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Citation

Jones, David S. 2016. Therapeutic Evolution or Revolution? Metaphors and Their Consequences. In *Therapeutic Revolutions: Pharmaceuticals and Social Change in the Twentieth Century*, eds Jeremy A. Greene, Flurin Condrau, and Elizabeth Siegel Watkins. Chicago: University of Chicago Press.

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Chapter 10

Therapeutic Evolution or Revolution? Metaphors and Their Consequences

David S. Jones

When Cleveland surgeon René Favaloro published his description of coronary artery bypass grafting in 1968, he launched one of the most important surgical procedures in the United States.¹ Speaking at a conference in Houston in 1985, he described 1968 as the “year of revolution.”² When interviewed a decade later, however, Favaloro used a different metaphor. As he described it, “The evolution took place in just a few months from patch graft to interposition graft to bypass graft.”³ So which was it: an evolution or a revolution? Debates about the meanings and merits of these two metaphors for historical change have been a fixture of the historiography of science and medicine for decades. Although historians do not argue as much about whether or not a particular development counted as a “scientific revolution” as they did when Thomas Kuhn’s *Structure of Scientific Revolutions* was fresh, the choice of “evolution” or “revolution” remains important, especially in the history of medicine and therapeutics. The two metaphors carry very different connotations for our understandings of how and why medical practice changes over time.

Revolutions, as the essays in this volume make clear, receive the lion’s share of attention from historians. Charles Rosenberg’s classic essay on the “therapeutic revolution,” revisited at

¹ René G. Favaloro, “Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion,” *Annals of Thoracic Surgery* 5 (1968): 334-339.

² Favoloro, quoted in *THI Today* (December 1985), p. 2, in John P. McGovern Historical Collections and Research Center (Houston Academy of Medicine), Institutional Collection #43 (Texas Heart Institute), Box 2, Folder “THI Today, 1985”.

³ Favaloro, “Oral History” (3 March 1997), in *Pioneers of Cardiac Surgery*, ed. William S. Stoney (Nashville: Vanderbilt University Press, 2008), pp. 357-368, on p. 364.

the end of this volume, has set the standard for therapeutic history for nearly forty years.⁴ Yet Rosenberg's 1977 essay principally focused on a nosological revolution that only secondarily transformed therapeutics. Others have written about the bacteriological revolution, the antibiotic revolution that followed, and the broader pharmaceutical revolution in the 1950s. Geneticists have for decades been making promissory claims about a genetic revolution that will introduce a new epoch of personalized, precision medicine.⁵ Historians of surgery have described the anesthetic and aseptic revolutions. One cardiologist, channeling Kuhn, has even described "The Structure of Cardiological Revolutions."⁶

Evolution, however, is also ubiquitous in the medical literature. Consider the field of cardiology, once named "the youngest child of medical evolution."⁷ Atherosclerotic plaques undergo "evolution,"⁸ as do cardiac surgery procedures,⁹ anesthetic techniques,¹⁰ and the

⁴ Charles Rosenberg, "The Therapeutic Revolution: Medicine, Meaning, and Social Change in Nineteenth-Century America," *Perspectives in Biology and Medicine* 20 (1977): 485-506.

⁵ David S. Jones, "The Prospects of Personalized Medicine," in *Genetic Explanation: Sense and Nonsense*, ed. Sheldon Krimsky and Jeremy Gruber (Cambridge: Cambridge: Harvard University Press, 2013), pp. 147-170; Reza Mirnezami, Jeremy Nicholson, and Ara Darzi, "Preparing for Precision Medicine," *New England Journal of Medicine* 366 (2012): 489-491.

⁶ Burton E. Sobel, "The Structure of Cardiological Revolutions," *Circulation* 87 (1993): 2047-2054. Sobel described three revolutions: a "social revolution" that led to declining prestige of the profession, the revolution of interventional cardiology, and the revolution of molecular and cellular biology.

⁷ Louis Faugères Bishop and John Neilson, *History of Cardiology* (New York: Medical Life Press, 1927), 71.

⁸ Peter Libby, Paul M. Ridker, and Attilio Maseri, "Inflammation and Atherosclerosis," *Circulation* 105 (2002): 1135-1143.

⁹ Floyd D. Loop, Delos M. Cosgrove, Bruce W. Lytle, Robert L. Thurer, Conrad Simpfendorfer, Paul C. Taylor, and William L. Proudfit, "An 11-Year Evolution of Coronary Arterial Surgery," *Annals of Surgery* 190 (October 1979): 444-454.

¹⁰ A.S. Keats, "Evolution of Anesthesia for Cardiac Surgery," *Cleveland Clinic Quarterly* 48 (1981): 75-79.

specialties of cardiology and cardiac surgery.¹¹ Doctors can use electrocardiograms to follow a heart attack's "electrocardiographic evolution."¹² New operations and instruments have been evolved.¹³ When cardiac surgeons began to face competition from the new field of interventional cardiology, many realized that "only our ability to evolve will guarantee our survival."¹⁴ Even patients joined the effort: "Patients undergoing coronary bypass grafting have undergone an evolution in recent years."¹⁵ At times physicians have explicitly debated which metaphor -- evolution or revolution -- offers the more apt description for whatever therapeutic changes happen to interest them, whether heart-lung machines, statin therapy, or endovascular repair of abdominal aortic aneurysms.¹⁶ A revolution itself, such as that produced by transesophageal echocardiography, can undergo evolution.¹⁷

The language of evolution has been entrenched in the history of medicine as well. In April 1913, for instance, William Osler gave lectures at Yale titled the "Evolution of Medicine."

¹¹ Ellis J. Jones, William S. Weintraub, Joseph M. Carver, Robert A. Guyton, and Caryn L. Cohen, "Coronary Bypass Surgery: Is the Operation Different Today," *Journal of Thoracic and Cardiovascular Surgery* 101 (1991): 108-115.

¹² Anthony P. Fletcher, Sol Sherry, Norma Alkjaersig, Fotios E. Smyrniotis, and Sidney Jick, "The Maintenance of a Sustained Thrombolytic State in Man," *Journal of Clinical Investigation* 38 (1959): 1111-1119.

¹³ Michael E. DeBakey, "Changing Concepts in Thoracic and Vascular Surgery," *Journal of Thoracic and Cardiovascular Surgery* 38 (1959): 145-165.

¹⁴ Michael Mack, Ralph Damiano, Robert Matheny, Hermann Reichenspurner and Alain Carpentier, "Inertia of Success: A Response to Minimally Invasive Coronary Bypass: A Dissenting Opinion," *Circulation* 99 (1999): 1404-1406.

¹⁵ Jones and others, "Coronary Bypass Surgery."

¹⁶ F. Trojette, A. Benamar, S. Beloucif, D. Foure, H.J. Poulain, "Clinical Experience with the Mini-extracorporeal Circulation System: An Evolution or a Revolution?" *Annals of Thoracic Surgery* 77 (2004): 2172-2176; P. Rehfield, C. Kopes-Kerr, and M. Clearfield, "The Evolution or Revolution of Statin Therapy in Primary Prevention: Where Do We Go from Here?" *Current Atherosclerosis Reports* 15 (2013): 298; C. Lee, C.S. Barroso, and P.J. Troped, "Endovascular Aneurysm Sealing for Abdominal Aortic Aneurysm Repair: Evolution or Revolution?" *Cardiovascular and Interventional Radiology* 37 (October 2014): 1129-1136.

¹⁷ J.R.T.C. Roelandt, I.R. Thomson, W.B. Vletter, P. Brommersma, N. Bom, D.T. Linker, "Multiplane Transesophageal Echocardiography: Latest Evolution in an Imaging Revolution," *Journal of the American Society of Echocardiography* 5 (1992): 361-367.

He sought to tell the story of medical progress. Even though the path might not have been linear, medical theory and practice improved with evolution: “like a living organism, truth grows, and its gradual evolution may be traced from the tiny germ to the mature product. Never springing, Minerva-like, to full stature at once, truth may suffer all the hazards incident to generation and gestation.”¹⁸ As the editors describe in their introduction to this volume, Fielding Garrison praised Osler’s “panoramic survey” of the painful evolution of medicine from superstition to rationality. Garrison hoped that Osler’s narrative of evolutionary progress would be an inspiration to students and other readers.¹⁹

Even though historians of medicine have since learned to be skeptical of positivism and Whiggish “just-so” stories, evolution remains widespread in historians’ writing. Historians have published essays on the evolution of medical ideas, for instance of the term “chancre,” of Darwin’s concept of pangenesis, of clinical trials, or of Harvey Cushing’s thoughts about specialization.²⁰ They have traced the evolution of medical techniques, including endotracheal anesthesia, prophylactic enucleation of the eye, bronchial casts, or frozen sections (and the impact of those on the evolution of surgical pathology).²¹ And they have narrated the evolution

¹⁸ William Osler, *The Evolution of Medicine* (New Haven: Yale University Press, 1922), 219.

¹⁹ Field H. Garrison, “Preface,” in Osler, *The Evolution of Medicine*, xiii.

²⁰ Harry Keil, “The Evolution of the Term Chancre and Its Relation to the History of Syphilis,” *Journal of the History of Medicine and Allied Sciences* 4 (1949): 407-416; Gerald L. Geison, “Darwin and Heredity: The Evolution of His Hypothesis of Pangenesis,” *Journal of the History of Medicine and Allied Sciences* 4 (1969): 375-411; Abraham M. Lilienfeld, “Ceteris Paribus: The Evolution of the Clinical Trial,” *Bulletin of the History of Medicine* 56 (1982): 1-18; Samuel H. Greenblatt, “Harvey Cushing’s Paradigmatic Contribution to Neurosurgery and the Evolution of His Thoughts about Specialization,” *Bulletin of the History of Medicine* 77 (2003): 789-822.

²¹ Noel Gillespie, “The Evolution of Endotracheal Anaesthesia,” *Journal of the History of Medicine and Allied Sciences* 1 (1946): 583-594; R.K. Blach, “Prophylactic Enucleation in Sympathetic Ophthalmitis: The Evolution of an Heroic Form of Treatment,” *Medical History* 15 (1971): 190-192; Andrew Davies, “The Evolution of Bronchial Casts,” *Medical History* 17 (1973): 386-391; James R. Wright, “The Development of the Frozen Section Technique, the

of medical institutions, from the Mayo Clinic to health services in India.²² Such articles rarely invoke anything more than the most superficial idea of evolution as a process of gradual, progressive change over time.²³

What are we to make of the co-existence of evolution and revolution in medicine and its histories? Both words are often used casually in English, without careful attention to their specific meanings or connotations. The meanings of “evolution” have themselves evolved over time, and many discordant meanings remain in use today.²⁴ From the Latin *evolver*, to rollout or unroll (as in unrolling a scroll), evolution first appeared in English in the mid-seventeenth century. It was used in different ways, to describe the wheeling movement of dancers, the course of childbirth, or the working out of God’s plan for creation. By the eighteenth century it increasingly implied a gradual change in a system from a simpler to a more complex state, as in embryological development. This meaning generalized in biology to describe the transformation of organisms over time. “Revolution,” as described elsewhere in this book, has followed an equally complex course, from a revolving movement in space or time, to violent upheaval and

Evolution of Surgical Biopsy, and the Origins of Surgical Pathology,” *Bulletin of the History of Medicine* 59 (1985): 295-326.

²² H.P. Tait, “Health Services in India and Burma: Their Evolution and Present Status,” *Medical History* 16 (1972): 184-193; W. Bruce Fye, “The Origins and Evolution of the Mayo Clinic from 1864 to 1939: A Minnesota Family Practice Becomes an International ‘Medical Mecca,’” *Bulletin of the History of Medicine* 84 (2010): 323-357.

²³ One essay, for instance, on the evolution of the concept of febrile seizures, describes how “Beginning in the mid-nineteenth century and continuing as a gradual process to the present, this thinking has changed dramatically.” See John W. Gardner and Robert C. Dinsmore, “Evolution of the Concept of the Febrile Seizure as It Developed in the American Medical Literature, 1800-1980,” *Journal of the History of Medicine and Allied Sciences* 50 (1995): 340-363, on p. 341.

²⁴ “Evolution,” *Oxford English Dictionary*, 3rd edition (March 2008), available at www.oed.com; Raymond Williams, “Evolution,” in *Keywords: A Vocabulary of Culture and Society*, revised edition (New York: Oxford University Press, 1983), 120-123; Robert J. Richards, “Evolution,” in *Keywords in Evolutionary Biology*, eds. Keller and Elisabeth A. Lloyd (Cambridge: Harvard University Press, 1992), 95-105, on p. 95; Richard C. Lewontin, “Organism and Environment,” in *Learning, Development, and Culture*, ed. H.C. Plotkin (New York: John Wiley & Sons Ltd., 1982), pp. 151-170, especially 152-156.

the overthrow of an established social or political order.²⁵ By the nineteenth century the sudden overthrow of revolution was contrasted against the gradual, organic reforms of evolution.²⁶ But this distinction was never perfect, with evolution in biology including ruthless struggles between species and dramatic extinctions. Do doctors and historians actually intend any of these specific meanings when they use “revolution” or “evolution” in their writing? Cardiological revolutions do not involve violent overthrow, and the evolution of cardiac surgery does not rely on surgeons’ differential reproductive success.

There is meaning in the words nonetheless. Evolution and revolution are both models of change over time. It is easy to see the appeal of a claim of revolution for scientists, and for their historians: it pronounces a radical break from the past, confident and triumphant. Progress is implied by the decisiveness of the rupture. Such rhetoric is good for marketing, especially when contrasted against the cautious gradualism of evolution. But evolution has its own appeals, especially its reassuring connotations of progressive improvement. Roy Porter defined the stakes well in his 1986 essay on scientific revolutions.²⁷ He described the juxtaposition of evolution and revolution as a contrast between continuity and cataclysm. He argued that if historians would not stake a claim about this distinction, they put themselves “in danger of defaulting on the task of assessing overall patterns of science.”²⁸ However, they had to proceed with caution. Porter advocated a narrow definition of scientific revolutions: they ought to involve a self-conscious

²⁵ “Revolution,” *Oxford English Dictionary*, 3rd edition (March 2010), available at www.oed.com; Raymond Williams, “Revolution,” in *Keywords*, 270-274.

²⁶ Williams, “Evolution,” 122; Williams, “Revolution,” 273.

²⁷ Roy Porter, “The Scientific Revolution: A Spoke in the Wheel?” in *Revolution in History*, ed. Porter and Mikuláš Teich (Cambridge: Cambridge University Press, 1986), 290-316.

²⁸ Porter, “The Scientific Revolution,” 300. He writes: “is it helpful to picture the course of the history of science as revolutionary? Or might it not make better sense to stress its ‘evolutionary’ aspects, its continuities and accommodation to the wider socio-intellectual environment? These large questions matter, not least because, with the irresistible rise of specialization, scholarship becomes myopic and fragmented” (300).

process of challenge, resistance, and struggle, the deliberate “overthrow of an entrenched orthodoxy.”²⁹ By this standard, the seventeenth century did bring some revolutionary changes to the sciences, but the changes in nineteenth century medical theory that Rosenberg described were merely a crisis, not a revolution.³⁰ Even though he winnowed the list of scientific revolutions, Porter also warned against a “retreat into an *evolutionary* metaphor of science’s development, on some specious analogy with the dictum *natura non facit saltum*.”³¹ What he wanted was deliberate, thoughtful, discussions of the pace and character of scientific change. His demand remains relevant today.

It is not enough simply to debate what counts, or not, as revolution or evolution. Instead, much can be gained through serious engagement with the theory and language of revolution and evolution in pursuit of the best possible accounts of scientific change. Porter, and the other essays in this book, did this with revolution. Something similar can be done with evolution. Relevant concepts, and their components, can be made into meaningful guides for historical analysis. Evolutionary biologists have developed an elaborate theoretical apparatus to understand the processes of organismic evolution, with analyses of niches, fitness, competition, the Red Queen hypothesis, extinction, taxonomy, island biogeography, and morphospace. Some of these ideas, such as the niche, have already been adapted by historians. Other aspects can be adapted to history as well, an exercise that can be thought provoking and even productive.

It is, of course, important not to be cavalier when borrowing ideas across scholarly disciplines. Richard Lewontin, a noted evolutionary theorist, has warned scholars in other fields not to appropriate concepts of evolution, because evolutionary theory was developed to explain

²⁹ Porter, “The Scientific Revolution,” 300.

³⁰ Porter, “The Scientific Revolution,” 308.

³¹ Porter, “The Scientific Revolution,” 309.

biological change, not social change, and its concepts cannot be casually applied across the latter domain.³² Scholars have long contested efforts to apply evolution to psychology, sociology, and social policy.³³ Similar concerns exist with history. Applying biological theory to history risks naturalizing what are actually social, economic, and political processes. Moreover, theories of evolution, like those of revolution, carry connotations of progress. These can confound understandings of progress in medicine, something that has long been a vexing issue for historians. Used carefully, however, the language of evolution can be a valuable tool for historians to think with.

Niche

In basic ecological and evolutionary theory, a niche is the space or role in an environment occupied by a particular species. Bees pollinate flowers, bats eat mosquitoes, and so forth. Historians of medicine have taken up the niche concept in two different ways. In *Last Resort*, Jack Pressman explained why lobotomy worked in the 1940s but not forty years later.³⁴ He offered the niche as an intuitive, ecological metaphor. The efficacy of a treatment can only be understood in the context of the particular problem the treatment offers to solve: “the extent to which a treatment flourishes is directly dependent upon the specific features of the day’s clinical landscape. In the long haul, viability is a matter of ecology, not virtue.”³⁵ In the 1930s, asylums overflowed with patients, hopelessness, and horror. Psychiatrists desperately sought new

³² Richard Lewontin, Conversation with the Author, 23 May 2011.

³³ For one revealing exchange, see Stephen J. Gould, “Darwinian Fundamentalism,” *New York Review of Books* 44 (12 June 1997): 34–37; Steven Pinker, with a reply by Gould, “Evolutionary Psychology: An Exchange,” *New York Review of Books* 44 (9 October 1997).

³⁴ Jack Pressman, *Last Resort: Psychosurgery and the Limits of Medicine* (Cambridge: Cambridge University Press, 1998).

³⁵ Pressman, *Last Resort*, 14; see also p. 160.

treatments. Lobotomy, which could calm some patients (albeit at the cost of damaging their personality), offered “human salvage.” It appealed to patients, their families, and psychiatrists. Pressman’s metaphor was explicit: “from an ecological perspective, the treatment rapidly penetrated into a niche of almost limitless size that as yet had no competitors.”³⁶

Ian Hacking used niche models to explain the history of dissociative fugues and other diseases that appear in a society only to vanish at some future date: “I argue that one fruitful idea for understanding transient mental illness is the ecological niche, not just social, not just medical, not just coming from the patient, not just from the doctors, but from the concatenation of an extraordinarily large number of diverse types of elements which for a moment provide a stable home for certain manifestations of illness.”³⁷ He argued that four “vectors” defined the extent of the niche: medical taxonomy (or nosology), cultural polarity, observability, and release. As these vectors change over time, so do the niches, and the diseases themselves: “To postulate a niche for an illness is to make two kinds of claims, one positive, one negative. In the presence of the relevant vectors, the illness flourishes; in their absence it does not.”³⁸ For both Pressman and Hacking, the metaphor of the niche provided an analytic framework that accounted for changing diseases and treatments over time.

While the niche concept has clear value, it introduces some risks. As Lewontin has warned, invocation of a biological concept like “niche” in a historical analysis might reify the phenomena being studied. This is a risk, since existing scholarship on changing diagnostic categories and therapeutic practices has shown that there is little natural about these dynamics. Historians have described many cases in which interested groups have, in effect, created niches

³⁶ Pressman, *Last Resort*, 190.

³⁷ Ian Hacking, *Mad Travelers: Reflections on the Reality of Transient Mental Illness* (Charlottesville, Va.: University of Virginia Press, 1998), 13.

³⁸ Hacking, *Mad Travelers*, 82.

for diseases or treatments. Patient activists have pushed diseases onto the medical agenda. Pharmaceutical executives have publicized diseases to create new markets for their products. When diuretics and tricyclic antidepressants appeared in the 1950s, Merck and other companies distributed educational materials to popularize the diseases -- hypertension and depression -- that the drugs could treat.³⁹ This set the precedent for many diseases (and their drugs), from social anxiety disorder to restless leg syndrome and erectile dysfunction.⁴⁰

Historians have often analyzed these cases an alternative metaphor, that of the market. While market analyses have obvious relevance and value, they focus on just one aspect of the phenomena -- money. Niche models offer a broader approach that can incorporate other dynamics. Moreover, the risk of naturalization can be minimized by emphasizing the social factors that define the niche. Pressman described overflowing asylums, psychiatrists in search for respect, and legislatures concerned by growing mental health budgets. Hacking's vectors were intellectual and cultural, from medical theorizing about epilepsy to the new popularity of cycling. However, avoiding the biological baggage of niche can be tricky to do. Hacking, for instance, equivocates, suggesting that there had to be "an ecological niche in which the construction could thrive."⁴¹ This just begs the question.

Tensions about whether a niche is natural or constructed are embedded deep in the origins of the word itself. "Niche" has been used since the eighteenth century to describe the lair

³⁹ David Healy, *The Antidepressant Era* (Cambridge: Harvard University Press, 1997); Jeremy A. Greene, *Prescribing by Numbers: Drugs and the Definition of Disease* (Baltimore: Johns Hopkins University Press, 2007).

⁴⁰ Ray Moynihan and David Healy, "The Fight Against Disease Mongering: Generating Knowledge for Action," *PLoS Medicine* 3 (2006): e191.

⁴¹ Hacking, *Mad Travelers*, 101.

of an animal or a suitable place for a person. This usage was borrowed from architecture.⁴²

“Niche” first appeared in English in 1610 to specify a space, often in cathedrals, built to house statues and relics; it replaced an older Latin term, *aedicula*, meaning a small house.⁴³ The derivation of “niche” itself remains contested. Some trace the word to a French source, also *niche*, meaning a kennel for a dog, or possibly *nichier*, meaning to make a nest. Others prefer an Italian source, *nicchio*, for seashell.⁴⁴ In either case, the architectural term “niche” has its roots, ironically, in nature. The ambiguity about whether a niche is natural or constructed simply recapitulates this etymology.

Recent developments in evolutionary theory offer a possible solution to this tension. When ecologists developed niche theories in the 1910s and the 1920s, they focused on characteristics of an organism’s environment (e.g., availability of food and shelter, competition and predation, etc.).⁴⁵ In 1957, however, G. Evelyn Hutchinson re-conceptualized the niche as a property of the species in relation to its environment.⁴⁶ This definition introduced the distinction between the fundamental niche (i.e., that which was possibly achievable by a species) and the realized niche. Meanings of “niche” shifted again in the 1970s when Richard Lewontin popularized the idea of “niche construction.”⁴⁷ Beavers build dams, grazers alter the species

⁴² James R. Griesemer, “Niche: Historical Perspectives,” in *Keywords in Evolutionary Biology*, 230-240. Caroline Jones, at the Massachusetts Institute of Technology, alerted me to this history: Mark Jarzombek to Caroline Jones, 24 June 2009, email shared with author.

⁴³ “Niche,” Oxford English Dictionary, available at www.oed.com. For the evolution of *aedicula* in medieval cathedral architecture, see John Summerson, “Heavenly Mansions: An Interpretation of Gothic,” in *Heavenly Mansions and other Essays on Architecture* (London: Cresset Press, 1949): 1-28.

⁴⁴ Online Etymology Dictionary, available at <http://www.etymonline.com>.

⁴⁵ Griesemer, “Niche.”

⁴⁶ Griesemer, “Niche,” 238-239; Robert K. Colwell, “Niche: A Bifurcation in the Conceptual Lineage of the Term,” in *Keywords in Evolutionary Biology*, 241-248.

⁴⁷ Richard Lewontin, “Adaptation,” *Scientific American* 239 (September 1978): 212-230, on p. 215. See also: F. John Odling-Smee, Kevin N. Laland, Marcus W. Feldman, “Niche

compositions of fields where they graze, and trees create myriad niches around themselves. As Lewontin later explained, organisms “are not simply *objects* of the laws of nature, altering themselves to bend to the inevitable, but active *subjects* transforming nature according to its laws.”⁴⁸ By shifting the focus from adaptation to construction, evolution becomes a coupled process in which organisms are functions of their environment and environments are functions of their organisms.⁴⁹

Understood in light of these modern formulations, the niche becomes a productive model for historians of medicine. It has both ecological connotations, suggesting an opportunity within an environment, and architectural connotations, suggesting a built space (which can encompass market strategies). In the simplest application, a therapeutic niche might simply be a disease or symptom in need of treatment. The rise of coronary artery disease in the twentieth century, for instance, opened a niche for a diverse assortment of pharmaceutical and surgical treatments. But the niche is not simply a phenomenon of the physical disease environment; the niche is also a social process. It might be the recognition of the need to manage some aspect of the burden of

Construction,” *American Naturalist* 147 (1996): 641-648. As they explain, “The idea here, in retrospect, is obvious: “Organisms, through their metabolism, their activities, and their choices, define, partly create, and partly destroy their own niches” (641).

⁴⁸ Richard C. Lewontin, “Organism and Environment,” in *Learning, Development, and Culture*, ed. H.C. Plotkin (New York: John Wiley & Sons Ltd., 1982), 151-170, on p. 163.

⁴⁹ Richard Lewontin, “Gene, Organism, Environment,” in *Evolution from Molecules to Men*, ed. D.S. Bendall (Cambridge: Cambridge University Press, 1983), 273-285; Clive G. Jones, John H. Lawton, and Moshe Shachak, “Positive and Negative Effects of Organisms as Physical Ecosystem Engineers,” *Ecology* 78 (1997): 1946-1957; F. John Odling-Smee, Kevin N. Laland, Marcus W. Feldman, “Niche Construction,” *American Naturalist* 147 (1996): 641-648; K.N. Laland, F.J. Odling-Smee, and M.W. Feldman, “The Evolutionary Consequences of Niche Construction: A Theoretical Investigation Using Two-locus Theory,” *Journal of Evolutionary Biology* 9 (1996): 293-316. For a discussion of how niche construction can be applied to the human social sciences (e.g., human niche construction, social learning, cultural inheritance, etc.), and a vigorous debate about that approach, see Kevin N. Laland, John Odling-Smee, and Marcus W. Feldman, and Commentators, “Niche Construction, Biological Evolution, and Cultural Change,” *Behavioral and Brain Sciences* 23 (2000): 131-175.

disease. There was a lag of several decades, for instance, between the rise of coronary disease and decisions by physicians and health officials to commit substantial resources against it. New disease concepts (e.g., atherosclerosis, coronary thrombosis), new technologies (e.g., the electrocardiogram), and new specialties (e.g., cardiology) all converged between the 1920s and 1950s to open the therapeutic niche for coronary artery disease.

Theories of niche construction suggest that a therapeutic niche will be altered by the treatments that attempt to fill it. Antibiotics have changed their niche by triggering the emergence (evolution) of antibiotic resistant bacteria.⁵⁰ Chris Feudtner has described the transformation (or niche construction) of diabetes.⁵¹ Before insulin, diabetes was an acute disease, with patients wasting away and then dying from ketoacidosis and hyperglycemic coma. After insulin, diabetes became a chronic disease, with patients developing diabetic retinopathy, nephropathy, neuropathy, and vascular disease. Each new complication opened a new therapeutic niche. The success of bypass surgery in the 1970s inspired cardiologists to develop angioplasty, which has now displaced bypass surgery from much of its niche. The complications of angioplasty, including restenosis and stent thrombosis, have created secondary niches, for platelet inhibitors and antiproliferative agents, that could not have been imagined in the 1950s. Used with attention to the subtleties that have been developed by evolutionary biologists, niche theory can be a valuable tool for historians of medicine.

Fitness

⁵⁰ Robert Bud, *Penicillin: Triumph and Tragedy* (New York: Oxford University Press, 2007); Scott Podolsky, *The Antibiotic Era: Reform, Resistance, and the Pursuit of a Rational Therapeutics* (Baltimore: Johns Hopkins University Press, 2014).

⁵¹ Chris Feudtner, *Bittersweet: Diabetes, Insulin, and the Transformation of Illness* (Chapel Hill: University of North Carolina Press, 2003).

When doctors and patients think about therapeutics, they often focus on the most fundamental outcome: did the treatment work? This can be surprisingly difficult to determine. Outcome can be assessed from the perspective of the physician or the patient; by changes in symptoms, laboratory values, imaging studies, or life expectancy; after short, medium, or long intervals; and with case series, cohort studies, randomized trials, and meta-analyses. Historians have also been extremely interested in efficacy. As Rosenberg explored in his classic essay on therapeutic revolutions, and revisits in the next chapter, one of the most interesting puzzles has been understanding how and why assessment of efficacy changes over time. Bloodletting, now dismissed by biomedical scientists, was popular in western medicine for over two thousand years. It must have worked. The crucial challenge is to understand what work it did.⁵²

The concept of efficacy has productive parallels with the concept of fitness. Darwin used “fit” and “fitted” throughout *Origin*, but it was only in the 1866 edition, influenced by Alfred Russel Wallace and Herbert Spencer, that he began to use “survival of the fittest.”⁵³ Population geneticists have defined fitness as differential reproductive success, something that is not an absolute attribute of an organism but a measure of its success in a particular environment. Since reproductive success is sometimes random (e.g., an extremely “fit” organism could die in an accident), biologists have developed a “propensity” interpretation of fitness that distinguishes potential and realized fitness.⁵⁴

It takes some tinkering to adapt evolutionary concepts of fitness to history of medicine. Treatments do not reproduce in any biological sense. Success is determined instead by the beneficial effect of a treatment on patients and the perception of that effect among physicians

⁵² Rosenberg, “The Therapeutic Revolution,” 1977.

⁵³ Diane Paul, “Fitness: Historical Perspectives,” in *Keywords in Evolutionary Biology*, 112-114.

⁵⁴ John Beatty, “Fitness: Theoretical Contexts,” in *Keywords in Evolutionary Biology*, 115-119.

and patients. However, at an abstract level, fitness can do useful work for historians. First, it actually is possible to think of fitness in terms of a treatment's ability to generate progeny.⁵⁵ As physicians work to improve treatments, whether pharmacological or procedural, they produce derivatives. Penicillin gave rise to methicillin, ampicillin, amoxicillin, and many other antibiotics. The first β -blockers produced derivatives that diversified and filled other niches. Balloon angioplasty has inspired an ever-growing lineage of catheter-based interventions. If success at producing derivatives yields one with higher clinical efficacy, then the parent therapy dies out -- a victim of its own reproductive success. Second, it is possible to think of therapeutic fitness in terms of a treatment's ability to expand a therapeutic niche. While sildenafil can produce erections, what really made it successful was its ability, through marketing, to transform the embarrassing problem of impotence into the profitable diagnosis of erectile dysfunction. In a similar way, it is possible for treatments to achieve success by creating sub-niches (segmenting the market?) for a series of treatments. The niche of hypertension now has space not just for one fittest antihypertensive, but for many fit diuretics, β -blockers, and more.

The distinction between potential and realized fitness is useful as well. Doctors often think about both the optimal outcomes that can be achieved with a treatment and those realized in actual clinical practice. In this respect, randomized clinical trials measure potential fitness, while realized fitness is experienced by patients in routine clinical practice -- this is the distinction between efficacy and effectiveness. The problem of non-compliance fits in here as well, as one of the many barriers that stands between potential and realized fitness.⁵⁶ Does a

⁵⁵ One example is provided by Walter Sneader, discussed in more detail below.

⁵⁶ Jones, "Technologies of Compliance: Surveillance of Self-Administration of Tuberculosis Treatment, 1956-1966," *History and Technology* 17 (Winter 2001): 279-318; Greene, "Therapeutic Infidelities: 'Noncompliance' Enters the Medical Literature, 1955-1975," *Social History of Medicine* 17 (2004): 327-343.

treatment work? That cannot be answered simply, just as a biologist cannot say whether or not an organism is fit. Like biologists who assess fitness in the context of a specific niche, physicians and historians must assess efficacy in the context of the problem being treated, the outcomes most valued by the patients and doctors, and the ability of the health care system to deliver the treatment.

Competition

Competition, one domain in which differential fitness reveals itself, has come to be seen as nearly synonymous with natural selection. It plays a key role in evolutionary theory. Biologists define it specifically as “the simultaneous reliance of two individuals, or two species, on an essential resource that is in limited supply.”⁵⁷ What is the limited resource in medicine? There are many possibilities. Illness episodes generate the need for treatment (and the opportunity for reimbursement). Patients host illness episodes. Health care resources are deployed to treat them. Competition for episodes, patients, and resources takes place between different treatments (e.g., medications or surgery for coronary disease), providers (e.g., cardiologists, cardiac surgeons, nutritionists), institutions (e.g., from neighborhood clinics to national referral centers), and insurers. While overt competition was once considered unseemly in medicine, it is now routine, and billions of dollars are spent each year advertising to gain advantage. Each of these aspects of competition offers a productive target for historical analysis.

What determines the outcome of competition? Success in medicine is fickle. The best treatments, doctors, or health care systems do not necessarily outcompete the others. Doctors have sought to adjudicate competition between treatments with randomized clinical trials, but

⁵⁷ Evelyn Fox Keller, “Competition: Current Usages,” in *Keywords in Evolutionary Biology*, 68-73, on p. 68.

there have been many obstacles to trials' power.⁵⁸ Success can come from better efficacy or from fewer side effects. Selective serotonin reuptake inhibitors, for instance, displaced tricyclic antidepressants not because of superior efficacy but because of increased safety (especially in overdose). Marketing campaigns have pushed many blockbusters to prominence even when those blockbusters had no significant advantage over existing treatments.⁵⁹ Sometimes the cultural meanings of diseases and their treatments matter most. Anne Pollock has shown how racial dynamics have influenced the popularity of treatments for hypertension (e.g., guidelines once recommended diuretics for black patients and ACE inhibitors for white patients) and heart failure (e.g., the approval of BiDil for patients who self-identify as black).⁶⁰ The fittest might survive, but there are many ways for a treatment to be fit.

The Red Queen Hypothesis

In classic Darwinian theory, organisms struggle to adapt themselves to their environment. Biologists now recognize that niches change constantly over time, a result of both environmental change and shifting competitive landscapes as other species come and go. This has important consequences for adaptation and natural selection: organisms must adapt to something that is constantly changing. Invoking a scene from Lewis Carroll's *Through the Looking-Glass*, evolutionary theorist Leigh van Valen in 1973 named this the Red Queen hypothesis.⁶¹ As the

⁵⁸ Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990* (Cambridge: Cambridge University Press, 1997).

⁵⁹ Greene, *Prescribing by Numbers*; Joseph Dumit, *Drugs for Life: How Pharmaceutical Companies Define Our Health* (Durham: Duke University Press, 2012); Healy, *Antidepressant Era*.

⁶⁰ Anne Pollock, *Medicating Race: Heart Disease and Durable Preoccupations with Difference* (Durham: Duke University Press, 2012).

⁶¹ Leigh Van Valen, "A New Evolutionary Law," *Evolutionary Theory* 1 (1973): 1-30, especially pp. 17-22. See also Lewontin, "Adaptation": 215.

Red Queen told Alice, in her world “it takes all the running you can do, to keep in the same place.”⁶² In biological terms, organisms might evolve constantly just to maintain a stable level of fitness in the changing environment. Subsequent theorists have introduced variants. One, restricting the Red Queen hypothesis to competitive interactions between species, coined a new phenomenon, the Court Jester effect, to analyze efforts by organisms to track random changes in their physical environments.⁶³ As a 2009 article explained, the “Red Queen model stems from Darwin, who viewed evolution as primarily a balance of biotic pressures, most notably competition.” The Court Jester model, in contrast, argues “that evolution, speciation, and extinction rarely happen except in response to unpredictable changes in the physical environment, recalling the capricious behavior of the licensed fool of Medieval times.”⁶⁴

The challenge of adapting to a changing niche provides a powerful intuitive model for understanding the fundamental task of medicine and public health: to provide relief from the diseases that afflict human populations. Physicians and public health officials seek to define and then eclipse the burden of disease.⁶⁵ The problem is that the burden of disease is never static. It changes constantly in response to changing physical and social environments, the evolution of pathogenic micro-organisms, the advent of new and dangerous technologies (e.g., cars,

⁶² Lewis Carroll, *Through the Looking-Glass, and What Alice Found There* (London: Macmillan and Co., 1872).

⁶³ Anthony D. Barnosky, “Distinguishing the Effects of the Red Queen and Court Jester on Miocene Mammal Evolution in the Northern Rocky Mountains,” *Journal of Vertebrate Paleontology* 21 (2001): 172-185. A recent analysis invokes another piece of fiction (Tolkien’s *Lord of the Rings*) to mark a different distinction. Organism-environment mismatches, whether from Red Queen or Court Jester effects, can cause both increased extinction rates and decreased origination rates of new species, a phenomenon of “evolutionary sterility that we call the Entwines effect.” See Tiago B. Quental and Charles R. Marshall, “How the Red Queen Drives Terrestrial Mammals to Extinction,” *Science* 290 (2013): 290-292, on p. 291.

⁶⁴ Michael J. Benton, “The Red Queen and the Court Jester: Species Diversity and the Role of Biotic and Abiotic Factors Through Time,” *Science* 323 (2009): 728-732, on p. 728.

⁶⁵ David S. Jones, Scott H. Podolsky, and Jeremy A. Greene, “The Burden of Disease and the Changing Task of Medicine,” *New England Journal of Medicine* 366 (2012): 2333-2338.

cigarettes), or the impact of decisive medical interventions (e.g., smallpox vaccination).

Physicians and public health officials must struggle to keep up. Since innovation takes time, evolving medical therapies inevitably lag behind the changing burden of disease.

Physicians and medical researchers, for instance, set out to master bacterial disease in the 1880s. They studied patients, identified causative micro-organisms, and then sought “magic bullets” that could cure the diseases, from immunizations and serotherapies early in the twentieth century to the “antibiotic revolution” in the 1950s analyzed in this volume by Scott Podolsky and Anne Kveim Lie. By that point, however, the burden of disease in the United States and other developed economies had shifted: cardiovascular disease and cancer had displaced infections as the leading causes of death.⁶⁶ Medical scientists took on these new challenges, supported by major investments in health care and research (e.g., the National Cancer Institute, the National Heart Institute). By the early 2000s physicians could celebrate dramatic successes against coronary artery disease (e.g., diuretics, β -blockers, ACE inhibitors, statins, bypass surgery, angioplasty, anti-smoking campaigns, etc.) and cancer (e.g., cytotoxic chemotherapy, surgery, radiation therapy, targeted chemotherapies, etc.). The burden of disease, however, continues to shift, with neuropsychiatric conditions rising to new prominence (e.g., depression, dementias, substance use). Medical science and public health will hopefully produce solutions to these conditions, but the burden of disease will surely shift once again.

A second Red Queen effect has played out in parallel. Just as medical and public health practitioners and institutions struggled to keep pace with the changing burden of disease, clinical researchers have struggled to produce knowledge of therapeutic efficacy that keeps up with changing therapeutic practice. Definitive assessment of efficacy often requires long-term follow

⁶⁶ Thomas McKeown, *The Role of Medicine: Dream, Mirage, or Nemesis?* (Princeton: Princeton University Press, 1979).

up (e.g., three- or five-year survival). Clinical trials that assess such outcomes necessarily last many years: design, patient recruitment, implementation, follow up, and analysis all take significant time to complete. Trial outcomes often are not published until five to ten years after the design of the intervention protocol. Are the ensuing results relevant? It depends on assumptions about therapeutic evolution. If you believe, as many patients and doctors do, that treatments improve over time, then a trial's results are undermined before they are even published. They reflect treatment as it existed ten years previously, an ancestral -- and more primitive -- form.

Consider the trials of coronary angioplasty. By the mid-1990s angioplasty had become a routine treatment for stable coronary disease even though there was little convincing evidence that it added value beyond optimal medical therapy. To produce decisive data, investigators from fifty sites designed the COURAGE trial to detect any incremental benefits provided by angioplasty.⁶⁷ They enrolled 2287 patients between June 1999 and January 2004 and followed them through June 2006. Over a mean follow-up of 4.6 years, they found no significant differences in rates of death, heart attacks, or hospitalization for acute coronary syndromes. This study, published in March 2007 in the *New England Journal of Medicine*, was trumpeted in the press as a "blockbuster." Shares of Boston Scientific, a leading stent manufacturer, fell and stent use dropped 10% within a month.⁶⁸ Supporters of angioplasty rushed to the procedure's defense. Since enrollment began in 1999, most COURAGE patients (97.7%) received bare metal stents.

⁶⁷ William E. Boden, Robert A. O'Rourke, Koon K. Teo, and others, "Design and Rationale of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial," *American Heart Journal* 151 (2006): 1173-1179; Boden, O'Rourke, Teo, and others, "Optimal Medical Therapy with or without PCI for Stable Coronary Disease," *New England Journal of Medicine* 356 (2007): 1503-1516.

⁶⁸ Keith J. Winstein, "Stent Implants Declined in April -- Doctors Attribute Drop To Study Showing Drugs May Have Similar Benefits," *Wall Street Journal*, 17 May 2007; Winstein, "A Simple Health-Care Fix Fizzles Out," *Wall Street Journal* 11 February 2010.

In 2003, however, drug-eluting stents designed to prevent restenosis became available in the United States.⁶⁹ Most cardiologists assumed that the new stents would outperform the old stents. As a result, “one could very reasonably hypothesize” that the outcomes of COURAGE would have been better had drug-eluting stents been used.⁷⁰ And since drug-eluting stents had already come to dominate the marketplace, critics argued that COURAGE was obsolete on arrival. Its negative results need not diminish enthusiasm for the variants in current use. The evidence base, always running, can never catch up.

Extinction

Most species that have ever existed have gone extinct.⁷¹ The same holds true in medicine. Many once popular therapies have vanished, with competition probably the most common cause of extinction. When chlorpromazine appeared in the mid 1950s, lobotomy was made “redundant” and went extinct.⁷² Chlorpromazine and other “typical” antipsychotics have since been driven close to extinction by newer (and heavily marketed) “atypical” antipsychotics. Sometimes a new competitor wipes out whole lineages. In the 1960s surgeons utilized many different approaches to coronary revascularization; nearly all of them disappeared with the emergence of bypass surgery in 1968.⁷³ Changes in the niche can be important as well. As Condrau and Kehr describe in this volume, the decline of tuberculosis in the United States and Europe eliminated the need

⁶⁹ Dean J. Kereiakes, “PCI Is No Better than Medical Therapy for Stable Angina? Seeing Is Not Believing,” *Cleveland Clinic Journal of Medicine* 74 (2007): 637-642. See also Barnaby J. Feder, “First, A New Artery Stent Study; Now, Questions about What It All Means,” *New York Times*, 28 March 2007.

⁷⁰ Kereiakes, “PCI Is No Better”: 640.

⁷¹ John Damuth, “Extinction,” in *Keywords in Evolutionary Biology*, 106-111.

⁷² Pressman, *Last Resort*, 401.

⁷³ Jones, “Surgical Practice and the Reconstruction of the Therapeutic Niche: The Case of Myocardial Revascularization,” in Thomas Schlich and Chris Crenner, *Innovation in Surgery* (Rochester: University of Rochester Press, forthcoming), ***.

for rest cures, sanatoria, thoracoplasty, and a host of other once-popular interventions. Smallpox vaccine sowed the seeds of its own demise by eradicating its own niche. If enough individuals find ways to control coronary disease through lifestyle and prevention, then bypass surgery and countless other treatments might disappear as well.

While studies of the extinction of specific treatments can be productive, historians can also follow the lead of evolutionary biology and look at broader patterns in therapeutic evolution. How have rates of speciation and extinction changed over time? Have periods of massive therapeutic proliferation (e.g., the “antibiotic revolution” as Burgess Shale?) typically been followed by periods of therapeutic mass extinction, as competition winnows out unfit therapies? It is necessary to organize the data of therapeutic evolution before it is possible to see its patterns.

Taxonomy

Scholars in many fields, confronted with large data sets, have sought ways to organize them. In natural history this became the science of taxonomy. Taxonomy is not simply about description and sorting. Instead, it requires that arguments be made about affinity: which things are most closely related? Taxonomists have long debated the merits of taxonomies based on morphology or genealogy.⁷⁴ This distinction is relevant in medicine as well. Doctors can classify diseases according to organ system or etiology, but ambiguities always persist. Does it make sense to define a category of pneumonia, regardless of whether it is caused by staph or strep, or do strep infections form the “natural kind” regardless of whether they strike lung, throat, or

⁷⁴ David C. Hull, *Science as a Process: An Evolutionary Account of the Social and Conceptual Development of Science* (Chicago: University of Chicago Press, 1990).

skin?⁷⁵ The situation is different for classifying therapies. Many writers, especially in review articles and textbooks, offer typological classifications of medications. Psychiatric drugs can be divided into antidepressants, antipsychotics, mood stabilizers, or anxiolytics. Antihypertensives can be divided into diuretics, vasodilators, β -blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and presumably others yet to come. But treatments, like species, have evolved over time. This makes it possible for physicians and historians to produce therapeutic genealogies. The different ways of classifying raise important questions for historian of medicine.

First, medical taxonomies, like biological taxonomies, changed over time as medical knowledge changed and as doctors made new claims about affinity. Taxonomies of fever changed with the rise of germ theory.⁷⁶ The classification of substance use has swung between vice and disease.⁷⁷ The shifts can be abrupt, especially when a bureaucratic power imposes a new taxonomic order. In 1892, for instance, the Department of the Interior issued new rules for physicians who worked on Indian reservations.⁷⁸ Consumption, which had been a constitutional disease in 1891, along with cancer, anemia, dropsy, and rheumatism, became tuberculosis, an infectious disease, like chicken-pox, diphtheria, measles, and influenza. Theorists of cartography have long argued that maps are not simply descriptions of geographic space. Instead, maps are

⁷⁵ Ian Hacking, *The Social Construction of What?* (Cambridge: Harvard University Press, 1999); Geoffrey C. Bowker and Susan Leigh Star, *Sorting Things Out: Classification and Its Consequences* (Cambridge, MA: MIT Press, 2000).

⁷⁶ Christopher Hamlin, *More than Hot: A Short History of Fever* (Baltimore: Johns Hopkins University Press, 2014).

⁷⁷ Sarah W. Tracy, *Alcoholism in America: From Reconstruction to Prohibition* (Baltimore: Johns Hopkins University Press, 2005).

⁷⁸ For the old nomenclature, see *Annual Report of the Commissioner of Indian Affairs to the Secretary of Interior* (Washington: Government Printing Office, 1891), 806-812. For the new nomenclature, see *Annual Report of the Commissioner of Indian Affairs to the Secretary of Interior* (Washington: Government Printing Office, 1892), 919-925.

arguments, the product of strategic decisions about what data to represent and how to represent them.⁷⁹ Taxonomies function similarly, making arguments about the affinity, etiology, or genealogy of diseases or therapeutics.

Second, superimposing genealogy on top of typological taxonomy reveals important boundary crossings in the history of therapeutics. Walter Sneader, for instance, has used evolutionary taxonomy to organize knowledge of pharmacology and trace its history in his “genealogical approach to drug discovery.”⁸⁰ Some lineages develop methodically, with all progeny staying within the same therapeutic class as the prototype. Penicillin gave rise to many generations of antibiotics, selected (designed) to be long acting (e.g., procaine penicillin), resistant to penicillinases (e.g., methicillin), broad spectrum (e.g., ampicillin), or orally absorbed (e.g., amoxicillin).⁸¹ Other lineages are full of surprises. Consider the descendants of epinephrine. Analogs (i.e., adrenergic agonists, e.g., albuterol) remain a mainstay of asthma therapy. Antagonists (i.e., β -blockers, e.g., propranolol), developed to protect the heart against adrenaline surges, proved useful not just for coronary artery disease but also hypertension. Some researchers developed derivatives with less neurotoxicity (e.g., atenolol) to make hypertension regimens more tolerable. Other researchers, intrigued by the vivid dreams produced by lipophilic β -blockers, sought more psychoactive derivatives, a pursuit that yielded the serotonin and norepinephrine reuptake inhibitors that have transformed the treatment of depression.⁸² Many

⁷⁹ Dennis Wood, *The Power of Maps* (New York: Guilford Press, 1992); Wood and John Fels, *The Natures of Maps: Cartographic Constructions of the Natural World* (Chicago: University of Chicago Press, 2009).

⁸⁰ Walter Sneader, *Drug Prototypes and Their Exploitation* (New York: John Wiley & Sons, Ltd, 1996), ix. In the preface to Sneader’s work, historian John Swann describes how Sneader, by “walking us step-by-step through the evolution,” is able to “document the modern revolution of real therapeutics” (vii)

⁸¹ Sneader, *Drug Prototypes*, 463-482.

⁸² Sneader, *Drug Prototypes*, 264-281.

other pharmaceutical lineages have jumped across functional classes. Antimalarials produced antihistamines and then antipsychotics.⁸³ B-vitamins gave rise to drugs for tuberculosis (e.g., isoniazid) and depression (e.g., iproniazid and other monoamine oxidase inhibitors).⁸⁴

The ways in which drug lineages transgress therapeutic class reveal not just the complexity of pharmacology (e.g., the subtlety of drug-receptor interactions), but also the important role of serendipity. Researchers who develop derivatives for one purpose often stumble across drugs useful for another purpose. This resembles the processes of exaptation described by biologists. Just as feathers likely evolved as insulation before they enabled flight, drug derivatives often find unanticipated applications.

Similar processes take place in surgery. Between 1920 and 1970 surgeons developed a bewildering diversity of surgical procedures to treat coronary artery disease. Sometimes a lineage preserved its function even as its form changed completely. For instance, techniques to slow the body's metabolism by reducing thyroid function evolved from surgical resection of the thyroid in the 1930s to destruction of thyroid tissue with radioactive iodine in the 1950s. Exaptation has been common, with techniques developed in one area of surgery (e.g., saphenous vein interposition grafts to repair renal artery stenosis) finding application elsewhere (e.g., coronary artery disease). Once coronary artery bypass surgery achieved a foothold in its niche, it underwent adaptive radiation and gave rise to many variants, including recent attempts at minimally invasive procedures. The adaptive radiation of the angioplasty lineage has been even more dramatic (and profitable), with balloon techniques giving rise to atherectomy, laser ablation, stents, and many others.

⁸³ Sneader, *Drug Prototypes*, 661-679.

⁸⁴ Sneader, *Drug Prototypes*, 410-415.

Questions of lineage and taxonomy often become relevant for policy. How much change can accumulate in a therapeutic lineage while preserving functional identity? When is new evidence and regulatory oversight required to ensure that the treatment still works as its predecessors did? According to the 1976 Medical Device Amendment, a new device can be approved expeditiously if it is substantially equivalent to an existing device -- the 510(k) process. This policy has been exploited by device manufacturers. One analysis of artificial hip implants included a branching tree diagram that traced the genealogical relations between 63 current implants and their ancestral forms.⁸⁵ The authors argued that, despite serial claims of substantial equivalence, significant changes had accumulated in the lineage over its many generations, and these required new regulatory oversight. At what point has speciation, and thus the need for renewed regulatory scrutiny, taken place? It is not always clear. Generic drugs raise similar questions. What kinds of similarity produce sufficient taxonomic affinity such that a generic drug can be assumed to be therapeutically -- and bureaucratically -- interchangeable with the parent drug? As Jeremy Greene has shown, distinctions are made not just on the structure of the active ingredient, but also on the binders and fillers that might affect bioequivalence, and the shapes, colors, and tastes that might affect pill-taking behavior.⁸⁶

Island Biogeography

Taxonomies raise questions not just about change over time, but also about the distribution of diversity over space. For instance, evolutionary theorists have studied how variation emerges in geographically isolated populations ever since Darwin's famous voyage to

⁸⁵ Brent M. Ardaugh, Stephen E. Graves, and Rita F. Redberg, "The 510(K) Ancestry of a Metal-on-Metal Hip Implant," *New England Journal of Medicine* 368 (2013): 97-100.

⁸⁶ Greene, *Generic: The Unbranding of Modern Medicine* (Baltimore: Johns Hopkins University Press, 2014).

the Galapagos Islands. As local varieties emerge, the isolated locales become sites for speciation. These intuitions were formalized in 1967 by Robert MacArthur and E. O. Wilson in their analyses of how so many species can exist on islands. Subsequent work has examined the ways in which islands become sources of novelty (i.e., speciation). Sometimes new species form when an existing species expands to occupy an open niche, subsequently splitting into two. At other times new species form when a geographic or behavioral barrier divides the group into two diversifying lineages.⁸⁷ The combination of isolation and small population size contributes to the rapid pace of change.

Medical geographers and historians have long wondered about the distribution of disease, especially the dynamics that influence the emergence of new pathogens in isolated regions and their potential dissemination.⁸⁸ The island biogeography of medical practice deserves similar attention. Jeremy Greene, in this volume, explores the significance of geographic variations in drug availability and pricing. A distinct literature exists about practice variation in surgery. From J. Alison Glover's 1938 description of a 27-fold disparity in tonsillectomy rates across London neighborhoods to the colorful maps of the *Dartmouth Atlas of Health Care* today, physicians have mapped striking disparities in medical practice between hospitals, cities, regions, and nations.⁸⁹ As John Wennberg and Alan Gittelsohn concluded in 1975, geographic variations in

⁸⁷ Robert J. Whittaker and José María Fernández-Palacios, *Island Biography: Ecology, Evolution, and Conservation*, 2nd ed. (New York: Oxford University Press, 2007).

⁸⁸ Tom Koch, *Cartographies of Disease: Maps, Mapping, and Medicine* (Redlands, CA: ESRI Press, 2005).

⁸⁹ Glover, J. Alison. "The Incidence of Tonsillectomy in School Children." *Proceedings of the Royal Society of Medicine* 31 (1938): 1219-1236; Center for the Evaluative Clinical Sciences, *Dartmouth Atlas of Health Care* (Chicago: American Hospital Publishing, 1996). For a discussion, see Jones, *Broken Hearts: The Tangled History of Cardiac Care* (Baltimore: Johns Hopkins University Press, 2013). For a critique of the Dartmouth approach, see Michael E. Chernew, Lindsay M. Sabik, Amitabh Chandra, Teresa B. Gibson, and Joseph P. Newhouse, "Geographic Correlation between Large-Firm Commercial Spending and Medicare Spending,"

medical practice “are a rule for which there is yet no exception.”⁹⁰ If practice variation simply reflected variation in the underlying burden of disease (i.e., if there were a perfect correlation between the biogeography of disease and the biogeography of medical practice), then it would not be interesting. However, an extensive body of research by physicians has concluded that much of the variation appears to be “unwarranted,” reflecting not the application of evidence based medicine to local burdens of disease, but instead the influence of physician supply, reimbursement practices, financial conflicts of interest, medical uncertainty, idiosyncratic differences in physicians’ beliefs and practices, and myriad other influences on medical decision making. Health policy experts have long seen the existence of unwarranted variation as a problem. As Frederick Robbins, president of the Institute of Medicine, wrote in 1983, “‘it looks bad, and it looks bad because it is bad. It is not an appropriate way for a profession to behave.’”⁹¹ Physicians and analysts have worked to identify the causes of unwarranted variation and purge it from medicine.

Historians can offer different perspectives. The first is epistemological: why did physicians become concerned about geographic variations when they did? The variations have existed for centuries.⁹² When Glover identified them in 1938, his work triggered no interest in the problem. It was only in the 1960s and 1970s that the problem received attention in the United

American Journal of Managed Care 16 (2010): 131-38; Newhouse and Alan Garber, “Geographic Variation in Health Care Spending in the United States,” *JAMA* 310 (2013): 1227-1228.

⁹⁰ John Wennberg and Alan Gittelsohn, “Health Care Delivery in Maine. I. Patterns of Use of Common Surgical Procedures,” *Journal of the Maine Medical Association* 66 (May 1975): 123-130, 149, on p. 127.

⁹¹ Frederick Robbins, quoted in John K. Iglehart, “From the Editor,” *Health Affairs* 3 (Summer 1984).

⁹² For most of this history, doctors argued that geographic variations in medical practice were an appropriate response to variations in environmental conditions. See, for instance, John H. Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America 1820-1885* (Cambridge: Harvard University Press, 1986).

States, in the setting of two developments: concern about the skyrocketing costs of health care and the emergence of evidence-based medicine.⁹³ It is not difficult to understand why documentation of unwarranted variation has been an affront to the aspirations of evidence-based medicine. Advocates of this movement have sought to discipline medical practice and bring it into conformity with the dictates of clinical data. Historians can contribute to this endeavor, for instance by helping to chart the forces that pull medical practice out of alignment with evidence-based medicine. Or they can choose to complicate the endeavor. Is it plausible that medicine could ever be a fully rational science, isolated from social, economic, and political influences? Few historians think this likely. Their analyses of historical contingency and the importance of local context can reveal the inevitable limits of evidence-based medicine.

The second perspective turns the problem of geographic variation into an opportunity. Historians, informed by biologists' theories of island biogeography, could argue that local variation in medical practice is actually a good thing. Isolation and local variation produced new traits and species in organismic evolution. Something similar has played out in the history of medicine. Different physicians and health care institutions have developed different approaches to particular clinical problems. In the ideal situation, doctors share and compare practices and contribute to medical progress. Aseptic surgery first developed in a particular late nineteenth century German surgical culture and then spread widely.⁹⁴ Directly observed therapy, developed to improve compliance with outpatient tuberculosis regimens in Madras in the 1950s, became a

⁹³ Jones, *Broken Hearts*. The research, when it did emerge, focused almost exclusively on surgery. Greene, in this volume, describes how practice variation in drug prescriptions also existed, and had become a subject of intense interest among pharmaceutical companies. Yet the literatures about surgical variation and pharmaceutical variation have remained distinct, produced by different kinds of analysts, published (or not) in different venues, and motivating different kinds of policy interventions.

⁹⁴ Thomas Schlich, "Asepsis and Bacteriology: A Realignment of Surgery and Laboratory Science," *Medical History* 56 (2012): 308-334.

mainstay for treatment of many diseases in many places.⁹⁵ But these are the best case scenarios.

There has never been an efficient system that evaluates different local practices and determines if one really is better than another. This is, of course, the nature of island biogeography. The barriers to exchange -- physical, cultural, or otherwise -- that foster local variation and innovation can impede their dissemination.

Morphospace

One last concept is particularly thought provoking. As Hutchinson formulated his niche theory in 1957, he realized that a niche was defined not just by two or three features of the environment and organism, but by innumerable factors. It was not simply a three-dimensional space, like an architectural niche, but an “ n -dimensional hypervolume ... every point in which corresponds to a state of the environment which would permit the species S_1 to exist indefinitely.”⁹⁶ This concept of the niche as a multidimensional hypervolume inspired a secondary idea, that of an n -dimensional trait space. As Steven Jay Gould wrote in 1991, “morphospace” represents the “full range of the abstract (and richly multivariate) space into which all organisms may fit.”⁹⁷ Any creature, real or imagined, occupies just a small patch. Conceptualized this way, morphospace presented Gould and his fellow biologists with a challenge: “we need to measure density, range, clumping, and a host of other properties that

⁹⁵ Ronald Bayer and David Wilkinson, “Directly Observed Therapy for Tuberculosis: History of an Idea,” *Lancet* 345 (1995): 1545-1548.

⁹⁶ G. Evelyn Hutchinson, “Concluding Remarks,” *Cold Spring Harbor Symposium on Quantitative Biology* 22 (1957): 415-427.

⁹⁷ Stephen Jay Gould, “The Disparity of the Burgess Shale Arthropod Fauna and the Limits of Cladistic Analysis: Why We Must Strive to Quantify Morphospace,” *Paleobiology* 17 (1991): 411-423, on p. 420.

determine differential filling of this totality; and we must be able to assess the variation in this differential filling through time.”⁹⁸

Morphospace provides evolutionary biologists with a teachable moment about contingency and developmental constraints. Large tracts of morphospace, once occupied, are now empty (e.g., trilobites, dinosaurs), the contingent result of meteor strikes and other causes of mass extinctions. But most morphospace has never been occupied. If you imagine every possible form a living creature could take (photosynthetic elephants! winged horses! dragons!), you quickly realize that most of these things ever existed. There are no six-limbed vertebrates. There are no talking horses. Instead, you find isolated clusters of creatures, with vertebrates in one region, crustaceans in another, trees someplace else, and an enormous -- but still finite -- cloud of bacteria. The lesson here is about constraint. Evolution works with a limited substrate: extant species. Since embryological development imposes constraints on how much one generation can vary from its parents, new species cluster near existing species and only slowly move into unfilled space. There is a wide gulf between realized and potential creatures.

Morphospace provides historians of medicine with two useful thought experiments. Thinking about disease space (pathospace?) is simple enough at first: it is the task of nosology and disease taxonomy. However, as you define the possible axes of disease space to capture every type of disease that does exist and begin to wonder about every type of disease that might exist, it quickly becomes an exercise in morbid imagination, one pursued enthusiastically in horror films and science fiction. Zombie viruses are simply the most recent in a long line of appalling imagined diseases. Fiction aside, disease space raises an important question about the

⁹⁸ Gould, “The Disparity”: 420. Gould admitted that this task was “dauntingly difficult” (420) at best, and possibly “logically intractable” (421). See also Benjamin Blonder, Christine Lamanna, Cyrille Violle, and Brian J. Enquist, “The *n*-Dimensional Hypervolume,” *Global Ecology and Biogeography* 23 (2014): 595-609, on p. 603.

social determinants of disease: to what extent do we control which swathes of disease space are occupied? Many diseases exist now because of decisions people have made about how to structure their societies, from smoking-related illnesses to obesity, substance abuse, lead poisoning, or car accidents. Our hunter-gatherer ancestors were presumably spared these diseases. What about our descendants? It is possible to imagine a world free of lung cancer, bronchitis, and emphysema. If tobacco use ceased, those diseases would almost certainly slip back into the domain of diseases that could be imagined, but do not actually exist.

The thought experiment is even more productive with therapeutics. Imagine an n -dimensional trait space for medical interventions, not just a pharmacospace or a surgerispace, but a therapospace, a remedispace -- an iatrospace. The dimensions would allow the full range of conceivable interventions (pharmaceutical, surgical, interactional, natural, synthetic, magical, religious, specific, universal, etc.) for every possible disease. Within this iatrospace could be found the actual treatments that do exist, abandoned treatments that once were popular, and ideal future treatments towards which medical research strives: magic bullets for cancer, drugs that reverse dementia, a vaccine for HIV, or an electromagnetic wand that dispels depression. As patients and doctors know too well, existing treatments occupy but a tiny fraction of potential iatrospace. The history of these shortcomings is, in part, a history of constraint. There are limits on what surgery can accomplish, and even though thousands of biologically-active compounds have been tested, it has not been possible to find a perfect drug for every clinical problem. Furthermore, just as natural selection can only work with existing species, doctors largely use existing treatments to produce subsequent, incremental derivatives.

But unlike in biology, physicians can influence how iatrospace gets filled. They can consciously imagine the space of potential therapeutics, recognize gaps that exist, and work to

fill them. Rational drug design, one of the many promissory sciences of contemporary biomedicine, demonstrates this well. As doctors characterize the mechanisms of disease in ever increasing detail and improve the resolution of their map of the n -dimensional volume of disease space, they identify new destinations in iatrospace. Advances in cancer science allowed doctors to move beyond surgical resection to cytotoxic chemotherapy, radiation, and now targeted kinase inhibitors. While there have been a few dramatic successes, many promising areas of iatrospace have not been reached. This model can help understand therapeutic failure as well. Psychiatrists, for instance, do not yet have a detailed enough map of psychiatric disease space to identify specific targets for therapeutic intervention. It might even be possible to construct a taxonomy of medical practice according to barriers to a total eclipse of different segments of the burden of disease. In some areas, as in psychiatry, the problem is our understanding of disease space. In others, as is increasingly the case in oncology or infectious disease, the challenge is finding an actual molecule that performs a well-characterized function within iatrospace.

These abstractions of n -dimensional hypervolumes, of disease space or iatrospace, bring together different threads of evolutionary theory. They provide domains in which not only niches, but also taxonomy, fitness, extinction, adaptive radiation, and many others play out. While evolutionary biology remains a distant analogy for the development of medical theory and practice, the theories of evolutionary biology can inspire productive theorizing within history of medicine.

The Problem of Progress

Historians of medicine can adapt theories and metaphors from evolutionary biology and develop new modes of description, new arguments about causation, and new perspectives on the

dynamics of change over time. But historians must think carefully if they do so. Is the analogy specific enough for evolutionary theory to add real value when applied to non-biological systems? Can our understanding of efficacy really be enhanced by insights about fitness or the therapeutic niche? The rhetoric of evolution, like that of revolution, requires careful handling by historians of medicine. It is important to think not just about the potential creative insights it offers, but also about the potential downsides of evolutionary concepts. The most relevant dilemma with evolution for historians of medicine, as with revolution, is the problem of progress.

Progress has long been associated with the varied meanings of evolution. “Progress” entered English from Latin in the fifteenth century, to mean a step forward, as on a march or journey. The movement was not necessarily positive, as seen in the usage (which continues) of “the progress of a disease.”⁹⁹ Through an association with “evolution,” however, “progress” gradually gained the meaning of movement from worse to better, first as “an inherent principle of development of higher forms,” and then more broadly to “an inherent process of social and historical improvement.”¹⁰⁰ Most eighteenth and nineteenth century writers saw progress in idealist terms, though some became increasingly concerned about the costs of progress.

The association of evolution with progress has long been a bugaboo for biologists.¹⁰¹ Traditional evolutionary thought assumed that evolution brought progress, as seen in ubiquitous imagery of the great chain of being. It is true that there are creatures living today that are more complex than the most complex creatures two billion years ago, and it is unlikely that anyone living now would trade their human existence for that of a unicellular critter from eons past.

⁹⁹ Raymond Williams, “Progressive,” in *Keywords*, 243-245, on p. 244.

¹⁰⁰ Williams, “Progressive,” 244, 245.

¹⁰¹ Richard Dawkins, “Progress,” in *Keywords in Evolutionary Biology*, 263-272, on p. 263.

Nonetheless, the scientific literature now takes a much more nuanced approach to progress. Phylogenetic lineages are full of dead ends. Some species lose functions over time (e.g., eyeless cave fish). A trait might satisfy a local selective pressure and proliferate, but decrease fitness in the long run (e.g., possibly the giant antlers of the Irish elk). Mass extinctions occurred repeatedly, with lineages vanishing sometimes for explicable causes and sometimes seemingly at random. At a global scale, evolution has actually maintained something of a status quo: if you plot complexity on the x-axis and the number of species achieving that level of complexity on the y-axis, the median organism on earth for billions of years has always been, and still remains, a bacterium.¹⁰² Nothing about natural selection or ecological dynamics as now understood necessitates progress.

Progress has been a similar problem in history of medicine, even among writers who would not self-identify as Whigs. Osler, Garrison, and many more recent historians have celebrated the progress of medicine. When doctors talk about treatments, practices, and institutions evolving, a sense of progress is part of this discourse. The assumption is that the new is better than the old, with evolution producing ever better understandings and interventions. In the 1960s, however, some historians of medicine turned away from these positivist assumptions and towards meta-narratives of relativism, skepticism, and critique. But progress is hard to set aside. Just as no one would want to live the life of an archaic bacterium, there are few who would choose to give up modern medical technology and live with medicine as it existed even 50, let alone 100 or 200 years ago. Historians have tried to find a balance by acknowledging the possibility of progress without accepting its inevitability.

¹⁰² Variation around this mean, however, has increased. This accounts for the appearance of more complex life forms over time.

Historians of medicine who are attuned to assumptions of evolutionary progress can offer perspective on progress in the medical literature. Physicians often deploy several different rhetorics of progress to generate faith and enthusiasm in new therapies -- and to discount the need for scholarly or regulatory scrutiny. In some cases they accentuate the merits of a break from the past. For instance, when coronary artery bypass grafting launched in the late 1960s, it was the latest in a long series of surgical attempts to treat coronary artery disease. Since prior techniques had ended in disillusionment, skeptics often assumed that the new operation would be no different. They demanded that bypass surgery be subjected to rigorous trials. Surgeons did not deny this history; rather, they denied its relevance. They argued that past surgical treatments had failed because they had relied on inadequate diagnostic technology. The advent of coronary angiography in the 1960s, however, allowed surgeons to visualize the coronary arteries before making a decision about surgical intervention, a “leap forward in our ability to read coronary disease that can be fairly likened to the impact of the invention of the printing press on the written word.”¹⁰³ This diagnostic revolution ruptured any kind of historical continuity. As surgeon Donald Effler explained, “Whatever surgical efforts were expended before are of historical interest only, and it does little good to dwell on past failures.”¹⁰⁴

In other cases doctors place their emphasis on gradual progress. A physician might develop a variant on an existing treatment and make a claim of incremental, evolutionary progress: the new is similar enough to the old, but improved, so that it should be trusted at the outset. This strategy allows doctors to tweak the dose of an approved regimen or adjust an operation in an attempt to make it safer, quicker, cheaper, or more effective. As long as everyone

¹⁰³ Donald Effler, “Surgery for Coronary Disease,” *Scientific American* 210 (1968): 36-43, on p. 38.

¹⁰⁴ Effler, “Myocardial Revascularization at the Community Hospital Level,” *American Journal of Cardiology* 32 (1973): 240-242, on p. 240.

assumes that the tweak is positive, then there is no need for new clinical trials or regulatory review. For instance, just as the Food and Drug Administration allows expedited approval if a new device is substantially equivalent to an existing device, it also grants the benefit of the doubt if the device involves “incremental innovations” of an existing device.¹⁰⁵ Is this wise? It depends on assumptions of progress. Device manufacturers argue that if the first device was safe and effective, then their slightly improved device should be safe and effective as well, hopefully more so. This intuition has worked well in many instances: incremental change has allowed for the safe flourishing of numerous medical devices and operative procedures. But device companies have now spawned so many generations of derivatives that some new devices bear little resemblance to the distant ancestor on which their approval relied, and many have been approved without specific clinical evidence. Consider implantable devices used to control cardiac arrhythmias. Between 1979 and 2012, the Food and Drug Administration granted 77 formal premarket approvals and an additional 5829 supplements, 37% of which involved a change in design.¹⁰⁶ Several of these devices failed, a consequence of unfulfilled assumptions of progress.

The challenge for historians is to use the language and theories of evolution skillfully. Evolutionary language can certainly imbue historical writing with assumptions of progress, just as assumptions of progress still pervade popular understandings of organismic evolution. However, biologists have learned to disentangle evolution and progress and tell stories about the multiple possible outcomes of evolution. Historians should also be able to invoke medical

¹⁰⁵ Benjamin N. Rome, Daniel B. Kramer, and Aaron S. Kesselheim, “FDA Approval of Cardiac Implantable Electronic Devices via Original and Supplement Premarket Approval Pathways, 1979-2012,” *JAMA* 311 (2014): 385-391, on p. 388.

¹⁰⁶ Rome and others, “FDA Approval,” on p. 390.

evolution (or revolution) and simultaneously subject the question of progress to the scrutiny it requires.

Evolution or Revolution?

Physicians, patients, and historians share an interest in the dynamics of medical change. Physicians and patients want rapid progress. Historians want to understand the dynamics and causes of change (and, when they get sick, most hope that medical science has progressed!). The rhetoric of revolution holds much appeal, for physicians celebrating an innovation or for historians drawing attention to the importance of their object of study. A claim of revolution is a demand for attention. However, as Roy Porter warned, historians must take care not to be drawn into the drama and over-state the claim. The essays in this volume provide a nuanced view of the subtleties and stakes of revolutionary claims. What about the opposing metaphor, of evolution? The rhetoric of evolution also looks to progressive improvement, but with reassuring gradualism in place of frightening rupture. If revolutionary change satisfies those who are dissatisfied with existing practice and want something fundamentally new, then evolutionary change reassures those who want gradual improvement of existing practice.

Historians need not adjudicate whether evolution or revolution is better. Instead, they can make two important contributions. First, they can mine scholarship on revolution and evolution, whether from political science or biology, to develop tools to refine our understanding of the past. Porter defined strict standards for revolution (i.e., a self-conscious overthrow of an existing scientific orthodoxy) and used those to characterize purported scientific revolutions. Historians can adapt concepts of evolution to analyze and understand change over time. Second, they can attend closely to language and its connotations. Whether the model is evolution or revolution,

one core consequence seems to be the same: the expectation of a better future. However, there is nothing inherent in the theory of either evolution or revolution that ensures progress. In fact, there is much in the dynamics of evolution, whether of niches, competition, Red Queen effects, or morphospace that argues against progress. While progress is a possible outcome of organismic evolution, it is not an inevitable one. When it takes place, it requires specific explanation. The same holds true for medicine and its history.