Graham's lab in Oxford's Zoology Department. There, equipped with the purified

[89] Tim Stewart interview.

[90] Add. 83882 , 'Conference Literature, 1980', Anne McLaren papers, The British Library.

[91] Costantini & Lacy 1981.

Fig. 4-5. Elizabeth Lacy in Chris Graham's Oxford laboratory, 1982.

Courtesy of Frank Costantini.

rabbit beta globin DNA from Maniatis's lab, the couple learned the elaborate techniques of mouse embryology (Fig. 4-5).

While trying to come up with a promising project, Lacy and Costantini were immersing themselves in the lively network of mammalian development in Oxford and Europe more generally. After Graham returned from the Cell Biology Congress in West Berlin where he had heard Ruddle's paper, he encouraged them to pursue pronuclear microinjection. On their visit back to the USA for the Christmas holidays of 1980, Lacy and Costantini went to Yale, where Gordon taught them the technique, the couple thus becoming the first adopters of an uncertain but promising technology. Armed with expertise in molecular biology, their own source of DNA to work with, and growing competency in embryology, the two pursued gene transfer experiments.

Lacy and Costantini went to some length to maintain their genetically modified mice that they referred to as founders, and incorporated them into further genetic experiments. From about 100 mice, 24 showed the rabbit globin DNA in their liver samples – a significant increase in efficiency of the procedure compared to Gordon's 2–3 out of 70. However, in order to establish the strains of these animals, the couple went on to cross the 'successful' males with unmodified female mice of a different strain. A fraction of the second-generation animals that were born as a result showed the rabbit gene, with even more copies than the first-generation parents.

Lacy and Costantini reported these early results in a letter to *Nature,* which was submitted in July 1981 and published in November.[92] They invoked the familiar Mendelian ratios ("These fractions are: one out of four progeny for mice 4 and 23, two out of four for mouse 7, and two out of six for mouse 13."[93]), even though the small sample size could not support a statistical analysis. They also highlighted the possibility of keeping the lines of animals with large inserts of foreign DNA, that could become a permanent resource to be bred and studied. The conclusion foregrounded what they saw as the next step in the gene transfer work and its key potential: the spatial and temporal exploration of specific gene expression in a living mammal, from conception to death:

> With such strains of mice it will be possible to examine the expression of the rabbit beta globin gene and to investigate whether expression is restricted to specific tissues and/or developmental stages. If the rabbit sequences are integrated into mouse chromosomes, presumably different strains will contain the rabbit genes at different chromosomal locations. This will allow us to investigate how the host chromosomal environment influences the expression of a foreign gene.[94]

Finally, also in November 1981, a paper from the Brinster-Palmiter collaboration came out in *Cell*.[95] The paper confidently claimed that the HSV *tk* gene was expressed strongly and predictably under the control of the metallothionein-1 promoter – a control DNA element that regulated expression and could be activated by injecting mice with heavy metal salts. Moreover, it proposed models of the molecular mechanism of gene integration, suggesting that the inserted plasmid

---

[92] Ibid..

[93] Ibid., 92.

[94] Ibid., 93–4.

[95] Brinster, et al. 1981.

likely underwent a series of duplications before being integrated. This publication marked the beginning of a series of highly successful experiments that Brinster and Palmiter would orchestrate, and it offered a hope of control over foreign genes, especially since Thomas Wagner's claims were not taken seriously.

This was not exactly the first publication from Brinster's lab on the subject, though. A 1980 *Nature* paper had described the production of protein from RNA injected into embryo cytoplasm.[96] A note added in proof to another RNA article in *Science*, published in January 1981, claimed that DNA injection had been achieved with Carlo Croce at Wistar, without revealing further detail. In a 1998 interview, Brinster said that his group had succeeded in inserting genes into mice by the end of 1980, and that "[t]hese were tantalizing and encouraging results but certainly did not warrant publication."[97] The comment – rather transparently hinting at Ruddle's haste – does, however, open up a question: what counted as publishable for these different groups?

For Ruddle, the experiment was an extension of a research programme aimed at gene mapping, and he expressed hopes that it could be used to study the sites where foreign genes integrate, and therefore to map mouse genes further. Expression and transmission were desirable criteria that the group went on to pursue, but the focus was mainly at the gene level. For Brinster and Mintz, the promise of developmental questions that the system could answer made tracing expression a key priority, as well as observing how genes could affect the embryo or be used to trace lineage. Similarly, Thomas Wagner's fascination may have lain in whether a foreign gene could integrate into the mouse genome based on his ideas about DNA repair after fertilisation, but his engagement with a biotech company put a stress on demonstrating protein products.

The need to publish novel results was a bigger pressure, as routine replications would not secure much credit. As a result, a range of experimental programmes were pursued to establish these unmet criteria. The overall effect of these efforts, and of the independent publications, was to establish the credibility and efficiency of the new technique. The multiple invention of the genetically modified mice not only reflected the general interest in such a project or the availability of

[96] Brinster, et al. 1980.

[97] Brinster 1998.

techniques and molecules to perform such work – it was also integral to turning claims into inventions as reports from reputable labs confirmed Ruddle's initial result. Revisiting Merton's claim as to the ubiquity of multiple discoveries, the confirmation that they confer on experimental results should be thematised. Especially in a case where credit for such events is negotiated amicably, the social process of establishing a claim as a discovery or an invention is much more rapid and straightforward. In subsequent years, as a citation pattern was established and more dramatic results reported, transgenic mice were embraced by the laboratories who could afford the funding, time and expertise to make them. In the process, the name and properties of these animals were defined.

§5. "These mice, that we call transgenic"

Credit for discoveries and inventions is necessarily decided retrospectively, and can result in bitter feuds about priority, but it can also be distributed between different actors. I have shown the communication strategies employed in making such claims, which routinely involved popular science and general-interest media as well as traditional journals. As a result, certain exclusions did take place: Thomas Wagner was not a major part of the re-telling of the story either in its immediate aftermath or later, and Jaenisch's work was less prominent, though his older experiments with Mintz remained a common 'precursor'. This final section will examine the establishment of a citation pattern that fortified the distributed priority, and show the different reinterpretations that were still possible within this framework.

While other laboratories were announcing their results of microinjection into mouse eggs, the Yale group was the first to start assimilating and reviewing the work. In 1981, Ruddle co-authored several reviews of gene transfer with his lab colleagues.[98] These mainly focused on somatic cell manipulation, but also mentioned microinjection into zygotes. But in December 1981, Ruddle and Gordon published a high-profile paper in *Science* that reported their success at breeding second-

[98] Ruddle 1981, Klobutcher & Ruddle 1981, Scangos & Ruddle 1981.

generation offspring that also carried the inserted HSV *tk* gene.[99] While only 3 pages long, the paper also functioned as a summary and programmatic statement for a new field.

The *Science* paper referenced previous publications from the authors' laboratory, and the groups at Fox Chase, Ohio, Oxford, and even unpublished collaborative work from Kurt Bürki at Illmensee' lab at the University of Geneva with Axel Ullrich at Genentech.[100] Gordon and Ruddle did, however, ignore the new microinjection work done in Hamburg by Jaenisch and colleagues. This *Science* paper was submitted on 30 September 1981, and revised on 30 October, and the summary of Jaenisch's experiments appeared in *Nature* on 15 October. However, Gordon and Ruddle's article did cite the Lacy and Costantini paper that was published on 5 November 1981, also in *Nature,* so the editing clearly continued in response to peer review, but given the connection between the two laboratories Ruddle must have seen the preprint of the Oxford paper in advance and could also have acted as a referee.

In this paper, Gordon and Ruddle coined the word 'transgenic' to describe their mice: "The feasibility of producing such genetically transformed mice, which we call 'transgenic' mice, depends upon several factors."[101] *Transgenic* is derived from *gene*, and the prefix *trans-* indicates otherness and crossing boundaries, as opposed to *cis-,* which indicates the same side. The pair of prefixes were in common use in molecular biology, when talking about control of DNA function – thus, trans-factors usually meant proteins that interact with DNA, while the cis-factors are bits of the sequence that control or enable such interactions. However, the practical etymology was much more local and related to the research genealogy of the Yale lab. It was derived from 'transgenome', a word Frank Ruddle had coined when describing bits of alien chromosomes inserted into somatic cells through chromosome-mediated gene transfer.[102] The naming was decided internally,

[99] Gordon & Ruddle 1981.

[100] While Illmensee attempted similar experiments as early as 1978 (see chapter 3 §1), this project was most likely aided by Peter Hoppe's 1979 sabbatical in the Geneva lab. The work was published as Bürki & Ullrich 1982.

[101] Gordon & Ruddle 1981: 1244.

[102] Ruddle & McBride 1977.

after Gordon came up with a list of names for consideration. As he recalls, this included "pecalomice",[103] "transgenomic mice", even "mighty mice", by analogy with the cartoon character.[104]

Names can be important in biology, and sometimes remain linked to individuals and their research agendas. Many examples are at hand in developmental biology. The tension between Mintz and Tarkowski over 'allophenic' vs. 'chimaeric' mice has been discussed in chapter 1. In 1981, Cambridge University-based Martin Evans and Matthew Kaufmann cultured what are now known as mouse embryonic stem cell, which they called EK cells (for Evans and Kaufman – the name did not stick, however), to parallel 'EC cells', a name given to teratocarcinomas that were a major reference point for their work.[105] Similarly, the coinage of 'transgenic' contributed to securing the Yale group's authority in the field. Despite competition, the word was quickly adopted by other groups working on gene transfer in mice, notably Brinster and Palmiter, became commonplace and was extended to other animals, plants and bacteria, even though it was not used widely in the media until 1985. This adaptation was one of the many ways in which a retrospective narrative of invention was accepted, despite early doubts about the utility of the Yale methods and the real meaning of their data.

The parallel work that happened in the laboratories involved working synthetically to establish a cumulative narrative of invention, as problems were consecutively 'resolved' by serial publication: gene expression, germline integration and its likely molecular structure. The need to make further claims about the microinjection work was a response to the pressure for novelty in journal articles, and reflected the theoretical commitments of specific groups. I argue that the rapid pace of publication, enhanced by the liberal communication with mainstream media, facilitated the establishment of the success of the new kind of experiment. Reliance on journals that offered rapid publication, such as *PNAS,* further facilitated the transition from uncertainty that Ruddle was keen to emphasise to the press early on, to a perception of a new field and a new means of investigating genes in a living animal.

---

[103] By analogy with Michael Wigler's term 'pecalosome', largely equivalent to 'transgenome'. 'Pecalosome', that never stuck, appears to be derived from the Yiddish word *pekl*, meaning package or bundle.

[104] Gordon interview.

[105] Evans & Kaufman 1981.

The change is traceable through outsider accounts of the field. If early descriptions, both in scientific periodicals and newspapers, placed microinjection alongside many other attempts to insert genes into animal cells, increasingly commentators treated transgenic mice as a separate agenda. By transforming a group of parallel results into a sequence of successes, a productive set of promises was elaborated, for instance in the *Nature* comment piece on the work from Hamburg and Oxford, which claimed that genetic engineering had entered a new era: "if it has indeed been possible to insert a cloned gene sequence into the mammalian genome so that it functions correctly, the wider implications are enormous. Leaving aside the controversial question of gene therapy in humans, it seems certain that the genetic manipulation of agriculturally important animals will quickly follow".[106]

Giving the new object a name helped crystallise a new approach, and the coinage as well as priority allowed the Yale scientists to define the terms of the game, literally and metaphorically. With exchanges between the competing laboratories, their wide and rapid communication, a successful new thing – a transgenic mouse – became real, through the discovery narrative of an apparent collective. This narrative, however, was unstable and could be revisited in the later years, especially where questions of property and biotechnological interest came into play. Through the 1980s, as the focus on microinjection of plasmid DNA into the pronucleus of a fertilised egg persisted, the papers from Jaensich's group were occasionally omitted in review articles, as was Thomas Wagner's contribution (Table 4-2).

Yet, while the Ohio-Jackson work may have been sidelined in the journals, Thomas Wagner and Peter Hoppe remain the inventors of transgenic technology from the perspective of the US Patent and Trademarks Office as supported by a highly unusual adjustment to their patent that was granted in 2005, after its power had expired, which legitimised most of the original application claims[107] – unlike the more contained 1989 patent. At the same time, the patent had little impact on university research and was not contested from therein, and in public discussions was eclipsed by the 1988 Harvard mouse patent, the first to be granted on an animal as a product of an inven-

[106] Hogan & Williams 1981.

[107] US Patent 6,872,868.

Table 4-2: Allocation of credit in the major reviews of transgenic technology, 1983–1990. Papers cited as a pioneering contribution are indicated with a tick, and in most cases the exact contributions – demonstrating successful microinjection, gene expression or germline transmission – are detailed.

Review	Gordon et al. 1980	E. Wagner et al. 1981	T. Wagner et al. 1981	Harbers et al. 1981	Costantini & Lacy 1981	Brinster et al. 1981
Gordon, 'Transgenic mice…', *Developmental Genetics*, 1983	✓	✓	✓	✓	✓	✓
Gordon & Ruddle, 'Gene-transfer into mouse embryos…' *Methods in Enzymology* 1983	✓	✓	✓	—	✓	✓
Palmiter & Brinster, 'Germline transformation of mice', *Annual Review of Genetics*, 1986	✓	✓	✓	✓	✓	✓
Hogan, Lacy & Costantini, *Manipulating the Mouse Embryo*, 1986	✓	✓	✓	✓	✓	✓
Jaenisch, 'Transgenic animals', *Science* 1988	✓	✓	—	✓	✓	✓
Gordon, 'Transgenic Animals', *International Review of Cytology*, 1989	✓	✓	❊	—	✓	✓
Hanahan, 'Transgenic mice as probes into complex systems', *Science*, 1990	✓	✓	—	✓	✓	✓
E. Wagner, 'On transferring genes into stem cells and mice', EMBO medal review, *EMBO Journal*, 1990.	✓	✓	✓	—	✓	✓

❊ The Wagner-Hoppe paper is not cited with the other pioneering contributions here, but is mentioned as a claim of gene expression of rabbit beta globin that others could not replicate.

tion. Even if most of Wagner's competitors still think his first expression results were most likely a curious artefact,[108] his priority is registered by the US government.

The curious thing about this recent Wagner patent is that it was issued two years *after* it would have expired, and has largely symbolic value. At this point, I also wish to emphasise that despite active measures to secure priority, it was not the ultimate goal, nor did the scientific decorum ever break down. These strategies were mostly acceptable in the climate of the 1980s, and few printed records of the story survive beyond ephemeral newspaper publications. The diversity of interests and plans for the new animals, as well as the sheer number of pioneer groups, prevented a bitter controversy, while opening up space for diverse lines of experimentation and keeping the moral economy of research in balance.

Conclusion

Through multiple publications in journals with cross-disciplinary readership, claims were made about a new living mammalian system for the study of gene function and further molecularisation of development, employing the most promising techniques from molecular biology. But the work to register the advance went far beyond journals. The scientific paper, especially after World War II, is a genre that necessarily conceals irregularities, uncertainty and debate as much as it reveals the proposed facts. The mediation of these mice was incorporated into existing narratives of genetic engineering and biomedical work more broadly.

The key criteria brought together in the very word 'transgenic' – gene expression, germline integration and insertion into the genome – were articulated early, but also left the future open. Until 1983 the question of what transgenic mice were for was by no means settled, nor were techniques standardised or easy to adapt by labs that did not carry a similar combination of expertise and resources. While priority order was not explicitly articulated in journal papers, it mattered at the time, and was contested more widely via the general press. While all of the scientists I have interviewed admit independent co-invention, most of them predictably emphasised that they were the

[108] Gordon 1989b: 186; various interviews.

ones that did the experiment that *really* mattered. For Jaenisch, transgenic mice were invented in 1974 during the Mintz collaboration. For Thomas Wagner, his mice were the first to show gene expression that came out of molecular biological considerations about the state of DNA in the sperm cell, which had not been fully recognised. Similarly, Erwin Wagner and Timothy Stewart suggested that while the Yale mice may have been the first transgenics, theirs were certainly the first unambiguous evidence of the technology working. Finally, Brinster's subsequent high-throughput collaboration with Richard Palmiter became so defining for the field that the animals born out of their 1982 experiment, discussed in the next chapter, are sometimes quoted as the first transgenic mice.

Chapter 5. Bespoke animals: Adoption of transgenic technology, 1982–1988

Histories of successful laboratory animals have tended to focus on dissemination of an organism from a single place, often its key supplier. For example, *Drosophila* strains from the Columbia Fly Room, Jackson mice, the Wistar rat were all promoted, shared or sold by the scientists and other actors who domesticated these animals.[1] New organisms enter biological research with difficulties associated with domestication, standardisation, building infrastructure and the establishment of experimental credibility. Transitions to new research organisms are only worth the effort when new scientific agendas are being articulated. Thus, the switch of some drosophilists to the fungus *Neurospora* allowed them to open up a new agenda in biochemical genetics, but also to move up the career ladder more rapidly.[2] Importing *Xenopus* from South Africa started as an experimental physiology project, but gained traction when the frogs began to be used routinely for pregnancy testing.[3] Sydney Brenner's choice of the nematode worm *C. elegans* allowed for a molecular take on tracing development, which combined multicellularity with simple and predictable differentiation.[4] The recent explosion of organisms used in developmental biology is a reflection of the evolutionary focus and the rise of evo-devo, enabled through the molecular transformations of the 1970s and 80s when cross-species comparisons were made more straightforward by reduction to the level of DNA sequence.[5]

Unlike new laboratory species, transgenic mice fitted within existing infrastructures. Moreover, their epistemic value relied heavily on the established status of mice as the genetic animals best suited to studying human pathology. At the same time, despite the initial publicity and multiple claims for the viability of gene transfer into mice, the credibility and utility of that approach were not self-evident. A group of users had to become converts to the interdisciplinary procedures for

---

[1] Kohler 1994, Clause 1993, Rader 2004.

[2] Kohler 1994: 233–42.

[3] Gurdon & Hopwood 2000, Olszynko-Gryn 2013.

[4] de Chadarevian 1998, Ankeny 2000.

[5] Davies 2007, Gilbert 2009, Hopwood 2011.

making the new animals. For molecular biologists in particular, using transgenic mice would often mean transitioning to an unfamiliar organism.

Historians of technology often employ the diffusion metaphor when they talk about how innovations spread. While perhaps more appropriate in a commercial context where mass-produced items may be sold and used with subsequent modification, this metaphor tends to place the agency firmly in the hands of inventors and designers. The spread of a given technology is thus imagined as an ever-expanding contagion, ironing out geographic variation and the historical fluctuations in its popularity and credibility.[6] Turning the tables and focusing on adoption instead restores agency to the users who may or may not find a new technology attractive or affordable. Users determine whether or not an innovation is successful and able to replace existing alternatives or create new niches for use. Experimental animals – moving in networks between suppliers, stock centres and laboratories – become legitimate research subjects when a large enough fraction of users and external observers can be convinced of their utility and promise.

This chapter addresses the adoption of transgenic technology in the 1980s, considering the major events and avenues of their dissemination. I begin by discussing the giant 'supermice' produced through growth hormone gene injections in 1982. These animals were the first and soon the dominant success story, because they displayed the immediately visible effects of gene transfer, and their images circulated widely between scientific and lay publications. In section 2, I trace the early adoption of transgenic mice in the USA and beyond. Some scientists picked up the techniques independently, building on their experience with related methods, but many were aided by courses, conferences and personal contacts with established researchers. Section 3 reflects on the strategies of making new knowledge with transgenic mice in 1983–88 and considers the relationship between mice and other animal systems in the molecular age. I argue that the most dramatic utility of transgenic mice was the ability to study gene expression in a whole mammal, and show how the perceived limitations of technology could be recruited to pose new questions. Finally, section 4 considers the relationship between transgenic research and the traditional sites of mouse genetics and supply, especially the Jackson Lab. The mouse genetics community was not

[6] Edgerton 2007, 2010.

involved in transgenic work and did not supply transgenic mice until the mid-1990s, because of its limited communication with the growing transgenic community, diverging practices of establishing new stocks and the knowledge that could be made with them. Unlike the large-scale crosses and mutagenesis assays, transgenic research was a local, bespoke operation.

§1. Supermice

As I have shown in chapter 4, the coverage of the 1980–81 gene transfer experiments with mouse embryos steered media narratives away from any serious controversy. Yet unlike the daily press, longer journalistic investigations continued to take a more critical approach to future possibilities stemming from genetic intervention, especially genetic testing in the workplace, prenatal diagnosis and gene therapy. Following the tradition of long-form reportage on the new biology, these stories reviewed multiple strands in biological research. Transgenic mice were occasionally incorporated into the narrative of the genetic revolution. Some pieces were optimistic; when considering the implications of reproductive and genetic technologies for cattle breeding, *Business Week* envisioned vast progressive changes to agricultural industry, referring to Thomas Wagner and Ralph Brinster among other scientists.[7] Other articles, while fascinated with the scientific advances, raised concerns. In the March 1982 issue of *OMNI*, Yvonne Baskin combined the stories of the Yale gene transfer, Martin Cline's gene therapy attempts and IVF to raise questions about the future of human genetics:

> News articles glibly refer to a future when we will program our cattle to put all their energy into producing milk and we'll engineer our crops to survive on salt water. Will we use our burgeoning knowledge to enhance the individual? Or will we use it to make individuals, like cattle and plants, to suit society's needs?[8]

After the Cline affair, genetic modification of humans was at the crux of such discussions. "Brave New Babies", a November 1982 episode of the BBC science documentary series *Horizon*, used the footage of Jon Gordon microinjecting mice in a montage of recent biomedical advances. Narrated

[7] Anon. 1982d.

[8] Baskin 1982.

by the bioethicist Jonathan Glover, it included eerie discussions with the presenter's children and a sinister vision of a clinic where parents could choose the desired features of their future child.[9]

Increasingly ready to engage with the media coverage, eminent biologists were discussing these issues. At the 1982 Banbury meeting in Cold Spring Harbor, leading experts on gene transfer met to discuss the future of gene therapy. Attendees included Brinster, Costantini, Illmensee, Jaenisch and Ruddle as well as the likes of French Anderson, Richard Axel, Paul Berg and Victor McKusick. Banbury meetings were initiated post-Asilomar in 1978 as a space to discuss potential biohazards, and the published proceedings had been technical and dense. The 1983 publication, *Gene Therapy: Fact and Fiction,* was by contrast a cheap and slim paperback that aimed to address a broader audience and combined summaries of discussions with transcribed dialogue.[10] The overall conclusion was that germline gene therapy was an unlikely and impractical outcome of the gene transfer experiments, and the somatic approaches were to be pursued. Similar arguments were presented at the congressional hearings on gene therapy in November 1982. Transgenic mice did not feature prominently, but were mentioned by Barbara Sanford, director of Jackson lab, as a potential step on the path towards germline therapy.[11]

When talking to the press, pioneers of transgenesis tried to distance themselves from any application to the human germline, but at the more esoteric conferences transgenic animals were all the rage when it came to gene function and development. The new mice were the highlight of the June 1982 meeting of the Society for Developmental Biology, where Mintz and Palmiter presented their most recent work on the HSV *tk* gene expression. As *Nature* reported, the general mood was that "real progress towards understanding the control of gene expression and development may be at hand".[12]

---

[9] BBC Horizon, 'Brave New Babies', first aired 15 November 1982. As Chris Graham, who appeared in the episode, recalls, "I didn't read [the script], because there were two very advanced children of [Glover's]... discussing philosophy for long periods... and it was immediately apparent that everyone would remember these precocious children rather than the point of the programme." Graham interview with Sarah Franklin and Martin Johnson.

[10] Friedmann 1983.

[11] Barbara Sanford, Testimony to the Human Genetic Engineering Hearings before the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, November 16–18, 1982. Folder 7, Box 37, Papers of Barbara Sanford, Head of JAX, 1981–87, The Jackson Laboratory archive, Bar Harbor, ME.

[12] Petri 1982: 399.

Among the first groups to insert genes into mice, Brinster and Palmiter were at the forefront of controlling foreign gene expression, having used the metallothionein promoter that could be switched on in the presence of heavy metal salts. Seeking to continue the collaboration, the two scientists were considering other genes to inject into mouse embryos that would have clear effects and had potential relevance to human health or agricultural improvement. Other labs were moving to explore more pertinent genes, too. Thus, Ruddle's group experimented with interferon DNA, while Karl Illmensee and Axel Ullrich worked on the human insulin gene. On his way to meet Brinster in person for the first time in late 1981, Palmiter stopped over to give a seminar at Roswell Park, Buffalo. where he learned of a dwarf strain of mice that could potentially be treated by a growth hormone gene. Shortly afterwards, he obtained the recently-cloned rat growth hormone gene from Ron Evans at the Salk Institute, spliced it with the metallothionein promoter and sent it off to Brinster who had started building a colony of the little mice. But even before these animals were ready for experiments, Brinster discovered that injection of the growth hormone plasmid into normal strains also had the envisioned effect – the modified mice grew much larger than normal.[13] In Brinster's recollection, "The giant mouse experiment was a fantastic experiment. That is the experiment that made everybody, including us, stop and say, 'This is incredibly powerful.' That you could enter the germ line and make a change like that".[14] The experiment became the biggest news story in early transgenic research.

Brinster and Palmiter outlined this work in a letter that appeared in the 16 December 1982 issue of *Nature,* and the front cover carried a photograph of a giant mouse next to its regular kin (Figs. 5-1, middle & 5-1a).[15] This was not the first time that the group's work made journal covers. In November 1981, when Brinster and Palmiter's first gene transfer paper had been published in *Cell*, two transgenic mice had also featured on the cover of the journal (Fig 5-1, left) In November 1983, a similar image appeared on the cover of *Science*, accompanying a paper of theirs on the transfer of the human growth hormone gene.[16] (Fig. 5-1, right) The use of journal covers to highlight research

[13] Palmiter interview, Brinster & Arechaga 1998.

[14] Quoted in Stratton 2012.

[15] Palmiter, et al. 1982.

[16] Palmiter, et al. 1983.

Fig. 5-1. Brinster and Palmiter's mice on journal covers.

Left to right, *Cell*, 15 November 1981; *Nature*, 16 December 1982; *Science*, 11 November 1983.

was a relatively recent development in the early 1980s. *Science* had first put a photograph on its cover in October 1959, with an editorial announcing the redesign and speculating as to the difficulties in obtaining images for every issue,[17] and through the 1960s, journal covers frequently featured abstract photographs. *Nature* used most of its cover as an advertising space until the 28 May 1971 issue, when a larger black-and-white image took about half of the cover, with issue highlights listed underneath. In the 1970s, despite printing on cheaper paper, *Nature*'s cover images became more prominent, and authors were encouraged to submit images as "artwork".[18] Colour photographs made it to the covers of *Science* only in 1976, with *Nature* and *Cell* following suit in 1978. This trend was driven not only by declining colour printing costs, but also by the proliferation of popular science periodicals in the late 1970s, which in turn took their aesthetic guidance from mainstream weekly magazines. By contrast, more specialised periodicals, as well as *PNAS* – where most of the transgenic papers had appeared at that point – kept the table of contents on their front cover.

Striking visualisation of experimental results in these relatively new spaces conferred an additional advantage to the scientists attempting to make their research stand out. The images in Fig 5-1 show pairs of mice – apparently siblings – with their tails clipped for molecular analysis, and

[17] DuShane 1959.

[18] Anon. 1978b.

Fig. 5-1a. "Gigantic mice" on the cover of Nature, 16 December 1982.

framed by a plasmid map in the *Science* image. They alluded to before-and-after advertising images and the genre of juxtaposing dwarfs and giants, which had been used in much older work on growth hormone injections.[19] The giant mouse images spread through the scientific and general press to a remarkable degree, and their significance persisted in recollections. Thus in 1989, the co-inventor of the OncoMouse Philip Leder said of the result: "It was… this uncanny evidence of functional expression, that made us sit up and realize that transgenics was [sic] more than just some technological stunt."[20]

A sizeable final section of the *Nature* paper elaborated the potential applications of growth hormone gene transfer: the production of bigger cattle, the synthesis of valuable protein in farm animals, and the development of mouse models for gigantism to study the effects of growth hormone gene expression. In parallel with the *Nature* paper, Brinster and Palmiter wrote a less technical piece for *Trends in Biochemical Sciences* (*TIBS*), which also appeared in December 1982. Reviewing their own work and the research of others, the conclusion summarised an agenda for future work and press discussion: "Clearly the introduction of new genes into animals promises to have considerable importance in addressing fundamental scientific questions regarding gene regulation and may, in addition, be put to practical or commercial use."[21] In a final bit of journal publicity, *Nature* commissioned a companion News & Views piece, titled "Mouse and supermouse". Jeffrey Williams, a slime mould researcher at the Imperial Cancer Research Fund laboratories in Mill Hill, London, noted that this was "the first time that genetic engineering [had] been used to alter the phenotype of an animal in such a profound manner" and the "culmination of a series of elegant experiments performed by Palmiter, Brinster and their colleagues over the past few years."[22] The article also hinted that the technique might be used to produce strains of commercially valuable farm animals and improve meat yields, as well as placing these 'supermice' – a name that stuck – within the recent advances that could lead towards gene therapy, with a qualifier indicating that human embryo modification was unlikely ever to be considered in the clinic.

---

[19] See e.g. photographs of 'giant' dachshunds and rats in a 1948 issue of *Life* magazine: Anon. 1948.

[20] Quoted in Patrusky 1989: 16.

[21] Brinster & Palmiter 1982: 440.

[22] Williams 1982.

The University of Pennsylvania Press Office was eager to advertise Brinster's work as a breakthrough. In a press release accompanied by the manuscript of the group's *Nature* paper, embargoed until publication, the experiments were described as opening a "new era in genetic engineering."[23] A United Press International wire, with a photograph of the mice, spread the news rapidly through the US and beyond.[24] On 16 December, the day the article was published, Brinster's giant mice made it to the front page of *The New York Times* and *The Washington Post* and appeared inside *The Wall Street Journal*, and the British *Guardian* and *Times* (via the *Nature-Times* News Service).[25] All articles focused on the agricultural applications of the mice, envisioning the potential for giant cattle. As the London *Times* put it, "The parallel development of an outsized breed of cattle could have obvious appeal to both farmers and steak-eaters."[26] On 27 December, the giant mice made it to *TIME* magazine. Dramatising the significance of the experiment ("It was the sort of biological alchemy that abounds in science fiction"), the article featured a small photograph from the *Nature* cover, captioned "Next step: enormous cattle", and a brief interview with Brinster and Palmiter. The two were eager to speculate about the implications of their experiments. They emphasised that any modification to humans was premature and unlikely to be attempted, while suggesting less threatening outcomes. Brinster said, "If we can make bigger mice we can make bigger cows," while Palmiter noted that, "in a sense, the big mice are models of pituitary gigantism in humans."[27]

Once again, the major focus of the initial newspaper coverage was on the scientific advance and the work that went into making these mice. Often, the animals were taken lightly. Editorials in *The Washington Post* and *The New York Times* made tongue-in-cheek remarks about the new need for bigger mousetraps, or perhaps bigger cats.[28] Introducing the report from Philadelphia, the CBS

---

[23] 'Experiments introduce new era in genetic engineering,' press release, Box 18 Folder 20, Biographical Files, University Relations: News and Public Affairs Records (UPF8.5), University of Pennsylvania Archives.

[24] Clippings, University Relations News and Public Affairs Records, Biographical Files (Collection UPF 8.5B) Box 18, Folder 22. University of Pennsylvania Archives, Philadelphia, PA.

[25] Schmeck 1982b, Cohn 1982, Anon. 1982e, Veitch 1982, Anon. 1982g.

[26] Ibid.: 2.

[27] Anon. 1982f: 53.

[28] Anon. 1982a.

anchor remarked, "however you feel about mice, you probably think they're big enough."[29] To Palmiter's delight, the story was also picked up by the comedian Johnny Carson on the Tonight Show. In Carson's monologue, full of incredulity over anyone wanting bigger mice, "one mouse kicked out the door to the lab and said, 'I want a cheeseburger and I want it now!'"[30]

Unlike the first stories of gene transfer into mice that received fleeting attention, the supermouse persisted in the news, aided by the impressive images. Journalists were able to use the story to revisit the recent government report on *Splicing Life,* published on 16 November 1982. The document was authored by the recently-founded (and short-lived) US President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which weighted the ethical issues of human genetic manipulation against the benefits that biotechnology might bring to the ailing economy. While the report explored issues around manipulating life, it came short of any recommendations to limit research, except to reject human-animal hybrids.[31] Schmeck's later opinion piece in the *New York Times* described the report as raising "thorny ethical issues" about extending this work to farm animals or, especially, humans.[32] Similarly, the last paragraph of an article in Boston's *Christian Science Monitor* referred to the continued opposition to any human genetic modification from US church leaders and the caution urged by bioethicists. Another *New York Times* editorial, from 29 December 1982, took a more sober tone.[33] Using the giant mice as a segue to the discussion of *Splicing Life*, it argued that the Commission had tiptoed around the pertinent issues such as banning human genetic intervention, while entertaining experiments that no one had been planning to undertake.[34]

In November 1983, Brinster and Palmiter published another paper featuring a new batch of supermice, this time produced with the human growth hormone gene under the metallothionein

---

[29] Evening news, CBS, 16 December 1982.

[30] 'Tonight Show Starring Johnny Carson', NBC, 16 December 1982.

[31] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research 1982.

[32] Schmeck 1982a.

[33] Cowen 1982. Despite being founded and owned by The First Church of Christ, Scientist in Boston, CSM is not in any meaningful way a Christian Science or otherwise religious publication, aside from its religious section.

[34] Anon. 1982b.

promoter. These mice, superimposed on a schematic plasmid map, made the cover of a special issue of *Science* that featured papers from the biological frontier of molecular techniques (Fig. 5-1a, right). The introduction of the human gene led to renewed coverage of supermice that followed the pattern of late 1982 very closely. That the gene was human made some uncomfortable, although Mintz's group had already been inserted the human beta globin gene into mice by in 1981. An unidentified clipping from the University of Pennsylvania archive, likely from a Seattle newspaper just after the *Science* publication, offers a rare glimpse into private letters that Palmiter received as it quoted from one such letter at length:

> ...when I read this (an article about the experiment), my blood began to boil, my stomach turned and my mind cranked up some revolting thoughts!!! To me the marriage of human tissue – no matter how minute – is an abomination when connected with animal, bird, insect or plant life... to read about this at Christmas was a double blow to my senses... What kind of MONSTERS do you have working with you? Is nothing sacred??[35]

The quotation, with its preservation of the idiosyncratic style of the original letter, was clearly included as a sympathetic gesture towards the scientists. The other letters cited in the piece were much less dramatic – for instance, one suggested gorilla genes should be spliced into sheep to make more wool. In the conclusion of the article, Palmiter was given the final word to point out that it made little difference, "chemically", that the gene was human. In all sorts of news settings, Palmiter and Brinster continued to evoke practical uses, implicitly including possible applications in medicine, and sought to frame their experiments in safer terms.

Before anyone seriously proposed that a particular transgenic mouse could be a useful model of human pathology, the widespread coverage and the context of debates around genetic engineering turned supermice into models of the moral and ethical dilemmas to come. Scholars of human-animal relations have repeatedly pointed at how animals are used to mimic and perform important cultural anxieties and ambiguities.[36] The light-hearted take on the supermouse drew on a long history of using mice in laboratories. The familiar place of the animal in a laboratory allowed

---

[35] Colin Wilson, "Mighty Mouse Experiment Draws Protest" [news clipping, date and name of publication not identified]. University Relations News and Public Affairs Records, Biographical Files (Collection UPF 8.5B) Box 18, Folder 22, University of Pennsylvania Archives, Philadelphia.

[36] Ritvo 1989, Haraway 1993, Fudge 2002. See also Davies 2012.

journalists and activists to rehearse cultural debates with a 'safe' species.[37] Yet such safety was not inherent in the mouse species but came out of the specifics of the communication process, as science reporters emphasised scientists' perspectives and subsequently used supermice to introduce issues about human genetics. The difference between the mouse – a familiar experimental animal ensconced in the laboratory – and other mammals is starkly visible in later debates around the first attempts to introduce genes into farm animals, again spearheaded by Brinster, which proved significantly more controversial. In 1984, Jeremy Rifkin recruited the US Humane Society to file lawsuits against the US Department of Agriculture for collaborating with Brinster, and to raise publicity around similar experiments attempted by Thomas Wagner with pigs, sheep and cattle. With this renewed media attention, the older images of giant mice were occasionally featured, this time with a new ability to become controversial.[38]

With the circulation of supermouse images, transgenic animals were made visible as they became incorporated into different narratives about farm animals and humans. Yet these remarkable creatures yielded no significant controversy in the context of increasingly positive media coverage of biotechnology in the USA. Rather, as I show in the next section, the circulation of the images played a role in the wider acceptance of transgenic technology among molecular and developmental biologists and their scientific, regulatory and lay audiences.

§2. Adopting transgenesis

While the possibility of human genetic intervention occupied many column inches in 1982–3, the mouse work continued at full pace. If for certain science journalists the images of supermice hinted at the future of human genetic intervention, for molecular biologists they demonstrated the success of directed gene expression in mammals: a central criterion for the utility of transgenic technology. Expression and germline transmission had already been claimed in 1981. But while previous experiments had established the expression of viral genes though mundane assays, and evidence for the production of foreign beta globin proteins in mice had been contest-

[37] Rader 2004, 2007.

[38] Rifkin 1984, Beardsley 1984.

ed,[39] the growth hormone experiments showed the dramatic effect that a foreign gene could have on the physiology of an organism.

These images were thus a testament to the power of transgenic technology. For a *Boston Globe* piece on the first supermouse paper, several prominent scientists were asked for their opinion on the experiment. David Baltimore, a celebrated molecular biologist and head of MIT's newly-established Whitehead Institute, remarked, "This demonstrates that you can put a gene into an embryo and have it function at a high level in the resulting organism". Another MIT biologist, Philip Sharp, described the work as "the most striking demonstration of success" in animal gene transfer. With supermice, Brinster's lab established a firm place at the forefront of transgenic research, and their giant mice were often picked up as a key breakthrough in transgenesis, and to date they are occasionally referred to as the 'first transgenic mice'.[40]

In 1983–85, accounts of gene transfer into mice also began appearing in textbooks dealing with genetics and biotechnology, often accompanied by the supermouse images. Fincham's *Genetics* (1983) mentioned the experiments by Thomas Wagner as well as Lacy and Costantini.[41] The first edition of Karp's *Cell Biology* (1984) featured the supermouse image, as did the second edition of Benjamin Lewin's *Genes* (1985).[42] Moreover, a drawing of the mice made it to the cover of *Recombinant DNA: A Short Course* (1983) by James Watson, John Tooze and David Kurtz (Fig. 5-3).[43] The book was published under the *Scientific American* brand, with illustrations in its characteristic style. It targeted a broad audience, primarily undergraduate students, and summarised the key developments in recombinant research and their applications to biology. A whole chapter was devoted to gene transfer in higher organisms, with a particular focus on Brinster's experiments and Jaenisch's viral work.

---

[39] Lacy, et al. 1983, Gordon 1989a

[40] See e.g. *Nature*'s Mouse Genome timeline, www.nature.com/nature/mousegenome/timeline/mouse15.html or the Life Sciences Foundation biotechnology timeline, lifesciencesfoundation.org/events-A_transgenic_mammal.html, both accessed on 16 August 2014. Many timelines of genetic engineering have featured supermice rather than the earlier experiments, sometimes with a clarification that they weren't strictly the first, starting with Watson, et al. 1983.

[41] Fincham 1983. John Fincham was a noted *Neurospora* geneticist who would become the Balfour Professor of Genetics at Cambridge University in 1984.

[42] Karp 1984, Lewin 1985.

[43] Watson, Tooze & Kurtz 1983.

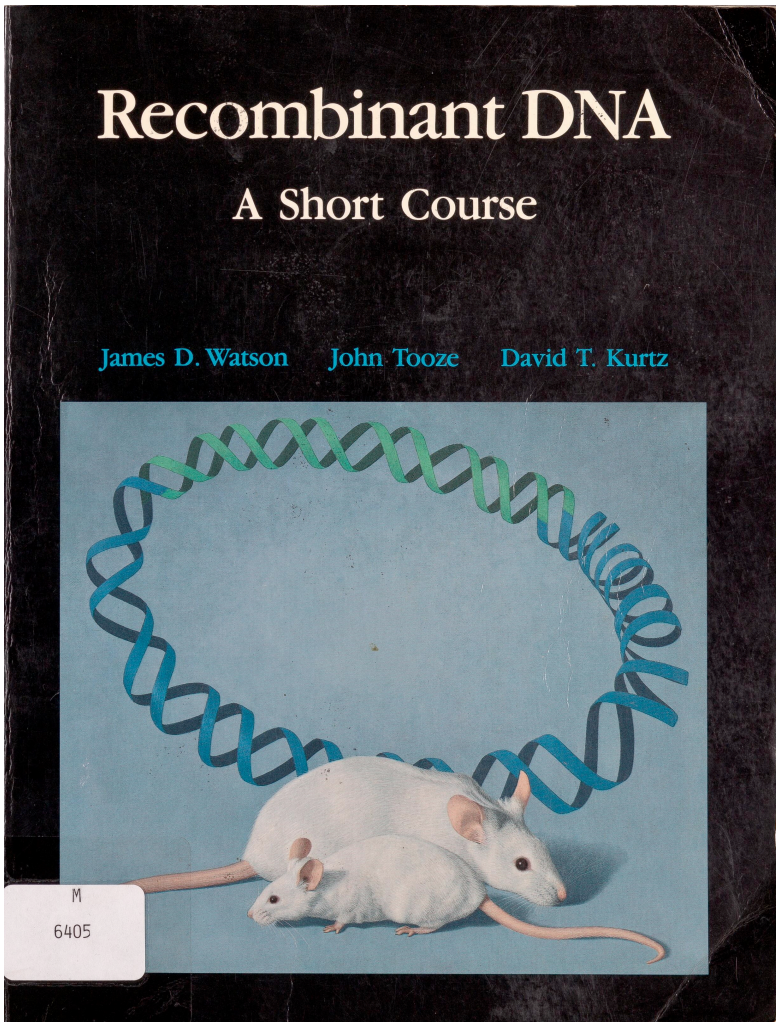


Fig. 5-3. Recombinant icons. Cover of Watson, Tooze & Kurtz 1983, image by Marvin Mattelson.

The highly-publicised promise of transgenic mice made them an attractive research system for those labs that were well-placed to adopt them. The combination of skills, know-how and instruments and infrastructure was unusual and costly, yet between 1982 and 1985, a number of laboratories succeeded in adopting the technology, some with relative ease: elite institutions at the cross-roads of academic exchanges, with existing animal colonies and developmental biologists on hand. A series of courses spread the techniques through direct hands-on teaching from experts in the field. Other places succeeded in relative isolation, with little or no immediate contact with experienced scientists.

The postdocs involved in making the first transgenic mice were in an enviable position career-wise and some of the leading molecular biologists were eager to recruit them. Philip Leder, who had received one of the first major university-industry grants in molecular biology at Harvard with money from the chemical giant DuPont, attempted to recruit Gordon, who took up a position

at the Mount Sinai medical school in New York instead.[44] Leder then hired Tim Stewart, who offered the embryological expertise and was eager to learn molecular techniques that he was unable to pick up in Mintz's lab. He began working with the new gene called c-*myc* at Harvard, a project that later gave birth to OncoMouse.[45] Yale's George Scangos secured a permanent position at Johns Hopkins, only to move back to Connecticut in 1986, to work in Frank Ruddle's start-up company, Molecular Diagnostics. Erwin Wagner secured a post at the European Molecular Biology Laboratory (EMBL) in Heidelberg, a major institution where he set up transgenic facilities. Frank Costantini and Elizabeth Lacy had been approached by James Watson to join Cold Spring Harbor, but both ended up securing permanent positions in New York City, at Columbia and the Sloan Kettering Institute, respectively.

The transit of postdocs was one early and safe way to spread the new techniques. Such direct exchange of skill was not, however, essential. Many classic studies in history and sociology of experimentation stressed the difficulty with which experiments travel and become replicated, and therefore the importance of personal demonstration and contact to make novel instruments work. But such replication challenges were not always insurmountable at a distance.[46] While personal contact aided the adoption of transgenesis in specific labs, pronuclear microinjection relied on well-established instruments and procedures that could be honed under the right conditions. After all, most transgenic pioneers devised pronuclear microinjection independently.

Several sites with expertise in mammalian embryo manipulation succeeded at replicating the technique from published descriptions. With the country's considerable tradition of mammalian development, British centres were in a particularly strong position. At the Agricultural Research Council's Animal Research Station in Cambridge, a key site for farm-animal genetics and embryology, Azim Surani set up a transgenic mouse project. After working on mouse parthenogenesis, Surani's main interest was the epigenetic differences between maternal and paternal chromo-

---

[44] Gordon interview

[45] Kenney 1986. The introduction happened via Shirley Tilghman, then based at Fox Chase, who had been a colleague of Leder's at NIH.

[46] Shapin & Schaffer 1985, Schaffer 1989, Collins 1985. For a recent case study of replication from printed description, see Lynch, et al. 2008: 83–112.

somes in the embryo, and the techniques for introducing new genes into mice offered the promise of exploring their fate and regulation. His lab assistant, Sheila Barton, was crucial to helping Surani make microinjection work. Barton had trained as a historian and entered the world of development as a secretary to Bunny Austin, eventually becoming extremely skilled at micromanipulation, recognised for her gold hands. Ironically, she taught one of the transgenic pioneers, Thomas Wagner, to actually perform pronuclear microinjection when he visited Surani, an old friend, in early 1982. The microinjections for Wagner's previous work had been done by Peter Hoppe at the Jackson Lab, and Wagner was eager to learn the embryological technique, despite Barton's observation that he was "ambidextrous – lousy with both hands".[47]

At Anne McLaren's MRC Mammalian Development Unit in London, Robin Lovell-Badge started microinjecting genes into mouse eggs after his move from Cambridge in 1982. He had been involved in another pioneering project, the isolation of mouse embryonic stem cells in Martin Evans's lab in Cambridge, and this system occupied the rest of his time in McLaren's unit.[48] McLaren's 1983 report to the MRC emphasised that pursuing recombinant DNA was a good strategy, confirmed by "the evident eagerness of molecular biology laboratories to acquire from us the methodologies of mammalian development."[49] She also expressed a continued commitment to gradually integrating molecular tools throughout her unit. However, the opinions of some referees of McLaren's work illustrate the community's ambivalence about embracing the molecular approach wholeheartedly and indicate a skepticism less frequently aired in publications. Jonathan Slack stated that "There is no doubt that solutions to the major problems of developmental biology will come about through a combination of micromanipulative skills with modern molecular biology. It is rare to find both in the same laboratory and I think they are quite right to claim this as a major strength."[50] Martin Evans's report saw the encroachment of molecular tools as both illuminating and threatening to the study of mammalian development, and encouraged McLaren to maintain a firm footing in traditional embryological and genetic approaches. Along similar

---

[47] Surani, unrecorded interview; quote from the T. Wagner interview.

[48] Board sub-committee visit 11/11/83, FD 12/1199, MRC papers, UK National Archives, Kew.

[49] Ibid.

[50] Ibid.; all the following quotes in this paragraph come from the referee reports in the same document.

lines, Chris Graham commended the unit for a new generation of PhD students who combined both molecular and embryological skills, but felt the transgenic project was a risk that "requests the Unit to become an injection factory for gene cloners (à la Brinster) or to increase their post-doctoral investment in the work, or to be very, very lucky."

While some embryologists were not convinced, a number of molecular biology laboratories showed strong interest in picking up the techniques of mammalian embryology and soon several workshops and courses were established to address this demand. The Molecular Embryology of the Mouse course at Cold Spring Harbor was the first and most influential. It was initiated by Brigid Hogan, a British molecular biologist working on teratocarcinoma cells at the British NIMR. In England, Hogan had been learning the techniques of mammalian development first-hand, and remembers her frustration at the lack of clear recipes or handbooks. The mystique of embryology with its emphasis on the complexity of embryonic manipulation and manual talent was maintained, with pervasive local beliefs about what made experiments succeed. Hogan had envisaged a course that could synthesise these techniques, but received negative responses from most embryologists. It took James Watson to broker the arrangement and set up such a course at Cold Spring Harbor, after a conversation with Hogan at a 1982 teratocarcinoma symposium there. Cold Spring Harbor had an established tradition of running summer courses in biological techniques, from phage genetics in the 1950s to the key course on recombinant DNA that had started in 1981 and was collated into the very successful 1982 handbook, *Molecular Cloning*.[51]

James Watson's clout helped the course start smoothly within a year. He had a strong interest in running a transgenic project at Cold Spring Habror, and persuaded Douglas Hanahan to start one. Watson approached Lacy and Costantini to help run the course, got the mouse colony organised, and secured sponsorship from Leica and Zeiss, which provided micromanipulators and microscopes. The two-week Molecular Embryology of the Mouse course was launched in summer 1983, with Costantini and Lacy on board (Fig. 5-4).[52] Lacy and Costantini's own experience in transi-

[51] Maniatis, et al. 1982. Hogan, interviewed by Sarah Franklin and Martin Johnson; Hogan, unrecorded interview; Hogan to James Watson, 30 September 1982, James D. Watson papers, Cold Spring Harbor Laboratory Archives, JDW/2/2/765.

[52] A major success since that first summer, the course is still running.

tioning from molecular techniques to embryo manipulation proved helpful. From the early days, it attracted major figures in mammalian embryology, including McLaren. Structured around an invited lecture followed by hands-on lab demonstrations, with full support from the Cold Spring Harbor infrastructure, it was an efficient way to transmit mouse transgenesis techniques. It was also an opportunity to raise awareness of other aspects of mammalian development among molecular biologists. IVF and embryo transfer, isolation of stem cells, making chimeras, nuclear transfer and teratocarcinoma work were all included alongside basic introductions to mouse development and the routine but crucial advice on animal husbandry and running mouse facilities.

Much of the demand for learning how to make transgenic mice came from molecular biologists eager for a new system to extend their ongoing work on gene expression. According to Costantini, "at the beginning, pretty much everyone who came wanted to learn how to make transgenic mice. A lot of them weren't so interested in learning other stuff. They would bring their DNA, and their boss said, 'don't come [back] without knowing how to make a transgenic mouse.' And then, over time, I think it started to get a more diverse bunch of students."[53] Other institutions followed suit. The Jackson Lab included transgenesis in its established 'Short course' on mouse and human genetics.[54] Peter Hoppe did much of the teaching on the new techniques there, though Lacy and Costantini participated in the 1985 course. In Europe, EMBL ran an annual workshop on gene expression in mammalian development, with a stronger focus on newly-available embryonic stem cells. These, however, were lecture courses without practical demonstrations.[55] In Britain, Brigid Hogan attempted to replicate the Cold Spring Harbor course at NIMR in 1985, but without comparable resources and strict requirements that all visitors should have Home Office licences to work with animals, it did not become a recurring event.[56]

In 1986 the handouts from the Cold Spring Harbor course were compiled into a handbook, *Manipulating the Mouse Embryo: A Laboratory Manual*, authored by Lacy, Hogan and Costantini.[57]

---

[53] Lacy & Costantini interview.

[54] For the history of the Jackson course, see McKusick, et al. 1999.

[55] EMBO-EMBL 1984 workshop videos, kindly provided by Erwin Wagner.

[56] Hogan, unrecorded interview.

[57] Hogan, et al. 1986.

Fig. 5-4. Participants in the first Molecular Embryology of the Mouse course at Cold Spring Harbor, 1983.

Back row: Peter Rigby, NIMR • Douglas Hanahan, CSHL • ? • Brigid Hogan, NIMR • ? • ?

Middle row: Kathie Raphael, CSIRO, Australia • Tadatsugu "Tada" Taniguchi, Japanese Foundation for Cancer Research • Anne McLaren, UCL • ? • Lee Silver, CSHL • Frank Costantini, Columbia • Minoo Rassoulzadegan, Nice University • Elizabeth Lacy, Sloane Kettering

Front row: Denise Barlow, NIMR • ? • Bryan Crenshaw, UCSD • ? • Lisa Stubbs, CalTech.

Whereas its hugely influential predecessor, *Molecular Cloning*, had been routinely referred to as the "Bible", Hogan, Lacy and Costantini's output was labelled "the Mouse Book". Beyond detailed advice on how to make transgenic mice, it included materials on general mammalian development and other techniques such as nuclear transfer and stem cell culture, a brief history of mouse embryology, as well as information on setting up a mouse colony. It was intended to be used at the bench, as evidenced not only by its clear step-by-step recipes and a wealth of diagrams and photographs, but also by its comb-binding, which meant it could be laid down flat and photocopied more easily – a printing choice increasingly employed by the Cold Spring Harbor Laboratory Press.

The Mouse Book was favourably reviewed. In *Trends in Genetics*, the Cambridge embryologist Martin Johnson noted that "all laboratories that aspire to the genetic manipulation of the mouse should buy at least two copies immediately – my single copy is never there when I need it, a sure sign of its value."[58] A review in *Genetical Research* praised the book's contribution as an introduction to mammalian development at large: "this book is probably unique in its coverage of mammalian developmental biology, and will be welcomed by anyone who has tried to plough through embryology texts in search of information relevant to mammals."[59] The handbook also did well commercially, even though it never quite matched the success of *Molecular Cloning* or the Press's monoclonal antibody series.[60]

Similar books appeared in 1986–7, embracing a wider focus on molecules and mammalian development. Janet Rossant and Roger Pedersen's *Experimental Embryology of the Mouse* was a collection of chapters from prominent biologists, and it aimed to become a more theoretical introduction for any "serious student of mammalian development", focusing on the state of the art. It recognised the role of transgenic mice in raising the status of the field: "For the many molecular biologists who have discovered the mouse embryo in their quest for transgenic mice, it will provide an introduction to the wider issues of mammalian embryogenesis."[61] Similarly, Marilyn Monk's *Mammalian Development*, an instalment in the extensive 'Practical Approach' series from IRL Press, was a British multi-authored handbook with a broader scope.[62] Azim Surani, Sheila Barton and two postdocs in Surani lab wrote their contribution on transgenic mice. While these volumes were favourably reviewed, they did not become as widely used as the Mouse Book.

The success of the Cold Spring Harbour course was partly owing to its ability to bring in heavy sponsorship, and in fact, Watson may have considered extending the laboratory's own transgenic work into a commercial venture.[63] The 1980s saw a dramatic expansion of the biotech industry

---

[58] Johnson 1986: 298.

[59] Simons 1987.

[60] Judy Cuddihy, the handbook's managing editor, email to author, 3 Jan 2014.

[61] Rossant & Pedersen 1986: ix.

[62] Monk 1987.

[63] Hogan interview, personal communication.

and reorganisation of biomedical research. Beyond the success stories of Genentech and Cetus, the 1980s was a decade of hybrid arrangements between universities and industry. Major pharmaceutical and chemical companies – Pfizer, Monsanto, DuPont – funded high-profile collaborations.[64] The Whitehead institute, founded with a major donation in 1982 and affiliated with MIT after protracted faculty debates, became a new site for exciting molecular work, giving its first director, David Baltimore, extensive control over hiring and research strategies.[65] Transgenic technology followed the early success stories of biotech and many institutions were keen to introduce it into their routine. A 1985 opinion piece in *Nature,* tellingly titled 'DNA makes protein makes money,' listed the various recombinant systems used in biotechnological production, and then remarked: "Now that the [transgenic] technique has been established... it offers the possibility of investigating the mechanism of tissue-specific gene expression and maybe eventually of producing useful proteins in the milk of cows or in the eggs of chickens" (Fig. 5-5).[66]

Some commercial applications for transgenic animals were envisioned, but the bigger biotechnology firms also pursued cutting-edge research to build reputations and attract university scientists. Seeking to attract the best scientific talent to a new industry, Genentech built on the collaboration between Axel Ullrich and Karl Illmensee and in 1984 recruited Tim Stewart to set up its own transgenic facilities. Following prominent research universities and the NIH intramural programme, Baltimore offered Jaenisch a place at the Whitehead institute and invested in building proper mouse infrastructure.[67] Yet the commercial entities keen to attract transgenic research were not limited to the biotech hubs of the Bay and Boston areas. Smaller start-ups emerged, some of them led by transgenic pioneers. Frank Ruddle was involved in two related ventures, Molecular Therapeutics and Molecular Diagnostics in West Haven, Connecticut, where George Scangos moved in 1986 to organise transgenic mouse research, taking a sabbatical from his tenure-track position at Johns Hopkins, and eventually fully moving into industry. In Ohio, Thomas Wag-

---

[64] Kenney 1986.

[65] See Kevles 1998.

[66] Emtage 1985: 185

[67] Jaenisch interview; Baltimore interviewed , Jackson Laboratory Oral History, 1986.

Fig. 5-5. The golden eggs of biotechnology. Drawing in *Nature* that accompanied Emtage 1985.

ner was heavily involved with the foundation of an animal biotechnology research institute and Embryogen, a company intended to commercialise its outputs.

The Ohio story showcases heavy state support for the 'private science' of biotechnology, and demonstrates alternative modes of funding and network-building.[68] Wagner's original work on gene transfer was partially funded by the Detroit-based Genetic Engineering, Inc. which would have held an exclusive licence under the Ohio University/Jackson patent on microinjection filed in June 1981. From the very start, the Ohio University administration was backing Thomas Wagner's work to put the institution on the map and raise revenues. Charles Ping, the University President, managed to secure an important and lucrative alliance with the state administration, which largely relied on Wagner's research and the promise biotechnology held for employment and economic growth in a 'rust-belt' state. Ohio University opened the Institute for Animal Biotechnology in 1984 with a grant from the Thomas Alvaro Edison programme, a fund initiated by the new Democrat governor Dick Celeste to provide seed capital for innovative projects. The same year, the university bought out the Genetic Engineering, Inc. claim to the exclusive licence, and established its own spin-off company, Embryogen.

---

[68] The detailed history of Embryogen and Edison Animal Biotechnology Institute is found in papers of Charles J. Ping, his assistant Alan Geiger and the notes and drafts for the history of Ping's administration by Peg Black, eventually published as Riffe 2004. Ohio University Archives, Athens, Ohio. This account also draws on T. Wagner and Holtzman interviews.

The agricultural promise of transgenic technology loomed large in corporate strategy. It was made feasible by Brinster's collaboration with USDA researchers in Beltsville, Maryland that started in 1984 and resulted in transgenic sheep and pigs.[69] In 1985, Azim Surani reported the production of transgenic sheep at the Animal Research Station in Cambridge, a project enthusiastically promoted by its funder, the recently renamed UK Agricultural and Food Research Council.[70] Sheep transgenesis was also pursued the Edinburgh site of the Institute for Animal Physiology and Genetic Research (IAPGR),[71] and a spin-off company, Caledonian Transgenics, was founded to commercialise this work in 1986. The global reach and the promise of real applications encouraged agricultural institutions to build up their molecular portfolios. Thus, in the Soviet Union, a collaborative project focusing on transgenesis and embryo transfer in farm animals was established at the All-Union Institute for Animal Husbandry in the Moscow satellite town of Dubrovitsy. Led by Lev Ernst, the project relied on the infrastructure of Soviet research institutes.[72] With one microinjection facility available and limited molecular expertise on site, Ernst followed the Brinster example and secured DNA supply from a molecular biology laboratory at the Moscow State University.[73]

Biotech companies and universities interested in agricultural applications of animal transgenesis created alternative networks through which individuals, skills, DNA and animals travelled. While Wagner was being delicately excluded from the citation history of transgenic mice (see Chapter 4 §5), the fledging patent application ended up creating a new legitimacy – and controversy – for his claims when it was granted in 1989. Furthermore, despite Embryogen's struggle to attract investors willing to pour money into the Ohio facilities, and the company's ultimate merger with another start-up and move to New Jersey, Wagner's involvement in a state-private enterprise opened

---

[69] Hammer, et al. 1985

[70] Agricultural and Food Research Council 1986: 8–9, 25

[71] IAPGR was a short-lived conglomerate built by AFRC on the basis of Edinburgh Animal Breeding Research Organisation and Babraham institute outside Cambridge that existed between 1986 and 1993, after the council closed a large number of research units during the shortage of funding under Thatcher's government, including the Animal Research Station in Cambridge. In 1993, Babraham regained its autonomous status and the Roslin Institute was formed on the basis of the Edinburgh site, where Dolly was cloned in 1996.

[72] NII, *nauchno-issledovatsl'skiy institut,* 'scientific research institute', a specialised non-teaching facility.

[73] Alla Madich, unrecorded interview and email to author, 10 February 2014

other doors. Thus, Ohio built connections with emerging Asian institutions, for instance Beijing Agricultural University and provincial biotechnology centres in China, as well as universities in Japan and Malaysia. Finally, Wagner's position as scientist-entrepreneur, a new identity forged by the rise of biotech, secured him an invitation to the US Congress's Office of Technology Assessment (OTA) Committee on Biotechnology in 1986, and he was a prominent voice in congressional investigations and media debates on transgenic research and animal patenting.

The success of transgenic experiments was constructed in the early 1980s in a highly visible fashion. A number of laboratories invested in the new technique, hoping to capitalise on a new experimental system through publications, expanding knowledge and, in some cases, by attracting funding and building hope of future profits. A network of courses and personal contacts, with active engagement from several pioneers, helped with the transmission of elaborate techniques, though a number of laboratories picked the skills up independently. Through different strategies, new laboratories embraced transgenesis and adapted it to their infrastructure and research programmes. Moreover, with the expansion of commercial interest in genetic engineering and encouragement of private funding for biomedical research, new networks were being built around the commercial exploitation of transgenic technology. In the early days, these connections were driven by the agricultural promise.

§3. Making knowledge with transgenic mice

Unusually, the mouse was the first animal for which a novel molecular technology had been implemented, while other laboratory animals lagged behind. This state of affairs did not last. Between 1982 and 1985, gene transfer was achieved in other animals key to developmental biology. The use of P-elements (transposable genetic elements that 'jumped' in the genome) to transfer genes into *Drosophila* was reported in 1982 by Gary Rubin with Allan Spradling, both molecular biologists working with the fly at the Carnegie Department of Embryology.[74] Gene transfer attempts were also performed with the nematode *C. elegans,* with genome integration and germline

[74] Rubin & Spradling 1982, Spradling & Rubin 1982.

transmission announced in 1986.[75] These experiments did not receive attention comparable to mice outside of the embryological community, but their profile was high within. With the proliferation of eukaryotic experimental systems suitable for molecular intervention, these species were being used to elaborate new knowledge about gene action in higher organisms. The emphasis on molecular genes as a unifying focus of research, aided by the ability to splice and hybridise genes between species, made comparisons between different experimental organisms more straightforward.

In 1985, the Cold Spring Harbor Symposium on Quantitative Biology celebrated its 50th anniversary with a meeting on 'The Molecular Biology of Development'. It was organised by Joe Sambrook, a molecular biologist at Cold Spring and co-author of the *Molecular Cloning* handbook. In his foreword to the published proceedings, Sambrook explained the choice of topic:

> In recent years... developmental biology has undergone a dramatic change and has matured from a descriptive to an analytical science. There is no doubt in my mind that this change stems almost entirely from two technical advances – the ability to use molecular cloning to isolate and characterize wild-type and mutant versions of genes that control or are expressed at specific developmental stages and, second, the ability to generate transgenic organisms in which the expression of the introduced gene(s) is correct both spatially and temporally.[76]

Such emphasis could be expected from a molecular biologist and a Cold Spring Harbor event, and the programme reflected such excitement. Yet the opening and closing remarks at the symposium, by John Gurdon and Gerry Rubin, respectively, presented two contrasting perspectives.[77] Rubin's concluding lecture celebrated the newly available methods such as gene transfer, *in vitro* mutagenesis and antisense RNA – which he characterised as 'non-classical' or 'surrogate' genetics – and highlighted the variety of species with which new molecular knowledge of development was being produced: mice, but also *Drosophila* (his organism of choice), *C. elegans*, yeast and *Xenopus*. Gurdon's introductory lecture emphasised the historical achievements of experimental embryology and downplayed the importance of genetics, as he urged his audience to keep in mind

[75] Fire 1986.

[76] Sambrook 1985: xv.

[77] Gurdon 1985, Rubin 1985.

the ambitious developmental questions of determination, axis formation and patterning. Recognising the promise of gene transfer, to which he himself had greatly contributed, he reminded the audience that the traffic between molecular biology and embryologists had been two-directional, and suggested that to answer the big developmental questions, studies of protein interactions and using cell-free systems had to be taken seriously alongside transgenic organisms.

Transgenic mice were certainly a highlight of the symposium, with leading researchers reporting their latest work. However, it was a consensus of the meeting that their utility left something to be desired. In *Drosophila*, a single gene integrated into the genome on a P-element showed reasonably predictable levels of expression – something emphasised in discussions around the fly publications.[78] In mice, integration of foreign genes happened at random into unknown genomic positions. The DNA itself did not insert as a single copy, but replicated into tandem repeats through a mystifying mechanism. The levels of expression could vary widely and seemed to correlate poorly with the number of gene copies that ended up in the mouse genome.[79] Jaenisch's approach, which relied on retroviruses with a single copy integration, circumvented that problem, but it involved the extra step of purifying the viruses and was more likely to give rise to mosaic animals with genes in only some tissues.

Transgenic researchers were aware of this lack of control and emphasised it in talks (Fig. 5-6). At the same time, it did not remain merely a limitation. Unpredictable integration and the lack of correlation between gene copies and expression levels became resources to articulate further questions. Thus, random insertion could give rise to mutations, some of them resulting in embryonic lethality, and several were reported at the Cold Spring Harbor meeting. Such mutants had been the staple of developmental genetics since the 1930s. However, with transgenic mice, the disruptive gene was known and a molecular probe could be designed to map and sequence the affected chromosomal region, offering a molecular take on gene hunting.

Molecular tinkering with the injected DNA constructs drove attempts to circumvent unpredictable expression and define the key elements that were required. It fit well with the intense inter-

[78] Petri 1982.

[79] Rubin 1985: 908.

est in eukaryotic gene regulation from molecular biologists. While the possibilities of genetic therapies and agricultural promises captured media attention, the immediate attraction of transgenic mice in their early years was the ability to examine eukaryotic gene function in space (across tissues) and time (during development). In 1982–88, a great variety of gene constructs were injected into mouse embryos, connecting experts across fields. Here, I will consider two examples of research with transgenic mice to illustrate the broader pattern of their use: the study of control sequences in human globin genes and work with oncogenes as the genetic basis of cancer.[80]

As Chapter 2 showed, much impetus behind recombinant DNA research was to provide a new way to investigate and understand eukaryotic genes. With the ability to isolate genomic or cDNA, the study of expression exploded.[81] The second edition of Benjamin Lewin's *Gene Expression* (1980) was devoted to eukaryotic chromosomes, after the 1974 text on bacterial expression, and was a completely different text intended as another volume rather than an update.[82] Over a thousand pages, the book struggled to reflect the dramatic amounts of new knowledge made in only three years. Studies of the structure of eukaryotic chromatin – the combination between DNA and various protein that packaged it into chromosomes – and the effect of different sequence regions on expression levels was booming. Introns – regions of DNA sequence not found in the final RNA transcript – were a hot topic in the late 1970s.[83]

Promoters, well-described by bacterial molecular biologists, were already instrumental in the first gene transfer experiments. These elements initiated RNA transcription from DNA, and had to be located upstream of the gene, with their specific position in the sequence affecting the rate of RNA production. Yet in eukaryotes, other regulatory elements worked at a long distance away from the gene were being identified. These 'enhancers' were first described in 1981 in the familiar tumour virus SV40. Their striking feature was demonstrated by Paul Berg in the same year, as he

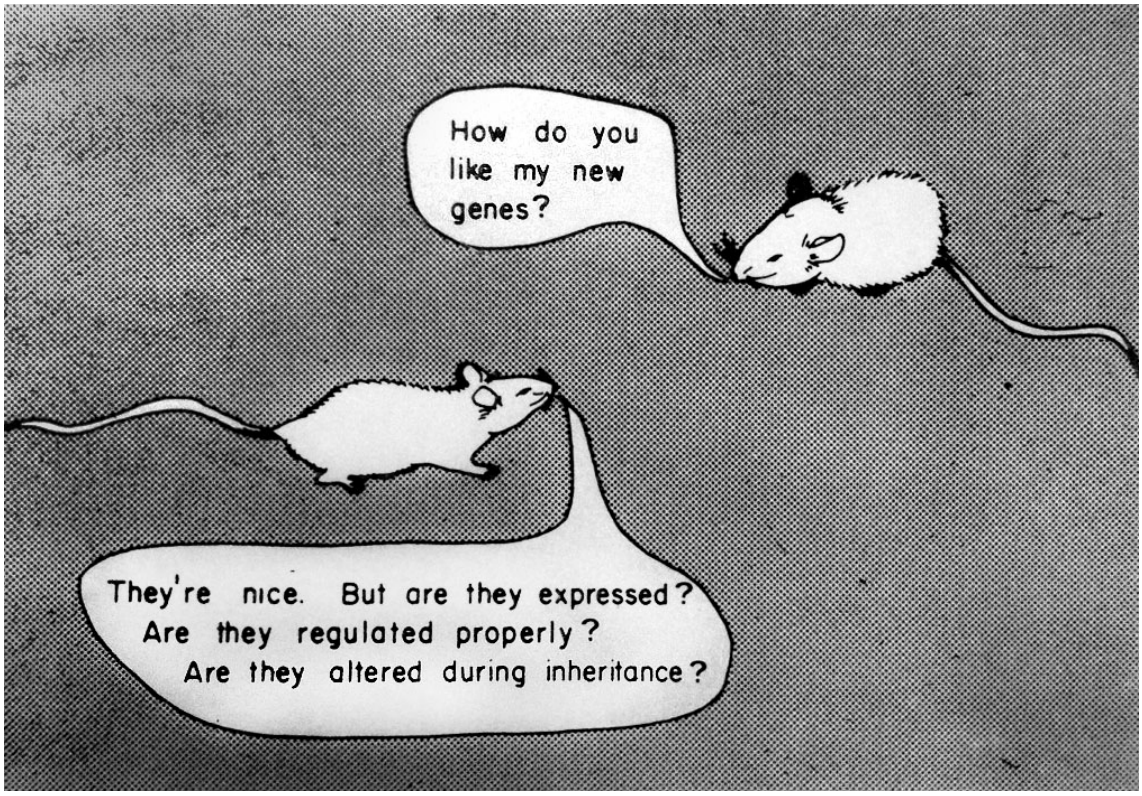
---

[80] For more extensive reviews of the trajectories in of early transgenic research, see Camper 1987, Gordon 1989a, Hanahan 1989, Patrusky 1989.

[81] Echols 2001: 344–7.

[82] Lewin 1980.

[83] Morange 1998: 204–14.



showed that removing these bits of DNA and moving them downstream of the gene did not reduce expression. Initially, enhancers were suspected to be specific viral elements. However, by 1983 similar sequences were detected in lymphocytes, suggesting they were cellular elements that the viruses hijacked and moved, and the search for new enhancers continued.[84]

The vast majority of gene expression analysis in this period was performed in cultured cells or cell-free systems. Work with transgenic mice could build on *in vitro* experiments by showing whether the foreign gene expression was limited to the predicted tissues and to what extent the existing control elements could mimic expected quantities of protein. Human globin genes were a major genetic system for such projects as they were among the first genes to be cloned. Developmental changes in the way human haemoglobin is made – the embryonic, foetal and adult molecules combine different globin subunits – were another attraction. Unlike other genes, significant expression of foreign beta globin in transgenic mice had not been achieved. Lacy and Costantini continued working with beta globins in New York, and while they managed to detect some expression, tissue specificity was a problem. They could detect the rabbit beta globin mRNA in some

[84] Patrusky 1986.

tissues – skeletal muscle and testes – but not the expected blood cells.[85] By 1985, however, the team published a paper with a mouse-human beta globin gene hybrid, including some mouse and human regulatory sequences upstream and downstream of the gene. The result showed specific expression in red blood cells, even though the levels remained low.[86] In the same year, Brinster, Palmiter and collaborators at the universities of Alabama and Cincinnati reported tissue-specific expression of human beta globin with a different construct.[87] Removing prokaryotic sequences from the plasmids or phage vectors improved the levels, and was recommended for all subsequent transgenic experiments.[88]

In 1987, after years of experimenting with the globin genes in cultured cells, Frank Grosveld and George Kollias at NIMR constructed a beta globin DNA that showed predictable expression. Through a contact with Hogan, Kollias had attended the second Cold Spring Harbor course and brought transgenic techniques into Grosveld's lab.[89] Drawing on extensive work on globin promoters and enhancers in culture, studies of thalassaemia patient cells and transgenic experiments, Grosveld and Kollias designed a control sequence that they expected to combine all the crucial features required for expression. The resultant transgenic mice showed very high expression, comparable to the levels observed in humans. Significantly, the levels of human globin protein also correlated with the number of foreign genes that incorporated into the germline – an indication that their combination of promoters and enhancers alone was sufficient to generate normal expression. This region, that they labelled the Dominant Control Region, became a key part in the regulator model of globin genes.[90]

---

[85] Lacy, Roberts, Evans, Burtenshaw & Costantini 1983.

[86] Chada, et al. 1985.

[87] Townes, et al. 1985.

[88] Hogan, Costantini & Lacy 1986: 159–60.

[89] Frank Grosveld's brief recollection, as recorded and kindly shared by Alan Palmer at NIMR, email to author, 25 October 2012.

[90] Grosveld, et al. 1987, Evans, et al. 1990. This analysis also relied on the structure of chromatin in the globin locus, as the key control elements showed hypersensitivity to DNase, a non-specific restriction enzyme. Such hypersensitivity implied that chromatin was unravelled at the locus to enable access to transcription factors that initiate RNA synthesis from the DNA template.

In parallel with the globin work, other groups made transgenic mice with new eukaryotic genes that had receiving dramatic attention circa 1980. These were oncogenes, associated with the molecular processes behind carcinogenesis. The research into origins of cancer, in which mice played a central role, had oscillated between emphasising genetic and environmental causes. Providing animals for cancer research persisted as a key agenda for mouse genetics, as the disease became a major locus of biomedical funding. Viruses were an important research programme for cancer causation in the 1930s and again in the 1960s and 70s, with major interest in animal tumour viruses that I discussed in Chapter 2.[91] In 1975, Dominique Stehelin, Harold Varmus and Michael Bishop used Southern blotting with a viral probe to detect a Rous sarcoma virus gene (later labelled *src*) in the chicken genome. While this result is celebrated as the beginning of oncogene research, work from other groups, detection in different species and alternative methods that relied on gene transfer were required to make a convincing case for their importance in cancer causation.[92] In only a few years, oncogenes became the dominant concern of carcinogenesis studies and a key instrument for research.[93]

Several laboratories pursued inserting oncogenes into the mouse germline. Brinster and Palmiter attached the viral *src* gene to their metallothionein promoter in the summer of 1982, with no tumours in the resulting mice. However, in the same summer, an experiment that relied on improving expression of the thymidine kinase gene by SV40 enhancers led to unexpected brain tumours. Palmiter's construct included a large part of the viral 'early' region. In subsequent studies, Brinster and Palmiter showed that the control region in the virus and the T-antigen gene were sufficient for tumour formation, thus demonstrating that SV40 T-anitgen was an oncogene.[94] In Leder's Harvard lab, Tim Stewart was working with the cellular *myc* oncogene involved in Burkitt's lymphoma – Leder's long-term interest. Learning the molecular techniques, Stewart combined the gene with a promoter and enhancer sequence from the mouse mammary tumour virus (MMTV), in the hope that it would be a 'strong' control element. Gene expression was targeted to

---

[91] Löwy & Gaudillière 1998a, Löwy & Gaudillière 1998b, Gaudillière 1998a, 2001, 2003b.

[92] Morange 1998: 221–4.

[93] On oncogenes, see also Angier 1988, Morange 1993, 1997a, Fujimura 1996: 116–36.

[94] Brinster, et al. 1984.

the mammary tissue, leading to breast tumours in resulting mice. Papers from both groups were published in *Cell* in June and October 1984, respectively, and both experiments featured on the cover (Fig. 5-7).[95]

Famously, a patent was filed on the Harvard mouse, in line with the agreement Philip Leder had with DuPont who sponsored his research and move to Harvard. It would appear that they responded to the promise of disease models that had been articulated in anticipation of successful gene transfer into mice, most coherently by Mintz. Yet Leder and Stewart's mice were not initially presented as models of breast cancer. The major utility of these animals, reflected in the patent claims, was as instruments for expression analysis and carcinogen testing, potentially superior to the non-transgenic mice that had been used for similar purposes. They were presented as a source of novel tumour cell lines that could be derived from different tissues, and a means of studying the MMTV promoter sequences further.

Gene expression was one of the major issue at stake: was the mere presence of a single oncogene sufficient to cause tumours, or was gene regulation to blame?[96] On top of that, the slow emergence of tumours fit with the already-articulated multi-step models of carcinogenesis, in which several things had to go awry for a tumour to emerge.[97] With further results form Brinster, Hanahan and Wagner reported in 1985, mice were promoted over cell culture as tools for dissecting multi-step carcinogenesis. In a 1987 experiment, Leder's group showed that when mouse strains with different oncogenes were crossed, tumour development increased dramatically in offspring that carried two oncogenes.[98] While this work relied heavily on knowledge generated *in vitro*, transgenic researchers argued their mice were genetic animals that were best-suited to help solve genetic problems.[99]

---

[95] Hanahan, Wagner & Palmiter 2007.

[96] On the tensions between oncogene mutation versus regulation as a main event in cancer causation, see Morange 1997a.

[97] Ibid., Keating & Cambrosio 2012: 306–14.

[98] Sinn, et al. 1987.

[99] Rigby 1985; Hanahan 1988, 1989.

Fig. 5-7. Transgenic mice with oncogenes on the cover of *Cell*, 1984. *Left*, cross-section of a brain tumour from the Brinster-Palmiter paper, June 1984. *Right*, mouse with a visible breast tumour from the Leder-Stewart article, October 1984.

For developmental biologists, the utility of transgenic mice was less immediate. Insertional mutations were a promising line of work, but creating new lines was slow.[100] Some oncogenes were implicated in differentiation and cell division, and the haemoglobin system held the promise of developmental switches to be determined. However, the interest in gene regulation fit well with a molecular take on differentiation that had been promoted in the 1970s by the like of Gurdon, Markert and Davidson. Thus, Azim Surani's work on genomic imprinting – the idea that alleles of the same gene could behave differently depending on whether they were on a paternal or maternal chromosome – initially relied on making parthenogenetic embryos by moving two male or two female pronuclei into a mouse zygote. While Illmensee had claimed such constructed embryos viable, both Surani and Davor Solter's group argued their development was in fact severely abnormal. Surani proposed that the same genes could be regulated by means external to their DNA sequence, or epigenetically, and undertook a molecular demonstration to make a case for imprint-

[100] That embryonic mutations would lead to identifying important genes was also not immediately obvious. Gerry Rubin remarked: 'The major limitation of this approach is that only a small minority of embryonic lethal mutations will be in genes with functions of developmental interest. As Mary Lyon put it, "A lot of things can cause a mouse embryo to go wrong early." – Rubin 1985: 907.

ing. In 1987, Surani's postdoc Wolf Reik – a former PhD student of Jaenisch's – made transgenic mice with a gene whose methylation could be assessed. Methylation – presence of added methyl groups on chromatin – was known to affect expression *in vitro*. Crucially, the pattern of methylation in the resulting mice changed depending on whether it was inherited from the mother or the father in subsequent crosses.[101]

Transgenic mice were thus being embraced as a means to investigate gene function where differences between tissues could be demonstrated and controlled. The ability to detect promoters and enhancers was assumed to correlate with gene numbers, and showed sufficient conditions for expression. Moreover, the very limitations of transgenesis by pronuclear microinjection were recruited to pose new questions and generate novel experimental agendas. The promise of transgenic mice had been accepted before reliable gene expression was achieved, but the very process of controlling expression was informative for molecular biologists. These results were not challenged in print, but rather integrated into the growing knowledge about eukaryotic genes. The heavy focus on DNA made comparisons between systems as diverse as mice and yeast increasingly productive, especially since nucleic acid hybridisation showed high levels of evolutionary conservation between many gene families.[102] To revisit Rubin's summary of the 1985 Cold Spring Harbor meeting: "The surprising finding of evolutionary conservation of a number of DNA sequences known to encode important functions has provided a way to relate observations made in diverse systems. The use of sequence cross-homology as a tool to utilize the advantages or advances of one experimental system in another was a recurring theme in this year's Symposium."[103]

Heralded by the supermouse, the study of gene expression was thus the primary focus and most celebrated application of transgenic mice in the 1980s. Yet, while most studies maintained a molecular focus without a clear goal at medical translation, transgenic researchers were not blind to the world of biomedicine, and biotech and medical researchers paid attention. As noted already,

---

[101] Reik, et al. 1987. Surani's embryological experiments were published as Surani & Barton 1983, Surani, et al. 1984

[102] The RNA and DNA hybridisation experiments across species were known as "zooblots". The focus on comparing protein and DNA sequences across species had received sustained attention in molecular studies of evolution since the 1970s, building on earlier serological and electrophoretic studies, and has been a major influence for evo-devo approaches – see Suárez-Diaz & Anaya-Muñoz 2008, Suárez-Díaz 2014.

[103] Gurdon 1985, Rubin 1985.

while the studies may have focused on specific gene expression, the genes selected often had potential medical relevance – insulin, interferon, globin genes and oncogenes were all hot subjects. Moreover, the number of transgenic researchers entering new niches in the biotech industry was considerable. While most early projects focused on the production of valuable proteins in animals and attempts to breed better farm animals, and not disease models per se, relevance to human health remained on the agenda, and became a priority after 1987. Thus, in their studies of oncomice, Brinster, Leder and Hanahan built links with cancer researchers and clinical scientists who provided detailed descriptions of the cancers his mice developed. Between 1987 and 1990, a flurry of reviews and papers on transgenic animals targeted clinical audiences through medical journals, increasingly employing the language of "models".[104]

They easily achieved a high profile due to their novelty, scarcity and the ability to claim *in vivo* analysis. This status was reflected in the publication pattern. Even as the scale of transgenic work expanded considerably and entered more disciplines, the majority of transgenic papers were published in high-profile journals – 'bridge' publications covering multiple fields such as *Science*, *Nature* or *PNAS*, or generalist biological journals like *Cell* (Fig. 5-8). Yet such experiments were few in comparison to cell culture studies, they required more time, a rare combination of expertise and animal infrastructure. As I discuss in the next section, this focus on individual gene expression and the scarcity of transgenic animals affected the way they were produced and defined.

[104] E. g. Murphy, et al. 1987, Pattengale, et al. 1989, Sepulveda, et al. 1989.

§4. "A boutique operation": Standards and scales

Today, transgenic mice are easily available through university 'core facilities' – to which their production was outsourced in the 1990s – as well as the Jackson Lab and the many commercial suppliers, both new and established. Yet most early users had to rely on their own ability to introduce foreign DNA into the germline, or find willing collaborators. The resulting strains could then be studied in more detail or crossed to observe the effects of multiple genes or control elements, yet the primary style of research was to produce new animals with an ever-expanding number of available cloned genes and control elements. The husbandry, record-keeping, disease management and breeding of transgenic mice relied on established practices of mouse genetics that were propagated through demonstration, handbooks and existing institutional experience.[105] Yet, despite their place as tools and iconic symbols in the molecular interpretation of mammalian development, the established mouse *genetics* community was barely involved in transgenic work until the 1990s. The focus on specific genes was the core interest for molecular biologists, and many cloned genes remained to be introduced and studied. Some transgenic experiments paid attention to the genetic background of the strains they were using and the designed mouse stocks had to be maintained, much like novel mutant strains produced through classical genetic means. But as this section will show, the institutional separation of transgenic research from traditional mouse genetics created modes of production and exchange outside of the usual supply networks.

Despite its role in all things murine, the Jackson Lab did not begin advertising transgenic mice until 1993, and even then served largely as a repository for external providers. The Lab was also marginal in research with transgenic animals.[106] Thomas Wagner's collaborator Peter Hoppe continued to work on making transgenics there, but anecdotal evidence suggests that he was hard-hit by the Illmensee affair as the prime collaborator and co-author on the mouse cloning paper. He taught the techniques of mammalian development, including pronuclear microinjection, at the Jackson Short Course in Mammalian Genetics, but did not publish any further work on transgene-

[105] On genetic standardisation of mice, see Rader 2004, Birke, et al. 2007. On the importance of non-genetic parameters in lab animal standardisation, such as physiology, disease management or environment, see Clause 1993, Kirk 2008, 2010, 2012, Leonelli, Ramsden, Nelson & Ankeny Forthcoming, 2014.

[106] Since then, the Jackson Lab has become a major transgenic producer and supplier.

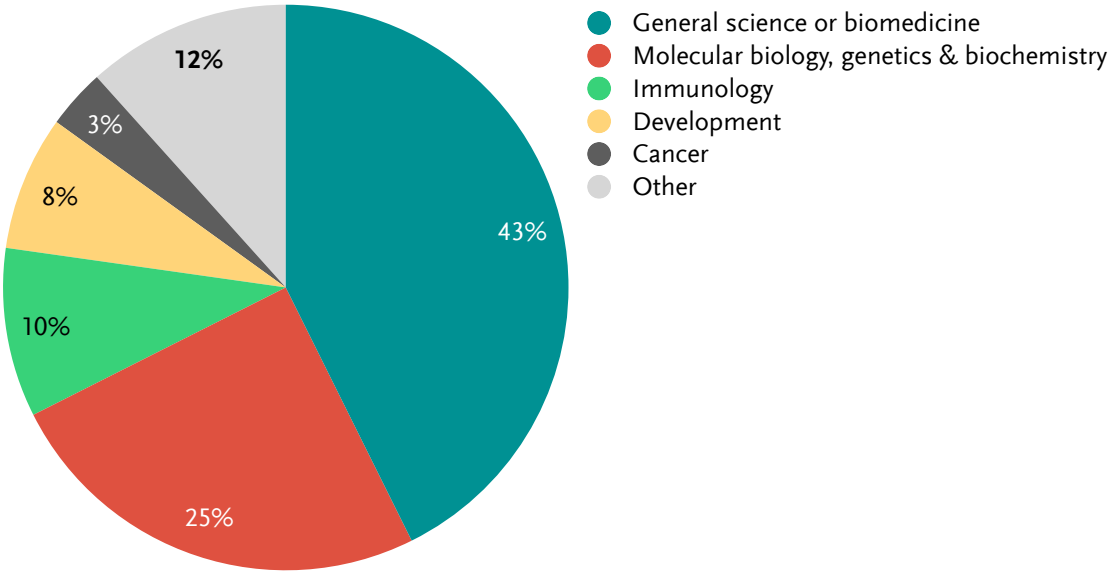


Fig. 5-8. Articles on transgenic mice by journal type, 1985–1990.

Data obtained using Web of Science core database search for 'transgenic AND mouse', with relevance confirmed by title and abstract. Only journals that published more that two papers on transgenic mice throughout the six-year period were included in the analysis, with a total of 558 papers. Categorisation of journals is as follows:

General
PNAS
Nature
J. Experimental Medicine
Cell
Science
J. Clinical Investigation

Mol. biology, genetics & biochemistry
Molecular & Cellular Biology
EMBO Journal
Nucleic Acids Research
J. Biological Chemistry
Molecular Biology Medicine
Biochemical & Biophysical Res. Comm-s.
Biomedica Biochimica Acta
Molecular General Genetics
Somatic Cell And Molecular Genetics

Immunology
J. Immunology
European J. of Immunology
Current Topics in Microbiology & Immunology
Immunology
Thymus
Immunogenetics

Development
Genes & Development
Development
Developmental Genetics
Developmental Biology

Cancer
Oncogene
Oncogene Research
Cancer Research

Other
Endocrinology
J. Virology
Neuron
American J. of Pathology
Molecular Endocrinology
J. Cell Biology
J. Neuroscience Research
Scandinavian J. of Rheumatology
Diabetes
Kidney International
Tsitologiya

sis until 1987.

As an institutional strategy, leaders of the Jackson Lab focused the limited resources elsewhere. As a global repository of mouse strains, the lab was heavily involved in the techniques of embryonic cryopreservation. Another example of a technology that came from the intersection between mouse embryology and farm animal research, the ability to safely freeze and thaw embryos and transfer them to surrogate females had been established as a feasible technology in 1977 at a Ciba foundation meeting in London.[107] In 1978, Jackson started its cryopreservation programme, with 281 strains stored this way by the summer of 1982;[108] similar efforts were made at the MRC Harwell unit in Britain. The Jackson Lab did recruit two molecular biologists in 1983 to establish cDNA libraries from well-known inbred strains of mice, in line with the institution's archival mission, and to study cancer in existing mouse lines. In a 1986 oral history interview commissioned by the lab, David Baltimore, who had spent his high-school summers at the Jackson student courses, lamented that the laboratory was unlikely to become an efficient site for molecular research. While predicting an important role for the lab in mouse supply and quality control, Baltimore felt that the narrow research focus, remote location and 9-to-5 work ethic were inadequate to rewrite the mouse in the language of DNA.[109]

Community-wide, there was some effort to integrate transgenic mice into the existing genetic standards. In 1984, a group of the International Committee on Standardised Genetic Nomenclature for Mice met at the Jackson Lab to discuss symbols for mouse globin genes, and in the process produced standard designations for transgenic mice. Their guidelines were published in the *Mouse Newsletter* as part of a 90-page nomenclature update.[110] The transgenic designations suggested criteria for what a geneticist would count as a good mouse. There were multiple options for the exclusion and inclusion of extra information, but the basic structure was as follows, to take an example: Tg(12OCU*Hba*)N33. Tg stood for transgenic; the number in parentheses designated the

[107] Ciba Foundation 1977

[108] Anon. 1982c

[109] David Baltimore, interviewed by Susan Mehrtens on 12 November 1986, Jackson Lab Oral History Collection.

[110] International Committee on Standardised Genetic Nomenclature for Mice 1985. On the role of nomenclatures, see Bangham 2014.

chromosome into which the gene had integrated (here, chromosome 12); the three-letter code in capitals indicated the species that the gene came from (here, OCU for the rabbit, *Oryctolagus cuniculus*); the italicised or underlined three letters represented the standard gene abbreviation (*Hba* for alpha-globin). The numbers after the brackets designated the *Newsletter* code for the institution where the mouse was made (N for NIH), and the the final number referred to the serial number of the insertion at that institution.

The same document recognised the unwieldiness of this nomenclature by suggesting that full names be reserved for Materials and Methods sections. Despite this allowance, the Jackson nomenclature set itself against the established short names of existing transgenic mice, named locally after the gene of interest. The laboratories that produced transgenic mice were happy to maintain their own naming systems in the scientific press, adding to the credit contribution they received in collaborative papers and future applications. The suggested nomenclature was not picked up. In 1989, when the committee published its nomenclature recommendations alongside the list of known mouse strains and genes – over 800 pages long – transgenic designations remained tucked away as a few paragraphs in the section on globin genes, while inbred, congenic and recombinant strains received a chapter each.[111]

By contrast, existing accounts suggest that transgenic *Drosophila* were readily integrated into the practices and institutions of fly genetics.[112] While also used heavily in gene expression studies, fruit flies modified with P-elements could be readily used in large-scale mutagenesis screens and in mapping projects via 'chromosome walking' that allowed mapping of unknown elements adja-

[111] Lyon 1989. *Congenic* and *recombinant* here refer to different means of crossing inbred mice, with no relevance to gene transfer or recombinant DNA techniques, and this usage predates 1970. Congenic or coisogenic mice are made by crossing two inbred strains so that a locus from one strain is transferred to a different inbred line, becoming the only genetic difference with the normal animals from this recipient strain. A transgenic strain can also be congenic, although none were recognised in 1989. 'Recombinant inbred' strains contain unique, approximately equal proportions of genetic contributions from two progenitor inbred strains.

[112] Weber 2007; Rasmuson-Lestander 1995, Rubin & Lewis 2000

cent to the known marker on the chromosome.[113] Such approaches, however, were too laborious in mice, and chromosome walking was not achievable with any ease.[114]

A number of factors might explain the gap between mouse genetics community and transgenic researchers. First, most scientists working with transgenic mice were trained in molecular biology or mammalian development, and often had worked with different species before. Communication networks had few overlaps – few transgenic labs contributed to the *Mouse Newsletter*, and few genetic labs carried the molecular expertise. Finally, the experimental focus, costs and genetic uncertainties of making transgenic mice made Jackson-style practices of genetic purity that had been established for inbred lines a secondary concern.

On one level, genetic specificity was a selling point for transgenic mice. Accessing and editing individual genes and observing the effects in a well-studied mammal was a major attraction. The emphasis on bespoke production and designer genes – a term that had spread through news articles on genetic engineering since the mid-1970s – was not limited to transgenic animals. Monoclonal antibodies, another major biomedical innovation of the 1970s that attracted much more dramatic commercial interest promised to produce antibodies against any substance.[115] In her neo-Marxist analysis of biotechnology, Melinda Cooper has argued that genetic intervention replaced the industrial emphasis on mass production and reproduction of standardised life forms in biomedicine with a destandardisation project.[116] The tension between standards and specificity is also thematised in studies the of more recent uses of transgenic mice, in which the animals are described as simultaneously made-to-order and relying on established genetic standards.[117]

---

[113] 'Chromosome walking' relies on in situ hybridisation on giant *Drosophila* 'polytene' chromosomes in salivary gland cells, so that the cloned gene or a P element can be mapped with high resolution. The labelled part of the chromosome can then be cut with restriction enzyme, identified with Southern blotting, and the extra bits of the chromosome that have been restricted then used as the next probe further along the chromosome – hence 'walking'. A similar approach was initially used to compile sequences in the public Human Genome Project initiative.

[114] E. Wagner interview.

[115] Keating & Cambrosio 1995, de Chadarevian 2011, Marks forthcoming.

[116] Cooper 2008:15–50.

[117] Haraway 1997: 96–101, Birke, Arluke & Michael 2007: 49–51.

These studies tend to conflate the worlds of mouse genetics and transgenic work – an understandable state of affairs since the mid-1990s, but one that ignores the historicity of "transgenic models" and the work involved in the uneasy reconciliation of the supply and maintenance of transgenic and inbred mice that had taken place in the preceding decade.[118] The divisions between the different institutions can be linked to the style and scale of research. Where a new mouse mutant had been discovered, whether spontaneously or as part of a planned mutagenesis screen, for instance by exposing mice to radioisotopes or chemicals, it had first to be treated as a genuine novelty rather than as an anomaly to be ignored.[119] To produce a recognised inbred strain, it then had to be crossed to its siblings or parents for at least twenty generations, where ideally an individual mutation would be the clear source of variation in future crosses.

The focus of most inbred strains remained on a single gene or a locus, with extensive inbreeding designed to make the remaining background uniform. Yet the core aim of the process was to make these mice useful in future crosses for large-scale mapping projects, or, crucially, for research into diseases in which concerns about genetic purity could be black-boxed. By contrast, transgenic mice were designed with a specific construct in mind that was central to the immediate investigation. If a mouse showed the presence of the foreign gene, its most likely destiny was that it would be killed, its organs separated, homogenised and assessed for tissue-specific expression. In most experiments, which specific strain the modified embryos came from was unimportant. The vast majority of transgenic experiments relied on the first-generation ($F_{1)}$ hybrids between common inbred strains – a strategy that had been common in mouse embryology where hybrids were valued for their recalcitrance to manipulation (see Chapter 1 §2). Not all experiments would require further breeding, and many mice were discarded in the hope that they could be derived again.[120]

If there was an interest in establishing a new strain, the resulting transgenic "founder" mice were then bred to hybrids of similar crosses, allowing researchers to follow foreign genes through generations. The husbandry section of the Mouse Book dedicated four short paragraphs to the gen-

---

[118] As does Fiona Murray's analysis of sharing oncogene mice, Murray 2010.

[119] Gaudillière 2004: 193–201. On contemporary analysis of designating aberrant mouse as a novel mutant rather than an anomaly, see Davies 2013, esp. 139–145.

[120] Hogan, Costantini & Lacy 1986: 153–6.

eration of transgenic mouse lines, paying more attention to the pseudopregnant surrogates and sterile males required to make them receptive to embryo transfer after microinjection.[121] While noting that some experiments would require specific inbred strains if the genetic background was important for specific purposes, the handbook recommended using the F_1 hybrids in most cases and stressed the limitations of microinjection. It also had to warn against killing the founder mice to assess their gene expression until a line was securely established and several generations of offspring were able to show clear presence of foreign DNA.

There were also issues of cost and scale. My oral history interviews, researcher survey and analysis of transgenic papers in the late 1980s show that few mice had been sent off indiscriminately, in the manner of plasmids, but were mostly exchanged among collaborators with a view to shared authorship on resulting publications.[122] First, little could be gained by using others' strains that had already been published, as the key attraction of the technology was the ability to examine new molecular constructs. Second, production of transgenic mice was resource-intensive and uncertain. A 1989 report described microinjection as tedious and inefficient, estimating the cost of the instrumental set-up at $50,000, with an annual colony cost that could fall anywhere between $10,000 and $100,000, depending on size.[123] The timeframes required to establish new lines were often unaffordable, given the inefficiency of the procedure. Certain injected elements – for instance the growth hormone gene – reduced fertility. Despite the relative standardisation of pronuclear microinjection, its success rate remained low and was a continuous source of concern. To quote a review in *BioTechniques,*

> Typically, if 100 eggs are collected, approximately 85 will be suitable for injection, 60 will survive the injection, 6 of the implanted zygotes will be born and 1–2 of the mice will be transgenic. The inherent inefficiency of this process can be a source of frustration for the beginner.[124]

---

[121] Ibid.: 87–8. This was not expanded in the second edition, Hogan, et al. 1994: 123–4, even though a section on pathogen-free animal housing was added.

[122] This sharing pattern is consistent with the findings for oncomice in Murray 2010.

[123] Office of Technology Assessment 1989. In 1993, GenPharm, a California start-up that planned to supply transgenic and knock-out mice commercially, estimated costs to establishing a *single* new transgenic line at $ – National Research Council 1994.

[124] Camper 1987: 641–2.

With local difficulties in making transgenic mice, concerns more pressing than genetic purity occupied most workers. Yet despite these difficulties, the genetic status of mice was recruited to promote transgenic research. In 1989, the US Congress Office of Technology Assessment published a report on *Patenting Life* in its *New Developments in Biotechnology* series, largely in response to the OncoMouse patent granted the year before. In its review of transgenic technology, it noted that despite the limited number of labs involved in such work – it estimated several hundred worldwide – and the scarcity of experts with the right skills, mice remained a promising animal for genetic modification. It listed several advantages for the species: being a "warm-blooded mammal with many similarities to humans in genetics and physiology", small and inexpensive, with well-known genetics and physiology compared to other mammals and "available in a variety of different, well-characterized, genetically consistent lines for use in different types of studies".[125]

The invention of a different method for inserting or removing genes helped bridge the divisions between transgenic research and mouse supply. It relied on homologous recombination in embryonic stem cells that finally allowed the selection of cells in which foreign DNA was integrated at a known site, or where a wild-type gene was removed. The latter approach yielded 'knockout mice', the subject of the 2007 Nobel Prize, first reported in 1989.[126] They allowed the generation of strains in which specific genes could be removed and phenotypes observed, making the strains – rather than individual animals – more valuable to outsiders. These new techniques, alongside the expanding number of conventional transgenic strains, generated an interest in integrating molecular embryology with mouse genetics.

Another nomenclature case illustrates these changes, as a new effort to establish transgenic designations was undertaken by a committee at the Institute of Laboratory Animal Resources at the US National Resource Council. Chaired by Jon Gordon, the Committee on Transgenic Nomenclature published a report in 1992 that offered a minor update on the existing but underused guide-

[125] Office of Technology Assessment 1989: 95.

[126] Thompson, et al. 1989, Capecchi 2005, 2007

lines, but it had more impact as the research interests shifted since 1984. The report highlighted the need to organise the boutique operation, citing several reasons:

> *Duplication of effort*. Many different transgenic animals already exist (perhaps as many as 10,000 strains). Without a catalog, investigators might needlessly reproduce existing models.
>
> *Loss of valuable transgenic models*. Many transgenic models are not relevant to the research programs of the laboratories in which they are made [...] In the absence of an effective method to make their existence known, such models would probably be discarded, even though they might be extremely valuable to investigators in other laboratories.
>
> *Loss of information*. Many of the subtleties of gene regulation are discernible only by comparing the expression of closely related transgenes in different strains.[127]

In 1993, Jackson Lab created a resource and offered to supply researchers with transgenic and knockout mice, insisting that it would only accept mice with no intellectual property restrictions.[128] In the same year, the NIH gave a major grant to develop a database at Oak Ridge that then moved to Johns Hopkins. TBASE, as it was called, used the transgenic nomenclature in its computerised entries, making the management of cumbersome designations more straightforward.[129] These changes went a long way towards centralising supply and easing communication of transgenic animals, and set up the infrastructure that made these organisms much more routine in the 1990s.

Conclusion

From giant rodents to patented beings, transgenic mice created a new niche for research into the molecular genetics of higher animals. Their novelty and the dramatic results obtained in the early work attracted many biologists to the new technique. With multiple models of communication and sustained attention from molecular biologists, courses and handbooks allowed the technology

---

[127] Anon. 1992

[128] Anderson 1993, National Research Council 1994

[129] Woychik, et al. 1993

to be adopted in laboratories that could afford to venture into a new system. The difficulties associated with their production and considerable costs – financial, but also temporal – were a limiting factor that kept the work concentrated in under a thousand laboratories worldwide. The powerful and widely-circulating images of supermice promised a controlled way to study genes and make new kinds of animals. However, in practice multiple issues with controlling gene expression remained, especially in comparison with tissue culture and *Drosophila*. Yet these very problems were recruited to generate new questions about gene expression and attempts to control them made new knowledge about DNA elements, demonstrated in a whole animal.

The prominent research questions, low efficiency of the procedures, limited control over integrating genes and limited communication with the established sites of mouse genetics restricted the circulation of the new animals. Transgenic mice were both valuable and difficult to make and maintain, but their scientific worth was also more transient given the dominant scientific interests in the 1980s. The difference of scales between the local small laboratories and the big animal suppliers made widespread circulation and integration of transgenic animals into preexisting mouse networks problematic, and it was not a priority for either side. Much like in the case of gene mapping and sequencing, scaling up local laboratory practices required articulated agendas, resources, a critical mass of researchers and a new social order. With the expansion of transgenic enterprise – both academic and commercial, – conflicts over intellectual property, and new technologies such as knockout animals, transgenic research went through a series of standardisation attempts, centralisation of information and outsourced production. To this day, however, the craft-like procedures and local difficulties mean that making transgenic animals remains, to quote one researcher, a "boutique operation".[130]

[130] As described by Carlisle Lindel, transgenic researcher who learned the techniques as a postdoc at the Salk institute in 1986, currently with Transposagen Biopharmaceuticals. Email to author, 23 January 2014.

Conclusion: Transforming mice, transforming biology

This thesis has presented a multi-sited analysis of the development and early adoption of a hybrid set of techniques and a novel laboratory animal. Transgenic mice were born and made at a time of significant shifts in the way biological research was funded and regulated, especially in the USA. While the sparse historiography of 1980s biology has understandably focused on controversy, biotech enterprise and expansion of intellectual property in academic research, transgenic mice offer a less polarising case study that is better suited to highlight continuities as well as changes in this period.

Introducing isolated DNA into mice had been envisioned since the 1960s, but the strategy for such a feat moved between disciplines and fashions in biomedical research: somatic cell geneticists, mouse developmental biologists and animal virologists variously imagined using their pet systems to manipulate mouse genetics in a molecular vein. Attempts to introduce foreign genetic material into the germline predated recombinant DNA, as manifested most clearly by the Jaenisch-Mintz experiments of 1972–74. However, these various experiments alone were not sufficient to generate a large-scale programme of inserting isolated genes into mice, and researchers often pursued more pragmatic and immediate goals. New networks built around eukaryotic DNA and the circulation of experts, techniques and molecules made gene transfer into mouse embryos feasible. This agenda aligned the growing interest in higher animals as objects of molecular analysis with isolation and exchange of genes and control sequences, simplified dramatically by the recombinant DNA methods.

The multiple and rapid success of pronuclear microinjection conferred credibility on the new method. Moreover, the competition for priority pushed the groups to elaborate the new properties of these new animals and pursue avenues of communication to a variety of audiences. These interventions steered away from controversy, but raised the profile of the new animals, epitomised by the dramatic images of supermice. The subsequent adoption of transgenic mice relied on their high profile, as well as the diversity of collaboration strategies and interests of the pioneer groups. In the 1980s, they were first and foremost a tool to study molecular gene function in

a whole developing animal and as such new mice had to be produced constantly, with little demand to exchange strains. However, within the wider changes in the biomedical patronage, commercial ventures were increasingly creating new networks for research, outside of the established sites.

While genetics provided a crucial set of knowledge, tools, practices and infrastructure for transgenic mice, it did not play a direct role in their invention and early adoption. These mice were made possible by a new alliance between molecular biologists working with viruses and isolated genes, and mouse embryologists drawing on the prestige and promise carried by the cutting-edge field of genetic modification. The molecularisation of the mouse embryo happened as new practices centred around molecules took centre stage in the 1980s, linking diverse groups of scientists and interested observers through exchanging DNA and driving interest in molecular explanation, and they met some resistance.[1] Transgenic mice were not the sole or indeed most common way to apply molecular thinking and methods to the developing mouse embryo, but they were certainly the most symbolic and widely-publicised case in this transition.

The place of the mouse in biomedical researched transformed in this period. Domesticated as a genetic mammal useful for studies of cancer, the post-war uses of the species diverged. The practices of genetic purity that were to sustain mass-production of mice relied on the dramatic scaling up of mouse work in institutions such as Oak Ridge and Harwell. Such expansions of scale enabled previously-difficult mapping projects, expanded the infrastructures and focused the attention of key suppliers on maintaining the animals genetically standardised and free of disease. Yet these major projects, underwritten by the dramatic expansion in biomedical research in the USA and Europe, were challenged successfully by the outsiders who promoted different strategies for handling variation. In a new niche, the mouse embryo became an experimental object that combined techniques of mammalian embryology with genetic promise. By investing resources into culture techniques and building connections across disciplines, the growing community of mouse embryologists propelled their research object from a marginal and difficult embryo to a widely used system.

[1] On defining molecularisation in terms of circulation, practice and building new alliances, see de Chadarevian & Kamminga 1998: 1–2

This ability to attract new workers drew on the changing conceptualisation of embryology as developmental biology, and the molecular promise attached to the mouse. Existing mouse infrastructure eased transitions from other laboratory animals. In the 1960s, a substantial fraction of these questions relied on the promise of molecular analysis and intervention, as molecular biology was receiving greater funding and many practitioners were eager to expand the knowledge generated in bacteria and viruses to animals. The mouse became the only mammal suited for the job, and the challenges of embryonic manipulation and slow work were outweighed by its unique attractions in the menagerie of laboratory life – availability, comparatively low cost, genetic status and established connections to human biology. The existence of the quasi-embryonic teratocarcinoma cells were another crucial link to the molecular world in the 1970s.

These transitions made transgenic mice possible, and these modified animals invited researchers, politicians and journalists to imagine a world where genetic engineering could be done with mammals. Despite the claims to human and farm animal applications, transgenic mice were not immediately made as models of human disease. Most dramatically, transgenic mice conferred the credibility of a whole developing living animal on molecular analyses of gene function. This work relied on the dramatic attention they received from molecular biologists and other outsiders, as well as the ability to ease comparisons with other species and *in vitro* systems by referring to conserved molecular genes and the uniform techniques used for their analysis.

But long before they were made into models of human conditions, transgenic mice allowed science writers, journalists and policy makers to approach the future of genetic intervention in humans. Despite severe public discomfort with genetic manipulation, journalists covered these animals in neutral tones, marginalising the activist voices and using the new experiments to reflect on changes in biology, future therapies and enterprise. Used extensively in laboratories for over 80 years, mice themselves did not invoke a clear ethical threat and their origin in universities kept them away from the controversies that centred on privatising biological research until the OncoMouse patent.

Circulation and exchange were crucial in transforming the species. The simultaneous generation of transgenic mice through microinjection relied on extensive movement of individuals, tech-

niques and materials. While insertion of foreign genetic material into mouse embryos predated 1980, most notably in Rudolf Jaenisch's viral programme, it was the availability of isolated genes and the comfortable mastery of embryo manipulation that made the first gene transfer projects viable. I have shown that the power of recombinant DNA technology lay not only with the technical abilities it offered – these were continuous with earlier approaches to gene transfer – but in their portability, the focus on eukaryote biology and the new networks of sharing isolated genes. These networks existed within a moral economy that resembled older cases of exchange in laboratory animal biology in its emphasis on sharing and due attribution balanced against the motivations of maintaining priority. Unlike these older economies, however, these networks were rather decentralised, partly as a result of the dramatic expansion of biological research in the 1950s and 60s, but also because cloned genes were highly mobile and extremely attractive. The dramatic pace of recombinant research made spontaneous sharing the rule.

Another distinctive feature of recombinant DNA exchanges was that the troubled political climate emphasised containment of genetically modified organisms. Yet as I have shown, despite the common complaints about the stringency of the NIH guidelines and their real effects on career trajectories, isolated molecules could travel easily though the postal system or with individuals moving between laboratories. The effect of the guidelines was to limit the initial circulation of recombinant molecules to certain elite institutions, and while sharing was likely, accessing these networks relied on offers of collaboration or the fortuitous moves of a postdoc.

In analysing the circulation of materials and claims, I have emphasised the themes of proximity and distance. Being in the right place and combining expertise was a crucial precondition for extending novel molecular work to mouse embryos. Thus, Jaenisch's position at Salk brought him in contact with Paul Berg who would share some techniques. Mintz's and Ruddle's strategies to bring molecular and developmental biologists together in one laboratory paid off. At the same time, divisions of labour within these groups made this speculative work manageable and provided a safeguard for junior scholars in case they had failed. Other collaborations – Brinster and Palmiter, as well as Thomas Wagner and Hoppe – achieved similar results by keeping molecular and embryological work separate between sites, each playing to their strengths. Such divisions were

maintained by the former group and were productive in terms of making transgenics in the 1980s, with others emulating distant collaborations. However, as transgenic techniques were adopted widely through courses, a more synthetic approach took hold. That Frank Costantini and Elizabeth Lacy were involved in teaching at the Cold Spring Harbor course was largely a matter of proximity, with both of them based in New York City. However, their own experience in transitioning from molecular biology to mouse development no doubt contributed to the success of teaching diverse audiences all aspects of the process.

Between laboratories, the competition and isolated communication were productive, as rumours encouraged others to attempt similar work, while the credit for making a genetically modified mouse was up for grabs. But that the claims came from multiple sites within a very short period of time also generated credibility around the technique. That the news of the 1980 gene transfer was confirmed so rapidly at multiple sites, many of them eager to communicate to broad audiences, ended up crystallising the criteria around what counted as a transgenic mouse and allaying initial suspicions of artefact and uncertainties as to the fate of injected DNA.

Taking the circulation of knowledge and materials seriously delivers a more complete picture of the way science functioned on a middle scale in this period and beyond, because it can accounts for spatially and temporally distributed changes in ideas, practices and values while still tracking the local. The focus on circulation offers a specific explanation for the dynamics of a laboratory innovation, as transgenic mice were made as a desideratum, project, a potential result, a promising entity, a new word in the process of these interactions between multiple actors, technical traditions and audiences. Partially overlapping networks of communication and material exchange, relying on established infrastructures, drove the adoption of transgenic mice in multiple directions, and, despite considerable costs and experimental uncertainties, made them a fascinating and useful tool to generate and answer molecular questions about eukaryotic genes.

This heavy focus on the molecular gene, combined with the difficulties and costs of production and control of gene integration, imposed limits on the scale of transgenic work and sharing, and defined the place of the modified lines.. Despite commercial interest in animal gene transfer and subsequent expansion of transgenic enterprise, in the 1980s the vast majority of transgenic mice

were produced in university laboratories, and travelled through academic networks. They were a risky investment, especially when synthesising proteins in *E. coli* or making therapeutic and diagnostic products with monoclonal antibodies was a safer bet. Private initiatives did emerge, but the most successful ones revolved around sponsorship for established university sites. These arrangements offered an alternative sources of funding and communication networks, minor in scale but increasingly important in the 1990s and beyond.

Direct intervention into the germline made transgenic mice resemble *Drosophila* as a 'breeder reactor', where new mutants could be generated and published. However, if the explosion of the fruit fly strains at a single location in the Columbia Fly Room provided conditions for extensive crosses and mapping experiments, the diverse vectors of transgenic research, attention to specific cases of gene expression and the greater cost of maintaining strains made the stocks much more transient. This bespoke mode of production placed little value on maintaining all the mutants, many of them potential failures, and kept a distance between transgenic workers and the traditional sites of mouse supply. Since most research questions relied on the ability to make new mice with a gene of interest rather than obtain existing strains, the enthusiastic but troubled commercialisation attempts were premature.

The tension between local production – characteristic of both molecular and developmental biology laboratories – and expanding scales was typical in this period. Gene mapping initiatives encountered similar problems in converting local molecular projects into the global networks of sequencing consortia, where competition, credit and potential commercial spin-offs had to be negotiated against the common good. A new social order had to be established and enforced to enable large-scale collaboration and making comparable results.[2] Moreover, potential for monetising research were a tension that affected the circulation and imposed controls on sharing.

Beyond the patronage, the changes in mediation of new science circa 1980 were symptomatic. They were caused by these very hybrid university-industrial arrangements and the emerging biotech industry, as well as the expansion of science reporting. Biologists have been addressing wide

[2] Hilgartner 2004

audiences throughout the field's existence, and embryologists and molecular biologists were all too familiar with controversy before 1980. But the new incentives to communicate wide and far were considerable. Multi-directional communication could not only turn the work safe in an environment of severe mistrust towards genetic manipulation, as it did with the Yale gene transfer experiment or supermice. It was also a means to establish claims to priority and control the narratives and expectations about a novel technology. As science sections expanded and reports of genetic advances and failures became commonplace, the saturation of science stories in the media became dramatic. Media relations became a routine part of conducting high-stakes biological research.

Nowhere did this become clearer than in the next phase of the story. On 12 April 1988, the US Commissioner of Patents Donald Quigg held a press conference to announce the first US patent on an animal, Leder and Stewart's 'Harvard mouse'. While the decision followed the logic of *Diamond v. Chakrabarty*, the news caused a dramatic controversy.[3] Capitalising on its exclusive licence deal with Harvard, DuPont moved to commercialise the new intellectual property which it marketed as OncoMouse™ and supplied via Charles River, the commercial animal supplier, at $50 a mouse (compared to $5–10 per inbred animal).[4] After the controversy, the US Patent and Trademarks Office (USPTO) established a moratorium on issuing patents on further animals. The Ohio University application for the microinjection process was granted in 1989, but its lawyers had dropped the product claim, so it did not cover the resulting animals.[5] Three more patents on mice were granted in 1992, to Ohio University, Bay Area start up GenPharm and Cambridge University.

It remained unclear whether the Harvard patent extended to academic users, especially as university research was increasingly expected to generate commercial spin-offs. Most transgenic workers in a university setting ignored the intellectual property issues and continued producing their own animals.[6] Yet resistance was growing, driven not so much by the price-tag as DuPont's

---

[3] This decision was also likely in the light of the 1987 USPTO deliberations over *Ex parte Allen*, when the Office decided a patent could have in principle been granted to a polyploid oyster had the application met all the requirements. Kevles 2002a, 2002b. See also Haraway 1997: 79–118, Fuller 2008, Robins 2008, Murray 2010.

[4] National Research Council 1994: 23, Murray 2010: 361

[5] US Patent 4,873,191 wrapper, obtained from the USPTO.

[6] Ibid.

prohibitive policy on breeding the animals, which required approval for mouse exchange and an annual update on all published and unpublished research. The small scale of the potential market for individual transgenic animals was another issue. The hope to mass-produce OncoMice as carcinogen test animals, with the claim that they could offer greater sensitivity would did not justify the price tag and restrictions; established mouse strains were reliable, cheap and good enough for the task. Furthermore, the patent's claims and DuPont advertising did not address the disanalogy between having select oncogenes activated in every cell, and clinical carcinogenesis. Similarly, despite receiving the patent on pronuclear microinjection in 1989, Ohio University made much larger profits from Hybriwix™, a rapid DNA isolation and testing method patented in 1989 by Diagnostic Hybrids, another spin-off with Thomas Wagner as co-founder.[7]

Products of individual collaborations and sustained labour, transgenic mice were still presented as first and foremost tools to study gene regulation.[8] With the need to introduce new genes for future work, establishing existing models required larger scales and many more converts, as well as alliances with clinicians. The costs required to develop and maintain new strains were not justified by the small academic market. In response to another patent granted on a knockout mouse in 1992, and similarly strict conditions of distributions, a group at the Cold Spring Harbour course staged a rebellion that led to a major National Academy of Sciences meeting.[9] While no simple solutions were found, the resulting discussion highlighted commercial limitations on transgenic research, to the extent that the NIH discouraged mouse patent applications from its grantees except in the most promising cases. Storage, line maintenance and standards were the key issues, and the NIH was urged to set up a facility to exchange transgenics.

The issues of infrastructures were a pressing concern. In 1991, David Baltimore penned the editorial for the first issue of *SEARCH*, the Rockefeller University's short-lived magazine dedicated to biomedical research.[10] He declared that the 1990s would be 'The Decade of the Mouse'. Recruiting

---

[7] T. Wagner interview; Holtzman unrecorded interview.

[8] National Research Council 1994: 16

[9] Anderson 1993, National Research Council 1994

[10] Baltimore 1991. Shortly after the editorial was published, Baltimore was forced to resign his post at Rockefeller after a protracted investigation over alleged fraud by a faculty member at the Whitehead Institute turned sour. The allegations revolved around immunoglobulin research that partially relied on transgenic mice. See Kevles 1998.

the "new experimental capabilities" in molecular manipulation, Baltimore argued that the "lowly mouse, a pest to many, is man's and woman's best surrogate. Although so different from us – four-footed, not very intelligent, a life span of two or three years, a gnawing rodent," the animal was now "the ideal tool for investigating the functions of all mammalian genes, whether or not they have been associated previously with disease". The enthusiastic conclusion called to improve animal supply and infrastructure for the glorious future of American science: "Fully realizing the potential of The Decade of the Mouse will test both our institutional flexibility and America's commitment to rapid progress in health research".

The continuities and changes during the 'Decade of the Mouse' require further critical examination. The focus on the alliances between academic, state and commercial institutions would help expand the historical understanding of the conditions familiar to today's researchers. Synchronising mouse genetics and transgenic work, the role of knockout mice and the establishment and marketing of disease models are all part of this story. The role of animal agriculture is another important direction for future research. Farm animal modification was the first trajectory for applying transgenesis globally, and a lot more controversial than mouse work. Farmer associations and property traditions were a key part of the debates and legislation around patenting life. Furthermore, agricultural workers provided some of the crucial technologies in dealing with the embryos, shipping and freezing them. Looking at crops and horticulture has adjusted our view of the history of genetics, and the plant GMO debates were the loudest and most lasting.[11] Yet despite some historical attention,[12] the animal farm remains a gap in our understanding of the life sciences in the twentieth century, a missing area to be taken seriously alongside the laboratory and the clinic.

[11] Fitzgerald 1990, Palladino 1993, Bauer & Gaskell 2002, Kloppenburg 2004, Charnley & Radick 2013, Curry 2013, 2014.

[12] See e. g. Clarke 1998, 2007; Franklin 2007a, 2007b; Wilmot 2007; Woods 2004, 2007, 2012.

Sources

Oral history interviews

By the author:

Recorded Interviews:

Frank Costantini and Elizabeth Lacy, 13 December 2011, New York City.

David Dickson, 7 September 2011, London.

Jon Gordon, 10 December 2011, New York City.

Rudolf Jaenisch, 29 January 2013, Cambridge, MA.

Richard Palmiter, 8 June 2012, Seattle.

Frank Ruddle, 8 December 2011, New Haven, CT.

George Scangos, 9 May 2012, Cambridge, MA.

Harold Schmeck Jr., 6 December 2011, phone interview.

Tim Stewart, 31 May 2012, San Francisco.

Erwin Wagner, 22 February 2013, Madrid.

Thomas Wagner, 25 January 2013, Greenville, SC.

Unrecorded interviews:

Brigid Hogan, 23 December 2013, Skype interview.

Steven Holtzman, 11 February 2013, phone interview.

Azim Surani, 29 November 2012, Cambridge, UK.

Keith Willison, 12 September 2013, London.

Alla Madich, 1 February 2014, Cambridge, UK.

By other interviewers:

David Baltimore, interviewed by Susan Mehrtens on 14 December 1986. Transcript obtained from the Joan Staats Library, Jackson Laboratory, Bar Harbor, ME.

Jim Dahlberg, interviewed on 4 June 2001, Cold Spring Harbor Oral History Collection, available at library.cshl.edu/oralhistory/speaker/jim-dahlberg.

Chris Graham, interviewed by Martin Johnson and Sarah Franklin, 16 February 2012, C1324/02, British Library.

Brigid Hogan, interviewed by Johnson & Franklin, 24 July 2007, C1324/09, British Library.

Mary Lyon, interviewed by Johnson & Franklin, 20 February 2007, C1324/04, British Library.

Archives

Full references to specific items are given in citations.

British Library, London.

Anne McLaren papers, Add. 83830–83981.

Cold Spring Harbor Laboratory Digital Archives

Correspondence, James D. Watson Collection, JDW/2/2. Available online at http://libgallery.cshl.edu/collections/show/3.

Glasgow University Archive.

Papers of Malcolm Feguson-Smith, UGS 188. Available online through the Wellcome Library, wellcomelibrary.org/using-the-library/subject-guides/genetics/makers-of-modern-genetics/digitised-archives/malcolm-ferguson-smith.

Jackson Laboratory Archives, Bar Harbor, ME

Papers of Barbara Sanford, Director, 1981-87, Box 37, RG1.

National Archives, Kew, London, UK

Papers relating to the Developmental Biology Unit, MRC papers, FD 12/1198–99.

National Library of Medicine, NIH, Bethesda, MA

W. French Anderson papers, 101291466.

Paul Berg papers, 101584580. Available online at profiles.nlm.nih.gov/ps/retrieve/Collection/CID/CD.

Joshua Lederberg papers, 101584906. Available online at profiles.nlm.nih.gov/ps/retrieve/Collection/CID/BB.

Ohio University Archives, Athens, OH

Charles J. Ping papers, Office of the President Record, Series 1, UA00001.

Alan Geiger papers, UA00272.

Peg Black research on Charles Ping, UA00413.

Othmer Library, Chemical Heritage Foundation, Philadelphia

Records of the Gordon Research Conferences, 2001.016.001.

Rockefeller Archives, Tarrytown, NY.

Elaine Diacumakos papers, RU450.

Wellcome Library Archives

Francis Crick papers, PP/CRI. Available online at wellcomelibrary.org/using-the-library/subject-guides/genetics/makers-of-modern-genetics/digitised-archives/hans-gruneberg.

Hans Grüneberg papers, PP/GRU. Available online at wellcomelibrary.org/using-the-library/subject-guides/genetics/makers-of-modern-genetics/digitised-archives/francis-crick.

University of Pennsylvania Archives, Philadelphia

University Relations News and Public Affairs Records, Biographical Files, UPF 8.5B.

Yale University Archives, New Haven, CT

News clippings and articles about Yale University, RU64.

Audio-Visual Materials

The Boys from Brazil. DVD. Directed by Franklin J. Schaffner. 1978; London: ITV Studios Home Entertainment, 2003.

"Brave New Babies", *Horizon,* BBC2. First aired 15 November 1982. Accessed through the British Film Institute

"The Cline Affair", *Horizon*, BBC2. First aired 15 February 1982. Accessed through the British Film Institute

Evening News, CBS, 4 September 1980 and 16 December 1982. Accessed through the Vanderbilt Television News Archive.

Evening News, NBC, 11 September 1980. Accessed through the Vanderbilt Television News Archive.

Tonight Show Starring Johnny Carson, NBC, 16 December 1982. Courtesy of the Carson Entertainment Group.

Patents

Leder, Philip and Timothy A. Stewart. 1988. Transgenic non-human mammals. US Patent 4,736,866, filed 22 June 1984 and issued 12 April 1988.

Wagner, Thomas and Peter Hoppe. 1989. Genetic transformation of zygotes. US Patent 4,873,191, filed 12 June 1981 and issued 10 October 1989.

———. 2005. Transgenic mammals. US Patent 6,872,868, filed 24 May 1995 and issued 29 March 2005.

Bibliography

Abir-Am, Pnina G. 1985. Themes, Genres and Orders of Legitimation in the Consolidation of New Scientific Disciplines: Deconstructing the Historiography of Molecular Biology. *History of science* 23 (1):73–117.

———. 1999. The First American and French Commemorations in Molecular Biology: From Collective Memory to Comparative History. *Osiris* 14:324–72.

Agricultural and Food Research Council. 1986. *Annual Report, 1985–86*. Milton Keynes: Powage Press.

Alberts, Bruce, Dennis Bray, Julian Lewis, Martin Raff, Keith Roberts, and James D. Watson. 1983. *Molecular Biology of the Cell*. New York & London: Garland.

Alexandre, H. 2001. A History of Mammalian Embryological Research. *International Journal of Developmental Biology* 45 (3):457–67.

Anderson, Carl W., ed. 1978. *Genetic Interaction and Gene Transfer*. Brookhaven Symposia in Biology 29. Upton, NY: Brookhaven National Laboratory.

Anderson, Christopher. 1993. Researchers Win Decision on Knockout Mouse Pricing. *Science* 260 (5104):23–4.

Anderson, W. French, Lillian Killos, Linda Sanders-Haigh, Peter J. Kretschmer, and Elaine G. Diacumakos. 1980. Replication and Expression of Thymidine Kinase and Human Globin Genes Microinjected into Mouse Fibroblasts. *Proceedings of the National Academy of Sciences of the USA* 77 (9):5399–403.

Anderson, W. French, and Elaine G. Diacumakos. 1981. Genetic Engineering in Mammalian Cells. *Scientific American* 245 (1):106–21.

Andreopoulos, Spyros. 1980. Gene Cloning by Press Conference. *New England Journal of Medicine* 302 (13):743-6.

Angier, Natalie. 1988. *Natural Obsessions: The Search for the Oncogene*. Boston: Houghton Mifflin.

Ankeny, Rachel A. 2000. Fashioning Descriptive Models in Biology: Of Worms and Wiring Diagrams. *Philosophy of Science* 67:S260–S272.

———. 2001. Model Organisms as Models: Understanding the 'Lingua Franca' of the Human Genome Project. *Philosophy of Science* 68 (3):S251–S261.

Ankeny, Rachel A., and Sabina Leonelli. 2011. What's so Special about Model Organisms? *Studies In History and Philosophy of Science* 42 (2):313–23.

Anon. 1948. Growth Hormone: New Method for Extracting Pituitary-Gland Secretion Makes it Possible to Build Muscle and Bone in Humans. *Life*, 11 October.

Anon. 1978b. Guide to Authors. *Nature* 275 (5676):iii.

Anon. 1979. On the Way to a Clone. *Science News* 116 (4):68.

Anon. 1980a. Editorial: Scares About Genetic Manipulation. *Nature* 287:96.

Anon. 1980b. Science, Technology and the Press: Must the "Age of Innocence" End? *Technology Review* 82 (March/April):46–56.

Anon. 1982a. Editorial: Bring Back the Shmoo. *New York Times*, 22 December, A22.

Anon. 1982b. Editorial: The Rules for Reshaping Life. *New York Times*, 29 December, A18.

Anon. 1982c. Embryo Freezing: Preserving Vital Genetic Resources for the Future. *JAX: The Jackson Laboratory* 28 (4):3.

Anon. 1982d. The Livestock Industry's Genetic Revolution. *Business Week*, 21 June, 124–32.

Anon. 1982e. Mice Double in Size as Scientists Insert a New Growth Gene. *Wall Street Journal*, 16 December, 20.

Anon. 1982f. Mighty Mice: Gene Transfers Create Giants. *TIME*, 27 December, 53.

Anon. 1982g. US Team Produces Giant Mice. *The Times*, 16 December, 2.

Anon. 1992. Standardized Nomenclature for Transgenic Animals. *ILAR Journal* 34 (4).

Anon. 2013. Our People: In Memoriam: Frank Ruddle, Pioneer in Human Gene Mapping and Former ASCB President. American Society for Cell Biology. Available at http://www.ascb.org/index.php?option=com_content&view=article&id=1029:our-people-in-memoriam-frank-ruddle-pioneer-in-human-gene-mapping-and-former-ascb-president&catid=121:news-a-information&Itemid=402. Accessed on 11 October 2013.

Appel, Toby A. 2000. *Shaping Biology: The National Science Foundation and American Biological Research, 1945–1975*. Baltimore & London: Johns Hopkins University Press.

Ashley, Mike. 2007. *Gateways to Forever: The Story of the Science-Fiction Magazines from 1970 to 1980*. Liverpool: Liverpool University Press.

Asimov, Isaac. 1980. What's Fueling the Popular Science Explosion? *Saturday Review*, August, 22–6.

Assmus, Alexi. 1993. The Creation of Postdoctoral Fellowships and the Siting of American Scientific Research. *Minerva* 31 (2):151–83.

Austin, Colin R. 1961. *The Mammalian Egg*. Oxford: Blackwell.

Baltimore, David. 1974. Tumor Viruses: 1974. *Cold Spring Harbor Symposia on Quantitative Biology* 39:1187-200.

———. 1991. The Decade of the Mouse. *SEARCH: The Rockefeller University Magazine* 1 (1):1.

Bangham, Jenny. 2013. *Blood Groups and the Rise of Human Genetics in Mid-Twentieth Century Britain*, PhD Thesis, Department of History and Philosophy of Science, University of Cambridge.

———. 2014. Writing, Printing, Speaking: Rhesus Blood-Group Genetics and Nomenclatures in the Mid-Twentieth Century. *British Journal for the History of Science* 47 (2):335–61.

Baskin, Yvonne. 1982. Spare Genes. *OMNI*, March, 52–4, 109–14.

Bauer, Martin W. 2012. Public Attention to Science 1820–2010 – a 'Longue Durée' Picture. In *The Sciences' Media Connection – Public Communication and Its Repercussions*, edited by S. Rödder, M. Franzen and P. Weingart. Houten: Springer.

Bauer, Martin W., and George Gaskell, eds. 2002. *Biotechnology: The Making of a Global Controversy*. Cambridge: Cambridge University Press.

Beardsley, Tim. 1984. Genetic Manipulation: Rifkin Strikes against Gene Transfer Experiments. *Nature* 311 (5986):495.

Begley, Sharon, and John Carey. 1980. Of Baby Mice and DNA. *Newsweek*, 15 September, 27.

Bennet, William. 1979. Science Goes Glossy. *The Sciences*, September.

Berg, Paul, and Janet E. Mertz. 2010. Personal Reflections on the Origins and Emergence of Recombinant DNA Technology. *Genetics* 184 (1):9–17.

Biagioli, Mario. 2006. *Galileo's Instruments of Credit: Telescopes, Images, Secrecy*. Chicago & London: University of Chicago Press.

Biggers, John D. 1987. Pioneering Mammalian Embryo Culture. In *Preimplantation Mammalian Embryo*, edited by B. D. Bavister. New York: Plenum

———. 1998. Reflections on the Culture of the Preimplantation Embryo. *International Journal of Developmental Biology* 42 (7):879–84.

———. 2001. Research in the Canine Block. *International Journal of Developmental Biology* 45 (3):469–76.

Biggers, John D., and P. J. Claringbold. 1954. Why Use Inbred Lines? *Nature* 174 (4430):596–7.

Biggers, John D., and Anne McLaren. 1958. "Test Tube" Animals. *Discovery*, October, 423–6.

Billington, W. D. 1971. Review of *Methods in Experimental Embryology of the Mouse* by Keen A. Rafferty. *The Quarterly Review of Biology* 46 (1):81.

Birke, Lynda. 2012. Animal Bodies in the Production of Scientific Knowledge: Modelling Medicine. *Body & Society* 18 (3/4):156–78.

Birke, Linda, Arnold Arluke, and Mike Michael. 2007. *The Sacrifice: How Scientific Experiments Transform Animals and People*. West Lafayette, IN: Purdue University Press.

Boddé, Tineke. 1982. Biologists and Journalists: A Look at Science Reporting. *BioScience* 32 (3):173–5.

Bonneuil, Christophe. 2008. Producing Identity, Industrializing Purity: Elements for a Cultural History of Genetics. In *A Cultural History of Heredity Iv: Heredity in the Century of the Gene. Preprint 343*, edited by H.-J. Rheinberger, S. Müller-Wille and J. Dupré. Berlin: Max-Plank-Institut für Wissenschaftgeschichte.

Bourgeois, Suzanne. 2013. *Genesis of the Salk Institute: The Epic of Its Founders*. Berkeley: University of California Press.

Brandt, Christina. 2012. Stem Cells, Reversibility and Reprogramming: Historical Perspectives. In *Differing Routes to Stem Cell Research: Germany and Italy*, edited by R. G. Mazzolini and H.-J. Rheinberger. Berlin: Duncker & Humblot.

———. 2013. Hybrid Times: Theses on the Temporalities of Cloning. *History and Philosophy of the Life Sciences* 35 (1):75–81.

Brannigan, Augustine. 1981. *The Social Basis of Scientific Discoveries*. Cambridge: Cambridge University Press.

Brattain, Michelle. 2007. Race, Racism, and Antiracism: UNESCO and the Politics of Presenting Science to the Postwar Public. *The American Historical Review* 112 (5):1386–413.

Brauckmann, Sabine. 2006. A Network of Tissue Cultures and Cells: The American Society of Cell Biology. *Archives Internationales d'Histoire des Sciences* 56:295–308.

Brenner, Sydney. 1979. Introduction to *Human Genetics: Possibilities and Realities.* Ciba Foundation Symposium 66, edited by R. Porter and M. O'Connor. Amsterdam: Excerpta Medica.

Brinster, Ralph L. 1964. *Studies on the Development of Mouse Embryos* in Vitro, PhD Thesis, School of Veterinary Sciences, University of Pennsylvania.

———. 1974. The Effect of Cells Transferred into the Mouse Blastocyst on Subsequent Development. *The Journal of Experimental Medicine* 140 (4):1049–56.

———. 2013. Dr Brinster's Presentation for the Brinster Symposium. YouTube video, posted by Penn Vet on 18 July 2013. http://www.youtube.com/watch?v=JjJcWaxXHGA. Accessed on 25 September 2013.

Brinster, Ralph L., and Juan Arechaga. 1998. Embryo Culture, Stem Cells and Experimental Modification of the Embryonic Genome: An Interview with Ralph Brinster. *International Journal of Developmental Biology* 42 (7):861–78.

Brinster, Ralph L., Howard Y. Chen, Albee Messing, Terry van Dyke, Arnold J. Levine, and Richard D. Palmiter. 1984. Transgenic Mice Harboring SV40 T-Antigen Genes Develop Characteristic Brain Tumors. *Cell* 37 (2):367–79.

Brinster, Ralph L., Howard Y. Chen, and Myrna E. Trumbauer. 1981. Mouse Oocytes Transcribe Injected Xenopus 5S RNA Gene. *Science* 211 (4480):396–8.

Brinster, Ralph L., Howard Y. Chen, Myrna E. Trumbauer, and Mary R. Avarbock. 1980. Translation of Globin Messenger RNA by the Mouse Ovum. *Nature* 283 (5746):499–501.

Brinster, Ralph L., Howard Y. Chen, Myrna Trumbauer, Allen W. Senear, Raphael Warren, and Richard D. Palmiter. 1981. Somatic Expression of Herpes Thymidine Kinase in Mice Following Injection of a Fusion Gene into Eggs. *Cell* 27 (1):223–31.

Brinster, Ralph L., and Richard D. Palmiter. 1982. Induction of Foreign Genes in Animals. *Trends in Biochemical Sciences* 7 (12):438–40.

———. 1984. The Transfer of New Genes into Mice. In *Transfer and Expression of Eukaryotic Genes*, edited by H. S. Greenberg and H. J. Vogel. London: Academic Press.

Britten, Roy J., and Eric H. Davidson. 1969. Gene Regulation for Higher Cells: A Theory. *Science* 165 (3891):349–57.

Broad, William J. 1978. Librarian Turned Entrepreneur Makes Millions Off Mere Footnotes. *Science* 202 (4370):853-7.

Broad, William, and Nicholas Wade. 1982. *Betrayers of the Truth: Fraud and Deceit in the Halls of Science*. New York: Simon & Schuster.

Brown, Donald D. 1993. Developmental Biology Has Come of Age. In *Evolutionary Conservation of Developmental Mechanisms*, edited by A. C. Spradling. New York: Wiley-Liss.

Bucchi, Massimiano. 1998. *Science and the Media: Alternative Routes in Scientific Communication*. London & New York: Routledge.

Bud, Robert. 1993. *The Uses of Life: A History of Biotechnology*. Cambridge: Cambridge University Press.

———. 2009. History of Biotechnology. In *Cambridge History of Science, Vol. 6: The Modern Biological and Earth Sciences*, edited by P. J. Bowler and J. Pickstone. Cambridge: Cambridge University Press.

———. 2010. From Applied Microbiology to Biotechnology: Science, Medicine and Industrial Renewal. *Notes and Records of the Royal Society* 64 (Suppl. 1):S17–S29.

Burian, Richard M., and Denis Thieffry. 2000. Introduction to the Special Issue "From Embryology to Developmental Biology". *History and Philosophy of the Life Sciences* 22 (3):313–23.

Burke, Bob, and Barry Epperson. 2003. *W. French Anderson: Father of Gene Therapy*. Oklahoma City: Oklahoma Heritage Accociation.

Bürki, Kurt, and Axel Ullrich. 1982. Transplantation of the Human Insulin Gene into Fertilized Mouse Eggs. *EMBO Journal* 1 (1):127–31.

Camper, Sally A. 1987. Research Applications of Transgenic Mice. *BioTechniques* 5 (7):638–50.

Capecchi, Mario R. 2005. Gene Targeting in Mice: Functional Analysis of the Mammalian Genome for the Twenty-First Century. *Nature Reviews. Genetics* 6 (6):507–12.

———. 2007. Nobel Lecture: Gene Targetting, 1977–Present. Available at http://www.nobelprize.org/nobel_prizes/medicine/laureates/2007/capecchi_lecture.pdf. Accessed on 23 January 2013.

Chada, Kiran, Jeanne Magram, Kathryn Raphael, Glenn Radice, Elizabeth Lacy, and Frank Costantini. 1985. Specific Expression of a Foreign Beta-Globin Gene in Erythroid Cells of Transgenic Mice. *Nature* 314 (6009):377–80.

Chambon, Pierre. 1978. Summary: The Molecular Biology of the Eukaryotic Genome Is Coming of Age. *Cold Spring Harbor Symposia on Quantitative Biology* 42: 1209–30.

Charnley, Berris, and Gregory Radick. 2013. Intellectual Property, Plant Breeding and the Making of Mendelian Genetics. *Studies in History and Philosophy of Science* 44 (2):222–33.

Chasis, Herbert. 1964. Preface to the Meeting on the Role of Genes in Development. *Journal of Experimental Zoology* 157 (1):vii.

Ciba Foundation. 1977. *The Freezing of Mammalian Embryos.* Ciba Foundation Symposium 52. Amstrerdam: Elsevier.

Clarke, Adele E. 1998. *Disciplining Reproduction: Modernity, American Life Sciences and "the Problems of Sex"*. Berkeley & Los Angeles: University of California Press.

Clarke, Adele E. 2007. Reflections on the Reproductive Sciences in Agriculture in the UK and US, ca. 1900–2000+. *Studies in History and Philosophy of Biological and Biomedical Sciences* 38 (2):316–39.

Clause, Bonnie T. 1993. The Wistar Rat as a Right Choice: Establishing Mammalian Standards and the Ideal of a Standardized Mammal. *Journal of the History of Biology* 26 (2):329–49.

Cohen, Bernard L. 2000. Guido Pontecorvo ("Ponte"), 1907–1999. *Genetics* 154 (2):497–501.

Cohn, Victor. 1981. Biologists Report Transfer of Gene from Rabbit to Mouse to Offspring. *Washington Post*, 8 September, A12.

———. 1982. Day of the 'Super-Mice'. *Washington Post*, 16 December, A1, A7.

Colaianni, Alessandra, and Robert Cook-Deegan. 2009. Columbia University's Axel Patents: Technology Transfer and Implications for the Bayh-Dole Act. *Milbank Quarterly* 87 (3):683-715.

Collins, Harry. 1985. *Changing Order: Replication and Induction in Scientific Practice*. Chicago & London: University of Chicago Press.

Consolazio, Willam V., and Margaret C. Green. 1956. Federal Support of Research in the Life Sciences. *Science* 124 (3221):522–6.

Cooper, Melinda. 2008. *Life as Surplus: Biotechnology and Capitalism in the Neoliberal Era*. Seattle: University of Washington Press.

Corvini, Margaret. 1979. Restrictions Governing DNA Research Eased. *Yale Daily News*, 5 April.

Costantini, Franklin, and Elizabeth Lacy. 1981. Introduction of a Rabbit Beta-Globin Gene into the Mouse Germ Line. *Nature* 294 (5836):92–4.

Cowen, Robert C. 1982. Experiment on Mice Highlights Concern over Genetic Engineering. *Christian Science Monitor*, 20 December.

Cozzens, Susan E. 1989. *Social Control and Multiple Discovery in Science: The Opiate Receptor Case*. Albany, NY: State University of New York Press.

Creager, Angela N. H. 2013. *Life Atomic: A History of Radioisotopes in Science and Medicine*. Chicago & London: University of Chicago Press.

Crowe, Nathan. 2014. Cancer, Conflict, and the Development of Nuclear Transplantation Techniques. *Journal of the History of Biology* 47 (1):63–105.

Crowe, Nathan, Michael R. Dietrich, Beverly S. Alomepe, Amelia F. Antrim, Bay Lauris ByrneSim, and Yi He. Manuscript under review. The Rise of Developmental Biology: Research Diversification and Discipline Formation.

Curry, Helen Anne. 2013. Industrial Evolution: Mechanical and Biological Innovation at the General Electric Research Laboratory. *Technology and Culture* 54 (4):746–81.

———. 2014. From Garden Biotech to Garage Biotech: Amateur Experimental Biology in Historical Perspective. *British Journal for the History of Science* 47 (3):539–65.

Daston, Lorraine. 1995. The Moral Economy of Science. *Osiris* 10:2–24.

Daston, Lorraine, and Gregg Mitman, eds. 2005. *Thinking with Animals: New Perspectives on Anthropomorphism*. New York: Columbia University Press.

Davidson, Eric H. 1968. *Gene Action in Early Development*. New York: Academic Press.

Davies, Gail. 2012. What Is a Humanized Mouse? Remaking the Species and Spaces of Translational Medicine. *Body & Society* 18 (3/4):126–55.

———. 2013. Mobilizing Experimental Life: Spaces of Becoming with Mutant Mice. *Theory, Culture & Society* 30 (7-8):129-53.

Davies, Jamie. 2007. Developmental Biologists' Choice of Subjects Approximates to a Power Law, with No Evidence for the Existence of a Special Group of 'Model Organisms'. *BMC Developmental Biology* 7 (1):40.

de Chadarevian, Soraya. 1998. Of Worms and Programmes: *Caenorhabditis elegans* and the Study of Development. *Studies in History and Philosophy of Biological and Biomedical Sciences* 29 (1):81–105.

———. 2000. Mapping Development, or How Molecular Is Molecular Biology? *History and Philosophy of the Life Sciences* 22 (3):381–96.

———. 2002. *Designs for Life: Molecular Biology after World War II*: Cambridge University Press.

———. 2003. Portrait of a Discovery: Watson, Crick, and the Double Helix. *Isis* 94 (1):90–105.

———. 2006. Mice and the Reactor: The "Genetics Experiment" in 1950s Britain. *Journal of the History of Biology* 39 (4):707–35.

———. 2011. The Making of an Entrepreneurial Science: Biotechnology in Britain, 1975–1995. *Isis* 102 (4):601–33.

de Chadarevian, Soraya, and Harmke Kamminga. 1998. Introduction to *Molecularizing Biology and Medicine: New Pratices and Alliances, 1910s–1970s.*, edited by S. de Chadarevian and H. Kamminga. Amsterdam: Harwood.

De Robertis, Edward M., Ronald A. Laskey, and John B. Gurdon. 1977. Injected Living Cells as a Biochemical Test Tube. *Trends in Biochemical Sciences* 2 (11):N250–3.

DeBakey, Louis. 1976. *The Scientific Journal: Editorial Policies and Practices; Guidelines for Editors, Reviewers, and Authors*. St. Louis: C. V. Mosby.

Dembart, Lee. 1980. Scientists Transfer Virus DNA to Mice. *Los Angeles Times*, 9 September.

Dewey, Michael J., David W. Martin, Gail R. Martin, and Beatrice Mintz. 1977. Mosaic Mice with Teratocarcinoma-Derived Mutant Cells Deficient in Hypoxanthine Phosphoribosyltransferase. *Proceedings of the National Academy of Sciences of the USA* 74 (12):5564–8.

Diacumakos, Elaine G. 1973. Methods for Micromanipulation of Human Somatic Cells in Culture. *Methods in Cell Biology*, 7: 288–311.

——— 1979. Introduction of Macromolecules into Viable Mammalian Cells by Precise Physical Microinjection. In *Introduction of Macromolecules into Viable Mammalian Cells*, edited by R. Baserga, C. Croce and G. Rovero. New York: Alan Liss.

Diacumakos, Elaine G., Scott Holland, and Pauline Pecora. 1970. A Microsurgical Methodology for Human Cells in Vitro: Evolution and Applications. *Proceedings of the National Academy of Sciences of the USA* 65 (4):911–8.

Dickson, David. 1988. *The New Politics of Science*. Chicago & London: University of Chicago Press.

Dietrich, Michael R., and Brandi H. Tambasco. 2007. Beyond the Boss and the Boys: Women and the Division of Labor in Drosophila Genetics in the United States, 1934–1970. *Journal of the History of Biology* 40 (3):509–28.

Dunwoody, Sharon. 1986. The Scientist as Source. In *Scientists and Journalists: Reporting Science as News*, edited by S. M. Friedman, S. Dunwoody and C. L. Rogers. New York: Free Press.

Dupuis, Mark. 1980. Yale Researchers Hope Experiments Lead to Cure of Genetic Disorders. *Norwalk, CT, Hour*, 5 September, 3.

DuShane, Graham. 1959. New Garb. *Science* 130 (3379):829.

Echols, Harrison. 2001. *Operators and Promoters: The Story of Molecular Biology and Its Creators*. Berkeley: University of California Press.

Edelsen, Edward. 1980. Gene-Splicing: Will It Create a Monster? *New York Daily News*, 7 September.

Edgerton, David. 2007. *The Shock of the Old: Technology and Global History since 1900*. London: Profile Books.

———. 2010. Innovation, Technology, or History: What Is the Historiography of Technology About? *Technology and Culture* 51 (3):680–97.

Edwards, Robert G. 1968. Explosive Biology. *Nature* 218 (5145):987.

Edwards, Robert, and Patrick Steptoe. 1980. *A Matter of Life: The Story of a Medical Breakthrough.* London: Hutchinson.

El-Badry, Hamed M. 1963. *Micromanipulators and Micromanipulation*. New York: Academic Press.

Emery, Michael , Edwin Emery, and Nancy L. Roberts. 2000. *The Press and America: An Interpretive History of the Mass Media*. 9th ed. Boston: Allyn and Bacon.

Emtage, J. S. 1985. DNA Makes Protein Makes Money. *Nature* 317 (6033):185-6.

Epstein, Steven. 1998. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley & Los Angeles: University of California Press.

Evans, Martin J., and M. H. Kaufman. 1981. Establishment in Culture of Pluripotential Cells from Mouse Embryos. *Nature* 292 (5819):154–6.

Evans, Michael J., and Jerry B. Lingrel. 1969. Hemoglobin Messenger Ribonucleic Acid. Distribution of the 9S Ribonucleic Acid in Polysomes of Different Sizes. *Biochemistry* 8 (3):829–31.

Evans, Todd, Gary Felsenfeld, and Marc Reitman. 1990. Control of Globin Gene Transcription. *Annual Review of Cell Biology* 6:95–125.

Falconer, Douglas. 1993. Quantitative Genetics in Edinburgh: 1947–1980. *Genetics* 133 (2):137–42.

Fekete, Elizabeth. 1947. Differences in the Effect of Uterine Environment Upon Development in the Dba and C57 Black Strains of Mice. *The Anatomical Record* 98 (3):409-15.

Fekete, Elizabeth, and C. C. Little. 1942. Observations on the Mammary Tumor Incidence of Mice Born from Transferred Ova. *Cancer Research* 2 (8):525-30.

Fincham, John R. S. 1983. *Genetics*. Bristol, London & Boston: Wright PSG.

Finn, Bernard S. 2009. Bell and Gray: Just a Coincidence? *Technology and Culture* 50 (1):193–201.

Fire, Andrew. 1986. Integrative Transformtion of *Caenorhabditis elegans*. *EMBO Journal* 5 (10):2673–80.

Fitzgerald, Deborah Kay. 1990. *The Business of Breeding: Hybrid Corn in Illinois, 1890–1940*. Ithaca, NY: Cornell University Press.

Fleck, Ludwik. 1981. *Genesis and Development of a Scientific Fact*. Chicago: University of Chicago Press. Original edition, 1935.

Fox, Allen S., William F. Duggleby, William M. Gelbart, and Sei Byung Yoon. 1970. DNA-Induced Transformation in *Drosophila*: Evidence for Transmission without Integration. *Proceedings of the National Academy of Sciences of the USA* 67 (4):1834-8.

Fox, Allen S., Sei Byung Yoon, and William M. Gelbart. 1971. DNA-Induced Transformation in *Drosophila*: Genetic Analysis of Transformed Stocks. *Proceedings of the National Academy of Sciences of the USA* 68 (2):342-6.

Franklin, Sarah. 2007a. 'Crook' Pipettes: Embryonic Emigrations from Agriculture to Reproductive Biomedicine. *Studies In History and Philosophy of Biologal and Biomedical Sciences* 38 (2):358–73.

———. 2007b. *Dolly Mixtures: The Remaking of Genealogy*. Durham, NC & London: Duke University Press.

———. 2013. *Biological Relatives: IVF, Stem Cells and the Future of Kinship*. Durham, NC & London: Duke University Press.

Franzen, Martina, Peter Weingart, and Simone Rödder. 2012. Exploring the Impact of Science Communication on Scientific Knowledge Production: An Introduction. In *The Sciences' Media Connection – Public Communication and Its Repercussions*, edited by S. Rödder, M. Franzen and P. Weingart. Houten: Springer.

Fredrickson, Donald S. 2001. *The Recombinant DNA Controversy: A Memoir; Science, Politics, and the Public Interest, 1974–1981*. Washington, D. C.: ASM Press.

Freeman, Carol, Elizabeth Leane, and Yvette Watt. 2011. *Considering Animals: Contemporary Studies in Human–Animal Relations*. Furnham: Ashgate.

Friedmann, Herbert C. 2004. From "Butyribacterium" to "E. Coli": An Essay on Unity in Biochemistry. *Perspectives in Biology and Medicine* 47 (1):47–66.

Friedmann, Theodore. 1983. *Gene Therapy: Fact and Fiction, Biology's New Approaches to Disease*. New York: Cold Springs Harbour Laboratory Press.

Fudge, Erica. 2002. A Left-Handed Blow: Writing the History of Animals. In *Representing Animals*, edited by N. Rothfels. Bloomington, IN: Indiana University Press.

Fujimura, Joan H. 1996. *Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer*. Cambridge, MA & London: Harvard University Press.

Fuller, Michael. 2008. Twenty Years of Transgenic Animals: Are Some Inventions so Important as to not Be Entitled to Full Patent Protection? *World Patent Information* 30 (2):139–43.

Gardner, Richard L. 1968. Mouse Chimaeras Obtained by the Injection of Cells into the Blastocyst. *Nature* 220 (5167):596–7.

Gardner, Richard L., and Alan J. Munro. 1974. Successful Construction of Chimaeric Rabbit. *Nature* 250 (5462):146–7.

Garfield, Eugene. 1973. ISI's *Press Digest* Helps Narrow the Gap between the Scientist and the Layman. *Current Contents*, 16 May, 5–6.

———. 1986. *The Scientist*: How It Began. *Current Contents*, 18 August, 3–6.

Garfield, Eugene, and Esther Lederberg. 1977. Is the Curent System of Scientific Communication Adequate to the Age of Plasmid Engineering? In *Plasmids: Medical and Theoretical Aspects*, edited by S. Mitsuhashi, L. Rosival and V. Krčméry. Prague: Avicenum.

Gaudillière, Jean-Paul. 1998a. The Molecularization of Cancer Etiology in the Postwar United States: Instruments, Politics and Management. In *Molacularizing Biology and Medicine: New Pratices and Alliances, 1910s–1970s.*, edited by S. de Chadarevian and H. Kamminga. Amsterdam: Harwood.

———. 1998b. Mouse. In *Insturments of Science: A Historical Encyclopedia*, edited by R. Bud and D. J. Warner. London: The Science Museum.

———. 2001. Making Mice and Other Devices: The Dynamics of Instrumentation in American Biomedical Research (1930–1960). In *Instrumentation: Between Science, State, and Industry*. Dodrecht: Kluwer.

———. 2002. Paris-New York Roundtrip: Transatlantic Crossings and the Reconstruction of the Biological Sciences in Post-War France. *Studies in History and Philosophy of Biological and Biomedical Sciences* 33 (3):389–417.

———. 2004. Mapping as Technology: Genes, Mutant Mice and Biomedical Research (1910–65). In *Classical Genetic Research and Its Legacy: The Mapping Cultures of Twentieth Century Genetics*, edited by H.-J. Rheinberger and S. Müller-Wille. London & New York: Routledge.

———. 2009. New Wine in Old Bottles? The Biotechnology Problem in the History of Molecular Biology. *Studies in History and Philosophy of Biological and Biomedical Sciences* 40 (1):20–8.

Gaudillière, Jean-Paul, and Ilana Löwy. 2003. Making Heredity in Mice and Men: The Production and Uses of Animal Models in Postwar Human Genetics. In *Heredity and Infection: The History of Disease Transmission*, edited by J.-P. Gaudillière and I. Löwy. London: Routledge.

Geison, Gerald L., and Manfred D. Laubichler. 2001. The Varied Lives of Organisms: Variation in the Historiography of the Biological Sciences. *Studies in History and Philosophy of Biological and Biomedical Sciences* 32 (1):1–29.

Gilbert, Scott F. 1996. Enzymatic Adaptation and the Entrance of Molecular Biology into Embryology. In *The Philosophy and History of Molecular Biology: New Perspectives*, edited by S. Sarkar. Dodrecht: Kluwer.

———. 2005. Salome Gluecksohn Waelsch. *Jewish Women: A Comprehensive Historical Encyclopedia*, http://jwa.org/encyclopedia/article/waelsch-salome-gluecksohn. Accessed on 14 April 2013.

———. 2009. The Adequacy of Model Systems for Evo-Devo: Modeling the Formation of Organisms/Modeling the Formation of Society. In *Mapping the Future of Biology: Evolving Concepts and Theories*, edited by A. Barberousse, M. Morange and T. Pradeu. Berlin: Springer Science+Business Media.

Gilbert, Scott F., and Karen A. Rader. 2001. Revisiting Women, Gender, and Feminism in Developmental Biology. In *Feminism in Twentieth-Century Science, Technology and Medicine*, edited by A. N. H. Creager, E. Lunbeck and L. Shiebinger. Chicago and London: University of Chicago Press.

Gitschier, Jane. 2013. Problem Solved: An Interview with Sir Edwin Southern. *PLoS Genetics* 9 (3):e1003344.

Goodell, Rae. 1980. The Gene Craze. *Columbia Journalism Review* 19 (4):41–5.

———. 1986. How to Kill a Controversy: The Case of Recombinant DNA. In *Scientists and Journalists: Reporting Science as News*, edited by S. M. Friedman, S. Dunwoody and C. L. Rogers. New York: Free Press.

Goodfield, June. 1981. *Reflections on Science and the Media*. Washington, D. C.: American Association for the Advancement of Science.

Gordon, Jon W., George A. Scangos, Diane J. Plotkin, James A. Barbosa, and Frank H. Ruddle. 1980. Genetic Transformation of Mouse Embryos by Microinjection of Purified DNA. *Proceedings of the National Academy of Sciences of the USA* 77 (12):7380–4.

Gordon, Jon W. 1983. Transgenic Mice – A New and Powerful Experimental Tool in Mammalian Developmental Genetics. *Developmental Genetics* 4 (1):1–20.

———. 1989. Transgenic Animals. *International Review of Cytology* 115:171–229.

———. 2003. *The Science and Ethics of Genetic Engineering: Mendel's Maze.* Hoboken, NJ: Wiley-Liss.

Gordon, Jon W., and Frank H. Ruddle. 1981. Integration and Stable Germ Line Transmission of Genes Injected into Mouse Pronuclei. *Science* 214 (4526):1244–6.

Gore, Rick. 1976. New Biology I: The Awesome Worlds within a Cell. *National Geographic* 150 (3):355–95.

Gottweis, Herbert. 1998. *Governing Molecules: The Discursive Politics of Genetic Engineering in Europe and the United States*. Cambridge, MA & London: MIT Press.

Graham, Chris F. 2000. Mammalian Development in the UK (1950–1995). *International Journal of Developmental Biology* 44 (1):51–6.

——— 2008. Andrzej Krzysztof Tarkowski Abroad, in Photos and Correspondence. *International Journal of Developmental Biology* 53 (2/3):171–8.

Graham, Frank L., and Alex J. van der Eb. 1973. A New Technique for the Assay of Infectivity of Human Adenovirus 5 DNA. *Virology* 52 (2):456-67.

Greenberg, D. S. 1966. "Bootlegging": It Holds a Firm Place in Conduct of Research. *Science* 153 (3738):848–9.

Grosveld, Frank, Greet Blom van Assendelft, David R. Greaves, and George Kollias. 1987. Position-Independent, High-Level Expression of the Human Beta-Globin Gene in Transgenic Mice. *Cell* 51 (6):975–85.

Grüneberg, Hans. 1943. *The Genetics of the Mouse*. Cambridge: Cambridge University Press.

———. 1954. Variation within Inbred Strains of Mice. *Nature* 173 (4406):674–6.

Gurdon, John B., T. R. Elsdale, and M. Fischberg. 1958. Sexually Mature Individuals of *Xenopus laevis* from the Transplantation of Single Somatic Nuclei. *Nature* 182 (4627):64–5.

Gurdon, John B., Jerry B. Lingrel, and Gérard Marbaix. 1973. Message Stability in Injected Frog Oocytes: Long Life of Mammalian Alpha and Beta-Globin Messages. *Journal of Molecular Biology* 80 (3):539–51.

Gurdon, John B. 1974a. *The Control of Gene Expression in Animal Development*. Oxford: Clarendon Press.

———. 1974b. Molecular Biology in a Living Cell. *Nature* 248 (5451):772–6.

———. 1985. Introductory Comments. In *Molecular Biology of Development. Cold Spring Harbor Symposia on Quantitative Biology, Volume 50*. Cold Spring Harbor: Cold Spring Harbor Laboratory Press.

Gurdon, John B., and Nick Hopwood. 2000. The Introduction of *Xenopus laevis* into Developmental Biology: Of Empire, Pregnancy Testing and Ribosomal Genes. *International Journal of Developmental Biology* 44 (1):43–50.

Gurdon, John B., and Doug A. Melton. 1981. Gene Transfer in Amphibian Eggs and Oocytes. *Annual Review of Genetics* 15 (1):189-218.

Gurdon, John B., Doug A. Melton, and Edward M. De Robertis. 1979. Genetics in an Oocyte. In *Human Genetics: Possibilities and Realities.* Ciba Foundation Symposium 66. Amsterdam: Excerpta Medica.

Gutteling, Jan M., Anna Olofsson, Björn Fjæstad, Matthias Kohring, Alexander Goerke, Martin W. Bauer, and Timo Rusanen. 2002. Media Coverage 1973–1996: Trends and Dynamics. In *Biotechnology: The Making of a Global Controversy*, edited by M. W. Bauer and G. Gaskell. Cambridge: Cambridge University Press.

Gwynne, Peter, Mariana Gosnell, Sharon Begley, Anthony Collings, and Stephen H. Gayle. 1978. All About Clones. *Newsweek*, 20 March, 54–5.

Hamburger, Viktor. 1988. *The Heritage of Experimental Embryology: Hans Spemann and the Organizer*. New York & Oxford: Oxford University Press.

Hammer, Robert E., Vernon G. Pursel, Caird E. Rexroad, Robert J. Wall, Douglas J. Bolt, Karl M. Ebert, Richard D. Palmiter, and Ralph L. Brinster. 1985. Production of Transgenic Rabbits, Sheep and Pigs by Micro-injection. *Nature* 315 (6021):680–3.

Hanahan, D. 1988. Dissecting Multistep Tumorigenesis in Transgenic Mice. *Annual Review of Genetics* 22 (1):479–519.

Hanahan, Douglas. 1989. Transgenic Mice as Probes into Complex Systems. *Science* 246 (4935):1265–75.

Hanahan, Douglas, Erwin F. Wagner, and Richard D. Palmiter. 2007. The Origins of Oncomice: A History of the First Transgenic Mice Genetically Engineered to Develop Cancer. *Genes & Development* 21 (18):2258–70.

Hansen, Bert. 2009. *Picturing Medical Progress from Pasteur to Polio : A History of Mass Media Images and Popular Attitudes in America*. New Brunswick, NJ: Rutgers University Press.

Haran, Joan, Jenny Kitzinger, Maureen McNeil, and Kate O'Riordan. 2007. *Human Cloning in the Media: From Science Fiction to Science Practice*. London & New York: Routledge.

Haraway, Donna J. 1993. When Man Is on the Menu. In *Zone: Incorporations*, edited by J. Crary and S. Kwinte. Cambridge, MA: MIT Press.

———. 1997. *Modest_Witness@Second_Millennium.FemaleMan©_Meets_OncoMouse™*. New York & London: Routledge.

———. 2007. *When Species Meet*. Minneapolis: University of Minnesota Press.

Harbers, Klaus, Detlev Jähner, and Rudolf Jaenisch. 1981. Microinjection of Cloned Retroviral Genomes into Mouse Zygotes: Integration and Expression in the Animal. *Nature* 293 (5833):540–2.

Harris, Henry. 1995. *The Cells of the Body: A History of Somatic Cell Genetics*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Henig, Robin Marantz. 2004. *Pandora's Baby: How the First Test Tube Babies Sparked the Reproductive Revolution*. Boston: Houghton Mifflin.

Hilgartner, Stephen. 1990. The Dominant View of Popularization: Conceptual Problems, Political Uses. *Social Studies of Science* 20 (3):519–39.

———. 2004. Making Maps and Making Social Order: Governing American Genome Centers, 1988-1993. In *From Genetics to Genomics: The Mapping Cultures of Twentieth-Century Genetics*, edited by J.-P. Gaudillière and H.-J. Rheinberger: Routledge.

———. 2012. Staging High-Visibility Science: Media Orientation in Genome Research. In *The Sciences' Media Connection – Public Communication and Its Repercussions*, edited by S. Rödder, M. Franzen and P. Weingart. Houten: Springer.

Hogan, Brigid, Rosa Beddington, Franklin Costantini, and Elizabeth Lacy. 1994. *Manipulating the Mouse Embryo: A Laboratory Manual*. 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Hogan, Brigid, Franklin Costantini, and Elizabeth Lacy. 1986. *Manipulating the Mouse Embryo: A Laboratory Manual*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Hogan, Brigid, and Jeffrey G. Williams. 1981. Integration of Foreign Genes into the Mammalian Germ Line: Genetic Engineering Enters a New Era. *Nature* 294 (5836):9–10.

Holmes, Frederick Lawrence 2001. *Meselson, Stahl and the Replication of DNA: A History of the "Most Beautiful Experiment in Biology"*. New Haven & London: Yale University Press.

Hopwood, Nick. 2000. Producing Development: The Anatomy of Human Embryos and the Norms of Wilhelm His. *Bulletin of the History of Medicine* 74 (1):29–79.

———. 2007. A History of Normal Plates, Tables and Stages in Vertebrate Embryology. *International Journal of Developmental Biology* 51:1–26.

———. 2009. Embryology. In *The Cambridge History of Science Volume 6: Modern Life and Earth Sciences*, edited by P. J. Bowler and J. V. Pickstone. Cambridge: Cambridge University Press.

———. 2011. Approaches and Species in the History of Vertebrate Embryology. In *Vertebrate Embryogenesis*, edited by F. Pelegri. New York: Humana Press.

Howlett, Peter, and Mary S. Morgan, eds. 2011. *How Well Do Facts Travel? The Dissemination of Reliable Knowledge*. Cambridge: Cambridge University Press.

Hughes, Sally Smith. 2001. Making Dollars out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980. *Isis* 92 (3):541–75.

———. 2011. *Genentech: The Beginnings of Biotech*. Chicago & London: University of Chicago Press.

Illmensee, Karl. 1980. Genetic Manipulation of the Early Mouse Embryo. *Results and Problems in Cell Differentiation* 11:75-86.

———. 1981. Experimental Manipulation of the Mammalian Embryo: Biological and Genetic Consequences. In *Mammalian Genetics and Cancer: The Jackson Laboratory Fiftieth Anniversary Symposium*, edited by E. Russell. New York: Alan Liss.

International Committee on Standardised Genetic Nomenclature for Mice. 1985. Nomenclature for Transgenic Mice. *The Mouse Newsletter* 72:21.

Jacob, François. 1977. Evolution and Tinkering. *Science* 196 (4295):1161–6.

———. 1998. *Of Flies, Mice and Men*. Translated by G. Weiss. Cambridge, MA: Harvard University Press.

Jacobs, Paul. 1980. Doctor Tried Gene Therapy on 2 Humans. *Washington Post,* 8 October, A1, A15.

Jaenisch, Rudolf. 1976. Germ Line Integration and Mendelian Transmission of Exogenous Moloney Leukemia-Virus. *Proceedings of the National Academy of Sciences of the USA* 73 (4):1260-4.

———. 1977. Germ Line Integration of Moloney Leukemia Virus: Effect of Homozygosity at M-MuLV Locus. *Cell* 12 (3):691-6.

———. 1980. Retroviruses and Embryogenesis: Microinjection of Moloney Leukemia Virus into Midgestation Mouse Embryos. *Cell* 19 (1):181-8.

Jähner, Detlev, and Rudolf Jaenisch. 1980. Integration of Moloney Leukemia Virus into the Germ Line of Mice: Correlation between Site of Integration and Virus Activation. *Nature* 287 (5781):456-8.

Johnson, Martin. 1986. Review of "Manipulating the Mouse Embryo: A Laboratory Manual". *Trends in Genetics* 2:298.

Karp, Gerald. 1984. *Cell Biology*. New York: McGraw-Hill.

Kay, Lily E. 1988. Laboratory Technology and Biological Knowledge: The Tiselius Electrophoresis Apparatus, 1930–1945. *History and Philosophy of the Life Sciences* 10 (1):50–72.

———. 1993. *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology*. New York & Oxford: Oxford University Press.

———. 2000. *Who Wrote the Book of Life? A History of the Genetic Code*. Stanford: Stanford University Press.

Keating, Peter, and Alberto Cambrosio. 1995. *Exquisite Specificity: The Monoclonal Antibody Revolution*. Oxford: Oxford University Press.

———. 2012. *Cancer on Trial: Oncology as a New Style of Practice*. Chicago & London: University of Chicago Press.

Keller, Evelyn Fox. 1995. *Refiguring Life: Metaphors of Twentieth-Century Biology*. New York: Columbia University Press.

———. 2000. *The Century of the Gene*. Cambridge, MA & London: Harvard University Press.

Kelty, Christopher M. 2012a. This Is Not an Article: Model Organism Newsletters and the Question of /`Open Science/'. *BioSocieties* 7 (2):140–68.

Kendig, Frank. 1979. Whether or not the First Test-Tube Baby is a Hoax isn't the Issue; Rather, it is Whether or not Scientific Journals have a Monopoly on the Disclosure of New Information. *OMNI*, February, 6.

Kenney, Martin. 1986. *Biotechnology: The University-Industrial Complex*. New Haven & London: Yale University Press.

Kevles, Daniel J. 1985. *In the Name of Eugenics: Genetics and the Uses of Human Heredity*. Berkeley & Los Angeles: University of California Press.

———. 1993. Renato Dulbecco and the New Animal Virology: Medicine, Methods, and Molecules. *Journal of the History of Biology* 26 (3):409–42.

———. 1998. *The Baltimore Case: A Trial of Politics, Science, and Character.* New York: W. W. Norton.

———. 2002a. *A History of Patenting Life in the United States with Comparative Attention to Europe and Canada: A Report to the European Group on Ethics in Science and New Technologies*. Luxembourg: Office for Official Publications of the European Communities.

———. 2002b. Of Mice & Money: The Story of the World's First Animal Patent. *Daedalus* 131 (2):78–88.

———. 2007. Patents, Protections, and Privileges: The Establishment of Intellectual Property in Animals and Plants. *Isis* 98 (2):323–31.

Kiernan, Vincent. 2006. *Embargoed Science*. Urbana, IL and Chicago: University of Illinois Press.

Kirby, David A. 2003. Science Consultants, Fictional Films, and Scientific Practice. *Social Studies of Science* 33 (2):231–68.

———. 2011. *Lab Coats in Hollywood: Science, Scientists, and Cinema*. Cambridge, MA: MIT Press.

Kirk, Robert G. W. 2008. "Wanted-Standard Guinea Pigs": Standardisation and the Experimental Animal Market in Britain, ca. 1919–1947. *Studies in History and Philosophy of Biological and Biomedical Sciences* 39 (3):280–91.

———. 2010. A Brave New Animal for a Brave New World: The British Laboratory Animals Bureau and the Constitution of International Standards of Laboratory Animal Production and Use, circa 1947–1968. *Isis* 101 (1):62–94.

———. 2012. "Standardization through Mechanization": Germ-Free Life and the Engineering of the Ideal Laboratory Animal. *Technology and Culture* 53 (1):61–93.

Klobutcher, Lawrence A., and Frank H. Ruddle. 1981. Chromosome-Mediated Gene Transfer. *Annual Review of Biochemistry* 50:533–54.

Kloppenburg, Jack Ralph. 2004. *First the Seed: The Political Economy of Plant Biotechnology, 1492–2000*. Madison, WI: University of Wisconsin Press.

Knorr Cetina, Karin. 1999. *Epistemic Cultures: How the Sciences Make Knowledge*. Cambridge, MA: Harvard University Press.

Kohler, Robert E. 1994. *Lords of the Fly*. Chicago & London: University of Chicago Press.

Kolata, Gina. 1998. *Clone: The Road to Dolly and the Path Ahead*. London: Penguin.

Korzh, Vladimir, and Uwe Strähle. 2002. Marshall Barber and the Century of Microinjection: From Cloning of Bacteria to Cloning of Everything. *Differentiation* 70 (6):221–6.

Krimsky, Sheldon. 1984. *Genetic Alchemy: A Social History of the Recombinant DNA Controversy*. Cambridge, MA: MIT Press.

Krumholz, Harlan. 1979. DNA: Does It Spell Danger? *Yale Daily News*, 18 January, 6.

Lacy, Elizabeth, Sally Roberts, Edward P. Evans, Mike D. Burtenshaw, and Franklin Costantini. 1983. A Foreign Beta-Globin Gene in Transgenic Mice: Integration at Abnormal Chromosomal Positions and Expression in Inappropriate Tissues. *Cell* 34 (2):343–58.

Landecker, Hannah. 2004. The Lewis Films: Tissue Culture and "Living Anaromy," 1919–1940. In *Centennial Hiustory of the Carnegie Institution of Washington. Volume V: The Department of Embryology*, edited by J. Maienschein, M. Glitz and G. E. Allen. Cambridge: Cambridge University Press.

———. 2007. *Culturing Life: How Cells Became Technologies*. Cambridge, MA & London: Harvard University Press.

Lane, Charles D., Gérard Marbaix, and John B. Gurdon. 1971. Rabbit Haemoglobin Synthesis in Frog Cells: The Translation of Reticulocyte 9S RNA in Frog Oocytes. *Journal of Molecular Biology* 61 (1):73–91.

Latour, Bruno. 1999. Circulating Reference: Sampling the Soil in the Amazon Forest. In *Pandora's Hope. Essays on the Reality of Science Studies*. Cambridge, MA & London: Harvard University Press.

Latour, Bruno, and Steve Woolgar. 1986. *Laboratory Life: The Construction of Scientific Facts*. 2nd ed. Princeton: Princeton University Press.

Lederberg, Joshua. 1966. Remarks. *Current Topics in Developmental Biology* 1 (1):ix–xiii.

Ledley, Robert S., and Frank H. Ruddle. 1966. Chromosome Analysis by Computer. *Scientific American* 214 (4):40–6.

Ledoux, Lucien, ed. 1971. *Informative Molecules in Biological Systems*. Amsterdam & London: North-Holland Publishing Company.

Leonelli, Sabina. 2007. Growing Weed, Producing Knowledge: An Epistemic History of *Arabidopsis thaliana*. *History and Philosophy of Life Sciences* 29 (2):55–87.

Leonelli, Sabina, Edmund Ramsden, Nicole Nelson, and Rachel A. Ankeny. Forthcoming, 2014. Making Organisms Model Human Alcoholics: Situated Models in Alcohol Research. *Science in Context*.

Lewenstein, Bruce V. 1989. Magazine Publishing and Popular Science after World War Ii. *American Journalism* 6 (4):218–34.

———. 1995. From Fax to Facts: Communication in the Cold Fusion Saga. *Social Studies of Science* 25 (3):403–36.

Lewin, Benjamin. 1972. New Genes for Old? *New Scientist* 54 (792):122–4.

———. 1980. *Gene Expression 2: Eucaryotic Chromosomes*. Chichester: John Wiley & Sons.

———. 1985. *Genes II*. New York: John Wiley & Sons.

Lewis, Ricki A. 2001. *Discovery: Windows on the Life Sciences*. Malden: Blackwell Science.

Lewis, W. H., and E. S. Wright. 1935. On the Early Development of the Mouse Egg. *Contributions to Embryology* 25 (148):115–43.

Lin, Teh Ping. 1966. Microinjection of Mouse Eggs. *Science* 151 (3708):333–7.

Lindee, M. Susan. 1994. *Suffering Made Real: American Science and the Survivors at Hiroshima*. Chicago & London: University of Chicago Press.

Liu, Chih-Ping, Doris L. Slate, Roy Gravel, and Frank H. Ruddle. 1979. Biological Detection of Specific mRNA Molecules by Microinjection. *Proceedings of the National Academy of Sciences of the USA* 76 (9):4503–6.

Löwy, Ilana. 2000. The Experimental Body. In *Medicine in the Twentieth Century*, edited by R. Cooter and J. V. Pickstone. Amsterdam: Harwood.

Löwy, Ilana, and Jean-Paul Gaudillière. 1998a. Disciplining Cancer: Mice and the Practice of Genetic Purity. In *The Invisible Industrialist: Manufactures and the Production of Scientific Knowledge*. Basingstoke: Palgrave Macmillan.

———, eds. 1998b. *The Invisible Industrialist: Manufactures and the Production of Scientific Knowledge*. Basingstoke: Palgrave Macmillan.

Lurquin, Paul F. 2001. *The Green Phoenix: A History of Genetically Modified Plants*. New York: Columbia University Press.

Lynch, Michael E. 1988. Sacrifice and the Transformation of the Animal Body into a Scientific Object: Laboratory Culture and Ritual Practice in the Neurosciences. *Social Studies of Science* 18 (2):265–89.

Lynch, Michael E., Simon A. Cole, Ruth McNally, and Kathleen Jordan. 2008. *Truth Machine: The Contentious History of DNA Fingerprinting*. Chicago & London: University of Chicago Press.

Lynch, Michael E., and Kathleen Jordan. 1992. The Sociology of a Genetic Engineering Technique: Ritual and Rationality in the Performance of the Plasmid Prep. In *The Right Tools for the Job*, edited by A. Clarke and J. H. Fujimura. Princeton: Princeton University Press.

Lyon, Mary F. 1990. L. C. Dunn and Mouse Genetic Mapping. *Genetics* 125 (2):231–6.

———, ed. 1989. *Genetic Variants and Strains of the Laboratory Mouse*. 2nd ed. Oxford: Oxford University Press.

Maienschein, Jane. 2014. *Embryos under the Microscope: The Diverging Meanings of Life*. Cambridge, MA: Harvard University Press.

Maienschein, Jane, Marie Glitz, and Garland E. Allen, eds. 2004. *Centennial Hiustory of the Carnegie Institution of Washington. Volume V: The Department of Embryology*. Cambridge: Cambridge University Press.

Maleszewski, Marek, and Andrzej K. Tarkowski. 2008. Early Mammalian Embryo: My Love. *International Journal of Developmental Biology* 52 (2/3):163–9.

Maniatis, Tom. 2012. On the Road from Classical to Modern Molecular Biology. *Nature Medicine* 18 (10):1499–502.

Maniatis, Tom, E. F. Fritsch, and Joseph Sambrook. 1982. *Molecular Cloning: A Laboratory Manual*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Marks, Lara. 2001. *Sexual Chemistry: A History of the Contraceptive Pill*. New Haven & London: Yale University Press.

———. forthcoming. *The "Lock and Key" of Medicine: Monoclonal Antibodies and Their Transformation of Healthcare*. New Haven & London: Yale University Press.

Marshall, Eliot. 1998. Embargoes: Good, Bad, or "Necessary Evil"? *Science* 282 (5390):860–7.

Martin, Paul A. 1999. *From Eugenics to Therapeutics: Science and the Social Shaping of Gene Therapy*. PhD Thesis, University of Sussex.

Marx, Jean L. 1980. Gene Transfer Moves Ahead. *Science* 210 (4476):1334–6.

———. 1981. Globin Gene Transferred. *Science* 213 (4515):1488.

McBride, O. Wesley, and Harvey L. Ozer. 1973. Transfer of Genetic Information by Purified Metaphase Chromosomes. *Proceedings of the National Academy of Sciences of the USA* 70 (4):1258.

McKinnel, Robert G. 1978. *Cloning: Nuclear Transplantation in Amphibia. A Critique of Results Obtained with the Technique to which is Added a Discourse on the Methods of the Craft*. Minneapolis: University of Minnesota Press.

McKusick, Victor A. 1984. The William Allan Memorial Award. Presented to Frank H. Ruddle, PhD, at the Annual Meeting of the American Society of Human Genetics, Norfolk, October 30–November 2, 1983. *American Journal of Human Genetics* 36:941–3.

McKusick, Victor A., Juergen Naggert, Patsy Nishina, and David Valle. 1999. 40 Years of the Annual "Bar Harbor Course" (1960–1999): A Pictorial History. *Clinical Genetics* 55 (6):398–415.

McLaren, Anne. 1976. *Mammalian Chimaeras*. Cambridge: Cambridge University Press.

———. 1996. Speaking Volumes: 'Preimplantation Stages of Pregnancy'. *Times Higher Education Supplement*, 8 March, 20.

McLaren, Anne, and Donald Michie. 1954. Are Inbred Strains Suitable for Bio-Assay? *Nature* 173 (4406):686–7.

———. 1955. The Importance of Being Cross-Bred. In *New Biology 19*, edited by M. L. Johnson, M. Abercrombie and G. E. Fogg. Harmondsworth: Penguin.

Merton, Robert K. 1973. *The Sociology of Science: Theoretical and Empirical Investigations*. Chicago & London: University of Chicago Press.

Mertz, Janet E., and John B. Gurdon. 1977. Purified DNAs Are Transcribed after Microinjection into *Xenopus* Oocytes. *Proceedings of the National Academy of Sciences of the USA* 74 (4):1502–6.

Miller, David, Martin Brinkworth, and David Iles. 2010. Paternal DNA Packaging in Spermatozoa: More Than the Sum of Its Parts? DNA, Histones, Protamines and Epigenetics. *Reproduction* 139 (2):287–301.

Mintz, Beatrice. 1964. Synthetic Processes and Early Development in the Mammalian Egg. *Journal of Experimental Zoology* 157 (1):85–100.

———. 1967. Mammalian Embryo Culture. In *Methods in Developmental Biology*, edited by F. H. Wilt and N. K. Wessels. New York: Thomas Y. Crowell Co.

———. 1974. Gene Control of Mammalian Differentiation. *Annual Review of Genetics* 8 (1):411–70.

———. 1978a. Gene Expression in Neoplasia and Differentiation In *The Harvey Lectures, Series 71 (1975–1976)*. New York: Academic Press.

———. 1978b. Teratocarcinoma Cells as Vehicles for Mutant and Foreign Genes. In *Genetic Interaction and Gene Transfer*, edited by C. W. Anderson. Upton, NY: Brookhaven National Laboratory.

———, ed. 1958. *Environmental Influences on Prenatal Development*. Developmental Biology Conference Series, 1956. Chicago: University of Chicago Press.

Mintz, Beatrice, and Claire Cronmiller. 1981. METT-1: A Karyotypically Normal in Vitro Line of Developmentally Totipotent Mouse Teratocarcinoma Cells. *Somatic Cell and Molecular Genetics* 7 (4):489–505.

Mintz, Beatrice, and Karl Illmensee. 1975. Normal Genetically Mosaic Mice Produced from Malignant Teratocarcinoma Cells. *Proceedings of the National Academy of Sciences of the USA* 72 (9):3585–9.

Mintz, Beatrice, and Elizabeth Russell. 1957. Gene-Induced Embryological Modifications of Primordial Germ Cells in the Mouse. *Journal of Experimental Biology* 134 (2):207–37.

Moga, Thomas Traian. 1994. Transgenic Animals as Intellectual Property (or the Patented Mouse That Roared). *Journal of the Patent & Trademark Office Society* 76 (7):511–45.

Monk, Marilyn, ed. 1987. *Mammalian Development: A Practical Approach*. Oxford: Oxford University Press.

Monod, Jacques, and François Jacob. 1961. General Conclusions: Teleonomic Mechanisms in Cellular Metabolism, Growth in Differentiation. In *Cellular Regulatory Mechanisms,* Cold Spring Harbor Symposia on Quantitative Biology, Volume 26. Cold Spring Harbor: Cold Spring Harbor Laboratory Press.

Morange, Michel. 1993. The Discovery of Cellular Oncogenes. *History and Philosophy of the Life Sciences* 15 (1):45–58.

———. 1997a. From the Regulatory Vision of Cancer to the Oncogene Paradigm, 1975–1985. *Journal of the History of Biology* 30 (1):1–29.

———. 1997b. The Transformation of Molecular Biology on Contact with Higher Organisms, 1960–1980: From a Molecular Description to a Molecular Explanation. *History and Philosophy of the Life Sciences* 19 (3):369–93.

———. 1998. *A History of Molecular Biology*. Translated by M. Cobb. Cambridge, MA & London: Harvard University Press.

———. 2000. François Jacob's Lab in the Seventies : The *T*-Complex and the Mouse Developmental Genetic Program. *History and Philosophy of the Life Sciences* 22 (3):397–411.

———. 2005. What History Tells Us. I. The Operon Model and Its Legacy. *Journal of Biosciences* 30 (3):313–6.

———. 2009. What History Tells Us. XVI. A Third Pillar for Molecular Biology: Molecular Embryology. *Journal of Biosciences* 34 (1):17–20.

Morgan, Lynn M. 2009. *Icons of Life: A Cultrual History of the Human Embryo*. Berkeley & Los Angeles: University of California Press.

Mowery, David C., Richard R. Nelson, Bhaven N. Sampat, and Arvids A. Ziedonis. 2004. *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer before and after the Bayh-Dole Act in the United States*. Stanford: Stanford Business Books.

Mueller, C., Adolf Graessmann, and M. Graessmann. 1980. Microinjection: Turning Living Cells into Test Tubes. *Trends in Biochemical Sciences* 5 (3):60-2.

Müller-Wille, Staffan. 2007. Hybrids, Pure Cultures, and Pure Lines: From Nineteenth-Century Biology to Twentieth-Century Genetics. *Studies in History and Philosophy of Biological and Biomedical Sciences* 38 (4):796–806.

Müller-Wille, Staffan, and Hans-Jörg Rheinberger. 2012. *A Cultural History of Heredity*. Chicago & London: University of Chicago Press.

Mulligan, Richard C., Bruce H. Howard, and Paul Berg. 1979. Synthesis of Rabbit Beta-Globin in Cultured Monkey Kidney Cells Following Infection with a SV40 Beta-Globin Recombinant Genome. *Nature* 277 (5692):108–14.

Murray, Fiona. 2010. The Oncomouse That Roared: Hybrid Exchange Strategies as a Source of Distinction at the Boundary of Overlapping Institutions. *American Journal of Sociology* 116 (2):341–88.

Murphy, D., A. Bishop, G. Rindi, M. N. Murphy, G. W. Stamp, J. Hanson, J. M. Polak, and Brigid Hogan. 1987. Mice Transgenic for a Vasopressin-SV40 Hybrid Oncogene Develop Tumors of the Endocrine Pancreas and the Anterior Pituitary. A Possible Model for Human Multiple Endocrine Neoplasia Type 1. *American Journal of Pathology* 129 (3):552–66.

Myers, Greg. 1990. *Writing Biology: Texts in the Social Construction of Scientific Knowledge*. Madison, WI: University of Wisconsin Press.

Nathoo, Ayesha. 2009. *Hearts Exposed: Transplants and the Media in 1960s Britain*. Basingstoke: Palgrave Macmillan.

National Research Council. 1994. *Sharing Laboratory Resources: Genetically Altered Mice*. Washington, D.C.: The National Academies Press.

National Science Foundation. 1983. *Science Indicators 1982*. Washington, D. C.: National Science Board, National Science Foundation.

Nelkin, Dorothy. 1995. *Selling Science: How the Press Covers Science and Technology*. New York: W. H. Freeman.

Nelkin, Dorothy, and M. Susan Lindee. 1995. *The DNA Mystique: The Gene as a Cultural Icon*. New York: W. H. Freeman.

Nisbet, Matthew C., and Bruce V. Lewenstein. 2002. Biotechnology and the American Media: The Policy Process and the Elite Press, 1970–1999. *Science Communication* 23 (4):359–91.

Office of Technology Assessment, U. S. Congress. 1989. *New Developments in Biotechnology 5: Patenting Life*. Washington, DC: U. S. Congress, Office of Technology Assessment.

Olby, Robert. 1997. Mendel, Mendelism and Genetics. Available at http://www.mendelweb.org/MWolby.html#s3. Accessed on 12 March 2013.

Olszynko-Gryn, Jesse. 2013. When Pregnancy Tests Were Toads: The Xenopus Test in the Early NHS. *Wellcome History* 51:1–3.

Oppenheimer, Jane. 1966. The Growth and Development of Developmental Biology. In *Major Problems in Developmental Biology*, edited by M. Locke. New York: Academic Press.

Oudshoorn, Nelly. 1994. *Beyond the Natural Body*. London: Routledge.

Oudshoorn, Nelly, and Trevor J. Pinch. 2003. *How Users Matter: The Co-Construction of Users and Technologies*. Cambridge, MA: MIT Press.

Palladino, Paolo. 1993. Between Craft and Science: Plant Breeding, Mendelian Genetics, and British Universities, 1900–1920. *Technology and Culture* 34 (2):300–23.

Palmiter, Richard D., and Ralph L. Brinster. 1985. Transgenic Mice. *Cell* 41 (2):343–5.

Palmiter, Richard D., Ralph L. Brinster, Robert E. Hammer, Myrna E. Trumbauer, Michael G. Rosenfeld, Neal C. Birnberg, and Ronald M. Evans. 1982. Dramatic Growth of Mice That Develop from Eggs Microinjected with Metallothionein-Growth Hormone Fusion Genes. *Nature* 300 (5893):611–5.

Palmiter, Richard D., Gunnar Norstedt, Richard E. Gelinas, Robert E. Hammer, and Ralph L. Brinster. 1983. Metallothionein-Human GH Fusion Genes Stimulate Growth of Mice. *Science* 222 (4625):809–14.

Papaioannou, Virginia E. 1998. The Coming of Age of the Transgenic Era. *International Journal of Developmental Biology* 42 (7):841–6.

———. 1999. The Ascendency of Developmental Genetics, or How the *T* Complex Educated a Generation of Developmental Biologists. *Genetics* 151 (2):421–5.

Papaioannou, Virginia E., and Françoise Dieterlen-Lièvre. 1984. Making Chimeras. In *Chimeras in Developmental Biology,* edited by N. L. Douarin and A. McLaren. London: Academic Press.

Papaioannou, Virginia E., Michael W. McBurney, Richard L. Gardner, and Martin J. Evans. 1975. Fate of Teratocarcinoma Cells Injected into Early Mouse Embryos. *Nature* 258 (5530):70–3.

Parry, Bronwyn. 2004. *Trading the Genome: Investigating the Commodification of Bio-Information*. New York: Columbia University Press.

Patrusky, Ben. 1986. Gene Enhancers. *Mosaic* 17 (3):36–44.

———. 1989. Genetics in the Round: Transgenic Animals. *Mosaic* 20 (2):12–23.

Pattengale, P. K., T. A. Stewart, A. Leder, E. Sinn, W. Muller, I. Tepler, E. Schmidt, and P. Leder. 1989. Animal Models of Human Disease. Pathology and Molecular Biology of Spontaneous Neoplasms Occurring in Transgenic Mice Carrying and Expressing Activated Cellular Oncogenes. *American Journal of Pathology* 135 (1):39–61.

Paulson, Andrew. 1976a. Biology Plans Review of Recombinant DNA. *Yale Daily News*, 1 November, 3.

———. 1976b. DNA Debators Confront Panel. *Yale Daily News*, 2 November, 1.

Pellicer, Angel, Erwin F. Wagner, Adele El Kareh, Michael J. Dewey, Arnold J. Reuser, Saul Silverstein, Richard Axel, and Beatrice Mintz. 1980. Introduction of a Viral Thymidine Kinase Gene and the Human Beta-Globin Gene into Developmentally Multipotential Mouse Teratocarcinoma Cells. *Proceedings of the National Academy of Sciences of the USA* 77 (4):2098–102.

Petri, William. 1982. Transgenic Organisms and Development. *Nature* 299:399–400.

Pincus, Gregory. 1936. *The Eggs of Mammals*. New York: Macmillan.

Porter, Ruth, and Maeve O'Connor, eds. 1979. *Human Genetics: Possibilities and Realities*. Ciba Foundation Symposium 66. Amsterdam: Excerpta Medica.

Portugal, Franklin H. 1977. Cell Transformation with Herpes Simplex Viruses. *Nature* 269 (5625):196.

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. 1982. *Splicing Life: A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings*. Washington, D. C.: US Government Printing Office.

Proctor, Robert N., and Londa Schiebinger, eds. 2008. *Agnotology: The Making and Unmaking of Ignorance*. Stanford: Stanford University Press.

Rabinow, Paul. 1996. *Making PCR: A Story of Biotechnology*. Chicago & London: University of Chicago Press.

Rader, Karen A. 1998. "The Mouse People": Murine Genetics Work at the Bussey Institution, 1909–1936. *Journal of the History of Biology* 31 (3):327–54.

———. 2004. *Making Mice: Standardizing Animals for American Biomedical Research, 1900–1955*. Princeton: Princeton University Press.

———. 2007. Scientific Animals: Reflections on the Laboratory and Its Human-Animal Relations from *Dba* to Dolly and Beyond. In *A Cultural History of Animals in the Modern Age*, edited by R. Malamud. Oxford & New York: Berg.

Rafferty, Keen A. 1970. *Methods in Experimental Embryology of the Mouse*. Baltimore: Johns Hopkins University Press.

Rasmuson-Lestander, Åsa. 1995. The Drosophila Stock Centers and Their Implications for Developmental Biology. *International Journal of Developmental Biology* 39 (5):765–8.

Rawling, Alison. 1994. The AIDS Virus Dispute: Awarding Priority for the Discovery of the Human Immunodeficiency Virus (HIV). *Science, Technology & Human Values* 19 (3):342–60.

Reik, Wolf, A. Collick, Michael L. Norris, Sheila C. Barton, and M. Azim Surani. 1987. Genomic Imprinting Determines Methylation of Parental Alleles in Transgenic Mice. *Nature* 328 (6127):248–51.

Richmond, Marsha L. 2001. Women in the Early History of Genetics: William Bateson and the Newnham College Mendelians, 1900–1910. *Isis* 92 (1):55–90.

Riffe, Florence Clark. 2004. *The Philosophy of Community: Ohio University in the Ping Years, 1975–1994* Athens, OH: Ohio University Special Publications.

Rifkin, Jeremy. 1984. Notice of Proposed Actions under NIH Guidelines for Research Involving Recombinant DNA Molecules. *Federal Register* 49 (37016), 20 September.

Rigby, Peter W. J. 1985. Hybrid Oncogenes: A Multi-Purpose Tool for Studying Multi-Step Processes. *Nature* 315 (6015):96–7.

Rigby, Peter W. J., Marianne Dieckmann, Carl Rhodes, and Paul Berg. 1977. Labeling Deoxyribonucleic Acid to High Specific Activity in Vitro by Nick Translation with DNA Polymerase I. *Journal of Molecular Biology* 113 (1):237-51.

Ritvo, Harriet. 1989. *The Animal Estate: The English and Other Creatures in Victorian England*. Cambridge, MA & London: Harvard University Press.

Robbins, Louise E. 2002. *Elephant Slaves and Pampered Parrots: Exotic Animals in Eighteenth-Century Paris*. Baltimore: Johns Hopkins University Press.

Robins, Rosemary. 2008. Inventing Oncomice: Making Natural Animal, Research Tool and Invention Cohere. *Genomics, Society and Policy* 4 (2):21–35.

Rorvik, David M. 1978. *In His Image: The Cloning of a Man*. Philadelphia: J. B. Lippincott.

Rossant, Janet, and Roger A. Pedersen. 1986. *Experimental Approaches to Mammalian Embryonic Development*. Cambridge: Cambridge University Press.

Rubin, Gerald M. 1985. Summary of the Molecular Biology of Development Symposoum. *Cold Spring Harbor Symposia on Quantitative Biology* 50: 905–9.

Rubin, Gerald M., and Edward B. Lewis. 2000. A Brief History of *Drosophila*'s Contributions to Genome Research. *Science* 287 (5461):2216–8.

Rubin, Gerald M., and Allan C. Spradling. 1982. Genetic Transformation of *Drosophila* with Transposable Element Vectors. *Science* 218 (4570):348–53.

Ruddle, Frank H. 1973. Preface to *Genetic Mechanisms of Development.* Soceity for Developmental Biology Symposium 31, edited by F. H. Ruddle. New York & London: Academic Press.

———. 1981. A New Era in Mammalian Gene-Mapping – Somatic-Cell Genetics and Recombinant DNA Methodologies. *Nature* 294 (5837):115–20.

———. 2001. Hundred-Year Search for the Human Genome. *Annual Review of Genomics and Human Genetics* 2 (1):1–8.

Ruddle, Frank H., and Raju S. Kucherlapati. 1974. Hybrid Cells and Human Genes. *Scientific American* 231 (1):36–44.

Ruddle, Frank H., and O. Wesley McBride. 1977. New Approaches to Cell Genetics: Co-Transfer of Linked Genetic Markers by Chromosome-Mediated Gene Transfer. In *The Molecular Biology of the Mammalian Genetic Apparatus: Its Relationship to Cancer, Aging and Medical Genetics,* Vol. 2, edited by P. O. P. Ts'o. Amsterdam: North-Holland.

Sambrook, Joe. 1985. Foreword to Molecular Biology of Development symposium. *Cold Spring Harbor Symposia on Quantitative Biology* 50:xv.

Santesmases, María Jesús. 2009. From Prophylaxis to Atomic Cocktail: Circulation of Radioiodine. *Dynamis* 29:337–63.

Scangos, George A., Kenneth M. Huttner, Saul Silverstein, and Frank H. Ruddle. 1979. Molecular Analysis of Chromosome-Mediated Gene Transfer. *Proceedings of the National Academy of Sciences of the USA* 76 (8):3987-90.

Scangos, George A., and Frank H. Ruddle. 1981. Mechanisms and Applications of DNA-Mediated Gene-Transfer in Mammalian-Cells – A Review. *Gene* 14 (1-2):1–10.

Schaffer, Simon. 1989. Glass Works: Newton's Prisms and the Uses of Experiment. In *The Uses of Experiment: Studies in the Natural Sciences*, edited by D. Gooding, T. J. Pinch and S. Schaffer. Cambridge: Cambridge University Press.

Schmeck, Harold M. 1979. Injection of a Gene Cures Flaw in Cell. *New York Times*, 10 October, A14.

———. 1980. 3 at Yale Report Key Transplants of Genes to Mice. *New York Times*, 4 September, A1, A14.

———. 1981a. Biotechnology No Longer Provokes Intense Concern. *New York Times*, 15 December, C1, C6.

———. 1981b. Gene Therapy: Scientists Take First Steps toward Curing the 'Incurable' Disorders. *New York Times*, 8 September, C1–C2.

———. 1982a. Bigger Mousetraps and Thorny Ethical Issues. *New York Times*, 19 December, E18.

———. 1982b. Rat Gene Implant in Mice Reported. *New York Times*, 16 December, A1, B13.

Schneider, Keith. 1988. Harvard Gets Mouse Patent, a World First. *New York Times*, 13 April, A22.

Schweiger, Hans-Georg, ed. 1981. *International Cell Biology 1980–1981: Papers Presented at the Second International Congress on Cell Biology, Berlin (West), August 31-September 5, 1980*. Berlin, Heidelberg & New York: Springer-Verlag.

Secord, James A. 2004. Knowledge in Transit. *Isis* 95 (4):654–72.

Sell, Susan K. 2003. *Private Power, Public Law: The Globalization of Intellectual Property Rights*. Cambridge: Cambridge University Press.

Sepulveda, Antonia R., Milton J. Finegold, Billie Smith, Betty L. Slagle, Janet L. DeMayo, Rong-Fong Shen, Savio L. C. Woo, and Janet S. Butel. 1989. Development of a Transgenic Mouse System for the Analysis of Stages in Liver Carcinogenesis Using Tissue-Specific Expression of SV40 Large T-antigen Controlled by Regulatory Elements of the Human α-1-antitrypsin Gene. *Cancer Research* 49 (21):6108–17.

Serpente, Norberto. 2011. Cells from Icons to Symbols: Molecularizing Cell Biology in the 1980s. *Studies in History and Philosophy of Biological and Biomedical Sciences* 42 (4):403-11.

Shapin, Steven, and Simon Schaffer. 1985. *Leviathan and the Air-Pump: Hobbes, Boyle, and the Experimental Life*. Princeton: Princeton University Press.

Siddiqi, Obaid. 2002. Guido Pontecorvo: 29 November 1907 – 25 September 1999. *Biographical Memoirs of Fellows of the Royal Society* 48:375–90.

Silver, Lee. 2008. Obituary: Salome Gluecksohn-Waelsch, 1907–2007. *Nature Genetics* 40 (4):376.

Simons, Paul. 1987. Review of "Manipulating the Mouse Embryo: A Laboratory Manual". *Genetics Research* 49 (2):175–6.

Sinn, Eric, William J. Muller, Paul K. Pattengale, Isidore Tepler, Rachel Wallace, and Philip Leder. 1987. Coexpression of MMTV/v-Ha-*ras* and MMTV/c-*myc* Genes in Transgenic Mice: Synergistic Action of Oncogenes *In Vivo*. *Cell* 49 (4):465–75.

Slack, Jonathan M. W. 2000. A Short History of the British Society for Developmental Biology. *International Journal of Developmental Biology* 44 (1):79–83.

Smith, Andrew. 1958. Brave New Mice. *Daily Telegraph*, 6 October.

Snell, George D. 1951. Hybrids and History. The Role of Race and Ethnic Crossing in Individual and National Achievement. *Quarterly Review of Biology* 26 (4):331–47.

———, ed. 1941. *Biology of the Laboratory Mouse*. Philadelphia: Blakiston.

Snow, Michael H. L., and Anne McLaren. 1974. The Effect of Exogenous DNA Upon Cleaving Mouse Embryos. *Experimental Cell Research* 86 (1):1–8.

Sobotta, Johannes. 1895. Die Befruchtung und Furchung des Eies der Maus. *Archiv für mikroskopische Anatomie* 45 (1):15–93.

———. 1902. Die Entwicklung des Eies der Maus vom Schlusse der Furchungsperiode bis zum Auftreten der Amniosfalten. *Archiv für mikroskopische Anatomie* 61 (1):274–330.

———. 1911. Die Entwicklung des Eies der Maus vom ersten Auftreten des Mesoderms an bis zur Ausbildung der Embryonalanlage und dem Auftreten der Allantois. *Archiv für mikroskopische Anatomie* 78 (1):271-352.

Southern, Edwin M. 1975. Detection of Specific Sequences among DNA Fragments Separated by Gel Electrophoresis. *Journal of Molecular Biology* 98 (3):503–17.

Speroff, Leon 2009. *A Good Man. Gregory Goodwin Pincus: The Man, His Story, the Birth Control Pill*. Portland, OR: Arnica.

Spradling, Allan C., and Gerald M. Rubin. 1982. Transposition of Cloned P-Elements into Drosophila Germ Line Chromosomes. *Science* 218 (4570):341–7.

Srinivasan, Ashwin, ed. 2009. *Donald Michie on Machine Intelligence, Biology and More.* Oxford: Oxford University Press.

Stamhuis, Ida H., and Arve Monsen. 2007. Kristine Bonnevie, Tine Tammes and Elisabeth Schiemann in Early Genetics: Emerging Chances for a University Career for Women. *Journal of the History of Biology* 40 (3):427–66.

Stern, Curt. 1940. Recent Work on the Relation between Genes and Developmental Processes. *Growth* Suppl. 1:19–36.

Stevens, Hallam. 2013. *Life out of Sequence: A Data-Driven History of Bioinformatics*. Chicago & London: University of Chicago Press.

Stevens, Leroy C. 1970. Development of Transplantable Teratocarcinomas from Intratesticular Grafts of Preimplantation and Postimplantation Mouse Embryos. *Developmental Biology* 21 (3):364–82.

Stewart, Timothy A., and Beatrice Mintz. 1981. Successive Generations of Mice Produced from an Established Culture Line of Euploid Teratocarcinoma Cells. *Proceedings of the National Academy of Sciences of the USA* 78 (10):6314–8.

Strasser, Bruno J. 2011. The Experimenter's Museum: Genbank, Natural History, and the Moral Economies of Biomedicine. *Isis* 102 (1):60–96.

Stratton, Kelly. 2012. Beyond Luck: Penn Vet's Ralph L. Brinster, VMD, PhD, Earns National Medal of Science for a Lifetime of Breakthroughs. *Bellwether: The Newsmagazine of the University of Pennsylvania School of Veterenary Medicine* 76:4–7, 36.

Stroun, Maurice, Philippe Anker, Pol Charles, and Lucien Ledoux. 1966. Fate of Bacterial Deoxyribonucleic Acid in *Lycopersicon esculentum*. *Nature* 212 (5060):397–8.

Suárez-Díaz, Edna. 2014. The Long and Winding Road of Molecular Data in Phylogenetic Analysis. *Journal of the History of Biology* 47 (3):443–78.

Suárez-Diaz, Edna, and Victor H. Anaya-Muñoz. 2008. History, Objectivity, and the Construction of Molecular Phylogenies. *Studies In History and Philosophy of Biologal and Biomedical Sciences* 39 (4):451–68.

Suárez-Díaz, Edna, and Vivette García-Deister. 2015. That 70s Show: Regulation, Evolution and Development Beyond Molecular Genetics. *History and Philosophy of the Life Sciences* 36 (4):503-24.

Summers, William C., and Wilma P. Summers. 1977. [^{125}I]deoxycytidine Used in a Rapid, Sensitive, and Specific Assay for Herpes Simplex Virus Type 1 Thymidine Kinase. *Journal of Virology* 24 (1):314-8.

Surani, M. Azim, and Sheila C. Barton. 1983. Development of Gynogenetic Eggs in the Mouse - Implications for Parthenogenetic Embryos. *Science* 222 (4627):1034–6.

Surani, M. Azim, Sheila C. Barton, and Michael. L. Norris. 1984. Development of Reconstituted Mouse Eggs Suggests Imprinting of the Genome During Gametogenesis. *Nature* 308 (5959):548–50.

Tarkowski, Andrzej K. 1961. Mouse Chimaeras Developed from Fused Eggs. *Nature* 190:857–60.

———. 1998. Mouse Chimaeras Revisited: Recollections and Reflections. *International Journal of Developmental Biology* 42 (7):903-8.

Tatum, Edward 1958. A Case History in Biological Research. Nobel Lecture. Available at http://www.nobelprize.org/nobel_prizes/medicine/laureates/1958/tatum-lecture.html. Accessed on 13 August 2012.

Taylor, Gordon Rattray. 1968. *The Biological Time Bomb*. London: Thames & Hudson.

Thackray, Arnold, ed. 1998. *Private Science: Biotechnology and the Rise of the Molecular Sciences*. Philadelphia: University of Pennsylvania Press.

Theiler, Karl. 1972. *The House Mouse: Development and Normal Stages from Fertilization to 4 Weeks of Age*. New York: Springer.

Thomas, Charles A. 1978. The Fanciful Future of Gene Transfer Experiments. In *Genetic Interaction and Gene Transfer.* Brookhaven Symposia in Biology 29, edited by C. W. Anderson. Upton, NY: Brookhaven National Laboratory.

Thompson, E. P. 1971. The Moral Economy of the English Crowd in the Eighteenth Century. *Past & Present* 50 (1):76–136.

Thompson, Simon, Alan R. Clarke, Angela M. Pow, Martin L. Hooper, and David W. Melton. 1989. Germ Line Transmission and Expression of a Corrected *hprt* Gene Produced by Gene Targeting in Embryonic Stem Cells. *Cell* 56 (2):313–21.

Tofano, Daidree, Ilse R. Wiechers, and Robert Cook-Deegan. 2006. Edwin Southern, DNA Blotting, and Microarray Technology: A Case Study of the Shifting Role of Patents in Academic Molecular Biology. *Genomics, Society and Policy* 2 (2):50–61.

Tooze, John. 1973. *The Molecular Biology of Tumour Viruses*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Toufexis, Anastasia. 1980. Moving Towards Designer Genes. *TIME*, 15 September, 76–81.

Townes, Tim M., Jerry B. Lingrel, Howard Y. Chen, Ralph L. Brinster, and Richard D. Palmiter. 1985. Erythroid-Specific Expression of Human Beta-Globin Genes in Transgenic Mice. *EMBO Jounal* 4 (7):1715–23.

Turney, Jon. 1998. *Frankenstein's Footsteps: Science, Genetics and Popular Culture*. New Haven & London: Yale University Press.

US Department of Health and Human Services. 1981. *Recombinant DNA Research. Volume 6: Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules", January 1980 – December 1980*. Washington, D. C.: US Government Printing Office.

US Department of Health, Education and Welfare (DHEW). 1979. *Laboratory Safety Monograph: A Supplement to the NIH Guidelines for Recombinant DNA Research*. Washington, D. C.: US Government Printing Office.

US House of Representatives Committee on Interstate and Foreign Commerce. 1978. *Developments in Cell Biology and Genetics: Hearing before the Subcommittee on Health and the Environment, 31 May 1978*. Washington, D. C.: US Government Printing Office

Veitch, Andrew. 1982. How Supermouse Holds the Key to Weighty Matters. *The Guardian*, 16 December, 4.

Vettel, Eric J. 2006. *Biotech: The Countercultural Origins of an Industry*. Philadelphia: University of Pennsylvania Press.

Waddington, C. H. 1969a. A Matter of Life and Death. *New York Review of Books*, 5 June.

———. 1969b. Gene Regulation in Higher Cells. *Science* 166 (3905):639–40.

Wade, Nicholas. 1977. *The Ultimate Experiment: Man-Made Evolution*. New York: Walker.

Wade, Nicholas, and Gina Kolata. 1980. Human Gene Treatment Stirs New Debate. *Science* 210 (4468):407.

Wagner, Erwin F., Timothy A. Stewart, and Beatrice Mintz. 1981. The Human Beta-Globin Gene and a Functional Viral Thymidine Kinase Gene in Developing Mice. *Proceedings of the National Academy of Sciences of the USA* 78 (8):5016–20.

Wagner, Erwin F. 1990. EMBO Medal Review: On Transferring Genes into Stem Cells and Mice. *The EMBO Journal* 9 (10):3024–32.

Wagner, Thomas E., Peter C. Hoppe, Joseph D. Jollick, David R. Scholl, Richard L. Hodinka, and Janice B. Gault. 1981. Microinjection of a Rabbit Beta-Globin Gene into Zygotes and Its Subsequent Expression in Adult Mice and Their Offspring. *Proceedings of the National Academy of Sciences of the USA* 78 (10):6376–80.

Wagner, Thomas E., and Jeung S. Yun. 1979. Fine Structure of Human Sperm Chromatin. *Archives of Andrology* 2 (4):291-4.

Wagner, Thomas E., Julianne E. Sliwinski, and D. B. Shewmaker. 1978. Subunit Structure of Eutherian Sperm Chromatin. *Archives of Andrology* 1 (1):31-41.

Ward, David C. 1972. Informative Molecules in Biological Systems. *Yale Journal of Biology and Medicine* 45 (6):606-7.

Watson, James D. 2000. The Dissemination of Unpublished Information. In *A Passion for DNA: Genes, Genomes and Society*. Oxford: Oxford University Press.

———, ed. 1978. Chromatin. Symposium Held at Cold Spring Harbor, June 1-8, 1978, *Cold Spring Harbor Symposia on Quantitivative Biology* 42.

Watson, James D., and John Tooze, eds. 1981. *The DNA Story: A Documental History of Gene Cloning*. San Francisco: W. H. Freeman.

Watson, James D., John Tooze, and David Kurtz. 1983. *Recombinant DNA: A Short Course*. New York: Scientific American Books.

Weber, Marcel. 2007. Redesigning the Fruit Fly: The Molecularization of *Drosophila*. In *Science without Laws: Model Systems, Cases, Exemplary Narratives* edited by A. N. H. Creager, E. Lunbeck and M. N. Wise. Durham, NC & London: Duke University Press.

Weiner, Charles. 1979. The Recombinant DNA Controversy: Archival and Oral History Resources. *Science, Technology, & Human Values* 4 (26):17-9.

Weiss, Rick, and Norman Oder. 1980. Yale Biologists Find New Gene Process. *Yale Daily News*, 5 September, 1.

Whitten, Wesley K. 1956. Culture of Tubal Mouse Ova. *Nature* 177 (4498):96.

———. 1957. Culture of Tubal Ova. *Nature* 179 (4569):1081–2.

Whitten, Wesley K., and John D. Biggers. 1968. Complete Development in Vitro of the Pre-Implantation Stages of the Mouse in a Simple Chemically Defined Medium. *Journal of Reproduction and Fertility* 17 (2):399–401.

Whittingham, David G., and John D. Biggers. 1967. Fallopian Tube and Early Cleavage in the Mouse. *Nature* 213 (5079):942–3.

Wigler, Michael, Saul Silverstein, Lih-Syng Lee, Angel Pellicer, Yung-chi Cheng, and Richard Axel. 1977. Transfer of Purified Herpes Virus Thymidine Kinase Gene to Cultured Mouse Cells. *Cell* 11 (1):223–32.

Wigler, Michael, Raymond Sweet, Gek Kee Sim, Barbara Wold, Angel Pellicer, Elizabeth Lacy, Tom Maniatis, Saul Silverstein, and Richard Axel. 1979. Transformation of Mammalian Cells with Genes from Procaryotes and Eucaryotes. *Cell* 16 (4):777-85.

Williams, Jeffrey G. 1982. Mouse and Supermouse. *Nature* 300 (5893):575.

Williamson, Bob. 1976. First Mammalian Results with Genetic Recombinants. *Nature* 260 (5548):189–90.

Willison, Keith R. 1980. *Microinjection of Mammalian Eggs*. PhD Thesis, MRC Laboratory of Molecular Biology, University of Cambridge.

Wilmot, Sarah. 2007. Between the Farm and the Clinic: Agriculture and Reproductive Technology in the Twentieth Century. *Studies in History and Philosophy of Biological and Biomedical Sciences* 38 (2):303–15.

Wilson, Duncan. 2011. *Tissue Culture in Science and Society: The Public Life of a Biological Technique in Twentieth Century Britain*. Basingstoke: Palgrave Macmillan.

Wilt, Fred H., and Norman K. Wessels. 1967. *Methods in Developmental Biology*. New York: Thomas Y. Crowell Co.

Wolff, Jon A., and Joshua Lederberg. 1994. An Early History of Gene Transfer and Therapy. *Human Gene Therapy* 5 (4):469–80.

Wolstenholme, G. E. W., and Mauve O'Connor, eds. 1965. *Preimplantation Stages of Pregnancy.* Ciba Foundation Symposium. London: Churchill.

Woods, Abigail. 2004. *A Manufactured Plague: The History of Foot and Mouth Disease in Britain, 1839–2001.*. London: Earthscan.

———. 2007. The Farm as Clinic: Veterinary Expertise and the Transformation of Dairy Farming, 1930–50. *Studies In History and Philosophy of Biologal and Biomedical Sciences* 38 (2):462-87.

———. 2012. Rethinking the History of Modern Agriculture: British Pig Production, c. 1910–65. *Twentieth Century British History* 23 (2):165–91.

Woychik, Richard P., John S. Wassom, and David Kingsbury. 1993. TBASE: A Computerized Database for Transgenic Animals and Targeted Mutations. *Nature* 363 (6427):375–6.

Wright, Susan. 1986. Molecular Biology or Molecular Politics? The Production of Scientific Consensus on the Hazards of Recombinant DNA Technology. *Social Studies of Science* 16 (4):593–620.

———. 1994. *Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering, 1972–1982*. Chicago & London: University of Chicago Press.

Yanchinski, Stephanie. 1980. Opening the Pandora's Box of Biology. *New Scientist*, 11 September.

Yardley, William. 2013. Harold M. Schmeck, Jr., 89, Times Science Writer, Dies. *New York Times*, 9 April, A17.

Yi, Doogab. 2008a. Cancer, Viruses, and Mass Migration: Paul Berg's Venture into Eukaryotic Biology and the Advent of Recombinant DNA Research and Technology, 1967–1980. *Journal of the History of Biology* 41 (4):589–636.

———. 2008b. *The Recombinant University: Genetic Engineering and the Emergence of Biotechnology at Stanford, 1959–1980*. PhD thesis, Princeton University.

———. 2011. Who Owns What? Private Ownership and the Public Interest in Recombinant DNA Technology in the 1970s. *Isis* 102 (3):446–74.

Zallen, Doris T., and Richard M. Burian. 1992. On the Beginnings of Somatic Cell Hybridization: Boris Ephrussi and Chromosome Transplantation. *Genetics* 132 (1):1–8.

Zuckerman, Harriet, Jonathan Cole, and John T. Bruer. 1991. Interview with Salome Waelsch. In *The Outer Circle: Women in the Scientific Community*, edited by H. Zuckerman, J. Cole and J. T. Bruer. New York: W. H. Norton.