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HISTORICAL NOTE

Stanislav Klikovich (1853–1910)

Pioneer of nitrous oxide and oxygen analgesia

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Fig. 1. Stanislav Sigismund Klikovich (1853–1910).

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Stanislav Sigismund Klikovich (Fig. 1) (alternative Polish and German spellings Klikowicz and Klikowitsch respectively) was born of Polish parentage on 31 August 1853, in the province of Vilno which at that time was part of Russian-occupied Poland. Although he studied and worked in Russia he maintained a close affiliation with the Polish community there, and it is in a Polish publication by Marian Kus[1] that a comprehensive account of his life appears.

He studied medicine at the Academy of Medicine and Surgery in St Petersburg and, in 1876, he graduated with the diploma of Physician and Surgeon which he obtained '*cum eximia laude*'. Thereafter he began working with the famous physician Professor Botkin at the Clinic of Internal Diseases where, with Botkin's encouragement, he began his studies on nitrous oxide; as a result of this research he was awarded an MD on 23 April 1881 at the age of 27 years. The substance of his thesis is available as a book published in Russian entitled 'Nitrous Oxide and Experiences with its Therapeutic Administration'.[2] Specific parts of the book are also presented in German[3–5] and the following accounts are based on these sources.

At the time of Klikovich's research, nitrous oxide had become established as a useful anaesthetic agent, unconsciousness resulting mainly from the hypoxia which occurred during its administration. Klikovich introduced the concept of using a mixture of nitrous oxide and oxygen to provide analgesia without loss of consciousness or risk of hypoxia. He was the first physician to make a detailed study of nitrous oxide and oxygen mixtures for this purpose, although in 1800 Sir Humphrey Davy had discovered the analgesic properties of nitrous oxide and had suggested its use to minimise pain during minor surgery.[6]

Preparation and storage of nitrous oxide

Although nitrous oxide was commercially available from London, Klikovich prepared the gas in his laboratory to avoid the high cost of transporting the cylinders to Russia. Ammonium nitrate was heated in a glass retort and the evolved gas was purified by passage through two Wolff bottles, the first containing ferrous sulphate acidified with sulphuric acid and the second containing potassium hydroxide solution (Fig. 2).

The nitrous oxide was then stored in a zinc plated gasometer 177 cm in height and 80 cm in diameter to which oxygen was added so that an 80% nitrous oxide–20% oxygen mixture was present. The mixture could also be stored in gutta percha cushions but both nitrous oxide and oxygen diffused out of the cushions and nitrous oxide diffused more rapidly than oxygen; the result was, that after a few hours, the quantity and potency of the remaining mixture was considerably diminished. In order to overcome this problem Klikovich recommended transferring the mixture to a glass bottle (Fig. 3). Two glass tubes (a, b) were passed through the cork of the bottle which was partially filled with water. The gutta percha cushion was connected via tubing (d) to tube (b) and tube (a) was connected to tubing (c) which extended below the level of the glass bottle and opened into a beaker. Compression of the cushion or aspiration of tube (c) caused gas to flow from the cushion to the bottle where it displaced water which flowed into the beaker. Clamping tubes (d) and (c) facilitated storage of the gas in the bottle. Filling a funnel (f) with water caused gas to flow from the bottle along tubing (d) to a mouthpiece (e). The rate of flow of the gas through the mouthpiece could be regulated by the height to which the funnel was raised above the level of water in the bottle. Klikovich used this ingenious apparatus for administration of the gas mixture in a number of his clinical studies.

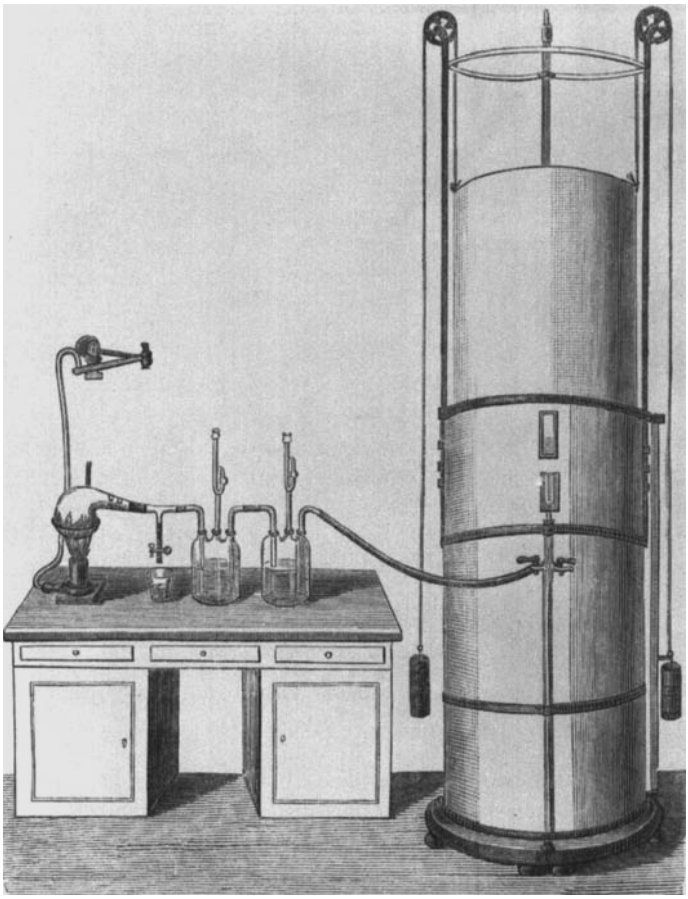

Fig. 2. Method of preparation of nitrous oxide used by Klikovich.[2] Ammonium nitrate was heated in the retort on the right, purified by passage through the Wolff bottles containing ferrous sulphate acidified with sulphuric acid and potassium hydroxide respectively and stored in the gasometer on the right.

Laboratory and animal studies

As a result of *in vitro* experiments on blood, Klikovich confirmed that nitrous oxide did not chemically combine with haemoglobin but existed in simple solution in the plasma. In subsequent studies on animals he showed that pure nitrous oxide caused asphyxia but the addition of 20% oxygen to the nitrous oxide rendered the mixture safe for administration.

Clinical research and applications of the nitrous oxide and oxygen mixture

Having established the safety of the nitrous oxide–oxygen mixture in animal experiments, Klikovich then proceeded to study the effect of the mixture on healthy volunteers with particular reference to cardiovascular and respiratory function during its

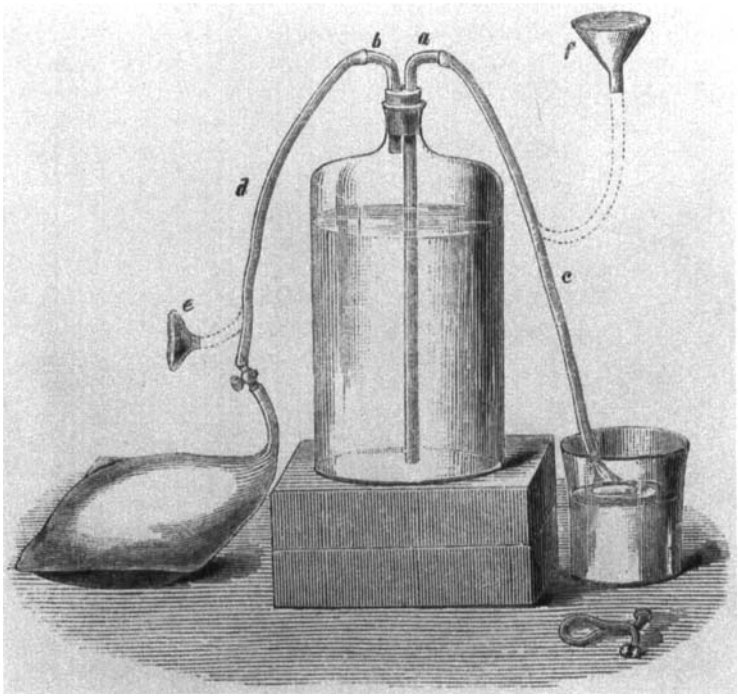

Fig. 3. Method of storing and controlling the flow of nitrous oxide and oxygen mixtures (see text).

inhalation. Satisfied that there were no undesirable side effects, he began to administer it to ill patients, particularly those with cardiovascular or respiratory disorders.

His description of the effect of the mixture on a clergyman with a severe anginal attack to whom he gave the mixture is of great interest. He writes 'The patient seemed to be dead, he implored us not to touch him. The cyanotic fingers of his left hand clutched his chest over the heart convulsively clutching, as if he would tear a hole in his chest. Terror showed on his pallid face, his head inclined to the left and glances to his heart showed clearly that it was there that danger threatened. Wide open eyes, dilated pupils, slow glances, beads of sweat on the forehead, everything indicated he was in a state of agony prior to death. Through clenched teeth he murmured "Wife—Death—Am Dying". His state left no question concerning the experimental trial of nitrous oxide and lack of time permitted one only to notice the rapid irregular feeble pulse and the infrequent and superficial breathing. The nitrous oxide mixture was given within two minutes of the start of his attack. There was no question of his inhaling anything himself but a mask was held in front of his mouth and nostrils and the nitrous oxide mixture delivered by pressure on the rubber reservoir bag. The situation began to change in less than a minute, the patient began making short but deep inspirations, the pulse became fuller and the facial pallor diminished. The patient took a hand away from his chest and pressed the mask to his mouth. After a while he took his other hand away too and leaning back said with a smile "That's better".'

Klikovich found that patients with respiratory disorders, particularly asthma, derived marked relief during acute attacks by inhalation of the nitrous oxide and oxygen mixture. There is little evidence of its widespread use for this purpose although

Smolinskii claims success in using it in asthmatics[7] and Rice describes administering it with benefit to a patient who developed an acute asthmatic attack while in the dental chair.[8]

Klikovich also described his successful use of the mixture in other situations, for example to provide analgesia during cervical polypectomy, to diminish vomiting and to alleviate attacks of coughing.

Research into the analgesic effects of the nitrous oxide and oxygen mixture during labour

Of all the clinical work, which Klikovich undertook, undoubtedly his most interesting and valuable contribution was in the obstetric field, where he was the first clinician to use a mixture of nitrous oxide and oxygen to provide analgesia during labour. This work was carried out while he was House Surgeon to Professor Botkin and was conducted in the Maternity Department of the Clinic of Professor Slavyansky.

Klikovich recorded detailed observations on 25 women in labour to whom he had given the nitrous oxide/oxygen mixture. The following account describes how he taught the women to inhale the mixture in order to achieve the maximum benefit: 'She should breathe out as fully as possible and then inhale as deeply as possible from the mouthpiece. If the inspired mixture is kept for a short time in the lungs before being expelled, the effect is achieved quicker and the gas consumption is greatly reduced. The woman must be warned that she may feel intoxicated for a short time, which often disturbs subjects who have not been warned to expect it. Inhalation should begin a minute or half a minute before the expected pain; usually from 2 to 6 inhalations are enough to give the desired effect. The first inhalation must be started early, for it is extremely important to ensure that the analgesic action of the gas is felt during the first labour pain. Encouraged by success, the woman will very quickly learn to take deep breaths and to hold the mouthpiece herself and to apply it to her mouth at the beginning of every subsequent pain. If, however, the inhalations are started late, the commencing pain will often prevent the woman from taking deep breaths and the anaesthesia will not be completely successful.'

The following is the first account of the use of a mixture of nitrous oxide and oxygen in labour and indicates the precision with which Klikovich noted all his observations.

'*Case* 1. Delivery No. 100, M.S., aged 23 years, 1-para; admitted to the maternity home on 10 June 1880 at 10 a.m. Pains began at 6 a.m. On admission the cervix was dilated, the os admitted 1½ fingers, and the membranes were ruptured. Contractions lasting about 30 seconds occurred at intervals of 2–2½ minutes and were extremely painful. The birth passages were normal and the presentation was R.O.A. The pregnancy was full-term.

Under the influence of three inhalations of nitrous oxide a contraction which had started followed an almost painless course, although a very strong uterine contraction could be felt manually. The patient did not lose consciousness but was simply surprised to find that her head spun as if she were drunk, and she insisted that she be allowed to continue inhaling the gas. All contractions during which no nitrous oxide was given were painful as before. Dilatation of the birth passages and expulsion of the fetus took place perfectly normally. The cervix was completely dilated at 6.25 p.m., the head began to engage at 6.40 p.m., the child was born without the slightest

sign of asphyxia at 6.50 p.m. and the placenta was expelled 5 minutes later. The patient coped excellently with each stage of labour and, when requested, breathed through her mouth and relaxed her abdominal muscles. In her own words she had been able to relax so easily because under the influence of the gas she had felt no pain. The total gas consumption was about 3 cubic feet of mixture, of which about 1 cubic foot was used during the second stage' (1 ft^3 is approximately 28·25 litres).

Klikovich established that there was no prolongation of labour during inhalation by noting the frequency, duration and strength of uterine contractions before and after inhalation, by abdominal palpation. He also recorded contractions quantitatively by means of a manometer attached to tubing passed through the cervix into the uterine cavity. In all of the cases he studied he was unable to find any problems in the puerperium either in the mothers or in the infants which could not be attributed to a cause other than nitrous oxide.

Klikovich's conclusions from his obstetric research

Many of the conclusions which Klikovich reached as a result of these detailed studies still apply today:

'(1) Its complete safety with respect to the life of the mother and fetus and its freedom from the risk of protracting labour.

(2) Its undoubted analgesic action in all stages of labour.

(3) The fact that consciousness is not lost during a high degree of analgesia such as is attainable by the use of the suggested mixture of nitrous oxide and oxygen and, consequently, the possibility of utilising the accessory forces of labour (such as the abdominal muscles).

(4) The absence of vomiting and, in many cases, the cessation of existing vomiting; the absence of a period of excitation and of disorders following anaesthesia—nausea, headache, dyspepsia, etc.

(5) The anaesthesia can be continued throughout labour without cumulative action, for during the pause between pains the effect of the preceding inhalations passes off almost totally.

(6) The presence of a physician to administer the anaesthetic is not necessary.

The chief disadvantages of nitrous oxide for use in obstetrics are its relatively high price and its non-portability.'

The subsequent career of Stanislav Klikovich

After completing this research, Klikovich returned to Vilno as a military doctor for a time, and then spent two years travelling in Western Europe. During this period he visited France, Germany and England and worked in the clinics of a number of famous men, among them Koch and Virchow. On his return to Russia in 1886 he became an Associate Professor and in 1890 a Lecturer in Internal Diseases. Soon afterwards he was evacuated to Novograd where he worked as a lecturer and military doctor, and, after the Revolution of 1905, he was evacuated to Kazan where he died following a stroke, on 2 February 1910 at the age of 56 years.

It appears that the majority of his research was undertaken in the first few years after qualification and it might be postulated that the unsettled political climate which existed during his lifetime may have contributed to the premature interruption

of his promising academic career. Although a number of European physicians did attempt to use the analgesic technique described by Klikovich, unfortunately it did not become established. It was not until 1911 that Guedel[9] devised the first machine for self administration of nitrous oxide and air in obstetrics. In 1934 Minnitt[10] developed his gas–air machine by modifying the McKesson oxygen therapy apparatus and this remained in use for over 30 years despite the severe degrees of hypoxia which often existed during its use. A growing awareness of the harmful effects of maternal hypoxia on the fetus led to the introduction of apparatus which delivered nitrous oxide and oxygen mixtures similar to those which Klikovich had shown to be safe in use almost 70 years previously.[11] In 1961 at Tunstall's[12] request, premixed 50% nitrous oxide and oxygen was developed by the British Oxygen Company and subsequently introduced into obstetrics where it continues to provide safe and satisfactory analgesia in labour.

It is hoped that tribute will at last be given to Klikovich who, during an era of relatively improverished scientific research made a most outstanding contribution to nitrous oxide analgesia, but owing to an unfortunate combination of circumstances failed to achieve the recognition he so richly deserved.

Summary

The career and work of Stanislav Klikovich (1853–1910) has been reviewed. He was born in Russian occupied Poland and was a pioneer of the use of analgesic concentrations of nitrous oxide in oxygen for many painful conditions including childbirth. He based his clinical work on sound research and animal and human experimentation and recognised that the analgesic state was distinct from anaesthesia.

Acknowledgments

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Fig. 1 is taken from a book by A. Bogdanov entitled '*Materials for the history of scientific and applied activities in Russia in the realms of zoology and allied branches of knowledge during the last 35 years 1850–90*' published in Moscow in 1892. Figs 2 and 3 come from the Thesis by Klikovich.[2]

References

1. Kus, M. (1966). The merits of Stanislav Klikowicz in advancing obstetric analgesia.* *Polsk. Tygodnik Lekarski*, **21**, 602.
2. Klikovich, S. (1881) *Nitrous oxide and experiences with its therapeutic administration.** A. M. Kotomin, St Petersburg.
3. Klikowitsch, S. (1881) Ueber das Stickostoffoxydul als Anaestheticum bei Geburten. *Archiv für Gynaekologie*, **18**, 81.
4,5. Klikowitsch, S. (1883) Das Stickostoffoxydul and Versuch seiner anwendung in der Therapy. *Virchows Archiv: Abteilung A: Pathologische Anatomie*, **94**, 148 and 227.
6. Davy, H. (1800) *Researches chemical and philosophical chiefly concerning nitrous oxide or dephlogisticated nitrous air and its respiration.* Biggs and Cottle, Bristol.

7. SMOLINSKII, K.I. (1960) Use of nitrous oxide with oxygen in paroxysms of bronchial asthma.* *Sovetskaia Meditsina*, **24,** 114.
8. RICE, V. (1970) Nitrous oxide/oxygen mixture and asthma. *British Dental Journal*, **128,** 476.
9. GUEDEL, A.E. (1911) Nitrous oxide-air anesthesia, self-administered in obstetrics, a preliminary report. *Indianapolis Medical Journal*, **14,** 476.
10. MINNITT, R.J. (1934) New techniques for self-administration of gas–air analgesia in labour. *Lancet*, **i,** 1278.
11. MCANEMY, T.M. & DOUGHTY, A.G. (1963) Self-administered nitrous oxide/oxygen analgesia in obstetrics. *Anaesthesia*, **18,** 488.
12. TUNSTALL, M.E. (1961) Obstetric analgesia. The use of a fixed nitrous oxide and oxygen mixture from one cylinder. *Lancet*, **ii,** 964.

* Translations of Polish and Russian titles.