THE DEVELOPMENT OF ANESTHESIA

(continued)

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Intravenous Anesthesia and Related Procedures

The discovery of a method of conveying liquors directly into the blood stream is attributed to Sir Christopher Wren, the famous architect (fig. 26), by his contemporaries, Oldenburg (86) and Clarck (87). The first experiments were carried out in 1657, at the home of the French ambassador, the Duc de Bordeaux. Wren was at that time professor of astronomy at the University of Oxford. Wren ligated the veins of a large, lean dog. Having made an opening on the side of the ligature toward the heart, he then introduced a syringe into this opening. The syringe, formed from an animal bladder to which a quill had been attached, was filled with a solution containing opium in one case and an infusion of crocus metallorum in another. Wren found that opium, administered intravenously, soon stupefied but did not kill the dog. A large dose of crocus metallorum, however, similarly administered to another dog, induced vomiting and death. Wren probably was unaware of the anesthetic results of his intravenous administration of opium, for his investigation was made mainly in the hope of discovering a new therapeutic procedure. According to Sturgis (88), Wren also injected beer and wine into the blood stream, probably to determine their therapeutic effects.

Apparently, as suggested by Jarman (89), the first genuine attempt at intravenous anesthesia was made in 1665. At that date Sigismund Elsholtz injected a solution of an opiate to obtain insensibility. At about this time (February, 1665) Richard Lower (fig. 27) transfused blood to animals for the first known time. On June 15, 1667, Jean-Baptiste Denis of Montpellier transfused blood to a man for the first known time. The account of Dr. Lower's experiments was published in the *Philosophical Transactions* of the Royal Society for December, 1666, and Dr. Denis' experiment was published in the same *Transactions* for March, 1667 (87). In all these early experiments the blood of animals, preferably lamb's blood, was used. In some of the cases of Denis, however, the blood of a calf was used. Lower and Edmund King (90) also transfused blood to a man, Arthur Coga, on November 23, 1667. In the case of the transfusion of blood to humans, it was hoped to

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bring about sanity by this therapeutic measure, for the patients who underwent the procedure were demented. Because of the severe reactions which followed these early attempts at transfusion and the death of one of Denis' patients (probably not from the transfusion, but from poisoning) the transfusion of blood to human beings was prohibited by law in France, and in 1670 by an act of Parliament in England. The transfusion of blood was therefore abandoned for many years.

FIG. 26. Sir Christopher Wren, who discovered a method of administering medicine intravenously. (Reproduced from the frontispiece to Ann. Med. Hist. for July, 1929. Courtesy Paul B. Hoeber, Inc.)

James Blundell (91), the distinguished English obstetrician and physiologist, reopened the subject of the transfusion of blood. Many of his patients had died because of puerperal and postpartum hemorrhage. Blundell felt that transfused blood might have saved them. Postulating that when blood is to be transfused to an animal, it should be obtained only from an animal of the same species, he was the first to transfuse human blood to a patient (September 26, 1818). Unfortunately, the patient was at the point of death and could not be revived by this therapeutic measure. Blundell transfused blood on many other occasions, and, according to Sturgis (88), of 10 patients to whom blood was transfused, 5 died and 5 lived. Despite the failures, Blundell be-

lieved in the therapeutic benefits of the transfusion of blood, and predicted that the world would sometime realize its value.

Another procedure related to the transfusion of blood and to intravenous anesthesia is the intravenous administration of saline solutions to patients suffering from shock. According to Adams (34), Latta of Leith, Scotland, introduced this practice in 1831. Many investigators in the latter part of the nineteenth century, as mentioned by Hirsh (91), demonstrated the effectiveness of infusing a physiologic solution of

FIG. 27. Richard Lower, who was the first man known to transfuse blood to animals. (Reproduced from Stirling, William: *Some Apostles of Physiology*, London, Waterlaw and Sons, 1902. Permission applied for from the publisher.)

sodium chloride in cases of surgical as well as traumatic shock. For a time the intravenous use of sodium chloride superseded that of whole blood, obviating the problem of coagulation as well as the problem of the procuring of blood donors.

Theodor Bischoff (92) performed some very interesting experiments in 1835. He demonstrated that when the whole blood of one animal was injected into an animal of another species, toxicity and death resulted. Bischoff found, however, that the injected animal would tolerate defibrinated blood. John Braxton-Hicks, according to Hirsh (91), opened up the field of the use of chemical anticoagulants in 1868.

He added sodium phosphate to blood used for transfusion, noting its anticoagulant properties.

It was not until 1914, however, that much real progress was made in the problem of anticoagulation. At that time A. Hustin (93, 94) of Belgium described a new method of transfusion in which a solution of glucose and sodium citrate was used as an anticoagulant. In the same year Professor Luis Agote (95) of Buenos Aires transfused citrated blood successfully. In 1915, Richard Lewisohn (96) of New York City reported a means of regulating the dosage of sodium citrate, so that its efficiency as an anticoagulant would be insured but its toxic characteristics would be overcome. After using the method experimentally with no ill results, he reported that he had transfused blood successfully to 2 patients with this new method.

Besides the problem of clotting, there remained the problem of discovering why, in the course of transfusion, some human blood was not compatible with other human blood. For even when human blood was used exclusively in transfusions, severe reactions resulted in many cases. Karl Landsteiner (97), in 1900, and Samuel G. Shattock (98), working independently in the same year, reported on the incompatibility of different types of human blood. In a footnote to Landsteiner's article it was pointed out that all blood could be divided into three types. The fourth type, according to Sturgis (88), was discovered by two students, DeCastello and Sturli, in 1902. Solution of the problem of the compatibility of the blood and the problem of coagulation is the basic discovery on which the successful transfusion of blood rests. Recently the blood bank, by means of which it is possible to keep blood in storage for thirty days, has been developed. Blood serum and plasma are now being used to some extent to replace whole blood (99), and may be of utmost importance in war medicine.

The first monograph on intravenous anesthesia to be printed was that of Pierre-Cyprien Oré (100) (fig. 28) (1875). He published a preliminary report on this subject in 1872 (101). Oré experimented with the intravenous injection of chloral hydrate into animals. After successful experimentation on animals he was able to produce general anesthesia among human beings by this method. Oré reported the first case in which he had employed this type of anesthesia for a human being to the French Academy of Sciences on February 16, 1874. Oré was very enthusiastic about intravenous anesthesia with chloral hydrate, and believed it to be superior to inhalation anesthesia with ether or chloroform. But inhalation anesthesia continued to be favored and intravenous anesthesia was not used for several years. As Greene (102) has suggested, Oré's drug (chloral hydrate) was not well suited to anesthetic purposes. Its anesthetic action was slow in disappearing and the required dosage for purposes of surgical narcosis was close to the toxic dosage.

Before and after the introduction in 1903 of the barbiturates, which were to revolutionize the use of intravenous anesthesia, other drugs were employed. In 1899, H. Dresser of Munich introduced methylpropylcarbinol urethane (hedonal) (34), and in 1905, N. P. Krawkow and his associates at Petrograd demonstrated the value of hedonal as

ÉTUDES CLINIQUES

SUR

L'ANESTHÉSIE CHIRURGICALE

PAR LA MÉTHODE

DES INJECTIONS DE CHLORAL DANS LES VEINES

PAR LE D^r ORÉ

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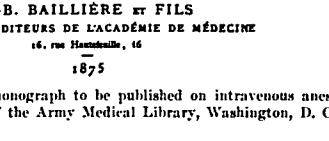

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1875

FIG. 28. Title page of the first monograph to be published on intravenous anesthesia. (Reproduced by courtesy of the Army Medical Library, Washington, D. C.)

an anesthetic agent for intravenous use (34). At about this time Fedorow of St. Petersburg reported favorable results in 530 cases in which he used hedonal as an anesthetic agent in a physiologic solution of sodium chloride (89).

In 1909 Bier (34) used the regional intravenous method to obtain anesthesia of the limbs. He injected a solution of procaine hydrochloride into the veins near the site of the proposed operation. In the

same year Ludwig Burkhardt of Germany reported on the use of chloroform and ether injected intravenously for general anesthesia (34). The difficulties in administration were so great that the intravenous use of ether and chloroform was soon discarded. In 1912 J. Goyanes of Madrid reported on the intra-arterial use of procaine hydrochloride (34).

Paraldehyde as an anesthetic agent for intravenous use was reported on in 1913 by H. Noel and H. S. Souttar (103). In the years after the first World War the intravenous use of paraldehyde became marked, and, according to Greene (102), this agent has retained a small but lasting position in the field of intravenous anesthesia. It is employed chiefly to produce basal anesthesia for some major operations and to produce complete anesthesia for some minor operations.

Elisabeth Bredenfeld (104) of Switzerland in 1916 reported on the intravenous use of morphine in combination with scopolamine. In the same year C. H. Peck and S. J. Meltzer (105) suggested the clinical use of magnesium sulfate as an intravenous anesthetic agent. Another anesthetic agent that was employed intravenously was ethyl alcohol. It was so used experimentally by Nakagawa (106) of Japan in 1921. M. G. Marin (36) of Mexico established the clinical use of this agent in 1929. In 1929, also, Martin Kirschner (107) reported on the intravenous use of tribromethyl alcohol in amylene hydrate (avertin).

According to Greene (102), none of the aforementioned preparations, with the exception of paraldehyde, attained lasting favor. Anesthesia produced intravenously with these agents either could not be uniformly controlled or was not so reliable or safe as anesthesia obtained by inhalation. Furthermore, the introduction of endotracheal anesthesia in 1909 (which will be considered in a subsequent issue) made available a procedure that was safer than intravenous anesthesia, in terms of the anesthetic agents then known.

Foundation for the relatively recent and continued success of intravenous anesthesia was the development of the barbiturates. Barbital (veronal), the first of these agents, was synthesized in 1902 by Emil Fischer (108) (fig. 29) of Berlin, one of the greatest physiologic chemists of all time. The first barbiturate was a long acting drug, very slow in producing anesthesia, and, consequently, it left patients in a deep sleep which disappeared only after twenty-four to forty-eight hours. Other long acting barbiturates included phenobarbital, soneryl, dial, and neonal. In 1920 Bardet (5) of France experimented with the anesthetic qualities of somnifen (a combination of veronal and alurate), and in 1924 Fredet (34) and Perlis introduced the intravenous technic of administration of this drug. In the same year dial (di-allyl-barbituric acid) was used as an anesthetic agent by Bogendörfer (109) of Wurzburg.

Pernoston or pernocton was the first barbiturate widely used for general intravenous anesthesia. It was introduced by R. Bumm (34) of

Germany in 1927. Its action was quicker and for that reason it was a more satisfactory anesthetic than the aforementioned barbiturates.

In 1929 somnifen, according to Geyer (110), was injected intramuscularly for the production of anesthesia. In the same year L. G. Zerfas and J. T. C. McCallum (111, 112) reported on the intravenous use of sodium amytal for anesthesia. In 1929, also, John S. Lundy

FIG. 29. Emil Fischer, who synthesized the first barbiturates. (Reproduced from Moore, F. J.: *A History of Chemistry.* New York, McGraw-Hill Book Co., 1918. (Reproduced by permission of publisher.)

(113) reported on the barbiturates as anesthetic, hypnotic, and antispasmodic agents, with special reference to sodium amytal. According to Adams (34), this particular barbiturate was used more frequently in the United States from 1929 to 1933 than any other agent for the production of intravenous anesthesia. According to Greene, sodium amytal is still widely useful in the medical management of patients who have neurologic and psychiatric disturbances, but with the advent of even shorter acting barbiturates its use as an anesthetic agent has been displaced.

The intravenous use of pentobarbital sodium (nembutal) was reported on by R. H. Fitch, R. M. Waters, and A. J. Tatum (114) in 1930. Lundy (115), in the same year, after an extensive study of sodium amytal and neonal, concluded that anesthesia produced intravenously with these barbiturates was not justified because of the untoward results incident to their use. In 1931 (116), however, he advocated the intravenous use of pentobarbital sodium as a hypnotic agent.

Advancement in the practical use of intravenous anesthesia was brought about by the discovery of evipan. It was first synthesized by the chemists, Kropp (109) and Taub. H. Weese and W. Scharpff (117) reported in 1932 on its pharmacologic and clinical effects. This new derivative of barbituric acid was very rapid in its hypnotic action. Likewise, the duration of its anesthetic effect was very short. Early in 1933 Weese (118) reported on an improved compound, evipan-natrium (evipal sodium or evipal soluble), as an anesthetic agent for intravenous use. Evipal soluble, because of its rapid destruction within the body, was found to produce very safe anesthesia for minor operations of short duration. According to Geyer (110), more than 4,000,000 patients have been operated upon with the aid of this anesthetic agent, administered intravenously. One of the earliest papers on the clinical use of evipan was published by Jarman and Abel (119) in 1933.

In 1934 Lundy (120) introduced the technic of intravenous administration of pentothal sodium (sodium ethyl-methyl butyl thiobarbituric acid). He also experimented with a related barbiturate, sodium allyl secondary butyl thiobarbituric acid, but concluded that pentothal sodium was the better of these two for anesthetic purposes. Lundy also found pentothal sodium to be considerably more potent than evipal sodium. Moreover, pentothal sodium afforded better surgical relaxation than did the other barbiturates. Since its introduction in this country, pentothal sodium has been widely used. At the Mayo Clinic it had been used alone or in combination with other types of anesthetic agents in 31,931 operations (121) up to and including December 31, 1941. J. R. Fulton (122) recently recommended the intravenous use of pentothal sodium under skilled direction for wartime conditions. He also advocated the intravenous use of pentothal sodium as an anesthetic measure in the treatment of fresh burns. The Medical Research Council of Great Britain (123) has also recommended anesthesia with pentothal sodium as well as that produced with gas and oxygen, prior to the local treatment of severe burns.

Another short acting barbiturate, eunarcon, was introduced as an intravenous anesthetic agent by Otto Gandow in 1936 (124). The use of still another barbiturate, sodium isoamyl-ethyl-thiobarbiturate, was reported in 1938 by S. C. Cullen and E. A. Rovenstine (125).

According to Lundy and his associates (126), the scope and safety of intravenous anesthesia have been increased by the simultaneous use of oxygen or of a mixture composed of 50 per cent oxygen and 50 per

cent nitrous oxide. Intravenous anesthesia also is of great value as a method of induction for other forms of general anesthesia and to supplement spinal, local, and regional anesthesia, when indicated. Recently, Mousel (127) has suggested that intravenous anesthesia be favored particularly in cases in which diathermy or cautery is to be used, for intravenous anesthesia eliminates the hazard of fire and explosion. For the same reason, intravenous anesthesia is of great value for the reduction of a fracture under the roentgenoscope. Another advantage of intravenous anesthesia in operations on the head and neck, as suggested by Greene (101), is elimination of anesthetic apparatus from the field of the operation. To patients undergoing short operations, the rapid and pleasant transition from consciousness to complete anesthesia constitutes the chief advantage of intravenous anesthesia.

(To be continued.)

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