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The Introduction of Hedonal: A Russian Contribution to Intravenous Anesthesia

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The modern era of intravenous anesthesia began in March, 1871, when Ore' administered chloral hydrate in a series of 44 dogs.[1] Three years later, "he reported to the French Academy of Sciences the first case in which he had employed this type of anesthesia for a human being."[2] Ore's monograph on intravenous anesthesia followed in 1875.[3] Despite Ore's enthusiasm for the method and reports in the contemporary literature by other Frenchmen, a significantly high mortality rate prevented further development of intravenous anesthesia until after the turn of the century.[4]

The next stage in the development of intravenous anesthesia is associated with the use of hedonal for general anesthesia (fig. 1). According to Adams, "Hedonal was the first anesthetic agent for intravenous administration that produced fairly adequate surgical anesthesia with a moderate degree of safety."[4] The initiative for using intravenous hedonal as an agent for general anesthesia belonged to Nicholas Krawkow (1865–1924). The first such use of hedonal in a surgical patient took place in St. Petersburg in 1909, where Krawkow (fig. 2) was Professor and Chairman of the Department of Pharmacology at the Military Medical Academy, the finest Russian medical school of the time.[5]

The investigations that finally resulted in the use of hedonal for intravenous anesthesia should be traced to the Schmiedeberg Laboratory of Pharmacology in Strassburg (Germany). In 1885, Oswald Schmiedeberg, the founder of German experimental pharmacology, was the first to experiment with urethane. He studied the hypnotic effect of ethylurethane and suggested that it could be used as a hypnotic agent. Ethylurethane was found to be a very weak hypnotic drug, and Schmiedeberg hypothesized that replacement of ethyl by a higher molecular weight chain should result in a stronger hypnotic action.[6] Dresser, in Munich, made use of Schmiedeberg's suggestion; the ethyl radical in ethylurethane was replaced by methypropylcarbinol, and, thus, in 1899, hedonal was synthesized.[7] This drug was used as a hypnotic agent in the treatment of patients with insomnia.

Krawkow and several associates began to investigate the pharmacological properties of hedonal in 1901. The choice of this topic was, probably, influenced by the research experience that Krawkow had early in his scientific career. He spent some time with Schmiedeberg, who studied the hypnotic effect of urethane. At the end of the 19th century, the Schmiedeberg laboratory was the center of world pharmacology. Many young physicians from different nations worked there under the direction of Schmiedeberg, and some of them later became leaders in pharmacology in their own countries.[8] Krawkow is regarded as the founder of pharmacology in Russia, and John A. Abel, who also worked in the Schmiedeberg laboratory, became a leader in the specialty in the United States.[9]

In the beginning of his work with hedonal, Krawkow did not consider the possibility of using hedonal as a sole intravenous anesthetic in humans, primarily because of low solubility of the agent in water and the necessity to use it in large quantitites, 100–300 mg/kg. However, his thinking on this matter was dramatically changed by publication of Burkhardt's study on the intravenous use of the volatile anesthetics chloroform and diethyl ether for induction of anesthesia.[10] Krawkow analyzed the results obtained by Burkhardt, and concluded that, if chloroform and diethyl ether could be used for intravenous anesthesia, hedonal had definite advantages over them as an intravenous anesthetic.

This conviction was partially based on experiments with oral administration of hedonal performed in Krawkow's laboratory by Lampsakow in 1901.[11] These experiments showed that hedonal could cause a deep and long-lasting surgical anesthesia without a state of excitement. In addition, arterial blood pressure was decreased less by hedonal than with chloroform at comparable levels of anesthesia. This characteristic was the basis for Krawkow's suggestion to use a combination of

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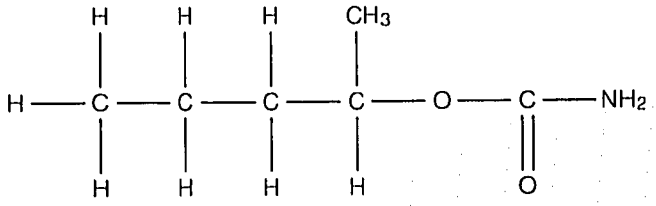
hedonal and chloroform for anesthesia, with the hedonal being administered orally 1 h before inhalation of chloroform. Such a combination was successfully used in surgical patients in 1903 by Fedoroff and his associates.[12,13]

After Krawkow read the paper by Burkhardt,[10] he invited a young surgeon named Jeremitsch into his laboratory to perform a systematic experimental study on intravenous hedonal for anesthesia. Jeremitsch tried a maximal hedonal concentration that did not require heating the solution to keep the drug from precipitating, *i.e.*, 0.75% hedonal in normal saline. For induction and maintenance of 4-h anesthesia in dogs, 200–300 mg/kg of the drug was required. Jeremitsch obtained basically the same results using intravenous administration of hedonal as those described earlier by Krawkow and Lampsakow for oral administration of this agent: deep surgical anesthesia without any significant preanesthesia excitement and post-anesthesia vomiting.

Krawkow's next step was dictated by his association with Sergei Fedoroff (1869–1936), who was Professor and Chairman of the Department of Surgery in the same St. Petersburg institution where Krawkow worked, the Military Medical Academy. Krawkow and Fedoroff were close friends and, in 1903, had performed joint research project to assess the combination of hedonal and chloroform for anesthesia in humans.

As a result of an agreement between Krawkow and Fedoroff, Jeremitsch moved from the experimental laboratory into the operating room of the hospital to continue his work with intravenous hedonal in surgical patients. In these patients, Jeremitsch used a method of interrupted injections of hedonal.[14] A 0.75% solution of hedonal was placed in a flask and forced by air pressure to flow through a rubber tube and the hollow needle into a vein (fig. 3). A volume of solution sufficient to produce general anesthesia was injected; the needle was then withdrawn and reinserted for further injections as they became necessary.

Hedonal intravenous anesthesia was used for the first time on December 7, 1909. The patient was an elderly man with a malignant lesion of the leg. Ninety minutes before surgery, the patient received 3.0 gm hedonal per os. The patient fell asleep, but was awake on the operating table. He received 275 ml of 0.75% hedonal in normal saline, iv. A surgical level of anesthesia was reached in 4 min without excitement; the respiratory and cardiac rhythms remained regular. For maintenance of anesthesia, two additional infusions of hedonal were used: first, 75 ml of the solution, and the next, 25 ml. The patient was asleep for about 6 h postoperatively; no nausea or vomiting occurred after anesthesia.[15] Jeremitsch reported on this first successful administration of hedonal for intravenous anesthesia at the



Hedonal (methylpropylcarbinol urethane)

FIG. 1. Hedonal (chemical structure).

9th Congress of Russian Surgeons 12 days after the case.

The first 44 cases of anesthesia with intravenous hedonal (they were performed in the Department of Surgery in the Military Medical Academy) were summarized by Jeremitsch.[14] Operations such as enterostomy, nephrectomy, cholecystectomy, amputation, and appendectomy were performed on patients whose ages ranged from 9 to 65 yr. In this series, the shortest oper-

FIG. 2. Nicholas Krawkow, M.D. (1865–1924).

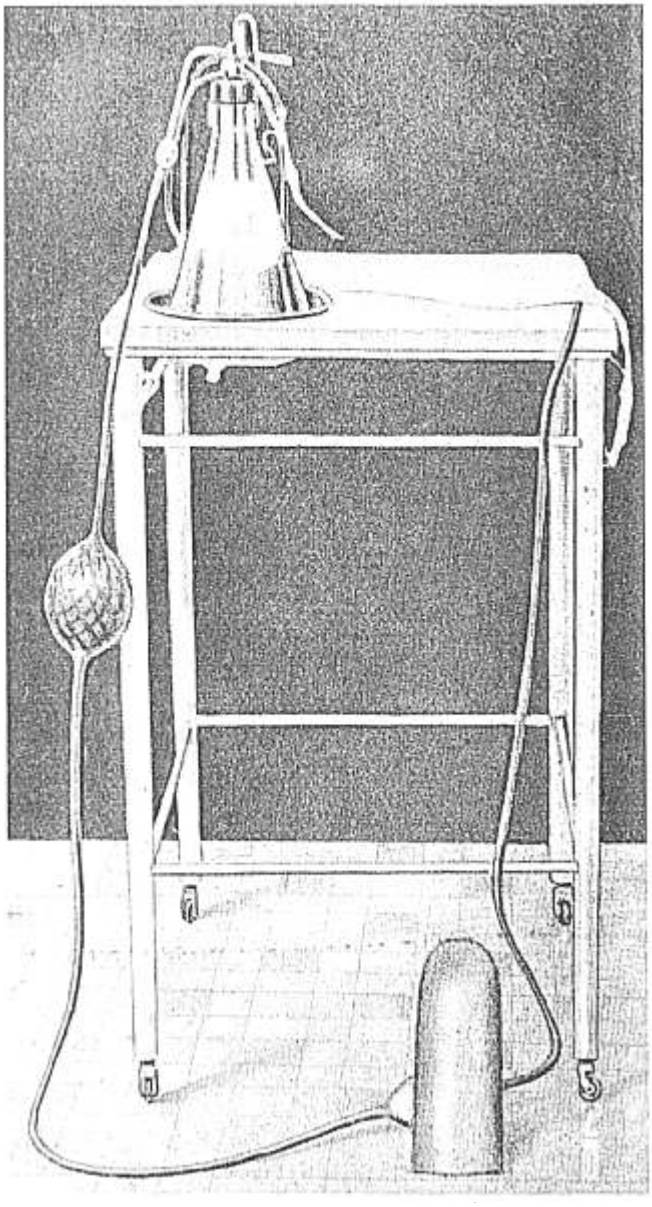


FIG. 3. Jeremitsch's apparatus for the administration of intravenous hedonal.[14]

ation lasted 14 min and the longest 2 h, 42 min. The total amount of hedonal solution injected varied from 325 to 1100 ml (0.75%). In two cases, satisfactory anesthesia was not obtained; in one, the vein isolated was very small, and the injection was carried out with difficulty. In the other instance, of varicose veins, the injection was made into the greater saphenous vein, and anesthesia was not induced after injection of 800 ml of solution. In one case, there was respiratory depression attributed to too rapid injecion of the solution. No case of local thrombosis occurred.

After Jeremitsch's presentation at the 9th Congress of Russian Surgeons in 1909, intravenous hedonal began to be used by several Russian surgeons, including Sidorenko,[16] Polienoff,[17] and Oppel.[18] In 1911 at the Congress of the German Surgical Association, Fedoroff summarized results from 530 cases of intravenous anesthesia with hedonal collected by these investigators and including Jeremitsch's cases.[19] Of the deaths that occurred in this series, none were directly attributed to hedonal. Temporary cessation of respiration occurred in eight of 530 cases; in each instance, normal breathing resumed after a few moments of artificial respiration. According to Lastotschkin's estimate, by 1913, there were more than 1,000 published cases of hedonal anesthesia from at least seven Russian hospitals.[20]

From Russia, use of intravenous hedonal spread to Germany and England, where the technique was received favorably by many workers.[21,22] In 1912, Page reported the use of hedonal in 75 cases.[21] In this series, there were no direct deaths from anesthesia. Dobson reported 434 cases in which this anesthetic agent was used.[22] The mortality in this series of cases was 10.1%, while it was 6.4% in a series of cases in which inhalational anesthetic agents were used. The author attributed nine deaths directly to hedonal. In five cases, death was caused by acute pulmonary edema. At necropsy, pneumonia was found in eight cases. In all of these cases, the patients received more than 1200 ml of hedonal solution during anesthesia. Dobson suggested that pulmonary edema can be avoided by not administering more than 1200 ml of hedonal solution.

At the International Congress of Medicine in London in 1913, Sargeant reported 43 cases in which cranial operations were performed during hedonal anesthesia.[21] Comparing hedonal anesthesia with inhalational anesthesia produced by chloroform and diethyl ether, Sargeant found a mortality rate of 20% with chloroform, 13% with diethyl ether, and 3% with hedonal. Mennell, speaking at the same meeting, indicated the untoward effects of intravenous hedonal anesthesia were due to infusing the hedonal solution too quickly and using too much.[23]

After the use of hedonal for intravenous anesthesia was reported, the search for other possible intravenous anesthetics continued. In 1913, Noel and Souttar[24] described anesthetic effect of paraldehyde given intravenously. Three years later, Peck and Meltzer[25] reported the results of the intravenous administration of magnesium sulfate. Ethyl alcohol was used intravenously by Naragawa[26] in 1921, and by Cardot and Laugier[27] in 1922. Barbiturates began to be tried for intravenous anesthesia in 1921. A mixture of the diethylamines of diethyl- and diallyl-barbituric acid (Somnifen) was used by Bardet[28] in France. Although barbiturates were synthesized in 1903 (Fisher and von Mering[29]), their very low solubility in water and extremely prolonged dura-

tion of effect delayed the search for intravenous anesthetics in this class of hypnotic agents. However, the sodium salt of sec-butyl-(2-bromoallyl)-barbiturate (Pernoston) had greater water-solubility, and Pernoston, introduced by the German obstetrician, Bumm, in 1927,[30] was the first barbiturate to gain widespread use as an intravenous anesthetic. The first short-acting barbiturate with a fast onset of action, hexobarbital (Evipan), was produced by Kropp and Taub[4] and the first report of its use as an intravenous anesthetic was published in 1932.[31]

Hedonal could not compete with barbiturates as an intravenous anesthetic. The drug did not have adequate water solubility, acted too slowly, and had a very long duration of action. Laboratory and clinical investigations of hedonal for anesthesia continued until about 1930.[32,33] At that time, the wide use of barbituric acid derivatives for intravenous anesthesia had begun; this development effectively put an end to further use of hedonal.

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