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Frogs Featured Prominently in Basic Science Contributing to Anesthesiology

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Frog anatomy is sufficiently similar to that of humans such that frog dissection was long a popular endeavor in introductory science classes. Indeed, Luigi Galvani (1737-98) taught medical students with the aid of frog dissection. In the course of his preparation of frog specimens near a static electricity generator, he accidentally discovered that electricity caused excised skeletal muscles to contract.[1] Of course, despite their five fingers, frogs are imperfect human models. The amphibians have remarkable features that facilitated basic science experiments of importance in the history of anesthesia.

Lack of coronary arteries

For example, the frog heart lacks coronary arteries. The blood within the heart chambers perfuses the spongy muscle. Since there is no need for an arterial perfusion pressure, an excised frog heart will continue to beat for a long time when placed in saline solution, provided that certain additives are present. The original additives were blood or egg white or other rich biological fluids. No perfusion apparatus was required. It is hard to overstate the inspirational importance of this observation of an extracorporeal working organ to physiology.

In 1847, Carl Ludwig (1816-95) invented the rotating drum kymograph ("wave writer"), a device for graphically recording pressures or muscle displacements as a function of time.[2] This device was a tool of physiology for many decades before the availability of electronic instruments. In 1856, he applied it to measure the ventricular pressure pulses of isolated frog hearts. Consequently, the Frank-Starling Law of the Heart was first observed by Ludwig student Otto Frank (1889-1980) in experiments with frog hearts.[3] An elaborate perfusion apparatus was later required for the mammalian experiments of Starling (1866-1927).

Since a frog heart will not beat in ordinary saline solution, Sydney Ringer (1835-1910) was taken aback in 1882 when excised frog hearts did beat in apparently simple saline.[4] He learned that the saline had been prepared for him with tap water instead of distilled water, and he concluded that low concentrations of inorganic ions, in addition to Na^+ and Cl^-, are required by the heart. Thus was born Ringer's solution, an eponym well known to anesthesiologists. This inorganic solution dispelled the suspicion that extracorporeal beating of the heart required blood or other life-derived organic matter.

Calcium and potassium are the cations Ringer found to be required to be added to the saline. In discovering that extracellular calcium is required for systole of the frog heart, Ringer anticipated the cardiac L-type calcium channel.[5] Ringer observed that high levels of potassium arrest the frog heart in diastole. He thus pointed to an important cardioplegia strategy for modern heart surgery.

Ringer stopped isolated frog hearts with the muscarinic agent pilocarpine and restarted them with atropine.[6] He may have thereby been the first pharmacologist to compete an antagonist against an agonist at a drug receptor.

Otto Loewi (1873-1961) shared a 1936 Nobel Prize with Henry Dale (1875-1968) for demonstrating chemical neurotransmission by acetylcholine. The lack of frog coronary arteries was essential to Loewi's classic experiment. He left the vagus nerve attached to excised frog hearts.[7,8] The hearts contained a very small volume of esterase-free Ringer's solution (one heart-full). Stimulation of the vagus slowed the heart, and much of the acetylcholine escaped cardiac esterase action and diffused into the small volume of Ringer's solution without excessive dilution. The heart-full of acetylcholine solution then replaced the contents of a second heart, and that heart slowed. Loewi set up the experiment in the middle of the night after it came to him in a dream for the second time.[9] He could not clearly remember the first dream since he let it go until morning! The subsequent identification of the neurotransmitter of the frog vagus as acetylcholine was facilitated by Loewi's finding that the vagus substance ("*vagusstoff*") is stabilized by physostigmine.

Absent rib cage and diaphragm

Frogs have no ribcage and no diaphragm and therefore do not employ negative-pressure ventilation (Fig. 1).[10] Their throat muscles propel air into the lungs under positive pressure. To an appreciable extent, human polio victims were able to mimic this "glossopharyngeal breathing" during breaks from mechanically assisted ventilation.[11]

Unfortunately, humans cannot copy an additional frog ability, that of breathing through the skin. Since transcutaneous gas

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The C. Ronald Stephen Resident Essay Contest

The Anesthesia History Association (AHA) sponsors an annual contest for the best essay on the history of anesthesia, pain medicine or intensive care. This contest is open to all residents and fellows in anesthesiology. The purpose of the contest is to promote interest in the history of anesthesia and to advance professionalism in the specialty. Additionally this contest offers residents and fellows the opportunity to present their paper at a national meeting and to publish the results of their research. The Resident Essay Contest is named for Dr. C. Ronald Stephen an anesthesiologist who was a revered teacher, researcher, clinician and anesthesia historian. Dr. Stephen died at age 90 in 2006.

The essays must be written in English and be approximately 3,000 to 5,000 words in length. Judging will be in two stages. In the first stage the finalists will be chosen. These finalists will be announced at the AHA dinner meeting during the American Society of Anesthesiologists annual meeting. From these finalists, the winners will be chosen on the basis of both content and delivery during the spring meeting of the AHA. All the finalists will present their papers in a session of the AHA attended by a panel of judges. The panel of judges will make their final decision based on originality, appropriateness of topic, quality of the research, and delivery. Because the final judging will be at the time of the presentation at the spring meeting of the AHA, all who enter must agree to attend the meeting at which the presentations are made. Essays must be submitted by the 10th of September 2009, in order to be eligible for presentation at the spring AHA meeting of the following calendar year. If not received by that date they will be considered for the next year's contest.

The first, second, a*nd* third place winners receive $500 $200 and $100 respectively. Awards will be made during the AHA spring meeting. The three winners are required to submit their essays to the peer-reviewed Bulletin of Anesthesia History for possible publication.

To enter, essays should be sent to:

William Hammonds, MD, MPH
Professor, Department of Anesthesiology and Perioperative Medicine
Medical College of Georgia
1120 15th Street
Augusta, GA 30912
whammonds@mcg.edu

Entries must be received on or before September 10, 2009.

April 4, 2009

Letter to the Editor, Bulletin of Anesthesia History

Dear Editor,

The photograph of Dr. Ralph Waters from Dr. Lucien Morris's archives on the back page of the January 2009 issue of the Bulletin is of extraordinary interest. The presence of Professor Sir Robert Macintosh in the group with Dr. Waters perhaps symbolizes the close relationship between the two men: a particular example was the attempt by Sir Robert to model the academic department he founded in Oxford in 1937 on that established by Dr. Waters in Wisconsin.

In the book published by the Wood Library containing the text of the presentations at the Waters 75th Anniversary Meeting in 2002, the late Dr. Carlos Parsloe relates Dr. Waters reluctance to attend the meeting in Sao Paulo in 1964. He was persuaded to come and in his Opening Address to the Third World Congress talked about the 'ghosts' of the past. Dr. Waters virtually completely disconnected himself from the world of anesthesia upon his retirement in 1948 and many have wondered why. This writer has speculated that he suffered from depression. Any comments?

Yours respectfully,

Gerald Zeitlin

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The *Bulletin*, formerly indexed in Histline, is now indexed in several databases maintained by the U.S. National Library of Medicine as follows:

1. Monographs: Old citations to historical monographs (including books, audiovisuals, serials, book chapters, and meeting papers) are now in LOCATORplus (locatorplus.gov), NLM's web-based online public access catalog, where they may be searched separately from now on, along with newly created citations.
2. Journal Articles: Old citations to journals have been moved to PubMed (www.ncbi.nlm.nih.gov/PubMed), NLM's web-based retrieval system, where they may be searched separately along with newly created citations.
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Frogs. . . *Continued from Page 21*

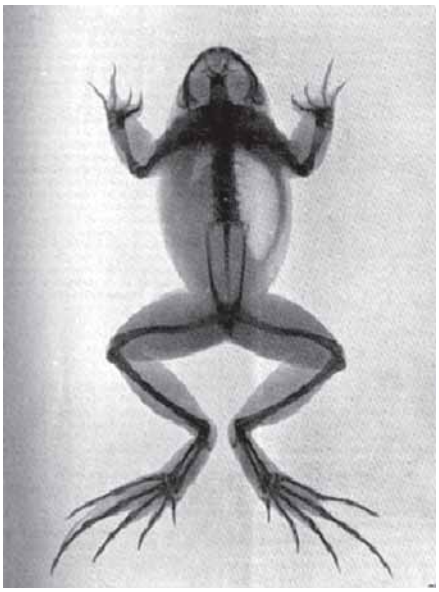

Fig. 1. Röntgenogram of a frog (1896). There is no rib cage. Immediately following Röntgen's announcement of his eponymous rays, E. Waymouth Reid and Johannes Kuenen wrote, "The clearness with which the several bones have come out is so remarkable that we consider the picture well worth reproduction".[10] For years thereafter, the quality of a frog image was the measure of the resolving power of radiographic equipment. The image may have been the first published chest film; the authors did not explain the collapse of the left lung. The image is reprinted by permission from Macmillan Publishers Ltd.

exchange does not involve skeletal muscle, the process makes the frog relatively tolerant of neuromuscular blocking agents. Frogs, then, were much used by Claude Bernard (1813-78) in his celebrated experiments on the mechanism of action of curare, which paralyzes skeletal muscle.[12,13] Those 19th-century experiments very nearly established chemical neurotransmission before the 20th-century work of Loewi and Dale. For instance, Bernard showed that curare blocked muscle contraction when nerves were electrically stimulated but not when muscles were directly stimulated by electricity.

Transcutaneous gas exchange also renders frogs remarkably tolerant of anesthesia overdose. Moderate doses of ether would stop frogs from breathing, but prolonged apnea was reversible. The irreversible overdose was the massive amount of ether required to stop the frog heart. Though John Snow (1813-58) is remembered as a superb clinician rather than a laboratory investigator, even he had to see this phenomenon for himself.[14,15] Duplicating the frog experiments of "the Parisian physiologists" (Bernard et al.), he related that, "if placed in air containing but 20 or 30 per cent of vapour of ether, [frogs] very quickly became affected, probably from the rapid absorption of the vapour by the skin: in a minute or two the respiration ceases, and they have every appearance of being dead, except that the heart can be seen pulsating on the under side of the chest. If they are now withdrawn, the circulation continues, the ether gradually evaporates by the skin, and respiration recommences, in a period varying from 5 to 15 minutes, according to the length of the previous exposure to the vapour." Snow's experiment was an impressive bit of *réanimation.*

Snow intended some of his frog experiments to dispel the common notion that inhaled anesthesia acts by depriving the nervous system of oxygen. He explained, "Although etherization and asphyxia resemble each other in some respects, yet the rapidity with which frogs are affected with ether, whilst they are so very slowly asphyxiated by privation of air, proves that they differ widely, and shows clearly enough that the effects of the vapour of ether are not due to its excluding part of the oxygen of the air by the space it occupies, as might at first, perhaps, be supposed."

Fully aquatic tadpoles permitted observation of pressure reversal and cutoff in general anesthesia

Another anatomic feature of frogs was of help in investigations into the fundamental mechanism of general anesthesia. Though they are phylogenetically higher than fish, frogs have a fully aquatic larval phase, complete with gills. Tadpoles were the subjects of two experiments that are most easily performed in aquatic organisms and have long intrigued investigators of anesthesia: pressure reversal and "cutoff."

Enormous ambient pressure reverses general anesthesia. Because water is virtually incompressible, such pressure can be applied without grossly changing the concentration of the anesthetic agent in the water holding anesthetized tadpoles. Dramatically, anesthesia-immobilized animals resume activity when a piston applies high pressure (circa 100 atm) to their swimming medium.[16] The experiment is most cleanly performed in the absence of a gas phase so that partial pressures of gases and volatile anesthetics in the water do not appreciably change with the change in hydrostatic pressure. Experiments in air are complicated by the toxicity of high partial pressure of oxygen and by the anesthetic action of high pressure nitrogen. However, helium has much less anesthetic activity than nitrogen and eventually permitted the demonstration of pressure reversal of anesthesia in mice.[17,18]

Anesthesia cutoff refers to an abrupt loss of anesthetic potency when a series of related anesthetic molecules are increased to a certain size, perhaps corresponding to the thickness of the neuronal cell membranes.[19] For instance, straight chain alcohols of the formula CH_3-$(CH_2)_n$-OH exhibit increasing anesthetic potency as n increases from 1 to 11, but higher alcohols of the series cease to provide anesthesia. The loss of anesthetic potency when the series goes from C11 to C12 is the "cutoff." length. Since many of the active alcohols of the series have low vapor pressure, it is easier to apply them as aqueous solutions to tadpoles than to administer them as inhaled vapors.

Egg laying

Although pressure reversal and cutoff provide important clues as to the mechanism of general anesthesia, it must be conceded that the mechanism is still mysterious. However, frogs have another feature that permits further understanding of anesthesia. Frogs have large, easily manipulated egg cells, and these have been made to express ion channels from nervous tissue. These expressed ion channels can then be studied with the aid of micro-electrode techniques which earned a 1991 Nobel Prize for frog researchers **Erwin Neher (1944-) and Bert Sakmann (1942-).**[20,21] Frog egg experiments increasingly point to ligand-gated ion channels as the receptors of anesthetic drugs.[22-30]

Cold-bloodedness

The cold-bloodedness of frogs influenced anesthesia for cardiac surgery. Procedures involving cardiopulmonary bypass frequently involve profound systemic hypothermia. Often, the thermally uncorrected $PaCO_2$ and arterial pH are maintained at 40 mmHg and 7.4. This practice is termed á-stat management, while holding the corrected values at 40 and 7.4 is termed pH-stat.[31,32] The symbol á refers to the á-proton of the imidazolium group of histidine residues of enzymes. With á-stat practice, the percent ionization of that group remains constant with cooling. Important or not, this finesse point was not initially conceived by cardiac anesthesi-

ologists. R. Blake Reeves (-2001) introduced the concept in order to explain the constancy of uncorrected "blood gas" values of winter-chilled bullfrogs.[33]

Concluding remarks

There are many who decry the use of animals as subjects in scientific experimentation. Even Françoise (Fanny) Marie Bernard née Martin (b. 1819), wife of Claude Bernard, was an antivivisectionist. It is to be hoped that advances in anesthesia will help to further allay the many ethical concerns that have been voiced on this topic. Perhaps extensive scientific knowledge of the physiology of amphibians will help to preserve their endangered populations.

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Carlos P. Parsloe, M.D., Dies at Age 89 in Sao Paolo, Brazil

by Lucien Morris, M.D.
and
John W. Severinghaus, M.D.

The ex-president of the World Federation of Societies of Anesthesiology (WFSA), Dr. Carlos Parsloe, died January 19, 2009, of heart failure in Sao Paolo, where he had practiced for nearly 55 years. He was one of the world's best loved and most traveled anesthesiologists.

He was born November 28, 1919, in Santos, Brazil, where his father was employed by the American Consulate. He obtained his M.D. from Faculdade Nacional de Medicina da Univesidade do Brasil in Rio de Janeiro in 1943. In 1945, 9 months into an unsatisfactory internship at Illinois Masonic Hospital in Chicago, he sought a residency. Finding all the good posts in Medicine, Surgery and Obstetrics filled, he chose anesthesia because a two year residency was immediately open in Madison, Wisconsin. He had not previously heard of Ralph Waters, the world's first Professor of Anesthesia at the University of Wisconsin, now considered the "father" of academic anesthesia. Parsloe began his residency in Madison in October 1946. He regarded this accidental opportunity as the major turning point in his life. Indeed, many of the world's early leaders of academic anesthesia trace their educational roots to "Aqualumni," the residents of Waters.

While at the University of Wisconsin he met and married Edith Elenore Reidhauser, a nursing student from Neenah-Menasha, WI. In 1949 he attended (in Buenos Aires) the First Latin American Congress in Anesthesiology and the Second Argentinean Congress of Anesthesiology, the start of a lifelong career of participating in professional meetings.

Dr. Carlos Parsloe giving the Waters toast at the AHA 2006 Annual Dinner Meeting in Chicago, IL.

In 1948, after visiting by car all the major anesthesia training centers in the U.S.A., he returned to Brazil with Edith and began practice in Santos at Santa Casa da Misericórdia Hospital.

In 1952 Parsloe accepted an invitation from the new chair of anesthesia, O. Sidney Orth, to return to Madison as a Clinical Assistant and a Research Associate. He might have remained at UW had he not been invited to join a new medical school in Ribeirão Preto, Brazil, in 1954 by its founder Professor Zeferino Vaz. He expected to found the first Department of Anesthesiology in Brazil. On arrival at that remote inland post, landing on a gravel strip, he learned from the surgeon in chief that anesthesia would not be an independent department but part of Surgery. He refused the appointment, and instead joined an anesthesia group led by Dr. Luiz Rodrigues Alves in Sao Paolo with which he spent the rest of his professional career. The physicians primarily served at Hospital Samaritano but were free to work elsewhere on request.

Photo of Elinor Severinghaus and Carlos and Edith Parsloe at Yosemite in October 2007. Photo by Dr. John Severinghaus.

Parsloe recalled beginning the first case of the day on a Monday in a new, well equipped State Hospital. His patient almost immediately turned cyanotic with no cause so he disconnected the anesthesia machine, and the color normalized. He and a nurse ran to warn all twenty operating rooms that the oxygen and nitrous oxide lines must have been switched. All patients were saved but one who had suffered irreversible brain damage.

Dr. Parsloe enthusiastically joined and contributed his efforts to several national and international anesthesiology societies during his long career. He was a long standing member of the American Society of Anesthesiology (ASA) and perhaps the most regular attendee at the annual ASA meeting. He served as Chairman and member of the Board of Directors of the Brazilian Society of Anaesthesiology, President of the Sao Paulo State Society of Anaesthesiologists (1973), the editorial boards of the Brazilian Journal of Anesthesiology (*Revista Brasileira de Anestesiologia*) and *Survey of Anesthesiology*, and was awarded the annual prize of the Confederation of Latin American Societies of Anesthesiology (CLASA, 1981).

In 1974, at the invitation of Lucien Morris, Parsloe was visiting professor in the Department of Anesthesiology at the Medical College of Ohio in Toledo, Ohio.

Among the many career honorariums and distinctions, Parsloe was named an Honorary Fellow of the Royal College of Anaesthetists (FRCA) in 1986 and in 1989 an Honorary Member of the Association of Anaesthetists of Great Britain and Ireland (AAGBI), and the Australian and New Zealand College of Anaesthetists (ANZCA).

During the 1960 Second World Congress (in Toronto) of the WFSA, as chair-

man of the Scientific Committee, Brazilian Society of Anesthesiology Organizing Committee, he was instrumental in bringing the Third World Congress to Sao Paolo in 1964. With Jack Moyers from Iowa City, he developed principles and organized Visiting Education Teams for WFSA, becoming an Executive Committee member in 1972-1980, Vice President from 1980-1984 and President from 1984-1988. In his acceptance speech in Manila in 1984, he chose two words to "epitomize the quadrennium": COMMUNICATION AND COOPERATION which he believed to be the key words for human accomplishment.

He was named Honorary President of the Tenth World Congress of Anaesthesiologists in The Hague, Netherlands, 1992.

His autobiography, "The Lifelong Apprenticeship of an Anesthesiologist" [Careers in Anesthesiology, Vol III, Wood Library-Museum of Anesthesiology, Park Ridge IL, 1999] includes fascinating sketches of nearly primitive anesthesia practices by untrained students, nurses or aides in Brazil in the 1940s.

Carlos Parsloe devoted enormous efforts to improving the scientific, ethical and humanitarian training of physicians choosing anesthesia careers. In 1987 at the ASA annual meeting in San Francisco, he spoke briefly at the Anesthesia History Association dinner, a group with which he had been associated since its foundation in 1982 in Rotterdam.

In 2002, on the celebration of the 75th anniversary of the foundation of the Waters program for graduate physicians in Anesthesia, Carlos and Edith returned to Madison to pay tribute to Ralph Waters (see photo).

In 2008 he attended the 55th Brazilian Congress of Anesthesiology in São Paulo, was celebrated by his colleagues, and delivered two addresses, one at the opening in which he emphasized the importance of friendship in our lives, considering himself very fortunate.

Dr. Parsloe was an avid traveler. During his term as President of the WFSA (1984-1988), he visited anesthesia departments around the world, especially in less developed countries in Africa, Asia and Latin America. Over his entire career, he is thought to have visited and befriended more physician anesthesiologists and departments than anyone in history. He will be sorely missed by family, friends and colleagues throughout the world.

He is survived by his wife Edith, three children (Diana, Roberto and Patricia), five grandchildren and a great grandson.

Untapped Sources for Anesthesia History*

by Amos J. Wright, M.L.S.
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Primary sources for anesthesia history research typically include such standards as professional medical books and journal articles and the surviving correspondence and other materials of departments and individuals. This article describes some additional sources for such research: newspapers and popular magazines; dissertations and theses; patents, and other resources. These sources have always been available to the dedicated researcher and sometimes indexed in such print tools as *Reader's Guide to Periodical Literature* or indices of individual major newspapers such as the New York *Times* or *The Times, London.* Indeed, several articles have been published about anesthesia history using newspaper accounts as sources.[1-6] Today these sources are even more available via the combination of vast electronic databases and the Internet. Many of the databases are proprietary and thus require a subscription, fee-for-use, or access [on site or remotely] to a library that subscribes. However, a growing number of these resources are free for anyone to use.

What follows are a selection and some discussion from the many examples that could have been chosen. My argument is that much fascinating and useful information about anesthesia history can be found in these sources. Based on my own informal wanderings through newspapers, I suspect that crimes committed in the U.S. and elsewhere with chloroform have been much more numerous than previously believed, and as a few examples of many possible will show, that use continues today. The easy availability of chloroform also seems to have made it a popular method of choice for suicides in the nineteenth and well into the twentieth centuries. Articles in newspapers and popular magazines can also provide information about public attitudes toward anesthesia and which anesthetic innovations have reached public awareness. Patents offer not only a window into practical aspects of equipment development and design, but also possible hints of "roads not taken." Doctoral dissertations and masters theses can provide a look at what aspects of anesthesia practice were important at academic medical centers in particular times and places. Many anesthesia books from the nineteenth and early twentieth centuries, now in the public domain, are beginning to appear in significant numbers in large scale scanning projects such as Google's and the Internet Archive's. Finally, there are many resources typically used by genealogists that can provide much useful material to anesthesia historians as well.

**A version of this material was presented at the Anesthesia History Association annual meeting in Nashville, Tennessee, in April, 2007.*

1. Newspapers

Many full-text newspapers from the nineteenth and twentieth centuries are becoming available in free databases as part of the many large-scale scanning projects currently underway by libraries and other non-profit entities. Numerous other newspapers are available in proprietary databases that commercial firms such as Proquest or Ancestry.com make available to library and individual subscribers. [Figure 1]

In some cases, such as the *Daily Mirror,* the database can be searched and citations found for no cost, but a fee must be paid for the full text.

Brooklyn *Eagle*
[Free; Figures 2 and 3]

Colorado's Historic Newspapers
[Free]

***Daily Mirror* (London)**
[Proprietary]

Google News Archive [Free]

New York *Times* Archive [Free]

Chronicling America [Free]

Ancestry.com [Proprietary]

Figure 1

A search in the Brooklyn *Eagle* database for "chloroform" and that word combined with various others gives some idea of the amount of material available about one anesthetic drug in just one newspaper over six decades. [Figure 4]

A selection of articles from various other newspapers illustrates the variety of topics available.

Colorado's Historic Newspaper Collection
www.cdpheritage.org/collection/chnc.cfm

"Effects of Chloroform" Ft. Collins *Weekly Courier* 14 December 1899

"Dr. Osler has evidently changed his mind. No one hears of his asking anybody to pass him the chloroform." Castle Rock *Journal* 10 November 1905

"Gem Bandits Get $500,000; Woman is Chloroformed Following New Year Party" Creede *Candle* 6 January 1923

New York *Times* Archive 1851-1980
www.nytimes.com

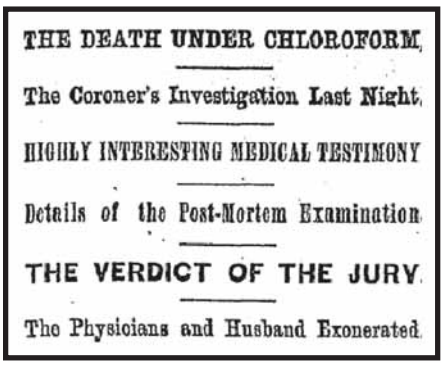
"Nurse commits Suicide; Places Her Head in a Pan of Chloroform" 28 October 1901

"Chloroform Thieves Led by a Doctor? Police Think some One with Medical Knowledge is Robbing East Site Flats; Whole Familes Drugged" 29 January 1908

"Anaesthetics for Plants; Experiments Show That Ether and Chloroform Hasten Growth" 3 July 1910

Washington *Post* via Google News Archive
news.google.com/archivesearch

"Chloroformed By His Wife" 10 February 1886



THE DEATH UNDER CHLOROFORM.

The Coroner's Investigation Last Night.

HIGHLY INTERESTING MEDICAL TESTIMONY

Details of the Post-Mortem Examination

THE VERDICT OF THE JURY.

The Physicians and Husband Exonerated.

Fig. 2. Headlines from an article in the Brooklyn Eagle *on February 22, 1870*

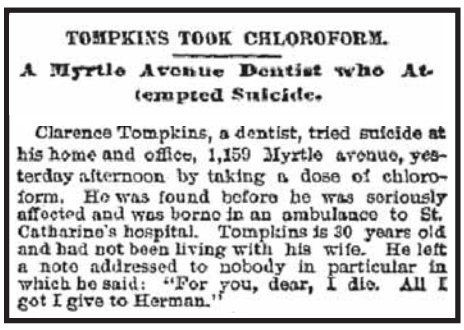
"Fatal Effects of Chloroform; Two Lady Patients Die While Under the Influence of the Drug" 17 February 1890

"Masked Burglars Use Chloroform" 24 December 1899

Other Newspapers and Media: A Tiny Sample

Huntsville [Alabama] *Weekly Democrat* 7 June 1882
"BIRMINGHAM, ALA., June 3.
Mr. George Allen, a machinist in the shops of the North & South Alabama Railroad, died yesterday about 2 o'clock in a dentist's chair, in the office of Dr. Eubank, a dentist of this city, from the effect of chloroform, administered by two well known physicians of Birmingham, for the purpose of extracting a tooth. Mr. Allen had been suffering for some days from the effect of a previous attempt to draw the tooth, and, unknown to the physicians, had already taken several doses of morphine. He leaves a wife and several children."

Birmingham [Alabama] Iron Age 10 July 1884
[Available in the Birmingham Public Library's Digital Collections at www.bplonline.org]



TOMPKINS TOOK CHLOROFORM.

A Myrtle Avenue Dentist who Attempted Suicide.

Clarence Tompkins, a dentist, tried suicide at his home and office, 1,159 Myrtle avenue, yesterday afternoon by taking a dose of chloroform. He was found before he was seriously affected and was borne in an ambulance to St. Catharine's hospital. Tompkins is 30 years old and had not been living with his wife. He left a note addressed to nobody in particular in which he said: "For you, dear, I die. All I got I give to Herman."

Fig. 3. Brooklyn Eagle, *January 9, 1893*

"A Mysterious Stranger/A Deaf Mute Found Dosing Himself with Chloroform."
On a Saturday afternoon this individual was found sitting on a box in front of the City Hotel "with a small vial and a handkerchief in his hands, in a rather peculiar and comatose condition." Further investigation discovered the cause of his condition. "…the man had, during the day, purchased four ounces of chloroform at Hughes' drugstore…" He had also bought some at Nabors and Morrow's drugstore and tried but failed at two other drugstores.

Cleburne New Era 17 April 1906 [from Cleburne County, Alabama]
"Charles Bolt was chloroformed several days ago in his room at the Morris Hotel in Birmingham by a professional crook. A gold watch and $37 in money were taken by the robber. However, the man has been caught and landed in jail and Mr. Bolt has recovered his property."

Gloucestershire Echo 12 April 2007:
"A trainee chartered accountant killed himself with Chloroform after storming out of work when a colleague taunted him about never making the coffee, an inquest heard. Stuart Baldwin, 24, bought the old-fashioned anaesthetic over the internet after resigning from his job as a financial controller with Online Packaging, the Gloucester inquest was told."

TV3 News Auckland NZ 25 April 2007:
"On each occasion, he gave the [10] women alcoholic beverages laced with sleep-inducing chemicals, such as chloroform, before raping them as they slept, leaving two of them dead, the indictment said."

Sky News Isleworth UK 24 April 2007:
"He also used chloroform to drug his victims and this, the court was told, led to the death of Australian Carita Ridgway in 1992."

Chronicling America
www.loc.gov/chroniclingamerica

This effort, a joint project of the Library of Congress and the National Endowment for the Humanities, debuted on March 21, 2007. By late November 2008, more than 680,000 total pages of public domain newspapers from ten states had been digitized for the period 1880 to 1910. Over the next 20 years the project is expected to include newspapers from all U.S. states and territories from 1836 to 1922. On November 21, 2008, I ran searches on various words and phrases and got these results:

Brooklyn *Eagle* 1841-1902

"Chloroform"	**1,730 items**
"Chloroform & murder"	**243 items**
"Chloroform & burglary"	**56 items**
"Chloroform & robbery"	**104 items**
"Chloroform & death"	**479 items**
"Chloroform & suicide"	**169 items**

Fig. 4. Articles from the Brooklyn Eagle *using "chloroform" and other search terms.*

Term	Results
Anaesthesia	210
Anesthesia	128
Chloroform	6,274
Laughing gas	100
Nitrous oxide	102

Times, London, Digital Archive 1785-1985

In January, 2009, I accessed a free trial version of this proprietary database at infotrac.galegroup.com/itweb/free4_tda by using the word "trial" without quotes in the password box. A search of "chloroform" in titles only produces just over 100 articles. Searching the same word full text produces more than 2,500 results, over 500 of them in advertisements!

Scotsman Digital Archive
archive.scotsman.com

This archive of Scotland's national newspaper offers free searching of all issues from 1817-1950. Copies of articles are available for a fee. A search of "chloroform" in the full archive resulted in over 1000 results, including this article:

The Scotsman, 19 June 1934
"Rare Form of Poisoning"
"Due to Delayed Action to Chloroform"

Ancestry.com
www.ancestry.com

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Ancestry is one of the largest commercial genealogical resources. One of their many proprietary databases is devoted to scanned newspapers from around the U.S.

2. Popular Magazines

Here are a few sample articles on chloroform found via *Readers' Guide Retrospective*, a proprietary database from the H.W. Wilson Co.:

"Chloroforming flowers" *Harper's Weekly* 54: 25, November 19, 1910
Colvin FH. "Shall we chloroform 'em at 40?" *Magazine of Business* 56: 59, July 1929
Cook G. "Chloroform" [poem] *Cornhill Magazine* 113: 489-490, April 1916
"Effect of ether & chloroform on plants" *Scientific American* 96:166, February 23, 1907
Girdner JH. "Chloroform—Its Uses and Dangers" *Munsey's Magazine* 27: 501-502, July 1902
Payne W. "Chloroform at sixty?" *Saturday Evening Post* 199: 35, April 2, 1927
Waugh FA. "Children need not be chloroformed" *School & Society* 33: 665-667, May 16, 1931

The *Time* magazine archive from 1923 to 2002 is freely available at www.time.com and contains such as articles as these:

"Will Ether Be Superceded?" [Luckhardt and Carter and ethylene] 17 March 1923
"New Anesthetic" [Dr. Fredet of Paris, "sommifere"] 4 August 1924
"Useful Poison" [Griffith and curare] 21 February 1944

There is also the frightening "Lung Explosion" article published 2 February 1931, which begins:

"In a Los Angeles hospital last week a Mrs. Maude Branton, 43, clergyman's wife, inhaled ether, oxygen and nitrous oxide as anesthetic for an operation. This mixture of gases is explosive. In Mrs. Branton's case something ignited the mixture in her lungs. The mixture exploded, the lungs burst, Mrs. Branton died. A coroner's jury decided that no one was to blame."

3. U.S. Patents via Google
www.google.com/patents

A search of Google's free U.S. patents database will produce some fascinating results, as noted below. Names of patent applicants can be searched, as well as individual terms such as anesthesia or anaesthesia, anesthetic, cyclopropane or phrases such as nitrous oxide. A search combining chloroform and anaesthesia produces results beginning in 1869. The U.S. Patent Office also offers free searching at patft.uspto.gov, but the patents from 1790 to 1975 are searchable only by issue date, patent number or current U.S. classification. In both databases, the full patent application is available.

Sample patents via Google:

"Holder for Gas-Inhalers"
US 340778
8 January 1885

"Chloroform Dropper"
US 859157
27 June 1905

"Anesthesia Mask"
US 955821 13 October 1909

"Preparation of Cyclopropane"
US 2261168
30 April 1937

"Spinal Anesthetic Solution"
US 2340425
15 May 1940

Curiosities abound in the patent records. Archelus H. Mitchell, a resident of Selma, Alabama, has two patents listed:

US Pat. 1236591 - Filed Jul 21, 1916
ARCHELUS H. MITCHELL, Of SELMA, ALABAMA. ANESTHETIZING AND RESUSCITATION APPARATUS.
Specification of letters Patent.
Patented Aug. 14, 1917.

US Pat. 1924797 - Filed Apr 29, 1932
... MOTOR VEHICLE Archelus H. Mitchell, Selma, Ala. Application April 29, 1932.

Mitchell's 1916 patent consisted of a mixing chamber; valve-controlled air, oxygen and gas inlets; wash bottles connected that chamber and another mixing chamber; and connection valves between the wash bottles and the oxygen and gas inlets. Whether a prototype of this machine was ever built is unknown. Why an individual in this small Alabama town at the time of World War I was interested in anesthesia machines or, much later, motor vehicles also remains a mystery.

4. Dissertations and Theses

Dissertation Abstracts
Dissertation Abstracts is a proprietary database from a company called ProQuest; access is offered by many academic and large public libraries. The database indexes mostly U.S. academic dissertations and theses primarily since 1950. Some Canadian and European items are also included.

Locator [NLM catalog] locator.gov
The U.S. National Library of Medicine's card catalog indexes the many theses and dissertations owned by NLM. These include 44 items in the Washington University School of Medicine Thesis Collection, ca. 1867-1871. One of those, exact date unknown, is John Thad Johnson of Georgia's thesis on chloroform.

Many individual libraries and archives have collections of medical dissertations and theses. Some institutions include Drexel University College of Medicine, Archives and Special Collections, Women Physicians 1850s-1970s; the University of Pennsylvania; and the University of Michigan Libraries [1851-1878].

Many listings of such theses and dissertations have been published in both the journal and monographic literature. Just one example, from 1849, gives the list of University of Pennsylvania medical graduates in April of that year, along with states of residence and graduating essay topics. There we find "Etherization" by John R. Jameson, from Marshall, Mississippi.[7]

Two dissertations by University of Pennsylvania medical students from Alabama indicate the possibilities for further research. Their biographical hints sound fascinating!

Charles F. Henry
"Etherization as a surgical remedy" [presented 17 February 1853]
b. 8-29-1828, Mobile, Alabama
A.B., University of Alabama, 1847
Tutor, modern languages, UA, 1851-2
Surgeon, Russian army, Crimean War

d. 7-22-1862, Warm Springs, Ga.

Nathaniel Friend
"Anaesthesia in Labour" [presented 19 January 1857]
b. 7-6-1834, Boligee, Alabama
d. 9-27-1877, Lampasas, Texas
A.B., University of Alabama, 1855
Professor of chemistry, Howard College [now Samford University], 1856-7
Surgeon [Major], C.S.A.
Superintendent of Education, Greene Co., 1865-6

[Biographical information about Henry and Friend was taken from Palmer TW, comp. *A Register of the Officers and Students of the University of Alabama 1831-1901*. Tuscaloosa: University of Alabama, 1901]

A Random Selection of Other Dissertations
Johannes Quistorp, "Die Anaesthesie" University of Rostock, Germany, 1718
William P.C. Barton, "A dissertation on the chemical properties and exhilarating effects of nitrous oxide gas, and its application to pneumatick medicine." University of Pennsylvania, 1808
John Harvey, Jr. "Ether in Surgical Operations" University of Pennsylvania, 1851
Charles H. Sackrider. "Ether and Chloroform" University of Michigan, 1856
Louise Schneider, "Anaesthesia in Natural Labor" Female Medical College of Pennsylvania, 1879
Richard Charles Adams, "Intravenous Anesthesia" University of Minnesota, 1940
Dan C. Lortie, "Doctors without Patients: the Anesthesiologist, a New Medical Specialist" University of Chicago, 1949
Donald E. Soltero, "A Clinical Evaluation of Automatic Anesthesia" University of Minnesota, 1951

5. Public Domain Books

Two major book scanning projects by Google and the Internet Archive are making hundreds of thousands of public domain books available for free download. A number of anesthesia titles are included in these projects; and as the scanning of major research libraries continues, even more become available on a regular basis. Google and the Internet Archive are in a sense beginning the anesthesia full-text project I outlined a few years ago.[8] Why not explore some of these classics yourself and perhaps give some on a CD or USB drive to residents? Below is a selection of titles recently found via these two projects; some titles are available from both projects.

Google Books books.google.com

Davy H. *Researches, Chemical and Philosophical: Chiefly Concerning Nitrous Oxide.* 1800
Dreiser T. *Plays of the Natural and Supernatural.* 1916 [This collection contains Dreiser's play, "Laughing Gas." (9)]
Flagg PJ. *The Art of Anaesthesia.* 1922
Hertzler AE. *Surgical Operations with Local Anesthesia.* 1916
Murphy EW. *Chloroform: Its Properties and Safety in Childbirth.* 1855
Rogers B. *The Semi-Centennial of Anaesthesia, October 16, 1846-October 16, 1896.* 1897
Sansom AE. *Chloroform: Its Action and Administration.* 1865
Warren JC. *Effects of Chloroform and of Strong Chloric Ether, as Narcotic Agents.* 1849

Internet Archive archive.org

American Year-Book o f Anesthesia and Analgesics, vols. 1 and 2. 1916 and 1920
Braun H. *Local Anesthesia: Its Scientific Basis and Practical Use.* 1914
Davis CH. *Painless Childbirth; Eutocia and Nitrous Oxid-Oxygen Analgesia.* 1916
Gordon HL. *Sir James Young Simpson and Chloroform (1811-1870).* 1897
Heineck AP. *General and Local Anesthesia.* 1901
Hewitt FW. *The Administration of Nitrous Oxide and Oxygen for Dental Operations.* 1911
Hirschel G. *Text-book of Local Anaesthesia for Students and Practitioners.* 1914
Lyman HM. *Artificial Anaesthesia and Anaesthetics.* 1881

6. Genealogical Sources

Records used frequently by genealogists can also be useful to any historical researcher. These record types include census, birth and death, marriage, passport, ship passenger arrival and departure records and many more. Anyone doing biographical research on individuals connected with anesthesia history should seriously consider using these records to add depth and even new knowledge about such individuals. Historical researchers would do well to peruse a book or two of the many aimed at beginning genealogists, such as Holly Hansen's *The Handybook for Genealogists* [11th ed. 2005] and Christine Rose's *Complete Idiot's Guide to Genealogy* [2nd Ed., 2006]. Two basic web sites in this area are Ancestry.com, consisting mostly of proprietary content and RootsWeb.com, a massive collection of free resources and databases. A large index site maintained by Cyndi Howells is at www.CyndisList.com. The Church of Jesus Christ and Latter-Day Saints also maintains an important genealogical site at www.familysearch.org.

7. Court Records

Legal information is available in several proprietary databases offered by academic or large public libraries. Such databases can be used to find information beyond the public press on cases related to anesthesiologists and anesthetic agents that have entered the legal system. Examples of these databases include:

LegalTrac 1980 to date
Citations and full text from law reviews and journals, bar association journals, legal newspapers,etc.

LexisNexis Legal Research
Federal, state and international legal materials

Westlaw Campus Research
Statues, cases, public records

Some older legal records are becoming available for free on the web. The proceedings of the Old Bailey, London's Central Criminal Court, from 1674 to 1913 were opened to public searching last year. A group of English universities developed this resource of 197,745 individual trials. The database is at www.oldbaileyonline.org. A search of this database in November, 2008, for "chloroform" resulted in 72 items between 1849 and 1912.

Conclusion

This article has explored some resources relatively untapped for anesthesia history research. Other sources could have been included. For example, there is the vast and contantly growing FictionMags database at www.philsp.com/homeville/FMI/0start.htm which indexes magazine fiction—and some other content—primarily from the 19th and early 20th centuries and primarily from British and American pub-

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lications. A look at the title index for "chloroform" turns up two short stories, "Chloroformed!" by Elaine Hamilton in the July 19, 1930 issue of *Detective Story Magazine* and "Chloroforming the Apache Kid" by Emma Allen in the May 1904 issue of *Everybody's Magazine.*

My hope is that since many of these resources are becoming more easily available, and often free to access, via digital databases, they will be more useful to future anesthesia historians. Even more of these type resources will be available in the years to come. In addition, such sites as YouTube and similar video sharing sources will provide resources for serious research. YouTube has already become a de facto research tool for many.[10] At least one history professor is already using YouTube for "primary source" videos.[11] A recent article describes YouTube videos as sources of information for patients and families about their surgical anesthetic experiences. Such current use videos will become primary sources for historians in the future.[12] A YouTube for medicine, icyou.com, has developed in the past couple of years.[13] The possibilities for anesthesia history research in these "untapped" sources seem endless.

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6. Haddad FS. First newspaper announcements of the first public demonstration of ether anesthesia. *Middle East J Anesthesiol* 1992 Oct;11(6):583-5.

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13. Johnson C. The new tube in town: a video-sharing site for healthcare. *Medicine on the Net* 2009 Jan;15(1):1-4.

Why Was there a Four-Decade Delay before Anesthesia was Introduced in 1846?*

by David A. E. Shephard, M.D.

Introduction

Customarily, anesthesia is regarded as having been introduced on October 16, 1846, because it was then that William Thomas Green Morton showed, *in public*, that ether could induce sleep and analgesia and so make painless surgery possible.[1] Likewise he is generally accorded priority in the 'discovery' of anesthesia. Yet other individuals had used an anesthetic agent earlier. American dentist Horace Wells 'anesthetized' persons with nitrous oxide in December 1844;[2] physician and surgeon Crawford Long used ether in Jefferson, Georgia, in several surgical operations beginning on March 30, 1842;[i3] medical student William Clarke also used ether during a dental extraction in Rochester, New York, two months earlier;[4] and in 1823 English physician and surgeon Henry Hickman demonstrated the *principle* of anesthesia by making animals unconscious with carbon dioxide and then operating on them without causing them pain.[5] In addition, as early as 1800 English chemist Humphry Davy suggested that nitrous oxide might be of value in surgery.[6] Therefore in terms of relief of pain in surgical patients the *idea* of anesthesia, albeit in the form of an anodyne, was evident in 1800. Moreover, at that time the requisite knowledge of nitrous oxide, and also ether, and the necessary equipment were available to support the introduction of anesthesia into clinical practice had anyone followed up on Davy's suggestion. But no one did. Why? And why was anesthesia not introduced for another 46 years?

Historians and anesthesiologists have proposed answers to those questions, but the questions do not appear to have been fully answered. The purpose of this essay is to discuss the solutions to the 'historical puzzle.'[7] The influence of romantic literature on the medical understanding of pain and suffering that have been proposed and to add a further solution. The thesis of this discussion is that the delay in the advent of anesthesia resulted from the existence of conflicts of ideas among individuals and of ethics within society, both of which had to be resolved before the idea and the principle of induced insensibility in surgical patients could be accepted. That took time – even four decades. In that period, however, extraordinary progress was made in medicine and equally extraordinary progress was made in reforming society. All that had to take place before anesthesia could come to pass.

Davy's Suggestion of 1800 and Hickman's Demonstration of 1824

An appropriate starting point for the discussion is the situation in 1800. At that moment, chemistry was riding a huge wave of success, for gases such as carbon dioxide, nitrous oxide, and oxygen had all been discovered in the previous half-century. The suggestion by Humphry Davy (Figure 1) that year that nitrous oxide might be useful in surgery was symbolic of the promise of the research by natural scientists such as Joseph Priestley in England[8] and the formulation of the principles of chemistry by Antoine Lavoisier in France.[9] Moreover, it was apparent before 1800 that all this work would become clinically relevant. As early as 1772, Priestley, who discovered nitrous oxide that year[10] and oxygen (probably with Carl Scheele also[11]) perhaps in 1774, announcing it in 1775,[12] went so far as to say that "very great medicinal use" would come from those "different kinds of airs."[13] Similarly, Thomas Beddoes, whom Davy worked for, opened the Pneumatic Medical Institution specifically to make 'medicinal use' of those 'airs.'[14] The fact that no one followed up on Davy's suggestion is therefore somewhat surprising.

It is even more surprising as one delves into Davy's ideas. The passage in which he suggested a surgical use of nitrous oxide is instructive when it is read in its complete form. Davy wrote that "as nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage in surgical operations in which no great effusion of blood takes place,"[15] which indicated his interest in the analgesic effects of nitrous oxide as well as the psychological effects. Though he was thrilled by the euphoria and the enhancement of sensibility — he wrote that objects around him were "dazzling" and he felt "an highly pleasurable thrilling" in the chest and extremities[16] – he also noted the relief of pain: headache on one occasion was relieved "after the third inspiration"[17] and the pain from a wisdom tooth "always diminished after the first four or five inspirations" of the gas.[18]

Fig. 1. Humphry Davy (1778-1829).

Most authorities believe that Davy regarded nitrous oxide simply as an anodyne and not anything resembling anesthesia,[19] which anyway was then an alien concept and would be until Hickman described his experiments of 1823 the following year. But Davy did express some caution about the use of the gas. He stated that it could produce "peculiar changes in the composition of the blood" and that in the presence of "stimulating substances" more oxygen and nitrogen "must be combined with the blood in respiration."[20] His own experience suggested to him that breathing nitrous oxide on one occasion had led to the formation of injurious nitrous acid, and he was determined not to repeat "so rash an experiment."[21] As far as Davy's suggestion about use of the gas in surgery is concerned, the efficacy of nitrous oxide in patients in whom blood loss was excessive would not only be undermined by the hemorrhage but might well be dangerous, even lethal, as oxygen was lost with the blood.[22] Nor did Davy change his views about nitrous oxide: by 1828, if not earlier, he thought that there was no way of inducing insensibility safely[23] – a point that recalls the potentially hazardous nature of some of Davy's experiments with nitrous oxide.[24] Davy did understand that nitrous oxide relieved pain, but only one historian

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Delay. . . *Continued from Page 33*

has adduced evidence that Davy might have thought of nitrous oxide as more than an anodyne. According to Frederick Cartwright, Davy in 1800 (but before he wrote his *Researches*) interjected a separate note on a page of an essay on pleasure and pain and the intellect that simply read "removing physical pain of operations."[25]

For Davy's contemporaries, his caution with respect to nitrous oxide may therefore have deterred others from following up his suggestion for a possible surgical use of nitrous oxide. Thus it is not surprising that only one reference to use of nitrous oxide as clinical analgesic has been found —that of W.D.A. Smith, who stated that it had been considered in the context of dental extractions in 1820.[26]

Not until 23 years had elapsed after Davy made his original suggestion was a further significant advance made. This was when Henry Hickman (Figure 2) induced unconsciousness and analgesia in small animals and was able to operate on them without causing any pain. He reported the results of his work, which he described under the rubric of 'suspended animation,' in two versions, in February 1824 and then August 1824. As with Davy's report, it is instructive to consider in some detail what Hickman wrote.

Four of Hickman's observations are worthy of note here. First, he stated that "there is not an individual who does not shudder at the idea of an operation, however skillful (sic) the Surgeon or urgent the case, knowing the great pain that the patient must endure …," adding that he himself "frequently lamented, when performing … duties as a Surgeon that something has not been thought of whereby the fears may be tranquillised and suffering relieved."[27] Second, he amplified that statement later by concluding that it was "rather singular" that no one had carried out experiments to see whether operations might be carried out in animals "in a torpid state."[28] Third, Hickman's success with carbon dioxide led him to conclude that it should be possible to do the same thing, "with perfect safety and success" in surgical operations in humans.[29] And, fourth, he was quite prepared to practice what he preached, for he said he would be quite willing to undergo what he termed 'suspended animation' should he ever have to have surgery.[30]

Those statements of Hickman suggest that, by 1824, he had both formulated the *concept* of inhalational anesthesia and put it into practice, albeit in animals. This

Fig. 2. Henry Hill Hickman (1800-1830).

appears to have been the first time anyone had thought of making someone 'torpid' so that submission to a surgical operation was not painful. This was a remarkable step. What had led him to do so?

As a surgeon, and as a sensitive individual, he wished to minimize his patients' suffering and he wondered how to do so. Hickman trained in medicine at a time when physicians had begun to think of death as a process, and even as a reversible process if appropriate measures were taken. That concept developed in part as a result of steps that were taken in the 18th century to revive drowned persons were revived, one of the measures being intubation of the trachea and inflation of the lungs.[31] Hickman might have been familiar with a book on 'apparent death' by James Curry that was published in 1815.[32] Curry referred to suffocation by noxious gases, pointing out that the suffocating effects of carbonic acid could be lessened if it were mixed with other gases and if the lungs were ventilated. Hickman's thought process might also have been shaped by the ideas of two other individuals. One was Henry Goldwyer, whom Hickman, then a medical student in Edinburgh, might have heard lecture on asphyxia.[33] Goldwyer defined asphyxia as a temporary 'suspension' of the vital functions arising from a deficiency of atmospheric air, and he explained that noxious gases, including carbonic acid, were taken into the lungs, then having, as Xavier Bichat suggested, an effect on the brain.[34] The other individual who might have influenced Hickman was London surgeon Benjamin Brodie, who described experiments on carbon dioxide he had performed on January 23, 1821.[35] However, it is by no means certain that Hickman actually heard Brodie, but he could conceivably have heard about them.

In using the word 'suspension,' Goldwyer was using a term that was commonly used in Hickman's day with respect to reversible loss of vitality as well as to its literal meaning of absence of the pulse. Thus it is not surprising that, once Hickman had conceived the idea of using carbon dioxide – which, as he wrote, in his experience had never proved lethal[36] — he would also use the term 'suspended animation' to describe the reversible state of insensibility that he induced.[37] By 1823, therefore, there was enough evidence to suggest that experiments with suspended animation were feasible and that carbon dioxide was as safe as any other inhalational substance.

In conceiving and conducting his experiments, Hickman went much further than Davy. In 1800, Davy had simply made a *suggestion*, and a suggestion that is likely to have been made with nitrous oxide just as an anodyne. In 1823, Hickman actually demonstrated the *principle* of anesthesia. Moreover, unlike Davy, he had no reservations about hemorrhage,[38] which had limited the suggestion about the use of nitrous oxide in surgery. Hickman's research was the groundwork for anyone who wished to study further the topic of pain associated with surgical operations, but no one came forward. No one seemed at all interested in testing the practicability of inducing gaseous sleep and analgesia in the surgical setting, either with carbon dioxide, or with nitrous oxide, or even with ether, which had been known to physicians since the 16th century – and which Paracelsus had shown could put chickens to sleep.[39] Hickman's work was ignored, both in England and in France,[40] even though he had actually demonstrated the principle and the *fact*, of inhalational anesthesia. Why was Hickman's work ignored, just as Davy's had been?

Previous Answers to Questions on the Delayed Introduction of Anesthesia

Delay in the introduction of innovations into clinical medicine is not uncommon, and anesthesia is no exception. The hypnotic effect of ether was first observed in the 16th century;[41] the paralytic effect of curare was discussed by Claude Bernard in 1857;[42] and the numbing effect of cocaine was apparent to Albert Niemann in 1860.[43] In each of these instances, no one envisioned clinical relevance, and only much later were the findings applied in anesthesia. One reason for the delay in the

introduction of anesthesia, then, is the limitation of the human capacity for envisioning applications of valid observations.

But there are other reasons why anesthesia was not introduced soon after 1824, let alone soon after 1800, and, similarly, and why it was introduced in 1846 rather than 1800 or 1824. These can be conveniently discussed by considering how each fits into a spectrum of opinion. They may broadly be considered in two classes: those relating to the work of Davy and Hickman in the context of medicine, and those relating to changes in attitudes within society.

At one end of the spectrum is anesthesiologist E.M.Papper, who wrote about Davy and the members of the 18th-century romantic movement with whom he was associated.[44] Papper argued that the advent of anesthesia was a consequence of the stimulus of the romantic movement in literature. Poets like William Wordsworth and Samuel Taylor Coleridge, as well as Beddoes and Davy, who were members of that movement, were especially interested in the possibility of heightening sensibility in their lives as well as being concerned about the individual and human suffering. They believed that there was no need to see pain as the consequence of Fate or of the mortal condition. Here, the therapeutic efforts of Beddoes and the research on nitrous oxide conducted by Davy fit in well. Davy, in particular, spearheaded the interest in the euphoric effects of nitrous oxide and likely diminished the interest in its analgesia effects. However, as historians Margaret Jacob and Michael Sauter point out, the first romantics were primarily concerned with the search for pleasure and the augmentation of individual consciousness. None of them engaged in a serious quest for a holy grail of pain relief.[45] Papper may have been correct in believing that romanticism was relevant to the way they thought about scientific matters, but he went out on a limb in speaking about the relationship of love and compassion to the advent of anesthesia. His point was that love in the sense of compassion and anesthesia in the medical sense are corollary forces; or that "anesthesia is inconceivable unless there is compassion derived from love."

More specifically, Margaret Jacob and Michael Sauter addressed the questions as to why no one followed up on Davy's suggestion of 1800. Davy and his colleagues were enthusiastic about their experiences with nitrous oxide, but Davy's note of caution limited the enthusiasm. This must be borne in mind when Davy's suggestion as to the use of the gas when there might be a 'great effusion' of blood. For Davy, as for Beddoes, blood was the source of life and sensation, and if blood was lost during a surgical operation so, too, was oxygen lost and, as well the analgesic effects of nitrous oxide would be diminished.[46] Even after Davy left Beddoes' Institution in 1801, he remained cautious about the use of nitrous oxide, believing that there was no way that insensibility could be induced safely. Davy became president of the Royal Society in 1820, and caution noted by a man in his position would have been taken seriously.

Another historian who has discussed the work of Davy, and Hickman also, is Stephanie Snow – a descendant of part of the family of the great John. She said that "a new concept of an unfeeling, yet living, body became possible through the new physiological and anatomical knowledge of the 1820s onwards," and that by the 1840s a few medical individuals were ready to accept the idea of artificial suspension of sensibility of the body,[47] though her evidence here is limited. However, it is implicit in her remarks that time was required for new knowledge in medicine, especially in anatomy and physiology, to accumulate and for new ideas to seep through the medical consciousness, and that only then was the time right for the advent of anesthesia. Of Davy, Snow pointed out that he (and many physicians and surgeons) believed that pain fulfilled a physiological function, for its presence marked the return to health,[48] though one could readily state the opposite. In relation to Hickman, Snow made the point that one difference between him and Davy was that he believed he had some control over the process that, if uncontrolled, would lead to death.[49] In other words, 'suspension' was transient, not permanent. Snow's argument supports the belief that ideas about death as a process and that the process might sometimes be reversible process.

Norman Bergman also wrote at some length on Davy. In his opinion, Davy likely thought of nitrous oxide as one more anodyne, not a be-all and end-all solution to the problem of pain in surgical operations. Davy's suggestion was consistent with an action that was based on the Brunonian system of asthenia (or decreased excitability) and sthenia (or increased excitability). Nitrous oxide would help to prevent the diminished excitability of the pain of surgery and, in cases of hemorrhage, to act synergistically with blood loss to increase excitability.[50] It was this rather than the thought of actual patient comfort during surgery that interested Davy. There is no evidence that the possibility of pain-free surgery ever occurred to Davy.[51]

In terms of the delay in the introduction of anesthesia, then, we can draw three conclusions about Davy and three about Hickman. Concerning Davy, first his suggestion of 1800 was, at most, a very tentative suggestion about analgesia; second, no one who read his writings is likely to have thought that nitrous oxide would make an unusually efficacious anodyne for surgical patients; and, third, his reservations, even though they were only mild, would have tended to hold back further research on the gas. As far as Hickman is concerned, first, while he was *the* pioneer in inhalational anesthesia, and a man whose ideas were ahead of his time,[52] his term 'suspended animation' had negative connotations that were related, for example, to grisly stories such as burial of someone who was still alive. And, as Bergman pointed out, such unfavorable associations tended to make some physicians reluctant to use anesthesia,[53] even after it had been shown to be efficacious. Two further points about Hickman are that he was not especially tenacious in pressing forward with further experiments, and he died early, in 1830.

At the other end of the spectrum are historians who have considered the nature of the larger society in the latter part of the 18th century and the early part of the 19th. Among anesthesiologists, two whose views have contributed significantly to discussions of the delay in the introduction of anesthesia are Nicholas Greene[54] and Donald Caton.[55] Greene held that one prerequisite for the 'discovery' of anesthesia was the development of the concept that each individual is responsible for the welfare of fellow members of society. Not only could political freedom and individual well being in the broadest sense not develop in the absence of a humanitarian attitude in society and nor could a desire within a society to correct ailments and suffering among its members develop. Beginning late in the 18th century, society in the West became more sensitive, though only gradually, but it was certainly manifest by the 1830s. At the same time, ideas about pain could only change as medical research showed that pain had a biological origin and occurred as a response to a physical stimulus. Again, beginning late in the 18th century, the practice of medicine began to develop a more objective basis as rational analysis replaced dogma and superstition and as treatment based on evidence replaced gunshot therapy in the form of bleeding and purging. We see this in

Delay. . . *Continued from Page 35*

William Withering's use of foxglove for heart failure[56] and Edward Jenner's understanding of the antagonism between cowpox and small pox.[57] Knowledge of anatomy, physiology, pharmacology, and pathology grew greatly in the early years of the 19th century, so that not only was diagnosis and treatment organ-specific but also there was a more objective basis for the understanding of the management of pain – and for the justification of doing so without thinking that one was interfering with 'God's plan.'

Caton extended Greene's argument and emphasized the secularization of pain. He pointed out that liberal thinkers like Jeremy Bentham and John Stuart Mill did much to change people's attitudes about pain and suffering. Bentham classified pain into natural, man-made, and divine causes, which led to the realization that the physical and mental components of pain might be studied scientifically. The management of pain became accepted as a social goal, which was an important advance in that the concept of anesthesia could not be accepted otherwise, and Caton attributed the absence of follow up to the work of Davy and Hickman to the fact that amelioration of pain was not a social goal in their day, while it was in Morton's – and hence his success and the cessation of the delay in the introduction of anesthesia. Nor was the active amelioration of pain acceptable in 1842, and the reluctance of Crawford Long (Figure 3) to publish his work soon after using ether on March 30, 1842, is explicable on this basis. As William Hammonds and John Steinhaus have reminded us, Long's daughter stated that the people in his town considered him reckless and perhaps mad.[58]

A New Perspective: The Significance of Conflicting Opinions

The contributions of the foregoing historians have done much to answer the question as to why there was a four-decade delay in the introduction of anesthesia. However, they do not seem to have emphasized one other aspect of the context of the delay; namely, the conflicts that had to be resolved before anesthesia could be introduced. There were two sets of conflicts: those that concerned *ideas among individuals* and those that concerned *ethical beliefs within society*. And the opinions underlying those conflicts were often forthright.

Concerning conflicts among individuals, on one side stand Davy and Hickman, whose ideas contained the seeds of the wonderful concept of anesthesia. However, those seeds were sown on the barren soil of the orthodox, and in effect negative, ideas of a number of early-19th century physicians and surgeons and lay persons. Some surgeons countered any suggestion that anesthesia was possible. Some argued that it was senseless to search for a solution of the problem of pain control during surgery: that, as French surgeon Louis Velpeau believed, it was a 'chimera.'[59] Other surgeons held that the idea of inducing coma to obtund operative pain as an alternative to the traditional anodynes such as opium and alcohol was philosophically wrong. Scottish surgeon John Bell, for example, asked, "Who would lose, for fear of pain, this intellectual being?"[60] In other words, it was reckless to deliberately endanger a patient's integrity by inducing coma. A third view was the common one that pain was good because it expedited healing.[61] Yet another medical opinion was that of London surgeon Benjamin Brodie, who believed that ether was a poison[62] – in the same way that Samuel Mitchill, in New York, was convinced that nitrous oxide was toxic.[63] Among non-medical individuals was Michael Faraday who, it is believed, wrote in 1818 advising against the use of ether because it had made one man unconscious for many hours.[64]

Fig. 3. Crawford Williamson Long (1815-1878).

As far as the conflicts within society are concerned, they arose mainly in the first three decades of the 19th century, when the new ideas about social reforms had the potential to reshape society. They ran the gamut of social issues: child labor, hours and conditions of work for adults in factories, conditions in mental hospitals and prisons, and slavery. The threat to the *status quo* was a potential source of conflict, as, too, were new ideas about pain. Was it, for example, not morally wrong, even ungodly, for human beings to take it into their own hands to try to abolish pain? Didn't God either punish or test us with pain? Fortunately for the good of those who suffered from pain, the writings of people like Bentham and Mill were able to influence society into taking a more positive view about pain management. But the belief that it was morally wrong for anyone to take active steps to obtund pain remained alive in society for years, and countless women in labor suffered as a result, even after anesthesia had been introduced. Religious thinkers and adherents took a very strong stand, as James Young Simpson found later when he used ether to relieve the pain of childbirth in 1848.[65] There were strong feelings on both sides, not all obstetricians opposing the clerics by any means. Eventually, the uproar died down somewhat after Simpson explained that the Biblical word 'sorrow' really meant 'effort,'[66] and more after John Snow anesthetized Queen Victoria in 1853 and again in 1857 with chloroform.[67]

Two other ethical issues generated conflict in society. One was antivivisection, which held back recognition of Hickman's work.[68] Many people in England were opposed to experimentation on animals, which may explain in part why Hickman appealed to the French, who had less marked distaste for animal research. The other issue was mesmerism, which was widely accepted and practiced in the 1830s and 1840s as a means of promoting painless surgery.[69] If mesmerism worked, why use a dangerous chemical like ether?

That may have been one of the reasons why Long did not immediately shout his message to the house tops. He feared that some of his colleagues would blame him for preferring dangerous ether to mesmerism. Those two sets of conflicts had to be resolved before progress could be made in society. They were resolved, though it took time. Not until the 1830s did the positive forces finally gain the upper hand, though, as Greene noted, this aspect of democratization and humanism occurred only in the West; there were no counterparts in Russian, Islamic, Hindu, and Far Eastern countries. By the 1840s the time was right for anesthesia to be introduced. The notes of caution sounded by Davy and Faraday did not seem to be followed by disaster and death when nitrous oxide and ether were used in recreational circumstances. It is therefore understandable that the delay in the introduction of anesthesia came to an end in the West, and in the 1840s.

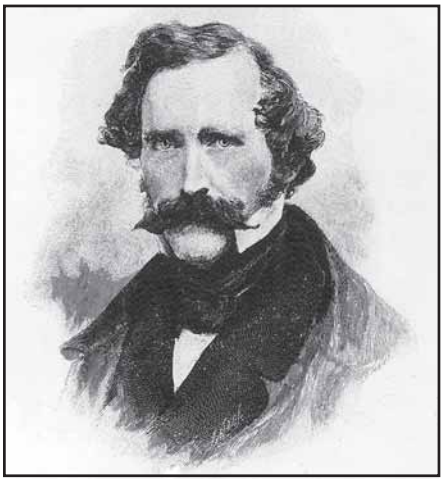

Fig. 4. William Thomas Green Morton (1819-1868).

Concluding Comment

For a new concept to be understood and accepted, the time and the circumstances have to be right. With respect to the introduction of anesthesia, the time was right in 1800, for physicians were familiar with both ether and nitrous oxide. Both had potent effects on the nervous system, and ether was an established therapeutic agent. The wherewithal for the introduction of anesthesia – the pharmacological knowledge, the substances themselves, and the equipment – was all available in 1800. The circumstances, however, were not entirely right. They were not right from the point of view of social attitudes, and they were not right medically. Surgeons were concerned about inflicting pain on their patients and some endeavored to diminish it. In 1767, Benjamin Gooch stated that pain was "a dreadful symptom …[and]the utmost attention is required to prevent or remove it,"[70] and in 1784 James Moore wrote *A Method of Preventing or Diminishing Pain in Several Operations*,[71] in part to describe his technique of compressing limb nerves and the consequent loss of feeling in the limb. However, his technique was not entirely efficacious. Davy had made a useful suggestion, but he urged caution that deterred attempts to pursue research on nitrous oxide.

Nor were the circumstances right even in 1824, when Hickman demonstrated the *principle* of anesthesia, even though he used carbon dioxide in animals. A short while before Hickman conducted his experiments, James Wardrop, another surgeon, in 1819 advocated induction of syncope and unconsciousness by means of bloodletting, withdrawing as much as 50 ounces of blood,[72] but this had no greater practical benefit than Moore's nerve compression. Nor had the circumstances as far as social reform changed significantly, and they would not do so until after the results of the reforms of the 1830s began to be evident.

Then the 1840s dawned. Even then, in 1842 the circumstances were not yet entirely suitable, for Long was circumspect about his own experience to make known his use of ether. His reluctance is understandable. Well trained, he wished to acquire a reasonable number of cases before reporting them, and that would take a while in a small town; ether was not regarded as safe as mesmerism. Ether was seen by many people as a recreational drug, used in 'ether frolics' – but which caused the analgesia and amnesia that did in fact serve as the basis for his use of it.[73]

So we come to William Morton (Figure 4) and 1846, when both the time and the circumstances finally were right. Only then did the delay in the introduction of anesthesia come to an end. But this fact raises a final point of some irony. On the one hand, we have to accept that 'failure' marked the endeavors of Davy, Hickman, Clarke, and Long as far as the introduction of anesthesia is concerned, even though they were sensitive individuals whose conduct and aspirations were motivated by a desire to diminish human suffering and by a vision of relief of pain in surgery to a varying degree. On the other hand, the efforts of Morton were marked by 'success,' even though he has never been regarded as conducting himself in a particularly ethical manner, and, to the contrary, being dubbed a 'tarnished idol.'[74] We therefore have another illustration of conflict: between the ethical nature and vision of pain relief of Davy, Hickman, and Long on one side and the entrepreneurial and task-orientation of Morton on the other. To give Morton his due, he did try to find an anodyne that would enable him to reduce the pain his dental patients suffered, even though his motive may have been to increase his practice and make a good living. The entrepreneurial pragmatism of Morton trumped the humane vision of Davy and Hickman and Long, too. The introduction of anesthesia came not as a fairy-tale ending but as the outcome for a more business-like search for an aid to success in dentistry. As such, it also illustrates the vagaries of history.

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19. A statement by Norman Bergman concerning Davy is illustrative: "the thought of patient comfort during surgical operations probably never crossed his mind at any stage of his life." (p. 278) Margaret Jacob and Michael Sauter argued similarly in stating, of Davy and the 18th-century Romantic movement (also discussed below) that "pain never became a serious part of their quest." (2002). In sharp contrast stands F.F. Cartwright, who stated unequivocally that Humphry Davy discovered anesthesia (Humphry Davy's contributions to anaesthesia, *Proc Roy Soc Med* 1950;43:571-78).

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INVITATION

Dear Colleagues,

It is certainly a privilege and a great pleasure to invite you to the ***7th International Symposium on the History of Anaesthesia (ISHA)*** *to be held on the island of Crete, October 1st to 3rd,* ***2009****.*

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Send abstracts, inquiries etc., to:

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