Labor and Luck: The Birth of Modern Oxytocics
Mary Becker Rysavy
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Oxytocin is currently one of the most commonly used medications in the United States. A polypeptide hormone naturally secreted by the posterior pituitary gland, oxytocin stimulates the smooth muscle of a pregnant uterus to contract. Synthetic analogues of the hormone can be used to supplement the effects of this naturally occurring hormone during childbirth in order to cause a pregnant woman to go into labor, markedly strengthen her contractions if labor stalls, and help the uterus to contract down to normal size after delivery to stop postpartum bleeding. A 2011 study reported that oxytocin is prescribed in more than half of all deliveries in some U.S. hospitals.¹

Oxytocin has only been used in obstetrics since the middle of the last century; however, the complications of labor that oxytocin now treats have existed throughout history. In this study, I examine the history of this widely-used medication, as well as other uterine-contracting medications, known as oxytocics, that have aided in childbirth through the ages. The story of oxytocics involves anonymous midwives whose names have been lost to history, as well as Nobel prize-winning scientists, and it centers on an unlikely protagonist – ergot, an unsightly black fungus that grows on the grains of common rye. Discoveries made during the development of oxytocin paved the way for modern molecular biology, and the drug itself has transformed the field of obstetrics and saved innumerable maternal and infant lives.

**Rattlesnakes, Rose Oil, and Rye**

Women have experimented with substances to cause uterine contractions since as far back as written records exist. Early reasons for trying to induce labor included fetal demise and maternal comfort.\(^2\) In ancient Egypt, drinks prepared from honey, wine and fresh salt were given in an effort to hasten birth.\(^3\) The first-century Greek physician Dioscorides recommended the root of the plant *Cyclamen graecum* be tied around a woman’s pregnant abdomen to accelerate childbirth.\(^4\) Native Americans used concoctions of powdered rattlesnake rattles, infusions of bear claw scrapings and teas made from the inner bark of a pine or fir balsam as oxytocics.\(^5\) And, in 11\(^{th}\) century Italy, the female physician Trotula suggested several remedies for stalled labor, including drinking vinegar and sugar water, rubbing rose oil on the hips, and binding savory to a gravid abdomen.\(^6\)

While only history knows how these concoctions affected their users, one substance, the “long, black, hard, narrow pegs on the ears [of rye], internally white, often protruding like long nails from between the grains in the ear” did “awaken the pains of the womb.”\(^7\) These observations, recorded by 15\(^{th}\) century German botanist Adam Lonicer in his *Krauterbüch* (or Book of Herbs), led to the development of the first significant oxytocic in Western medicine. ‘Black pegs’ on rye described a fungus that became known as ergot,

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from the French word *argot*, or cock’s spur, due to its similarity to the red feathers on a rooster’s head.

Ergot was already well-known in the medical community for other reasons. The fungus was responsible for epidemics of a disease known as ‘ergotism’ that affected European villages and cities over many centuries. The disease, caused by eating bread made from ergot-contaminated rye, manifested as gangrene of the limbs and nervous dysfunction, and often led to death. It has been suggested that during at least one epidemic, midwives observed that ergotism in pregnant women led to miscarriage. Many reasoned that ergot might cause uterine contractions, and some began drying the fungus and administering its powder in small doses to women in labor for cases of prolonged labor or inefficient contractions.

French and German midwives had reportedly used ergot for many centuries, but the substance only became widely known throughout Europe in the 18th century, when it entered the medical literature of the time. Sometime after Loncier made the first known written observation of ergot’s effects, the substance was listed as *pulvis ad partum* – literally ‘birth powder’ – in the Edinburg Pharmacopeia, an official publication of medications used at the time. The powdered medicine likely became especially popular in the late 1700s after a 1756 conference of physicians in London reported that early induction of labor, whether by the use of ergot or by manually breaking the amniotic sac, could be used to prevent labor complications in women with small pelvises. Rather than wait until a large developing child reached full-term and was unable to pass through the

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10 Benrubi:430.
birth canal alive, physicians and midwives recognized that they could artificially induce labor several weeks early before the child grew too big. Ergot was often the method of choice for such inductions.

**Ergot in America**

Until the first decade of the 19th century, the most common method of inducing labor in the United States was venesection, or blood-letting. Amniotomy, the practice of slipping a long, hooked rod through the cervix to puncture the amniotic sac and release the fluid surrounding a baby in the womb, was also recognized as an effective induction method. Complications from infection following the breaking of the amniotic sac were extremely common, though, and long before the discovery of antibiotics, such infections often caused death of both mother and fetus. It was no surprise then that the use of ergot spread rapidly in American obstetrics once it was introduced.

That introduction came in 1807 when New York physician Dr. John Stearns wrote a letter to a physician colleague describing a substance he called *pulvis parturiens* about which he had learned from a rural Scottish midwife. The letter was published the following year as “An Account of the Pulvis Parturiens, a Remedy for Quickening of Childbirth” in the *Medical Repository* of New York. Stearns reported that ergot “expedites lingering parturition, and saves the [obstetrician] a considerable portion of time, without producing any bad effects on the patient.” He wrote that it was most useful for cases in which “pains are lingering, have wholly subsided, or are in anyway incompetent to exclude the fetus.” Stearns warned that ergot could cause nausea and vomiting if used in too high a dose, and
that its use should not be taken on without certainty that the infant was in proper position to be delivered due to the extremely strong contractions ergot could produce.\textsuperscript{11}

Many other physicians soon began using ergot during deliveries. Not only did it speed labor as Stearns suggested, but it also helped to stem excessive bleeding following delivery. It provided new recourse for physicians who otherwise had few options to assist a distressed woman in labor.\textsuperscript{12}

American acclaim for ergot was short-lived, however. Backlash against its use began just a few years after Stearns’ initial article. Criticism stemmed from severe side effects that some physicians observed when administering the drug. Dosing, timing, and other factors modify the effects of many drugs, and ergot was no exception to this principle. Ergot causes extremely intense contractions and, if administered before the cervix is fully dilated, it can result in large tears to the lining of a woman’s birth canal, or worse, a rupture of the uterus – often leading to death for mother and infant. Moreover, the effective dose of ergot could vary widely depending on where it was obtained, how it was prepared, and other factors. The consequences of such variation could be significant: While ergot stimulated contractions in a woman who otherwise might have waited for many hours without progressing in labor, too much of the drug could cause the uterine muscles to contract excessively, to the point of pushing the head or umbilical cord of the infant so hard against the closed cervix that an infant might suffocate.\textsuperscript{13}

\textsuperscript{13} Ibid.
Ergot’s most notable critic was Dr. David Hosack, a New York physician perhaps better remembered for his care of Alexander Hamilton following Hamilton’s deadly duel with Aaron Burr. Hosack helped found New York’s Bellevue Hospital, which included a lying-in ward specifically set up to attend to women in childbirth, and it was there that Hosack observed ergot in practice. In an 1824 letter to obstetrician James Hamilton, Hosack attested to several cases in which he used ergot on a healthy mother and fetus, only to have the infant be delivered stillborn. Hosack sardonically suggested that the name *pulvis ad partum* should be changed to *pulvis ad mortem* (‘death powder’).14

Hosack argued that ergot could prove useful in controlling postpartum hemorrhage, but he urged extreme caution in its use to hasten labor. Others in the medical profession did not come to a clear consensus regarding ergot use for some time afterward. Most physicians of the time agreed that administration of the medicine after delivery of an infant was useful to prevent postpartum hemorrhage and shock; however, they disagreed about whether the drug should be administered immediately following birth or after the delivery of the placenta. Additionally, although most realized the dangers of ergot’s use, they were hard-pressed not to use it when a woman in stalled labor asked her physician for *some* sort of intervention.15

Many physicians, such as Dr. James Hamilton, the recipient of Dr. Hosack’s letter, turned completely against the use of ergot. Hamilton instead argued for the use of other means to induce or speed labor when necessary, such as herbal teas or enemas.16 Dr. David

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15 Leavitt:144-47
Davis, a 19th-century British expert on difficult deliveries and one of the developers of modern forceps, accepted the use of ergot when absolutely necessary, but also had many doubts. He recognized, however, that a great benefit could be achieved if a safe oxytocic substance was discovered:

“If ergot of rye, or anything else which might be safely administered to a woman in labour through the medium of the stomach, could be really proved to possess, in any considerable degree, a parturient influence on the uterus; it is obvious that it would form a most important addition to our material medica as it could not fail, in a certain class and proportion of cases, to supersede the use of mechanical instruments in the practice of midwifery.” 17

Birth In The Era Of Molecular Biology

Although other practices such as the use of herbal teas and enemas to stimulate labor persisted, ergot remained the most important oxytocic drug well into the early 20th century. Physicians continued to search for a substance with ergot’s capacity to contract uterine muscle without the deleterious side effects that Hosack and others had described. As scientists developed the techniques of molecular biology in the early 20th century, several laboratories in the United States and Europe set out to isolate the active ingredient within ergot in hopes it could be distilled and given in controlled amounts. Scientists had recently discovered methods for separating out the component parts of complex substances, and they worked to pry the active ingredient within ergot from others that caused nausea, high blood pressure, and other side effects. In the end, it was the brilliant

work of a British physiologist, Henry Hallet Dale, and his scientific successor, American chemist Vincent du Vigneaud, which led to the discovery of the exact medication physicians hoped to find.

Dale was a recent Cambridge graduate with a degree in physiology when he joined the Bourroughs Wellcome research laboratory in 1904 and followed his mentor’s suggestion to work on isolating the uterotonic component of ergot. Dale was not initially keen on the idea, calling the uterine actions project the “morass of ergot.” However, he recruited a strong research team and his collaboration with chemist George Barger resulted in the isolation of one of the first components of ergot to be identified: ergotoxine. Unfortunately, ergotoxine was not the pure substance the researchers had hoped it to be. It had a much slower action than ergot and caused severe nausea and vomiting, so it was never useful in clinical practice. However, the duo each went on to gain acclaim for the work that stemmed from that initial project. Dale discovered a vasodilator substance present in ergot, which he later characterized as acetylcholine – a principle molecule in nerve transmission, familiar to all medical practitioners, and the foundation of medications used in nearly all disciplines of medicine. Barger developed techniques for characterizing and synthesizing biologic hormones, methods he later used to describe and synthesize thyroxine, the primary hormone produced by the human thyroid gland.18

Dale received the Nobel Prize in Physiology or Medicine for his acetylcholine research and later became the director of the British National Institute for Medical Research. While he did not continue to study ergot, his initial work with Barger eventually led to the 1932 discovery by H.W. Dudley and Chassar Moir of ergometrine, the purest

uterotonic component of ergot.\textsuperscript{19} Ergometrine, while not the first-line oxytocic in modern practice, remains an available nonstandard treatment for postpartum hemorrhage. Dale’s work also set the foundation for other laboratories to isolate additional ergot derivatives, including ergotamine, which is a drug still used today in the treatment of migraine headaches.\textsuperscript{20}

Additionally, Dale is remembered for having discovered the hormone that causes uterine contractions \textit{in vivo}, natural oxytocin – the synthetic form of which has become the standard oxytocic in modern medical practice. Through his use of cat models to study the effects of endocrine hormones on various organs in the body, Dale observed that extractions from the pituitary gland of an ox produced uterine contractions in the pregnant cat.\textsuperscript{21, 22} It was Dale who named the pituitary substance he had discovered ‘oxytocin’ from the Greek \textit{oxutokia}, meaning ‘swift delivery.’

Following Dale’s discovery, many scientists sought to concentrate oxytocin hormone for obstetrical purposes. Labor inductions in the early 20\textsuperscript{th} century were most often performed by amniotomy, or by manual dilation of the cervix, but both methods remained dangerous for mothers and infants due to extremely high infection rates. Derivatives of ergot, like ergometrine, were valuable oxytocsics for the treatment of postpartum hemorrhage, but they were slow-acting and tended to cause nausea, making them less than ideal for frequent use in labor induction and other obstetric indications.

\textsuperscript{19} Dudley, HW and Moir, C. The substance responsible for the traditional clinical effect of ergot. \textit{British Medical Journal}. 16 Mar 1935:520-523
Vincent du Vigneaud, a chemist from Illinois interested in the structures of peptides, would solve the great problem of synthesizing oxytocin for medical use. When du Vigneaud set out as a researcher in the 1920s, many basic tenets of molecular science that are now taken for granted were as yet unknown. Du Vigneaud began his career studying insulin and was one of the first scientists to propose that it was a protein. With an interest in the molecular structure of hormones, du Vigneaud began to study the pituitary extract that Dale had described in 1906. By 1928, du Vigneaud had concentrated pituitary extract, and he then helped to identify the unique structures of the two hormones present in the extract, vasopressin and oxytocin.

Throughout the 1930s, du Vigneaud’s studies centered on trying to synthesize proteins from their component molecules. He maintained a specific interest in oxytocin, focusing in particular on its sulfur content, an element important in his studies of insulin. During this time, he also synthesized vitamin H, or biotin, one of the essential molecules for human metabolism. Du Vigneaud took a hiatus from his central research during World War II to assist in the study of penicillin; he played a key role in the first isolations of small amounts of the synthetic drug. Finally, decades after he began, du Vigneaud succeeded in synthesizing a molecule identical to the oxytocin hormone in 1953. He wrote, “If the synthetic product truly represents oxytocin, which it does in so far as we have been able to ascertain, then it would constitute the first synthesis of a polypeptide hormone.” Two years later, du Vigneaud won the Nobel Prize in Chemistry for this accomplishment.

Over the next several years, synthetic preparations of oxytocin, such as Pitocin® and Syntocinon® became widely available for use in medical practice. During the 1960s, obstetricians refined techniques for using oxytocin for induction of labor, and the practice became common for medical indications such as maternal hypertension and toxemia, fetal distress, or prolonged pregnancy. A study from 1965 showed that about 2% of all deliveries at a major Pennsylvania hospital were induced with oxytocin.25

The field of obstetrics at this time was also changing in other ways. Widespread antibiotic availability transformed all of medicine following World War II, and the field of obstetrics particularly benefited. Puerperal infections resulting from the performance of an amniotomy, Cesarean section, or simple contamination were no longer life-threatening events. The medical approach to pregnancy and labor changed greatly. Even if synthetic oxytocin was unsuccessful in effecting delivery, obstetricians could quickly rush to the operating room to perform a Cesarean section and rescue both mother and baby.

It is important to note that medical research into the best possible oxytocic substances continued even after identification of oxytocin and derivation of the synthetic hormone. In the 1970s, prostaglandins were found to produce uterine contractions. It was determined that their uterine-contracting effect is not as strong as oxytocin; however, they are extremely effective at helping the cervix soften and dilate, allowing the infant head to pass from the uterus into the birth canal.26 Prostaglandins have proved to be a good companion to oxytocin for induction of labor in the modern delivery room. Although the synthetic production of oxytocin standardized the dosage of this potent drug, it did not

resolve all the possible complications associated with it. Just as ergot was long ago noted to provoke fetal distress, perineal tears or uterine rupture if a woman’s cervix was unready for strong contractions pushing against it, oxytocin is also limited by the readiness of the cervix to allow a baby’s head to pass. Thus, the induction of labor today usually begins with preparation of the cervix with prostaglandins, followed by slow infusions of oxytocin.27

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The history of oxytocin reflects the struggle of physicians and midwives to reduce the complications of birth that have threatened the lives of women and infants throughout history. Early midwives gave women herbal teas and mixtures of roots, and they watched many patients die from stalled labor and postpartum bleeding. In light of such experiences, the discovery of ergot was exciting for midwives and physicians who worked to prevent complications wherever possible. Spurred by both the amazing positive effects and the horrible negative consequences of early ergot use, physicians turned to science in search of a drug that could increase uterine contractility without risking the life and health of the laboring woman. The story of oxytocics, from a humble plant fungus to a protein worthy of a Nobel Prize, is the story of the quest for a pure and safe medication to make labor less difficult and less fatal. Safe and careful management of labor are possible today thanks in great part to the advances made through the use and study of ergot and the research that led to the synthesis of oxytocin – now one of the most valuable medications of the modern delivery ward.