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“Standardization through Mechanization”:

Germ-Free Life and the Engineering of the Ideal Laboratory Animal

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Abstract

“In all his work,” *Science News-Letter* reported on 17 August 1940, “Reyniers follows a slogan of his own, follows it so zealously as to make it almost a fetish: standardization through mechanization.”¹ Utilizing new technologies that he designed and built, James Reyniers came to “wide notice in the world of science” due to his innovative approach to standardizing organisms for use as experimental tools. “Ordinarily, when a scientist wants to study an unknown germ (or drug, or nutrient) he tries it out on an experimental animal,” *Life* magazine explained in September 1949 when reporting Reyniers’s innovative technologies. “But since all laboratory animals are invariably contaminated by a host of unknown germs, he can never be absolutely sure that results he sees are really caused by the agent he is testing. This problem ... can be solved only by using animals whose bodies contain no germs at all. Now, for the first time, such animals are available.”² Reyniers had extended the bacteriological ideal of pure culture to encompass the whole organism, creating “bacteriologically blank” organisms, or “biological *tabula rasa*,” which he believed formed ideal tools for experimental science.

The appeal of a germ-free animal as an experimental tool was inspired by the debate between Emile Duclaux and Louis Pasteur on the question of whether microbes were detrimental or, as Pasteur believed, necessary for higher organisms to live.³ Although the idea of a germ-free animal as a standard bacteriological tool had been posited as early as the 1920s, early efforts failed to create and, most importantly, maintain germ-free higher organisms as generic experimental tools.⁴ Reyniers (1908–67) and Philip Charles Trexler (1911–) at the University of Notre Dame first perfected the routine production of germ-free animals, and they successfully maintained them over several generations. At Notre Dame germ-free animals were designed to be generic research tools from the start. Importantly, Reyniers and Trexler worked outside of any defined biological-research problem or disciplinary interest; instead, they had created a new identity of their own as “biological engineers.”

Reyniers, the senior of the two, coined the term “biological engineering” to capture his interest in the construction of generic tools for biological research. His interest in the material cultures of the biomedical sciences was driven by an abstract focus on the technologies that made research possible. This instrumental focus dominated Reyniers’s career. His publishing record, for example, exclusively reports new techniques, technologies, and technical solutions with a characteristic style. Reyniers explained *how* to use his tools and *why* researchers may want to, but always left the work of integrating the technologies within research programs to others.⁵ Many contemporaries assumed Reyniers and Trexler to be “technicians,” because the pair did not locate themselves in specific biomedical research.⁶ If technician he was, Reyniers’s prominence within the scientific infrastructure of the United States makes him quite unconventional. Reyniers, however, viewed the category as derisory and insisted that his work involved innovative research within the new discipline of biological engineering. This discipline, which rigorously applied the principle of “standardization through mechanization,” would systematically

produce the basic tools and technologies necessary to drive the expansion of the biomedical sciences.

Several historians have argued that standardization provides an important resource through which experimental tools and scientific theories become organized, stabilized, and made productive. Such studies have tended to emphasize the interconnectedness of scientific tools, theories, and knowledge. Joan Fujimura's study of standardizing practices in twentieth-century cancer research, for example, concludes that "[i]t is impossible to understand the theories, concepts, and facts apart from the experimental systems used to bring them into being."⁷ Reyniers and Trexler, however, dreamed of building generic experimental systems. This does not, however, mean that their work lacked an epistemological element; on the contrary, germ-free systems were developed according to their pragmatic philosophy of science, which was shaped by several epistemological questions: namely, how scientists might stabilize living objects to facilitate research; how local practices could be standardized without restricting novelty to the point of constraining experimental progress; and, above all, how the material cultures of experimental science could be mobilized to attain these aims. Reyniers's mantra of standardization through mechanization reflected an attempt to resolve these problems.

Standardization through mechanization combined an engineering logic with a generalization of the bacteriological concept of "pure culture" in order to materially embody within standard mechanical systems a generalized experimental approach useful for all biomedical sciences. Such an agenda does not compare easily to existing historical accounts of experimental tools, which are frequently framed around the question of how locally produced, contextually situated tools become generalized. To account for such transitions, analytical categories like "experimental systems," "model systems," "standard organisms," and "model organisms" have entered into the literature. These concepts have proved useful in enabling historians to symmetrically address the material, cultural, and experiential labor of experimental science. Yet the meanings of these terms are both interrelated and multiple. Complexity in their usage emerges from the fact that each has been drawn from the language of experimental science itself. The ambiguity of these terms, however, has been mobilized by historians as an explanatory resource. Thus model systems and model organisms have become much-used analytic categories, as the model concept can account for how scientific objects, knowledge, and practices travel from highly specific locations to wider communities.⁸ Angela Creagar's account of Tobacco Mosaic Virus, for example, draws on the capacity of "model" to mean both an object representing another *and* as an exemplar of how to go about studying a given phenomenon so as to account for the generalization of locally produced experimental practices.⁹

Reyniers and Trexler, however, were not developing models; instead, they believed that the germ-free animal, as a form of life isolated from all other life, was *literally* a pure form of life. By building "tools for the job" when the job remained critically underspecified, Reyniers and Trexler were developing a distinctive conjunction of epistemological and material practices in an attempt to provide standardized tools at the macro, rather than the micro, level. Although, to be sure, their work was local, the intent and target was always already general. Reyniers and Trexler shaped their goals at the general level, simply assuming that germ-free animals could, should, and would be integrated by others at the local level. Given this intricacy, situating the development of germ-free experimental systems within existing historiography is not straightforward.

Reyniers's work is of interest to historians of technology and biology, because the construction of standard experimental organisms presents a historical site at which the interests of the two meet.¹⁰ Like models, standards have become a category of strong

historical interest. Some historians, such as Fujimura, have persuasively argued that standards provide the means by which local practices and knowledge become generalized. Karen Rader also framed her study of C. C. Little and the Jackson Laboratory as a nuanced account of the ways in which the ambiguous meanings of standardization help explain the phenomenal uptake of inbred mice as research tools.¹¹ However, others are less convinced of the utility of standards as explanatory devices. There is broad consensus on what experimental systems do (in that they operate as machines for scientific research), but there is little agreement on what they consist of (beyond their being local assemblages of concepts, practices, and things) or how, if at all, the processes of standardization might operate within them. In his account of *D. melanogaster* as an experimental system, for example, Robert Kohler emphasized the importance of standardization, while Hans-Jörg Rheinberger has downplayed the utility of standardization as a useful analytic device in his historical study of test-tube protein synthesis.¹²

In place of standardization Rheinberger promoted the experimental system to the center of his work. For him, the experimental system was the complex yet basic unit of science:

Experimental systems are ... the genuine working units of contemporary research in which scientific objects and the technical conditions of their production are inextricably interconnected. They are inseparably and at one and the same time, local, individual, social, institutional, technical, instrumental, and above all, epistemic units. Experimental systems are thus impure, hybrid settings.¹³

Rheinberger asserted that it is the capacity for experimental systems to produce novelty that drives biomedical production. For this reason, he displaced the primacy of standardization yet did not wholly discount it; rather, Rheinberger constituted experimental systems from the tension between “technical objects” and “epistemic things.” Technical objects are those that are standard, known, and predictable and thus behave in a uniform manner; epistemic things, in contrast, are variable, unknown, surprising, and capable of producing novelty. Importantly, a given entity may move from one category to another, because nothing is permanently stabilized within an experimental system. Standardization thereby becomes a process managed within the experimental system—a process that is never forever achieved, but instead held in tension with the potential for variation and thus novelty. Within any experimental system, stabilization through standardization is a contingent state.

Reyniers believed that his germ-free isolators, combined with germ-free animals, formed a generic experimental system. However, despite germ-free animals capturing the scientific imagination between 1942 and the late '50s, they never became the generic tools Reyniers believed they should have been. This article explores the reasons for this by examining how Reyniers's principle of standardization through mechanization successfully operated across the boundaries of human, animal, and machine, yet failed to establish the germ-free animal as a productive boundary object. It argues that Reyniers's germ-free systems, despite his frequent appeals to the contrary, failed to succeed as a generic experimental system because the tension between standardization and the need to produce novelty was not adequately managed.¹⁴

Mechanizing Imprecision: Reyniers's Micrurgical System

Reyniers's mantra of standardization through mechanization developed from a philosophical understanding of bacteriology learned as an undergraduate at the University of Notre Dame (1928–30). Believing the cell to be the basic unit of life, Reyniers reasoned that bacteriology could only be successful when it isolated and manipulated cells within a “pure culture.” Existing micrurgical tools had been constructed at local sites to suit local research practice (micrurgy being the manipulation of micro-objects).¹⁵ This, Reyniers complained, had

caused “almost as many isolators [to be] designed as there have been workers, and as many methods for using such instruments as there have been individual problems.” What was really required, he went on, was a micrurgical system that standardized all the necessary instruments and techniques of investigation, while embodying enough plasticity to allow for the production of research novelty. Such a system would use mechanization to routinize techniques of micrurgical investigation, while allowing researchers flexibility in integrating the technology within their research programs. One way in which Reyniers built in plasticity was to allow for a degree of imprecision regarding the object of analysis, which could range from the isolated cell through chains of cells to tissue.¹⁶ In this way Reyniers believed that his “theory of standardization through mechanization” could replace locally produced instruments with a single “micrurgical system.”¹⁷

Between 1930 and 1936 Reyniers designed, constructed, and perfected his micrurgical system. He believed a properly designed machine should manage the tension between standardization and the production of novelty by decreasing reliance on tacit skills, while still allowing for experimental innovation. “[W]hatever design is used,” he and Trexler wrote in 1943, “it must realize latitude of control without losing too much to manipulative control.”¹⁸ Building skill into the machine would obviate reliance on human operators’ tacit skills.

Reyniers’s emphasis on mechanization stemmed from his background growing up in an engineering-minded family. He never obtained nor sought formal doctoral training; instead, he claimed expertise “along mechanical lines by virtue of family background and associations.”¹⁹ His father’s engineering company, Reyniers and Sons of Chicago, built and supplied many of his technologies. When Trexler was appointed Reyniers’s “biological apprentice” in 1932 he spent four years at Reyniers’s father’s machine shop acquiring his engineering skills, while working to develop micrurgical and isolator technologies.²⁰

Reyniers and Trexler can be located within the historical trajectory of what Philip Pauly labeled the “engineering standpoint in biology,” within which the “[o]ntological and epistemological aspects of science [were] subordinated to technics,” and the “image of the biologist [was] not the naturalist, philosopher, or physician, but the engineer.”²¹ Reyniers and Trexler were essentially “tool men,” drawing their identity from the early twentieth-century tradition of American machine-shop culture, rather than from the biological laboratory.²² From this perspective, the problems of biological research became a series of technical problems to be solved by the innovative engineering of machine and organism.²³

Reyniers’s micrurgical system was well-developed by the mid-1950s and “made easily and cheaply in any machine shop.”²⁴ The system consisted of an innovative mechanical isolator; a working surface to which nutrients could be added; a moist chamber for maintaining consistent temperature and humidity; a mechanical microscope; and an apparatus for monitoring operational factors (for example, temperature).²⁵ The isolator itself united micro-instruments (for example, pipettes or needles) with mechanized methods of manipulation capable of working with single biological units, ranging from cells to tissue. The design principles that informed Reyniers’s approach were simplicity, utility, reliability, and affordability, although the latter became less important to him (but not to Trexler).

Reyniers’s interest in germ-free isolators, which isolated units of life within from the world without, developed as a byproduct of the micrurgical system. He first employed mechanical barriers in response to unwanted bacteria invading cell cultures within the system, aiming to create an isolator that could maintain a sterile environment. Germ-free chickens, and later guinea pigs, were subsequently developed as a mechanism to test and monitor the microbial security of the isolators.²⁶ Reyniers initially used germ-free animals to render microbial

contamination visible, placing them in a role akin to the contemporary “sentinel” animal. Signs of infection in a germ-free animal indicated that a mechanical barrier had failed. Environmental isolators, however, proved far more difficult to engineer than the micrurgical system. Early isolator models suffered several mishaps, the most alarming being a tendency toward explosion when the inside air pressure was miscalculated. The adoption of a rigorous, albeit expensive, steel design in the late 1930s overcame this and several other teething problems.

In the decades after World War II the germ-free isolators that made Reyniers and Trexler’s reputation extended the philosophy of isolating single biological units to encompass higher organisms. However, the germ-free isolator and animal developed interdependently, emerging from the logic of standardization through mechanization. Each was reliant upon the other for their existence and status. Sustaining the germ-free animal *as germ-free* was the test of a successful isolator and the guarantor that the “mechanical barrier” was maintaining a sterile environment within. Yet the production of germ-free animals required the preexistence of a sterile environment in the form of a mechanical isolator. It was this “chicken-and-egg” instability that inspired Reyniers’s shift of focus from the isolator as a standard tool to the animal itself. Rethinking the limits of his unit theory, Reyniers realized that increasing the reliability of germ-free isolators might enable the mass production of germ-free animals. Higher organisms, “free of all life other than that produced by the protoplasm of the individual,” might then become the new basic unit of biological research.²⁷ Rather than an auxiliary device to test and monitor microbial sterility, Reyniers transformed the germ-free animal into the purpose for which germ-free isolators were built.

The Germ-Free Animal as a Standard Experimental Tool

It is worth reiterating that Reyniers was not working within an established biomedical discipline or research problem. This absence of a recognizable disciplinary context, experimental problem, or epistemic thing, however, does not imply the absence of a guiding epistemology. With the germ-free animal, Reyniers’s unit theory was developed into a fully articulated philosophy of science wherein “purity” was the guarantor of reliable knowledge: “the need for isolating ‘pure units’ from the natural complex in which they exist forms the basis of analysis ... whether these pure units are compounds, bacteria, animals, or mathematical symbols does not alter the philosophy.”²⁸ Although influenced by his early encounter with bacteriology, this was not the reason he developed germ-free animals; rather, he viewed the animals as mechanically standardized tools to be used by all biological researchers within local experimental systems.

By 1940 the Reyniers steel isolator was capable of providing sterile environments for the production and maintenance of germ-free animals over multiple generations. The design of isolator units for specific purposes mechanized many of the operating skills, while preserving plasticity of use by allowing units to be fitted together in a variety of ways to suit specific research activities. Each unit at its most basic was an airtight metal cylinder fitted with a window, a pair of rubber gloves to manipulate contents, inlet and outlet openings for ventilation, a supply inlet with integrated autoclave, and high-pressure steam mechanics for sterilization²⁹ (fig. 1).

Yet, the principle of simplicity—a guiding logic at the heart of standardization through mechanization—began to show its limits in the Reyniers steel isolator. To standardize human labor, thereby “mechanizing” laboratory work, Reyniers’s design multiplied simple yet repetitive operations that made the labor involved intensive and monotonous. Preparation alone consisted of an eight-step sterilization process, taking even experienced technicians five to six hours of repetitive activity. The entire process demanded full

attention, as technicians attended to the vacuum, heating, high-temperature steam, air filtration, and rigorous checking of the security of the microbial barrier. Ironically, Reyniers's mechanization, which he thought would produce a standardized system requiring few tacit skills in its operator, was quite the opposite; the monotonous nature of the work required a personality capable of maintaining concentration during prolonged and repetitive labor.³⁰

Producing germ-free animals also required the careful co-engineering of biological life and machine. One key site of connection was the uterus, which was assumed to protect the young within a sterile environment in a way analogous to the mechanical isolator. Creating a germ-free animal began with the removal of an intact uterus from near- to full-term females, an operation performed within a specially designed surgical isolator (fig. 2). The uterus was then passed through a series of disinfection procedures involving total immersion in germicide-filled dunk tanks, before being introduced to a second surgical isolator. Here, progeny were released from the uterus and either hand-reared or passed to "foster parents."

For each species, timing gestation periods, developing practices for hand-rearing prenatal animals, and identifying nutritional needs and methods to safely sterilize foodstuffs, along with other factors, had to be worked out by trial and error. Such work was replete with setbacks, including mechanical failures, such as the time when a thermostat became stuck, leading to overheating in the isolators wiping out ten years of work in a single hour.³¹ More often, however, explaining failures in the maintenance of germ-free life was more difficult due to the complexities of integrating machine, human, and animal.

One particularly vexing problem was nutrition. Whether microbes formed a necessary element in the life processes of higher organisms had remained an open question since the first debates between Duclaux and Pasteur. Early work on germ-free animals at Notre Dame had established a pattern of initial success, followed by the gradual loss of animals over time; some believed that these failures confirmed Pasteur's views that germ-free life was impossible. Reyniers, however, could not accept the notion that microbes were necessary components of healthy higher organisms. Despite widespread theorizing positing links between microbes and essential nutritional processes, such as the production and metabolism of vitamins, Reyniers insisted on the possibility of germ-free living.³² The problem of sustaining animals within a germ-free state was not to be understood as a limit of nature, but instead a problem of proper engineering. Reyniers believed that the sterilizing processes rendered foodstuffs nutritionally poor or poisonous. Through trial and error and introducing regimes of vitamin supplements, he eventually succeeded in maintaining germ-free guinea-pigs, mice, rats, rabbits, cats, dogs, and monkeys over full lifespans. The answer for Reyniers always lay in properly engineering the system.

By 1946 Reyniers had established germ-free animals as self-sustaining breeding populations within a vastly enlarged system.³³ The original steel isolators were subsequently renamed the Reyniers Germ-Free System II and relegated to use for small-scale germ-free production and research work (although there was nothing "small" about the space required by or the price demanded for these machines). The new Reyniers Germ-Free System I isolator reflected growing ambitions to establish Notre Dame as the global center of germ-free animal production. By upscaling the familiar steel cylindrical chamber to the size of a small room, System I could house up to a thousand small mammals or lesser numbers of larger animals, including dogs, goats, larger monkeys, pigs, and cattle. System I was intended to mass-produce germ-free animals to serve as generic tools for biomedical research³⁴ (fig. 3). The scale of System I required everything involved to be increased, from the labor and number of the team to the daily production of sterilized animal feedstuffs. Its most profound effect, however, was on social ordering.

Paradoxically, the work of isolating life from all other life forms only emphasized the interdependence of human, animal, and machine. Further, Reyniers's formulation of the design of robust machines located that robustness within a widespread awareness of the fragility of the system. Any failure in the mechanical barrier would undermine the whole. As the scale of germ-free work expanded, ever more was at stake in operating even the simplest aspect of the system. Overly mechanizing the work of technicians was counterproductive, because simplicity, repetition, and routine brought the hazards of complacency and boredom, which increased the risk of minor mistakes that could "in a matter of seconds, ruin an experiment on which many persons have been working on painstakingly for months."³⁵ Consequently, the principle of standardization through mechanization was gradually tempered as the engineering of human components grew in importance.

Reyniers also took steps to engineer work cultures to be socially unified. Allowing a technician to think or act as an isolated individual was to risk disaster, because such occurrences were thought to divorce individuals from the wider impact of their actions. Technicians were encouraged to practice "submerging their own interests for the good of the entire organization and its program."³⁶ Day-to-day labor with the Reyniers system prioritized holistic cohesion over individual action.

The ways that germ-free labor created interdependencies were most evident in the design and operation of the Reyniers Germ-Free System I isolator (fig. 4). Each stage of entry into the isolator, which required wearing a rubber "diving suit" before passing through a vigorous germicidal shower and bath, reminded personnel of normal microbial interactions within the outer world. Further, Reyniers's codependent work culture took on added resonance as the "diver" depended for his survival on outside colleagues who maintained the air supply and monitored his well-being through portholes. Within the highly claustrophobic artificial environment of the isolator, constrained by protective gear and dependent on an outside supply of air, the routine work of caring for the animals became demanding and otherworldly for team members. The life of the human technician, as well as the germ-free animals housed within, relied upon the team operating as one.

One way to achieve social cohesion was to rotate team members across all jobs, so as to shape each individual as a "jack of all trades." Fighting complacency through managed variations in routine, this method also increased the functionality of the team, while simultaneously emphasizing how each role affected those of others and the whole. Even Reyniers submitted to this practice, adopting a hands-on approach that he doubtless enjoyed, but also deployed in order to overcome the tacit social barriers that came with his managerial seniority. To encourage social cohesion, Reyniers made much of the age of his comparatively young team (in 1950 the team had an average age of 35). The notion of a shared investment in learning on the job, as opposed to formal academic training, also built a collective coherence, resulting in Reyniers being playfully nicknamed "Doc" in reference to the fact that he lacked a doctorate—and bore that lack with pride. Reyniers's built a managerial approach around the notion that "there were no specialists on this team, everyone did a little bit of everything" and therefore all roles were "vitally important to the whole."³⁷ In this way the ethos of standardization through mechanization radiated beyond material technologies to shape wider work cultures.³⁸

In 1946 Reyniers's growing operation moved to its own institute, the Laboratories of Bacteriology, University of Notre Dame (LOBUND). Germ-free science had produced much positive publicity for Notre Dame and helped establish its scientific credibility. In 1948 the *Indianapolis Star* announced that "[t]he world of tomorrow is here today for Notre Dame University's guinea-pigs." The article, which was broadly representative of many popular interpretations of germ-free work, explained how Reyniers's creation of germ-free

animals promised a better world. The germ, long an object of public fascination, was now on the verge of being tamed, promising a longer, healthier future for all—a claim illustrated by a picture of a “[m]onkey peering at [the] dirty world outside [and] find[ing] it in a glum state.”³⁹ By touring universities and speaking at conferences across the globe, Reyniers courted both scientific and public acclaim, recognizing that global recognition strengthened his institutional position.⁴⁰ In 1950 the National Science Foundation (NSF) appointed Reyniers to its board, and in 1954 he received the Pasteur Award in recognition of his “pioneering work in germ-free research.”⁴¹ Such prestige helped him establish and preserve LOBUND’s independence from the wider managerial infrastructure at Notre Dame.⁴²

Fostering a public and professional image of himself as the figurehead of a futuristic science of germ-free life formed part of a wider strategy. Reyniers’s hope was to position LOBUND as an obligatory passage point within the emerging auxiliary infrastructure supporting the growth of biomedical sciences. The aim was to establish the germ-free animal as *the* generic tool for biomedical research, and in so doing locate LOBUND—as the leading manufacturer of such animals—as a central hub in the emerging biomedical world. Although Reyniers courted publicity to serve this wider agenda, he also recognized the pressing need for financial investment in order to maintain the independence of his new institute. The increasing ambitions of Reyniers’s germ-free systems were equaled by increasing costs. As early as the mid-1930s Reyniers had become a strategizer and fundraiser and undertook work as an industrial consultant, the latter occasionally doubly productive when clients agreed to support his wider research. W. K. Kellogg Company, for example, in 1939 awarded Reyniers his first outside grant.⁴³ Such piecemeal accumulation of supporters faded in importance when, during World War II, Reyniers attracted military support for his research, thus obtaining the substantial revenues that made the transition from small- to large-scale germ-free isolators possible.

Reyniers’s Germ-Free System and Centralized Production

In 1942 Reyniers complained to the National Academy of Science (NAS) that biologists were being recruited “to the armed services where they are generally used in positions that ignore their special talents.”⁴⁴ At Notre Dame, he argued, “special equipment not available elsewhere in the country” existed that could be used to investigate “the adaptation of the organism to the machines of war,”⁴⁵ yet there was no mechanism by which Reyniers could prevent members of his team from being recruited for other work—meaning that the unique facilities at Notre Dame could not be best utilized. He explained that his isolators could be used to contain microbes within, as opposed to isolating life from microbes without, thereby offering a means to safely work with dangerous pathogens.⁴⁶ Edwin Broun Fred, the chair of the NAS’s Subcommittee on Biological Warfare, was convinced of the merit of Reyniers’s proposal. He arranged for the Notre Dame team to be recruited into the U.S. Navy and posted under Reyniers’s command, a move that opened the way for considerable military investment in Reyniers’s isolator systems.⁴⁷ Reyniers, however, very nearly imperiled this new arrangement by refusing to move his work to a military installation. Such a move would delay progress, he insisted, because the “great variety of skills and techniques (mechanical, engineering, chemical, physical and bacteriological)” were already in place at Notre Dame and promising to “yield results in the shortest possible time.” Reyniers eventually won a compromise: he and his team would remain at Notre Dame while some isolators were shipped to and installed at Fort Detrick in Frederick, Maryland, where the research element of the work would occur.⁴⁸ The war years were subsequently spent engaged in classified biological-warfare projects, the most important work being in building, supplying, and maintaining isolator systems for research into biological warfare. Reyniers’s team also developed mechanisms for the transport and dissemination of airborne pathogens like typhus.⁴⁹ These contributions successfully established the military utility of Reyniers’s

systems, the Office of Naval Research (ONR) remaining a principal supporter of LOBUND for over a decade after the end of the war.⁵⁰

The refusal to leave Notre Dame was more than an attempt to secure investment in Notre Dame's research infrastructure. Reyniers was fastidious in retaining proprietary control over his germ-free technologies; for example, he micro-managed paperwork at LOBUND to ensure that all patentable technologies were attributed to the Department of Defense, because it allowed patents to be retained by grantees.⁵¹ Reyniers further guarded his isolators by ensuring that their sole manufacturer was his father's firm. Consequently, it was all but impossible for anybody to obtain Reyniers's germ-free systems without his permission. Retaining absolute control over his steel-isolator system formed part of Reyniers's wider strategy of establishing LOBUND as the leading supplier of germ-free animals. Believing that such animals would become the generic tool for biological and biomedical research, Reyniers hoped that controlling their production would catapult LOBUND onto the world stage as a key player in the development of post-World War II science.

The germ-free animal was, in Reyniers view, the scientific tool of tomorrow available today. His persuasive selling of the germ-free concept brought substantial investment in LOBUND. By mobilizing the language of efficiency and industry to his own advantage, he made those interested in using germ-free animals an offer that was difficult to refuse: namely, that one could either invest a large amount of money and time in establishing facilities and the required technical expertise or, on the other hand, one could choose to invest a much smaller amount of both by setting up a laboratory at LOBUND, where the ready availability of animals and onsite expertise would allow work to commence within a much shorter timeframe.⁵² Among others, the ONR, Parke, Davis & Company, the Regional Poultry Research Laboratory, W. K. Kellogg, the Zoller Memorial Dental Clinic of Chicago, and the Atomic Energy Commission accepted Reyniers's logic.

For those that did not Reyniers had a secondary argument: multiple sites and systems of production were undesirable, because they would inevitably lead to the proliferation of production standards. That said, the adoption of germ-free over conventional animals had to be encouraged, and it was impractical to expect the world to come to Notre Dame. Through the early 1950s Reyniers worked to develop the means by which germ-free animals could be centrally produced at LOBUND and distributed worldwide. Due to the growing number of adjunct laboratories being built at LOBUND, small isolators had already been adapted to serve as *transfer* and *receiving* units, which allowed the germ-free animals to be securely transported throughout the growing institute (which had expanded to occupy sixteen additional buildings in response to the influx of outside researchers). Long-distance transportation was more difficult though not impossible. The first reliable method was achieved by reengineering a Studebaker-Packard station wagon to form a mobile isolator capable of circulating filtered air for the duration of the journey (fig. 5).

Later trials demonstrated a more economic yet equally secure solution by dispensing with the need for circulated air in favor of using simple microbial filters. With some trial-and-error calculations of nutritional requirements, germ-free animals could subsequently be shipped in box-like transport units. These were originally constructed from widely available aluminum roasting pans fixed with rubber seals and clamps to create an airtight barrier and fitted with a sterile locking system to allow for direct attachment to isolators.⁵³ Once the method was refined, Reyniers's transport units RTR-1A and RTR-2A made possible the shipment of germfree animals from LOBUND to any country accessible by air.⁵⁴

At this time, those working in laboratory animal science were interested in centralized production as a possible means to counter the problem of maintaining standards when practices of use differed by location.⁵⁵ Reyniers may well have believed that his model of centralized production was designed to work with, and not against, scientific and industrial trends.⁵⁶ Nevertheless, his resistance to allowing others to purchase his systems rankled those who struggled to gain access to them.⁵⁷ In those instances when Reyniers did allow the purchase of his steel isolators he was less than cooperative in rendering the process easy. In 1949, for example, the National Institutes of Health (NIH) entered into an agreement to undertake research at LOBUND on dysentery; however, in 1952 the NIH opted to establish its own small-scale facilities upon the requests of the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis and Metabolic Diseases, the National Institute of Dental Research, and the National Cancer Institute. It was not until 1956, however, that Reyniers steel isolators were delivered to the NIH. In view of the delay the NIH's sanitary engineering branch had begun developing its own germ-free equipment, as well as exploring the use of alternative isolators obtained from Bengt Gustafsson of the University of Lund in Sweden.⁵⁸ In 1955 Theodore Hesburgh, the president of Notre Dame, had to step in when Reyniers refused the Walter Reed Army Institute of Research's request to establish its own large germfree facility. The episode was widely viewed as damaging to the reputations of LOBUND and the University of Notre Dame, and to Catholic science generally.⁵⁹

Reyniers could not have chosen a worse time to critically damage his reputation or make LOBUND the object of widespread criticism, because during the previous year the university had allocated a 1,700-acre plot of land to accommodate LOBUND's future expansion and applied to the NSF to support its planned building program.⁶⁰ The impressive array of supporters was not enough to quash the informal concerns that reached Lawrence Blinks, Louis Levin, and John Wilson of the NSF's Division of Biological and Medical Sciences. They were so uneasy about Reyniers's behavior that they began an unprecedented investigation of LOBUND prior to making their decision on further investment. Most seriously, they wanted to know if Reyniers had deliberately acted to restrict the development of rival germ-free facilities; they also were concerned about the absence of academic activity at LOBUND, evident in the institute's apparent failure to make any tangible contribution to biomedical knowledge beyond the germ-free systems. Their informal inquiries did little to assuage these concerns; on the contrary, Reyniers's blustering instead confirmed the total absence of basic aspects of a scientific and academic infrastructure. LOBUND lacked, for example, a well-developed research culture and was found to have no formal system for the training of students.

Consequently, Conrad Elvehjem, a nutritional biologist from the University of Wisconsin, was asked to chair an independent Ad-hoc Advisory Committee on Microbiological Facilities tasked with formally investigating LOBUND and recommending ways that germ-free research could best be federally supported.⁶¹ Elvehjem's report agreed that the germ-free animal may be a "potentially valuable tool for biological and medical research," but rejected the model of centralized research. Innovative answers to complex problems, Elvehjem insisted, "come most rapidly if they are approached in different laboratories and by several different investigators."⁶² While LOBUND had done much to develop germ-free systems, Reyniers's resistance to collaboration with others, combined with an absence of "effective and adequate communication of results," had prevented any such synergy. More worrisome for Elvehjem were the widely reported difficulties "in the procurement of equipment by those institutions which desired to initiate programs of germ-free research," which "prevented workers who might have made contributions" from doing so. Rather than lauding Reyniers as an innovator, the report portrayed him as having retarded the development of the field to such an extent that little was actually known about the utility of

germ-free animals as experimental tools. Thus he forcefully dismissed Reyniers's claim that "the appropriate techniques needed for the production and use of germ-free animals cannot be readily duplicated at several institutions" as "contrary to modern concepts of research."⁶³ Progress could only be made, Elvehjem concluded, when the production and use of germ-free animals were incorporated within "a strong center for creative work in biological and medical research" stocked with "active researchers" across the biological disciplines—everything, in short, that LOBUND lacked.

Reyniers, of course, fundamentally rejected this assessment. In a detailed rebuttal he reasserted his belief "that establishing germ-free production facilities was in no way an easy task," and claimed that the absence of rivals should properly be understood as evidence of this fact. He went on to assert that his willingness to collaborate with others was evident in the fact that LOBUND had made possible the "shipment of strains of germfree animals to other smaller institutions."⁶⁴ At the heart of this dispute were different conceptions of the purpose of the work undertaken at LOBUND and the meaning of "research." Reyniers believed that his institute was pioneering a new field of "biological engineering," of which germ-free isolators were a result. For Reyniers, research included everything from the building and perfection of isolator systems to the development of hand-rearing techniques and nutritional regimes for different species. Understanding either the properties of germ-free life or their utility for biological research, however, was of little direct interest to the biological engineer. Reyniers believed that the answers to these questions were the work of others, principally those who would use the germ-free animal in their research. Reyniers had long struggled to establish the identity and expertise of the biological engineer as far more than that of a skilled technician. Describing Trexler to Fred in 1942, for example, Reyniers emphasized that "[t]his man is not a technician but a fully qualified professional bacteriological engineer."⁶⁵ Fred nonetheless continued to believe Reyniers to be a "marvelous technician [who] devotes his entire time to building new apparatus but never is known to accomplish any research."⁶⁶

Reyniers's lack of interest in the practical use of germ-free animals, the absence of any formal academic program at LOBUND, and his refusal to loosen his grip on the isolator systems all confirmed the image of him as an innovative technician, but not a research scientist. For these reasons the NSF refused to invest in the expansion of the LOBUND, a result that initiated a power struggle over the future of the institute. As president of the university and also as a Catholic priest Hesburgh was deeply troubled by what appeared to be LOBUND's fall from grace. Consequently, he replaced Reyniers as a NSF board member in 1954 and further made it an objective to reform LOBUND. Seeking to reestablish the institute as a high-profile example of what Catholicism could contribute to science, he integrated LOBUND within the university's Department of Biological Sciences.⁶⁷ Hesburgh's reforms, intended to provide a graduate program and a broad base of research expertise in the biological sciences, were a clear response to the NSF report. Reyniers, not incorrectly, viewed these changes as a formal rejection of the worth of biological engineering. Biological scientists and administrators increasingly viewed the separation of the production of germ-free animals (and the technologies that made this possible) from the study of their properties and applied uses as detrimental to the project of establishing such animals as the basic tool of biological research. Reyniers refused to accept this, resisting to such an extent that he was asked to resign from his own institute in 1957.⁶⁸

Trexler's Germ-Free System and Dispersed Production

Reyniers's departure presented Trexler with an opportunity. Having long been in his superior's shadow, Trexler was now free to articulate his quite different views on the way to establish germ-free systems within the wider biomedical sciences. His alternative vision for

the future of LOBUND assumed that the full potential of germ-free life would only be realized if germ-free research became a research discipline in its own right. The creation of a new science of “gnotobiotics” (literally, known life) had first been suggested in 1949, but gained little support from Reyniers, who noted that this would imply a proliferation of germ-free isolator systems.⁶⁹ In 1984 Trexler recalled their disagreement:

Reyniers was of the opinion that the Federal government should support [LOBUND] in much the same way as the large astronomic laboratories and centers for nuclear physics. I held the opposite view that the production of these animals should be made simple and relatively inexpensive so that research could be carried on in any laboratory in which these were the appropriate animals. Unfortunately we never did succeed in reconciling these difficulties.⁷⁰

Despite Reyniers’s views, Trexler had begun to develop a new isolator based on the principles of simplicity, economy, and adaptability. His new approach was inspired by his work on the diver suit for the System I isolator, which had demonstrated the versatility and strength of plastic, while providing methods to chemically decontaminate plastics without damaging them.⁷¹ Trexler subsequently experimented with new isolator designs that used plastic in place of steel; by 1957 he had developed a working prototype⁷² (fig. 6).

What came to be called the Trexler plastic isolator proved to be technically superior to the Reyniers steel isolator. It offered improved visibility and incredible flexibility in terms of design and construction, thus allowing more complex work to be undertaken within it. In this way, plastic construction brought with it a “plasticity of usage”; by ensuring that it was cheap to produce Trexler worked toward making the plastic isolator widely available, thereby allowing even small laboratories to experiment with germ-free research practices. His aim was to catalyze the formation of gnotobiotic science.

In 1961 Trexler established the Association for Applied Gnotobiotics in an attempt to consolidate a disciplinary and institutional identity for participants in germ-free research. A few years earlier the University of Notre Dame had established a Ph.D. program in the new discipline of gnotobiotics, a move that was influenced by the need to satisfy the NSF’s demands for a graduate program.⁷³ During the interim Trexler showcased the plastic isolator at scientific meetings across the country, emphasizing its design “with an eye to economy and mass-production” in order to realize the “potential of gnotobiotics” as a field of research in itself.⁷⁴ Despite these efforts, gnotobiotics struggled to establish itself as a research discipline akin to genetics; one reason was that the legacy of Reyniers made it difficult to separate LOBUND and germ-free research from its association with the production and supply of research tools. Gnotobiotics continued to be viewed by many as a field of expertise that was *auxiliary to* rather than *a discipline of* the biomedical sciences, which was evident in the name of the organization itself: the Association for *Applied* Gnotobiotics.

The growth of gnotobiotics was further retarded by an unintended effect of the proliferation of the plastic isolator. With Reyniers gone, LOBUND no longer adhered to his careful assigning of patentable technology to Department of Defense funding; instead, Trexler’s work was attributed to the NIH. Because the NIH was the stated source of funding for the new plastic technologies developed at LOBUND, Trexler’s patents entered the public domain. This was beneficial in one way, as it encouraged the proliferation of plastic isolators; by 1960 seven companies were marketing versions of Trexler’s design.⁷⁵ As a consequence, however, he found it difficult to attract investment in LOBUND, because the simplicity of its manufacture meant that researchers and commercial companies could develop their own systems. This, coupled with the withdrawal of federal financial support—the NSF did not agree to fund LOBUND again until 1964—gave the impression that large-scale investment in the development of isolator systems was over. Thus Trexler’s success

eroded the sustainability of his own position. His plastic isolators had made germ-free research practical for even the most economically challenged laboratory, while its design emphasis on flexibility and simplicity meant that their use proliferated without the need for LOBUND's expertise.

Furthermore, the widening access to germ-free production techniques undermined the credibility of germ-free animals as generic tools for biomedical research. Greater familiarity with such animals revealed them to be dramatically different from conventional organisms. Physiologically, for example, germ-free animals possessed fewer white blood cells, less lymphatic tissue, and virtually no antibodies. They grew faster and bigger than conventional animals (drawing comparisons with the recently discovered antibiotic growth effect), but aged slower. Germ-free males outlived females—the opposite of what was expected of conventional animals. Perhaps most disconcerting of all, germ-free bodies refused to decompose after death⁷⁶ (fig. 7).

These characteristics had been long known at LOBUND and assumed to be a point of interest for biomedical researchers. However, as one article explained in 1971, “[i]nitially, it was assumed that the germ-free animal is essentially a host without germs ... [t]hen it was learnt that, in addition, it is a host minus responses to germs.”⁷⁷ This was a problem, because the absence of such responses led to biological differences on such a scale as to undermine the ability of germ-free animals to represent “normal” life.⁷⁸ The Duclaux–Pasteur debate returned in a new form: Did the germ-free environment produce a normal animal freed from microbial contaminants, or were germ-free animals abnormal, because they were deprived of crucial microbial relationships? Answering this question depended on one's perspective and assumptions, but the practical consequences were similar. Complexity had resulted where simplicity had been promised; Pasteur's question had been reconfigured, but in no way demystified by the creation of germ-free life.

Germ-free animals, for example, had reduced metabolisms and cardiac outputs due, in part, to overly large ceca that, in turn, were associated with the absence of intestinal microbes. Until these complex interconnections were understood, it was impossible for germ-free animals to serve as standard experimental tools:

Under such circumstances, the design of an experiment and the interpretation of the results become major undertakings and users of the gnotobiotic animal find this “working in the dark” somewhat disconcerting. It still remains theoretically correct to regard gnotobiotic experimentation as an extension of the microbiologist's pure culture concept to all biological forms, yet in the case of multicellular organisms the complexity of interrelated functions considerably reduces the practical value of such generalizations.⁷⁹

By 1970 the utility of germ-free animals as experimental tools was highly specialized; the *potential* of germ-free animals as generic biomedical tools remained no more than that.⁸⁰

Despite their failures, the germ-free animal was, quite literally, the parent of what became a new standard laboratory animal. By adapting germ-free techniques, animals could be produced that were guaranteed to be free of specific microbes, pathogens, and parasites. This offered a solution to the long-held problem of endemic infections in laboratory animal stock. With the widespread adoption of plastic isolators, so-called specific pathogen-free (SPF) animals were relatively simple to produce. The main practical use for germ-free animals was to act as foster parents when establishing a new SPF population. By using SPF practices, laboratory animals could be pathogenically standardized in a way that was absolutely defined yet infinitely flexible; the end-user could refine the microbial load of his or her animals to suit local purposes. Trexler was quick to recognize the utility of plastic

isolators for this purpose, because gnotobiotic science had for him always encompassed any animal with a *known* microbial flora and not only, as Reyniers preferred, those in “pure” germ-free states. Consequently, when Trexler convened a workshop in 1962 at LOBUND to train participants in gnotobiotic techniques, he invited commercial laboratory animal breeders and one government breeder. Each was asked to agree to a one-year period of surveillance by Trexler, after which they would be given a certificate of gnotobiotic competence, thereby conferring credibility upon their claim to be producing pathogenically determined animals.⁸¹ Trexler’s isolators subsequently transformed the commercial laboratory animal industry, with Charles River Breeding Laboratories, for example, recruiting him to serve as a consultant director of research in 1965.⁸²

SPF animals succeeded where germ-free animals failed, because their health and microbial load was known and could be refined for local purposes, yet otherwise they biologically resembled normal animals. Within a decade of Trexler’s development of the plastic isolator it had become an integral tool in the field of laboratory animal science and the laboratory animal industry. William Lane-Petter, a leading architect of laboratory animal science, recognized the plastic isolator’s importance after seeing it demonstrated at a meeting of the Animal Care Panel. He immediately arranged to introduce it in Great Britain, with the hope that it could eradicate the problem of latent infections in laboratory animal stocks. By 1963 Lane-Petter was describing SPF animals as “the healthy animals we have been looking for for years” and predicting that “in a short time the questionable term ‘SPF’ etc will be forgotten, because all laboratory rats, mice and probably every other species will be of this standard of health.”⁸³

Reflecting on all this in 1984, Trexler reminded his audience that the term “gnotobiotics” had been coined from the Greek *gnostos* (known) and *bios* (life) so as to encompass the study of life forms whose microbial load had been completely defined. For him, it made little difference that SPF, as opposed to germ-free animals, had become standard experimental tools within the biomedical sciences, because both were properly understood as gnotobiotics. As he further explained:

Gnotobiotics as a science resembles genetics and in many respects the gnotobiotite is analogous to an inbred animal... The technology required to make the defined flora animal as readily available as inbred animals is now a realistic goal. When it is reached the use of [the] gnotobiotite will not be considered to be a special biology, i.e. gnotobiology, anymore than the use of an inbred animal is considered to be special inbred-biology.⁸⁴

In this view gnotobiotic science was only a temporary means by which germ-free systems were to be integrated within the biomedical sciences. Interestingly, the inbred strain (historically known as a pure line) and the gnotobiotite (or SPF) animal shared a historical lineage emerging from the “pure culture” concept; it is therefore no surprise that the two were perfectly compatible.⁸⁵ In 1960, for example, Elizabeth Russell of the Jackson Laboratory in Bar Harbor, Maine, predicted that “in the future genetic control and pathogen-free maintenance should in some cases be combined ... if either discipline is to have its full usefulness.”⁸⁶ This has indeed occurred. Yet where genetically standardized animals remain crucial tools in many fields of research, pathogenic standardization is now the de facto standard expected for *all* laboratory animals. As Lane-Petter predicted and Trexler hoped, SPF animals became such a successful standard that the term is now rarely used—all laboratory animals are now expected to possess a defined pathogenic record. As with all standards, success brought invisibility.

Conclusion

“My people,” Reyniers reflected in 1962 in an interview with *Popular Science*, “have always been machinists... My father, brother and I invented a whole line of germ-free equipment—apparatus to take care of anything from houseflies to fish to pigs.”⁸⁷ Throughout his life Reyniers characterized his work by looking to early twentieth-century engineering and machine-shop cultures, yet he cast germ-free life and the role of the biological engineer as being of the future. By 1962, for example, his germ-free systems were being used to breed monkeys to be sent to the moon. “One scientist even suggests germ-free men to explore space,” *Popular Science* stated in the interview, somewhat whimsically concluding that “[a]ll we need to do is keep a man in a germ-free cabinet for 25 years following birth, meanwhile teaching him how to fly a spacecraft.”⁸⁸ This tension between past practice and future promise might help explain Reyniers’s rejection of academic qualifications in favor of on-the-job learning, and also his refusal of the label of technician and preference for distributing animals as products, rather than his systems of production themselves. At a time of rapid change Reyniers aimed to define a new place for himself and his generic mechanized systems in the world of biological research. The changing fortunes of his work illustrate the complexities of relations among military, industrial, and academic biomedical research in the twentieth-century United States. The much-maligned linear model of university-based academic research applied within industrial contexts is too simplistic to account for Reyniers’s position.⁸⁹ To the extent that Reyniers acquired his expertise in an industrial setting and transferred it to academia, he could be characterized, following Wolfgang König, as one attempting to create an “industry-based science.”⁹⁰ Yet Reyniers struggled to establish himself within a university setting precisely because he applied universalizing engineering approaches at the expense of academic infrastructures and protocols. His attempts to establish LOBUND as an obligatory point of passage for biological researchers failed to work, and his efforts to keep his production systems out of the hands of researchers proved incompatible with the ethos of the post–World War II biomedical sciences.

Furthermore, Reyniers’s failure to develop a generic experimental system outside of a specific research question highlights the inseparability of scientific knowledge, objects, and their local conditions of production. His failure to establish the germ-free animal as a generic experimental tool derives mostly from the boundaries he erected between the technologies of production and the practices of use. This prevented the formation of productive interactions between experimental tools and conceptual theories, as well as between the producers and users of technologies.⁹¹ Although Reyniers intended the germ-free animal to play the role that Rheinberger described as “technical object,” how could this possibly have occurred while such animals remained so widely unknown? Reyniers refusal to allow widespread access to his systems of production meant that potential users only had his word to go on. Working outside of any determined research goal and having little interest in integrating germ-free animals within an experimental system that would serve as an exemplar, Reyniers simply expected the biomedical community to accept germ-free animals as technical objects. In order to integrate such animals within experimental practices there had to be the potential for change, novelty, or surprise—the very things that Reyniers’s system of centralized production, inspired by his philosophy of standardization through mechanization, was designed to prevent.

Rheinberger argues that experimental systems “cogenerate the phenomena or material entities and the concepts they come to embody. Practices and concepts thus come ‘packaged together.’” Reyniers, with his predefined practices detached almost entirely from concepts, offered a partial package at best.⁹² Only when Trexler made his plastic isolator widely available did it become possible for users and producers to engage with each other and begin

the work of defining the germ-free animal. In view of Timothy Lenoir's claim that the success of industrial scientists and engineers "depends in large part on their ability to build disciplines," Reyniers's insistence on working outside of any specified disciplinary user group may have contributed to the resistance to his work.⁹³ Trexler, in contrast, found a form of success by deliberately fostering interactions with end-users in the hope of creating a new discipline of germ-free science. Yet even when Trexler set out to connect users to his germ-free technologies, it proved self-defeating in regard to his desire to establish the disciplinary field of gnotobiology. Germ-free animals were found to be too artificial, too distant from "nature." When Reyniers prevented access to his systems of production this crucial problem had not been obvious; far from simplifying the animal, standardization through mechanization had revealed a host of unexpected relations between higher and lower organisms. Germ-free animals were overly standardized; they produced unexpected and excessive novelty to such an extent that they could not meaningfully represent known forms of life. Germ-free animals ultimately proved obstructive, rather than helpful, to biomedical investigation.

Historical studies have shown the role of standardization within the biomedical sciences to be contextual and complex. One reason for this is the need to maintain a productive tension between stabilization and the potential for novelty, together with the capacity to meaningfully represent "natural" forms of life. Managing and maintaining these tensions are the work of experimental systems. The efforts to render germ-free systems useful to biomedical science could occur only through the interfacing of systems of production with practices of use. When Trexler made germ-free systems and expertise widely available, the germ-free animal consequently found its place as a tool for creating animals with known biological flora. SPF organisms successfully managed the tension between stabilization and novelty without sacrificing meaningful correspondence to conventional forms of life. Now so ubiquitous as to be invisible, SPF animals succeeded where germ-free animals failed, because they embodied a standard that could be reconfigured to suit local research agendas, while also remaining highly defined and capable of meaningfully representing "natural" forms of life.⁹⁴ For this reason SPF animals have become *the* standard used today in laboratories around the world.

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University produced germ-free animals in 1946, but again tied their use to specific research interests: wound healing, transplantation, and foreign-body inflammation. In Japan, as in Sweden, the germ-free animal as a generic experimental tool only emerged in the 1950s, influenced by the work of Reyniers and Trexler. The Swedish work is summarized in Gustafsson, Bengt. Germ-free Research at the Institute of Histology, University of Lund. In: Tunevall, G., editor. Recent Progress in Microbiology: A Symposium Held at the VII International Congress for Microbiology; Stockholm. Oxford: 1958. 1959. p. 327-35.

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28. Reyniers, James A. The Production and Use of Germfree Animals in Experimental Biology and Medicine. *American Journal of Veterinary Research*. 1957; 18:678–87. [PubMed: 13444595] , quote on 678; see also Reyniers. *The Pure-Culture Concept and Gnotobiotics*; p. 3-16.
29. Reyniers, James A. Design and Operation of Apparatus for Rearing Germfree Animals. *Annals of the New York Academy of Sciences*. 1959; 78:47–79.
30. UDIS 99/25, "Lobund Laboratory Volume I 1952–1978" folder, LOBUND, in archives of the University of Notre Dame, Hesburgh Library, University of Notre Dame, South Bend, Indiana (hereafter HL-UND).
31. Gannon, Robert. Life in a Germfree World. *Popular Science*. Aug. 1962 :90–93. esp. 92.
32. For example, Élie Metchnikoff believed that certain bacteria in the gut were responsible for ageing via a process of auto-intoxication, while other bacteria were beneficial and necessary. His principle was adopted, extended, and widely publicized by John Harvey Kellogg, who was a physician and health reformer and brother of Will Keith Kellogg, the founder of the cereal company. See Kellogg, John. *Autointoxication or Intestinal Toxemia*. Battle Creek, Mich.: 1919. , esp. 307–14. For the wider debate about autointoxication in twentieth-century America,

- see Whorton, James C. *Inner Hygiene: Constipation and the Pursuit of Health in Modern America*. Oxford: 2000.
33. Reyniers, James A.; Trexler, Philip C.; Ervin, RF. Rearing Germfree Albino Rats. *LOBUND Reports*. 1946; 1:1–84. [PubMed: 20247584]
 34. Reyniers, James A. The Germfree Life Program of Lobund Institute, University of Notre Dame: A Summation from 1928–1958. *Recent Progress in Microbiology*. :261–87. (n. 4 above). esp. 262.
 35. “Lobund Institute for Research in the Life Sciences,” p. 6, PNDP40-Lo-1, “LOBUND (Laboratories of Bacteriology U.N.D.) 1940s–1980s” folder, in HL-UND.
 36. *Ibid*.
 37. Letter, James E. Murphy to James P. Conroy, 8 November 1967, UDIS116/08, “Reyniers, James A.—LOBUND” folder, in HL-UND. In a 1942 letter requesting funding, Reyniers wrote: “Undoubtedly at first glance, my age and formal education does [*sic*] not seem to warrant rank or consideration. However, when my record is examined it will be found that my age and lack of the conventional ‘moulding’ that invariably accompanies the doctorate have aided rather than hindered my progress” (letter, James A. Reyniers to E. B. Fred, 23 October 1942, “Reyniers, Dr. James A.: 1942–1943,” in NAA).
 38. Analogous to the way Kohler has argued that *Drosophila* shaped the genetics community; see Kohler (n. 12 above).
 39. Brooks, Ralph L. Exploring a Germfree World. *Indianapolis Star*. Apr 18.1948 :6–7., UDIS116/08, “Reyniers, James A.—LOBUND” folder, in HL-UND; Tombs, Nancy. *The Gospel of Germs: Men, Women and the Microbe in American Life*. Cambridge, Mass.: 1998.
 40. In 1953 alone Reyniers visited Italy, Spain, France, Germany, Belgium, Holland, Denmark, Sweden, Finland, and England; see “Lobund Chief Leaves on Tour,” UDIS116/08, “Reyniers, James A.—LOBUND” folder, in HL-UND.
 41. *Scientists in the News*. *Science*. Jun 4.1954 119:795.; Appel, Toby A. *Shaping Biology: The National Science Foundation and American Biological Research, 1945–1975*. Baltimore: 2000. Although he served as a representative of “Catholic” science, his appointment was equally influenced by his growing public and professional stature as the figurehead of the futuristic science of germ-free life.
 42. Appleton B. Lobund Comes of Age. *Scientific Monthly*. 1955; 80:57–58.
 43. The W. K. Kellogg Company asked no more than that he continue developing his germ-free isolators. The company was no doubt interested in the potential of germ-free animals in clarifying Metchnikoff’s unresolved question as to whether microbes in the gut were beneficial or detrimental to human health (see n. 32 above). Reyniers undertook a range of industrial consulting roles, earning from between \$2,400 to \$2,600 in 1942. See “Staff in Bacteriology, University of Notre Dame, Indiana, James Arthur Reyniers,” in NAA (n. 19 above).
 44. “The Biologist and War,” 3 September 1942, “Committees on Biological Warfare, Series 6: Name Files” (“Academy Files”), box 8, “Reyniers, Dr. James A.: 1942–1943,” in NAA.
 45. *Ibid*. Gerard James Fitzgerald has placed germ-free work at Notre Dame within wider U.S. biological-warfare research; see Fitzgerald. *From Prevention to Infection: Intramural Aerobiology, Biomedical Technology, and the Origins of Biological Warfare Research in the United States, 1910–1955*. Carnegie Mellon University; 2003. Ph.D. diss. For biological warfare in the United States generally, see Bernstein, Barton J. *The Birth of the U.S. Biological-Warfare Program*. *Scientific American*. 1987; 256:116–21. [PubMed: 3296173] ; Bernstein. *America’s Biological Warfare Program in the Second World War*. *Journal of Strategic Studies*. 1988; 11(no. 3):292–317.; and Regis, Ed. *The Biology of Doom: America’s Secret Germ Warfare Project*. New York: 2000. For Britain, see Hammond, Peter M.; Carter, Gordon B. *From Biological Warfare to Healthcare: Porton Down, 1940–2000*. Basingstoke, U.K.: 2002.
 46. In the latter use the isolator becomes more approximately an instrument (in the sense of Nicolas Rasmussen). As a means of producing germ-free animals, however, isolators served dual roles: as systems of production and maintaining the animals. Compare Rasmussen. *Making a Machine Instrumental: RCA and the Wartime Origins of Biological Electron Microscopy in America, 1940–1945*. *Studies in History and Philosophy of Science*. 1996; 27:311–49. [PubMed: 11613315]
 47. Letter, James A. Reyniers to E. B. Fred, 29 October 1942, “Reyniers, Dr. James A.: 1942–1943,” in NAA. For Fred, see Baldwin, Ira L. *Edwin Broun Fred, 1887–1981*. 1985 Washington, D.C.

48. Letter, Reyniers to Fred, 23 October 1942, in NAA (n. 37 above).
49. Letter, James A. Reyniers to E. B. Fred, 30 November 1942, "Reyniers, Dr. James A.: 1942–1943," in NAA. Although detailed information on this classified work has yet to be located, one report was titled "Sabotage: Contamination of City Water Mains from Building Connections" (letter, James A. Reyniers to E. B. Fred, 8 February 1943, "Reyniers, Dr. James A.: 1942–1943," in NAA).
50. "LOBUND Annual Report to Office of Naval Research" for the years 1958, 1959, and 1961, PNDP90-Lo-1, "LOBUND (Laboratories of Bacteriology U.N.D.) 1940s–1980s" folder, in HL-UND. For the growth of biology and "big science" within the context of the post-1945 military-industrial complex, see Galison, Peter; Hevley, Bruce. *Big Science: The Growth of Large-Scale Research*. Palo Alto, Calif.: 1992. ; Appel (n. 41 above); Lindee, Susan M. *Suffering Made Real: American Science and the Survivors at Hiroshima*. Chicago: 1994. ; and Kay, Lilly E. *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology*. New York: 1993.
51. Trexler, Philip C. "Development of Gnotobiotics and Contamination Control in Laboratory Animal Science. In: American Association for Laboratory Animal Science. , editor. *50 Years of Laboratory Animal Science*. Memphis: 2005. p. 121–28., esp. 123. On patents, see Kaufer, Erich. *The Economics of the Patent System*. London: 1989. ; Etzkowitz, Henry; Webster, Andrew. *Science as Intellectual Property*. In: Jasanoff, Sheila; Markle, Gerald E.; Petersen, James C.; Pinch, Trevor, editors. *Handbook of Science and Technology Studies*. Thousand Oaks, Calif.: 1995. p. 480–505.; Rasmussen, Nicolas. Of 'Small Men,' Big Science and Bigger Business: The Second World War and Biomedical Research in the United States. *Minerva*. 2002; 40(no. 2):115–46.; and Turchetti, Simone. *A Contentious Business: Industrial Patents and the Production of Isotopes, 1930–1960*. *Dynamis*. 2009; 29:191–217.
52. Compare this with Reyniers's letter to Fred, 29 October 1942, in NAA. The most basic germ-free system was estimated in 1954 to cost \$35,000, excluding the time and expense of training technicians on how to maintain and use it; see "Report of the Ad Hoc Advisory Committee on Microbial Facilities," circa 1955, p. 6, "Series 91153: Conrad Elvehjem. Committees," "National Science Foundation Germ-Free Animal Committee, 1955–56" folder, box 7, in Conrad Elvehjem Papers, University of Wisconsin–Madison (hereafter CEP-UWM). I would like to thank archivist David Null for assistance in locating this report.
53. Reyniers, James A.; Sacksteder, Miriam R. Apparatus and Method for Shipping Germfree and Disease-Free Animals via Public Transportation. *Applied Microbiology*. 1958; 6:146–52. [PubMed: 13521940]
54. *Ibid.*, 150–52.
55. The decades after World War II saw a global attempt to systematize the production, provision, and use of laboratory animals. Although centralized production was seen by some as the means to establish national supplies of standard laboratory animals, others thought it a high risk, as an outbreak of disease could wipe out an entire stock. See Kirk, Robert G. W. *A Brave New Animal for a Brave New World: Constituting Standard Laboratory Animals in Britain, c.1947–1968*. *Isis*. 2010; 101:62–94. [PubMed: 20575490]
56. For an analysis of the relations of "globalization" and "scientization" sensitive to the role of standardization, see Ramirez, Francisco; Drori, Gill S.; Meyer, John; Schofer, Evan. *Science in the Modern World Polity: Institutionalization and Globalization*. Palo Alto, Calif.: 2003.
57. For others the cost was simply prohibitive.
58. Wright, Willard H.; Phillips, Bruce P.; Lewton, Walter L. Recent Progress in Microbiology. *Germ-Free Animal Research at the National Institute of Health*; p. 314–26.(n. 4 above) On the history of the NIH, see Hannaway, Caroline. *Biomedicine in the Twentieth Century: Practices, Policies, and Politics*. Washington, D.C.: 2008.
59. Trexler. *Development of Gnotobiotics*. (n. 51 above)
60. "LOBUND Institute for Research in the Life Sciences," p. 16, in HL-UND (n. 35 above).
61. An account of this episode is given by Appel (n. 41 above), 89–90. Surviving archival records are found in "Subject Files of Dr. Alan T. Waterman, compiled 1951–1963," ARC identifier 579611/MLR, no. A1-1, series from "Record Group 307: Records of the National Science Foundation,

- 1907–2007,” box 2, “Division of Biological and Medical Sciences, LOBUND and Related Matters,” in Archives II, National Archives and Records Administration, College Park, Maryland.
62. “Report of the Ad Hoc Advisory Committee on Microbial Facilities,” p. 8, in CEP-UWM (n. 52 above).
 63. *Ibid.*, 9.
 64. Copies of Reyniers’s extensive correspondence on this issue can be found in “Series 91153: Conrad Elvehjem. Committees,” “National Science Foundation Germ-Free Animal Committee, 1955–56” folder, box 7, in CEP-UWM.
 65. “Staff in Bacteriology, University of Notre Dame, Indiana, Philip Charles Trexler,” in NAA (n. 20 above).
 66. “Note,” E. B. Fred, 4 February 1942, “Committees on Biological Warfare, Series 6: Name Files” (“Academy Files”), box 8, in NAA.
 67. Letter, Murphy to Conroy, 8 November 1967, in HL-UND (n. 37 above).
 68. Reyniers left in 1959 to set up his own germ-free life center in Tampa, Florida, now the Rumbaugh-Goodwin Institute for Cancer Research. He accepted an honorary doctorate from Notre Dame in 1961, suggesting that he harbored no resentments (UDIS130/04, “Reyniers, James A.—Honorary Degree Recipient 1908–,” in HL-UND). For Hesburgh’s own account of these events, see Hesburgh, Theodore M.; Reedy, Jerry. *God, Country, Notre Dame*. New York: 1990. p. 66–67.
 69. This term was coined so as to include both the production and study of germfree animals, as well as animals with a known set of organisms; see Reyniers JA, Trexler PC, Ervin RF, Wagner M, Lucky TD, Gordon HA. The Need for a Uniform Terminology in Germfree Life Studies. *LOBUND Reports*. 1949; 2:151–62.
 70. Philip C. Trexler, “The Evolution of Gnotobiotic Technology,” p. 4, circa June 1984, UDIS100/02, “Lobund Laboratory Conference: Bubble Boy (6/84); International Symposium on Germfree Research 1972–1984,” in HL-UND.
 71. Trexler, Philip C. U.S. Patent 2,779,331. 1957. filed 12 September 1952, and issued 29 January 1957
 72. Trexler, Philip C.; Reynolds, LI. Flexible Film Apparatus for the Rearing and Use of Germfree Animals. *Applied Microbiology*. 1957; 5:406–12. [PubMed: 13488447]
 73. Germfree Life Is Longer. *Science News-Letter*. Jul 1.1950 58:3.
 74. Trexler, Philip C. Progress Report on the Use of Plastics in Germfree Equipment. Proceedings of the Animal Care Panel. 1959; 9:119–25., quotes on 119. Significantly, Reyniers was not involved with the establishment of the Association for Applied Gnotobiotics, nor did he attend the occasional symposiums on gnotobiotic technology that followed; see List of Participants. *Laboratory Animal Care*. 1963; 13:670–84. Reyniers died on 3 November 1967, age 59.
 75. Promotion material for some of these companies dating from the 1960s can be found in the “Animal Welfare Institute Records,” carton 5.013, folders 17–20, in the Special Collections Research Center, North Carolina State University, Raleigh.
 76. Gnotobiotics, new PhD field. *Science News-Letter*. Jan 26.1957 71:62.
 77. Gordon HA, Pesti L. The Gnotobiotic Animal as a Tool in the Study of Host Microbial Relationships. *Bacteriological Review*. 1971; 35:390–429. quote on 410.
 78. Weathersbee C. Is Clean Living Bad for Mice? *Science News*. 1968; 93:456–57.
 79. Gordon; Pesti. p. 420
 80. Coates, Marie E. Gnotobiotic Animals in Research: Their Uses and Limitations. *Laboratory Animals*. 1975; 9:275–82. [PubMed: 1107656]
 81. Trexler (n. 74 above). Workshop participants were Blue Spruce Farms (Altamont, New York), Carworth Farms Inc. (New City, New York), Charles River Breeding Laboratories (Brookline, Massachusetts), Cumberland View Farms (Clinton, Tennessee), Fort Detrick (Frederick, Maryland), Manor Farms (Staatsburg, New York), Millerton Research Farms (Millerton, New York), National Laboratory Animal Company (Creve Coeur, Missouri), A. R. Schmidt Company (Madison, Wisconsin), Simonson Laboratories (Gilroy, California and St. Paul, Minnesota), and Taconic Farms Inc. (Germantown, New York). All but Blue Spruce Farms gained the certificate of competence; it subsequently went out of business.

82. "Information for a Non-faculty Research Appointment to Graduate School University of Notre Dame, Trexler, Philip Charles, 12th July 1983," UDIS100/02, "Lobund Laboratory Conference: Bubble Boy (6/84); International Symposium on Germfree Research 1972–1984," in HL-UND.
83. Lane-Petter, William. Laboratory Animals Centre Collected Papers. Vol. 12. London: 1963. Discussion; p. 54-55.quote on 55
84. Trexler. The Evolution of Gnotobiotic Technology; p. 5HL-UND (n. 70 above)
85. The notion of a "pure line" is attributed to Wilhelm Iohannsen; see Roll-Hansen N. The Genotype Theory of Wilhelm Iohannsen and Its Relation to Plant Breeding and the Study of Evolution. Centaurus. 1978; 22:201–35.
86. Russell, Elizabeth S. New Trends in the Use of Genetically Controlled Laboratory Animals in Biomedical Research. Proceedings of the Animal Care Panel. 1960; 10:167–76.
87. Gannon. p. 92(n. 31 above)
88. Ibid., 93.
89. Critiques of this model include Rasmussen, Nicolas. Picture Control: The Electron Microscope and the Transformation of Biology in America, 1940–1960. Palo Alto, Calif.: 1997. ; Gaudillière, Jean-Paul; Löwy, Iliana, editors. The Invisible Industrialist: Manufacturers and the Production of Scientific Knowledge. London: 1998. ; and Edgerton, David. The 'Linear Model' Did Not Exist: Reflections on the History and Historiography of Science and Research in Industry in the Twentieth Century. In: Grandin, Karl; Wormbs, Nina, editors. The Science–Industry Nexus: History, Policy, Implications. New York: 2004.
90. König, Wolfgang. Science-Based Industry or Industry-Based Science? Electrical Engineering in Germany before World War I. Technology and Culture. 1996; 36:70–101.
91. Oudshoorn, Nelly; Pinch, Trevor, editors. How Users Matter: The Co-Construction of Users and Technologies. Cambridge, Mass.: 2005. Albert de la Bruhèze, Adri; Oldenziel, Ruth. Manufacturing Technology, Manufacturing Consumers: The Making of Dutch Consumer Society. Amsterdam: 2009.
92. Rheinberger (n. 12 above), 28.
93. Lenoir, Timothy. Instituting Science: The Cultural Production of Scientific Disciplines. Palo Alto, Calif.: 1997. p. 292
94. On the invisibility of standards, see, for example, Lampland and Star (n. 10 above), 9–11.

FIG. 1. Standard Reyniers Germ-Free Steel RSU 300 Isolator (A), attached to a Reyniers Germ-Free Surgical RSU 100 Isolator (B). (Source: James A. Reyniers, "The Germfree Life Program of Lobund Institute, University of Notre Dame," in *Recent Progress in Microbiology: A Symposium Held at the VII International Congress for Microbiology, Stockholm, 1958*, ed. G. Tunevall [Stockholm, 1959], 261–87. All attempts to locate the copyright holder for this image were unsuccessful.)

FIG. 2.
Specialist variations of the Reyniers Germ-Free Steel Isolator. (Source: James A. Reyniers, "Design and Operation of Apparatus for Rearing Germfree Animals," *Annals of the New York Academy of Sciences* 78 [1959]: 47-79, © John Wiley & Sons, Inc. Reprinted with permission.)

FIG. 3.

Germ-free monkey having been delivered into an isolator being hand fed sterilized milk formula. (Source: "Germ-Free Research," *Chemical and Engineering News* 30 [7 July 1952]: 2826-27. All attempts to locate the copyright holder for this image were unsuccessful.)

FIG. 4. Reyniers Germ-Free System 1 Mass-Production Isolator. (Source: *Life* magazine, artist Donald Birren. All attempts to locate the copyright holder for this image were unsuccessful.)

FIG. 5. Mobile isolator for shipping germ-free animals. (Source: James A. Reyniers, "The Germfree Life Program of Lobund Institute, University of Notre Dame," in *Recent Progress in Microbiology: A Symposium Held at the VII International Congress for Microbiology, Stockholm, 1958*, ed. G. Tunevall [Stockholm, 1959], 261–87. All attempts to locate the copyright holder for this image were unsuccessful.)

FIG. 6. Trexler flexible plastic isolator, ca.1959. (Source: P. C. Trexler, "The Use of Plastics in the Design of Isolator Systems," *Annals of the New York Academy of Sciences* 78 [1959]: 29–36, © John Wiley & Sons, Inc. Reprinted with permission.)

fig. 7.
Germ-free rats were found to possess an enlarged cecum (bottom) compared to conventionally bred rats (top). (Source: Bengt Gustafsson, "Germfree Research at the Institute of Histology, University of Lund," in *Recent Progress in Microbiology: A Symposium Held at the VII International Congress for Microbiology, Stockholm, 1958*, ed. G. Tunevall [Stockholm, 1959], 327–35. All attempts to locate the copyright holder for this image were unsuccessful.)