Experimental Clinical Medicine and Drug Action in Mid-Seventeenth-Century Leiden

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SUMMARY: Leiden University boasted one of the most popular and influential medical schools of the mid-seventeenth century, drawing hundreds of students from across Europe. These students participated in the revival of frequent clinical instruction, anatomical and chymical experiments, and even tests of supposed disease-causing substances and remedies on living animals and humans. Comparing records of cases from the hospital clinic with the professors’ treatises and student-authored disputations shows that old and new theories of disease and drug action were hotly contested and often tested, including the claims of the leading professors at the school. Though notable exemplars of their work received sharp criticism and rejection from contemporaries and subsequent generations, Leiden students and professors united chymistry, postmortem autopsy, anatomical experiments, and clinical tests, often aiming at discovery. They enacted one, perhaps ephemeral, instance of experimental, clinical medicine well before its putative modern birth.

KEYWORDS: experiment, Leiden, clinic, students, professors, Franciscus Dele Boë Sylvius, Reinier de Graaf
In the mid-seventeenth century, Leiden University advertised a comprehensive medical education, with daily instruction in the many facets of medicine. For the morning lectures, Johannes Van Horne taught on the method of curing at the eighth hour, then Adolph Vorstius would begin instruction on the aphorisms of Hippocrates at the tenth. At the eleventh hour Johannes Antonides Vander Linden taught the method of recognizing and curing particular diseases according to rational medicine. Franciscus Dele Boë, known as Sylvius, instructed the students on the more serious and more frequent diseases encountered in practical medicine from the second hour. Johannes de Raey taught natural philosophy (Physica) at the fourth hour, and occasionally leveraged his medical degree to teach Cartesian “anatomy.” De Raey’s speculative Cartesian approach vexed other medical professors, who objected that “medicine must not be founded on philosophical speculations, but on experience [ervarentheyt].” At the same time, Vorstius demonstrated medicinal plants in the university botanical garden. Vander Linden and Sylvius also had the task of instructing the students at the public hospital, in alternate trimesters, and demonstrating “to ocular confidence [fidem oculatam] the causes of death in dissected cadavers.” This mix of controversy, tradition, and innovation catalyzed student-professor innovation. Though some of their work provoked harsh criticism soon and long after, students and professors still generated a productive culture of testing in an influential medical institution.

In this setting, a few students and professors experimentalized drug testing by constructing horrific vivisection experiments in which they could directly witness the effects of drugs and purported pathological substances in the living bodies of animals. In 1663 or 1664, a student at the university, Reinier de Graaf, captured or bought a series of dogs and surgically cut them into...
experimental apparatuses for viewing the effects of hydragogues, phlegmagogues, and cholagogues, drugs that supposedly purged water, phlegm, and bile.⁴ He and his mentor Sylvius also produced experimental support for Sylvius’s new medical system based on the production and interaction of bodily acids and alkalies. Sylvius’s clinical prediction that plague acted as a volatile alkaline substance found sure confirmation in animal tests: acids injected into the veins of sacrificed, tortured dogs coagulated the blood and caused heart failure; alkaline salts made the blood more fluid, causing internal bleeding and other effects.⁵ Daily instruction in the hospital clinic allowed Sylvius and his students to correlate the symptoms of patients with the predictions of the new system and the evidence from postmortem dissections of their experimental subjects. Throughout clinical treatments in the hospital, Sylvius and his students also tried out their diagnoses and chymical remedies on patients.⁶ Ultimately, only a patient’s recovery or the demonstrative results of postmortem autopsies could confirm the nature of the disease and the success of therapy. In Leiden, students and professors tested all sorts of interrelated things: theoretical and factual claims, laboratory chymicals, bodily fluids, anatomical structures, surgical techniques, new instruments, and, ultimately, drugs.

Previous studies have offered overviews of one aspect or another—experimental “physiology,” anatomy, or philosophical controversy—without sustained attention to the integrated community or the ultimate aim of therapy. Harm Beukers crafted erudite studies of clinical teaching at Leiden, as well as essential treatments of Sylvius’s chymistry.⁷ He has established beyond doubt that Sylvius “indeed performed substantial practical chemical work.”⁸ Certainly, Sylvius produced chymical remedies and very probably sought for the arcana of alchemical transmutation, yet Beukers explicitly left open for further research the question of
whether Sylvius conducted “significant original researches.” Beukers has also very briefly pointed to Sylvius’s vigorous clinical instruction, including his emphasis on dissections and his use of chymical remedies. Yet he left open for future research the testing of remedies on animal or human subjects, as well as the central place of chymical theory, such as affinity theory, and chymical tests and other laboratory phenomena in the defense of the new drugs and medical concepts.

This article aims to answer, at least in part, the question of how De Graaf and Sylvius came to make direct trials in living subjects, and why they did so. My argument here moves beyond and integrates aspects of the extant scholarship. So far, G. A. Lindeboom’s concise overview of experimental “physiology” at Leiden has been the most comprehensive short treatment, while E. D. Baumann’s biography remains the most extensive monograph of Sylvius. There are also useful overviews and focused studies of Reinier de Graaf’s works, especially his later investigations of generation. More recently, Pamela Smith has painted a portrait of Sylvius as a gentleman experimentalist who relied on the senses yet cultivated his elite social status. Finally, Tim Huisman’s elegant survey of the institution of anatomy at Leiden University sketches some of the anatomical work in the midcentury in the context of a diachronic cultural history. Harold Cook presents Sylvius as typifying “the best of Dutch experimental medicine,” whose integrated intellectual and manual work reflected the mobile, porous, and practically oriented nature of Dutch social commerce. The material here supports Cook’s succinct insight, and expands our view beyond Sylvius and his better-known students to the wider community, following the theme of medical testing. The culture of testing and collaboration also resonates with the broader values of commerce and networks of exchange Cook has highlighted in his
extensive studies. Finally, this study strongly supports Cook’s historiographic lesson about the interconnectedness of anatomy, chymistry, natural history, medicines, and instrumentation in “intertwined investigative projects.”

Here I will fill in many details not supplied elsewhere, especially the experimental testing of drugs performed by De Graaf and Sylvius, and draw together the lines of evidence to give a more complete picture of the competitive and collaborative culture of testing found in the Leiden medical school. In contrast to Matthew Cobb’s narrative of the later investigations of generation after several members left Leiden, I am interested in earlier and institutionalized forms of experimental culture, especially in the close, even daily practical and conceptual links uniting chymical experimentation, clinical therapy, postmortem dissections, and experimental vivisections.

My point here is not that midcentury Leiden must represent the origin of modern anatomo-chymico-clinical medicine. Too much work remains to be done, and there are earlier examples of clinical instruction, anatomical investigation, and chymical experimentation in medical faculties. Even at Leiden earlier in the seventeenth century, Otho Heurnius gave clinical instruction and made careful postmortem dissections of patients. Rather, my aim is to get a better sense of the actors and practices in this culture of testing and briefly point to the strikingly detailed appropriation of these and other practices to solve similar problems in nineteenth century.

These Leiden practices of testing drugs and medical systems, cutting to new discoveries of “the things themselves” in bodies living and dead, all with the aim of improved therapies, also cuts across the categories and discontinuities found in key studies of the history of European
clinical medicine. In brilliant and celebrated analyses from Michel Foucault, Erwin Ackernecht, and N. D. Jewson, medicine variously described in terms of practices, discourses, institutions, or cosmologies shifted in the late eighteenth and early nineteenth centuries into new forms enacted in and around the hospital clinic. This “new” medicine penetrated beneath the total complex of surface symptoms to concentrate on hidden pathological states later revealed in postmortem dissections. Scholarly responses to these germinal works present a vast literature, making any succinct claim in need of extensive support and articulation.

Yet the Leiden culture sketched here presents challenges to literature that portrays clinical teaching before the late eighteenth-century Parisian institution as aiming at the passive transmission of knowledge or unconcerned with pathological anatomy and medical experimentation. Though Leiden investigators lacked sophisticated notions of tissues, they still emphasized the interpretation of life and disease through the evidence of cadavers, and even the localization of disease states. Moving “vertically” from surface symptoms to hidden blockages, bodily chymicals, vessels, organs, and, at times, lesions was something Leiden professors and students did with regularity. Even if Boerhaave’s clinical practice was merely demonstrative, confined to small numbers of patients, declining, or otherwise limited, the earlier Leiden medical culture prized new discoveries produced by experiments on dozens of dissections, human and animal, during a student’s career. In the 1660s, many patients who died while in the hospital then had their bodies dissected immediately, or on the next day. Furthermore, students often authored their own disputations, and publicly defended their investigations and claims.

Of course, the historical complexities of the later clinics generated important and long-lasting innovations. In contrast, the number of patients at Leiden did not reach the tens of
thousands found in the later Paris hospitals, so physicians there did not have the same need to develop clinical statistics. In Leiden, physicians and students also continued to reason in part from the structures to the functions of organs, and God rather than brute Nature guaranteed all regularities.\textsuperscript{25} And there is little doubt that François Magendie and Claude Bernard would have rejected at least some of the conclusions and the system-building zeal of Sylvius, however much the Leiden professor sought to base his system in experiments anatomical, chymical, and practical.\textsuperscript{26} Yet the practice of Sylvius and De Graaf of producing phenomena experimentally seems at least partially in line with Bernard’s notion of experimental medicine: “Systems and doctrines proceed by affirmation and purely logical deduction; the experimental method always proceeds by doubt and experimental verification.”\textsuperscript{27} Grounding their suspicions and conclusions in phenomena perceptible to the senses, Leiden students and professors linked chymical and anatomical experiments, drug testing, clinical practice, and postmortem dissections in a productive concurrence of new technological devices, new operations, and evidence for new systems.

An Experimental Community: Competition and Collaboration in Leiden

Collaborative experimentation was the hallmark of anatomical-medical work at Leiden in the 1660s. As I have argued elsewhere, collaborative experimentation in anatomy at Leiden stretched at least from the early work of Sylvius and Johannes Walaeus in the late 1630s and early 1640s up to the 1660s.\textsuperscript{28} They developed the methods of William Harvey along the new directions his circulation of the blood opened up, such as the conversion of food to blood. To this more
anatomical tradition they fused chymical experimentation inspired in part by Jan Baptista van Helmont and Johann Rudolph Glauber.29

One of the sites for group work was the hospital. In 1636, Otto Heurnius and Ewaldus Screvelius founded a *collegium medico-practicum*, or a course in clinical instruction and demonstrations in the Caecilia Hospital.30 More active than his colleague Vander Linden, after his appointment to the faculty in 1658 Sylvius expanded the twice-weekly visits to the hospital to daily rounds with students. His clinical instruction became so popular that he requested and received an additional two benches for the dissection theater.31

His commitment to his system of chymical medicine did not blind him to useful clinical observations. For instance, Sylvius is still credited as the first European physician to link the appearance of pus-filled tubercles (*tubercula*) in the lungs with the other symptoms of phthisis.32 His postmortem autopsy of a patient with phthisis revealed these tubercles, and their pus emerged under the investigative knife.33 Combining detailed case histories of the patients in the hospital with autopsies allowed Sylvius to make novel links between pathological anatomy and the diagnostic signs of disease.

At least by early 1662, we have student accounts of Sylvius demonstrating his new system in clinical instruction, arguing that the alkaline bile and acidic pancreatic fluid play key roles in generating a chymical “effervescence” that controlled vital heat, produced localized disease states in various organs, and generated other general states such as fevers.34 Student case histories from 1659–61 and the later 1660s are extremely detailed, with many including clinical observations and therapies as well as theoretical explanations of the disease and treatments.35
A violent controversy with an erudite medical professor from Groningen, Anton Deusing (1612–66), provided Sylvius with the chance to defend and advertise his clinical teaching.\textsuperscript{36} In targeted letters and his major polemical work, \textit{In Sylvam Echo} (1663), Deusing wielded ancient and modern books as weapons against the novelty and consistency of Sylvius’s new medicine.\textsuperscript{37} Deusing was also something of a rival to Sylvius, since his own doctrines on the process of nutrition—though derived from other authors and not his own observations—were revisionist, and drew from recent authors such as Nathaniel Highmore, Walter Charleton, and Francis Glisson.\textsuperscript{38} Status and salaries hung on the controversy, which raged for several years and boiled over when the Leiden Curators intended to hire Deusing and pay him sixteen hundred guilders annually for his services (rivaling Sylvius’s colossal eighteen hundred guilders). It ended only when Deusing died in 1666.\textsuperscript{39}

In this seething polemical contest, Sylvius portrayed his successes in medicine as the result of Divine grace, with his charitable manner opposed to the beastly ways and itemized sins of his opponents. While Deusing “growls, moos, groans, froths, roars, howls, bellows, [and] barks” throughout his “shat-out Writings,” Sylvius claimed to present a model of open, free discourse better suited to the evidence of the senses about the “things themselves.”\textsuperscript{40} Here, he likely followed his anatomical hero, William Harvey, who had experimentally demonstrated the muscular, contractile action of the heart against Descartes and the Cartesians.\textsuperscript{41} In the preface to his 1651 work on generation, Harvey had contrasted learning based on books and philosophical opinions with his path: “a more new and difficult way, to find out the nature of things from the things themselves [\textit{ex rebus ipsis}].”\textsuperscript{42} Sylvius concurred, and added that human lives were at stake. Physicians did not dispute “about goat’s wool, but deal with human hide.”\textsuperscript{43} All the mess
and trouble of clinical practice and experimental trials—something Sylvius lamented frequently throughout his writings—remained the heavy price of effective knowledge and care.

Sylvius’s account of clinical discussions is valuable:

I led them to practical medicine by the hand, and from day to day in the public Hospital I led them to visiting the Sick, and I set out for them their complaints and otherwise noticeable Symptoms, and presently I asked their opinions, and the reasons for their opinions about whatever Disease was observed in the Sick, and its Cause, and about the Doctrinal Treatment, and as often as disagreement was therefore excited among them, I gently brought together those disagreeing among themselves, so that each one would be satisfied with the sought reasons from wherever, but, as much as possible, very solid reasons, and at last I also introduced or tossed in my own judgment about the singular cases. Moreover, in the following days, I exposed to them the varied successes of my prescribed medicines, and then, as before, again I examined the opinions of those coming together; and then at last the sick anxiously treated by us, as God was pleased, were either restored to their former health so that they departed happy, or followed their fate and, dying, left us their bodies to be dissected; and in the accurate opening and demonstration of their bodies it was revealed to all whether they had judged rightly or wrongly about that Disease, and from that the rest of the things considered.44

From the favorable presentation here, we can observe that the daily clinical instruction in the public hospital depended on attention to the sick patients and open discussion of the diseases signified by their symptoms, as well as their causes and treatments. These discussions were not rigidly demonstrative or dogmatic lessons, but open to disagreement and competition for recognition. Postmortem dissection determined whose explanation made the final cut; the
anatomical investigation of the dead bodies “revealed to all whether they had judged rightly or wrongly.”

Experimentation from the clinic and private rooms and laboratories anchored the most important claims for many new discoveries, and for Sylvius’s medical system. He repeatedly asserted that all of his teachings, “each and every one must be deduced or referred to Experiments, or to Reasonings deduced from preceding experiments.” He further divided experiments into three kinds: anatomical, chymical, and practical. Only experiments could “demonstrate these things to Sense . . . to satisfy those curious and worried about the truth of the matter.” Experiments dot Sylvius’s published works, and serve to confirm his doctrines and rebut those of his opponents. In the later “Additamenta” to the original disputations he authored, Sylvius countered his opponents’ criticisms with experimental reports. A few days after the July 10, 1660, public disputation On the Use of the Bile and the Liver, for example, a postmortem in the academic hospital involved inserting a tube into the bile duct and then inflating the liver and even forcing blood out of the heart and right axillary vein. Sylvius performed a similar experiments on September 15, 1660, to show that air injected into the hepatic artery inflated the gallbladder. A final inflation experiment on November 13, 1662, during a hospital postmortem showed an apparent connection from the hepatic artery to the aorta. All these experiments served as warrant for the claim that the alkaline bile could travel from its creation by chymical transmutation in the gallbladder up through vessels to the heart and beyond. The variability of animals and the difficulty of the work required repetitions and variations: “[D]issections must be made often, and the same experiments must be reiterated frequently
before anything can be determined with certainty in an affair which is controversial among the Anatomists.”

Sylvius also carried experimental programs into his daily lectures. He lectured on chymistry even prior to the establishment of a university laboratory in 1669. On March 14, 1661, for example, Sylvius gave a lecture on chymistry, highlighting the regular actions of fire, water, and spirit as solvents:

[F]ire, water, and spirit are the principal solvents of nature . . . acid spirits dissolve coagulated things by the salt, acid spirits coagulate fatty things; spirit acts especially in salt; fire acts in nothings except by the oil, and volatile salts coagulate those things that are dissolved by an acid spirit, such as metals. Thick bile grows green when an acid spirit is poured on it, and thus come the green excrements of infants, since indeed their odor shows them to be acidic. Hot water softens claws, and a scraping bony matter of the limb of crabs, found in a certain man’s stomach, was dissolved with the juice of a radish, and this experiment should be carried over to bones.50

Chymistry lectures under Sylvius were not just about pharmacy. Chymistry teaching with Sylvius involved the use of experimentation to discover principles and regularities.51 As he styled it, “Chymistry is the foremost Art of natural changes, in which changes, if I may say it, Nature itself is surpassed, and so Chymistry is uniquely necessary and extremely useful for building up a sound Medicine, and Natural Knowledge [Physica Scientia].”52 He paid close attention to the regularities of solution replacement series (related phenomena are now often discussed in terms of the activity series of metals). Due to the greater chymical “affinity” (affinitas) of iron particles for acidic aqua fortis, iron introduced into a solution of
copper and *aqua fortis* displaced the copper, which emerged from its bonding with the acid and fell to the bottom of the container. Sylvius drew from experimental laboratory results such as this as a general conception of chymical affinity that determined the regular reactions of bodily digestion and acid-alkali pathology.\(^{53}\) In his fine home on the Rapenburg, Sylvius stoked twenty chymical furnaces, with at least three laboratory spaces.\(^{54}\) The lecturer at the new university chymical laboratory opened in August 1669, Carel de Maets, had eight furnaces.\(^{55}\)

Anatomical experiments, too, revealed the regularities of nature across animal and human kinds and individual subjects. As Sylvius’s student De Graaf asserted, “that which Nature exhibits as more suppressed and more obscure in one kind, in another she unfolds more clearly and openly. Thus, no one can rightly determine the use \([usus]\) or office \([officio]\) of any one of the parts who has not seen the structure \([fabrica]\), situation, and connected vessels, and other accidents, and diligently pondered them himself.”\(^{56}\) Here De Graaf likely echoed the sentiments of Sylvius and William Harvey, whose comparative study of the motion of the heart and blood in snakes, fish, frogs, lizards, and a long list of other animals allowed him to establish universal characteristics of the parts and mark out conspicuous cases.\(^{57}\)

Finally, by “Practical experiments” Sylvius meant the sorts of tests recorded in medical *observationes* or *historiae*. Generically, these took the form of records of medical experience with patients, often in terms of case histories.\(^{58}\) Examples of successful treatment, or even failed regimens explained in terms of the theory employed, counted in favor of the suspicions or doctrines constituting the acid-alkali medical system.\(^{59}\)
These declarations of allegiance to experimentation were not mere rhetoric. Sylvius, in particular, rejected forming conclusions based on reasoning alone, and thought even his experimental work failed to generate true demonstrations (*demonstrationes*). As they approached true demonstrations, he “marked them off with the name of either *Opinions*, or *Suspicions*, or *Conjectures*. And I have also not hesitated to add here and there my *Doubts*.“⁶⁰ When he posited subvisible pores or particles, for example, he wrote only that “we suspect” (*suspicamur*) such things to exist.⁶¹ When he made inferences to bodily chymistry based on the regularities of laboratory chymistry, though, he remained confident in the teachings of this “foremost Art of natural changes.”⁶² Once established in the laboratory, and confirmed in animal experiments, these chymical regularities allowed the Leiden investigators to reason beneath the surface symptoms to the hidden causes and states of diseases. Postmortem dissections clinched their conclusions.

Tellingly, Sylvius and colleagues repeatedly performed difficult and even disgusting anatomical and chymical experiments, and often limited their claims to the constraints of experimentation. For instance, student disputations in December 1668 attacked Sylvius’s claim that the gallbladder produced bile by a process of alchemical transmutation, and then sent that bile throughout the body via the liver.⁶³ In their public discussion, students invoked the experiments of the eminent Italian anatomist Marcello Malpighi, whose ligation of the ducts connected to the gallbladder showed the bile originating in the liver. Even though he had not taken the time to replicate Malpighi’s findings, Sylvius accepted the experimental refutation of his views. Experiments made a difference, even against favored claims.
Johannes Van Horne was the other active promoter and performer of experimental dissections and vivisections on the faculty during this time. Van Horne’s father, Jacob, was fabulously wealthy as a director of the Dutch East Indies Company, one of the first “Lords Seventeen.” Johannes pursued his medical studies at Utrecht and Padua, where he took his medical degree, then traveled before returning to Leiden and then joining the faculty in 1651 as an extraordinary professor of anatomy. Van Horne worked on an anatomical atlas in the 1650s, a few plates of which were observed by the Danish polyhistor Ole Borch (1626–90) in the early 1660s, and have just been found. Van Horne was very much part of the group of cutting-edge anatomists in Leiden, which is shown especially in his 1652 observation of the lacteals in a human body, his later investigations of generation with Jan Swammerdam and other students, and his search for new methods for anatomical injections. After the death of a hospital patient, Van Horne and Sylvius sometimes performed the postmortem together, as on January 27, 1661, when the body of a woman called “Helena,” an adulteress, offered Sylvius the chance to find postmortem evidence of his acid-alkali chymical pathology, and Van Horne an opportunity to use bellows to uncover a connection between a cranial sinus and the nostrils. Professors and students both seem to have seized on any chance with a fresh cadaver, correlating bodily states and the predictions of new medical theories, or manipulating parts in the hope of making an anatomical discovery.

The collaborative community of anatomical research in Leiden tended to reduce or collapse the authoritative social distinctions between students and professors. Some of Sylvius’s lectures in the hospital used cutting-edge observations from his students’ private experimentation. Based on my review of hundreds of disputations held at Leiden University, I would argue that by the
1660s it was standard for a Dutch medical student to author his own disputation, sometimes supplying his own experimental work and clinical experience to support his claims.⁶⁸ Although the collections of disputations are incomplete in the earlier decades, medical students began regularly to author their own disputations around 1640. Many disputations, of course, were wholly derivative of extant authoritative sources, but even then usually identified the student as auctor on the dedication pages. Ku-ming (Kevin) Chang has argued, following Hubert Steinke, that in the eighteenth century Albrecht von Haller instituted a “new model” of disputation authorship, in which the student was given sole authorship—without attribution of any authority to the praeses—in exchange for experimental work.⁶⁹ The evidence from Leiden in the mid-seventeenth century shows an intermediate practice, in which many students supplied their own experimental work, even contradicting their professors, and most wrote their own disputations. A final section added to the disputation of Robert Padtbrugge, defended on April 27, 1663, details one such case.⁷⁰ First, Padtbrugge and his colleagues Jan Swammerdam and Nicolaus Steno began a trial sparked by their professor Vander Linden’s erudition.

In the month of February of this year we were going to make an experiment (the way having been shown by the truly learned Vander Linden), about whether Apoplexy follows after the carotid arteries are ligated, and I invited the most distinguished Young Men, Becker and Vonder Lahr so they could be ocular witnesses. I was separating the jugular vein, when—behold!—at once we saw in it a motion of emptying or subsidence during inspiration, and swelling in expiration. After the wound had been sewn up for two days (namely, the 8th), I opened the wound (as there and then in the abdomen [in the vena cava], where it is more manifestly conspicuous), and [we did] this because my friend Swammerdam was there, and Vonder Lahr and Becker were again present at the
meeting, as well as the most accurate Anatomist Steno. The next day Swammerdam showed our finding to the Celebrated Sylvius, who told about it that very day publicly in the Hospital, and he claimed that he did not know if we were the discoverers, and he asked if I could set up the vivisection again, that I would call it together. The third of the same month arrived, and I was with Van Home, my Promotor . . . and we observed no motion (or any pulsation) except the one already mentioned in either the jugular or the descending vena cava. And this is the same motion that the most celebrated Sylvius calls a motion of contraction in the additamentum no. 87 of his Medical Disputations (in my judgment, however, this kind [of motion] has not been discovered), and he admits that it is our discovery, lest anyone assume an improper opinion from another place.  

There are several details worth noting in this passage. First, it records what the students took to be an anatomical discovery and advances that discovery as a significant contribution to the extant knowledge on apoplexy, which appears summarized in the main text of the disputation. Even students at Leiden used experiments to test hypothesized connections between anatomical states and diseases. Second, it was presented as a last-minute addition to a disputation the student defended about a month after the confirmation of the initial discovery. This suggests both the epistemic importance accorded to vivisectional discoveries, and the occasionally haphazard nature of their appearance. Third, the discovery appears first as the result of an extramural collaborative vivisection performed by a group of students. Fourth, students quickly involved their professors. Swammerdam immediately communicated the result of the experiment to his mentor Sylvius, who described it in that very day’s clinical instruction in the hospital. Sylvius was not sure about possible precedents, which reveals the premium placed on establishing priority for anatomical experiments. Patibrugge then turned to further experimental vivisections with his Promotor, Johannes Van Horne, to confirm the phenomenon. Last, even as a student
Padtbrugge had enough confidence in his experimental skills to contradict the wording of Sylvius, who claimed to have seen a “contraction” of the jugular vein and descending vena cava in an experiment performed by Swammerdam in January of the same year. Swammerdam, in turn, would cite Padtbrugge’s observations in his 1667 disputation on respiration, which also contradicted Sylvius’s account of respiration by its embrace of Cartesian principles.

Padtbrugge’s account nicely illustrates the competitive, even aggressive nature of experimental discovery, as well as the close, daily ties between experimental collaboration and clinical instruction.

In fact, students were often free to dissect the cadavers in the hospital or in private after the demonstrations by Sylvius. At least nineteen student disputation from Sylvius’s tenure mention dissections or medicinal trials in the hospital, often with Sylvius as the active dissector or administrator of therapies. Most recount anatomical observations. These included observing a blood vessel full of exhalations, ostensibly formed from Sylvius’s proposed “effervescence” of bile and pancreatic fluid, and the concretion of blood in the heart and vessels of a patient diagnosed as an epileptic.

Of course, there is evidence of only a small group of students actually performing experiments. Out of an average of fifty-seven students matriculating in medicine each year from 1650 to 1672, roughly a third produced a doctoral disputation still extant. Only a handful of these report significant first-person experimentation, though many others report and use the experimental work of other students, and professors, as evidence in their arguments. Yet many of these students attended the daily clinical instruction, and certainly knew something of the
celebrated and publicized experimental work mentioned in the clinical lectures, the postmortem autopsies, and the frequent public disputations.

Students could import their own research interests and skills, too. In 1661 and 1662, Nicolaus Steno (Niels Stensen, 1638–86) published accounts of his discovery of a previously unknown duct, the parotid salivary duct, leading from the gland near the ear to the mouth.\(^80\) Steno’s work was an important early moment in the local participation in the wider “revival of the glands” in the 1660s.\(^81\) Steno had made his discovery in private rooms in Amsterdam prior to coming to Leiden, in a chance investigation of a sheep’s head, at the home of the anatomy lecturer Gerard Blaes (Gerard Blasius, ca. 1625–82).\(^82\) As Eric Jorink has pointed out, the precocious successes of Steno and Swammerdam were due, at least in part, to their intense collaboration and the frequent assistance of others in both private and public settings.\(^83\)

Students circulated experiments and demonstrations freely beyond their closer circles of friends. Robert Sibbald’s recollections of his time in Leiden illustrate this nicely, since in just the year and a half he studied there, Sibbald saw Sylvius dissect twenty-three human bodies in the hospital, performed dissections with Van Horne and Nicolaus Steno, even in his own private lodgings, and met with chymists and apothecaries.\(^84\) Strikingly, Sibbald’s observation of twenty-three bodies dissected by Sylvius in just a year and a half actually corroborates the eulogistic portrayal of Sylvius’s industry painted by Lucas Schacht (1634–89). In his funeral oration for his mentor, Schacht claimed that Sylvius had dissected more than three hundred human cadavers during his fourteen years at Leiden.\(^85\) Together, professors and students lived out a collaborative, competitive culture.
Students and Professors Testing Chymical Bodies and Remedies

Sometime in 1663, Reinier de Graaf captured or bought a dog. In private lodgings, he tied the dog securely and then surgically opened its abdomen. Taking the instruments from chymical analysis at hand, he attached a duck quill to a chymical flask, inserted the quill into the pancreatic duct of the dog, and secured the flask to the dog with a ring-and-cord cinch used by chymists. He kept the carefully tortured animal alive for seven or eight hours in order to collect and analyze the pancreatic fluid produced by a living dog apparatus. With the fluid safely in the flask, De Graaf used taste, color tests, coagulation tests, and an effervescence test to confirm his mentor Franciscus Sylvius’s conjecture that the fluid had to be acidic to balance and effervesce with the alkaline bile flowing into the intestine from a neighboring duct. I have described some aspects of De Graaf’s experimental work and Sylvian chymistry elsewhere. In the remainder of this essay I use De Graaf’s further experiments to explore more fully from the student side the concurrence of experimental anatomy, chymistry, postmortem dissections, and clinical practice. Since De Graaf’s work offers the most detailed and sophisticated discussions of in vivo testing of drugs, he will take center stage here.

Like other students, De Graaf published the history and results of his experiments in his public disputation, *Disputatio Medica de Natura et Usu Succi Pancreatici* (*Medical Disputation on the Nature and Use of the Pancreatic Fluid*). Unlike those of most of his peers, his disputation was ninety pages long and exhibited novel experimentation and argumentation on page after page. He successfully defended his disputation on December 17, 1664. De Graaf’s treatise on the pancreatic fluid moved from history to anatomy, experimentation, tasting, and pathology with ease. Here, we will only sketch the outlines of De Graaf’s pathology and therapy.
of the fluid. Following Sylvius and his version of Hippocrates, De Graaf understood the pancreas as the primary source of acidity in the body. Since bile was primarily responsible for enkindling the vital heat of the heart, pancreatic fluid could indirectly affect the action of the heart and even the heat of life by excessively tempering the alkaline bile. Given the vital importance of the bile and pancreatic fluid mixture, the balance God put into place worked most of the time.\textsuperscript{90}

With these conceptual tools, Sylvius’s urging, and a great deal of youthful enthusiasm, De Graaf proceeded to link many diseases to the various abnormal states of the pancreatic fluid. Despite these theoretical flourishes, De Graaf retained some grounding in experiment. Strikingly, De Graaf used \textit{in vivo} injections as a novel investigative technique by which the physician could experimentally determine both the pathologic effects of a chymical substance and directly test chymical remedies by trial.

Chymical color tests and the sense of taste could reliably track these changes of state from the natural to the preternatural, or diseased, state. In fact, De Graaf likely pushed his fellow students to new levels of devotion by urging the probative tasting of an arthritic patient’s urine. As might be expected, De Graaf found in the urine an acidic acridity that he ascribed to an excess of the pancreatic fluid.\textsuperscript{91} Strikingly, the practice of tasting chymicals from flasks and even diseased and dead bodies was widespread in 1660s Leiden medical instruction and investigations.\textsuperscript{92}

For De Graaf, variations in the pancreatic fluid generated a host of diseases. First, the fluid could be weakened whenever the primary, sharp matter from which it was prepared was not abundant enough in the food ingested, or bound too tightly to the blood.\textsuperscript{93} A blockage of the pancreatic duct by thickened or hardened phlegm could cause similar problems. The link
between acidity and disease could also be joined to the seasons and spicy foods. So, too, acidic melancholics are “less affected by the plague than the bilious.” As Sylvius had taught, the plague was caused by too-fluid blood resulting from an overabundance of alkaline bile.

Even in his section on pathology, De Graaf included empirical tests and experiments, first reasoning from chymical laboratory regularities. He expanded on Sylvius’s remarks on chymical affinity, arguing that scrutinizing certain laboratory reactions or “effervescences” (effervescentiae) would allow for an understanding of bodily chymistry. He continued: “The affinity [affinitas] of the acids with the things to be dissolved is either greater or lesser, and is more obvious if many metals are successively mixed into the same liquor.” Thus silver produces an effervescence when mixed with aqua fortis, and even after it is “wholly dissolved” introducing copper causes the aqua fortis to leave the silver and join to the copper. The silver gradually sinks toward the bottom of the container, “which change comes by the name of ‘precipitation’ among the Chymists.” Iron, in turn, will displace the copper in solution, and an alkaline substance such as roasted tartar or potash will displace the iron because the acid will “join itself much more tightly to that salt . . . and will scarcely ever suffer itself to be separated from it.” In these remarks, De Graaf sought to use laboratory-based chymical regularities to establish a general principle of chymical affinity, which he could then use to explain the selective action of digestion in purely material terms. With regular chymical affinities open to sensory and experimental confirmation, De Graaf, like Sylvius, had little need for speculative Galenic faculties of attraction or fanciful Cartesian pores-and-particles micro-mechanisms.

He also made direct chymical tests of bodily fluids and processes. Acidic pancreatic fluid generated black or rusty-colored bile, “since it sometimes either breathes out acid or corrodes the
copper when poured into a copper bowl, and it excites a manifest effervescence, which would not happen without an acid.” Second, he offered extended experimental reports as the main grounds for his pathological claims. The first involved correlating a color change of the bile in vivo with the changes of hue observed in laboratory spirit of vitriol mixed with the bile in vitro.

Having opened the small Intestine, I discovered the black [bile] turning into a green liquor . . . so I could become more certain about the true origin of the humor turning from black to green, I poured spirit of vitriol onto the bile brought out from its own little vessel and at once I placed those two I had brought together in the heat of the sun, and then a similar color followed from the black turning green. Hence I concluded that the color of this aforesaid humor found in the narrow Intestine had its origin from the bile poured in there, and from the acid salt of the Pancreatic Fluid then meeting it and so changing its color.

Having ostensibly established the chymical nature of the bile and pancreatic fluid, De Graaf turned to pathology and therapy.

In every edition, De Graaf presented his new theory of intermittent fevers as his most important contribution to the understanding and treatment of disease. In the third edition, for example, the remarks on intermittent fevers show additions and expansions, as De Graaf sought to position his account relative to ancient teachings and even cutting-edge doctrines, such as Richard Lower’s work on the heart. De Graaf deployed Van Helmont as well as the Hippocratic text On Ancient Medicine to argue against the traditional idea that fevers were caused by a putrefaction producing an increased heat. The formal definition of fever most common in the sixteenth century, and, with changes, in the seventeenth century, was “heat
contrary to nature,” or preternatural heat. In Sylvius’s account, presented as the topic of the tenth and final disputation of his Decade of collected disputations, intermittent fevers arise from the variable interaction of the acidic pancreatic fluid and the alkaline bile in the heart. Since laboratory distillation showed bile to contain a great deal of an alkaline lixivial salt and some oil, one could reason that its chymical components would mix with the supposedly acidic pancreatic fluid to produce a fiery effervescence. Thus, De Graaf and Sylvius at least attempted to trace the symptoms of diseases in the clinic back to the chymical qualities and effects established in the laboratory.

De Graaf used experiments from anatomy and chymistry to describe these very common intermittent fevers—fevers with irregular cycles in the presentation of their symptoms—as resulting from cycles of phlegmy blockages in the pancreatic ducts which are then dissolved by the built-up, stagnating acidic fluid. Excessive cold or too much phlegmy food could produce these blockages in the pancreatic ducts. The fluid would then build up, become stagnant and even more acidic and acrid, and then dissolve the blockage, breaking out and producing an excess of acid in the heart and body.

Injection experiments during a hospital postmortem of a patient suffering from an intermittent fever had demonstrated these same fatal blockages in the pancreatic ducts.

We observed such an obstruction in the Pancreatic Ducts a few months previous, in a certain woman who had suffered from an intermittent fever. In her dissection we infused through a Syringe a volatile and caerulean liquor into the larger Pancreatic Duct, which penetrated from there into many of the lateral Ducts, while in a very few of the ducts it stopped due to an obstruction.
Later, De Graaf added the historical details that this correlation of a fatal manifestation of an intermittent fever and blocked pancreatic ducts had occurred in the clinic in 1663, in collaboration with Sylvius.\(^{110}\)

De Graaf and his colleagues needed syringes and injection material to perform these postmortem exploratory and demonstrative anatomical injections. They could draw on mentions of injections via syringes found in sixteenth-century anatomical texts, as well as their own ingenuity and surroundings.\(^{111}\) De Graaf’s 1668 two-part work, *On the Organs of Men Devoted to Generation, and on Clysters and the Use of the Siphon in Anatomy*, advertised his skill and ambitions.\(^{112}\) There, he displayed his therapeutic clyster, developed from his work with duck quills used to *gather* fluid from a living body. The Musschenbroek workshop in Leiden advertised and sold De Graaf’s siphon apparatus for anatomical injections.

Therapeutic aims, especially the cure of fevers, and the drive to test and prove medicines, chiefly chymical remedies, fill much of De Graaf’s treatise on the pancreas. He also connected the neutralization model from Sylvius’s body chymistry with the symptoms of patients experiencing hot and cold. He first asserted that “Cold is tempered and destroyed by medicines breaking the Acid, and Heat is tempered by medicine tempering the Bile, and especially Acids.”\(^{113}\) Then, De Graaf went through a list of corresponding symptoms: the lumbar region is cold then hot in feverish patients, which region lies just under the first part of the small intestine in which the pancreatic fluid and bile flow together; the acid vapors produce belches, but also great pains as they spread throughout the lacteal veins and penetrate to the heart and then mix.
with the blood, thickening it; then they, in biting the heart (*cor mordicando*), increase the frequency of the pulse.\textsuperscript{114} Following Van Helmont and Sylvius, De Graaf prescribed alkaline salts to neutralize an excess of acidity in the pancreatic fluid.\textsuperscript{115}

Most strikingly, De Graaf proved the central doctrine that acids congeal the blood by in vivo experiments with horribly manipulated dogs.

If anyone has doubts about this, let him, as in my own example and that of others, gradually infuse a large amount of acid liquor into the vein of a living dog, and he will observe that not only is the blood accordingly coagulated and concreted, as afterward can be established by dissection without any outflow of blood, but when a notable quantity of the acid liquor arrives there in the right ventricle of the heart, the dog will soon be extinguished and suddenly die.\textsuperscript{116}

Thus, living dogs became experimental test subjects for checking and displaying the chymical pathology of excessive vascular acidity. De Graaf later attributed his first experience injecting acid into a vivisected animal to Swammerdam.\textsuperscript{117}

These experiments spread along lines of collaborative networks. Swammerdam reported experiments injecting the spirit of vitriol (containing sulfuric acid) and spirit of urine (containing ammonium carbonate) into the jugular vein of dogs to Ole Borch in Paris in 1664.\textsuperscript{118} Swammerdam’s postmortem report also stressed the coagulation of blood in the heart and arteries due to the acid spirit of vitriol, as well as the increased fluidity of blood produced by the alkaline spirit of urine. A few months later, Swammerdam repeated the injection of spirit of urine experiment for Thévenot, Borch, and a few others, with similar effects.\textsuperscript{119} Following De Graaf and Swammerdam, Van Horne also performed the
experiment of injecting acids and volatile salts into the veins of dogs, as reported in a student disputation of 1665.120

Like the supposedly definitive witness of the senses found in the clinical postmortem dissections, these in vivo experimental tests using the Swammerdam-De Graaf method became the ultimate guarantors of the major epistemic claims of the Sylvian acid-alkali system. Sylvius later incorporated De Graaf’s experimental pathology into his extensive treatise on the epidemic plague affecting Leiden around 1670, De Peste. He framed his treatise with religious piety, intoning repeatedly that God sends plagues to punish sinners, but investigating natural causes is the duty of the physician.121 As might be expected, Sylvius located the cause of the plague in excess vascular alkalinity caused by too much alkaline salt from the bile, and not enough tempering acid from the pancreatic fluid. After working through the various symptoms the plague presented, he anchored the truth of his claims about its acid-alkali pathology in infusion experiments. First, acids experimentally injected into test subjects caused both a quick death and manifest coagulation of the blood.

That the coagulation of the Blood depends on an Acid is proven [evincitur] by the infusion of Vinegar or Water of Vitriol, of Sulphur, or another substance mixed with Acid Spirit into the vein of a currently living animal, from whence the Blood will soon be powerfully coagulated; and if the infused liquor should reach as far as the Heart, the Animal will suddenly die, which is clearly different than in one who is similarly extinguished by the Plague.122
Direct in vivo injection tests granted the strongest confirmation of this acidity, but Sylvius also added parallel coagulation tests with milk, which he assumed everyone knew to be similar to blood.\textsuperscript{123}

The plague, however, seemed to kill by causing an excessive fluidity of the blood, preventing coagulation and causing eruptions from the nostrils, the uterus, and bodily orifices. A volatile salt, especially an acrid one, was known through its chymical properties and direct experimental tests to cause just this excessive fluidity.\textsuperscript{124} Just as with the in vivo test of the acids, Sylvius established the truth of this claim by experiments: “The truth of this remark, this assertion, is demonstrated [\textit{evincitur}] by taking whatever Volatile Salt you wish diluted in Water, and similarly mixed into a vein through a siphon; from which it will be observed that the coagulation of the Blood is impeded, nay rather, destroyed.”\textsuperscript{125} These direct experiments established that the blood became more fluid from the injection of an alkaline volatile salt, and allowed Sylvius to “plainly suppose,” rather than merely suspect, that “the pestilential Poison consists in a very Volatile and Acrid Salt.”\textsuperscript{126} But he still needed to move from anatomical and chymical experiments to his third type: practical experiments in the clinic.

After proving experimentally the effects of acids and alkaline salts in the blood, Sylvius constructed a long section drawing out in even more detail those correlations between the symptoms and treatments of plague victims and the chymical properties of the volatile, alkaline salt. The ultimate aim of medicine was the preservation of health, so the final goal of his treatise on the plague was to demonstrate that “the \textit{Cure of the Plague} plainly \textit{quadrare} \textit{with that same Volatile Salt}, and that the \textit{Precaution} is in agreement with Reason no less than Experience.”\textsuperscript{127}
Only someone well practiced in both the hospital clinic and the chymical laboratory could claim that both the plague and a volatile salt caused a similar litany of symptoms in human bodies: diminished hunger, increased thirst, increased nausea, vomiting, anxiety and chest constriction, ulcers, and irregular periods of stronger and weaker pulse. When the salt became more acrid or powerful, it generated chymical exhalations that irritated the heart muscle, causing it to contract with its “animal motion.” Even plague’s characteristic blackening and buboes appeared from the blackening and corroding action of acrid alkaline salt. To cure their patients, physicians needed to administer a neutralizing acid. Every day for eight months, Sylvius had treated himself with a prophylactic of one spoonful of wine vinegar each morning before visiting many patients infected with the plague. Different acids are needed for different constitutions—melancholics might not do so well with a daily regimen of wine vinegar—but acids cured many patients sick with plague.

Like De Graaf, Sylvius brought experimental anatomy, pathology, and clinical evidence together to build the case for his theoretical conclusions. For Sylvius, it was especially chymistry, “the admirable Art,” that provided the best additional evidence for his account of the pathology of the plague since it revealed the properties of the volatile, alkaline salt causing it. Where Cartesian explanations of secretion in terms of pores and particles did not “square” (quadrare) with the phenomena, chymical pathological tests did.

De Graaf had gone even further, though, and moved from experimental pathology to direct observation of the anatomical actions of drugs in live animals. Something very like the method used even today to test drugs appears at the very end of his disputation, as the capstone and call
De Graaf tested hydrogogues, drugs intended to rid the body of excess watery phlegm, against phlegmagogues, drugs intended to remove thicker humors.

I recently saw this in various dogs, to whom I had given hydragogic as well as phlegmagogic purgatives . . . at the same time as the purgation I immediately opened the abdomen along with the intestines in the living dogs. Having done this, I observed that in those dogs I had given cholagogic medicine, e.g., one drachm of diagredium, the Bile flowed much more copiously from the biliary Duct. Indeed, in another one I had given a hydrogogue [a water or phlegm-cleanser], two drachms of root of jalap, I noticed that the Pancreatic Fluid flowed more copiously from the Pancreatic Duct, although the Bile also flowed more copiously.135

Next, he applied another cholagogue, a drug intended to cleanse excess bile from the body, with similarly detailed observations of the anatomical effects.

And in another, to which I had given a cholagogue, the Pancreatic Fluid flowed out in a greater amount. I was able to collect a notable diversity, so that the Bile was cleansed by the cholagogues, and the Pancreatic Fluid copiously cleansed by the hydragogues. In making this experiment I observed other things worth noting at this point. First, that at the very time of the purgation, certainly, nothing was deposited through the mesentery arteries into the intestinal cavity, as many estimate who are content with speculations alone. . . . Second, in those in which I opened the abdomen two or three hours after they took the purgative, the lacteal veins were not apparent . . . [about which] we will postpone discussing [further], until we understand more deeply the powers of the other medicines, made more certain through more experiments.136
Note that De Graaf’s experimental report attends to the chronological sequence of anatomical events, as well as ephemeral phenomena such as the visibility of the lacteals. In De Graaf’s treatise, the best way to test a drug’s action was directly, avoiding “speculation alone” by attending to the “things themselves” in the living bodies of experimental animals.

Anatomy, chymistry, experimentation, and pathology all led to the promise of new therapies properly demonstrated through experimentation. Sylvius, for one, certainly thought that the apparent success of his chymical remedies, even the prized “secret” oily volatile salt, proved the essential truth of his theories of chymical anatomy and pathology.\textsuperscript{137} In turn, the anatomical experiments of De Graaf and his own laboratory chymistry demonstrated the truth of Sylvius’s chymical therapies. Even the plague outbreaks, one of which may have killed Sylvius in 1672, provided clinical evidence to support his claims that acids corrected the excess alkaline salts causing the dreaded plague itself. De Graaf and his mentor Sylvius prescribed drugs aimed at neutralizing bodily acids and alkalies, such as crab’s eyes, distilled vinegar, and various volatile salts, throughout their works and clinical case notes.\textsuperscript{138} We lack detailed records for later periods, but I suspect the experimental trials of the mid-1660s emboldened Sylvius to push for more extensive and expensive use of chymical medicines in the teaching hospital. In 1666, the university curators complained of his expensive, novel remedies used on the patients, most of whom were poor.\textsuperscript{139} Novel therapies could be trials for administrators, too.

Conclusions and Coda

Why make a trial? Why would De Graaf, or anyone else in midcentury Leiden, make such violent and complicated trials of drugs and pathological agents in bodies living and dead? In
short, because making trials was what ambitious students and professors did there. In that
culture, making trials could solve problems and generate new discoveries and treatments
according to the models of experimental anatomy, chymistry, and clinical practice integrated and
generated there. To understand the emergence and character of De Graaf’s in vivo trials of
pathological agents and drugs, we first cut a synchronic slice across the investigative community
in the medical school in 1660s Leiden. With key ideals, rhetoric, resources, and practices of the
community in hand, we then followed one line of De Graaf’s researches into the bodily effects of
chymical agents, pathological and therapeutic. Investigators at Leiden combined clinical
experience and experiments with other trials made in the chymical laboratories, the anatomical
theater, and private lodgings in order to generate novel philosophical and medical claims.
Making trials and crafting the instruments needed to perform them could also cultivate a
physician’s expertise and advertise his services.

De Graaf’s investigations here offer just one line of experimental investigation at Leiden,
and even only one theme of his broader research. We could also follow up the local work on the
heart and blood, respiration, muscle action, and reproduction for further examples of the
concurrence of experimental anatomy, chymistry, postmortem dissections, and therapy. This
integrated enterprise of investigation characterized a broad swathe of student life, as the
generally favorable reception of De Graaf’s researches presented in other students’ disputations
shows. Even later critics of the conclusions of Sylvius and De Graaf praised their experimental
skill and methods as exemplary. Thus, an investigative culture of experimentation developed
in Leiden in medicine before the celebrated institutionalization of the experimental physics
course in 1675, a course of study that was far more about rote demonstration of previously
established principles than discovery. It seems no coincidence that the cofounder of that course, Burchard de Volder, took his medical degree under Sylvius in 1664. Like his teacher, de Volder then rejected the Cartesian account of the heart’s action in favor of a more experimental, chymical explanation.

The experimental activity and usefulness of Leiden medicine was something that François Magendie, Claude Bernard, and many other “founders” of modern experimental medicine knew well. In 1823 the French Academy proposed a prize to be awarded to the researcher who could determine “by a series of chemical and physiological experiments what are the phenomena which follow one another in the digestive organs, during the act of digestion.” The leading submissions engaged texts from the seventeenth century in detail, and used the experimental methods of De Graaf and other Leiden investigators as models for solving similar problems of collecting and analyzing the bodily fluids and chemicals involved in digestion. Leuret and Lassaigne, as well as Tiedemann and Gmelin, quoted liberally from the seventeenth-century physicians from Leiden, and initially refined De Graaf’s method for making experimental fistulas and collecting fluids.

Later in his career, Bernard even made the frontispiece to De Graaf’s 1671 edition of the treatise on the pancreas an icon of the “new” experimental medicine: “In the frontispiece of his Treatise on the pancreatic fluid, did not Régnier de Graaf there take care to mark out, speaking in a symbolic manner, the connections between anatomy, experimental physiology, and medicine?” It is time we took on Bernard’s question, not as a rhetorical query or search for a founding myth, but as a call for greater historical attention to the diversity and significance of early modern medical testing.
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Figure 1. Bernard’s reproduction of De Graaf’s frontispiece displaying the integral relations among animal experimentation, human anatomy, and medical practice. Claude Bernard, *Leçons de Physiologie Opératoire* (Paris, 1879), 59. Courtesy, the Lilly Library, Indiana University, Bloomington.
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2 Ibid., 150.


4 Reinier de Graaf, Disputatio Medica de Natura et Usu Succi Pancreatrici (Leiden, December 17, 1664), 86–87.

5 Franciscus Dele Boë Sylvius, Opera Medica, editio nova (Utrecht, 1695), De Peste, 629–33.


Tijdschrift voor de geschiedenis der Geneeskunde, Natuurwetenschappen, Wiskunde en

8 Beukers, “Het laboratorium” (n. 7), 35.

9 Beukers, “Clinical Teaching” (n. 7), 145.

10 G. A. Lindeboom, “Dog and Frog: Physiological Experiments at Leiden during the
Seventeenth Century,” in Leiden University in the Seventeenth Century: An Exchange
of Learning, eds. Th. H. Lunsingh Scheurleer and G. H. M. Posthumus Meyjes (Leiden: University
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11 G. A. Lindeboom, Reinier de Graaf: Leven en Werken (Delft: Elmar B.V., 1973); H. L.
Houtzager, Reinier de Graaf: Gelukkig Geneesheer tot Delft (Delft: Reinier de Graaf Stichting,
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12 Pamela H. Smith, The Body of the Artisan: Art and Experience in the Scientific Revolution

13 Tim Huisman, The Finger of God: Anatomical Practice in 17th Century Leiden (Leiden:
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14 Harold J. Cook, “The New Philosophy in the Low Countries,” in The Scientific Revolution in
National Context, eds. Roy Porter and Mikuláš Teich (Cambridge: Cambridge University Press,
1992), 115–49, quotation on 126.

15 E.g., Harold J. Cook, Matters of Exchange: Commerce, Medicine, and Science in the Dutch
Golden Age (New Haven, Conn.: Yale University Press, 2007).
Ibid., 267.

Matthew Cobb, *Generation: The Seventeenth-Century Scientists Who Unraveled the Secrets of Sex, Life, and Growth* (New York: Bloomsbury, 2006). Cobb’s treatment of this earlier experimentation is brief and inaccurate. For example, De Graaf’s skill in handling the sensitivity and complexity of the living animals, his evidence adduced in support of Sylvius’s theory, as well as the details of his procedure are all incorrectly described (46–47). See Ragland, “Experimenting” (n. 3).


E.g., Foucault, *Birth of the Clinic* (n. 20), 72; Lindemann, *Medicine and Society* (n. 21), 100.

Pace Foucault, *Birth of the Clinic* (n. 20), 155 and 173.


Claude Bernard, *An Introduction to the Study of Experimental Medicine*, trans. Henry Copley Green (New York: Dover, 1957), 220. See also the importance of testing claims about drugs directly in animals (211).


Beukers, “Clinical Teaching” (n. 7), 139.


Henricus Bailly, *Disputatio Medica Inauguralis De Colica* (Leiden, 1662), thesis XV.

Sylvius, *Casus Medicinales*, in Sylvius, *Opera* (1695) (n. 5). See also the later cases recorded as *Collegium Nosocomium* in Franciscus Dele Boe Sylvius, *Opera Medica* (Geneva, 1681), 709–37.


Anton Deusing, *In Sylvam Echo* (Groningen, 1663).


Sylvius, “Epistola Apologetica,” in *Opera* (1695) (n. 5), 905.

Ragland, “Mechanism” (n. 28).

William Harvey, *Exercitationes de generatione animalium* (London, 1651) [unnumbered preface]; William Harvey, *Anatomical exercitationes concerning the generation of living creatures* (London, 1653) [unnumbered preface].

Sylvius, “Epistola Apologetica” (n. 40), 905.

Ibid., 907.
46 Ibid., 908.
47 Sylvius, Opera (1695) (n. 5), 1.
48 Sylvius, Decas, De bilis et hepatis usu [1663], in Opera (1695) (n. 5), 29.
49 Ibid., 29.
51 Ragland, “Chymistry and Taste” (n. 29).
52 Sylvius, Decas Disputationum Medicarum, 2.9, in Opera (1695) (n. 5), 13. Other authors cited Sylvius’s experimental, philosophical view of chymistry: Marchamont Nedham, Medela Medicinae (London, 1665), 504–5; Johann Joachim Becher, Institutiones Chemicae Prodromae (Amsterdam, 1664), 3–5.
53 Ragland, “Chymistry and Taste” (n. 29); Sylvius, Decas, 2.10–13 in Opera (1695) (n. 5), 13–14.
54 Beukers, “Het Laboratorium” (n. 7), 31.
55 Ibid.
56 Reinier de Graaf, Tractatus Anatomico-Medicus de Succi Pancreatici Natura et Usu [1671], in Opera Omnia (1678), 285.
57 William Harvey, Exercitatio anatomica de motu cordis et sanguinis in animalibus (Frankfurt, 1628), 47, 20–21.

59 Sylvius, Opera (1695) (n. 5), 256, 909; Sylvius, Casus Medicinales (n. 35), 30, 42; Sylvius, Opera, De Peste (n. 5), 90, 628.

60 Sylvius, “Epistola Apologetica” (n. 40), 908.

61 See, e.g., Sylvius, Opera (1695) (n. 5), 24.

62 Sylvius, Opera (1695) (n. 5), 13.

63 Sylvius, Decas (n. 52), 6.37; Sylvius, Idea Nova, in Opera Medica (1681) (n. 35), 219.

64 Huisman, Finger of God (n. 13), 76–97.


67 Borch, Itinerarium (n. 50), 1:69–70; Sylvius, Casus Medicinales (n. 35), 34.

68 Disputationen in the faculty of law were authored by students in the late sixteenth and early seventeenth centuries. Margreet Ahsmann, Collegia en colleges: juridisch onderwijs aan de Leidse Universiteit 1575–1630 in het bijzonder het disputeren (Groningen: Wolters-Noordhoff/Egbert Forsten, 1990).

Robert Padt-Brugge [Padtbrugge], Disputatio Medica Inauguralis De Apoplexia (Leiden, 1663).

Ibid., 6v.

Cutting or ligating arteries and veins in the neck in order to assess the effects appeared significantly in Galen’s critiques of Aristotle, which furnished exemplars into the early modern period. Baldasar Heseler, Andreas Vesalius’ First Public Anatomy at Bologna 1540: An Eyewitness Report by Baldassar Heseler, trans. and ed. Ruben Eriksson (Uppsala: Almqvist and Wiksells, 1959), 250–51. I am indebted to R. Allen Shotwell for this reference.

Sylvius, Decas (n. 52), 7.79–88.

Jan Swammerdam, Tractatus physico-anatomico-medicus de respiratione usuque pulmonum (Leiden, 1667), chap. 2. Swammerdam’s experimental work on respiration appeared as early as January 1663, and Sylvius quickly added it to the later editions of the disputations he authored, as well as a discussion arguing against the Cartesian explanation. Sylvius, Decas (n. 52), 7.79–88. Ragland, “Mechanism” (n. 28), 193–94.

Ole Borch to Thomas Bartholin, January 9, 1662, in Thomae Bartholini Epistolarum Medicinalium, Century III (The Hague, 1740), 416–25, 420. See also H. L. Houtzager, “Het experimenteel geneeskundige onderzoek in ons land ten tijde van Reinier de Graaf,” in Houtzager, Reinier de Graaf (n. 11), 53–82, esp. 61–62.

See the disputations by Christoforus Beeker and Hubertus Koen.


Several students cite the experimental work of De Graaf: e.g., Matthias Paisenius, *De humorum vitiiis eorumque restitutione* (1666); Daniel Wastelier, *De scorbuto* (1665); others mention experiments by Van Horne injecting acids: Hubertus Koen, *De syncope* (1665); or Sylvius curing dysentery with “one injection alone” with a clyster: Johannes Georgius Waxmuth, *De abortu* (1670), Cv.

Nicolaus Steno, *Disputatio anatomica de glandulis oris* (1661) and more fully as Nicolaus Steno, *Observationes anatomicae* (Leiden, 1662).


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86 For Ivan Pavlov’s construction of “dog technologies,” see Daniel Todes, Pavlov’s Physiology Factory: Experiment, Interpretation, Laboratory Enterprise (Baltimore: Johns Hopkins University Press, 2002).

87 Ragland, “Experimenting” (n. 3).

88 In 1664, disputations averaged about fifteen pages.

89 De Graaf, Disputatio (n. 4); Lindeboom, Reinier de Graaf (n. 11), 23.

90 De Graaf, Disputatio (n. 4), 51.

91 Ibid., 78.

92 Ragland, “Chymistry and Taste” (n. 29).

93 De Graaf, Disputatio (n. 4), 54–55.

94 Ibid., 58–59.

95 Ibid., 63.

96 Ibid., 62.

97 Ibid., 40.

98 Ibid., 42.

99 Ibid., 42–43.

100 Ragland, “Mechanism” (n. 28), 195.

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102 Ibid., 64–65.
De Graaf, Tractatus (n. 56), 336.

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Sylvius, Opera, De Peste (n. 5), 624.
122 Ibid., 626.
123 Ibid., 630.
124 Ibid., 626.
125 Ibid.
126 Ibid.
127 Ibid., 626–27.
128 Ibid., 629–33.
129 Ibid., 630.
130 Ibid., 649.
131 Ibid., 634.
132 Ibid., 652.
133 Ibid., 658.
134 Ibid., 628.
135 De Graaf, Disputatio (n. 4), 86–88.
137 Beukers, “Het Laboratorium” (n. 7).
138 Sylvius, Casus Medicinales and Collegium Nosocomium (n. 35).
139 Res. Cur. April 10, 1666, in Molhuysen, Bronnen (n. 1), 3:204; Beukers, “Clinical Teaching” (n. 7), 145.
140 Sylvius, Decas, 7, in Opera (1695) (n. 5), 30–35; Lindeboom, “Dog and Frog” (n. 10); Ragland, “Mechanism” (n. 28); Cobb, Generation (n. 17).
141 See the disputations of Daniel Wastelier, Matthias Paisenius, and Michael Genius.


Bernard, *Leçons* (n. 146), 58.