

edematous lingual follicles, most of which are hidden behind the blade of the laryngoscope. Furthermore, mechanical stimulation by the blade can exacerbate the edema formation. Our findings in this case demonstrate the necessity for fiberoptic laryngoscopy if time allows, when no abnormalities are noted by direct laryngoscopy.

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## The First Anesthetic Mixture

*To the Editor:*—Historians<sup>1-4</sup> quote John Gabb as the inventor of the first anesthetic mixture. Indeed, in May, 1848, Gabb<sup>5</sup> suggested mixing one part chloroform with two parts ether to provide a rapid, pleasant, and safe anesthesia. There is no evidence that he actually tried this mixture, but other practitioners did so shortly thereafter.<sup>6</sup> Gabb's idea was condemned by Jones<sup>7</sup> one week after its publication and by Snow<sup>8</sup> in 1849; both critics pointed out that the components' different volatilities would produce an unpleasant and dangerous anesthesia.

In fact, a Viennese dentist and surgical anesthetist preceded Gabb by several months. In December, 1847 or early January, 1848, Weiger<sup>8,9</sup> prepared a 1:4 chloroform-ether mixture\* and on January 15, 1848 reported several hundred anesthetics, stating

I mixed both drugs to combine the good properties of chloroform with those of ether . . . reaching the exact proportions after experiments on myself, my assistants, and technicians. . . . The induction is pleasant, without the sickening-sweet taste of chloroform nor the penetrating smell of ether. . . . Anesthesia is reached in 1 . . . 2½ minutes. . . . It gives such analgesia that the patient experiences no pain from the surgical stimuli even after return of his vision. . . . He wakes up cheerful . . . from pleasant dreams . . . and with full muscular strength. . . . The anesthetic's smell on his breath is slight and very transient. . . . I have used my mixture on several hundred patients . . . of all ages and conditions . . . and am convinced that we now have an anesthetic fulfilling all our wishes. . . . I recommend it to produce a rapid and safe anesthesia, free of sequelae, in all patients.<sup>8,9</sup>

Thus, Weiger, not Gabb, introduced "polypharmacy"<sup>1</sup> to anesthesia.

A German surgeon<sup>10</sup> reported using Weiger's compound in June, 1848. The famous "Vienna anesthetic" of the early 1850s may have derived from Weiger's mixture, although its origin is obscure<sup>11</sup> and its composition uncertain: some authors<sup>12,13</sup> describe it as one part chloroform and three parts ether; others<sup>2,11,14,15</sup> as one part chloroform and six or eight parts ether. A preparation with Weiger's proportions (1:4 chloroform-ether) is mentioned in the German literature<sup>13,16</sup> as "Lienhard's mixture." Buxton may have meant the same compound when he (mistakenly?) listed a "Linhart's mixture," of 1:4 alcohol-chloroform content, in his textbook.<sup>12</sup>

The Vienna anesthetic and, after 1872, Billroth's mixture (3:1:1 ether-chloroform-alcohol) were extensively used throughout the Habsburg empire and German speaking countries until World War I.<sup>2,14</sup> They were believed to be safer than chloroform because their ether and alcohol content diluted chloroform or offset its myocardial depression.

In Great Britain, except for Kidd's Vienna mixture<sup>11</sup> and the practitioners mentioned by Snow<sup>8</sup> in 1849, the mixtures were ignored until 1860, possibly because of Snow's vigorous condemnation.<sup>6,17</sup> Keys<sup>18</sup> and Clark<sup>19</sup> are mistaken in associating Thomas Nunneley with the alcohol-chloroform-ether (ACE) mixture in 1849; Nunneley at the time was experimenting with chloric ether, an alcoholic solution of chloroform.<sup>20</sup> Curiously, despite his opposition to mixtures, Snow, like J. C. Warren in Boston, preferred a 1:1 or 1:2 chloroform-alcohol preparation when he used a sponge or handkerchief rather than his inhaler.<sup>6,17</sup>

The concern over the many chloroform accidents and, possibly, Snow's death in 1858 led to a resurgence of the mixtures in Great Britain around 1860. The then three most popular mixtures were the 1:2 and 1:4 chloroform-ether solutions and George Harley's ACE mixture (1:2:3 alcohol-chloroform-ether). The Chloroform Committee of the Royal Medical and Chirurgical Society,<sup>21</sup> set up in 1864 to study the chloroform deaths, found the 1:2 and, especially, the ACE mixtures satisfactory and possibly safer than chloroform. The Committee, however, acknowledged the problem of the different volatilities of the liquid components, and some of its members gave up the mixtures—e.g. Kidd,<sup>11</sup> who adopted the chloroform-ether sequence, and Ellis,<sup>15</sup> the inventor of the first obstetric self-inhaler, in which chloroform and ether (mixed with alcohol) were separately vaporized to produce variable gaseous mixtures.

The mixtures, especially Harley's ACE and Hewitt's 3:2 ether-chloroform preparations, became popular in Great Britain, where they persisted until the late 1930s. They were used and recommended by such authorities as Buxton, Hewitt, Gardner, Bloomfield, Probyn-Williams, Minnitt, and Gillies.<sup>3,22</sup> They represented 6.2% of the 25,920 recorded anesthetics given in the United Kingdom in 1891.<sup>23</sup> The British Army extensively used ACE during World War I.<sup>13,24,25</sup>

Harley's ACE and Hewitt's mixtures were equally popular in the United States from the early 1860s until World War I, both in military<sup>24,26</sup> and civilian<sup>1,18</sup> practices. ACE was commonly used at the Mayo Clinic in the 1880s and 1890s, and the first anesthetic given by Charles H. Mayo (at the age of 12) was indeed ACE.<sup>1,18</sup> Both chloroform

\* All proportions in this article are given in weight; di-ethyl-ether is abbreviated to ether.

and its mixtures were condemned by the American Medical Association Committee on Anesthetics<sup>27</sup> in 1912 and rapidly disappeared from the American scene, although Guedel continued to use extensively anesthesol (a mixture of ethyl-chloride, ether, and chloroform invented by Meyer and also called anesthesol)<sup>13</sup> for the American Expeditionary Forces in World War I.<sup>25</sup>

The mixtures had been abandoned everywhere by the onset of World War II. The Germany Army briefly considered using ACE for the future hostilities in the late 1930s but gave it up because of disappointing laboratory and clinical evaluations.<sup>13,16</sup>

Other chloroform mixtures<sup>3,12,13,28</sup> also enjoyed a brief period of popularity at the turn of the century:

- Meyer's anesthesol and Fohl's rinaron: chloroform, ether, and ethyl-chloride;
- Wertheim's and the three Schleich's mixtures: chloroform, ether, and benzene,
- Otis' compound: chloroform, alcohol, and ethyl-bromide; and
- Regnaud's methylene: chloroform, and methyl-alcohol.

Nonchloroformic mixtures appeared later and up to the 1960s,<sup>28,29</sup> All rapidly lost their initial popularity:

- Rolland's somnoform in 1901: ethyl-chloride, ethyl-bromide, and methyl-chloride,
- Bourne's vinethene anesthetic mixture (VAM) in 1937: di-ethyl and di-vinyl-ethers;
- Willinger's neurolene in 1951: ether and trichlorethylene;
- Hudon's flu-ether in 1957: halothane and ether, and
- Howat's azeotrope in 1962: halothane and methyl-N-propyl-ether.

Flu-ether was not, as has been claimed by Hudon (cited by Hagelsten<sup>29</sup>), the first anesthetic azeotrope. Holtz (cited by Voigt<sup>16</sup>) had already prepared an azeotropic mixture of 7% alcohol and 93% chloroform in 1929. Distillation studies<sup>13,16</sup> have disproved the claim<sup>2</sup> that ACE is an azeotrope. To our knowledge, Buxton's claim<sup>12</sup> that Martindale's mixture (1:2:3 alcohol-chloroform-ether by volume) is azeotropic has never been substantiated. The interest in mixtures had disappeared when Howat (cited by Hagelsten<sup>29</sup>) presented his anesthetic azeotrope in 1962.

Our present anesthetics and techniques have made the mixtures unnecessary, but Weiger deserves to be remembered as anesthesia's first polypharmacist.<sup>1</sup>

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