Ethics & Medics

September 2021 Volume 46, Number 9

A Commentary of The National Catholic Bioethics Center on Health Care and the Life Sciences

Also in this issue: "Reflections on Revising Part 1 of the *ERDs*," by John F. Brehany

Gain-of-Function and Pathogenic Viruses

Thomas H. Fischer and Carr J. Smith

During a Senate hearing conducted on July 20, 2021, Rand Paul, a senator from Kentucky and an eye surgeon, and Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, engaged in a verbal exchange over what does, and does not, constitute gain-of-function research on viruses. Paul contended that a virus experimentally altered to increase its transmission from an animal to a human constitutes an example of gain-of-function. Fauci did not agree but did not proffer an alternative explanation.

This article clarifies issues surrounding gain-of-function research on viruses raised by the COVID-19 pandemic. Determining the appropriate role of this research is extremely important, as the long-term efficacy of current vaccine strategies reportedly declines over a period of months post-vaccination, necessitating optimal approaches to vaccine development.

Although the pandemic is ongoing, the widespread availability of vaccines and effective therapeutic strategies has hopefully advanced us to at least the end of the beginning of the crisis. The respite provided by this relative progress has facilitated retrospective analysis of etiological factors. Gain-of-function research has emerged as a potential link in the causal chain. Herein, we define *gain-of-function* within the context of virology research and briefly outline some of its risks and benefits.

Advantages and Disadvantages

Gain-of-function refers to the deliberate alteration of the genetic code of a virus, rendering it more infectious.[1] A virus thus altered can be used to better understand certain molecular aspects such as viral attachment to a host target cell, cellular penetration, and the process of hijacking the cellular machinery for reproduction. This knowledge can provide a starting point for drug and vaccine development. Research on the COVID family of viruses exemplifies the benefits of this line of inquiry.

Several important mechanisms have been elucidated. Before penetrating cells lining the blood vessels to facilitate its replication, the virus first attaches to the ACE-2 receptor. ACE-2 binding was elucidated by modifying a bat coronavirus to become more infectious to human primate tissues.[2] In addition, the cellular penetration step was characterized by engineering a bat coronavirus with a cleavage site easier to cut by the proteolytic proteins present in human tissues.[3] Understanding the COVID-19 binding and cleavage sites has played a valuable role in vaccine design and has provided information useful for the diagnosis and treatment of patients with COVID infection. Gain-of-function experimentation is among the more direct approaches to gaining information on the relationship between the genetic code of a virus and the individual steps (docking, cell penetration, and so on) of the infection and propagation processes.

Another advantage provided by gain-of-function research is the development of animal models for testing vaccines and antimicrobial therapeutics. Species differences between humans and animals render direct comparisons problematic. This can represent a particularly significant problem in vaccine development, where a few angstroms' difference in the orientation of a group of atoms can affect efficacy. One experimental approach to circumventing species differences is to bioengineer human proteins (such as the SARS-Cov-2 ACE-2 receptor) into specialized donor mice to obtain a humanized mouse. The humanized mouse can be infected with the pathogenic virus, facilitating analysis of the efficacy of human vaccines and therapeutics. A potential weakness of this approach is that a virus pathogenic to humans is frequently unable to strongly infect and sicken the humanized mice, because of interspecies differences. A set of cloning methods termed *reverse genetics* can be used to produce a more virulent virus to facilitate study in the humanized mice.[4]

Paradoxically, a hazardous virus is sometimes created to answer questions about a related hazardous virus. The risks versus benefits of gain-of-function experimentation was a major focus of a 2014 Institute of Medicine conference. The IOM risk-benefit analysis served as the preamble to the 2015 implementation of limitations on National Institutes of Health (NIH) gain-of-function research.[5] To protect lab personnel and the general public, gain-of-function research should be conducted only under highly specialized handling and manipulation procedures and be restricted to containment facilities with appropriate levels of handling stringency (biological safety levels one to four, four being the most protective). Concomitantly, much of the research with COVID family viruses takes place in BSL three and four facilities.

Performing gain-of-function virology in even the most stringent containment facilities minimizes but does not eliminate the infection of laboratory workers and ultimately the escape of pathogens into the general population. The regulations mandate that incidences of laboratory-acquired infections be extensively documented.[6]

As discussed in the IOM's 2015 report, not all gain-of-function experimentation presents a direct risk to humans. Investigators

frequently use viral constructs that are incapable of replication or are bioengineered with control systems. However, it is often difficult to discern the dividing line between innocuous gain-of-function studies and those with downside hazards. The result, even when institutional review processes are followed, can be an underestimation of risk.

Weaponization of Pathogens

The appropriate role of gain-of-function research is being debated against a backdrop of the potential weaponization of pathogens. Epidemics have played a major role in the outcome of many battles and sieges. Prior to the invention of antibiotics and other drugs, soldiers living in close quarters with poor sanitation were at high risk of spreading infectious diseases rapidly. Approximately half of the deaths suffered by American Civil War combatants were the result of disease. Even as late as World War II, American Marines fighting on tropical Pacific islands were debilitated by malaria and dysentery.

Weapons of mass destruction are usually classified as nuclear, chemical, or biological. Of these, biological weapons are the most difficult to accurately target and thus restrict their delivery to enemy forces. A superpower like the United States, which possesses accurate and powerful conventional weapons and a variety of nuclear weapons capabilities, would have little use for an offensive biological weapon. Weak adversaries and closed societies able to control entry and egress could potentially be willing to release a weaponized virus into the United States or another developed country. Also, there are theoretical scenarios where even an enemy with advanced technological capabilities could employ a biological weapon. For example, if an opponent had developed both a virus and an effective vaccine against it, following vaccination of its own troops, the advancing force could attempt to expose the defenders to an infectious agent. The ability to rapidly develop a vaccine following a biological attack could potentially be facilitated by gain-of-function research.

Several characteristics of the COVID-19 virus differ from an optimally designed biological weapon that could be directed by the inventing party. First, when the virus first infected humans, neither a vaccine nor an effective treatment was available. Second, even vaccinated individuals can experience reinfection. Third, asymptomatic individuals can infect others, necessitating invasive, high-technology testing to determine infection status. Fourth, the extreme infectiousness of the virus, and even more infectious manifestations like the delta variant, make it difficult to limit adverse effects to enemy combatants or civilians. Although COVID-19 does not share the characteristics of an idealized designer virus, this does not represent evidence against the lab-leak hypothesis or address whether coronavirus research conducted at the Wuhan Institute of Virology had potential military applications.

It can be difficult even for expert virologists to discern whether a particular gain-of-function experiment possesses a significant risk to humans. In general, if research employs a human pathogen intended for transmission in an animal model, the proposed research should be subjected to a serious risk-benefit analysis. The ethical challenge raised is balancing the potential knowledge to be gained versus the risk of introducing a new deadly or illness-inducing pathogen into the general population. If approved, the research should be subjected to honest and open audit and oversite.

This level of transparency is not in place in the authoritarian system under which the Wuhan Institute of Virology operates. Therefore, the possibility that the COVID-19 pandemic originated from a laboratory leak cannot be comprehensively evaluated, because of the deficit of cooperation by Chinese authorities. Also, an extensive search for an animal (zoonotic) origin has not yielded positive results. The indeterminate origin of the ongoing global pandemic and lack of transparency regarding any potential role for gain-of-function research in the pandemic argue that any further production of engineered viruses with increased virulence should be considered only under limited circumstances, following appropriate regulatory review, with ongoing monitoring.

Recent revelations regarding research conducted at the Wuhan Institute of Virology being indirectly funded by the NIH have intensified the controversy regarding gain-of-function research. Richard Ebright, a professor and laboratory director at Rutgers University, has proffered the opinion that "the documents make it clear that assertions by the NIH director, Francis Collins, and the NIAID director, Anthony Fauci, that the NIH did not support gain-of-function research or potential pandemic pathogen enhancement in Wuhan are untruthful."[7]

How the perception of gain-of-function research evolves as the COVID-19 pandemic drags on is unclear. Hopefully, the adverse consequences of such research will not become another exemplar of hubris leading to nemesis. The controversy over the specifics of gain-of-function should not obscure the overarching concerns about the safety of coronavirus research. Notably, in the same research grants to which Ebright alludes, the investigators traveled to remote bat caves, collected specimens, and grew viral cultures of unique coronaviruses in a laboratory housed within a city of eight million people. The wisdom of funding this protocol and these investigators, regardless of the involvement of gain-of-function, is questionable.

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Notes

1. National Research Council and Institute of Medicine, *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop* (Washington, DC: National Academies Press, 2015), 51–54; and Barbara Johnson, "Gain of Function Symposium: Potential Risks of Gain-of-Function Research I: Biosafety," National Academy of Sciences, YouTube video, posted December 15, 2014, https://youtu.be/bV_gwKLVOzA?list=UUBeoZcQRZ800s3bP2yJrFEw&t=32.
2. Michelle Becker et al., "Synthetic Recombinant Bat SARS-Like Coronavirus Is Infectious in Cultured Cells and Mice," *Proceedings of the National Academy of Science* 105.50 (November 26, 2008): 19944–19949, doi: 10.1073/pnas.0808116105.
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6. Johnson, "Gain of Function Symposium."
7. Richard H. Ebright (@R_H_Ebright), "The documents make it clear," Twitter, September 6, 2021, 9:33 p.m., https://twitter.com/r_h_ebright/status/1435053515785662464.

Reflections on Revising Part 1 of the *ERDs*

John F. Brehany

Second in a series that reviews the current ERDs *and reflects on what changes would be necessary or helpful in their next major revision.*

Introduction to *ERDs* Part 1

Part 1 of the *ERDs*, titled "The Social Responsibility of Catholic Health Care Services," exemplifies tthe new and more robust structure for guidance introduced with the 1995 *ERDs*.

The introduction to part 1 outlines five fundamental principles that undergird and should guide the Catholic health ministry in its social dimensions: (1) human dignity and the sanctity of human life, (2) the biblical mandate to care for the poor, (3) the common good, (4) stewardship of resources and subsidiarity, and (5) conscience and institutional integrity. Part 1 also contains nine directives. Directive 1 describes the nature of the Catholic health ministry and its relationship to Jesus Christ and the moral tradition of the Church. Directive 2 calls for mutual respect among all caregivers. Directive 3 unpacks the biblical mandate to care for the poor by listing persons who are most marginalized and vulnerable. Directive 4 calls for responsible medical research. Directives 5 and 9 stipulate the need for Catholic institutions and for all serving in them to adhere to the *ERDs*. Directive 6 calls for stewardship of resources and links this to the growing phenomenon of institutional collaboration (fully addressed in part 6). Directive 7 seeks to summarize the responsibilities of a Catholic institution to its employees, such as recognizing their right to unionize. Directive 8 references key issues of canon law for Catholic health ministries in starting or ending specific ministries and "alienating" property.

Part 1 still reads well after more than twenty-five years. Its principles, topics, and teachings appear so basic that it is hard to appreciate how new and unprecedented it was at the time. Past editions of the *ERDs* had little introductory material and began by stressing the duty of the Catholic hospital to the medical and spiritual needs of the patient—adopting and adapting, in a way, the traditional terms of the doctor–patient relationship. By contrast, part 1 begins by locating the Catholic health care ministry between two significant realities: the healing ministry of Jesus Christ and the US health care delivery systems, a complex sector in which the Catholic health ministry plays an integral part.[1]

Given the many thoughtful revisions in the 1995 *ERDs*, what grounds for improvement might justify changes in the next major revision? I suggest two sets of considerations: First, new external developments in medical technology or practice, health care delivery, or society (including law, culture, etc.) over the last twenty-five years could require changes. Second, issues in the *ERDs*' organization, structure, or formulations may justify some revisions.

Reflections on Revising the *ERDs* Part 1, Introduction

While most of the content in the introduction to part 1 is well-done, the greatest need for improvement can be found in the fifth principle, which references conscience and religious liberty. Briefly, the fifth principle addresses the right of Catholic health ministries to refuse to provide medical interventions that contradict Catholic moral teachings even when such demands are made based upon "conscience." This raises the question of how conscience is and should be addressed. The word *conscience* appears in the 1995 *ERDs* four times. Beyond the introduction to part 1, the other three occurrences (in the general introduction and directives 28 and 32) refer to the right and duty of persons to make decisions about medical interventions with a free and informed conscience. In hindsight this treatment of conscience was not sufficient at the time and is not sufficient now to withstand the challenges that have been growing since the mid-1990s.

The 1971 *ERDs* referenced conscience four times as well. But (in addition to covering the issues found in directives 28 and 32 noted above), the 1971 *ERDs* better defended the issue of respect for conscience, stating that no Catholic health institution or staff members could be coerced to violate their conscience or the *ERDs*.[2] Given the increasing efforts to diminish rights of conscience, as well as to threaten the institutional integrity of Catholic health care, the next edition should better define and defend the role of conscience for Catholics in health care.[3] Ongoing demands from clinicians or patients to pursue interventions that contradict Catholic moral teachings will also have to be addressed. Such demands, first raised in the early 1970s, are still being treated with sympathy today.[4]

Reflections on Revising the *ERDs* Part 1, Directives

Before making suggestions about specific directives, it is interesting to note that the title of part 1 references the *social* responsibility of Catholic health care. And the introduction's five principles, along with directives 4, 5, and 6, certainly reference the role of Catholic health care in society. However, a plurality of directives (directives 1, 2, 5, 7, and 9) address *organizational* ethics, something distinct from social responsibility. Issues of organizational ethics have grown in scope and complexity, in part because of the growth in laws and regulations since the 1990s. The next revision of the *ERDs* should better distinguish guidance devoted to social and organizational issues and strengthen guidance regarding the latter.

In this regard, directive 1 is of great importance. Its injunction that Catholic health care services must be "animated by the Gospel of Jesus Christ" provides both a goal and a distinctive criterion for strengthening some key directives (2, 5, 7, and 9) and for generating new directives if necessary.

For the purposes of this brief reflection, I take *animating* to mean that the Revelation of Jesus Christ, in word and action, should ground and supply the distinctive inspiration, motives, and goals for the implementation of Catholic health care. Many human goods and endeavors can and should be integrated therein, but the source and summit of all the Gospel contains should be ultimate.

Directive 2, for example, introduced a new topic into the 1995 *ERDs*: appropriate relationships and behaviors among associates. These are of tremendous concern to many organizations and are the subject of scholarly studies and industry standards. Since the early 1990s, for example, many secular and Catholic organizations have used third-party vendor tools to measure and improve employee

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September 2021

engagement, which correlates with productivity, retention, and patient satisfaction. (*Engagement*, by definition, transcends mere satisfaction to measure employees' feelings about workplace support and recognition, opportunities to improve, relationships, and even "meaning.") Such initiatives should be an occasion to integrate the rich resources of the Catholic moral tradition (e.g., theology of work, virtues) to ensure that the Gospel remains animating.

Without such integration, a significant piece of the culture of a Catholic health ministry could be shaped by alternative ethical terms and goals that, at best, compete with a Catholic worldview. For example, a Catholic hospital I once worked for hired Disney consultants to train associates on how to treat patients and one another. Those conducting the next revision of the *ERDs* should be cognizant of this important area of organizational ethics and encourage Catholic health ministries to intentionally integrate distinctive terminology, teachings, and standards of behavior from the Catholic moral tradition.

Directives 5 and 9 address the requirement that all who work within Catholic health care adhere to the *ERDs*. The *ERDs* were formulated for, and are often associated with, Catholic *hospital* care, but health care delivery has been moving outside hospital walls for decades. Health care systems, including Catholic health ministries, increasingly own and operate clinics and employ clinicians. And ethical conflicts have been growing in primary care as the "medical standard of care" has devolved from the routine provision of contraceptive drugs and devices to providing so-called gender-affirming drugs and supportive counseling.[5]

While directives 5 and 9 should apply to any Catholic-owned or -operated health entity, this new locus of health care delivery has proved hard to monitor. Moreover, Catholic bioethicists are arguing that violations of some Catholic moral teachings, such as on direct contraception and sterilization, can be tolerated in such Catholic-owned clinics.[6] These and other ethical challenges encountered in outpatient care should be addressed with new and more explicit guidance in the next revision.

Directive 7 mentions a range of issues relating to the responsibility of Catholic health care institutions to and for their employees, one of which, "just compensation and benefits," has become a contentious issue and a threat to the integrity of Catholic health care.

For more than two decades, activists have sought to leverage employer-provided health insurance to fund and validate a range of behaviors that violate key Catholic teachings. These efforts began with state-based contraceptive mandates and continued with Obamacare's HHS mandate and the Obama and Biden administrations' demand that all health insurance cover so-called gender-affirmative interventions. In addition, after the Supreme Court's *Obergefell* decision, same-sex partners in the United States have been accorded the same employee benefits as married couples.

Providing health insurance is financially, legally, and organizationally complicated. It also is a profound ethical endeavor. The next revision of the *ERDs* should establish the guidance Catholic health ministries need to provide "just compensation and benefits" while faithfully witnessing to the authentic goods of marriage, sexuality, fertility, and the family.

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Notes

1. Catholic Health Association of the United States, "U.S. Catholic Healthcare," updated March 2021, https://www.chausa.org/about/about/facts-statistics.
2. National Conference of Catholic Bishops, *Ethical and Religious Directives* (Washington, DC: NCCB, 1971), dir. 2.
3. Christine O'Riley, "Protecting the Free Exercise of Religion in Health Care Delivery," *National Catholic Bioethics Quarterly* 17.3 (Autumn 2017): 425–434, doi: 10.5840/ncbq201717344; and Edmund Pellegrino, "Catholic Health Care Ministry and Contemporary Culture: The Growing Divide," in *Urged on by Christ: Catholic Health Care in Tension with Contemporary Culture—Proceedings of the Twenty-First Workshop for Bishops*, ed. Edward Furton (Philadelphia: National Catholic Bioethics Center, 2007), 13–30.
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5. See Jason Rafferty, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," *Pediatrics* 142.4 (October 2018), e20182162, doi: 10.1542/peds.20182162.
6. Michael Panicola and Ron Hamel, "Catholic Identity and the Reshaping of Health Care," *Health Progress* 95.5 (September–October 2015): 52–53.

Ethics & Medics is a publication of The National Catholic Bioethics Center. Regular annual subscription rates for twelve issues include both the print version by mail and online access at www.ncbcenter.org/em: United States, $28; foreign $38; institutional $55. Individual copies are available for $3 each. To subscribe, please write to The National Catholic Bioethics Center, PO Box 596, Wynnewood, PA 19096, e-mail orders@ncbcenter.org, or phone (215) 877–2660. Publisher: Joseph Meaney, PhD. Editor: Edward J. Furton, MA, PhD. ISSN 1071–3778 (print), ISSN 1938–1638 (online). To submit an essay or request submission guidelines, please e-mail submissions@ncbcenter.org.