



Jointly Sponsored by the Medical College of Georgia Division of Continuing Education and the Anesthesia History Association

## **Anesthesia History Association 15<sup>th</sup> Annual Spring Meeting**

**April 16-18, 2009**



Augusta Marriott Hotel & Suites  
Two Tenth Street  
Augusta, Georgia 30901  
USA

Course Director  
William D. Hammonds, M.D., M.P.H.  
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Medical College of Georgia  
Augusta, Georgia



**MEDICAL COLLEGE OF GEORGIA  
DIVISION OF CONTINUING EDUCATION**

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**15<sup>th</sup> Annual Spring Meeting of the Anesthesia History Association  
April 16-18, 2009**

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Dr. Franklin L. Scamman.....owns stock in the following companies: Intuitive Surgical, Pfizer, Astra Zeneca, Stericycle, General Electric, IBM, and Gilead Sciences.

**The following planners and presenters do not have anything to disclose:**

Dr. Samuel Barros, Dr. George Bause, Dr. Jessica Booth, Ms. Caro Cassels, Dr. Ray Defalque, Dr. Adolph Giesecke, Dr. William Hammonds, Dr. Anthony Kovac, Dr. Patrick Laguerre, Dr. Katherine Macy, Dr. Jason McKeown, Dr. William McNiece, Dr. Don Nakayama, Dr. Olujemisi Odugbesan, Dr. Anup Pamnani, Ms. Norma Robinson, Dr. Raymond Roy, Dr. Mark Schroeder, Dr. David Shephard, Dr. Robert Strickland, Dr. Wendy Turner, Dr. David Wilkinson, Dr. Alexander Wolfson, and Mr. A. J. Wright.

# Anesthesia History Association 15<sup>th</sup> Annual Spring Meeting

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## **Schedule**

**Thursday, April 16, 2009**

### **Pre-Program**

8:45 AM – 10:00 AM      Tour of the Old Medical College  
*(optional)*

***Please meet in the lobby of the Augusta Marriott at 8:45 AM for a short drive to the Old Medical College. There is no charge for this tour.***

2:30 PM – 4:00 PM      Cruise of the Savannah River  
*(optional)*

***Please gather in the lobby of the Augusta Marriott at 2:30 PM for a two block walk to the dock where we will board the boat for the tour. The cost of the boat tour will be \$12.00. Cash only.***

### **Program**

3:30 PM – 5:00 PM      Early Meeting Registration  
*Outside Estes Exhibit Hall B*

6:00 PM – 7:00 PM      AHA Council Meeting  
*At the home of Dr. and Mrs. William Hammonds*

7:30 PM                      *Dinner at the home of Dr. and Mrs. William Hammonds*

**Friday, April 17, 2009**

7:00 AM – 7:45 AM      Meeting Registration and Continental Breakfast  
*Estes Exhibit Hall B*

7:45 AM – 8:00 AM      Welcome  
**Alvin C. Head, M.D.**  
Professor and Chair  
Department of Anesthesiology and Perioperative Medicine  
Medical College of Georgia

**Lois Taylor Ellison, M.D.**  
Medical Historian in Residence  
Provost Emeritus and Professor Emeritus of Medicine,  
Surgery, and Graduate Studies  
Medical College of Georgia

800 AM – 10:00 AM

Free Papers  
Session A  
*Estes Exhibit Hall B*

Moderator: **Robert A. Strickland, M.D.**  
Associate Professor  
Department of Anesthesiology  
Wake Forest University School of Medicine

“Managing Pain in Medieval England”  
**Wendy J. Turner, Ph.D.**  
Associate Professor  
Department of History, Anthropology and Philosophy  
Augusta State University

“Seishu Hanaoka (1760-1835)”  
**Don Nakayama, M.D., M.B.A., F.A.C.S.**  
Chair  
Department of Surgery  
Mercer University School of Medicine

“Introduction of Anesthesia is Like a Diamond with Many Facets”  
**Adolph H. Giesecke, M.D.**  
Professor of Anesthesiology Emeritus  
University of Texas Southwestern Medical Center

“Why was there a Four-Decade Delay, from 1800 to 1842, in the Advent of Anesthesia?”  
**David Shephard, M.D.**

“First Spinal Anesthesia for Obstetrics in the American Continent”  
**Samuel Barros, M.D.**  
Servicio de Anestesiología  
Hospital Clínico FUSAT

“Tins Amongst Silver and Gold: America’s First Mass-Produced Ether Inhalers”  
**George S. Bause, M.D., M.P.H.**  
Honorary Curator  
Wood Library-Museum of Anesthesiology  
Clinical Associate Professor  
Case Western Reserve University

10:00 AM – 10:30 AM

Break

10: 30 AM – 12:00 PM

Free Papers  
Session B  
*Estes Exhibit Hall B*

Moderator: **Robert A. Strickland, M.D.**

“Intravenous Administration of Ether, Methoxyflurane, and Halothane”  
**Raymond C. Roy, M.D., Ph.D.**  
Professor  
Department of Anesthesiology  
Wake Forest University School of Medicine

and

**Robert A. Strickland, M.D.**

Associate Professor  
Department of Anesthesiology  
Wake Forest University School of Medicine

“Therapeutic Spinal Anesthesia—Historical Perspective”

**Patrick Laguerre, M.D.**

Resident  
Department of Anesthesiology  
Wake Forest University School of Medicine

and

**Raymond C. Roy, M.D., Ph.D.**

“A Heptad of Hoosiers—Indiana University and  
Anesthesiology”

**William L. McNiece, M.D.**

Director of Pediatric Anesthesia  
Gopal Krishna Associate Professor of Pediatric Anesthesia  
Department of Anesthesiology  
Indiana University School of Medicine

“Anesthesia for the First Heart Transplant”

**Franklin L. Scamman, M.D.**

Professor  
Department of Anesthesia  
University of Iowa

12:00 PM – 1:30 PM

Lunch  
*Estes Exhibit Hall A*

“An update on the Crawford Long Museum”

**Lesa H. Campbell**

Co-Owner, Campbell Consulting  
Museum Projects Manager, City of Jefferson

1:30 PM – 3:00 PM

The C. Ronald Stephen Resident Essay Contest  
*Estes Exhibit Hall B*

Moderator: **William D. Hammonds, M.D., M.P.H.**

Professor, Anesthesiology & Perioperative Medicine  
Medical College of Georgia

“From the Killer Bean of Calabar to Neostigmine: The History  
of Anticholinesterases and their Use in Anesthetic Practice”

**Oluyemisi M. Odugbesan, MPA, M.D.**

Resident in Anesthesiology  
University of Nebraska Medical Center

“Charles Nathan Combs, M.D.: A Portrait of an Anesthesia  
Advocate”

**Katherine M. Macy, M.D.**

Fellow in Pediatric Anesthesiology  
Riley Hospital for Children  
Indiana University School of Medicine

“The Reluctant Anesthesiologist: Dr. Joseph Artusio and the  
early days of the Physician Anesthetist”

**Anup Pamnani, M.D.**  
Resident in Anesthesiology  
New York-Presbyterian Hospital/Weill Cornell Medical Center

3:00 PM – 3:30 PM

Break

3:30 PM – 5:00 PM

Free Papers  
Session C  
*Estes Exhibit Hall B*

Moderator: **William L. McNiece, M.D.**

“Rectal Ether Anesthesia: A Technique Evolves and Finally Disappears”

**Robert A. Strickland, M.D.**

“Open Flames in Operating Rooms”

**Raymond C. Roy, M.D., Ph.D.**, and **Robert A. Strickland,**

**M.D.**

“Anesthesia and Surgical Aspects of Base Hospital #28 from Kansas City and the University of Kansas in World War I”

**Anthony L. Kovac, M.D.**

Professor  
Department of Anesthesiology  
University of Kansas Medical Center

“TNS Before it was Named TNS”

**Jessica L. Booth, M.D.**

Resident  
Department of Anesthesiology  
Wake Forest University School of Medicine

and

**Raymond C. Roy, M.D., Ph.D.**

7:00 PM

Banquet Dinner  
*Estes Exhibit Hall A*

“The History of the Medical College of Georgia with References to the Beginning of Anesthesia”

**Russell R. Moores, M.D.**

Professor of Medicine  
Section of Hematology/Oncology  
Department of Medicine  
Medical College of Georgia

**Saturday, April 18, 2009**

7:00 AM – 8:00 AM

Continental Breakfast  
*Estes Exhibit Hall B*

8:00 AM – 10:00 AM

Free Papers  
Session D  
*Estes Exhibit Hall B*

Moderator: **William D. Hammonds, M.D., M.P.H.**

“The Legacy of Dr. Gunter Corssen”

**Jason L. McKeown, M.D.**  
Assistant Professor  
Department of Anesthesiology  
University of Alabama at Birmingham

“Speed in Hitler’s German” Methamphetamine 1938-45”

**Ray J. Defalque, M.D.**  
Professor  
Department of Anesthesiology  
University of Alabama at Birmingham

and

**A.J. Wright, M.L.S.**  
Associate Professor and Clinical Librarian  
Department of Anesthesiology  
University of Alabama at Birmingham

10:00 AM – 10:30 AM

Break

10:30 AM to 11:30 AM

Free Papers  
Session D (continued)  
*Estes Exhibit Hall B*

“Ralph M. Waters’ Florida Retirement Rest”

**Mark E. Schroeder, M.D.**  
Associate Professor  
Department of Anesthesiology  
University of Wisconsin School of Medicine and Public

Health

“Katharine Georgina Lloyd-Williams 1896-1973: A Life of  
Extraordinary Contribution”

**David J. Wilkinson, M.B., B.S., F.R.C.A.**  
Fifth Laureate of Anesthesia History  
Emeritus Consultant Anaesthetist  
Boyle Department of Anaesthesia  
St. Bartholomew’s Hospital

“Dr. Robert Hanham Collyer: The Strange Life of a  
Mesmerist, Phrenologist and Ether Controversy Jump-Up-  
Behinder”

**A.J. Wright, M.L.S.**

## First Spinal Anesthesia for Obstetrics in the American Continent

Samuel Barros, M.D.  
Servicio de Anestesiología, Hospital Clínico FUSAT  
Representative, History Committee of the Chilean Society of Anesthesia  
Rancagua, Chile

The first spinal anesthesia (SA) for general surgery was done by Bier in Kiel, August 16, 1898, and published on April 1899. It is well known that the first use of spinal anaesthesia for obstetrics was published by Oscar Kreis, on July 1900, with six cases.<sup>1</sup> This novel type of anesthesia was used very soon in France, and reports were done by Doléris and Malartic, on July 17, with five cases,<sup>2</sup> and by Jean Dupaigné on August 28, both in 1900.<sup>3</sup>

In the American continent, it is said that SA was used for the first time in obstetrics in USA by S. Marx, who reported six cases in the New York Medical News on August 25, 1900, and "over 40 cases of labor" in *The Philadelphia Medical Journal*, November 3, 1900.<sup>4</sup> William Ridgely Stone read before the Buffalo Academy of Medicine on November 27, 1900, an original communication about "Cocainization of the spinal cord by means of lumbar puncture during labor", saying that "it has been but little over three months since I did my first injection."<sup>5</sup>

In Chile, southernmost country of the world, the first SA for labor was done by Dr Alcibiades Vicencio Tholar, on June, 1900. He presented his first report, with 16 cases, at the monthly meeting of the Medical Association, on July 10.<sup>6</sup>

Dr. Vicencio was born in Santiago de Chile, April 22, 1859. His father was José Vicencio and his mother, of English origin, Catherine Tholar. He received his medical degree on May 28, 1883. The following year he was commissioned by the Chilean government to go to Germany for three years, to study gynecology and obstetrics. When he came back, his main activity was at the maternity unit of the San Francisco de Borja Hospital. In 1899, he was sent again to Europe and during his stay in Germany he knew about the use of spinal anaesthesia for surgery, from the papers of Bier and Tuffier. After returning from Europe, he used spinal anesthesia in his obstetrical patients on June 1900. Cocaine was used on the first patients, changing later to eucaine, considered less toxic.

After a visit of Gen. Baden-Powell to Chile, Dr. Vicencio was the founder and first President of the Boy-Scouts Movement, the first group of this kind created outside England. He died at the age of 54 on April 30, 1913. Dr. Kreis did his first spinal for obstetrics on June 8, 1900. Dr. Vicencio did it on June 15, just one week later, so he may be considered one of the firsts in the world, and perhaps the first in the American continent to use spinal anesthesia for pain relief in normal labor.

### References:

1. Caton D. *International Congress Series* 1242 (2002):173-176.
2. Doléris et Malartic. *Académie de Médecine* (1900) July 17.
3. Dupaigné J. *Académie de Médecine* (1900) August 28.
4. Marx S. *Philadelphia Med J* (1900) November 3.
5. Stone W. *R. Am. J. Obst* (1901) February 43; 2:857-859.
6. Ramírez. *Bol Soc Chil Obst Ginec* (1936) 1:338-342.



## Tins Amongst Silver and Gold: America's First Mass-Produced Ether Inhalers

George S. Bause, M.D., M.P.H.  
Honorary Curator, Wood Library-Museum of Anesthesiology  
Clinical Associate Professor, Case Western Reserve University  
Cleveland, Ohio

**Research Problem:** Investigate America's first significant mass-produced ether inhaler

**Methodological Approach:** Review of original and copied sources (serials, patents, etc.)

**Sources:** The U.S. Patent and Trademark Office, Washington, D.C. The Register of Wills of the City of Philadelphia, Pennsylvania. Newspaper archives in Philadelphia, Pennsylvania; San Francisco, California; and Panama. Archives and libraries at the American Dental Association, Chicago, Illinois; Grand Valley State University, Allendale, Michigan; the Massachusetts Historical Society, Boston, Massachusetts; the New York Historical Society, New York, New York; the University of North Carolina, Chapel Hill, North Carolina; the University of Pennsylvania, Philadelphia, Pennsylvania; and the Wood Library-Museum of Anesthesiology, Park Ridge, Illinois.

**Abstract:** After earning his M.D. from the University of Pennsylvania in 1830, Lewis Roper pursued dentistry vocationally and both photography and numismatics avocationally. After contesting in Philadelphia the legality of W.T.G. Morton's "Letheon" royalties, Roper began designing ether inhalers. Unexpectedly, by December 2, 1848, both of Roper's young daughters had died from diphtheria. In a cruel coincidence on that same day, Roper's intellectual offspring, his U.S. Patent for an "apparatus for administering ether," was announced by *Scientific American*.<sup>1</sup> On the day that the Roper girls' death notices were published, U.S. President James Polk announced the "abundance of gold" in California. As a Philadelphia tinner fashioned Roper Ether Inhalers, their inventor left his wife behind in Philadelphia and sailed to San Francisco to become yet another "Forty-Niner." Sadly, Roper's Gold Rush fortune never panned out, and a second business venture collapsed. The hapless Roper died at sea attempting to sail home from California. His estate auctioned off his tin ether inhalers, his silver-based photographic apparatus, and his spectacular collection of gold coins. In 1861, Dr. Charles T. Jackson cited the Roper Ether Inhaler as "by far the best," and noted that it would also "serve for...chloroform, or the mixture of ether and chloroform."<sup>2</sup>

### References:

1. Roper L: Apparatus for administering ether. US Patent 5850, October 10, 1848.
2. Jackson, Charles T. *A Manual of Etherization: Containing Directions for the Employment of Ether, Chloroform, and Other Anaesthetic Agents, by Inhalation, in Surgical Operations, Intended for Military and Naval Surgeons, and All Who May Be Exposed to Surgical Operations; with Instructions for the Preparation of Ether and Chloroform, and for Testing Them for Impurities. Comprising, Also, a Brief History of the Discovery of Anaesthesia.* Boston: J. B. Mansfield, 1861.

## TNS before it was Named TNS

Jessica L. Booth, M.D., and Raymond C. Roy, M.D., Ph.D.  
Department of Anesthesiology  
Wake Forest University School of Medicine  
Winston-Salem, North Carolina

In 1993 Schneider, et al., published a case report purportedly describing the first cases of transient neurological syndrome (TNS). TNS is characterized by radicular back or leg pain that appears 12-24 hours after resolution of a subarachnoid block and lasts up to 5 days.<sup>1</sup> Numerous case reports and clinical studies of TNS have subsequently appeared. Although lidocaine, in either hypo-, iso-, or hyperbaric solutions, is the most frequently reported offender, TNS can be caused by other local anesthetics.<sup>2</sup> Hyperbaric lidocaine was introduced into clinical use in 1948. We propose that several "TNS equivalent" descriptions appeared between 1948 and 1993 associated with lidocaine and as early as 1905 with other local anesthetics.

In 1905 it was reported that 12 of 27 gynecologic patients suffered "quite serious symptoms some days after the spinal injection [of stovaine], such as severe headache, ocular and spinal pains ... On the average the symptoms came two days after the injection, at times the spinal pain came on at the end of twelve hours..."<sup>3</sup> Sebrechts, who published detailed observations based on more than 40,000 spinal, described in 1934 "rachialgias" lasting several days post-operatively after subarachnoid injections of percaïne [dibucaine].<sup>4</sup> He proposed that these frequent symptoms of pain were caused by "a certain meningeal reaction." A case reported in 1952 described a gentleman who was administered spinal anesthesia for a sacral pilonidal cyst. He described paresthesias in both legs that began immediately post-operatively, lasted one week, and resolved spontaneously.<sup>5</sup> In 1969 a prospective review of 10,440 spinal anesthetics revealed 284 patients complained of transient back pain that was so severe that 91 patients would not recommend spinal anesthesia again.<sup>6</sup> Although more reports may exist in the literature, there is certainly evidence that TNS existed prior to 1993.

Although the mechanism for TNS is still not known, there is probably a final common pathway for all cases.<sup>7</sup> Explanations of why TNS was not recognized as a distinct clinical phenomenon until 1993 will be proposed.

### References:

1. Schneider M, Ettlin T, Kaufmann M, Schumacher P, Urwyler A, Hampl K, von Hochstetter A. Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. *Anesth Analg* 1993;76:1154-7.
2. Aguilar JL, Pelaez R. Transient neurological syndrome: does it really exist. *Curr Opin Anaesthesiol* 2004;17: 423-6.
3. "Spinal Stovainization in Gynecology." *The Medical News. A Weekly Medical Journal* September 23, 1905;87:603-4.
4. Sebrechts J. Spinal Anaesthesia. *Br J Anaesth* 1934;12:4-29.
5. Arner O. Complications following spinal anesthesia: Their significance and a technic to reduce their incidence. *Acta Chir Scand* 1952;167:7-145.
6. Phillips OC, Ebner J, Nelson AT, Black MH. Neurologic complications following spinal anesthesia with lidocaine: A prospective review of 10,440 cases. *Anesthesiology* 1969;30:284-9.
7. Umbrain V, Shi L, Lauwers M-H, Smolders I, Michotte Y, Camu F. Intrathecal lidocaine elevates prostaglandin E2 levels in cerebrospinal fluid: a microdialysis study in freely moving rats. *Br J Anaesth* 2008;101:717-22.

## Speed in Hitler's Germany: Methamphetamine 1938-45

Ray J. Defalque, M.D., and Amos J. Wright, M.L.S.  
Department of Anesthesiology  
University of Alabama at Birmingham  
Birmingham, Alabama

Synthesized by Ogata in 1919, methamphetamine was "re-invented" in 1937-8 by the Temmler Firm pharmacologist F. Hauschild who discovered its CNS and (lesser) CV stimulating actions. In 1938 the firm patented the drug as Pervitin (P) and released it on the German market. Cheap & sold OTC, it immediately became immensely popular with pleasure seekers (euphoria) and night workers (fatigue). By the end of 1939, physicians had reported brilliant successes in a variety of diseases (uncontrolled trials). Despite denials by the firm & most investigators, there were a few reports of abuse and addiction.

Dr. L. Conti, the Reich Health Minister, obsessed with protecting the "Volk's" health, warned physicians of P's dangers and in November 1939 ordered it sold by prescription only. Under his prompting, Dr. E. Speer, an influential psychiatrist, reviewed the literature and his experience and in January 1941 published his conclusions: P was useless in most medical conditions, dangerous when used for fatigue, and highly addictive. On July 1, 1941, Conti placed P on the list of controlled drugs with threats of severe penalties but with a waiver for researchers and army physicians. This, along with war-induced production problems, led to a marked decrease of P use by civilians at the end of WW2.

The use of P in the Wehrmacht significantly exceeded its civilian use. At the request of the Medical Inspector (Chief MO) Col. Prof. O. Ranke tested P on medical cadets while reviewing the results of the Dortmund Institute of Work Physiology. Ranke also distributed large amounts of samples to the MOs of motorized troops during the Polish and French campaigns. Reviewing all his findings, Ranke concluded that P was useful in exceptional, life-threatening cases of fatigue (driving accidents), but should be used sparsely and always under control of an MO. P was then accepted by the Wehrmacht's Medical Chief S. Handloser (Directive, April, 1941), provided it be used along Ranke's recommendations. There is good evidence that those recommendations were ignored and that large amounts of P were distributed by officers to their troops escaping the Russians. A morphine-pervitin preparation was also widely used for the evacuation of wounded soldiers.

Large amounts of P were also used in the Navy, but not in the Air Force. SS physicians also tested P for hunger, fatigue and hypoxia on inmates of concentration camps.

Two famous WW2 P addicts were H. Boell, the 1972 Nobel Prize of Literature, and E. Udet, the Luftwaffe general who introduced the "Stuka". He shot himself in 1941. The use of P by Hitler remains a controversial topic.

The post-WW2 fate of the firm Temmler and of Conti, Ranke, Handloser & Hauschild will be presented.

### Bibliography:

1. Neumann A. *Arztum ist immer Kaempfertum*. Duesseldorf, Droste Verlag, 2005:260-6.
2. Unger F, Hartmann V. Einsatz von Pervitin in deutschen Heer im 2. Weltkrieg. *Wehrmed Monatschr* 1994;38:374-81.
3. Tschimer M, et al., edit. *Wissenschaft im Krieg, Krieg in der Wissenschaft*. Marburg, Eigen Verlag, 1990:258-66.
4. Kudlien F. *Aerzte im Nationalsozialismus*. Koeln, Kieperhauser & Witsch, 1985:167-74.

## Introduction of anesthesia is like a diamond with many facets

Adolph H. Giesecke M.D.  
Emeritus Professor, Anesthesiology and Pain Management  
University of Texas Southwestern Medical Center  
Dallas, Texas

Anesthesia is one of the most valued discoveries in all of history. The grim thought of a being awake while a surgeon amputated a breast or sawed through bones, is frightful to contemplate. The ability to put an end to this kind of pain is certainly one of the greatest gifts that any man ever gave to his fellows. Scholars have been preoccupied for decades with heated discussions of "Who was first?"

The introduction of anesthesia can be compared to a beautiful diamond with many facets. One facet is the first public demonstration of ether anesthesia in Boston October 16, 1846, by Morton. A second facet is the first use of ether anesthesia for a surgical procedure by Crawford Long of Georgia on March 30, 1842. A third facet is the public demonstration of nitrous oxide anesthesia at Massachusetts General Hospital by Horace Wells in January 1844 which was only considered successful in retrospect. A fourth facet is the claim by Jackson that he suggested to Morton that ether was a more potent drug than nitrous oxide and therefore the credit for the discovery should be his. Most historians give the credit to Morton because news of his demonstration spread rapidly around the developed world and offered relief to thousands of patients.

However, another facet of the jewel has emerged from across the Pacific Ocean in the Land of the Rising Sun, where Dr. Seishu Hanaoka used an oral concoction of herbs, which he called "Tsusen-San" to induce general anesthesia for the excision of breast cancer in a 60-year-old woman named Kan Aiya on October 13, 1804. This was 38 years before Long and 42 years before Morton. The details of the case were carefully documented in a book which resides in the library of Tenri University, Japan.<sup>1</sup> Hanaoka performed over 400 surgical procedures using his herbal anesthesia. These cases have been recorded in several books called "Rare Diseases Treated by Hanaoka." The Wood Library-Museum has acquired a copy published in about 1850. Hanaoka required 20 years of careful research to develop the ingredients of his Tsusensan. His contribution to the introduction of anesthesia should be recognized and studied.



Dr. Seishu Hanaoka (1760-1835), the Great Master of Surgery and Anesthesia. Picture is from a scroll portrait of Hanaoka in the Wood Library Museum of Anesthesiology.

### Reference:

1. Matsuki A. New studies on the history of anesthesiology – a new study on Seishu Hanaoka's "Nyugan Ckiken Roku" (a surgical experience with breast cancer). *Masui* 2000;49(9):1038-43.

# Anesthesia and Surgical Aspects of Base Hospital #28 from Kansas City and the University of Kansas in World War I (WW I)

Anthony L. Kovac, M.D.  
Kasumi Arakawa Professor of Anesthesiology  
University of Kansas Medical Center  
Kansas City, Kansas

**Research Problem:** Analysis of anesthesia techniques used at a WW I Base Hospital

**Sources:** National WW I Museum archives, Kansas City, MO; Wood Library-Museum of Anesthesiology, Park Ridge, IL; Clendening and Dykes Library, University of Kansas Medical Center, Kansas City, KS; Google internet search

**Methodological approach:** archival, library and internet web research

Base Hospital #28 was a 2,500 bed general hospital recruited from the Kansas City area in 1917 and operated at Limoges, France, from July 1918 until May 1919.

Of 2,511 total admissions, 2,066 surgeries were performed for gun shot wounds (GSWs). Other surgeries were 178 for ENT procedures, 53 eye surgeries and 1,774 dental cases. Total deaths were 23, including 17 non-operative and 6 operative.

The majority of cases were general anesthesia provided by one anesthesiologist and three corpsman anesthetists. The type of anesthesia selected depended on the type of patient, surgery or anesthesia required for treatment. For preop meds, morphine (1/6 grain) and scopolamine (1/150 grain) were commonly given IM ½ hour before surgery.

Military surgeons were trained and skilled in the application of tourniquets and ligation of arteries to stop hemorrhage in severely bleeding patients. As all patients were triaged, special areas were available for the treatment of shock, hypothermia, and acidosis. If patients were in shock, regional local anesthesia with novocaine was used and was best for short surgeries of ½ to 1 hour duration. In order to minimize the effect of surgical shock, Dr. George Crile's anoci-association method was used with a balanced anesthetic technique of IM morphine, inhalation nitrous oxide/oxygen and local block.

Other general anesthesia techniques included the use of nitrous oxide/oxygen mixtures, chloroform, ether, or ethyl chloride. The Connell brass war SP model (officer's version, 1917) was commonly used by US and French forces and enabled delivery of nitrous oxide/oxygen mixtures. The Heidbrink anesthetizer machine allowed simultaneous administration of nitrous oxide and oxygen via a rebreathing bag, which equalized oxygen and nitrous oxide pressures via pressure reducing valves.

General anesthesia with a combination of chloroform and ether was administered by the drop method via masks. As chloroform had a rapid onset and better patient tolerability, it was initially given more often than ether for anesthesia induction. Chloroform given first by Schimmelbush mask, used a single layer of gauze followed by a second mask for ether, with two gauze layers. Patients breathed spontaneously without assistance. Oxygen was available for treatment of hypoxia and cyanosis.

## References:

1. de Tamowsky G. Military Surgery of the Zone of the Advance. (Medical War Manual #7) Lea & Felbegin, Philadelphia 1918. pp 71-86.
2. Crile GW. Nitrous oxide anaesthesia and a note about Anoci-Association, a new principle of operative surgery. *Surg Gynecol Obstet* 1911;13:170-3.
3. Clarke T. Anesthetics in military hospitals. *Am J Surg (Anes Suppl)* 1913;32:134-5.
4. Gwathmey JT. Anesthesia During the World War: in *Anesthesia*, The Macmillan Company, New York and London, 1924, pp 688-703.

## Therapeutic Spinal Anesthesia – Historical Perspective

Patrick Laguerre, M.D., Raymond C. Roy, M.D., Ph.D.  
Department of Anesthesiology  
Wake Forest University School of Medicine  
Winston-Salem, North Carolina

Ever since introduction of spinal anesthesia in the late 19<sup>th</sup> century, the intrathecal injection of local anesthetics has been used to treat non-surgical illnesses. Direct injection of local anesthetic into cerebral spinal fluid allows a relatively small dose of local anesthetic not only to block afferent and efferent pain pathways involved in intractable pain syndromes but also efferent autonomic transmission and sympathetic overactivity associated with strychnine poisoning,<sup>1,2</sup> tetanus,<sup>3,4</sup> hyperthyroidism,<sup>5</sup> and congestive heart failure.<sup>6</sup>

Strychnine poisoning is also successfully treated by intrathecal treatment of eucaïne. It may be necessary to give a general anesthetic to relax the opisthotonos before performing the spinal puncture.<sup>2</sup>

Spinal anesthesia is not administered with the purpose of providing or even assisting the anesthesia for the surgical procedure. The purpose is solely to anesthetize the part of the sympathetic nervous system which innervates the adrenal glands, and therefore, to reduce the secretion of epinephrine both immediately before operation and as a result of the increase in thyroxin in the circulation as a result of manipulation of the gland.<sup>5</sup>

Dr. Rovenstine, Dr. Farr and I treated a number of patients in pulmonary edema with spinal anesthesia...<sup>6</sup>

The objective of this paper is to present a history of early attempts to apply spinal anesthesia therapeutically and compare with current practice.

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## Charles Nathan Combs, M.D.: A Portrait of an Anesthesia Advocate

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“Anesthesia, than which no more precious gift was ever granted humanity, has been long in coming into the dignity it rightfully deserves, and it is only within the last few years that it has unfolded into a specialty of the highest importance.”<sup>1</sup> Charles Nathan Combs, M.D. spoke these bold words before the Indiana State Medical Association in 1908. He championed the cause of anesthesia being recognized as a medical specialty in its own right and wrote several papers advocating such. He passionately wrote about professionalism, continuing medical education, and an appreciation of history. During his medical career he was able to experience the satisfaction of seeing his dreams fulfilled as anesthesia did develop into a dignified specialty of utmost importance. Charles Nathan Combs was indeed a man ahead of his time.

Combs was born June 7, 1879, in Mulberry, Indiana, a small town fifty-five miles north-northwest of Indianapolis. He was no stranger to medicine. His older brother and father-in-law were physicians and eventually his own son would become a doctor. Combs graduated from Indiana University in 1900 and obtained his medical degree from the Medical College of Indiana in 1903. He started a general medical practice in Terre Haute, Indiana, in 1904 and quickly became interested in anesthesia under the preceptorship of Stephen Young, M.D. Young witnessed one of the first ether administrations in the Midwest in 1851 while a student in Cincinnati.<sup>3</sup> Young had a general medical practice in Terre Haute before limiting his practice to anesthesia in 1899. Combs was one of only four Hoosier physicians who were members of the American Association of Anesthetists in 1914.<sup>4</sup> He took postgraduate courses in 1916, studying anesthesia under [Elmer] McKesson, M.D., at Flower Hospital in Toledo.<sup>2</sup> Combs spent one year (1918-1919) enrolled in the Medical Reserve Corps in the army, during which he traveled to England and France. By 1921 he identified himself as solely practicing anesthesia.<sup>5</sup>



Charles Nathan Combs, M.D.  
(Image courtesy of the Wood  
Library-Museum)

Combs' passion for his medical profession was obvious through his involvement in multiple medical societies.<sup>2,5,7</sup> He was long a proponent of the local county medical societies and at various times served as secretary, vice-president, and president of the Vigo County (Terre Haute, IN) Medical Society. Combs also served at one point as president of the Terre Haute Academy of Medicine and the Aesculapian Society of the Wabash Valley. His involvement in the Indiana State Medical Association included a fifteen-year stint as secretary and a one-year term as president in 1926. Combs also served as chairman of the state's Section of Anesthesia in 1935, the same year he was secretary of the AMA's anesthesia section. He had been a delegate to the AMA two previous years. Combs had also been president of the Mid-Western Association of Anesthetists. He was a fellow with the American College of Anesthesiologists, American Society of Anesthetists, and the International College of Anesthetists. In 1939, Combs became a Diplomate of the American Board of Anesthesiology. He was deemed an honorary member of the Indiana Society of Anesthesiologists in 1950.

Amazingly, Combs also served Union Hospital in Terre Haute as secretary, president, superintendent, and medical director. He eventually became director of Indiana Blue Cross Hospital and was a member of the Indiana Advisory Hospital Planning Council. Impressive does not begin to describe the resume of this Hoosier physician.

Combs' presentation one hundred years ago to the Indiana State Medical Society demonstrated an enviable dedication and enthusiasm for the specialty he loved.<sup>1</sup> He stressed the importance of the anesthetist being a specialist, as opposed to an intern, family doctor, or nurse, all of whom were more likely to be interested in the surgery at hand rather than the patient. Combs was realistic and understood the lack of clinical training was a deterrent and he warned that those who chose this field may undergo "years without glory and with insufficient recognition."<sup>1</sup> So why would one want to enter this field? Simply for the love of the job, that is, protection of the patient. He listed the qualifications of a good anesthetist including the abilities to focus solely on the patient's condition, to calm a patient's fears, to display good judgment in the balance of ether administration, to be level-headed in times of crisis, and to know the dangers of complacency. Combs repeatedly stressed that anesthesia cannot be performed in a cookie cutter fashion as each case is unique in its anesthetic needs. He astutely attributed part of the famous Mayos' success to having specialized anesthetists that greatly decreased the mortality and morbidity of their cases. Every hospital was urged to have at least one physician dedicated to anesthesia. Combs also exhorted the surgeon and family doctor to select only specialists to perform the anesthetic so the patient might have the best possible outcome. He mused of a future time when the patient would choose his own anesthetist and pay him a specific fee. Combs expressed the need to push forward and not be content with current practices. "...while a beneficent Deity may never allow us to find a perfect anesthetic, lest we misuse the boon, yet we will not be satisfied short of the very best we can discover."<sup>1</sup>

How is the anesthetist to interact with the patient? Combs promoted a personalized approach.<sup>1,8,9,10,11</sup> According to him, the anesthetist should visit the patient the day before surgery to obtain a thorough physical exam and history, focusing on previous anesthetic history and any pulmonary, cardiac, or renal disease. However, one of the main goals of this visit was to gain the patient's confidence, discuss his fears, and explain how the anesthetic will be performed. Thus the patient would arrive in the operating room comfortable that he was in the hands of one looking out for his best interests. This prevention of "psychic shock" was highly important for a successful anesthetic. Once in the OR, focus on patient comfort was to continue. The anesthetist was to make sure the bed was well padded. Nitrous oxide could be given initially during induction to blunt the response of the strong ether. Another option was to place a few drops of essence of orange in the mask to help minimize ether's pungency. Once the patient was induced and surgery had begun, the anesthetist's job was far from over. Combs stressed he must remain vigilant. The anesthetist should pay attention as to progression of the surgery and anticipate the more stimulating parts so more ether could be dropped. On the other hand, ether should be slowed down during less stimulating times so as to avoid overdose. The patient's color and respirations should be monitored. If needed, a jaw thrust or pharyngeal tube should be inserted to relieve obstruction. At the conclusion of the operation, the anesthetist should accompany the patient back to his room.

What should the surgeon-anesthetist relationship look like? Combs advocated a team approach built upon mutual respect.<sup>1,8</sup> The two should have a rapport and understanding of each other such to minimize the need for conversation. The surgeon should focus on his surgery and trust the anesthetist to care for the patient. Combs quipped that there should be a sign at the head of the table that says, "Don't talk to the motorman."<sup>1</sup> The anesthetist should know when to ask for help from the surgeon if the patient is in dire straits, and the surgeon should trust this judgment. On the other hand, the anesthetist should not bother the surgeon with every concern for the patient. Combs stated, "If he is diffident or uncertain in the use of his armamentarium or if he is an alarmist, he is nothing but a fly in the surgeon's ointment."<sup>1</sup> Combs' view of the team approach was evident as he explained the situation in which the patient appears to be heading down the slippery slope of shock. Before the blood pressure gets too low, "the anesthetist should speak to the surgeon, and the two plan the remainder of the operation with the view of preventing what is otherwise unavoidable, and probably fatal shock."<sup>8</sup> Combs' belief in specialties working together for the benefit of the patient spilled out of the operating room.<sup>12</sup> In 1916, he and surgeon Dr. Leo Weinstein opened the Associated Physicians & Surgeons Clinic, which included services from surgery, anesthesia, family medicine, and radiography and laboratory. This clinic still exists today and offers comprehensive medical care from a wide range of specialties. It has grown to include AP&S clinics in eight counties covering two states.



Persisting in his goal to see anesthesia as a respected and distinct medical specialty, Combs penned an article in 1925 titled "The Anesthesia Department of a Hospital."<sup>9</sup> He once again stressed the importance of trained anesthetists being the cornerstone of a respectable institution, as poor surgical outcomes leads to poor reputation. Just as an untrained surgeon would not be acceptable at such an institution, neither should an untrained anesthetist. Combs also strongly yet tactfully argued against allowing a nurse anesthetist as the primary anesthetist. In his view, nurses could certainly possess many qualities of a good anesthetist, but the physician's extra training in physiology, pathology, and pharmacology gave them the advantage of "self-reliance, judgment and masterful poise in times of peril."<sup>9</sup> Of utmost importance to Combs was that every hospital should have a Department of Anesthesia headed by a physician specialist in anesthesia. The minimum standards for this department should include a selection of ether and ether masks, a gas-oxygen apparatus, a closed ether machine, ethyl chloride, chloroform, local anesthesia, and pharyngeal tubes. Patient safety measures were to involve preventing psychic shock, acidosis, pneumonia, backache, paralysis, and anesthesia and surgical shock. "Shock is prevented rather than treated."<sup>9</sup> Documentation was also vital and Combs promoted regular charting of pulse, respiration, pupil condition, skin color, and in severe cases, blood pressure. Amount and type of anesthesia given, time for induction and maintenance, degree of relaxation, surgical risk classification, and any anesthetic morbidity or mortality were also encouraged to be recorded.

In 1928, Combs celebrated twenty-five years of practice and took time to reflect on the progress of anesthesia during that quarter of a century.<sup>3</sup> He would serve as president of the Mid-Western Association of Anesthetists in 1929 and he presented "The Ascendency of Anesthesia in Its Public and Professional Relation" as his presidential address. Combs gave this address while attending the Seventh Annual Congress of Anesthetists in 1928. He expressed genuine excitement as it had come to fruition that new medical graduates were entering anesthesia as a well-organized and established profession in its own right. As Combs stated, "I have witnessed the pageant of another Cinderella emerging from the hearth as the poor handmaiden of Surgery and seen her blossom forth as the Princess of an independent research organization."<sup>3</sup> He recollected being a charter member of the American Association of Anesthetists and attending their inaugural meetings in 1912 and 1913, where he heard papers on intratracheal anesthesia, gasometer insufflation, and oxygen therapy. Combs exhorted the progress anesthesia had made around the globe and noted Canada, England, Australia, and New Zealand as other countries forging anesthesia societies. Research in anesthesia was progressing and there were at least four journals throughout the world dedicated to that end. Numbers had sprung from a group of around fifty anesthetists twenty-five years prior to around three thousand across the globe. Combs stressed that despite the amazing advancements that had been made in anesthesia, the best was yet to come. "It is my wish that we should sometime soon realize this prophetic hope – that among all the specialties of medicine none shall be more truly exalted and none more divine than anesthesia, and that it may describe not an ellipse, but a parabola – a never ending orbit of usefulness."<sup>3</sup>

Not only did Combs eagerly await future advances, he was well aware of lessons to be learned from history. His appreciation of history was evident from his membership in local and state historical societies.<sup>6</sup> An article he wrote in 1909 urged the secretary of the local medical society to take it upon himself to become a medical historian.<sup>13</sup> Combs listed multiple ways of preserving and recording medical data. He admitted such a task may seem overwhelming, but its accomplishment would later reveal itself to be "priceless." Combs himself was no stranger to recording histories. He authored histories of medicine in Vigo County, of the Aesculapian Society, of Union Hospital, of community theater in Terre Haute, and of the Indiana State Medical Association.<sup>6,7</sup> In 1944, Combs presented "The First Nitrous-Oxide Anesthesia Administered By Dr. Horace Wells, December 11, 1844 – A Memorial" before the Section of Anesthesia of the Indiana State Medical Society.<sup>14</sup> Also in 1944, his second paper on postoperative mortality noted "statistics are dull enough, but in one hundred years from now, who knows but what this paper will be as amusing as a table I recently unearthed?", referring to an 1812 study on survival vs. causes of death of 1,000 New Englanders.<sup>15</sup>

Continuing medical education was another cause advocated by Combs. He wrote a letter to the editor of the Journal of the Indiana State Medical Association in 1908 encouraging involvement in the local county medical society.<sup>16</sup> Combs outlined a plan to restructure the meetings to make them more appealing and educational to a wide variety of specialists. The plan proposed conducting weekly meetings, offering study materials in advance of the meetings, giving specialties equal footing within the society, and supporting the American Medical Association.

In terms of clinical anesthesia, Combs saw the significance of advancing medical knowledge. He presented two papers over twenty years apart on perioperative mortality.<sup>15,17</sup> Of note, the second paper was published ten years prior to Beecher and Todd's well-known 1954 article "A Study of the Deaths Associated with Anesthesia and Surgery."<sup>18</sup> Noting that this topic is not the most pleasant issue to discuss, Combs stressed its importance in order to try to better patient outcomes. "As these departed spirits paraded before my attention, I heard them say in sepulchral tones, 'What did you do to bring about my demise, or what did you fail to do that might have saved my life?'"<sup>15</sup> In his 1922 presentation, Combs documented his 7,000 anesthetics to date with a perioperative mortality rate of 5.1%.<sup>17</sup> He described a risk stratification class, Group A, B, C, or D, that he assigned to each patient. The assignment was based on the patient's expected mortality rate for that case, which Combs determined by the patient's condition and the type of patients' physical states was published nineteen years later.<sup>19</sup> Combs' paper then went through and divided presumably avoidable deaths into errors by the surgeon, anesthetist, general practitioner, and even the patient. In his 1943 presentation, Combs noted a decline in mortality to 3.7% in his last 5,000 cases and only 2.5% in his last 1,000.<sup>15</sup> He again divided the cases into expected or unexpected deaths with possible explanations and made comparisons to his 1922 data. Combs concluded the decline in perioperative mortality could be attributed to advances in medicine, such as the birth of sulfa drugs, and to advances in anesthesia, such as intratracheal anesthesia, spinals, Pentothal, and combined techniques. Even with advances in anesthesia, Combs wisely exhorted the anesthetist to continue with vigilant monitoring of the patient as he stated, "under all agents I have had near fatalities. Danger lurks in any one of them..."<sup>15</sup>

Advances in anesthesia are fruitless unless the anesthetist is willing to try the newer techniques. Combs could hardly contain his enthusiasm after using cyclopropane shortly after its introduction. He presented a paper in 1938 outlining his experience of 700 anesthetics utilizing cyclopropane, which Combs states "revolutionized my entire methodology."<sup>10</sup> He detailed the types of surgeries, anesthetic techniques, and outcomes of those cases. His routine of pre-medication and induction were explicitly recounted. Combs praised the many advantages of cyclopropane, but noted it should not be used haphazardly by those unfamiliar with it. He also stressed that the anesthetist is more important than the agent used and one should use whichever technique yields the best results for him. Combs' willingness to embrace and experiment new techniques was not lost on his colleagues, including surgeons. J. R. Yung, M.D. wrote in response to this paper, "We surgeons of Terre Haute feel that we can render service to a wider group of patients and that we have a lower mortality by having expert anesthetists who are alert to the advantages of newer agents and methods of anesthesia and select that which is best for the patient and type of operation to be performed."<sup>10</sup>

Being accepted by his local colleagues was not enough as Combs longed for anesthesia to be recognized on a broader scale. He was actively involved in the creation and early years of the Anesthesia Section of the Indiana State Medical Association (ISMA).<sup>20</sup> On March 30, 1934, the Indiana State Board of Medical Registration and Examination found that the practice of anesthesia was the duty of a licensed physician. Later that year, Floyd Romberger, M.D., spearheaded the process for the formation of the Anesthesia Section of the ISMA. He described Combs as his "lieutenant-in-chief" surgery being performed. Combs' group assignments are impressive when one considers Meyer Saklad, M.D.'s article on grading through the ultimately successful adoption of the proposal and formation of that Section on October 11, 1934. Combs served as founding Vice-Chair of the Section and succeeded Romberger as Chair the following year.

Outside of medicine, Combs led an active life.<sup>2,6</sup> He married Ethel Mattox in 1902, with whom he had three children. He was very active in the Rotary club, even serving as a delegate to their conventions in Vienna, Canada, and Mexico. Combs was also a member of the Vigo County and Indiana Historical Societies. Other hobbies he embraced included recording music, performing in theatrical productions, and collecting stamps. Combs continued to be an active member of the social and medical communities up to his death on February 7, 1960, following a brief critical illness.

Dr. Charles Nathan Combs was truly a pioneer in anesthesia. His tireless efforts to promote anesthesia as a vital and respectable medical specialty deserve recognition. He humbly stated in 1928, "My only contribution has been to exemplify as best I could the dignity, the meritoriousness of the art and to preach by precept and example anesthesia as a true specialty for graduates in medicine."<sup>3</sup> Combs could honestly say in his lifetime he witnessed a revolution in the reputation and technology of the specialty he so loved. Admitting he was discouraged from the lack of attention his early efforts were producing, Combs soldiered on. He eloquently summed up the evolution of his field in a way that should make any anesthesiologist proud. "Since then the idea of a surgical team has evolved and who occupies a higher position in it than the man at the head of the table? Who can describe that dramatic moment when the great surgeon pauses and asks, shall I proceed? What a responsibility for the anesthetist, what deference to his judgment."<sup>3</sup>

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## The Legacy of Dr. Günter Corssen

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From 1968 to 1977 the Department of Anesthesiology at the University of Alabama was chaired by a dynamic leader who energized and grew the department during a period of unprecedented societal change and medical progress. Dr. Günter Corssen was a tall, striking figure in an ankle-length lab coat who, with his German accent, commanded the attention of everyone in an operating room. He was a passionate and inescapable advocate for the use of intravenous anesthetics. Dr. Corssen is credited with pioneering the first human studies with the drug, ketamine. In fact, his most enduring legacy today is the widespread use of ketamine in clinical anesthesia, pain management and clinical research. Ketamine's novel properties as a potent anesthetic/analgesic and sometimes troublesome hallucinogen make it a controversial agent and amongst anesthesia practitioners, a popular topic for anecdotal conversation. I have found that the same can be said of the late Dr. Corssen. Indeed, his German military background, his unrestricted use of ketamine, his sometimes brash leadership style, all promote fascinating discussion. During my research I have engaged in conversations about Dr. Corssen with individuals who had a wide range of relationships with the man.

Günter Corssen was born February 6, 1916, in Bremen, Germany. He endured the crushing poverty of post-World War I Germany with his mother and brother. Hitler's rise to power was not enthusiastically received by all Germans including a teenage Corssen. He later, however, went to war as was expected of him. He became a decorated tank commander in the German army and was wounded numerous times. Because of his many injuries, Corssen was hospitalized for extended periods during his service. It was this experience that inspired him to study medicine. After the war, he finished his M.D. and Ph.D. at the University of Hamburg in 1950. He trained subsequently in gynecology. To better serve the group with whom he worked, he left for the United States in order to familiarize himself with anesthesia.

At the University of Texas Medical Branch in Galveston, Texas, Corssen diligently went to work and was immediately impressed by the practice of anesthesia. He quickly realized that the complexities of the job demanded the full attention of a medically-trained specialist. From that point forward, he championed the field of anesthesiology.

In 1959 Corssen accepted a position at the University of Michigan where over the next several years, his most important research would take place. Along with Domino, he pioneered the use of the fascinating "dissociative" anesthetic, ketamine, a derivative of phencyclidine which had been rejected earlier because of its powerful hallucinatory side effects. In 1966, they published a study of 130 human subjects in which the drug was used. Consequently, Parke-Davis Pharmaceuticals commercially produced Ketalar<sup>®</sup> after its approval by the Food and Drug Administration. Corssen, meanwhile, became a full Professor and left for Birmingham, Alabama, to become the third Chair of the Department of Anesthesiology at the University of Alabama.

### **Sources:**

All data were collected between January, 2009 and present by questionnaires and telephone conversations with family, friends and former associates of the late Dr. Corssen and by review of departmental records provided by Mr. A.J. Wright at the University of Alabama, Birmingham.

## A Heptad of Hoosiers – Indiana University and Anesthesiology

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Indiana's medical schools prior to 1909 form a tangled web of formations, mergers, name changes and disappearances. Since 1909 there has only been one medical school in Indiana – Indiana University School of Medicine (IUSM). Indiana University students and athletes just as Indiana residents as a whole are “Hoosiers”. This abstract will review a group of seven IU School of Medicine graduates who have gone on to important roles in anesthesiology.

**Lillian Barbara Mueller** – Mueller was a member of the IUSM Class of 1909, the first class to complete all four years at IU and the only women member of that class. After a short time in general practice, she became the first full-time anesthesiologist at Methodist Hospital in Indianapolis. She was the founding Secretary of the Section of Anesthesia of the Indiana State Medical Association in 1934. She headed Anesthesiology at City Hospital (Indianapolis) from 1940-1955.

**Emery Andrew Rovenstine** – Rovenstine was an Atwood, Indiana native and a 1928 IUSM graduate. Following graduation, Rovenstine entered general practice with a part-time anesthesia component in LaPorte, IN. Two years later he entered a residency in anesthesiology at the University of Wisconsin. Rovenstine went on to become the first Professor of Anesthesia at New York University and is honored annually by the delivery of the Emery Rovenstine lecture at the American Society of Anesthesiologists Annual Meeting.

**Vergil Kenneth Stoelting** – V. K. Stoelting was a native of Freelandville, IN, and a 1936 IUSM graduate. Following internships and a short time in general practice, he entered the United States military in 1942. His military experience included six months of training in anesthesiology with Ralph Waters at the University of Wisconsin and three years as Chief of Anesthesia at Ft. Leonard Wood. Following discharge, he completed a residency with Stuart Cullen at the University of Iowa. On September 1, 1947, he founded the Department of Anesthesiology at Indiana University retiring from the position on September 1, 1977.

**Charles Owen Hamilton** – Hamilton grew up on a farm southeast of Muncie, IN. He entered Indiana University proceeding on to IUSM and graduating in 1945. He completed his residency in anesthesia in South Bend, IN, where he practiced anesthesia from 1952 to 1987. Hamilton served as President of the Indiana Society of Anesthesiologists in 1957, as Assistant Secretary of the ASA in 1959 and as Secretary of the ASA from 1963 through 1967.

**David Longnecker** – Longnecker is a graduate of IU, IUSM and the IUSM Anesthesiology residency. He was a faculty member at the University of Missouri and the University of Virginia before becoming the Robert D. Dripps Professor and Chair of Anesthesiology and Critical Care Medicine at the University of Pennsylvania from 1988 to 2002.

**Ronald D. Miller** – Miller is a graduate of IU and in 1964 of the IUSM. He completed a residency in anesthesiology at the University of California, San Francisco. Following military service, he joined the faculty at UCSF and has been Chair of the Department of Anesthesiology since 1984.

**Robert Kenneth Stoelting** – R. K. Stoelting is a son of V. K. Stoelting, a graduate of IU and in 1964 of the IUSM. He completed a residency in anesthesiology at the University of California, San Francisco then served at the NIH for two years before joining the faculty at IUSM in 1970. He became Chair of the Department of Anesthesia at IUSM in 1977 and served as Chair until retiring in 2003. He now serves as President of the Anesthesia Patient Safety Foundation.

## **Seishu Hanaoka (1760 – 1835)**

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Seishu Hanaoka (1760 - 1835) successfully performed a surgical operation using a mixture of herbs and plants to induce unconsciousness in 1804. While his concoctions would not qualify as general anesthesia under modern concepts, his successful efforts to conduct surgery without pain came 38 years before Crawford Long and 42 years before William Morton. His place in medical history is largely unknown in the West.

His successful technique was the product of more than 20 years of experimentation that included tests on his mother and wife. The leading figure in medicine in feudal Japan, his story reflects the transition of Japanese politics and science from feudal isolationism to its opening to the West in the 1860s.

## From the Killer Bean of Calabar to Neostigmine: The History of Anticholinesterases and Their Use in Anesthetic Practice

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The history of neostigmine is both captivating and complicated. Its synthesis and use in anesthetic practice are the consequence of Man's infinite fascination with poisons and the accompanying tales of mythic proportions surrounding their procurement from exotic lands. Fueled by the popularity of discovering and collecting botanical specimens for new drugs, poisons and other chemicals, the tale of "the killer bean of Calabar" and its deadly paralytic effects sparked the quest for the plant that produced the bean, the alkaloid extract of which would come to play a central role in many aspects of clinical medicine and anesthesia. The discovery of the physiological properties of the Calabar bean could arguably be one of the most important medical contributions of the past 160 years, as it paved the way for the elucidation of the role of antagonism, particularly at the neuromuscular junction, which is the site of action for anticholinesterases used in clinical anesthesia.

In the early 1840's Scottish missionaries to the Calabar region of southeastern Nigeria began to report a form of justice in which the Calabar bean, also known locally as the *esére* bean or *chop nut*, or *drink doctor*, was used as judge, jury, and executioner of those accused of various crimes, particularly witchcraft. To the people of the Calabar region, or the Efik, death could only be due to extreme age. Any other cause of death was unnatural and thought to be due to the practice of witchcraft, using the power of *ifot*.<sup>1</sup> If the *abia ebok*, or traditional medicine man, was consulted and unable to cure a person of sickness and the person died, the *abia idiong*, or witch doctor, was often called upon to "divine the origin of the evil influence."<sup>2</sup> Whether a person was identified by the *abia idiong* as casting *ifot* against the patient or charged with witchcraft by another member of tribe, the accused then underwent a trial by ordeal where he or she was forced to consume Calabar beans, which are more appropriately called the fruit or the seeds of the *esére* plant.

The first written report, albeit obscure, of the use of the Calabar bean as an ordeal poison came from the diary of a Calabar man, Antera Duke. On June 15, 1787, he wrote "so wee hear King Aqua was mak all wife to Drink doctor so 11 wife Dead by the Drink Doctor."<sup>3</sup> The first written account from a European was from J. A. Holman, a blind lieutenant in the British Navy, who in his 1828 record of his travels around the world told of a slave's wish for safe harbor because his master wanted to "cut his head off, or to make him 'chop nut,' i.e., to oblige him to eat a poisonous nut, which produces speedy death, because he had free-mason (meaning witchcraft), and that his master had been sick ever since he had last flogged him."<sup>4</sup>

More often the first written record of an ordeal poisoning is incorrectly accredited to Daniell, a surgeon in the British Army and botanist, who wrote that in 1846 persons suspected of capital offenses were "forced to swallow a deadly potion, made from the poisonous seeds of an aquatic leguminous plant, which rapidly destroys life."<sup>5</sup> Another account by the Reverend Zerub Baillie describes guilty parties having to chew and swallow up to 20 or 30 seeds (Figures 1, 2, and 3).<sup>6</sup> More often than not, the condemned died a slow but painless death from paralytic asphyxia, which was viewed as confirmation of their guilt. The missionaries recounted foaming at the mouth and "gradual paralysis of all the voluntary muscles. The person has a stupid look, and a drunken gait. His limbs cease to obey him, his breathing become laborious, and he sinks and dies without any apparent suffering."<sup>7</sup> It was thought that death was the natural consequence of the interaction between the *esére* and the *ifot*, which was believed to exist in their stomach. Those who were able to vomit the seeds with no side effects were pronounced innocent, and those who regurgitated the seeds but still exhibited some symptoms of the poison were sold into slavery.<sup>8</sup>

The Efik so strongly believed the seeds had the power of divination and could specifically and infallibly reveal and execute witches that many who were falsely accused would insist on



swallowing the seeds in order to declare their innocence. However many with the authority to administer the seeds knew its potency was directly related to its maturity, and thus selected less potent seeds to show favoritism or more potent ones to ensure death, subsequently influencing the outcome of many ordeal trials. It was observed that less than half of a seed was enough to kill, while survival was possible when the seeds were swallowed whole without being chewed and were quickly purged.<sup>2</sup> The fortuitous observation proved to be beneficial on a few occasions when missionaries who were taken into captivity were forced to undergo an ordeal. Having witnessed the survivors vomit the beans they would immediately induce regurgitation and spare themselves the effects of the poison. Consequently, the missionaries who survived the ordeal were able to establish their credibility among the Efik as disciples of a new religion and settling any doubts their designated converts may have had about the source of their divination powers.

For the Efik the Calabar bean was more than just an instrument to carry out ordeals. It was also believed to have protective powers against the very witches it eliminated. The seed was often tied to a valued object, such as money, or an ailing body part, or kept in houses to protect the inhabitants from witches at night. One of the more peculiar uses of the seed was as a popular weapon of choice in duels. The challengers would selectively divide the bean, swallow their portion, and oftentimes watch each other die.<sup>9</sup> Though no formal reports of homicide could be found, it also stands to reason the Calabar bean was used as a powerful and surreptitious weapon, wielded by the hands of many revenge seekers. In addition, the Calabar bean was put into streams to poison fish much like the current practice of using cyanide salts to harvest salmon.<sup>10</sup> Fascinatingly, it was used as a lethal means of brandishing power in the turbulent political times that followed the death of a king. Analysis of witchcraft accusations suggests they were a “weapon of covert aggression to further political ambitions.”<sup>12</sup> The best recorded example is of the events that followed the death of the Great Duke Ephraim (Efiom Edem) of Duke ward in October 1834. The account comes from a converted Calabar man known as Mr. Young. Nearly 50 people were accused of witchcraft by the leaders of a neighboring Eyamba ward and made to “chop nut”. In his journal, Mr. Young wrote on the morning after the king’s death “all country and Calabar come, . . . so all our people chop nut. The name of them: Erim Coofee Duk chop, dead. His son chop, no dead. . . One Otto slave, dead, for street. Egbo Eshen, mother dead tonight. . . Duk wife chop nut this morning, all dead” The ritual persisted over several days until 40 people accused of witchcraft had been eliminated.<sup>11</sup> With the Duke ward swiftly weakened, the candidate from the Eyamba ward assumed the kingship.

Concerned and sometimes horrified by the sight of numerous ordeal poisonings, missionaries to Old Calabar of the United Presbyterian Church of Scotland kept diaries and began to disseminate their experiences in the Church’s monthly *Missionary Record*.<sup>12</sup> They estimated approximately 120 deaths each year and documented the morbid sequelae of the poisonings.<sup>13</sup> Though the missionaries deemed the practice of ordeals a social taboo, and the colonialists eventually attempted to ban the cultivation of the *esére* plant, the allure of the macabre only further stimulated European interest in obtaining the seeds. Still, it would be over 25 years from Holman’s account before it landed in the hands of any European scientists.

It is not completely clear as to why it took this long. It is likely the Calabar bean became steeped in a quagmire of competing political, economic, and religious interests. The Revered Hope Waddell blamed the difficulty in obtaining the seeds on King Eyo, one of the Calabar kings of the region, who had ordered the wholesale destruction of the *esére* plants. It is uncertain from the Efik point of view whether this was an attempt to establish a monopoly on the Calabar beans in order to capitalize on European curiosity or whether the destruction was in response to pressure from Waddell and other missionaries to prevent the indiscriminate application of the ordeal trial. It does seem the latter did eventually prevail. Between 1850 and 1851, around the time of prohibition of human sacrifices, the private use of the Calabar bean was banned and placed under the authority of the *Ekpe* or *Egbo* society, which controlled judicial issues.<sup>11</sup> The ordeal trials were finally outlawed in treaties with the British in 1878, but the memory and use of the Calabar beans as a subterfuge for murder persisted.<sup>2</sup> For example, as recently as 2001, a torso, fished out of the River Thames in London, was found to have fragments of the seeds in his lower intestine.<sup>14</sup>

Nevertheless Waddell was able to smuggle two seeds out of Calabar sometime between 1850 and 1855.<sup>15</sup> He sent them to a toxicologist named Sir Robert Christinson in Edinburgh, Scotland, the location of his parent church. Christinson suggested that John Hutton Balfour, who had also obtained some seeds from Baillie, plant them at Edinburgh botanical garden. He attempted to grow some of the seeds, which produced vines, but no flowers. Christinson then decided to investigate the physiological effects of the seeds. After observing the results of his experiments involving only two rabbits, he proceeded to ingest a portion of one seed, nearly killing himself in the process. Experiencing no symptoms with only six grains, or an eighth of a bean, he discovered that just twelve grains of the bean was potent enough to cause “severe symptoms in his own person, although the poison was evacuated by vomiting,” induced by the hot shaving water he had just been using.<sup>16</sup> Thoroughly satisfied he had gotten hold of a “very energetic poison,” he recounted his ordeal of tachycardia followed by arrhythmia, feelings of giddiness, faintness, and weakness without uneasiness or loss of consciousness. Christinson hypothesized the Calabar bean carried out its death sentence by painlessly paralyzing the heart. Consequent to his experimentation, Christinson proposed that extracts of the seed be used as a more humane way to execute criminals sentenced to death. Christinson did not continue to research the Calabar bean, but he did give his *Materia Medica* Laboratory of the University of Edinburgh to Thomas Richard Fraser, the man who contributed most to current knowledge about the physiological characteristics and therapeutic uses of the ordeal bean.<sup>13</sup>

A few years after Christinson’s first experiments, the seeds began to appear in Edinburgh in no short supply. Missionaries other than Waddell started carrying them back to Scotland. Fraser received a package of about 80 seeds from Baillie.<sup>17</sup> Many of the men who studied the Calabar bean around this time passed the excess of their supply on to other interested investigators. In addition there were several poisonings across Europe, including Glasgow, Edinburgh, and St. Petersburg as well as two infamous poisonings in Liverpool in 1864 and 1871. In 1864 fifty children were poisoned after eating seeds that had been swept off a ship.<sup>18</sup> Only one died as a result of their prompt treatment with atropine by one Dr. Cameron. Another nearly identical incident in Liverpool involving 17 children but no deaths occurred in 1871.<sup>19</sup> Such events were not surprising since the seeds (Figures 2 & 3), which resemble actual edible beans, are deep chocolate brown, about the size of a pecan, kidney shaped, odorless, and initially taste bean-like.

However, it was not until 1859 that another missionary, Reverend W. C. Thomson, who recorded several ordeals (Table 1)<sup>20</sup> and whom Balfour considered to be a “very good botanical observer,” was able to acquire the first flowering specimen, which he preserved in salt.<sup>21</sup> But Balfour had already received a flowering plant from his friend and former student, Baillie, who had preserved it in alcohol.<sup>21</sup> The gap between the arrival of the seeds in Britain and the identification of the *esére* plant was due, in part, to the lack of knowledge of the vast majority of the Efik about the plant that produced the seed. In his account to Watson, Thompson noted it was a “curious fact, that hardly any of these people know anything at all of the plant; indeed one may safely venture to say, that none of them are able to identify the plant in new situations, except by aid of the fruit.”<sup>18</sup> Armed with the description by Thompson of the *esére* plant in its natural habitat, Balfour gave the first comprehensive botanical description of the plant, which he named *Physostigma venenosum*, in January 1860 (Figure 4).<sup>21</sup> The extract of the Calabar bean was aptly named, physostigma or physostigmine, by Jobst and Hesse, the two scientists who were first to successfully isolate the active alkaloid in 1864. The following year Vee and LaVern also isolated the active alkaloid in crystallized form and named it eserine, after the Efik name for the Calabar plant and seed.<sup>22</sup>

The next event, and perhaps the one to ignite the most intense international interest, was the proclamation by an ophthalmologic surgeon from Edinburgh, Argyll Robertson, that an extract of the Calabar bean would be “an agent that will soon rank as one of the most valuable in the ophthalmic pharmacopoeia.”<sup>23</sup> It is likely Robertson learned of the Calabar bean and its properties from several sources. He was a member of the United Presbyterian Church of Scotland, and presumably an observer of the *Missionary Record*. As a resident physician in the Royal Infirmary of Edinburgh where Christinson worked, he most certainly would have been aware of the results of Christinson’s experiments. And finally, he did

attribute his quest for a substance that would “stimulate the muscle of accommodation and the sphincter pupillae” to his colleague, Fraser, stating his pursuit was “productive of no satisfactory results until [his] friend Dr. Fraser informed [him] that he had seen contraction of the pupil result from local application of an extract of the ordeal bean of Calabar.”<sup>23</sup> For his experiment, Robertson instilled the extract into his own eye and discovered it dilated the pupil, finding it applicable in “all instances where atropine is used to render examination of the eye.”<sup>23</sup> Subsequent to Robertson’s work and presentation at the German Ophthalmological Society in Heidelberg in 1863, several papers from scientists across Europe appeared on the various ophthalmic uses of physostigmine.

But it was Fraser’s research on the physiological effects of the extract that started the wealth of data that elucidated the systemic toxicity of physostigmine in both humans and animals. As a result of his experiments Fraser administered the extract to cases of *erysipelas*, *delirium tremens*, bronchitis, rheumatic fever, irritable stomach, and tetanus only if the patient had a bounding tachycardia because he considered a weak pulse to be a contraindication to its use.<sup>7</sup> Fraser found that upon administration of physostigmine into the bloodstream, death resulted in every mammal, except the *esére* moth.<sup>24</sup> Upon injecting various animals, he noted a slight tremor, starting in the posterior regions and progressing anterior, followed by paralysis, again initiated in the posterior region. He then hypothesized the drug mediated the resulting muscle paralysis by depressing the spinal cord.<sup>25</sup> This hypothesis was generally supported, but some scientists, including George Harley had other theories regarding the muscle paralysis. For example, Harley observed a lack of irritability or toxicity to the muscles themselves, and particularly to the myocardium, and thus was led to believe the poison acted “entirely on the motor nerve-system...and the nerves only.”<sup>16</sup> At the time Harley proposed this theory, knowledge of acetylcholine, cholinesterases, and cholinesterase inhibitors and their action at the myoneural junction was still over 50 years from being discovered.

Part of the problem in gaining a consensus about the site of action of physostigmine was the drug itself had no standard formulation. In 1855 Christinson discovered the active principle could be extracted with alcohol.<sup>16</sup> Unfortunately he only obtained 2.7 percent of an alcoholic extract containing the physiological properties of the seed.<sup>16</sup> Those who were carrying out experiments on the drug were using differing formulations of physostigmine and testing it on various species of mammals and amphibians, which seemed to exhibit little sensitivity to the toxicity of the drug.<sup>6</sup> With his dogged determination to pursue many remaining questions about this new drug, Fraser, like his mentor Christinson, also ingested the powdered kernel of the seed and kept meticulous records of their effects (Table 2).<sup>26</sup> In later experiments he tried to keep as many variables constant as possible by using only one species (guinea-pigs) and adjusting doses for bodyweight. In doing so he was able to determine the minimum lethal dose before studying the antagonistic effects of physostigmine. At that time Fraser noted the concept of antagonism had not been demonstrated with any significance. He stated, “antagonism between any two substances, in the sense of the lethal action of one being preventable by the physiological action of the other, had not previously been shown to exist by any certain and satisfactory evidence.”<sup>27</sup> An “inveterate investigator,” Fraser then studied a large number of animals to increase the statistical power of his experiments, and subsequently established his credibility on the subject of the antagonism between physostigmine and atropine.<sup>27</sup> Because he knew the minimum lethal dose, he then was able to authoritatively substantiate his theory by demonstrating that a dose of atropine could prevent a proven lethal dose of physostigmine from causing death (Figure 5).<sup>27</sup> Remarkably, it was over 130 years ago that Fraser established the current adequate doses and dosage frequency of atropine along with the endpoints by which to judge efficacy.

However, Fraser can only be acclaimed as the first to substantiate the theory of antagonism through vigorous scientific principles. He cannot be credited with the original discovery of antagonism between physostigmine and atropine. Kleinwachter and Niemetscheck of Prague achieved that accomplishment in 1864. Kleinwachter was challenged with treating four prisoners who were exhibiting the effects of atropine intoxication. Five prisoners had been cleaning rooms in the jail hospital when they came upon a medicine box containing a bottle of spirit of atropine solution. Thinking it was alcohol, they imbibed it. One immediately spat his mouthful out when he realized it was not alcohol. Another who

swallowed the spirits only exhibited dilated pupils. The third seemed to exhibit behavior as if he was drunk, and another was completely unconscious. The more severely affected were examined and found to have the classic symptoms of anticholinergic poisoning, including hyperthermia, anhydrosis, dry mouth, and cyanosis. When conventional methods of revival, including syrup of ipecac and black coffee, were unsuccessful, Kleinwachter, who was the jail medical doctor, administered an oral solution containing the extract of the Calabar bean to the unconscious prisoner. He used the other less severely affected prisoners as controls, leaving them to recover on their own. Kleinwachter carried out this small study upon the suggestion of his colleague Niemetschek, who was aware of the opposing effects between the Calabar bean extract and atropine on the pupil.<sup>28,29,30</sup> Surprisingly, all five men survived, and this anecdotal report paved the way for the current practice of using physostigmine in the management of atropine poisoning.

In 1900 Jacob Pal would again demonstrate the principle of antagonism when he observed the ability of physostigmine to reverse curare. He gave physostigmine to a curarised dog, on which he was investigating the innervation of the gut. He noted that four minutes after the intravenous administration of physostigmine, his curarised dogs showed strong muscle twitches, spontaneous respiration and salivation.<sup>31,32</sup>

By the time Pal demonstrated the reversal of curare using physostigmine, pharmaceutical companies had long been producing tinctures and solutions for the myriad of ails it was touted to cure. However, since no analog of physostigmine existed in other plant products whose composition was already known, it was particularly difficult to determine its constitution. Therefore each product in the possession of medical doctors and travelling salesmen differed in composition from one to the next. Because of this one could never be sure what percentage of the product was physiologically active, making it impossible to accurately determine clinical doses. Armed with the structural formula of physostigmine, which was finally identified by Stedman and Barger in 1925,<sup>33</sup> Dr. Percy Julian solved the constitution problem in 1935, when he somewhat embarrassed the English chemists King and Robinson,<sup>34</sup> who had thought they were the first to synthesize physostigmine, by convincingly pointing out that their reduction formulas “could not be realized in practice” and therefore, their product “must be assigned another constitution.”<sup>35</sup>

Shortly before Julian revealed the true character and method of synthesis of physostigmine, scientists were postulating that some sort of vagus substance was released at the cardiac nerve endings, the action of which was to slow down the heart rate. The questionable substance was confirmed by Otto Loewi in 1926.<sup>36,37</sup> Through a long series of experiments on atropine’s antagonistic effects on the bradycardia mediated by the vagus substance acting on myocardial muscarinic receptors, Loewi concluded the vagus substance was likely the choline ester, acetylcholine, as Sir Henry Dale had previously suggested in 1914, because its breakdown could be inhibited by physostigmine.<sup>36,38</sup>

Loewi’s experiments led scientists to question whether acetylcholine was also active at the myoneural junction, and his work was seminal in leading researchers to finally confirming acetylcholine as the nicotinic transmitter that acted at the myoneural junction. By the 1930’s scientists knew high dose acetylcholine could cause muscular paralysis, but they did not know if it was indeed the natural transmitter active at the myoneural junction or if its action could be prevented by curare. It was Dr. Mary Walker and her use of physostigmine on a myasthenic patient that would help answer the question in 1934.

Walker was a physician at St. Alfege’s in Greenwich, England, who was presented with the case of Mrs. M, a 56-year-old woman who had been intermittently suffering with symptoms of myasthenia gravis for 14 years. She believed the weakness and ptosis was due to “curare-like poisoning of the motor nerve-ending or of the myoneural junctions.”<sup>39</sup> Walker was aware of Pal’s demonstration of the antagonism of curare with physostigmine, and she knew that myasthenic patients were extremely sensitive to even small doses of curare. Subsequently, she hypothesized physostigmine would antagonize the effect of the curare-like poison. Walker gave injections of physostigmine to Mrs. M with the dramatic disappearance of the patient’s ptosis and increase in muscular strength. This remarkable result was hailed the “miracle at St. Alfege’s,” and Walker went on to propose the mechanism of action of

physostigmine was to act as an anticholinesterase at the myoneural junction. As a consequence of Walker's work physicians now knew they could use physostigmine to diagnose and treat myasthenia gravis. In addition Walker's experiments paved the way for the use of anticholinesterases in the reversal of curare, which was introduced into the field of anesthesia in 1912.

Almost three decades after Walker's "miracle" Arthur Lawen, a German surgeon from Leipzig, used a partially purified preparation of curare to produce surgical relaxation in an anesthetized patient.<sup>40,41</sup> Lawen's findings were largely disregarded for almost 30 years until psychiatrists started using it in 1940 in conjunction with shock therapy. In 1935 psychiatrists began using metrazol to induce convulsive shock therapy for the treatment of schizophrenia.<sup>42,43</sup> So violent were the tetanic convulsions that traumatic complications such as fractures of the humerus, femur, and spine were not uncommon. These hazards caused some in the field to abandon the treatment altogether. However, Dr A. E. Bennet, a psychiatrist in Omaha, Nebraska, thus sought a method of decreasing the severity of the convulsions while preserving the therapeutic benefit. In his experiments in 1940, Bennet administered curare before shock treatment and succeeded in eliminating all traumatic complications. Subsequently, he recommended curarization before shock treatment as the standard of care. Of note, he made no mention of any kind of reversal of neuromuscular blockade using anticholinesterases such as neostigmine, a synthesized by Aeschlimann and Reinert in 1931. They initiated their investigation in response to the desire for a compound similar to physostigmine without the characteristic effects on the central nervous system.<sup>44</sup>

The first reports of the use of anticholinesterases being used to reverse the effects of curare appeared in 1941, a year after Bennet recommended the use of curare in shock treatment. Another psychiatrist from Nebraska, R. W. Gray, repeated Bennet's experiment and reported only three of their 50 cases required mechanical ventilation and the administration of the neostigmine to restore spontaneous respirations.<sup>45</sup> Even though curare was widely being used in general anesthesia in the early 1940's, anticholinesterases were not.

In a short, three-page report, Harold Griffith and Enid Johnson of Montreal reported the first appearance of neostigmine in clinical anesthesia in 1942. At the suggestion of Dr. L. H. Wright, Griffith and Johnson began administering Intocostrin (a purified extract of curare) to patients who had been anesthetized with cyclopropane via facemask. Since they generally did not have trouble with abdominal relaxation during cyclopropane anesthesia, they intentionally lightened the anesthesia to the point where patients began straining their abdomens to investigate the effect of the curare. All 25 patients in their study maintained spontaneous respirations, and hence none required mechanical ventilation or reversal. However Griffith and Johnson did recommend an ampule of prostigmine always be available.<sup>46</sup> The world renowned anesthesiologist T. Cecil Gray touted Griffith's light anesthesia technique as one that revolutionized the "specialty by removing for all time the need for deep anesthesia," which was associated with high mortality rates.<sup>47</sup>

A few years later in 1945 T. C. Gray, the pioneer of the Liverpool Technique, published his results from a study involving 1000 patients who had received curare. He strongly recommended mechanical ventilation after administering curare, however he was less enthusiastic about reversal with physostigmine, which was only used three times out of the 1000 cases studied.<sup>47</sup> After his experience with more than 8000 cases of patients receiving curare, in which patients were given a test dose of 5 mg followed by another 10 mg dose, Gray observed patients being returned to the ward still partially curarized and the resultant pulmonary complications associated with post-operative atelectasis.<sup>48</sup> He subsequently perfected his clinical technique to include reversal, stating "it is so easy to give a dose of prostigmine and atropine. And in order to be quite certain it is now almost my invariable custom to do so. This injection of prostigmine should have the same sedative effect upon anaesthetists as do the 'hypnotic sutures' of Moynihan on surgeons."<sup>48</sup>

Gray's Liverpool Technique represented a paradigm shift in the practice of anesthesia, as he was able to demonstrate that patients were dramatically safer during surgery and still woke up quickly after reversal was administered and the inhalational agent turned off. Thus two

methods of general anesthetic practice evolved: one method, employed mainly in Britain and other parts of Europe, prescribed large doses of muscle relaxant and light general anesthesia; and the other method, utilized primarily in America, advocated rarely administering curare as a supplement to deep general anesthesia. The former group was more likely to routinely use neostigmine while the latter group found few indications for reversal, with the tendency to label the use of a cholinesterase inhibitor an error in technique. Many who felt this way would cite the case of Dr. Frederick Prescott, the first known individual to voluntarily receive tubocurarine in the absence of any other drug. He vividly described the horror of feeling like he was suffocating, drowning in his own saliva and not even being able to communicate or signal his distress to his colleagues after a 30 milligram dose of curare.<sup>49</sup> Even though he was given several doses of neostigmine, he still required mechanical ventilation for seven minutes, and he was not able to speak properly for 30 minutes.

As the use of neostigmine became more frequent, particularly in Britain, reports of deaths following the administration of reversal agents started appearing. In 1949 there were three deaths due to cardiac arrest following the administration of neostigmine. W. A. Bain and J. L. Broadbent were the first to propose a cause. At that time, it was common to administer neostigmine and atropine in the same syringe. Bain and Broadbent thought the cardiac arrest was secondary to the atropine potentiating bradycardia, which was the result of a partially blocked vagus nerve.<sup>50</sup> However, Hunter found that neostigmine always caused bradycardia, regardless of the timing of atropine.<sup>51</sup> A committee on these anesthetic deaths accordingly recommended neostigmine only be given after a dose of atropine had produced a definite tachycardia.<sup>52</sup> By the time the committee issued its recommendations, administering neostigmine and atropine simultaneously was already becoming more uncommon, as it started falling out of practice in 1951.<sup>53</sup> In the decades since neostigmine has become the mainstay of the balanced technique in the delivery of general anesthesia.

Since the introduction of neostigmine into anesthetic practice, there have been no other alternative reversal agents of non-depolarizing neuromuscular blocking agents (NMBA). Almost 70 years after the dawn of neostigmine, finally a suitable alternative is on the horizon. A historical milestone is about to be realized with the advent of suggamadex, a revolutionary cyclodextrin compound with the capability to reverse profound blockade induced by the amino steroid non-depolarizing NMBA. It accomplishes prompt reversal by forming inclusion complexes that are water soluble and it possess no direct intrinsic biological activity, thus circumventing the undesired side effects associated with neostigmine. The incorporation of suggamadex into clinical anesthesia will most assuredly change the face of clinical neuromuscular pharmacology and introduce a paradigm shift in the practice of anesthesia, the proportions of which have not been witnessed since the introduction of curare.

However, the arrival of any new reversal agent, including suggamadex, cannot fully be appreciated unless one understands the rich and storied past of its predecessors and the bold personalities of the scientists who studied them. From Christinson's and Fraser's valiant if not reckless decisions to include themselves as test subjects to the leaps of faith taken by the likes of Walker and Kleinwachter, the chronicle of the development of the poison contained in one seed into a drug crucial to the clinical practice of anesthesia is indeed enthralling. From the mouth of the Calabar River to the shores of Scotland, the ordeal bean of Old Calabar, replete with the supernatural power bestowed upon it by the Efik, has journeyed the eddies and swells of history to marvel those inquisitive and enterprising men and women who, based on their work with physostigmine, contributed a wealth of knowledge to the field of neuromuscular pharmacology and the role of agonists and antagonists as they relate to the reversal of neuromuscular blockade. From poison to panacea and toxic to therapeutic, the annals of how the killer bean of Calabar came to be neostigmine calls to mind a quote by the Swiss physician Paracelsus who said, "The right dose differentiates a poison and a remedy."

#### **Appendix:**



Fig. 1. Calabar beans. The label on the right container states that they were received from John Baillie, brother of Zerub Baillie, in 1862

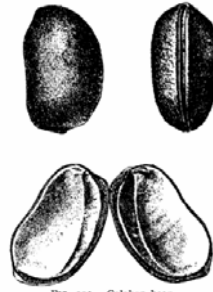


FIG. 130.—Calabar bean.

Fig. 2. Calabar bean in Sayre's Manual of Organic Materia Medica and Pharmacognosy<sup>54</sup>



Fig. 3. Physostigma venenosum and fruit



FIG. 121.—Physostigma venenosum—Portion of plant and fruit.

Fig. 4. Image from Calabar bean in Sayre's Manual of Organic Materia Medica and Pharmacognosy<sup>54</sup>

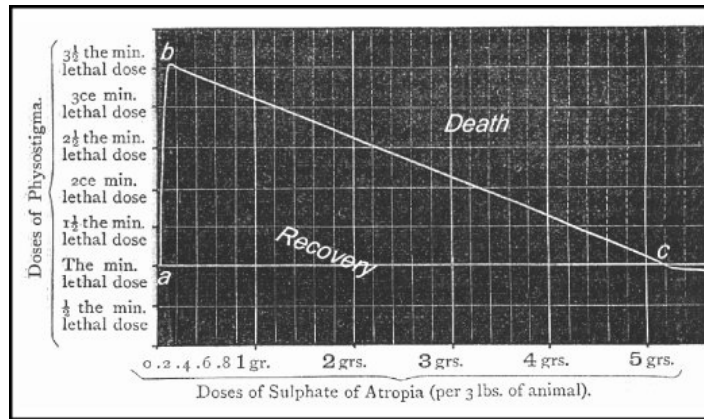


Fig. 5. An isobol representing the protective effect of atropine given 5 minutes before doses of physostigmine ranging from 0.5 to 3.5 times the minimum lethal dose<sup>27</sup>

- A dose of atropine as small as 0.15 grains (approx. 1mg) given 5 minutes before the MLD of physostigmine prevented death.
- The maximum amount of physostigmine that could be protected against by any quantity of atropine was of the order of 3.5 times the MLD (point b, the apex of the curve).
- The range of doses of atropine that could prevent death narrowed as the amount of physostigmine given increased (the horizontal distance between the relevant point on ab and that on bc).<sup>14</sup>

Table 1. Trials by ordeal observed by Thomson<sup>19</sup>

| Subjects (sex/age) | Amount ingested                    | Features   | Outcome  |
|--------------------|------------------------------------|--|----------|
| M adult            | Not known                          | Motionless   | Died     |
| M adult            | Not known                          | Motionless   | Survived |
| F adult            | About 1L                           | Vomited  | Survived |
| F 12-14y           | 1 bean (deliberate self-poisoning) | Unable to vomit - given an emetic  | Survived |
| F 20y              | Half a bean                        | Muscle twitching, profuse perspiration, repeatedly and urgently begged for water   | Survived |
| F 35-40y           | Several beans                      | Helpless, perfectly flaccid, head required support, intense nausea, constant flow of mucus from the mouth  | Died     |
| F 35-40y           | 21 bean                            | Vomited despite refusing an emetic   | Survived |
| M adult            | Not known                          | Profuse perspiration, vomited, celebrated with friends, later vomited again  | Died     |
| M 8y               | Not known                          | Flaccid, unable to support head, emptying of the bladder and rectum, unable to swallow, developed coma, frothy mucus from mouth and nose, feeble pulse | Died     |
| F elderly          | Not known                          | Flaccid  | Died     |
| F pregnant         | Not known                          | Aborted  | Survived |
| M adult            | 5-6 beans by mouth + a clyster     | Not known  | Survived |

F = female; M = male.

Table 1. Trials by ordeal observed by Thompson<sup>20</sup>

Table II. Features after ingestion of 650mg of powdered kernel<sup>26</sup>

| Minutes from ingestion | Heart rate (beats/min) | Observations  |
|------------------------|------------------------|---|
| 6                      | 74                     | None  |
| 19 <sup>a</sup>        | 72                     | Peculiar, slight epigastric sensation   |
| 15                     | 76                     |   |
| 20                     | 75                     | Epigastric sensation more marked  |
| 25                     | 77                     |   |
| 30                     | 72                     | Epigastric sensation continues at intervals but still slight  |
| 35                     | 69                     |   |
| 40                     | 66                     | Epigastric sensation recurred   |
| 45                     | 68                     |   |
| 50                     | 64                     | Slight giddiness. Intermittent sensation now extends from upper sternum to epigastrium and painful as when a large piece of food is swallowed suddenly. Belching in the middle of the sensation |
| 55                     | 65                     | Pulse full and regular. Frequent recurrence of the epigastric sensation with belching   |
| 60                     | 62                     | Pulse rather feeble, dizzy, vision dim  |
| 65                     | 62                     | Increased head symptoms, perspiring a little  |
| 70                     | 60                     | Pulse very small and wiry but regular, nausea, no recurrence of epigastric sensation since 50 min   |
| 75                     | 62                     | Copious total body perspiration. Unable to continue reading mainly because of dizziness. Slight difficulty walking  |
| 80                     | 60                     | Pulse thready and difficult to count  |
| 85                     | 60                     |   |
| 90                     | 58                     | Slight difficulty in breathing  |
| 95                     | 59                     | Pulse very feeble with occasional 'intermissions'   |
| 100                    | 56                     | Belching without the epigastric sensation. Considerable nausea and dizziness  |
| 105                    | 56                     | Pulse thready and intermittent  |
| 110                    | 58                     | Head symptoms greatly reduced. Less nausea and dizziness. Great difficulty walking. Breathing an effort   |
| 120                    | 60                     |   |
| 125                    | 59                     |   |
| 130                    | 60                     | Pulse rather fuller   |
| 140                    | 58                     | Felt sick and lay down  |
| Next morning           |                        | Uncomfortable. Poor appetite. Slight dizziness  |

<sup>a</sup> [sic] - probably 9.

Table 1. Effects after ingestion of 650 mg of powdered kernel<sup>26</sup>

### Acknowledgements:

The motivation for this essay came from my recollection of "Forgotten Genius," a documentary about Dr. Percy Julian and his synthesis of physostigmine, which aired on PBS in February 2007. At that time, I was excited something pertinent to the field of anesthesia was the subject of a documentary, and simply thought I had gained some knowledge that would one day prove useful in a round of Jeopardy. Little did I know that documentary would lead me to compose a historical essay. Moreover, little did I know the research would take me all the way back to Nigeria, from where my family originates.

Through extensive research, I have made every effort to ensure the accuracy of dates, names, quotes, and references. However, my research was by no means exhaustive. I wish to thank the reference librarians at the University of Nebraska Medical Center, who were instrumental in helping me obtain several key articles not available online. Indeed this essay would not have been possible without the availability of Google Books, which facilitated the research of rare historical texts from the 19<sup>th</sup> century, particularly those of the Royal Medical Society of Edinburgh, the Royal College of Physicians of Edinburgh, and the Edinburgh Medical Journal.

Finally, I wish to thank Ms Regina Ebong and Dr. Pam Smith for their help with the translation of the Efik words and contexts included in this essay. Slight variations exist in the spelling, and again, every effort was made to verify their accurate spelling and meaning.

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## **The Reluctant Anesthesiologist Dr. Joseph Artusio and the early days of the Physician Anesthetist**

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Anesthesiology was hardly considered a serious profession in 1944 when Dr. Joseph Artusio, a bright intern at Bellevue Hospital in New York City, considering a career in Internal Medicine, was drafted into the army. Having received a Bachelor of Science in Chemistry from St. Peters College and a medical degree from Cornell University, the New Jersey native was poised to embark on a distinguished career as an Internist. However, like many other doctors in training at the time, Dr. Artusio found his post-graduate training interrupted to serve his country in the Second World War.

With dreams of eventually completing residency training in Internal Medicine, the newly appointed First Lieutenant embraced his position as an assistant ward officer at the Army General Hospital in Lawson, Georgia. However, it came as a great disappointment, when two months later he was reassigned to the Army School of Anesthesia by his superiors. "I was absolutely furious!" he recalled in a later interview. When he approached his seniors about changing his assignment he was informed that he did not have a choice in the matter.<sup>1</sup> The Army was trying to encourage interest in the developing field of Anesthesiology. Being one of the youngest officers on staff, Dr. Artusio was arbitrarily assigned to work under Dr. Charles Mitchell; a respected anesthesiologist at the school.

This arbitrary assignment proved to be most fortuitous. Soon his sheer disinterest for the field was overcome by Dr. Mitchell's patient mentorship and immense knowledge of physiology and pharmacology. Further motivated by the fact that an Anesthesiologist assignment would mean a post some distance from the war front, he eagerly pursued his training. He soon became a specialist in the field and was even assigned to teach courses on the subject. As anticipated, an assignment to an aide station some distance from the Italian front soon followed. In no time, the reluctant anesthesiologist found himself at a replacement depot in a small town outside of Naples.<sup>1,2</sup>

Serving close to the Italian front proved to be a stimulating and inspiring time for the young Dr. Artusio. These early years were critical in cultivating his interest in what was to become an illustrious career. Among the war-time anecdotes he would recall in later years, were his frequent interactions with another important figure in Anesthesiology. The renowned Dr. Henry Beecher was the area anesthesiologist during the Italian campaign and frequently visited the local station hospitals. He regularly dispensed advice to staff anesthesiologists and brought them medical bulletins. It was at one of these meetings that Dr. Beecher warned Artusio of the dangers of using Pentothal in volume-depleted patients. Pentothal-based inductions were a frequent cause of mortality in wounded soldiers and its effects on the vascular bed, though common knowledge among modern day anesthesiologists, were unknown at the time. Dr Beecher's warnings did not go unheeded and his medical bulletins on the subject of Pentothal's vasodilatory effects led Dr. Artusio and his colleagues to eventually abandon its use in the hemorrhaging patient.<sup>1,2</sup>

His interest in Anesthesiology continued to blossom during the war. In no time Dr Artusio became widely considered one of the finest anesthesiologists in the Italian theater. The war also brought him true love and it was here that he met his future wife: a nurse anesthetist he worked with. A tour in the Philippines soon followed and, with the end of the war approaching, Dr. Artusio was faced with the dilemma of whether he should continue to pursue a career in Internal Medicine upon returning to the United States. When he expressed his desire to continue in Anesthesiology, his mentors discouraged him. In later years, he recalled the "horrified" reaction of one of his mentors, Dr. Dewitt Andrus, who was acting chief of Surgery at Cornell University at that time.<sup>1</sup> On hearing of his interest, Dr. Andrus promptly declared that Anesthesiology would always remain a field for nurses and would never become a medical field of any stature. In spite of this initial discouragement, Dr. Artusio persisted in

his new career choice and eventually completed residency training in Anesthesiology at New York Hospital.

This persistence, a trait that would characterize the remainder of his career, paid off. Dr. Artusio entered the field at one of the most interesting times in the history of the profession. The late 1940s and early 1950s were an exciting time to be an anesthesiologist. In spite of Dr. Andrus' prediction, physicians' interest in the field grew immensely during this time. The field of Anesthesiology did indeed grow in stature as a medical profession. Physician anesthetists were in great demand, supply was short, and newly trained anesthesiologists had a bright future ahead of them. As he neared completion of residency, Dr. Artusio had his eye on a private practice in Tarrytown, New York. However, Dr. Frank Glenn, the newly appointed chair of the Department of Surgery at New York Hospital, who had worked extensively with him, had different plans.

As was the case in programs across the country at the time, the Department of Anesthesiology at New York Hospital was a subdivision of the Department of Surgery. Dr. Glenn was looking for a replacement for the outgoing director. In spite of being a relative newcomer to the profession, he recognized Artusio's immense talent and offered him the position. Humbled by the offer, the newly trained anesthesiologist refused and requested that the position be given to someone else. He argued that the division would be better served by someone who was well-established in the profession and had considerably greater experience. Dr. Glenn was unrelenting in his conviction, however, and continued to urge him to take on the responsibilities of the position. It took some convincing but eventually Artusio relented and once again embarked on a path that would define his career.

The Department of Anesthesiology at New York Hospital flourished with Dr. Artusio at its helm. Under his capable guidance, it emerged as a separate division on par with all the other medical specialties in the hospital. What was initially conceived as a program to train residents, also started to produce top quality research. One such project involved the first human clinical trials of phenyltrimethylammonium compounds: an anticholinesterase class of chemicals with potent anticurare properties. Under Dr. Artusio's supervision, the trials concluded with great success. They lead to the development of Edrophonium which continues to be a compound of significant clinical value to this day. Some of the most interesting developments, however, came in the field of cardiac anesthesia.

At the time, the majority of cardiac procedures at New York Hospital consisted of valvulotomy of the mitral valve. The typical patient that presented with this pathology had suffered from rheumatic heart disease for several years and was functionally limited by significant heart failure. Severe hypotension and accompanying tachycardia were common on induction which resulted in considerable morbidity or the cancellation of the procedure. Diethyl Ether was the typical induction agent of choice. In order to limit vascular depression, the anesthesiologist frequently had to resort to administering low doses of the volatile anesthetic. The result was the occasional induction and maintenance of relatively light states of anesthesia during these major procedures. While anesthetizing a young girl with significant mitral valve disease with a low dose of Diethyl Ether, Dr. Artusio noted that the patient appeared to wake up mid-procedure and looked around the room. His reaction was one of great shock and he immediately deepened the patient's level of anesthesia by administering further agent. In spite of this incident however, the patient tolerated the procedure well. Much to his surprise she did not have any recall of the event on emergence from anesthesia. This observation flew directly in the face of the conventionally held belief that such a light level of anesthesia posed great danger to the patient. It was thought that light levels of anesthesia made the patient prone to significant reflex cardiac irritability and that the likelihood of ventricular fibrillation and sudden death were high during such states. The patient's remarkably stable course however, prompted Dr. Artusio to further investigate this state with surprising results.<sup>1,3</sup>

It turned out that it was possible to replicate this light "plane" of anesthesia with great consistency and this allowed it to be studied in great detail. Patients anesthetized to this level were able to follow commands and respond to questions and yet had no recall of events. Further, the analgesic properties of Diethyl Ether were fully maintained and patients

questioned mid-procedure with their thorax opened responded that they were entirely comfortable and experienced no pain. The use of a lower fraction of volatile anesthetic also limited the degree of cardiovascular depression and ensured a greater degree of hemodynamic stability in patients with compromised cardiac function. Soon “ether analgesia”, as the method came to be called, was regularly employed during mitral valvulotomy procedures at New York Hospital. The technique was soon replicated with excellent results at other institutions. In time other clinician-researchers defined similar light states of anesthesia using different anesthetic agents. The discovery of the effects of such light levels of anesthesia was a remarkable one. Aside from its clinical utility in patients with severe cardiac disease, it also introduced the concept of depths of anesthesia – a significant milestone in the modern understanding of anesthetic agents.<sup>4,5,6,7</sup>

Given the remarkable nature of the discovery and the degree to which it transformed the field of Anesthesiology a film demonstrating “ether analgesia” was commissioned in the spring of 1955 and screened nationally. In this extraordinary film, the viewer is introduced to a patient named “Edna” undergoing a mitral valvulotomy. The initial scenes of the film show Edna being induced with ether by Dr. Artusio to a level where she is able to correctly identify the name of her husband, the year of her birth and follow simple commands. Once in the operating room, she continues to follow commands and correctly answers the questions that Dr. Artusio poses to her. Then, in a dramatic gesture, the camera pans and displays to the viewers’ amazement Dr Glenn removing a rib and obtaining access to her heart without causing her the slightest discomfort. She continues to comfortably and with great hemodynamic stability respond to questions throughout the procedure. When interviewed a few days later, she displays no recall of the events. The film was well-received upon release and cemented Dr. Artusio and his colleagues’ reputations as pioneering physicians both within and outside the specialty of Anesthesiology.<sup>1,3</sup>

The next anesthetic challenge that garnered the interest of both Dr. Artusio and his close colleague Dr. Van Poznack, vice-chair of the Department of Anesthesiology at New York Hospital, was a significant one. The inhaled anesthetic agents available in the late 1950s posed a dilemma to anesthesiologists. Ether and Cyclopropane, while excellent anesthetic agents from a physiological standpoint, had one important flaw: they were extremely flammable. Their use in the operating room necessitated numerous cumbersome safety precautions and yet they posed significant danger to operating room staff. The non-flammable agents available at the time were also flawed, however, in that they either lacked potency as in the case of Nitrous Oxide or were too potent as in the case of Chloroform. Others also possessed significant toxicity, particularly renal and hepatic effects, which limited their use. It was in this setting that Drs. Artusio and Van Poznack took on the daunting task of creating a physiologically stable, non-flammable anesthetic agent that was both intermediate in its degree of potency and lacked significant tissue toxicity.

Through connections with the Dow and Abbott laboratories they were able to secure significant resources to aid in their quest. While Abbott provided the funding for the research, Dow made their Fluorine chemists and laboratories available to the project. This proved to be a particularly valuable collaboration. It allowed Dr. Van Poznack, who led the research team under Dr. Artusio’s guidance, to brainstorm fluorinated chemicals and create them readily in the laboratory. The convenience of this arrangement allowed the researchers to literally transfer ideas directly from the chalkboard to the clinical setting. Numerous new compounds were tested, many of which made it to the human phase of clinical trials. Finally, Methoxyflourane emerged as the novel new non-flammable agent they had been seeking.<sup>8,9</sup>

Methoxyflourane proved to be an incredibly useful volatile anesthetic agent for the anesthesiologist practicing in the late 1950s. It provided the physiological stability of Cyclopropane and Diethyl Ether and possessed excellent anesthetic and analgesic properties. The cumbersome safety procedures that flammable anesthetics necessitated became a thing of the past. In addition, Methoxyflourane displayed an intermediate level of potency that allowed for efficient delivery of anesthesia and analgesia with significant hemodynamic stability.<sup>10</sup>

In the summer of 1962 another film was produced displaying the remarkable anesthetic properties of this compound. In this film, a 64-year-old patient, scheduled for a gastrectomy secondary to a duodenal ulcer, is presented to a group of medical professionals. Dr. Artusio measures the patient's vital signs and begins a Methoxyflourane-based induction through a closed circle system using only pure oxygen as a diluent. Induction and onset of general anesthesia are achieved smoothly and within a few minutes. To further his point that Methoxyflourane provides ideal intubating conditions, Dr. Artusio forgoes the use of a neuromuscular relaxing agent. He intubates the patient using an endotracheal tube with ease. The patient's post intubation vital signs display little change from those obtained prior to induction much to the amazement of the spectators present.<sup>1</sup>

The film proved to be very effective in displaying the remarkable hemodynamic stability and excellent anesthetic, analgesic and relaxant properties of Methoxyflourane. The drug, marketed under the brand name Penthrane, eventually came to be widely used by anesthesiologists throughout the country. In subsequent years, as understanding of Methoxyflourane's properties progressed, it became apparent that it did indeed possess some degree of renal toxicity. Newer non-flammable agents were developed that lacked toxic tissue effects and provided similar levels of anesthesia and analgesia. It is hard to imagine however, that any of these subsequent discoveries would have been possible had the stage not been set by Artusio and Van Poznack and their pioneering work in those exciting times.

In spite of his significant accomplishments in the area of clinical research, Dr. Artusio also found the time to be a top notch educator. By 1969 he had compiled all the notes, used by the faculty in the department to teach medical students and residents, into a concise and organized form. With the help of Dr. Valentino Mazzia, he published a textbook called "Practical Anesthesiology". This publication became incredibly popular with residents and medical students alike. Although never updated, it became the foundation for a much larger and comprehensive series conceived in 1963.

The "Clinical Anesthesia" series edited by Dr. Artusio, since its inception over thirty years ago, continues to be one of the most highly regarded publications in the field of Anesthesiology. With the collaboration of a broad spectrum of his colleagues, many of them chairmen and gifted educators from departments across the country, Dr. Artusio and another close colleague Dr. Frank Yao collected and published a unique set of monographs. Each of these thoroughly dissected a single topic. The style and accessibility of information in these publications made them particularly popular among residents studying for the ABA licensing examination. The series continues to flourish to this day. Dr. Artusio recalled how the monograph entitled "A Method of Study" was actually conceived at the last minute to meet a publication deadline when another contributor failed to deliver a manuscript on time. In spite of being hastily drafted from mimeographs used to instruct residents, this particular edition conveyed in articulate and comprehensive manner information that was vital to the anesthesiologist-in-training. It became one of the most popular monographs in the series. Its emphasis on the basic sciences and their importance to the clinical practice of Anesthesiology was unique at the time. In time, the entire series became a valuable addition to every anesthesiologist's library.<sup>11</sup>

For a resident in Internal Medicine who reluctantly took on the practice of Anesthesiology, Dr. Joseph Artusio made some remarkable contributions. Over the course of his career, he became one of the longest serving chairmen in the history of the specialty, contributing over forty-five extraordinary years to the Department of Anesthesiology at New York Hospital. He is remembered to this day with great fondness at the institution. Ultimately his devotion to furthering the specialty is evident through the wide variety of endeavors he took on. As the President of the medical board of The New York Hospital and Chair of the committee to enhance the medical curriculum at Cornell University, he contributed to the medical education of innumerable medical students and residents. Highlights of his career include being one of the first thirty members invited to join the Association of University Anesthesiologists, his tenure on the Board of Governors of the American College of Anesthesiology, where he served as the Written Examinations Chairman for over 6 years, and his efforts in establishing the Society of Academic Anesthesia Chairmen. He also recalled with particular fondness, his

membership in the Society of Pharmacology and Experimental Therapeutics to which he dedicated a significant amount of his time.

As he celebrates his ninetieth birthday, at the time of this writing, Dr. Artusio can look back on a career that truly revolutionized the field of Anesthesiology. However, in spite of all his remarkable achievements, he will best be remembered as one of those daring physicians who was willing to take on an unpopular fledgling specialty and help transform it into the highly respected profession that it is today.

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## Intravenous Administration of Ether, Methoxyflurane, and Halothane

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Considerable experience with the intravenous (iv) administration of ether for surgical anesthesia in humans was obtained in the early 1900's in Germany by Burkhardt,<sup>1</sup> England by Rood,<sup>2</sup> and the United States by Honan.<sup>3</sup> Despite glowing reports, including smoother inductions and minimal postoperative nausea, it did not catch on because of "... *the necessity of the preliminary operation for finding the vein* [a "cut-down"]; ... *the danger of drowning the patient ... with excess fluid; the bleeding and oozing from the wound area are increased...*"<sup>4</sup> Attempts to reignite interest in iv administration of typically inhaled agents in humans occurred in the 1960's by Eger et al with ether,<sup>5</sup> especially when the operative procedure was a bronchoscopy or laryngoscopy, and Cascorbi et al with methoxyflurane in a lipid emulsion (Intralipid).<sup>6</sup> But high volumes of cold 5% ether-saline solution, up to 1000 ml in first hr and 500 ml in second hr, were required to maintain an adequate level of anesthesia, and iv methoxyflurane caused severe thrombophlebitis. Anesthesia was successfully induced and maintained with iv administration of halothane in a lipid emulsion to rats, cats, and dogs in the 1980's, but no human studies were reported. The iv administration of undiluted ether or halothane for purposes of substance abuse or attempted suicide resulted in severe acute respiratory distress syndrome, pulmonary edema, and right heart failure.<sup>7</sup> In the medical arena iv ether has been touted as treatment for gangrene secondary to arteriosclerosis,<sup>8</sup> compared unfavorably with electro-convulsive therapy as a treatment for affective psychoses,<sup>9</sup> and used in the modern era as a rare but controversial treatment for status asthmaticus.<sup>10</sup> Although inhaled agents have been given, or taken, orally, intravenously, and rectally, the inhaled route still remains the preferred route of administration.

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## Open Flames in Operating Rooms

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Open flames and ether vapors coexisted in close proximity in 19<sup>th</sup> and early 20<sup>th</sup> century operating rooms. Prior to arrival of electric lighting in the 1880's, and even for years after, candles or gas lamps illuminated surgical fields.

Etherisation can, with a little caution, be used by inhaler with candle or artificial light, where the more wasteful and diffused application by sponge would be inadmissible, from the danger of ignition.<sup>1</sup>

If ether is to be used, it must not be near an open fire or a lamp or gas jet, unless the light is so elevated as not to come in contact with the vapor, which being heavier than air settles down.<sup>2</sup>

It is necessary quite frequently to operate in a private house, with low ceilings, under the guidance of a gas or lamp light, either of which is sometimes brought near to the patient. Great care should be exercised on such occasions, for while accidents rarely happen, yet when they do, they are not only fraught with danger, but are keenly embarrassing to the surgeon and his assistants.<sup>3</sup>

Many anesthetists believed that inhalation of cold ether caused bronchial irritation and hypothermia. "The danger of bronchitis is due to the tendency of the cold vapor to freeze the lungs."<sup>4</sup> In 1876 Lawson Tait introduced a warm ether inhaler that used a spirit [alcohol] lamp flame to heat the ether vapor chamber.<sup>5</sup> In 1916, Gwathmey stated,

It takes much longer to kill an animal with warm ether than it does with cold... patients lose only 0.29°F with warmed ether vapor, against a loss of 1.02°F with the open drop method.<sup>6</sup>

Liquid nitrous oxide became commercially available in cylinders in the 1870's.

In those days nitrous oxide was neither as pure nor as dry as it is today and it was not unusual for the outlet valve of the cylinder to freeze up and cause the flow of nitrous oxide to cease. To avoid this embarrassing occurrence a small metal spirit lamp was commonly hung upon one of the cross bars so that its flame might play on the valve in use. Despite the proximity of this flame to the ether container it appears that explosions were seldom encountered, although there is at least one recorded.<sup>7</sup>

Fortunately from the perspective of fire and explosion hazards our anesthesia forefathers rarely used supplemental oxygen and administered the relatively unflammable chloroform or heavier than air ether.

... a lighted match or candle may be held two inches above the level of the ether in an open container for three minutes without ignition... [But] if a sponge, saturated with ether, is gently placed at one end of a table, or on the floor, or in an ordinary sink, and a lighted match held two feet away and close to the table, the floor, or the bottom of the sink, the vapor will quickly ignite and burn over a considerable surface.<sup>3</sup>

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## Anesthesia for the First Heart Transplant

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The first human-to-human heart transplant occurred December 3, 1967, at the Groote Schuur Hospital (GSH) in Cape Town, South Africa. The anesthetist was Dr. Joseph Ozinsky who obtained his MBChB degree from the University of Cape Town in 1949. He trained in anesthesia in Cape Town, Durban and London, obtaining his FFARCS (Ireland) in 1955. In 1958, he joined thoracic surgeon Christian Bernard at the GSH and by 1967 they had performed nearly 1000 operations using cardiopulmonary bypass.

On the afternoon of December 2, the donor was hit by a car and taken to the GSH. It was determined that her skull fractures and brain injury were terminal. Early the next morning, she was taken to OR "A" with relatively normal vital signs and prepared for heart and kidney donation. Shortly thereafter, the recipient, a 54-year-old man with end-stage ischemic cardiomyopathy, who had been hospitalized three weeks earlier in anticipation of transplant, was taken to OR "B" next door. Monitors for the recipient consisted of an oscillometric blood pressure, EKG, urinary catheter, temperature and a water manometer for CVP. Acid-base and carbon dioxide determinations were by the Astrup technique. Induction consisted of thiopental 200 mg slowly, followed by succinylcholine 100 mg. Following tracheal intubation, anesthesia was maintained with nitrous oxide, oxygen and intermittent halothane. After institution of cardiopulmonary bypass, anesthesia was maintained with halothane from a vaporizer in the oxygen line to the bubble oxygenator. Between 3 to 4 hours later, the patient was given a second dose succinylcholine, defibrillated and weaned from bypass. Rhythm control was established with a lidocaine infusion and circulation supported with isoproterenol. Meperidine 25 mg was given IM to prevent shivering. The oral tracheal tube was changed to nasotracheal and the patient taken to ICU. He was extubated the next morning. About two weeks later, the patient developed pneumonia. The night he died, a Bird ventilator was inadequate to ventilate him so Dr. Ozinsky hand ventilated him for several hours.

Gordon, an anesthetist currently at the GSH, in his recent article notes that "the actual agents used are less important than the skill of the administrator."

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## Ralph M. Waters' Florida Retirement Rest

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Ralph Waters wrote to the Dean of the Medical School on October 31, 1947, three weeks after his sixty-fourth birthday announcing his intention to retire in a year's time. Although he discusses his "primary object", that is, his concern for the "efficient continuation of the Department at Wisconsin" and the transition of leadership, he must have also been thinking of a sunny citrus grove next to a lake in central Florida.

In fact, he had been thinking about Florida for a long time. Letters to Noel Gillespie in the 1930s mention Waters' visits to his sister in Orlando and the pleasures of spring weather in the South when winter gripped Madison. In a July 1937 letter to Gillespie he asks, "Did I ever tell you that we had five acres of land on a little lake in central Florida.[?]...The land is burnt over turpentine forest with a few pine trees remaining. It is citrus land. We are proposing to clear the small second growth leaving the good pine trees and planting some little citrus trees next winter.... Grapefruit from one's own trees at the back door before breakfast makes the most delightful beginning of the day from a gastronomic standpoint."

With his retirement Waters moved with his wife, Lou, to Lake Lucy on Rural Route #3, Orlando, where his sister also owned property. In addition to tending his citrus grove, he remained an avid reader and active correspondent often sitting in the breezeway with a view of the lake. It was from here that Waters traveled to the 3<sup>rd</sup> World Federation of Societies of Anesthesiologists meeting organized by Carlos Parsloe in Sao Paulo, Brazil in 1964. Perhaps most pleasing, though, were the visits from old colleagues and students.

One special gathering, organized by Virginia Apgar, occurred on February 27, 1966, and included some 20 Aqualumni and friends. The attendees ate, talked, watched movies of previous Aqualumni gatherings and took more pictures. Greetings were sent from across the world and contributions resulted in a gift of \$2,500 for the Waters. Dr. Waters suggested he would use the money to replace trees lost in a recent cold snap.

Mrs. Waters died on February 12, 1975, and her remains were interred in a grove between the house and the lake. Dr. Waters continued to live at the house until his own death at age 96 in 1979. His cremated remains rest near those of his wife on the property.

The house remains in the family and is owned by Dr. Waters' granddaughter, Martha Tetlow, the daughter of John Waters. Patrick Sim and I were the guests of the Tetlow's at Waters' retirement home in October 2008 when the ASA met in Orlando.

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## Why was there a Four-Decade Delay, from 1800 to 1842, in the Advent of Anesthesia?

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The question as to why there was a delay in the advent of anesthesia from 1800 to 1842 has not been fully and convincingly answered. In 1800 Humphry Davy suggested a limited use for nitrous oxide in obtunding the pain of surgery,<sup>1</sup> but that *suggestion of anesthesia* was not followed up; and it was not until Crawford Long in 1842 used ether to abolish operative pain<sup>2</sup> in a patient that the *fact of anesthesia* was established (though not then publicly demonstrated). Remarkably, this delay, which has been likened to an 'historical puzzle,'<sup>3</sup> is not discussed in standard texts on anesthesia history, though some anesthesiologists<sup>3-6</sup> and some historians<sup>7,8</sup> have done so. However, other questions have arisen: Why was Davy's *suggestion of anesthesia* not followed up? What made Henry Hickman, in 1823, experiment with carbon dioxide, thus validating the *principle of anesthesia*? Why, too, was his endeavor ignored? And why was it Crawford Long, in rural Georgia in 1842, who finally *demonstrated the fact of anesthesia*? Those questions, which lie at the heart of the germinal period of the prehistory of anesthesia, form the context of the proposed paper.

The purpose of the paper is to provide an answer to those questions by stressing the scientific and medical aspects of the 'puzzle' rather than the esoteric and academic ones that have been asked by some authors. The approach is threefold. First, developments in the scientific, social and cultural background to the period from 1800 to 1842 will be reviewed because those developments form the background to the slow evolution of thinking about anesthesia in that period. Second, both the negative forces that impeded the formulation and the acceptance of the idea of anesthesia, and the positive forces that overcame them, will be evaluated. And, third, the nature and interests of Davy, Hickman, and Long will be emphasized in an effort to highlight more clearly the role, and the reasons, that each individual played in this period of the history of anesthesia. Such an approach, by focusing attention on the individuals concerned and the times they lived in, is likely to be more productive than approaches that are characterized by tenuous connections that are made between the events and individuals in this period and the apparent delay in the advent of anesthesia.

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## Rectal Ether Anesthesia: A Technic Evolves and Finally Disappears

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Plato stated that “necessity is the mother of invention.” This same precept is seen in the specialty of anesthesiology. As we all know, diethyl ether had many favorable qualities as a general anesthetic: stable hemodynamics; stable respiration; abdominal muscle relaxation; minimal, if any, metabolism; lack of renal or hepatic effects; and others. Oral secretions, vomiting, and the period of excitement were often reported problems that adversely affected an inhalational induction. And what about the patient who is having surgery about the face and neck? How does the surgeon do his task when the face is covered by the anesthesia mask?

Whether for the desire of a more pleasant induction or the absence of any interfering anesthesia equipment about the face, the idea for rectal anesthesia developed. Several references to rectal ether anesthesia appeared in 1847, but only Dr. Pirogoff in St Petersburg, Russia, apparently used this technic to any degree in humans.<sup>1</sup>

This topic next appeared in the medical literature in 1884. Dr. Daniel Molière on March 30 reported in the *Lyon Médical* his experiences with rectal etherization after the topic was recommended to him by a visiting Danish physician. Dr. Molière administered rectal ether to four patients, with the latter three patients receiving ether vapor after the flask of ether was placed into a 50 C water bath. Reported benefits were:

It suppresses the period of excitation; it permits one to regulate the dosage very exactly; it reduces to a minimum the amount of ether needed; it allows the surgeon opportunity to operate upon the face; it is a more agreeable method to those patients to whom the odor of ether is nauseating and objectionable.<sup>2</sup>

On May 3, 1884, Dr. William Bull in New York City, after reading about Molière's practice, reported his series of 17 patients to whom he administered rectal ether vapor.<sup>3</sup> Seven of these patients had the subsequent passage of “loose” stools, and two had blood in their stools. Bull disagreed with some of the possible benefits previously mentioned, stating that induction was prolonged and this technic did not suppress the period of excitement. Additionally, on several occasions he had to supplement the rectal ether induction with inhaled ether.

Other purported advantages of rectal ether anesthesia included: 1. “if vomiting occurs during etherization it does not interrupt the administration of the anaesthetic,” 2. “the secretion of mucus, which so frequently fills the mouth and air passages, has not occurred so far.” Another benefit was a decreased sense of suffocation during induction.<sup>4</sup>

Soon came the report of at least two deaths in New York City related to rectal ether administration.<sup>5</sup> One of the deaths was in a child, and the other was in a woman for a minor surgery in whom “after death the whole large intestine, together with the lower part of the small intestine, was found (to be) in a state of acute ulceration.” After a few more reports over the next several weeks, with some deaths involved, it seems that this practice disappeared until revisions were made in the technic.<sup>6,7</sup>

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## Managing Pain in Medieval England

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### Research Problem:

This paper, and PowerPoint presentation, will look at medieval physician's attempts (and some successes) at controlling both chronic and acute pain in patients. I will be examining several different physicians 'commonplace' books and medical reference materials. My research for this presentation will concentrate for the sake of time on the works of Gilbertus Anglicus (ed. Faye Marie Getz) and Bartholomeus Anglicus (Huntington Library rare book #82741), both twelfth-century physicians of England. I will incorporate some comparative material from other medieval medical works, such as BL Royal ms 12B xxv.

### Methodology:

Though this paper will not be limited to the pain of those with physical and mental disabilities, my research to date has concentrated on mental disabilities of the Middle Ages and in this research I am looking specifically to find out what type of pain care was available for the disabled in chronic pain. Gilbertus and Bartholomeus are both works for which I have seen both printed primary language editions, and for which I have seen the originals in the archives. I will stick primarily to original sources as I can and turn only to secondary works to fill in background.

To date, no work on the topic of pain care for the disabled in the Middle Ages has been done to my knowledge. There has been some work done on medieval pain and its care, medieval medicine generally, and medieval disability to a small extent.

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## **Katharine Georgina Lloyd-Williams 1896-1973: A life of extraordinary contribution.**

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Katharine (Kitty) Lloyd-Williams was born on 14 February 1896, in Wales. She was educated in Oswestry, Shropshire and Caterham, Surrey before attending Bedford Physical Training College from where she qualified with their diploma. After a few years teaching and working as a physiotherapist, she was encouraged to take up medicine and enrolled at the Royal Free Hospital in London in 1921 qualifying MBBS and LRCPMRCS in 1926 and 1927 respectively. She initially worked as a general practitioner and then moved into an increasing participation in anaesthesia. In 1929 she was granted an MD.

Her main interest in anaesthesia was in obstetric practice and in 1934 she published a small book on the subject.<sup>1</sup> She became consultant anaesthetist to the Royal Free Hospital and during the 2<sup>nd</sup> World War was the sole senior anaesthetist there full time. She became an honorary FFARCS when the Faculty was created in 1948 and became a founder member of their first Council, a unique honour in the male dominated profession of that time. While maintaining an active anaesthesia practice until her retirement in 1962 she then embarked on a major drive in education becoming Dean of her Medical School and then Dean of the Faculty of Medicine in the University of London.

A great believer in the equality of women she was a member and subsequent President of the Medical Woman's Federation. She was President of the Anaesthetic Section of the Royal Society of Medicine, became a CBE in 1956 and was appointed to the General Medical Council in 1961 where she served for 10 years.

After her retirement from active anaesthesia practice and her deanery in 1962 she moved back to Wales and spent time in gardening, travel and walking. Her health slowly worsened and in particular her eyesight and she died in Faro, Portugal, while away on holiday in January 1973.

Charming, beautiful, dynamic, an outstanding sportswoman and with time for all whom she met, Katharine Lloyd-Williams never married. She made a huge impact on her speciality and on medicine in general. Her role has been overlooked to date and this paper will explore all aspects of her life.

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## Dr. Robert Hanham Collyer: The Strange Life of a Mesmerist, Phrenologist and Ether Controversy Jump-up- Behinder

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In 1871 the second edition of a book appeared in London, from the publishing firm of Henry Renshaw, entitled *Mysteries of the Vital Element in Connexion with Dreams, Somnambulism, Trance, Vital Photography, Faith and Will, Anaesthesia, Nervous Congestion and Creative Function. Modern Spiritualism Explained*. The author was identified on the title page as Robert H. Collyer, M.D., “Registered by the Council of Medical Education. Original Discoverer of Anesthesia by the Inhalation of Narcotic and Stimulating Vapours, Discoverer of Electro-biology, Author of *The Physiology of the Brain and Nervous System*; Graduate of the Berkshire Medical College, Massachusetts; Member of the Massachusetts Medical Society; formerly Student of the London and Paris Schools of Medicine; late Principal Physician to the Cholera Hospital, Mexico.” To press his points, the author includes a quotation from the *Lancet* of June 11, 1870: “Dr. Collyer, to our minds, is the true modern pioneer, after all—the man who ran first.” Questions abound as to just what Dr. Collyer pioneered—if anything—and yet this title page only hints at the fascinating character he must have been.

Robert H. Collyer was born on March 5, 1814, in Jersey on the Channel Islands. One of his ancestors included his great-grandfather Joseph Collyer, the elder [1714?-1776], a translator and bookseller and the son of another Joseph Collyer [d. 1724], also a bookseller and treasurer of the Stationers’ Company. Joseph the elder’s first wife was Mary Mitchell Collyer, also a translator and novelist. Their son, Joseph the younger, was official engraver to Queen Charlotte in the late 18<sup>th</sup> century and a member of the Royal Academy in London.

Collyer thus had a distinguished pedigree, but left England for America, and by his own account “after a rough and trying voyage” arrived in New York on June 15, 1836. He had studied under Britain’s foremost advocate of mesmerism, John Elliotson, and in New York began to lecture “to overflowing houses” and then “accepted invitations to visit Philadelphia, Baltimore, Washington, South Carolina, and New Orleans.”<sup>1</sup> His lectures included demonstrations of painless tooth-pulling, a common ingredient in the mesmeric lecturer’s bag of tricks. Collyer received a medical degree from Berkshire Medical College [1823-1869] in Pittsfield, Mass. After Morton’s 1846 demonstration in Boston, Collyer became a vociferous advocate for his own priority, claiming that he had used anesthesia in 1842 and published an account the following year.

For the next three decades Collyer published numerous volumes in which he supported his claim. In an issue of February 6, 1847, the *Lancet* labeled him a member of “the class of jump-up-behinders” [p. 163], an assessment with which the distinguished anesthesia historian W. Stanley Sykes agreed.<sup>2</sup> Yet Collyer remains a fascinating figure whose vast published output touched on many fascinating subjects of his time.<sup>3-10</sup> This paper will explore what is known about Collyer and his claims to priority in several areas.

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