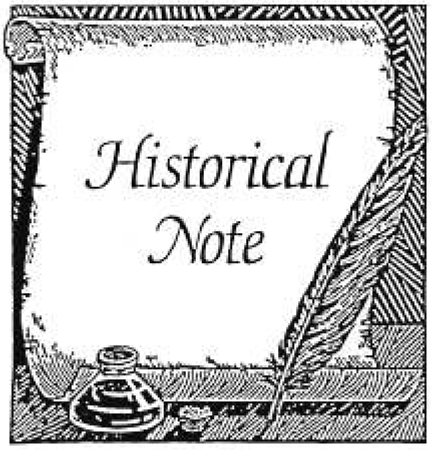

Arnold Adolph Berthold and the Transplantation of Testes

On February 8, 1849, Arnold Adolf Berthold (1803–1861) spoke at a meeting of the Royal Scientific Society in Göttingen [1]. He told the audience of an unusual experiment. He had removed the testes from six young male chickens. In two, he did nothing further; they served as what we would call controls. In two more, he put one of each chicken's testes back into its own abdominal cavity (chicken testes are intra-abdominal to begin with) without any attempt at connecting them with blood vessels. Over the next several months, both young castrated chickens grew into normal roosters. Their combs and wattles grew, they crowed, they fought, and they ran after the hens just as any normal rooster would. The implanted testes had actually become revascularized and did whatever testes do to keep roosters from behaving like capons. The two controls remained capons; they did not grow combs or wattles, crowed poorly, and were not at all interested in the hens. The difference was striking and clear. An autotransplant of an entire organ was a success.

Berthold did almost the same experiment with the remaining two animals but with a critical difference. In each of these two, he again implanted one testis into the abdominal cavity but implanted it into the other animal, a homotransplant. The result was quite clear. These testes "took" as well. They developed a good blood supply, actually contained actively motile spermatozoa, and caused the birds to grow combs and wattles, to crow, and to chase hens.

If done today, Berthold's experiment would be featured in medical and lay journals, most likely appear on television, arouse a wide range of interest, such as by immunologists or ethicists, and lead to speculation about easy transplants for many ailments. Did it have this impact in his own time? To answer this, even in a limited way, some assessment of Berthold's setting will help.

Who was Berthold? Why did he do what he did when he did? Were there predecessors or was his experiment an entirely novel idea? How did his colleagues react at the time? What influence did his success have on the later development of what came to be known as endocrinology?

Berthold was born on February 26, 1803, near Münster (in what is now Germany) to a hardworking master carpenter; the boy was the second youngest of six [2]. The family was not at all wealthy (there were no presents at Christmas), but his father's hard work kept them out of debt despite the trials of the Napoleonic wars, which swept over northwest Germany during Berthold's childhood. His early education was poor, but he then went to the "gymnasium" where he studied a classical curriculum including Latin and Greek. He was most attracted to the classes on natural history. His schooling done, he took his older brother's advice, decided to study medicine, and set out on August 1, 1819, with his brother, already enrolled as a student, for the university in Göttingen.

The university of Göttingen, technically the Georg-August-Universitat because it was founded by the Elector George Augustus (1683–1760) 85 years before, was then in Hanover, then an independent German-speaking kingdom. Hanover's ruler was an Elector because he was one of the few entitled to vote for the Holy Roman Emperor; by 1819 the Elector had also held the title of King since Napoleon's abdication in 1814. The Kings of Hanover in Berthold's student years at Göttingen were also the rulers of Great Britain, George III (1738–1820) and George IV (1762–1830), because from 1714 to 1837 the rulers of the two kingdoms were one and the same. Victoria (1819–1901) became Queen in 1837, but no woman could rule Hanover—it was against the law—so Ernest Augustus (1771–1851), her uncle and the fifth of George III's eight sons, became King of Hanover.

Hanover remained independent during Berthold's lifetime. It was invaded by Prussia in 1866 because the then King refused to declare neutrality in a Prussian dispute with Austria; after a brief war, Hanover became a Prussian province.

At Göttingen, Berthold was a well-read and hardworking student. The university had an excellent scientific faculty that included Karl Gauss (1777–1855) of the Gaussian distribution and Johann Blumenbach (1752–1840), Göttingen's outstanding physician. Berthold got his medical degree at age 20 on September 10, 1823. His career as a student was interrupted only by scarlet fever; he avoided military service when called earlier in

1823 because of his nearsightedness. The young physician stayed on at Göttingen for almost a year and then, as did many others, visited a number of German clinics and universities. He met J.L. Schönlein (1793–1864) and other physicians but retained a great interest in natural science. Finally, probably in 1825, he "settled" in Berlin to practice medicine but also began to experiment, e.g., on the effects of mercury and coal gas on the body. He seems to have "unsettled" himself later that same year and traveled again to several other German scientific centers as well as to Paris, where he attended lectures by G. Cuvier (1769–1832), E. Geoffroy St. Hilaire (1772–1844), and A.M.C. Dumeril (1774–1860), some of the 19th century's best-known biologists. By the fall of 1825, he had dropped the idea of medical practice (and written a paper on the parrot's thyroid gland) and come back to Göttingen as a lecturer (Privatdozent) in medicine. The 22-year-old physician-physiologist stayed at the university for the rest of his life; he became extraordinary professor of medicine in 1835 and ordinary professor (full professor) the next year at age 33. In 1840 he was also named director of the zoological division of the museum; perhaps it was in this capacity that he was able to do his experiments on chickens.

Berthold published on a wide variety of topics such as the length of pregnancy, myopia (his own problem), the formation of hair, and (another glandular topic) male hermaphroditism. A side venture into toxicology with Robert Bunsen (1811–1899; Ph.D., Göttingen, 1830)—whose burner we all know—led to an antidote for arsenic poisoning [3]. Berthold's forte was the teaching of physiology; in 1829 he published the first edition of his textbook of the physiology of man and animals. The text went through several editions and seems to have been widely used.

By the end of the 1820s, Berthold, not yet 30 years old, had settled into the steady, quiet life of a 19th century German professor. He was bright, well regarded, and he developed an excellent reputation. Blumenbach was nominally in charge but was old (by 1830 he was 78 years old). Berthold, along with the well-known surgeon, C.J.M. Langenbeck (1776–1851), essentially assumed the medical faculty's leadership in teaching anatomy and physiology (at that time—and until the turn of the century—physiology was seen by most as a part of anatomy) [4].

The politics of the time (the 1830s and 1840s) were fairly unstable. There was revolution in France in 1830 and a new king. England was unsettled; the Industrial Revolution swelled the ranks of workers who could not vote but were beginning to demand the franchise. Hanover was not immune to the revolutionary sentiment; the turmoil of 1830 led to a new constitution in 1833 that helped bring the people of Hanover and England more on a par under their common king. But when Ernest Augustus became King of Hanover in 1837, he abrogated the new constitution. The politically active faculty members protested. For their pains, seven faculty, known as the "Göttingen seven," were expelled from the university—including the brothers Grimm (known now for their fairy tales and not their philology)—and two actually were forced to leave the country. As far as we know, the medical and science faculty (except for the physicist W.E. Weber [1804–1891]) either did not protest or did not care for the new, more liberal constitution in the first place. Berthold, Langenbeck, Gauss, and the others apparently were unaffected by all this.

Eventually, the failing Blumenbach died at age 88 and in 1840 was replaced by Rudolf Wagner (1805–1864), another physician who, like Berthold, was mainly an anatomist and physiologist [4]. Wagner edited a "dictionary" of physiology and pathologic physiology that ran to four volumes over 13 years (1842–1855); Berthold contributed a 20-page section on sexual physiology, as it was then known, in the first volume in 1842.

Berthold was a good mentor as well as teacher. He encouraged the physiologist Carl Bergmann (1814–1865) to study both the production and regulation of body heat in different animals; Bergmann invented the words "poikilotherm" and "homeotherm" [4]. Conceptually he was responsible for the now obscure "Bergmann's Rule" (1845), which, based on largely observational data in birds, stated that in a group of related animals (mammals and birds), larger species—or larger animals within a single species—will live in the cooler parts of the available range. Bergmann postulated that this was so because larger animals lose less heat per volume per unit time. In the 1840s, Bergmann saw this simply as an example of sensible physiologic adaptation by the organism; there was no concept of survival advantage because Darwin did not come out publicly with his idea until 1859. Nevertheless, the idea of physiologic regulation (the maintenance of body temperature by changes in the rate of heat generation and loss) in the face of a stressful change (cold) in the organism's environment was a definite part of Göttingen's mode of physiologic thought. Berthold's support was key to Bergmann's work, and Berthold probably directed him to essential sources of information. Certainly Berthold was familiar with the general concept of physiologic regulation, an idea that may have contributed to his doing the testes transplants.

With Wagner, physiology at Göttingen got a boost. It is important to note, however, that "physiology" then was not the highly experimental science, often with isolated organs, tissues, and cells, that we now equate with "physiology." Then it was quite different and based on functional anatomy. The focus was mechanistic ("how does it work?"), as is ours, but not as strictly reductionist as our modern physiology. We assume that we could predict the total organism if only we knew enough about its parts; to the modern mind, it is a bit of a shock to realize that there was another way of doing physiology. Berthold's (and his colleagues') aim was to understand the organism as a whole and its harmonious integration, an idea that is now slowly making its way back 150 years later. Although they were aiming to understand the mechanics, the Göttingen physiologists (in contrast to modern physiology) felt that the organism itself had a uniqueness or "purpose" that could not be analyzed into its parts. The tools to apply to this task, the understanding of mechanisms within a harmonious whole, were comparative anatomy, the microscope, and a limited amount of vivisection. Even when chemical and physical approaches, such as the measurement of glucose or the observation of muscle contraction on a kymograph, were developed elsewhere in Germany and in France, the Göttingen style found little place for them; intellectually, they did not fit well (ideas and styles of thought do matter). Of course the chemical and experimental were the wave of the future; Göttingen did not seize this opportunity, and its physiologic style waned. We no longer think of an organism as having a mechanical "purpose."

Such was the intellectual climate of the life sciences in 1840s Göttingen. When the wave of revolution came through Europe in 1848 (France removed a king for a president, who fooled the French and rapidly became the emperor Napoleon III, and England barely escaped open revolt), the Göttingen faculty was untouched; the university was quiet and so was its faculty, at least politically. Rather, for Berthold, that was the year he did his rooster experiment, beginning on August 2 [1].

It is not easy to tell just why Berthold did the experiment in the first place. He had not tried it before as far as we know; perhaps he tried it a number of times—unsuccessfully—and simply did not talk of it until it worked (a practice still with us, to the consternation of those seeking negative data for meta-analysis). Quite likely his earlier studies, such as those on hermaphroditism, led him to consider how the testes contributed to the harmonious whole. Jorgensen's monograph [5] is the best treatment of this issue. After reviewing many of Berthold's writings and the three editions of his textbook of physiology—the last completed that same year, 1848—Jorgensen felt that Berthold started the experiment to test further potential sites of transplantation and to assess the effect of transplantation on the transplanted tissue itself. Berthold apparently did not begin with the idea of studying the effect of the transplant on the rest of the organism—in this case, the male chicken. The "sympathies," that is, the set of mechanisms responsible for maintaining harmony among the body's parts and which were thought to be largely neural (hence, our "sympathetic" nervous system), were the issue. Berthold realized from his study that nerves could not be the only means of having a "sympathetic" response and a maintenance of harmony; he realized that the circulating blood could be another sympathetic mediator.

It is doubtful that Berthold's conception of what the testis did—translated sometimes as "secretion"—matches ours. A common theory of organ function at the time was that blood itself was a functioning tissue and not simply a passive transporter of good things to the body's organs [6]. What some organs did was to transform the blood so that it might act in different ways on organs elsewhere in the body. Berthold does not say so but, in keeping with the physiologic thought of the time, his likely aims were to assess the body's overall effect on the newly located testis and to figure out how the testis, devoid of nerves, transformed the blood as evidenced by changes elsewhere in the body, e.g., the cock's comb and wattles. He never actually drew a conclusion that can be clearly interpreted as showing that he had an endocrine concept in mind [5, 7]. Berthold in fact operated well within the framework of Göttingen physiology.

Whatever Berthold thought about the mechanisms, was he not the first to succeed with a testis transplant? The answer is no. We now know well that John Hunter (1728–1793) did almost exactly the same experiment at least 80 years before Berthold [5, 8]. Hunter, the irascible younger brother of the more urbane William, was perhaps the most famous surgeon of the 18th century, in large part because he strove to put surgery on a scientific basis (both brothers had a high reputation; both were elected to the Royal Society in 1767). No one knows exactly when he did his testicular transplants because he never wrote up the work for publication (and many of his prolific notes were destroyed posthumously by his brother-in-law), but it was sometime before 1771. Hunter did both testicular autotransplants and transplants of rooster testes to the hen's abdomen (a visitor in 1771 noted that he saw many hens with testicular grafts). Hunter himself wrote in 1794 that he had done transplants to "the abdomen of a hen, and they had sometimes taken root there, but not frequently, and then had never come to perfection." Curiously, some of Hunter's specimens still exist today in his main legacy to us, the Hunterian Museum of the Royal College of Surgeons in London [5]. The testes in the hen's abdomen are clearly vascularized and histologically intact. Hunter's work is definitely not a myth and can be seen by any visitor.

But did Berthold know of Hunter's work? Berthold read widely and, despite Hunter's lack of formal publication and modern denials of Berthold's knowledge [7], Berthold did know about Hunter's chickens. The version of Berthold's work usually quoted [1] was in a widely read journal but was skimpy in the extreme. There is no real introduction or discussion, no mention of Hunter, and it reads like an extended abstract. However, in that same year, 1849, Berthold published almost the same article in the local medical journal [9] and clearly noted Hunter as an influence. This makes better sense because few ideas spring to mind totally without precedent (perhaps those who see Berthold as the first endocrinologist have a need to see him as without forebears).

So Berthold's work did not come as a "bolt from the blue" but grew reasonably out of the context of the time. He knew of Hunter's chickens, he had a reasonably consistent mode of physiologic thought, and—as seen in his association with Bergmann—he knew the need for explanations of physiologic regulation. This last sounds quite modern and seems similar to our biologic regulatory systems and "feed-back" loops, the stuff of modern endocrinology, but it is not the same. Berthold's harmonies and sympathies are, however, the beginning of the process of gathering data to show that, in fact, the body does have such biologic regulation. One needs to remember that not only was the concept of a hormone or internal secretion unknown in Berthold's time, but also that Berthold's study was done before Claude Bernard (1813–1878), the doyen of French physiology, developed his idea of the milieu interieur, which itself was not a sudden "eureka" but grew slowly in Bernard's mind over some years [6, 10].

If Berthold and his work were solidly placed in at least part of the mainstream of 19th century physiology, one would expect his work to be emulated and expanded, if not by him then by others. How was his work seen at the time? From all we can see from one and a half centuries later, Berthold's study had practically no effect at all. His own colleague, Wagner, repeated the experiment and it was not a success [5]. Berthold himself did some other work but never published it and clearly did not pursue the problem with any vigor. We do not know why; perhaps he did and was also unable to confirm his own work. Perhaps even more important was the fact that the Göttingen style and approach to physiology was rapidly displaced [4] by the new, attractive, and much more reductionist physiology of Carl Ludwig (1816–1895), now considered the principal "father" of modern physiology, so much so that few now know of the Göttingen organismic approach. Wagner's failure to repeat Berthold's success may have been a major factor in Berthold's failure to influence others and may have been seen by others as an indication that Berthold was simply wrong. Whatever the reason, and despite the clear success of both Hunter and Berthold, no one reported on this phenomenon again until the 1890s, after Brown-Sequard's claim of rejuvenation from testicular extract in 1889.

What then of the claims of modern writers that Berthold's "observations . . . established a new science" [7], that he did "the first experiment in endocrinology" [11], or that his work was "the foundation of modern endocrinology" [12]? Certainly Berthold and his work are not mythical, but such comments can only be read as efforts to make them legendary and to make them stand in retrospect for more than they were at the time. It is perfectly understandable for endocrinologists to seek older sources of our discipline (which is in reality only about 100 years old) and to find in Berthold a kind of hero struggling alone to lead the way down a new and glorious path. It is, however, bad history; moreover, the actual story is (to me, at least) more interesting and human. Berthold's work, rather than being a clear prelude to the endocrinology of today, is a kind of missed opportunity that we would do well to mull over. Are other such opportunities being missed today because of either limited or different visions? Or because of failure to get a grant?

Berthold can be seen as a "forerunner without immediate succession" [13] and his work as a "premature discovery" [14]. Of course, judging whether something is premature can only be done in retrospect; one may find that the apparent prematurity was actually due to active resistance by the scientific community to a scientific discovery [15, 16]. Why Berthold's experiment did not take root in his own time is not fully explained, but certainly it is an example of how science is more than just the collection of data with "true" knowledge then becoming apparent to anyone who can see. Science is also the social phenomenon of acceptance by others that the data are in fact "real" and, hence, credible.

Was Berthold wrong? Despite the tenets of formal science, no one knows how many times a scientific finding must fail to be confirmed before it can be considered wrong. We think—without thinking—that one failure is enough, but clearly that is not so. There is no more reason to accept one failure as "truth" than there is to see one success as "real." On the evidence, there is no reason to doubt Berthold, particularly in light of Hunter's precedent, but it runs against the grain of most modern immunology and transplantation. Nevertheless, empiric data are what count, not immunologic theory. Certainly testis transplants were not uniformly successful (though one would not know this from Berthold), but they did sometimes succeed. In fact, Berthold's work was confirmed in the 1890s [17] and again in the early 20th century [18].

How could this be? The puzzling empiric observation of successful testicular homotransplantation seems now to be yielding a rational explanation. Testis transplants into unmatched hosts do sometimes survive because the testis is somehow immunologically privileged. It seems that, in mice at least, the key is the testicular expression of the ligand for an activated lymphocyte cell-surface molecule (CD95) [19]. The foreign transplanted organ (the testis) is recognized as foreign by the host, and the host's lymphocytes are activated as expected. But the testis-specific production of the ligand for the activated lymphocyte's CD95 kills the lymphocyte when it tries to reject the testis, and so the testis survives. These data are new and need to be elaborated as well as extended to birds.

I doubt that many immunologists of today know of Berthold, but, although he is not really the "father" of endocrinology, his work remains as an example and a model and he may well still have something to teach us. And, after all, that is what he did best.

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Sources

1. Berthold AA: Transplantation der Hoden. Arch Anat Physiol Wissenschaft Med 1849; 42–6.
2. Rush HP: A biographical sketch of Arnold Adolf Berthold. An early experimenter with ductless glands. Ann Med Hist (new series) 1929; 1: 208–14.
3. Klein M: Berthold, Arnold Adolphe. Dictionary Scientific Biography 1970; 2:72–3.
4. Coleman W: Bergmann's rule: animal heat as a biological phenomenon. Stud Hist Biol 1979; 3: 67–88.
5. Jorgensen CB: John Hunter, A.A. Berthold, and the Origins of Endocrinology. Odense, Denmark, Odense University Press 1971.
6. Holmes FL: La signification du concept de milieu interieur. In La Nécessité de Claude Bernard, edited by Michel J, pp. 53–64, Paris, Méridiens Klincksieck 1991.
7. Forbes TR: A.A. Berthold and the first endocrine experiment: some speculation as to its origin. Bull Hist Med 1949; 23: 263–7.
8. Forbes TR: Testis transplantations performed by John Hunter. Endocrinology 1947; 41: 329–31.
9. Berthold AA: Über die Transplantation der Hoden. Nachrichten GA Univ Konigl Gesellsch Wissensch Göttingen 1849; 1–6 (Feb 19).
10. Holmes FL: Origins of the concept of the milieu intérieur. In Claude Bernard and Experimental Medicine, edited by Grande F, Visscher MB, pp. 179–91, Cambridge, MA, Schenkman 1967.
11. Setchell BP: Male Reproduction. New York, Van Nostrand Reinhold 1984.
12. Quiring DP: The transplantation of testes [by] Arnold Adolph Berthold. Bull Hist Med 1944; 16: 399–401.
13. Klein M: Sur l'article de Berthold: transplantation des testicules (1849). Arch Anat Histol Embryol 1968; 51: 380–6.
14. Stent G: Prematurity and uniqueness in scientific discovery. Sci Am 1972; 227 (Dec): 84–93.
15. Barber B: Resistance by scientists to scientific discovery. Science 1961; 134: 596–602.
16. Aronson N: The discovery or resistance. Historical accounts and scientific careers. Isis 1986; 77: 630–46.
17. Lode A: Zur Transplantation der Hoden bei Hahnen. Wien Klin Wochenschr 1895; 8: 345–6.
18. Pézard A: Sur la détermination des caractères sexuels secondaires chez les Gallinacés. Comptes Rend Acad Sci 1912; 154: 1183–6.
19. Vaux DL: Ways around rejection. Nature 1995; 377: 576–7.

Other Suggested Sources for the Curious

Kobler J: The Reluctant Surgeon: A Biography of John Hunter, Medical Genius and Great Inquirer of Johnson's England. New York, Doubleday and Co. 1960.

Kelly EC: Selections from the writings of John Hunter. Medical Classics 1940; 4: 401–527.

The political information was largely derived from the Encyclopedia Britannica, 11th edition (1910), various histories of Great Britain and France, and the Dictionary of National Biography.