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## Contradicting a Unitary Theory of General Anesthetic Action: a History of Three Compounds from 1901 to 2001

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This article tied for second place in the 2001 AHA Resident Essay Contest Award and has been peer reviewed and accepted for publication in the Bulletin of Anesthesia History.

The introduction of diethyl ether, chloroform, and nitrous oxide into clinical practice over 150 years ago revolutionized medicine and surgery. However, despite a long period of clinical use, it has been difficult to elucidate the molecular basis for general anesthesia. Even today this question continues to be a source of active inquiry and debate.

Although investigators in the last half of the nineteenth century proposed various theories for the actions of anesthetics, the first 'modern' theory for general anesthetic action came from the independent works of Meyer and Overton. The observation by Meyer and Overton, supported by extensive experimental investigation, was that the anesthetic potency of certain compounds ('narcotics' in the older terminology) varied in direct proportion to the partition coefficient in a lipid solvent such as olive oil. While these results did not prove any particular molecular target, the results were often interpreted to indicate the lipid membrane as the site of anesthetic action (the Meyer-Overton 'lipoid' hypothesis), described as follows by Meyer:

The narcotizing substance enters in a loose physico-chemical combination with the vitally important lipoids of the cell, perhaps with the lecithin, and in so doing changes their normal relationship to the other cell constituents, through which an inhibition of the entire cell chemism results.<sup>1</sup>

Although Meyer and Overton recognized limitations to their experimental

observations, their work was taken as the basis for a unified 'lipoid' theory of anesthesia. The Meyer-Overton theory is not the only unitary theory of anesthetic action. At least seventeen distinct unified theories have been proposed between 1847 and 1997 (see Table 1). It is nearly impossible to find a review article or book chapter on the mechanisms of anesthetic action that does not in some way mention the Meyer-Overton hypothesis or a related unified theory of anesthetic action.

While the legacy of Meyer and Overton has dominated investigations of general anesthetics, support for their hypothesis was hardly monolithic. In the last several decades in particular, unified theories of anesthesia have come under increasingly severe attacks and the general,<sup>2,3</sup> although by no means unanimous,<sup>4,6</sup> consensus is that anesthetics, as with most drugs in current medical use, act at protein receptor targets. A clear symbol of the 'changing of the guard' is illustrated by comparing two quotations from the 1990 and 1996 editions of the pharmacology textbook **The Pharmaceutical Basis of Therapeutics**. The 1990 edition reads:

Most theories of anesthetic action are based on the physicochemical characteristics of the anesthetic drugs. These proposals relate closely to the correlation between the potency of an anesthetic agent and the solubility of the drug in oil ... Interpretation of this fundamental result is thought to be crucial to the understanding of the action of anesthetics.<sup>7</sup>

In the 1996 edition of this text, the above passage was repeated but with the last sentence in the passage amended as follows:

Interpretation of this fundamental result, *once thought to be crucial to the understanding of the action of anesthetics, may be only an incidental finding*.<sup>8</sup> (italics added)

The following sections will focus on three compounds whose actions are inconsistent with the Meyer-Overton hypothesis. Two of the compounds,  $\alpha$ -chloralose and chloral hydrate, were anesthetics known to Meyer and Overton, and recognized at least by Overton as having properties which were difficult to explain by his hypothesis. The third compound, flurothyl (hexafluorodiethyl ether), is a volatile, fluorinated ether with convulsant properties which was discovered in 1957. While these three compounds posed a challenge for the Meyer-Overton hypothesis, their properties were mostly ignored by those favoring a unitary theory of anesthesia. The end of this manuscript will speculate on reasons for this.

### The Chemical Diversity of General Anesthetics

The chemical diversity of compounds that can produce general anesthesia is impressive and encompasses ethers (diethyl ether, isoflurane), alkanes (chloroform, halothane), alcohols (ethanol, chloral hydrate), chloralose, barbiturates, phenols (propofol), etomidate, steroidal compounds (alphaxalone), and inorganic

Continued on Page 4

# Anesthesia History at the ASA Annual Meeting October 2003

## Forum on the History of Anesthesia

*Sponsored by the Wood Library-Museum of Anesthesiology*

### Before It's Lost: Capturing the History of Subspecialization in Anesthesiology

*Objectives: The attendee will understand the impetus behind the formation of subspecialty societies in anesthesiology. The attendee will also learn about the documentary evidence and means to preserve the early history of sub-specialization.*

Moderator: Douglas R. Bacon, M.D., M.A.  
Associate Professor of Anesthesiology and the History of Medicine  
Mayo Clinic, Rochester, MN

The Perils and Pitfalls of Documenting Recent History—Can the WLM help?  
*Douglas R. Bacon, M.D., M.A.*

The Association of University Anesthesiologists  
*William K. Hamilton, M.D.*  
Professor Emeritus of Anesthesia  
University of California, San Francisco, CA

The Society of Cardiovascular Anesthesiologists  
*Roger Moore, M.D.*  
Past President, Society of Cardiovascular Anesthesiologists  
Assistant Treasurer, American Society of Anesthesiologists

Society for Education in Anesthesia—The History of Teaching?  
*Phil Liu, M.D.*  
Professor of Anesthesiology  
Harvard Medical School, Boston, MA

Society for Obstetrical Anesthesia and Perinatology—Caring for Mom and Baby  
*Gary Vasdev, M.D.*  
Assistant Professor of Anesthesiology  
Director of Obstetrical Anesthesia  
Mayo Clinic, Rochester, MN

The American Society of Regional Anesthesia—Even Better the Second Time  
*David Brown, M.D.*  
Professor and Chair, Department of Anesthesia  
University of Iowa

Society of Neurosurgical Anesthesia—Focused on the Brain  
*Maurice Albin, M.D., MSc.*  
Professor of Anesthesiology  
University of Alabama at Birmingham

Society for Ambulatory Anesthesia  
*Lydia Conlay, M.D., Ph.D.*  
Professor and Chairman, Department of Anesthesiology  
Baylor College of Medicine, Houston, TX

Society for Pediatric Anesthesia  
*Mark Rockoff, M.D.*  
Professor of Anaesthesia, Harvard Medical School  
Vice Chairman, Department of Anesthesia  
Children's Hospital, Boston, MA

## Panel on History

### APGAR at 50: A Celebration of the Remarkable Anesthesiologist Who Changed Neonatal Assessment and Obstetric Anesthesia

*Objective: After attending this panel the learner will gain an appreciation for the development of the APGAR score. The learner will also learn about the challenges of academic practice and the social milieu of anesthesiology in the late 1940s and 50s.*

*The learner will also gain an understanding of a small part of the history of anesthesiology that has everyday application.*

Moderators:

Douglas R. Bacon, M.D., M.A.  
Associate Professor of Anesthesiology  
Mayo Clinic, Rochester, MN

Maurice Albin, M.D., M.Sc.(Anes.)  
Professor of Anesthesiology  
University of Alabama at Birmingham

1. Obstetrical Anesthesia in 1950—  
Issues without Answer?  
*David Waisel, M.D.*  
Assistant Professor of Anaesthesia  
Harvard Medical School, Boston, MA
2. Neonatal Resuscitation:  
An Historical Perspective  
*George Gregory, M.D.*  
Professor of Anesthesiology, UCSF
3. The Columbia Department:  
A microcosm of Academic  
Anesthesiology in the 1950s  
*Douglas R. Bacon, M.D., M.A.*
4. Virginia Apgar—  
Anesthesiologist Extraordinaire  
*Selma Calmes, M.D.*  
Professor and Chair  
Dept. of Anesthesiology, UCLA
5. The APGAR Score  
*Randy W. Calicott, M.D.*  
Assistant Professor of Anesthesiology  
Wake Forest University  
Winston-Salem, NC
6. I Remember Ginny  
*Frank Moya, M.D.*  
Chairman, Frank Moya Continuing  
Education Programs, Inc.  
Coral Gables, FL

## Wright Lecture

The 2003 Lewis H. Wright  
Memorial Lecture  
of the  
Wood Library-Museum  
of Anesthesiology

*Tuesday, October 14, 2003*  
*12:50 PM – 1:50 PM*  
*ASA Annual Meeting*  
*The Moscone Center, Rooms 124-125*  
*San Francisco, CA*

**Peter L. McDermott, M.D., Ph.D.**  
Professor of History  
California Lutheran University  
Past President  
American Society of Anesthesiologists, 1993  
Thousand Oaks, California

**Fallacies and Useful Truths: An  
Overview of History and Science for  
the  
Anesthesiologist...  
or Lust, Torture and Depravity:  
The Anatomy of Derangement**

Introduction by  
Kathryn E. McGoldrick, M.D. and  
Susan A. Vassallo, M.D.

The Lewis H. Wright Memorial Lecture of the Wood Library-Museum honors a distinguished Pioneer in American Anesthesiology who gave himself tirelessly to dignify and accredit the discipline of anesthesiology as a clinical science and medical specialty. No part of the country was too far or too remote for him to reach with his advice and support. Because he had the wisdom to envision the value of the use of curare in anesthesia, he made his most significant contribution to anesthesiology in 1940 when he first suggested and later arranged for the clinical trials of this remarkable drug which has revolutionized the practice of anesthesiology for all time. In 1955, the American Society of Anesthesiologists recognized his contributions by according him their highest honor, the Distinguished Service Award. This Lectureship will serve to remind us now, and in the years to come, of his honored place in the specialty of Anesthesiology.

## Recent AHA Council Correspondence

Hello AJ:

Just a brief note about the last two days. I believe and it is my impression from those to whom I spoke, that the meeting was a splendid success. Ray and others will give you full details.

We were incredibly lucky with yesterday's weather and the tour of the Ether Dome and the Mt. A. Cemetery were enlightening, fascinating and gratifying. I am not one for too much hyperbole but one has to use these words.

Elliott M. did a splendid job despite his tendency to travel at high speed in the on the winding hilly roads in the leading HUMV (I think he thought he was in the Iraqi desert with the banditti all around), which twice left the rest of the procession viewing parts of the Great Graveyard we did not even know existed. So many people dead one would have liked to talk to. But the planned visits were superbly presented and deeply impressive.

A very well run meeting of Council at Illegal Seafood, came up with and voted positively on a number of stirring resolutions which of course you will hear about shortly.

While waiting for the evening reception, the VP of the AHA who is no longer used to rising at 6 a.m. was found asleep in the lobby at 7 p.m. by an attendant who threatened him with summary removal by a band of roving EMT's.

Today's program, which of course the present writer could only attend 62.5 % of (are ending prepositions still forbidden) contained the usual number of excellent original, creative, even moving, papers. Most gratifying to the elders were the residents' presentations. This despite the continuing designer incompetence on the part of the Westin's audiovisual department.

Congratulations to you and all organizers and helpers but particularly to Debbie Bloomberg who answers the eternal question, "What have we forgotten?"

All the best,

Gerald  
Gerald Zeitlin, M.D.

2003 History of Medicine theme issue. As an Associate Editor of msJAMA, I would like to invite contributions.

Issue Theme: History of Medicine  
Submission Deadline: August 20,  
2003

Issue Publication Date: November,  
2003

This issue will include essays on medical historiography, historical narrative and reflection on the relevance of history to medicine. Possible areas of interest for submissions might include:

- \* Compulsory vaccination programs and their opponents
- \* Historical epidemiology
- \* The historical context of the evidence-based medicine movement
- \* Medical biography
- \* Historical perspective on "hot topic" issues such as bioterrorism or The Emergency Health Powers Act
- \* Reflection on the writing of medical history

These suggestions are by no means meant to limit the scope of this issue. Authors are welcome to consider topics of their own choosing. Submissions should be in the form of short commentaries or highly focused editorial-style reviews of either 900 or 1,800 words. ***The deadline for submissions is August 20th.***

Please direct all inquires and submissions to rahul.rajkumar@yale.edu. msJAMA, the medical student section of JAMA (The Journal of the American Medical Association.) appears once a month as a Medline referenced section of JAMA and is edited by a team of medical students under the supervision of the JAMA senior staff. Authors publishing in msJAMA, usually research scientists or policy makers, have the opportunity to comment on cutting edge medical issues in a highly visible forum. Most importantly, they have the opportunity to influence and inspire the doctors of tomorrow.

\*\*\*\*\*  
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Associate Professor of Anesthesiology  
Director, Section on the History of  
Anesthesia  
Dept of Anesthesiology/Library  
University of Alabama at Birmingham  
ham

## Contradicting. . .Continued from Page 1

Theory	Authors
Dissolution and removal of fat-like substances in the brain (1847)	E. von Bibra & E. Harless <sup>57</sup>
Colloid theory (1875)	C. Bernard <sup>58</sup>
Meyer-Overton 'lipoid' hypothesis (1899-1901)	H.H. Meyer <sup>1,11</sup> and C.E. Overton <sup>14</sup>
Alteration of surface tension (1904)	J. Traube <sup>59</sup>
Action by achieving certain molar concentration in lipids (1937)	K.H. Meyer <sup>60</sup>
Thermodynamic activity (1939)	J. Ferguson <sup>61</sup>
Membrane volume occupation (1954)	L.J. Mullins <sup>62</sup>
Hydrate microcrystal theory (1961)	L. Pauling <sup>63,64</sup> and S.L. Miller <sup>65</sup>
Membrane disordering (1968)	J.C. Metcalfe et al. <sup>66</sup>
Membrane expansion (1972)	P. Seeman <sup>67</sup>
Critical volume hypothesis (1973)	K.W. Miller et al. <sup>68</sup>
Alteration of lipid phase transitions (1976-1977)	A.G. Lee <sup>69</sup> and J.R. Trudell <sup>70</sup>
Multi-site expansion hypothesis (1978)	M.J. Halsey et al. <sup>71</sup>
Proton-pump leak hypothesis (1980)	A.D. Bangham and W.T. Mason <sup>72</sup>
Disruption of hydrogen bonds (1990)	H. Brockerhoff et al. <sup>73</sup> J-S. Chiou et al. <sup>74</sup>
Alteration of membrane curvature (1991)	S.M. Gruner and E. Shyamsunder <sup>75</sup>
Alteration of membrane dipole potential (1995)	Z. Qin et al. <sup>76</sup>
Alteration of lateral membrane pressure (1997)	R.S. Cantor <sup>77</sup>

Table 1. Major unitary theories of general anesthesia formulated between 1847 and 1997

gases (nitrous oxide, xenon). Many of these chemical classes were known to Meyer and Overton. Indeed, Overton analyzed an extensive breadth of compounds including diethyl ether, chloroform and other halogenated alkanes, primary alcohols, halogenated alcohols, chloralose, nitriles, aldehydes, ketones, esters, amides, aromatic hydrocarbons, phenols, carbon dioxide, carbon disulfide, nitrous oxide, and opioids.

To support unified theories of anesthetic action, the chemical diversity of anesthetic molecules is often emphasized. The following statement from a recent edition of a medical pharmacology textbook is typical:

The shape and electronic configuration of the molecule is evidently unimportant, and the pharmacological action requires only that the molecule has certain physicochemical properties. The lack of chemical specificity argues against there being any distinctive 'receptor' for anesthetics.<sup>9</sup>

Despite the apparent non-specificity of a chemical structure required for anesthetic action, some scientists expressed doubts about the validity of the lipid hypothesis. For example, R.S. Lillie pointed out in 1916:

First it should be noted that substances belonging to the most various classes may have anaesthetic effects. This fact is overlooked in theories like those of Overton and Meyer, Traube, and others, which refer anaesthesia to the special properties of lipid-solvent substances[;] ... however, lipid-solubility or surface activity is not essential to narcotic activity; magnesium sulphate has long been used by naturalists to narcotize marine animals ... [Thus,] the parallelism between lipid-solubility and narcotic action is not an exact one, and many exceptions to the rule are known.<sup>10</sup>

Lillie touches on a fundamental problem with the Meyer-Overton hypothesis: the correlation between anesthetic potency and lipid solubility is impressive *for a certain group of compounds*, but exceptions to the rule exist. Meyer and Overton discuss observations that are difficult to explain based on a simple, unified theory. For instance, Meyer recognized that magnesium salts and opioids probably produced their anesthetic effects by a mechanism different than that of the 'alcohol lipoids', a finding that was definitively demonstrated by later research.<sup>11</sup> Meyer also proposed that the convulsions elicited by some compounds could result from affinity to 'cell constituents' other than the 'cell lipoids'.<sup>11</sup>

Exceptions to the Meyer-Overton hypothesis can be classified into three general categories.

(1) Highly lipid-soluble molecules which are not anesthetic or produce other physiological effects such as convulsions (e.g., volatile 'non-immobilizers', flurothyl).

(2) Molecules which possess low lipid solubility but yet are potent anesthetics (e.g.,  $\alpha$ -chloralose, chloral hydrate).

(3) Compounds which possess equal lipid solubility but unequal anesthetic potencies (e.g., anesthetic optical isomers).

Closer investigation of chloralose, chloral hydrate, and flurothyl will illustrate these categories.

### $\alpha$ -Chloralose

The chloralose molecules are an interesting class of anesthetic compounds, being essentially a hybrid of chloral hydrate and a sugar, with  $\alpha$ -chloralose resulting from the condensation of chloral (trichloroacetaldehyde) and glucose (Figure 1). (Chloral hydrate is formed from reaction of chloral with water). Although evaluated only briefly in the early part of the twentieth century as an anesthetic agent for humans,  $\alpha$ -chloralose has found extensive use in veterinary anesthesia<sup>12</sup> and as a rodenticide.<sup>13</sup> In his 1901 publication **Studies of Narcosis (Studien über die Narkose)**<sup>14</sup>, Overton found that anesthetic differences between  $\alpha$ -chloralose and its structural isomer  $\beta$ -chloralose were hard to explain. Overton summarized his experiments with the chloralose isomers as follows:

The phenomena of narcosis with  $\alpha$ -chloralose are not very easy to interpret ... Parachloralose [ $\beta$ -chloralose], which is only very slightly soluble in water in most solutions, has absolutely no narcotic effect. Tadpoles can live for weeks in saturated aqueous solution.<sup>14</sup>

A number of investigators returned periodically to the problems of the  $\alpha$ - and  $\beta$ -chloralose isomers and verified Overton's initial observations although problems with chemical purity and uncertainty about molecular composition plagued research with chloralose isomers until the mid-twentieth century.<sup>15</sup> Finally in 1940, T.C. Butler utilized high-purity  $\alpha$ - and  $\beta$ -arabinose optical isomers and synthesized two pairs of arabinochloraloses (i.e.,  $\alpha$ -*d*- and  $\alpha$ -*l*-arabinochloralose;  $\beta$ -*d*- and  $\beta$ -*l*-arabinochloralose) that showed anesthetic potency differences not only between the  $\alpha$ - and  $\beta$ - structural isomers but also between the respective optical isomer pairs.<sup>16</sup> Thus, the anesthetic properties of the chloralose molecules are inconsistent with the Meyer-Overton rule in several ways: (1)  $\alpha$ -chloralose is a more potent anesthetic than predicted by the Meyer-Overton rule, (2) optical isomers of  $\alpha$ -chloralose have different anesthetic potencies but by definition equal physico-chemical properties, and (3) the poorly water-soluble  $\beta$ -chloralose is inactive as an anesthetic. These results prompted Butler to point out:

Those theories which still enjoy any favor are either hedged about with so many protective reservations or

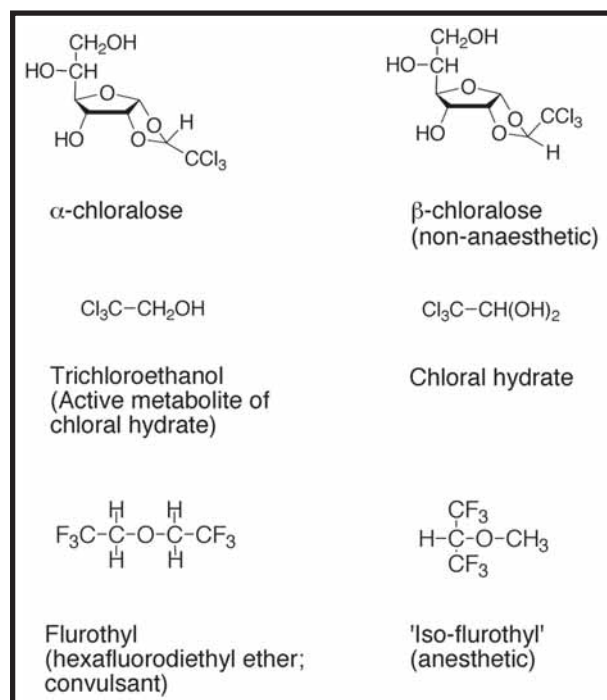


Fig. 1

are stated in such general terms that it is difficult to conceive of any feasible experiment which could give unequivocal support to any of them. None of the well-known theories gives special consideration to the role of asymmetry in the mechanism of narcosis ... Theories (such as that of Meyer and Overton) which seek to correlate narcotic activity with physical properties are of course inadequate to explain unequal activity of antipodes [i.e., optical isomers].<sup>16</sup>

Since Overton's theory was proposed, chloralose was ignored by those supporting a unitary theory of anesthesia. In contrast, Eccles and colleagues utilized the tools of electrophysiology to investigate the actions of  $\alpha$ -chloralose on synaptic transmission in the spinal cord beginning in the 1960s.<sup>17</sup> These studies and others revealed that  $\alpha$ -chloralose exerted barbiturate-like actions on synaptic transmission, including potent effects at inhibitory  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptors.<sup>18,19</sup> More recent research using recombinant GABA<sub>A</sub> receptors demonstrated that while  $\alpha$ -chloralose enhances GABA-mediated currents at concentrations equivalent to those that produce anesthesia in animals,  $\beta$ -chloralose is completely inactive at GABA<sub>A</sub> receptors.<sup>20,21</sup> Further,  $\beta$ -chloralose does not antagonize the actions of  $\alpha$ -chloralose at GABA<sub>A</sub> receptors,

showing that the binding site on the receptor discriminates between these two isomers.<sup>20,21</sup> These results finally provide a coherent pharmacodynamic explanation for the striking pharmacologic differences between the chloralose structural isomers nearly one hundred years after Overton's seminal experiments.

### Chloral Hydrate

Overton also had difficulty explaining the anesthetic actions of the highly water-soluble but poorly lipid-soluble compound chloral hydrate, stating, "[I]t does not seem improbable to me that the mechanism of action of chloral hydrate is more complex than is the case of most other

non-specific narcotics."<sup>14</sup> Much of the confusion surrounding the anesthetic properties of chloral hydrate was resolved in 1948 when T.C. Butler determined that chloral hydrate was metabolized to 2,2,2-trichloroethanol<sup>22,23</sup> (not chloroform as previously suggested<sup>24</sup>). Furthermore, trichloroethanol, and not the parent compound, accounted for all or nearly all of the anesthetic effects that resulted from administration of chloral hydrate to mammals.<sup>22,25</sup> Chloral hydrate was thus an example of a general anesthetic that was less potent than predicted by the Meyer-Overton hypothesis, because metabolism to another compound was required for its potent anesthetic actions. Butler summarized his findings as follows:

2,2,2-Trichloroethanol is a substance which, on intravenous injection, appears to be a more active narcotic than chloral hydrate. It is a substance the physical properties of which are more consistent with those of other typical narcotics of comparable activity than are those of chloral hydrate.<sup>22</sup>

This clashed with the view of general anesthetics as chemically inert molecules which non-specifically alter membrane lipids.

Following the work of Overton, chloral hydrate and trichloroethanol were

*Continued on Next Page*

## Contradicting. . . *Continued from Page 5*

scarcely discussed during investigations supporting unitary theories of anesthesia, even though the physical properties of trichloroethanol are better compatible with the Meyer-Overton correlation than those of chloral hydrate. A similar lack of attention was paid to the homologous anesthetic 2,2,2-tribromoethanol (Avertin), even though this compound was widely used in humans in the first half of the twentieth century.<sup>26</sup> Only in the 1990s did electrophysiology studies reveal that these two halogenated alcohol anesthetics potently modulate GABA<sub>A</sub> receptor function,<sup>21,27</sup> including prolongation of GABA<sub>A</sub> receptor-mediated inhibitory synaptic transmission of hippocampal neurons.<sup>28</sup> Chloral hydrate itself also modulates GABA<sub>A</sub> receptor function, albeit with a lower potency than trichloroethanol, but at concentrations similar to those which produce loss of righting reflex in tadpoles.<sup>21</sup> The research on chloral hydrate also resolved confusion about the homologous compound bromal hydrate, which is analogously metabolized to tribromoethanol.<sup>26,29</sup> It should be noted that chloral (or bromal) hydrate probably accounts for some of the anesthetic effect in tadpoles, whose inefficient drug metabolism would struggle to hydrolyze the hydrate present in the relatively large solution volume in which they are immersed for the loss of righting reflex assay.<sup>30</sup>

### Flurothyl

The properties of flurothyl (hexafluorodiethyl ether; Figure 1) presented a very different challenge for unitary theories of anesthesia than chloralose or chloral hydrate. Flurothyl was discovered during the active medicinal chemistry efforts of the mid-twentieth century to develop novel inhaled general anesthetics. To improve upon the shortcomings of diethyl ether and chloroform, special attention was paid to compounds which were non-explosive and less toxic. Advances in fluorine chemistry, stimulated by research during the Second World War yielded the modern generation of alkane and ether anesthetics including halothane, enflurane, isoflurane, and methoxyflurane.<sup>7,8</sup>

These efforts also resulted in the analysis of hundreds of other halogenated ethers and alkanes.<sup>31-34</sup> Many of these compounds were rejected because of chemical instability, unpleasant odor, and/or high toxicity and received no further attention. However, some compounds were

found to be potent convulsants despite chemical structures similar to compounds which were anesthetics. Flurothyl was one of the compounds with convulsant activity and no apparent anesthetic activity.<sup>35-38</sup> As described by Krantz and colleagues in 1957:

White rats exposed to the vapor hexafluorodiethyl ether [i.e., flurothyl] in concentrations as low as 30 ppm...convulsed violently within 30 seconds. There were marked clonic and tonic seizures, and there was some degree of emprosthotonus. The convulsions stopped promptly when the agent was removed from the inspired air. Repeated exposure...did not appear to produce injury to the animals.<sup>35</sup>

These properties were more striking with the characterization of 'iso-flurothyl' (1,1,1,3,3,3-hexafluoro-2-methoxypropane), a structural isomer of flurothyl which was a potent anesthetic without convulsive properties (Figure 1).<sup>39,40</sup> Flurothyl thus provided one of the first well-characterized examples of a highly lipid-soluble general anesthetic analog that lacked anesthetic properties. Despite intense investigation, research failed to provide an explanation consistent with unitary anesthesia theory for the pharmacologic properties of flurothyl, or of the differences between flurothyl and iso-flurothyl, although Koblin, Eger, and colleagues suggested that flurothyl may possess low potency anesthetic properties which are masked by its potent convulsant properties.<sup>40</sup> Following extensive investigation into the properties of flurothyl, Krantz and colleagues remarked in 1967, "Not any of the physicochemical properties or measurements conducted on the isomers, flurothyl and ISO[-flurothyl], revealed a marked difference which might be considered responsible for their respective pharmacologic responses."<sup>39</sup> As a historical sidenote, flurothyl ended up having an interesting but brief clinical history in humans when it was marketed under the trade name Indoklon as an inhaled chemical replacement for electroconvulsive therapy in psychiatry.<sup>35-37</sup>

As with chloral hydrate, a plausible molecular mechanism of action for flurothyl had to wait until the 1990s. A study published by Wakamori and colleagues in 1991 showed that flurothyl acted as a potent, non-competitive antagonist at GABA<sub>A</sub> receptors in brainstem neurons, in contrast to halothane and enflurane which

were positive allosteric modulators.<sup>41</sup> In retrospect, this explained the initial observation by Krantz et al.<sup>35,38</sup> that flurothyl convulsions closely resembled those produced by pentylenetetrazol and picrotoxin,<sup>42,43</sup> two compounds later shown to produce convulsions by acting as non-competitive GABA<sub>A</sub> receptor antagonists.<sup>44</sup> The differing properties of flurothyl and iso-flurothyl were finally explained in 2000 by the observation that flurothyl antagonized the function of recombinant GABA<sub>A</sub> receptors while iso-flurothyl enhanced GABA<sub>A</sub> receptor activity in a manner similar to that produced by isoflurane and sevoflurane.<sup>21,45</sup>

In addition to  $\alpha$ -chloralose, chloral hydrate, and flurothyl, more nettlesome problems for unitary anesthesia theories arose with other anesthetic compounds such as the barbiturates, etomidate, and steroid anesthetics. Examples mounted of isomers or close congeners of anesthetics which were inactive as anesthetics, convulsant, or even able to antagonize the actions of their anesthetic cousins. Further, like the arabinochloraloses, some classes of compounds such as the barbiturates, steroid anesthetics, etomidate, and halogenated ethers showed stereoselectivity in their anesthetic effects (Table 2).

### The Allure of Unitary Theories

Despite some shortcomings, unitary theories have held strong throughout most of the twentieth century. In the last two decades, however, unitary theories have been subjected to a sustained assault by a number of researchers, most prominently Franks and Lieb. Utilizing a combination of physical chemistry and electrophysiology, Franks and Lieb directly challenged the validity of lipid-based theories of anesthesia.<sup>3,46-49</sup>

Why have unitary theories of anesthetic action proven so compelling? There are several reasons. One, the desire to provide a straightforward answer to an important scientific question is very strong. T.C. Butler speculated on this issue in a 1950 review article:

The metaphysical desire for unification on the part of Claude Bernard and his intellectual heirs among the general physiologists may well have delayed arrival at a more satisfactory solution...Many workers of a later era, likewise impatient to find unifying principles of general physiology, have been led into a disregard of the logical steps needed to establish the relationship of various

Experimental Observation	First Year Described
<u>Barbiturates</u> Stereoisomers have different anesthetic potencies <sup>78</sup> Convulsant barbiturates described <sup>79</sup>	1934 1940
<u>Chloral hydrate</u> Anesthetic properties inconsistent with Meyer-Overton hypothesis <sup>14</sup> Metabolized to trichloroethanol, which is the active anesthetic compound in mammals <sup>22,25</sup>	1901 1948
<u>Chloraloses</u> $\alpha$ -chloralose lacks anesthetic activity <sup>14</sup> Arabinochloraloses show anesthetic potency differences between both optical and structural isomers <sup>16</sup>	1901 1940
<u>Etomidate</u> Stereoisomers have different anesthetic potencies <sup>80,81</sup> Stereoisomers equally soluble in lipid bilayers <sup>80</sup>	1975 1998
<u>Flurothyl</u> Convulsant properties described <sup>35,38</sup> Isomer 'iso-flurothyl' is anesthetic <sup>39,40</sup>	1957 1967
<u>Isoflurane</u> Stereoisomers have different anesthetic potencies <sup>82-84</sup> Stereoisomers equally soluble in lipid bilayers <sup>85</sup>	1992 1991
<u>Propofol (2,6-diisopropylphenol)</u> Alkylphenol analogs such as 2,6-di- <i>tert</i> -butylphenol inactive <sup>86-89</sup>	1980
<u>Steroid anesthetics</u> Inactive congeners of anesthetic steroids described <sup>90,91</sup> Stereoselectivity of steroid anesthetics shown <sup>92</sup>	1965 1996
<u>Volatile non-immobilizers</u> Highly lipid-soluble volatile alkanes and ethers found which lack anesthetic effects <sup>93-95</sup>	1994

Table 2. Experimental observations in conflict with unitary theories of anesthesia

phenomenon...The concept of one all inclusive phenomenon of 'narco-sis' does not rest on a very satisfactory logical basis.<sup>50</sup>

The Meyer-Overton hypothesis is elegant, compelling, and easily remembered by generations of physicians and scientists. Two, the practice of anesthesiology currently does not require a knowledge of general anesthetic pharmacodynamics.

Whether the anesthetics produce their effects by disordering lipids or modulating GABA<sub>A</sub> receptors does not affect clinical decisions, at least not for the foreseeable future. Three, general anesthetic drugs were in clinical use well before the concept of specific receptors was developed by pioneers such as Clark, Ehrlich, and Langley.<sup>51-53</sup> Although some of the initial research into specific protein targets began in the late nineteenth century, these theo-

ries were not widely disseminated until after the work of Meyer and Overton was entrenched. Four, unitary theories of anesthesia are versatile, as indicated by the large number of existing theories (Table 1), and difficult to disprove directly due to the technical problems in studying lipids. With a few exceptions such as Franks and Lieb, most researchers who oppose unitary theories do not have the experi-

*Continued on Next Page*

## Contradicting. . . Continued from Page 7

mental arsenal to challenge the theories directly.

These factors have led to a remarkable resilience of the legacy of Meyer and Overton. Borrowing the terminology of Kuhn from **The Structure of Scientific Revolutions**, the 'paradigm shift' from non-specific to specific mechanisms of anesthesia has progressed slowly.<sup>54,55</sup> Perhaps, for the unitary theories, the future will be as Max Planck wrote, "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents die, and a new generation grows up that is familiar with it."<sup>56</sup>

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# Goodbye Mac

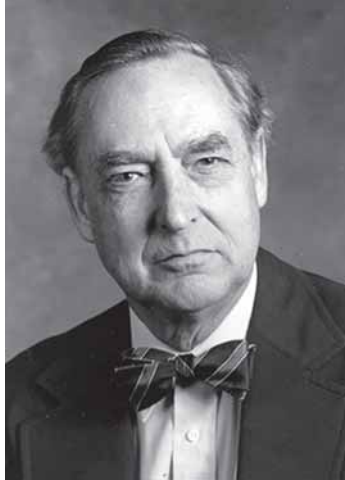
## Franklin B. McKechnie (1919-2003)

by Douglas R. Bacon, M.D., M.A.  
 Professor of Anesthesiology  
 Mayo Clinic  
 Rochester, MN

On June 12, 2003, Franklin B. McKechnie, long time Secretary-Treasurer of the Wood Library-Museum died at the age of 83. Frank was well known for his parliamentary expertise, dry wit, and bow ties. A friend to all, Mac had the unique ability to cut to the heart of an issue to resolve conflict. In addition to serving at the Wood Library-Museum, Frank was active in the Florida Society of Anesthesiologists, culminating in his presidency from 1968-1969. A registered parliamentarian, he was Vice Speaker of the House of Delegates of the American Society of Anesthesiologists (ASA) House of Delegates from 1974-1978 and Speaker from 1979-1983. Dr. McKechnie served as the ASA president 1985-1986. After completing his term as ASA President, he stayed involved in organized medicine serving as President of the Orange County Medical Society.

Mac was born in Boston Massachusetts on August 21, 1919. He received his undergraduate degree from Harvard University in 1942 and his medical degree from the Johns Hopkins School of Medicine in 1945. He served in the US Navy during 1945 through 1948, and returned to civilian life and an anesthesiology residency at the University of Indiana, remaining as an Instructor in pediatric anesthesia for a year. He left to become Assistant professor of Anesthesia and Pharmacology at the Albany Medical Center. In 1954 he moved south to Miami and was promoted to Associate professor, a rank he maintained when he moved two years later to the Medical College of Virginia. In 1960, Dr. McKechnie stopped traveling and entered the private practice of anesthesiology in Winter Park, Florida, from which he retired some thirty years later.

Dr. McKechnie was one of the second generation of American anesthesiologists who built upon the framework of the pioneers: Ralph Waters, John Lundy, Paul Wood and many others to create the "modern" practice of anesthesiology. Frank's area of special interest was the recovery room, a novel concept when he began his anesthesia residency in 1949 at the University of Indiana. He helped form the



Franklin B. McKechnie

both the Florida Recovery Room Association and the American Society of Post Anesthesia Nurses (ASPAN), inspired by a tragic case in Florida where a young child was left severely cerebrally impaired after a post-anesthesia care nurse failed to recognize that the patient was no longer breathing. Issues surrounding the immediate post operative care of anesthetized patients were Dr. McKechnie's lifelong area of expertise.

On June 21, 2003, a memorial service was held at St. John's Lutheran Church in Winter Park, Florida. Dr. McKechnie is survived by his wife Eleanor, three children, six grandchildren, three stepchildren, eleven step grandchildren and one step great-grandchild. Frank's guiding spirit, parliamentary expertise and keen wit and humor will be greatly missed.

*The following e-mails regarding Dr. McKechnie's passing were sent to the Editor of the Bulletin by Patrick Sim, Wood Library-Museum.*

Patrick,

I was saddened to receive your email with the news that Dr. McKechnie had died. Frank first involved me in the WLM by asking me to represent the Crawford W. Long Museum at the trustee meeting and I will always be grateful to him for that. I had Frank appointed to the BOD of the Long Museum. He was immensely popular with the citizens of Jefferson. In my report to the trustees about his visit to the Long Museum, I said that Frank's visit was the most exciting thing to happen in Jefferson since the statue of the Confederate soldier was placed on the village square. That visit is my most enduring memory of Frank. He charmed the entire city of Jefferson Georgia and was a great representative for the Wood Library-Museum of Anesthesiology.

Regards,  
 Bill

William Hammonds, MD, MPH

Dear Trustees and Friends of the WLM:

We received the sad news that Dr. Franklin B. McKechnie died on June 12, 2003 in Rochester, NY, while visiting his children. A memorial service will be held at 11:00 a.m. on Saturday, June 21, 2003 at St. John's Lutheran Church in Winter Park, FL, 1600 S. Orlando Avenue, Winter Park, FL 32789 (407-644-1783). A reception will follow at 1620 May Flower Court, Winter Park, FL 32792, from 2:00 p.m. to 4:00 p.m.

The McKechnie family has designated the Wood Library-Museum of Anesthesiology, among other charitable organizations, to receive donations in memory of Dr. McKechnie. Condolence may also be addressed to:

Mrs. Eleanor McKechnie  
 1620 Mayflower Ct., #B-116  
 Winter Park, FL 32792

Mr. Bruce McKechnie  
 146 Harrison Circle  
 Locust Grove, VA 22502  
 Telephone: 540-972-4770

PATRICK

Patrick Sim, Librarian

Wood Library-Museum of Anesthesiology

# Remembering Arnold Lee, a Colleague and a Dear Friend

by Hsueh hwa Wang, M.D.<sup>1</sup>

*Arnold St. Jacques Lee, P.E., mechanical engineer, whose career was dedicated to anesthesiology, is not widely known to the anesthesiology history community. Mr. Lee was associated with Columbia University, and later with the University of California, Los Angeles. It was at Columbia that he made significant contributions in anesthesia technology, collaborating with anesthesiologists at the Columbia program in the E. M. Papper Era. The contributions of Mr. Lee, and the impact of his contributions could best be felt by his colleagues of the Columbia days. It would not be unusual for anesthesiologists of a later generation to use, or hear of, instruments designed by Lee, but wonder who he was and how he designed them. To an even more recent generation of anesthesiologists, Mr. Lee's name is totally a strange one. Dr. Hsueh hwa Wang writes about Arnold Lee as a friend and a colleague. She is the widow of another leader of Columbia anesthesiology, Dr. Shih-hsun Ngai, who succeeded Dr. Papper, and preceded Dr. Henrik H. Bendixen, as chair of the anesthesiology department at Columbia. She is a physician researcher in pharmacology at Columbia. Professionally she has worked with Mr. Lee in anesthesiology and medical research instrumentation. They are also close family friends. Dr. Wang writes about Arnold Lee as a friend as well as a professional colleague, putting Mr. Lee in both a personal and a professional perspective in the history of anesthesiology. Mr. Lee's unique personality might have obscured his place in contemporary anesthesiology. Anesthesiology history, particularly contemporary anesthesiology history, is often recorded by personal reminiscence and accounts of similar nature. It is hoped that Dr. Wang's tale will instigate further study of an obscure and yet significant life and career like Arnold Lee's, so that his contributions will be better known, and his place in the history of the specialty properly recognized. Former colleagues, associates and friends of Mr. Lee will enjoy the story with fond memories, or with chuckles of bemused past encounters. For the professionals who have ever used or heard of the gadgets designed by Mr. Lee, his story will be an interesting re-*

*flection of the career behind those devices they use with wonder. For those youngest of generations of historians and anesthesiologists, Dr. Wang's story is a fascinating account of a colorful engineer who devoted his career to help improve clinical anesthesia.*

*Introductory Notes by  
Patrick Sim, Librarian  
Wood Library-Museum of Anesthesiology*



*Arnold and Shirley in 1995*

It is often the small things in life that matter. When I think of Arnold, what pops into my mind are mostly small things, in bits and pieces. It seems that I am looking into a kaleidoscope, watching these pieces twisting and falling, forming many images, some vague, some clear. But nonetheless, many are exhilarating and all are colorful.

**When I first met Arnold** I can't really remember when I first met Arnold. In 1964 Shirley<sup>2</sup> was working in my lab after she finished her anesthesia residency, and we were doing a cross-circulation experiment. It was probably the messiest and bloodiest experiment, ever. We therefore did not welcome visitors but I remember Arnold hanging around, many times. What was he doing in my lab? I hardly knew him and had not asked his advice or service. It only dawned on me much later that he was there to see Shirley!

In the fall of 1964, Shih-hsun<sup>3</sup> took his sabbatical leave at the Karolinska Institute in Stockholm and the whole family went with him. We returned in the summer of 1965, after another tour to Taiwan. In those days we hardly wrote letters or telephoned if there were no urgent matters. E-mail, of course, was non-existent. I was very surprised to get a wedding an-

nouncement from Shirley and Arnold just before we left for home. My immediate reaction was: How can Shirley, the dainty, graceful and elegant southern belle, marry this gorilla of a man?

**Arnold and Shirley** That was then, before I knew Arnold. Despite disparate outside appearances, Arnold and Shirley were not at all an incongruous couple. They complemented each other harmoniously in many ways, and were deeply devoted to each other. Arnold always tended to all of Shirley's needs. At Los Angeles, where Shirley worked at Cedar-Sinai hospital and had to leave the house at 6 AM, Arnold would get up at 4:30 AM to make two unbelievably fancy sandwiches for her – one to eat in the car on her way to the hospital, and one for lunch. And, when she came home, dinner would be waiting. I used to call Arnold the best house-husband. He sure was good to his "Shirley curly" (the curls had since long gone), and she was equally good to her "honey bunny".

**The Lees joined our family** Arnold and Shirley lived in the next town, very close to us, when they were first married. We got to know each other well very quickly. It seemed that they had joined our family. Arnold loved to eat. Even for a big man, to achieve a body mass of 280 pounds, lots of food must be consumed. He was a gourmet and also a gourmand, eating whatever was in sight. He loved Chinese food and ate and cooked practically nothing else. But there was one exception. He loved to make fancy blintzes which came from his Jewish background. He would wrap them with fresh farmer's cheese and cling peaches for Sunday brunch. The side dish was good, too – grilled filet mignon. I remember that, to announce "we are having blintzes at Arnold's" was a sure way to get the kids out of bed on Sunday mornings. Our two families spent a lot of time together, eating. We ate either at his house, or ours, or at a restaurant, two to three times a week during the years before they moved west. Once Arnold showed up at my lab in the early afternoon, announcing, "We are eating out tonight." I said "All right, but I don't know where my children are." "No problem," said he, "I will get them." He then went to my house in New Jersey, ly-

<sup>1</sup>The author is Professor Emeritus of Pharmacology, Columbia University. She is also the widow of Shih-hsun Ngai, M.D., formerly Professor Emeritus of Anesthesiology and Pharmacology, Columbia University.

<sup>2</sup>Shirley Markee, M.D.

<sup>3</sup>Shih hsun Ngai, M.D.

ing in wait, catching the kids one by one as they came home from school. At about 6 PM, his station wagon would pull into the Clinic Emergency entrance, parked illegally, with three captives in the back seat. He would then dash into the hospital to wind up the adults. Shirley and Shih-hsun were not always consulted for these ventures. Usually neither objected to a Chinese restaurant. And besides, they were not the cooks of the family. Over the years, Arnold was always in and out of our house for various reasons, for instance, taking the children to Friendly's for ice cream (sometimes before dinner when he noted that my dinner was nowhere near ready), or helping them with their science homework. The latter did not always work out, however. Once when Tu<sup>4</sup> was facing an exam in physics the next day, I asked Arnold to help her. When I got home, I saw Arnold sitting in the living room, reading a magazine, alone. "Where is the pupil?" I asked. "Upstairs, crying," he replied with a smirk on his face. Tu then came downstairs, saying in between sobs, "He is no help! He said the book is all wrong!" Exasperated, I said to Arnold, "The book may indeed be wrong, but you are impossible!" Several days later, when we were all walking together out of a restaurant, Johnny (about 9 at the time), asked Arnold to help him with his math. I told him that I could still do his math so there was no need to bother Arnold. Johnny answered, "But I want Arnold. I want to find out by myself why he is so impossible!"

**Favoritism** In order to boost his ethnic connection with us, he claimed that he was of Mongolian ancestry. Actually, Arnold did have some appearance of a Tartar, perhaps derived from mingling of Mongol origins into Eastern Europe over many centuries after invasions from the East. He gave himself a Chinese name "Lee Mongoo".<sup>5</sup> Although he was attached to all of us, he nevertheless singled two of us out as "special". One was my son Johnny, whom he loved dearly as his own son. Arnold took him under his wings from the beginning. He taught him numerous things, and took him to his lab in Fort Lee, NJ, on Saturdays. There he gathered a number of young boys there "to learn". It must have been interesting because these boys would go back, week after week. At least three became Ph.D. scientists, Johnny was one of them. When Johnny went to Pomona College and later to Cal Tech at Pasadena, Arnold and Shirley's house in

Los Angeles was his home away from home. He was always very serious with Johnny and the devotion went both ways. Arnold was scrupulously honest, showing his bias and favoritism tactlessly and shamelessly. We once visited LA while Johnny was at Cal Tech. Arnold had invited a houseful of people but Johnny was late to arrive from Pasadena. I noted a small plate of dumplings at the corner of the kitchen table and asked him if that was for appetizers, and if so, why it was such a small plate. "No," he said, "that is for Johnny. When he shows up he will be very hungry so I have to have something for him." Sure enough, when Johnny arrived, he went straight to the corner and devoured all the dumplings, oblivious of the people around him. He was used to the special treatment.

I was the other lucky special member to be Arnold's favorite. I still cannot come up with a reason how this came about. It must have begun with his interest in Chinese cooking. We did cook together, experiment together. But I think there was something else, nebulous perhaps, that put us on the same wavelength. He treated me affectionately, as a sister. He even called me "dajeh" which means big sister, as that was how my younger sister addresses me. Two reasons come to mind for Arnold's close relationship with me. First, he needed a listening ear. Mine was not always sympathetic but that was par for the course. Second, he needed a target to vent his frustration and when the need came he usually found some reasons (often trivial) to argue. My daughter Janet reminded me that our arguments usually ended with a "bet". The loser would buy a (whole) beef filet. My children watched us arguing with detached interest as they would get to eat the filet anyway, regardless of who won.

Arnold could be very argumentative and sometimes the exchanges would get out of hand. I would have to tell him to pick someone his own size and throw him out of my house. He would always come back the next day, however, as if nothing had happened. We did, however, talked a lot quite amicably with him doing most of the talking. We talked about everything. Politics? A little. Arnold hated the communists but to call him a conservative would be the joke of the century. Religion? Some. He was an atheist and the only religion that tickled his fancy (and mine) was Taoism. We mostly talked about people. His colleagues? Of course, among others, and there were many that he disliked. But Arnold was not the person to

gossip. In fact he was full of praise about some of the people that worked with him. Notably this included the machinist, Harry Applegate, who was with him from way back, and who made many pieces of his precision devices. Harry was an extremely capable mechanical engineer, soft-spoken and loyal. Heinz Rosskothén, an expert instrument maker from Germany employed by the Eye Institute was another super craftsman. Heinz had a very different personality and he worked with Arnold on Saturdays. He also made some very delicate cannulae for me for my experiments. Little by little Arnold told me almost all about himself and his family. His parents emigrated from Russia. He had an impoverished childhood growing up on a south New Jersey farm. He served in the army during the Second World War, was stationed in Germany and became fluent in German. The G.I. bill got him through college. He also told me about his first wife, his up-start company in South Jersey, but said very little if anything at all about his courtship with Shirley, other than "I never dreamt that she would marry me!"

Arnold also did a great deal for me for my laboratory. While he was in New York, he built a respirator for me, and checked my equipment in the lab almost constantly. So that made him a colleague of mine in science as well as in the culinary art. He wanted to learn some Chinese, but he was interested mostly in the formation of Chinese characters which made me research Chinese word origins, not an easy task. He spent literally hours in learning to pronounce my Chinese name correctly, while settling for a vulgarized Shihshh for Shih-hsun's name. While he treated the men folks of my family seriously and respectfully, he was anything but serious with me. I liked to tease him also. Once I caught him wearing a brown sock and a blue one. "Ever sort your socks, Arnold?" "Heck no! When I get to the last pair I would wash them all and out of the dryer they go to a basket. In the morning I grab a handful and choose two with the same color. But sometimes I goof." He had 8 or 10 pairs of shoes. "Trying to compete with Mrs. Marcos, Arnold?" "You don't understand. It is not easy to get size 13 shoes. And they hurt my feet, but not all hurt at the same place. So I have to rotate wearing them."

**Not sentimental but compassionate** Arnold would not be caught dead being sentimental, and he hid his emotions vigorously. When Johnny left Los Angeles for New York for his Post-Doctoral Fellow-

*Continued on Next Page*

<sup>4</sup>Family nickname of my older daughter, Mae

<sup>5</sup>李蒙古, meaning "Lee of Mongolia"

## Arnold Lee. . . *Continued from Page 11*

ship, I asked Arnold if he would miss him. “Nope.” “Perhaps a little bit?” “Nope.” But he actually was a very warm and compassionate man. He had deep feelings about the unfortunate people. Not those people at large which would not be in his character, but he did turn to some individuals to whom he offered his unqualified assistance. Raul Rodriguez, a maintenance man of Mexican ethnicity at UCLA did some work for him. Arnold realized that the man felt that his sons would go his route, not have a college education or at best go to a community college. Arnold tutored him in English, addressed his outlook, and saw to it that all his three sons went to reputable four year colleges. Shortly before Arnold died, he told Raul, “Take care of my wife, when I am not around anymore.” According to Raul, that was not a request, but a command. Shirley did not know any of this until Raul came forward and told her after Arnold’s death. Raul has been doing all the chores for Shirley, the house, the car and everything else, to this day. Arnold was an “all or none” man. You either were his friend, 100%, or he would have nothing to do with you. I felt lucky to be in the former category. In fact, I know he would walk the extra mile for me, and I, for him.

Highly intelligent but no compromise Arnold’s intellect definitely put him in a league by himself. We have a saying in Chinese, that “a person with high intelligence may sometimes appear dumb”.<sup>6</sup> That would be a befitting description of Arnold. With his aloofness, off-handed mannerism and immunity to praise or insult, sometimes he even looked dopey. He was widely read and the breadth of his knowledge, not in his discipline alone, left me in awe. Any subject that he knew, he knew in depth and he was very patient and methodical in explaining it to those who would listen. He could also explain things at any level. Once, Johnny as a lad asked him what a transistor was. He said “A transistor is a gadget that has one wire coming in and one wire going out. A little bit of juice comes in but a lot of juice goes out.” That seemed to satisfy the boy’s cu-

<sup>6</sup>大智若愚

<sup>7</sup>Raymond Fink, M.D., deceased, formerly Professor of Anesthesiology, Columbia University

<sup>8</sup>Arnold’s inventions were all patented. A complete list of his patents can be found integrated with his publications on the web site [www.medregs.org](http://www.medregs.org)

<sup>9</sup>M. Jack Frumin, M.D., deceased, formerly Professor of Anesthesiology, Columbia University

riosity. His interest was broad, but also selective. For instance, he had no feel for music and art; whereas, Shirley is an opera lover. He would travel to San Diego with her and take her to the opera house but had never accompanied her to a performance. This no compromise streak of his personality belied his integrity, but also accounted for his ultimate failure to have any of his inventions manufactured.

**Contributions to anesthesiology** Formally trained as a physicist, Arnold was also an excellent mechanical engineer and a first class craftsman. He undoubtedly was the major, if not the top contributor to Anesthesia technology and equipment of his generation. A letter from the late Dr. Ray Fink<sup>7</sup> to him stated, “You are the quintessential fearless expert witness of technological developments in anesthesiology....” This is an ageless statement. Arnold had designed and built numerous pieces of equipments, large and small, directly or indirectly related to anesthesiology and the details of these will be left for experts to describe and evaluate for posterity.<sup>8</sup> He had shown me many of his inventions and what impressed me most was the insight he had about a design, a problem, or a system. He had the vision to see what needed to be accomplished, and what could be done, before he embarked on a project. And he could also see what was hopeless and thus the effort should be abandoned. This insight, or vision, is what makes a genius.

Arnold had remarkable abilities to design electronic devices as well as mechanical ones. And, when digital technology came along, he mastered that very quickly also, and began designing instruments using digital rather than analog electronic techniques. Yet, perhaps owing to his training in mechanical engineering, Arnold would sometimes incline to make a mechanical device rather than an electronic one. The former could be visualized and easily quantified. An example is the Precision infusion pump he built for the delivery of potent pharmacological drugs. The pump was made to move tiny steps with each step delivering a minute amount of fluid. Greater volume was achieved by going to a higher gear. All the steps and gears were visible in a glass case, like the display of a wonderful Swiss watch.

Of the vast number of instruments he made, I only have personal experience with the Frumin Valve and the Frumin Respirator (animal model). He built a unit of the latter for me and also several for my colleagues in the Columbia’s Pharmacology department. The human model was es-

entially the same but with different sized bellows. Both were conceived by Jack Frumin<sup>9</sup> along with Arnold and should be called the Frumin-Lee Valve and Frumin-Lee Respirator. The former allows the animal (or person) to breathe in from an air source, be it anesthetic gas, oxygen or room air, and expire to room air with no mixing with the air intake. The latter is of ingenious design, is easy to use and has many built-in safety features. It was far superior to any commercial respirators available at the time. The superiority of the Frumin Respirator may primarily come from its gentle inflation of the lung, mimicking physiologically the natural state of breathing. A case in point was found at the neonatal intensive care unit at the Babies’ Hospital of Columbia Presbyterian Medical Center. There, Arnold built a tiny unit for small infants, where three other commercially made respirators were also available. When neonates needed to be ventilated, the baby placed on the Frumin Respirator often lived while those on the commercial ones died. The situation could be very exasperating when more than one baby needed to be ventilated. Nurses felt that they were playing God, to decide which baby would be put on the Frumin Respirator, thus allowed to survive. In a small, critically ill infant, the Frumin Respirator not only worked better, but could make the difference of life and death. The art of respirator design has come a long way from the sixties. Modern day respirators are now much better, more versatile and better monitored. Nevertheless, in his day, Arnold’s design was superior than others, and he was ahead of his time.

Arnold’s respirator really should have been made available to the general public. Arnold was in fact negotiating with Harvard Instrument Company to have it manufactured. The negotiations always broke down. I begged him to give in, for the sake of science. Money was not the big issue. Arnold was after neither money nor fame. He was, however, concerned that his design would be made without compromise and that they would actually be produced, not sequestered. He had his principle and would not compromise, and the respirator was never commercially made. Neither were his other inventions, except the Frumin Valves which were made by his friend Ed. Nailor in his garage, I believe. So, the real loser was society at large.

**Talent as Craftsman** As an excellent craftsman and machinist, and also a person of a wide spectrum of interests. Arnold turned out many items in his shop as a hobby for personal use and for friends. He

was famously known for his cutting boards, made from aged maple wood (or whatever hard wood he could find at the time) which he carefully stored in his basement. He had several templates, the pig being the most popular. His insignia was always carved at the rear end of the pig. Everyone in my family has an "Arnold's pig," plus some others.

He was so adept that he thought he could use any machine. Once while I was visiting him, he asked me to teach him how to use the sewing machine. He had borrowed one and wanted to make a cover for his king-sized comforter, using two huge sheets. It took me a while to get to know the machine, which was not as user-friendly as my faithful Singer. I told him to forget about it and to return the machine. Deft as he was, he could not learn to sew in a few hours on that machine. But of course, I made the (gigantic) cover for him that evening.

Last visit Arnold felt ill when he came east to attend the Memorial for Shih-hsun given by Columbia's Anesthesia department in November of 1999. He asked me to get him a doctor. One look at him and I noted that he was obviously jaundiced. I

told him he needed a thorough work-up, that it was best to get him back to LA as fast as possible, and I put him on the next flight. Sure enough, a simple work-up revealed a rather advanced state of a pancreatic cancer, obstructing the outflow of the upper gastrointestinal tract. He refused any intervention, even for palliative purposes, and chose to starve to death. He called me to go to see him. I told him that I had a meeting in Vancouver in March (2000) and would make a detour to LA on my way home. "It may be too late," said he. So I made a special trip to LA in mid February. After picking me up at the airport, we went, as usual, to his favorite Italian grocery store. My heart ached when I saw him painstakingly choosing many items, for Shirley and me, as he could not eat any of them. We later went to a discount supermarket where he bought 6 large (25 lb) sacks of kitty litter for their cats. "Why so many?" I asked. "These are too heavy for Shirley," was the reply. At his home he asked me to cook a lot of dishes for Shirley, to be put in the freezer. I did my best helping him to put the inventory of his machinery (stored in his garage) in order and made a list on the

computer. He grew weaker by the day as he could hardly keep anything down. When he took me to the airport we both knew this was farewell. After he dropped me off at the curb, I left my suitcase and ran around to the driver's side to say goodbye to him. But he did not want to say good-bye. He eased the car away slowly, without turning his head, just raising his hand to wave, leaving me in tears at the curb. The week after, Johnny went down from Berkeley and was with him at the end. He died in early March, 2000, while I was attending the meeting in Vancouver.

So exits Arnold Lee, a genius, a legend, and an unsung hero, stoic on the "outside" but warm and compassionate "inside". It was a privilege to be his dear friend.

## **Anesthesia History Association Eighth Annual Resident Essay Contest 2003**

The Anesthesia History Association (AHA) sponsors an annual Resident Essay Contest with the prize presented at the ASA Annual Meeting.

Three typed copies of a 1000-3000 word essay written in English and related to the history of anesthesia, pain medicine or critical care should be submitted to:

William D. Hammonds, M.D., M.P.H.  
Professor of Anesthesia  
Director of Pain Outcomes Research  
Department of Anesthesia  
University of Iowa  
200 Hawkins Drive, 6JCP  
Iowa City, IA 53342-1079  
U.S.A.  
william-hammonds@uiowa.edu

The entrant must have written the essay either during his/her residency or within one year of completion of residency. Residents in any nation are eligible, but the essay **MUST** be submitted in English.

This award, which has a \$500.00 honorarium, will be presented at the AHA's annual dinner meeting to be held in October, 2003, in San Francisco, California. This dinner is always held during the annual meeting of the American Society of Anesthesiologists.

***All entries must be received on or before August 23, 2003.***

# Pain for All to See

by Fred J. Spielman, M.D.

Professor

Department of Anesthesiology, University of North Carolina

On October 16, 1846, ether was given to Gilbert Abbott at the Massachusetts General Hospital by Boston dentist William Morton. This successful administration of anesthesia ended the era of the surgeon as "armed savage" and initiated more than a hundred and fifty years of life-saving improvements in the surgical care of patients. Ether, nitrous oxide, and chloroform abolished surgical pain, but a century would elapse before the establishment of the first chronic pain clinic.

Some of the techniques used to reduce or eliminate chronic pain originated hundreds of years ago. The analgesic effect of low temperature has been known for more than a thousand years. Hippocrates wrote about the use of ice and snow as a local anesthetic. In 1851, Dr. James Arnott described the use of ice-salt mixture to produce pain control in patients with cancer. Electricity in the treatment of pain was used as early as 600 BC when electric eels and torpedo fish were applied to painful areas. Benjamin Franklin experimented with a wide variety of electrical treatments for pain. Even the analgesic affects of the salicylates have been known for hundreds of years in the form of willow tree bark (*salix*).

Progress in chronic pain control required diverse ingredients, including the discovery of hollow needles, syringes, and local anesthetics. Alexander Wood (1817-84) popularized the hypodermic syringe for the treatment of neuralgia by injecting morphine and opium near the site of pain. This technique was ridiculed for nearly a century until the discovery of peripheral opiate receptors. In 1884, Carl Koller, a Vienna ophthalmologist, demonstrated the local anesthetic properties of cocaine on the cornea. The same year William Halsted used the principle of nerve blocking with the intraneural injection of cocaine for mandibular surgery.

During the latter part of the nineteenth century, the expanding knowledge of anatomy and of the mechanisms of pain stimulated experimentation with neurosurgery. In 1873, French surgeon Letevant published the first text on neurosurgery for pain control. Less than two decades later the first successful spinal rhizotomy was performed. In 1905, the significance of the anterior spinothalamic tracts was

discovered, and five years later the first cordotomy for pain relief was performed in a patient with cancer. Surgery soon offered a menu of destructive procedures to "cure" pain, and enthusiasm for operations eventually spun out of control. Creative neurosurgeons reasoned that if one could define the nociceptive pathways, the pain could be cured by simply destroying one or more of the pathways. Prominent surgeon Wilder Penfield stated, "All pain



*Roger Reacts to the Light by Christine Lamb Toubeau*

can be relieved, if it is really required, by cutting the proper sensory nerves or nerve tract in the proper place at the proper time." The introduction to the book, *Pain: Its Mechanisms and Neurosurgical Control*, published in 1955, contains the following quote: "Frontal lobotomy, although not strictly speaking a specific operation for the relief of pain, has become an invaluable method for controlling suffering from the varieties of intolerable discomfort for which no other solution is known." The application of neurosurgery to relieve chronic pain is employed infrequently now

because, as is acknowledged, indiscriminate application of destructive procedures produces an unacceptable loss of function; ablative procedures can result in severe iatrogenic pain, and nociceptive fibers serving a certain area of the body might not be confined to specific roots and tracts.

The goal of attacking the specific nerves responsible for chronic pain motivated physicians to experiment with a variety of drugs and techniques. In the latter part of the nineteenth century, peripheral nerve blocks were performed with chloroform, morphine, and osmic acid. In 1888, Corning published *Headache and Neuralgia*, in which he wrote about injecting cocaine for the treatment of femoral neuralgia and sciatica. Reporting in *Lancet* (1909), Harris described alcohol injection of the fifth cranial nerve to reduce the pain from cancer of the tongue. Enthusiasm for nerve blocks to treat a diversity of ailments lead to the 1926 publication in the *American Heart Journal*, "Paravertebral Alcohol Block in Cardiac Pain." Dr. George Swetlow used alcohol to interrupt cardiac afferent inflow in the treatment of intractable angina pectoris. Dogliotti, in 1931, was the first to use intrathecal alcohol to produce a chemical posterior rhizotomy for the treatment of intractable pain. In 1941, Wertheim and Rovenstine published their experience with suprascapular nerve block for the relief of refractory shoulder

pain. Writing in the *Journal of the American Medical Association*, the New York University anesthesiologists stated, "Therapy that includes narcotics with depression of bodily function and eventual addiction or the radical, often mutilating, surgical interventions as satisfactory remedies leave much to be desired. Any substitute that might promise to exempt bodily pain for even a relatively small number of sufferers has merit. Particularly is this true of therapeutic nerve block." Their message is still valid more than five decades later.

Surgeons frequently performed experi-

mental work with local anesthetics and nerve blocks. Gradually, nerve block clinics came under the jurisdiction of anesthesiologists who were proficient and knowledgeable with local anesthetics and regional anesthesia. The transition from nerve block to multispecialty pain clinics occurred shortly after the Second World War. With a better understanding of the nature of pain, the focus shifted from only nerve blocks to an integrated approach to treatment. In 1944, John Bonica, credited with starting the first pain clinic, was appointed a senior anesthesiologist at Madigan Army Hospital. This 7,700-bed hospital was filled with wounded soldiers. Dr. Bonica was called upon to diagnosis and treat causalgia, reflex sympathetic dystrophy, and phantom limb pain. He noted that rarely did these patients respond when only nerve blocks were administered. Dr. Bonica's early experience convinced him that complex pain syndromes could be more effectively diagnosed and treated by a multidisciplinary team. In 1948 the Philadelphia General Hospital opened a pain clinic in part "...because requests for the type of service which it could offer had become so numerous that it was impractical to continue to treat patients on the ward or in the operating room."

Soon after the establishment of chronic pain clinics, concerns were voiced about the role of the anesthesiologist. These criticisms were detailed in the publication, *The Anesthesiologist and Therapeutic Nerve Block: Technician or Physician*, written by Vandam and Eckenhoff, and published in *Anesthesiology* (1954). The authors were concerned that patients were being referred for treatment without adequate evaluation. Anesthesiologists were performing nerve blocks at the request of the referring physicians, without spending an appropriate amount of time in establishing the diagnosis. Rovenstine and Hershey (*Anesthesiology*, 1944) stated, "Much discredit has come to nerve blocking from the too frequent practice of 'trying a block' without accurate diagnosis. This is particularly true when patients are treated for pain following injury or of a chronic nature."

Although verbal imagery can paint poignant pictures of pain, visual renditions can be even more revealing. Art can portray a patient's suffering and some physical symptoms with a vividness that verbal descriptions often lack. For example, the painting that accompanies this essay, "Roger Reacts to the Light," depicts the severity and location as well as the patient's reaction to a migraine headache.

Both the painting and migraine headache share similar characteristics: striking, unusual, bright, strong, emotional, and unforgettable. The artist and chronic pain patient is Christine Lamb Toubeau. In the late 1980s Sandoz Pharmaceuticals Corporation undertook a national public education project; the centerpiece of the program was "Through the Looking Glass," a traveling exhibition of art created by headache sufferers to illustrate their pain. Sandoz solicited art from over 200 professional and amateur artists.

In the 1970s progress was made with regard to communication and dissemination of information among those health care workers who had an interest in chronic pain. In 1974, the International Association for the Study of Pain was founded. Since 1975 the association's journal, *Pain*, has been considered one of the most important publications in the field of pain research and therapy. The American Pain Society was established in 1978, and held its first national meeting the next year. Anesthesiologists have been a central force in chronic pain management and vital to its growth and prestige. Under the guidance and leadership of anesthesiologists, chronic pain has quickly evolved into a medical specialty responsible for cutting edge research, education of health care providers, and provision of unique and outstanding medical care to patients, and has raised the profession of anesthesiology to a higher plane.

#### Suggested Reading

1. Rovenstine EA, Hershey SG. Therapeutic and diagnostic nerve blocking; A plan for organization. *Anesthesiology* 1944; 5:574-582.

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

1. Monographs: Old citations to historical monographs (including books, audiovisuals, serials, book chapters, and meeting papers) are now in LOCATORplus (<http://locatorplus.gov>), NLM's web-based online public access catalog, where they may be searched separately from now on, along with newly created citations.

2. Journal Articles: Old citations to journals have been moved to PubMed (<http://www.ncbi.nlm.nih.gov/PubMed>), NLM's web-based retrieval system, where they may be searched separately along with newly created citations.

3. Integrated History Searches: NLM has online citations to both types of historical literature -- journal articles as well as monographs -- again accessible through a single search location, The Gateway (<http://gateway.nlm.nih.gov>).

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# Anesthesia History Association Spring Meeting, 2003

by *Gerald L. Zeitlin, M.D.*  
*Vice President, AHA*

The Spring meeting of the Anesthesia History Association was held in Boston on April 30 and May 1, 2003. One hopes this meeting will foreshadow a return of the American Society of Anesthesiologists Annual Meeting to the city where it all began. Boston is building a new and adequate Convention Centre near the South Boston waterfront.

Nearly 30 AHA members and guests joined Dr. Elliott Miller for a tour of the Ether Dome on the morning of April 30. We learned that the Bullfinch Building, the Ether Dome being its crowning glory, was built in 1818 and that between 1821 and 1868 more than 8000 operations were performed there. One of those is of particular interest to us! We admired the new painting of the Morton Demonstration by Warren Prosseri, a Boston artist, and were intrigued to hear that he used photos of contemporary Massachusetts General physicians as models for the famous figures from the past such as JC Warren and WTG Morton. We were also curious about the brass name labels on the backs of the seats in the steeply banked rows of the auditorium. In the front row we saw, among others, the names of Horace Wells and Charles Jackson, neither of whom was present of course, on October 16, 1846.

We enjoyed a rare clear and sunny Spring day for the afternoon visit to the Mount Auburn Cemetery. We were treated to excellent talks at the graves of such notables as Morton, Jackson, Jacob Bigelow, Charles Bulfinch, Oliver Wendell Holmes and Francis Parkman among others. We were a little saddened to see how the inscriptions on the Morton obelisk are being obscured by age and presumably, air pollution.

The next day was taken up with our academic program at the Westin Copley Place hotel - finely located next to the Boston Public Library and HH Richardson's Trinity Church.

In the opening plenary session Dr. Waisel gave us a more intimate view of the hero of his Anesthesiology article, Lt. Kornfield; not least because he showed us some dramatic photos of the beaches on D Day, 1944. Dr. Calmes amplified her studies of early women anesthesiologists with more research into the life of Mary Botsford. Prof. Sugioka had us laughing as he gave us a close-up view of Dr. Stuart

Cullen, an under-appreciated pioneer of our specialty. Kim Pelis, one of several academic historians who have increasingly graced our meetings in recent years, delved into John Snow's views of what was termed "surgical shock". Dr. Burt Dunbar vividly brought to life one of the most dramatic changes in the way we practice and yet one we have come to accept almost without comment i.e. the growth of day-case surgery.

Who of us was in practice before the mid 70's that does not remember making preoperative rounds after a long day in the operating room visiting patients who had no reason to be in hospital on the night before surgery, other than custom.

Dr. Ray Defalque revisited the old yet historically important question of who first realized the importance of a clear airway. Dr. Donald Wallace applied the concept of benevolence to the validation of sophisticated methods of pain relief during childbirth. Would that the authors of the influential book "Our bodies, our selves", that opened the minds of women to the way their bodies and emotions worked yet tried to denigrate all methods of pain relief as unnatural, had heard this talk. Our esteemed Wood Library librarian, Patrick Sim traced the reciprocal influence of three Chinese anesthesiologists who came to the USA, on the growth of the specialty in their homeland. He used the wonderful image of the leaf that falls from the tree that grew it, and thereby nourishes it.

Dr. Tungpalan and Dr. Curry, two more examples of the demonstration by Dr. Bacon that residents can contribute to the study of our history, gave exemplary talks on Colonic Analgesia and Subcutaneous Oxygen Therapy, respectively. Dr. Arunkumar, the winner of the 2002 Resident Essay Award told us the story of his attending, Dr. Jebson, a Britisher who was one of Prof. Sir Robert Macintosh's last two residents.

Dr. Anixter, another resident historian elegantly reviewed the dramatic improvements in the treatment and understanding of cardiac arrest from the early 30's to the present day. Dr. Sadhasivam told us about Sir C.V. Raman, the Indian scientific genius and Nobel Prize winner whose discovery of the so-called Raman effect led to the installation of mass spectrometers

that many of us old 'uns remember as our only means of following gas exchange in the anesthetized human. Dr. Bockstahler reminded us of another change in practice that we have incorporated almost casually and that is the use of dextran as a life-saving volume expander - first used on a large scale in the Korean war

At lunch Drs. Holzman and Dunbar and Patrick Sim entertained us with two training movies that the Canadian anaesthetist Digby Leigh made in the 40's and 60's that undoubtedly must have improved pediatric anesthesia care in that era.

After lunch, Dr. Donchin from Israel had us laughing once again with some of his vast collection of film clips that put our specialty into a sinister light, or a hilarious light as in Danny Kaye's movie 'The Secret Life of Walter Mitty'. Scott Maruna, a teacher and historian told us the remarkable story of an episode of what was thought to have been a case of mass hysteria in a small mid-Western town. He demonstrated through careful historical detective work that this episode had a rational and tangible explanation. Dr. Calmes related the tragic story of Dr. Hathaway, an alumnus of Dr. Waters' program, who became an addict probably in part due to overwork. He was lost to our specialty. Dr. Bill Hammonds made a nice comparison between the efforts of the apothecaries in England to take over the practices of physicians in England in the 17th century and the current similar efforts by our nurse-anesthetists. Dr. Mandabach summarized the growth of that most useful pediatric regional anesthetic, the caudal block.

The present writer has heard rumors that the attendees at this meeting considered it highly successful and enjoyable. Even if the rumors prove untrue, that is his opinion.





*Tour of the Etherdome:  
(from left to right) Dr.  
Gerald Zeitlin, Dr. Mark  
Schroeder, and Dr. Elliott  
Miller stand next to a  
horse-drawn ambulance at  
Mass. General.*



*Dr. Selma Harrison Calmes*

*Inside the  
Etherdome*



*Photos courtesy of  
Dr. Sukamar  
Desai, Dr. Gerald  
Zeitlin, and  
Patrick Sim.*

*Touring historic Mount Auburn  
Cemetery: Listening to Dr. Ray  
Defalque (far right) lecturing on the  
Ether Controversy are (from left to  
right) Dr. Elliott Miller, Dr. Sukamar  
Desai, and Dr. and Mrs. Richard  
Schwimmer.*



*Dr. David Mackey and  
Dr. Doug Bacon*



*Dr. Kenneth  
Sugioka*



# F. A. Duncan Alexander and the Multidisciplinary Management of Pain

by Adolph H. Giesecke, M.D.

Retired Jenkins Professor and Former  
Chairman  
Anesthesiology and Pain Management

This article has been peer reviewed and accepted for publication in the Bulletin of Anesthesia History.

An Aqua Alumnus refers to that elite group of anesthesiologists who were trained by the famous founder of the first academic department of anesthesiology in the world, Dr. Ralph Waters of the University of Wisconsin. F. A. Duncan Alexander MD was an Aqua Alumnus of the class of 1937. This article is a short summary of his life and career emphasizing his role in the development of the multidisciplinary management of chronic pain syndromes.

Like the other Aqua Alumni Dr. Alexander was extremely intelligent, highly innovative and very productive. Unlike the others he was an alcoholic in the times when recovery programs for addicted physicians were not available. His destiny was to be a medical vagabond. At each new location, he immediately impressed his patients and the staff with his charm and ability. He worked hard to spread the educational principles established by Dr. Waters; i.e., care for his patients, to teach those who wanted to learn and to perform some innovative research. Eventually, he would be found in the worst manifestations of his addiction and would be forced to move. W. B. Neff said it best in his article about all of the Aqua alumni in the Anesthesia History Newsletter, "Alex led a checkered career as he entered one teaching center after another only to disappear after several years of excellent performance; the reason being a bout with alcohol."<sup>1</sup> He is responsible for some significant achievements but he remains one of the least remembered of the illustrious Aqua Alumni.

Alexander was born in Arden, Ontario, Canada in 1908. His primary, secondary, collegiate and medical educations were all in Ontario.<sup>2</sup> He took 18 months of residency in anesthesiology in Madison, Wisconsin and six months at Bellevue Hospital New York as part of the exchange program between by Drs. Waters and Emory Rovenstine. He returned to Madison for another 14 months followed by a research fellowship in psychopharmacology. This fellowship led to some very important ob-



Figure 1. Dr. F. A. Duncan Alexander cropped from the group photograph of the Aqua alumni reunion of 1938. Photograph from the files of the Wood Library Museum.

servations.

In 1936 schizophrenia was being treated with a series of convulsive seizures induced by metrazol, an analeptic, or insulin, a hypoglycemic. Alexander proposed

substituting "nitrogen seizures."<sup>3</sup> These were anoxic seizures induced by inhalations of pure nitrogen. Much of the knowledge that we have about the progressive clinical manifestations of hypoxia come from Alexander's careful observations during these treatments.

In 1937, Alexander became director of anesthesia, gas therapy, blood banks and physiological services at Albany Hospital, New York. He held the academic title of Associate Professor of Anesthesiology, Physiology and Pharmacology at Albany Medical College. Working with Dr. Charles Martin he invented the "bazooka" for exhaled air, artificial ventilation. This device was patented in 1942 with the proper name of "Alexander Mouth-to-mouth Insufflator." A simple metal tube was fitted with a mouthpiece for the rescuer on one end and a mask adapter on the other end for the patient. Adult, pediatric or neonatal masks could be attached to provide sanitary mouth-to-mouth ventilation for all patients. Oxygen could be supplemented through a nipple and the inspiratory pressure could be adjusted

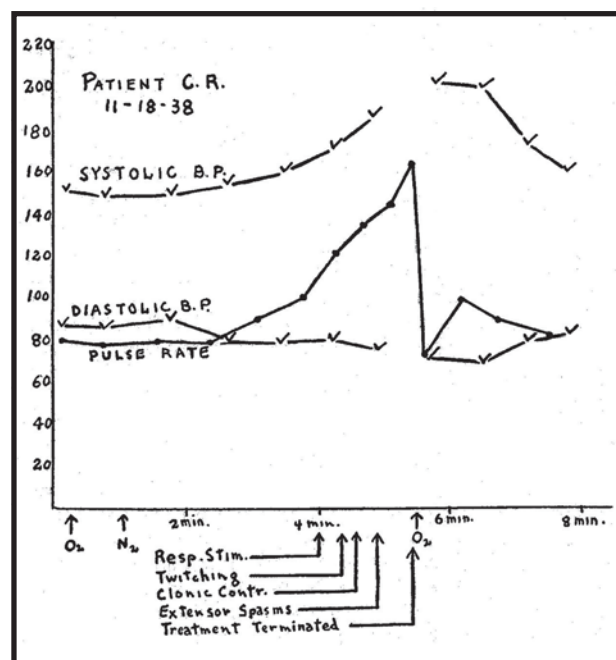


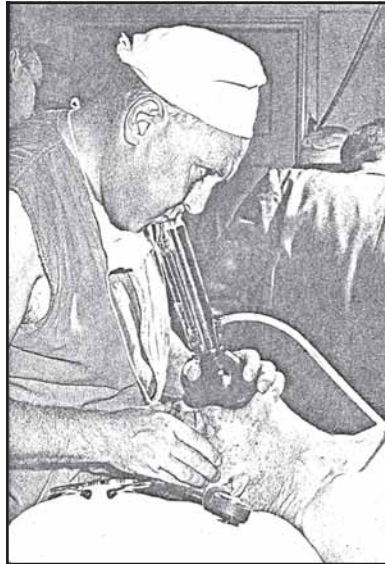
Figure 2. Graph of the progressive clinical manifestations of anoxia induced by breathing pure nitrogen to produce "Nitrogen Seizures" for the treatment of schizophrenia.<sup>2</sup> As a result of Alexander's observations we have accurate knowledge of the progressive clinical manifestations of anoxia. Reprinted with permission from the *American Journal of Psychiatry*.<sup>3</sup>

with a sliding pressure relief valve on the side.<sup>4</sup>

Alexander established an active training program in anesthesiology at Albany. His most important protégé was Dr. Benjamin Etsten, who became the chairman of anesthesiology at Tufts University, Boston from 1949 until he retired in 1974. Dr. Alexander was an effective lecturer and was in demand as a speaker for refresher courses and society meetings. His popularity grew and in 1942 he was elected First Vice-president of the American Society of Anesthesiologists.

That same year he joined the United States Air Force. According to his resume, he was chief of anesthesia and operating room section at three hospitals including the 160<sup>th</sup> General Hospital stationed in England. In his letters to his mentor, Dr. Waters, Alexander wrote enthusiastically about his activities.<sup>5</sup> This hospital "is the largest chest center in the U.K. ... We do about thirty open chest cases per week, mostly for foreign bodies in the lung, pleura, pericardium, heart and great vessels, but also many decortications." In a subsequent letter he reported doing "five hundred and seventy consecutive intrapleural cases of all kinds with a mortality of two. Astounding, isn't it?" This safety record was impressive in what might be considered the pioneer days of thoracic anesthesia. Alexander was proud of and stimulated by his success. He was extremely popular with his patients and colleagues but his addiction surfaced and became a problem. He narrowly escaped a military court martial, thanks to the timely intervention of a fellow Aqua Alumnus, Dr. Lucian Morris.<sup>6</sup>

After discharge from the Air Force in 1946, Dr. Alexander became the chief of anesthesia at the Veterans Hospital in McKinney, Texas, thirty miles north of Dallas. The hospital was a series of connected pavilions in a wooded section of the northern Texas prairie. In this peaceful setting, Alexander was able to do some of his best work. He was surrounded by veterans of World War II suffering from a variety of chronic pain syndromes associated with their wounds or other past stresses. Along with a neurosurgeon and a psychiatrist, he established a collaborative, multidisciplinary pain clinic to care for these unfortunate patients. Most authorities credit Dr. John Bonica with developing the concept of a multidisciplinary approach to pain problems. However, Dr. Bonica himself gives credit to F.A.D. Alexander for simultaneously and independently having a similar idea. Bonica writes, "At approxi-



*Figure 3. Dr Alexander performed mouth-to-mouth expired air ventilation with his "bazooka" circa 1942. Photograph from the files of the Wood Library Museum.*

mately the same time, FA Duncan Alexander had independently developed the same concept, initiating a multidisciplinary pain diagnostic and therapeutic program at the Veterans' Administration Hospital in McKinney, Texas in 1947."<sup>7</sup>

He was probably the first to demand radiological localization of needle placement before permanent nerve block.<sup>8</sup> He made large albums of x-ray photographs of needles in proper place for various blocks, followed by pictures showing the typical pattern of distribution of injected radio-opaque dyes when the tip of the needle is in the proper place. These albums are now in the possession of his grandson, Dr. David Jackson.

Dr. Alexander was present to welcome Dr. Pepper Jenkins in 1948 when Pepper became Chairman of Anesthesiology at Parkland Hospital and Southwestern Medical School in Dallas. Pepper admired the innovative work that Alexander was doing in the management of chronic pain, and the two became good friends. He made Pepper a consultant at the VA Hospital and in turn became a voluntary professor at the medical school.

He established a small residency-training program in McKinney. The best known of his trainees were Dr. Ivey Lambreth, who became president of the Texas Society of Anesthesiologists and Dr. Lewis Lewis, who became a committed friend. Dr. Lewis, who practiced pain medicine

in Los Angeles, CA, was the source of much of the information for this report.

Alexander served as president of the Collin County Medical Society. His occasional alcoholic indiscretions were tolerated by his fellow physicians, who respected his popularity and feared that a replacement would be impossible to recruit to this secluded area of Texas. However in 1955, the hospital was taken over by an ambitious administrator who forced Alexander to resign. Many would consider this a disgraceful end to a monumental achievement. The facts remain that Dr. Alexander brought the influence of the great Ralph Waters to academic anesthesiology in northern Texas and that he established the first pain clinic in the state.

Alexander moved to the University of Iowa as a Research Associate for two years and then became a consultant in medical education at Victory Hospital in Brooklyn, New York until 1958. He completed his career as an emergency room physician in Schenectady, New York, retiring in 1972. After retirement he lived in the home of Dr. Lewis Lewis, who looked after him until his death in 1983.<sup>9</sup>

Alexander was an enigma to his colleagues. He was a near genius full of ideas, all of which were potentially great. He lectured widely but did not publish much. He was an effective teacher in an informal clinical setting. He was manifestly popular with his colleagues and patients. He did important innovative work on physiology of hypoxia, adult and neonatal resuscitation, psychopharmacology and management of chronic pain. Although Bonica is generally credited with establishing the multidisciplinary pain clinic, Bonica himself writes that FAD Alexander simultaneously and independently established a multidisciplinary pain diagnosis and treatment clinic in McKinney, Texas. Alexander has faded from our memory because of his addiction to alcohol, which casts a dark shadow of disapproval over his career. One wonders what his career might have been if he had the advantage of the modern physician recovery programs, which have saved the lives, families and careers of hundreds of physicians.

## Appendix

Dr Alexander's Curriculum Vitae did not contain a complete listing of his publications. The listing below may not contain all of his publications, however it does include all publications listed in the Index Medicus between 1930 and 1955, which were his most productive years.

*Continued on Page 20*

# MedNuggets

by Fred J. Spielman, M.D.

Professor

Department of Anesthesiology, University of North Carolina

The blessings of anaesthetics to suffering humanity can hardly be exaggerated. The agony that many endured for want of them is too horrible to contemplate. The development of modern surgery would have been impossible without them.

–Editorial

*British Journal of Anaesthesia* 28:391, 1956

The general practitioner who sends a patient to a surgeon expects to give the anaesthetic, and if the surgeon fails to ask him, the general practitioner will in future send his patients to a surgeon who does.

–R.H. Orton

*The Medical Journal of Australia* 2:853, 1936

We do not believe in fussing with patients under spinal anesthesia. We do not ask them how they feel every few minutes, nor do we note their blood pressure every so often. We determine the blood pressure before and after injection, and again only when the patient shows symptoms of collapse.

–J.A. Joseph

*Surgery, Gynecology and Obstetrics* 45:649, 1927

I hope to see a device in the operating rooms, where it could be viewed by anyone, which will give information concerning the heart, its rate, its rhythm and its condition, as far as possible.

–John S. Lundy

*Surgical Clinics of North America* 29:1097, 1949

Manual dexterity and operative skill alone, important though they are, no more make a good anaesthetist than they do a good surgeon.

–A.R. Hunter

*Anesthesiology* 13:108, 1962

No patient should die as a result of the anesthetic alone.

–Paul H. Lorhan

*The American Surgeon* 18:727, 1952

Satisfactory teaching of students during a list of major operations has long since become impossible, as it is not easy to com-

bine responsibility to patient, surgeon, and student.

–G. F. Rawdon

*Anaesthesia* 3:110, 1948

Spinal anesthesia, carrying the highest anesthetic mortality, should not be used in trivial or minor operations.

–George Crile

*American Journal of Surgery* 23:102, 1934

There is certainly a definite need for air conditioning in hospitals. It not only provides comfort, but also has specific therapeutic and safety values. Freedom from oppressive heat and humidity conserves energy, lessens fatigue, and permits hospital personnel to perform their duties under the most favorable conditions.

–George J. Thomas

*Anesthesia and Analgesia* 36:32, 1957

It is obvious that one of the first principles of treatment in medicine is that when pain is present it should be relieved as soon as possible. Some, however, maintain that the pain of childbirth is an exception, and that any effort towards its relief is against the will of God.

–Dame A. Louise McLlroy

*Canadian Medical Association Journal* 24:21, 1931

The man who gives the anesthetic in a hospital is regularly the youngest man in the staff, a fresh graduate with theoretic teachings alone, or the example of another interne, as his guide.

–Editorial

*Journal of the American Medical Association* 31:613, 1898

Dentists, young and old, should be informed that they cannot learn how to administer anesthetics properly by seeing a few demonstrations or by taking a two or three day postgraduate course. There are far too many members of our profession who attempt the dual role of anesthetist and operator. In my opinion, in most instances, either the anesthesia or the operation is neglected.

–Thomas Conner

*Journal of the American Dental Association* 19:1931, 1932

Since so few anesthetics are administered skillfully, the laity readily accepts poor anesthetic results as inevitable.

–Frances E. Haimes

*Anesthesia and Analgesia* 6:25, 1927

It is true that anesthesia is available; it can be given by almost anyone, and frequently is, and this is not because such administration is the best or safest, but because of the appalling ignorance of the consequences by physicians, generally due to their historical attitude toward anesthesia.

–John B. Dillon

*Journal of the American Medical Association* 190:997, 1964

While surgeons know that a competent anaesthetist is one of the important factors in the operating-room for his own comfort, as well as for that of his patient, there is no class of work that has so little encouragement, and few are willing to follow this line of work long enough to become familiar with the first requirements of a good anesthetizer.

–Alice Magaw

*Surgery Obstetrics and Gynecology*

## Alexander. . .Continued from Page 19

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# The Book Corner

by Peter McDermott, M.D., Ph.D.

Complications: A Surgeon's Notes on an Imperfect Science. Atul Gawande, 269 pp., end notes. New York: Metropolitan Books, 2002. ISBN 0-8050-6319-6 (hbk.) \$24.

Thank God for young doctors and the opportunity they give us to discover our profession all over again! Dr. Gawande, a surgical resident at a Boston hospital and son of two physicians, has cast a critical, and at the same time affectionate, eye on current medical practices – the doctors' quest for certainty, the patients' search for cure and kindness, and the sometimes darkly lit terrain in which both operate. The author is a staff writer for *The New Yorker*. He comes with the uncommon ability of the professional journalist and the dedication of a caring physician. Divided into three sections – Fallibility, Mystery, and Uncertainty – the book discusses medical error, difficult diagnoses, and the troubling inevitability of doubt that is ever present in medical decision-making.

Woven through Gawande's analyses of large topics such as medical education, diagnostic and therapeutic complications, and the sometimes fragile relationship between physicians and those they serve, are specific case histories and personal, clinical experiences. Doctors who make mistakes are, well, all doctors. "Every doctor has things he or she ought to know but has yet to learn." Gawande looks at ways in which error can be minimized and cites

as the greatest success story that of anesthesiology – Jeep Pierce, Jeff Cooper, David Gaba and others – the formation of the Anesthesia Patient Safety Foundation, and the types of decision trees made commonplace in anesthesia by the ASA Committee on Standards of Care. Education and monitoring have demonstrated dramatically their power to anticipate and prevent morbidity and mortality. Critical incident analysis and crisis simulators, tools familiar to anesthesiologists, are also credited with improving patient outcomes. Another way of reducing adverse results is the standardization of services rather chillingly described in a visit to a Canadian hernia factory. Good results, little guessing are useful, but the extent to which systems can be stabilized and procedures mechanized is limited in the biological universe in which people function. Freely confessing some of his own mistakes, Gawande makes an important distinction between two of the responses to error that doctors sometimes employ. Guilt, he says, means I did something wrong for which I'm sorry. Shame means I'm the problem. I'm sure we have all inflicted those moral judgments upon ourselves at one time or another. Accepting responsibility, and the failure to do so, is skillfully analyzed. Some doctors go bad, but most adverse outcomes derive from good doctors, often from the evolution of small mistakes into catastrophes.

Gawande deals with some hard subjects:

what is the nature of pain, how can we succeed in relieving it? What are the faces of suffering, and how can we be more compassionate? Mind and body are separate yet connected. That is not as simple as it sounds.

Mysteries – the woman who could not stop throwing up, the man who could not stop eating, the woman who blushed, and other enigmas – are reminders for medical science that we have a way to go on our journey to knowing everything. Gawande has an amusing chapter on superstition relating to his being on-call one full-mooned Friday the 13<sup>th</sup>. He discounted the lunar and numerological significance of the date. A Taiwanese surgical colleague once muttered in my ear "Foo moo, pizzy wicken." It was a Friday and only exhausted hours later did I catch the "Full moon, busy week-end" he was predicting. In the factual error department: Gawande conflates Espanola with the Dominican Republic, the geographical omission of an entire country.

The inexactness of medical science and the physician's constant striving for competence seem like an impossible contest, but Gawande understands that uncertainty must remain a portion of the physician's daily diet. Living for what he calls "the alterable moment," that occasion, in which the doctor has the possibility of benefiting his or her patient, is the great joy and reward of the profession.

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## History of Anaesthesia Society

### ADVANCE NOTICE

#### *Sixth International Symposium on the History of Anaesthesia Queens' College Cambridge 15<sup>th</sup> to 18<sup>th</sup> September 2005*

Substantial Cash Prize  
(To be confirmed as the John Bullough Prize)

For all persons in training on 31<sup>st</sup> December 2004, there will be the opportunity to compete for the Trainee Prize at the Sixth International Symposium on the History of Anaesthesia. Essays on any topic in the history of anaesthesia will be accepted. This includes, but is not limited to anaesthesia, analgesia, pain medicine, critical care medicine, veterinary medicine. The best five papers will be presented before an international panel at the meeting, and the prize awarded, following adjudication. Papers deemed of sufficient merit, but not the final five, will also be offered the opportunity to present during the Symposium.

All papers and presentations are to be in English which will be the language of the Symposium. All papers must be received by Dr. Adams by 11<sup>th</sup> January 2005

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# From the Literature

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

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*Note: In general, I have not examined articles that do not include a notation for the number of references, illustrations, etc. I do examine most books and book chapters. Books can be listed in this column more than once as new reviews appear. Older articles are included as I work through a large backlog of materials. Some listings are not directly related to anesthesia, pain or critical care but concern individuals important in the history of the specialty [i.e., Harvey Cushing or William Halsted]. I also include career profiles of living individuals. Non-English materials are so indicated. Columns for the past several years are available as "Recent Articles on Anesthesia History" in the "Anesthesia History Files" at <http://www.anes.uab.edu/aneshist/aneshist.htm>. I urge readers to send me any citations, especially those not in English, that I may otherwise miss!*

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