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## I. THE CENTENNIAL OF CHLOROFORM \* † ‡

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CHLOROFORM anesthesia becomes one hundred years old in November 1947. Its history is voluminous, comprising a great part of the whole history of anesthesia. As with all great discoveries, the story has been written by many individuals.

*Production of the Drug.*—Often the general accumulation of knowledge and the mental attitude of the times set the stage upon which discoveries are made independently by two or more persons at the same time. An excellent example is afforded by the fact that chloroform was made in 1831 by three men independently of each other. In that year, Dr. Samuel Guthrie, Jr. (1, 2), a frontier doctor of Sackets Harbor, New York, distilled "three pounds of chloride of lime and two gallons of well flavored alcohol" to obtain "chloric ether," a solution of chloroform in alcohol and water, locally known as "Guthrie's Sweet Whiskey." A few months later, he published in *The American Journal of Science and Arts*, directions for purifying the product (3). Also in 1831, Eugène Soubeiran (4) of France and Justus von Liebig (5) of Germany each produced chloroform. In addition, Urdang refers (6, 7) to a German apothecary, Friedrich Moldenhauer, who unknowingly produced chloric ether in 1830, noting an ethereal odor while distilling potato spirit and chloride of lime in a search for fusel oil.

Jean Baptiste André Dumas (8), the famous French chemist, in 1834, determined the chemical composition of the substance and named it chloroform. This curious heavy liquid was chiefly regarded as a

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† Credit is given for assistance in this investigation to Dr. Ralph M. Waters, Dr. Erwin E. Ackerknecht, and Dr. George Urdang.

‡ A more detailed historical account is to be found in the recent extensive work of Barbara Duncum (16).

laboratory rarity, and found limited medical usage as "an agreeable and diffusible stimulant."

*Near Misses for Anesthetic Use.*—On several occasions the employment of chloroform as an anesthetic agent was missed by a narrow margin. Guthrie's early use of it is told in a letter (2) to his daughter shortly before his death in 1848.

"I could have made a fortune if I had gone to New York as I was urged last fall by making sweet whiskey which you remember taking when suffocated with charcoal. You see it called chloroform and the newspapers are beginning to give me the credit of discovering it. I made the first particle that was ever made and you are the first human being that ever used it in sickness. This is likely to prove the grandest discovery in medicine the world ever saw. By breathing it a few seconds the person falls apparently into a sweet sleep—when breasts, legs and arms may be cut away—painful labors ended and all without pain or injury."

Eli Ives, Professor of the Theory and Practice of Medicine in the Medical Institution of Yale College, in 1831, gave small doses of chloric ether by mouth (half a teaspoon every two hours) and by inhalation for respiratory troubles, with pleasing results. An interesting case report (9) follows:

"Mr. D. W. with pulmonic disease, has inhaled the chloric ether to obviate general debility and difficult respiration. The article has been effectual to obviate those symptoms, its immediate effect besides giving relief, is that of giving a pleasant sensation."

Daniel Smith (10) of Philadelphia, in 1832, noted the stimulating and intoxicating qualities of the agent on the living system. Black of Bolton, England, is quoted by Robinson (11) as recommending chloric ether in spasmodic asthma in 1833. In 1842 Dr. R. M. Glover (12) of Newcastle-upon-Tyne, England, published a study on the physiologic and medicinal properties of halogen compounds, in which he most certainly had produced anesthesia in animals by administering chloroform intravenously, intra-arterially, intraperitoneally and orally. He noted the depressant effect on heart, on blood pressure, and on respiration, dilatation of pupils, loss of voluntary muscle power, great prostration, profound coma, loss of response to noxious stimuli, and he detected odor of chloroform in the expired air. Though some of the animals recovered, he failed to grasp the clinical implication. An account of one of his experiments follows:

"Expt. 62d. Sixty minims of chloroform were very slowly injected into the jugular of a large shepherd's dog.

"Symptoms.—Irregular and hurried action of the heart; struggles; quick and forcible expiration, accompanied with a short bark; dilatation of the pupil; discharge of urine, and a temporary spasm, during which he was bent backwards. All this took place in two minutes. After this he lay still for three minutes; no respirations perceptible; the heart's action excessively feeble. He then began to breath again, and gradually recovered, the recovery being attended for some

time with great disorder of the respiration, loss of power over the voluntary muscles, and great prostration. Next day he was unwilling to move, and respirations continued laborious. Four days after the operation he was poisoned with prussic acid, when the lungs were found to retain marks of the great congestion produced by this class of poisons" (chlorine compounds).

Following the introduction of anesthesia with sulfuric ether in 1846, an eminent French physiologist, Flourens (13), in March of 1847, published an account of the anesthetic properties of chloroform in dogs. He considered the substance too toxic, and the account went unnoticed. Spurred by Morton's success with ether, Dr. Henry J. Bigelow (14) of Boston experimented with various agents, chloric ether among them, without success. Both John Snow (15) and Barbara Duncum (16) tell us that Mr. William Lawrence and Jacob Bell of England each tried chloric ether early in 1847 with little success—probably because of weak solutions.

*Simpson and Surgical Anesthesia.*—Prof. James Young Simpson of Edinburgh, not satisfied with the irritating qualities of ether in midwifery, sought new agents. A surgical colleague, Dr. Miller, gives us an account of the search (17). After suppers, Simpson and his assistants tested various substances by inhaling from tumblers. Upon trying chloroform they fell insensible under the table. On awakening, Simpson said to himself: "This is far stronger and better than ether." The incident occurred on November 4, 1847. Six days later, November 10, Simpson reported the clinical use of chloroform anesthesia to the Medico-Chirurgical Society of Edinburgh, and on November 12, he published his famous pamphlet "Notice of a New Anaesthetic Agent, as a Substitute for Sulphuric Ether in Surgery and Midwifery." On November 15 the pamphlet was reprinted (18) with the title changed to begin with the words "An Account of . . ." and a postscript of additional administrations was added. Four thousand copies of the November 15 paper were sold within a few days and many thousands afterward. Forthwith, Simpson employed chloroform enthusiastically in midwifery, championed its use for all operations and wrote prolifically and convincingly. Dr. James Syme, an Edinburgh surgeon of the same time, also actively promoted the use of chloroform. They administered small doses (half a teaspoon) of chloroform on a handkerchief, paying special attention to the respiration, but disregarding the pulse and circulation (19).

Although people earnestly sought relief of pain, they feared the mysterious loss of consciousness which came with this new blessing. And too, deaths occurred during anesthesia. The first one caused by chloroform (20) was that of a fifteen-year-old girl, Hannah Greener, at Winlaton near Newcastle-upon-Tyne, on January 28, 1848, while she was being anesthetized for removal of a toenail. Medical experimentation showed that when blood and ether were mixed in a tumbler a horrible mess resulted (21), and that in animals killed with chloro-

form the heart and lungs were engorged with black blood (22). Did not the same thing happen in the human body, and was not the lay press performing a disservice by playing up anesthesia to the public? Stern Scottish ecclesiasts objected to the relief of pain in childbirth because it was impious and against the Holy Writ, a circumvention of the primeval curse cast upon woman: "In sorrow shalt thou bring forth children" (Genesis III: 16). Simpson answered with scripture (Genesis II: 21), quoting the passage in which the Lord cast a deep sleep over Adam to remove the rib. This about stumped the preachers until they decided the rib episode was in the days before sin, hence there was no pain and no need for anesthesia.

*The Queen Establishes Precedent.*—Considerable impetus was given to anesthesia by the precedent set when Queen Victoria inhaled chloroform during the birth of her seventh and eighth child in 1853 and 1857. The anesthetist was John Snow (23) and not Simpson, as is sometimes stated. Without definite reference, Gwathmey (24) quoted some incredible figures from the Dublin Lying-in Hospital in which the use of chloroform reduced labor to only two hours and mortality to 1 in 320, while without chloroform, labor was twenty hours and mortality 1 in 11. Anesthetics were in use twenty years before antiseptics, and mortality from amputations was still 45 per cent. A survey in 1864 (25) showed that mortality following major operations with chloroform was no greater than without anesthesia.

*British Favored Chloroform.*—It is interesting to speculate as to why chloroform remained dominant in Great Britain, the British Empire, and much of the Continent, while in America ether remained in ascendancy. Presumably some of the reasons are to be found in the influence of teachers, the following of their students, the temperament, spirit and ideology of the times, and in historical pride. Chloroform had been introduced in Britain, it was their baby, and was it not far superior to anything which coarse Americans might think up? Ether was irritating, unpleasant, slow and inconvenient by the crude methods then in use, while chloroform, with its pleasantness, speed of action, full potency, and ease of administration, found ready acceptance. Simpson, by virtue of his fascinating personality, great ability, enthusiasm, and wide writings, did much to sell acceptance of chloroform. The trend was aided by Syme and in general by the influence of the Edinburgh School and its graduates. Nevertheless there were dissenters, chiefly Londoners, who used ether and were accused of being clumsy, stupid and incapable of administering chloroform.

Ether was America's baby. In the past there had been two wars with Britain, and why should Americans adopt a stepchild of the stodgy British—especially since chloroform was more dangerous and they could get on very well with their own products. After a brief trial, chloroform came to be seriously questioned in America (26), although its use continued to some extent, more in the Southern and Western

states. At the first scientific meeting of the American Medical Association (27) in Baltimore in May 1848, considerable attention was given to anesthesia, and the general impression on that occasion was in favor of ether because of its greater safety. In 1849, John Collins Warren (28) of Boston collected reports of eighteen deaths from chloroform and warned against its use. The British chose to acquire facility with the nicer agent; Americans chose to get along with the safer agent. A few Continental localities, such as Lyons in France, reverted to ether.

*The Ether-Versus-Chloroform Controversy.*—During the last half of the nineteenth century there raged a violent controversy of ether versus chloroform, largely within the British Empire itself. There have been a great many investigations, commissions and committees, and even today differences in opinion exist.

Numerous newspaper accounts and first-hand experiences with fatalities in Boulogne and Paris stimulated the French Academy of Medicine to appoint a Committee on Chloroform Accidents. Such men as Velpeau, Clocquet, and Poiseuille were on the commission and a precautionary report (29) was made on October 31, 1848, with the following conclusions: Chloroform should be classed as a poison, and as such should be entrusted only to experienced hands. It could be used to advantage if the toxic action were terminated before damage was done; this meant stopping administration as soon as narcosis was established. Only pure chloroform should be used, and it should be given only after digestion of food was complete. Much caution should be exercised in the presence of heart disease. Asphyxia was recognized as arising from inept administration, rather than from inherent properties of the drug; dangers of excluding air and of impeding respiration were stressed. Experiments for the committee showed that intravenous injection of 1 to 2 gm. of chloroform in dogs killed at once by cardiac standstill.

The anesthetist's patron saint, John Snow of London, through careful clinical and experimental work from 1847 to 1858, established trustworthy principles of inhalation anesthesia, and wrote a celebrated book: "On Chloroform and Other Anaesthetics" (15). Victor Robinson (11) evaluated him thus: "Compared to the attainments of Snow, the knowledge of the American pioneers of anesthesia was primitive and empirical." He came to use chloroform almost exclusively, though he recognized dangers and believed ether safer. He collected reports of fifty deaths from chloroform, and maintained that danger lay in the use of too concentrated vapor, which paralyzed the heart. Snow's inhaler limited vapor concentration.

Keys (30) stated that a Paris Commission in 1855 supported the Edinburgh contention that chloroform causes respiration to fail before the heart.

Hoff, (26) in an article containing an excellent bibliography, wrote that a committee of the Boston Society for Medical Improvement in

1859 advocated continued use of ether and discontinuance of chloroform.

After seventy meetings, a Committee Report to the Royal Medical and Chirurgical Society of London (25) in 1864, although admitting that ether was safer, concurred in the continued use of chloroform, and recommended mixtures of alcohol, chloroform and ether, as used earlier by George Harley (16). Two to four per cent chloroform vapor in air was thought safe. Fright was thought to contribute strongly to death during chloroform administration.

Back on the American scene, Dr. Hunter McGuire is stated to have said (24) that 40,000 administrations of chloroform were given in the Confederate Army without an anesthetic death, thanks to the splendid grade of chloroform captured from the Union Army.

Joseph Clover, as the leading anesthetist in Britain in the 1860's and 70's, gradually became converted to ether, and introduced the sequence of nitrous oxide induction to ether.

The "Glasgow Committee" (31) of the British Medical Association in 1879 stated:

"Chloroform has sometimes an unexpected and apparently capricious effect on the heart's action, the pressure being reduced with great rapidity to almost nil, while the pulsations are greatly reduced or even stopped. . . ."

The Committee deemed this a great source of danger, as it sometimes occurred after administration of chloroform had ceased. Since they would not recommend ether, they sought a new agent having the potency of chloroform, yet the benign effects of ether on the heart and respiration. Ethidene chloride was the answer to their prayer; but little came of it.

*The Hyderabad Commissions.*—Then came the famous Hyderabad Chloroform Commissions. Surgeon-Major Edward Lawrie was a former house surgeon and a disciple of Syme in Edinburgh. While directing a medical school in India in the late 1880's, Lawrie induced the native ruler, the Nizam of Hyderabad, to support researches to prove to all the world that Syme's teachings on chloroform were correct. One hundred forty-one dogs were used and the teachings were confirmed (32): namely that, if judiciously administered, chloroform could be given "so as to do good without the risk of evil." By gradually and continuously increasing the concentration, and with free breathing and free admixture of air, respiration invariably ceased before heart action; and artificial respiration started within thirty seconds always revived the animal. The administrator was to be guided *only* by the respirations, disregarding the pulse entirely. Primary cardiac syncope was believed nonexistent. Lawrie had given fifty thousand clinical administrations of chloroform without a fatality; so had Syme before him. Ether was considered capable of producing only semi-anesthesia (at least in the tropics).

Back in England, however, clinical experiences did not permit acceptance of these views; the state of the heart and circulation were considered paramount.

The American attitude in the 1880's and 1890's was summarized by Professor H. C. Wood, of the University of Pennsylvania, in his textbook "Therapeutics" (33). He stated that chloroform sometimes definitely killed by primary arrest of the heart. It killed without warning so suddenly that no forethought or skill or care could guard against the fatal result. Statistics seemed to indicate a mortality of about 1 in 3,000, and he thought hundreds of utterly unnecessary deaths had been produced by the extraordinary persistence in its use by a portion of the profession. He believed it ought *never* to be employed except under special circumstances, as on the battlefield.

Because of these disagreements, the Nizam granted another 1,000 pounds for the Second Hyderabad Chloroform Commission (34) in 1889. Thomas Lauder Brunton, a prominent physiologist from Great Britain, was delegated to assist. Four hundred and thirty animals were used, and the results were confirmed as before. Further, the Nizam provided funds for researches by the prominent Philadelphia pharmacologists, Hare and Thornton (35), who agreed essentially with the Commission.

*Clinicians Remained Wary.*—In the 1890's, the British Lancet (36) circularized doctors and hospitals throughout the world, collecting reports of 718 anesthetic deaths, in the ratio of 13 for chloroform to one for ether. Since chloroform was used six times as often as ether, it was concluded that the mortality from chloroform was twice that from ether.

Special Chloroform Committees of the British Medical Association published lengthy reports in 1901 (37) and 1910 (38). They concluded that danger to life was greater with chloroform than with other agents; ether was singularly safe. Since it was believed that chloroform produces benign or dangerous effects exactly in proportion to the strength of vapor, there was much concern over limiting vapor concentrations to 2 per cent or less by means of inhalers. They thought that the chief factor in safety was the administrator himself.

According to Hewitt (39), the French physiologist, Dastre, in 1893, maintained that chloroform vapor irritates nerve endings in the respiratory passage to produce reflex cardiac death, "syncope laryngoréflexe." Hewitt stated that Gaskell, Shore and others of England, in 1893, believed chloroform to have a direct paralyzing effect on the heart, causing it to dilate.

Embley (40) of Australia sought the cause of early sudden death during chloroform induction. In 1899 there had been 83 deaths from chloroform in England, of which 68 occurred before the start of the surgical procedure. From experiments on 300 dogs, Embley believed that strong chloroform vapors stimulated vagal activity to inhibit the

heart; this action was abolished by cutting the vagi of dogs or by giving large doses of atropine. He concluded that less than 1 per cent chloroform vapor should be used for induction until the vagus excitability had decreased.

Levy (41, 42) of England stated that there were 243 deaths from chloroform in England and Wales in 1911 (2 deaths in each three days). He believed there was no such thing as "initial overdose," or death through "vagal inhibition." From electrocardiographic records on cats, Levy concluded that the mode of sudden death early in the administration of chloroform was through ventricular fibrillation, the occurrence of which is quite unpredictable but is enhanced by injections of epinephrine. Levy's work has left a strong imprint on the thinking of anesthetists, even prompting some (43) to advise induction with ether before resorting to maintenance with chloroform.

*Liver Damage.*—Liver damage had been suggested in the earlier days of chloroform; an excellent summary is presented by Bourne (44). Dr. Leonard Guthrie, (45) of London, first called attention to it clinically in 1894 in reporting deaths of 9 children. Whipple and Sperry (46) of Johns Hopkins in 1909 demonstrated central necrosis in dogs, with complete regeneration in two or three weeks. Neudorfer of Vienna in 1886 used oxygen with chloroform, followed a year later by Kreutzmann of San Francisco; and in 1904 Gwathmey stated that chloroform with oxygen was twice as safe as chloroform with air (24). Goldschmidt, Ravdin, and Lucké (47) in 1936 stated: "The necrotizing effect of chloroform and of divinyl ether upon the liver cells of the dog is largely prevented by volatilizing the anesthetic with oxygen. This protective action of oxygen compares favorably with that of a high carbohydrate diet prior to the period of anesthesia."

*Chloroform Wanes.*—By the close of the nineteenth century, the use of chloroform was on the wane. With the advent of other agents and improved methods of administration, it has been relegated to the background. Chloroform, however, is still used to a limited extent on its one hundredth birthday. Those who employ it are somewhat reluctant to admit that they do so, because it has been condemned and they are fearful of censure. Cautiously administered, it continues to render admirable service as an analgesic in home deliveries. The advantage of nonexplosibility attracts some. There is a recent Australian report (48) of 3,000 administrations without accident. While using ether and chloroform as controls in evaluating newer anesthetic agents, Waters and his associates at the University of Wisconsin became interested in chloroform. Their recent evaluation (49) tends to support the findings of John Snow, Embley and Goldschmidt, rather than the Hyderabad Commissions or Levy.

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