

Vassily von Anrep, Forgotten Pioneer of Regional Anesthesia

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THE introduction of cocaine into medical practice by Koller¹ revolutionized surgery, starting with ophthalmology and spreading rapidly to urology, gynecology, otolaryngology, and general surgery. Amongst the many practitioners who contributed to development of this exciting new tool, William Halsted and Richard Hall are acknowledged as being the first to perform nerve blocks, *i.e.*, placing local anesthetic around a nerve to produce anesthesia in the nerve's distribution, as opposed to relying on surface or infiltration anesthesia, which others were using.²⁻⁴ A major early influence in the development of cocaine as a local anesthetic was the paper published in 1880 by Vassily von Anrep (1852-1927), in which he described the pharmacology of cocaine and suggested its use for surgery.⁵ In fact, there is evidence that Anrep was successfully using cocaine for nerve blocks (intercostal) and other techniques at least as early as, and probably before, Halsted and Hall. Anrep published an account of his work in Russian shortly after Koller's demonstration,⁶ but it seems he did not go on to develop local and regional anesthesia for surgery, unlike Halsted and Hall. Anrep's second paper⁶ has not, to our knowledge, been mentioned in any English-language publication of the subject until now. The aim of this paper is to describe Anrep's work and to reestablish him as one of the pioneers of regional anesthesia.

Background and Life

The (von) Anreps originated from Westphalia in the 13th century. The family settled in Livonia (later Estonia) and had a strong military tradition that included Vassily's parents. His father, Konstantin Joseph v. Anrep (1819-1852), was an officer in the Russian Navy and his mother, Julia Ozersky (dates unknown), was the daughter of a Russian general.⁷ Vassily (Basil; Wassili) Konstantinovich von Anrep was born on September 29, 1852 in the Liflyandskaya Guberniya district near St. Petersburg. He studied law at St. Petersburg University, changing after 1 year to medicine and graduating from the Medical Academy in 1876. During the Russian-Turkish War of 1877-1878 Anrep worked as an army physician. He then went to Germany to study alkaloids with Professor Michael Rossbach (1842-1894), professor of pharmacology and pharmacotherapy at the University of Würzburg,⁸ publishing his classic paper regarding the pharmacology of cocaine in 1880.⁵ In 1882, he married Prascovia Zatzepin (1857-1918), the widow of a St. Petersburg lawyer,⁷ and had two sons, Boris (1883-1969) and Gleb (1890-1955). Boris became a renowned artist based in London and Paris, whereas Gleb became an influential and prolific physiologist, conducting research in St. Petersburg (with Ivan Pavlov), London (originally with Ernest Starling), and Cambridge before finally settling in Cairo in 1931.⁹ There were also two stepsons, Volodya and Erast, from Prascovia's first marriage (fig. 1).

After his return to St. Petersburg, Anrep was appointed to a succession of governmental medicopolitical posts, culminating in Chief Medical Inspector at the Ministry of Health in 1904. During this time he also founded the Institute for Experimental Medicine and the Women's Medical Institute in St. Petersburg. After the 1905 Revolution he served as a member of the State Duma (People's Parliament) and was Chairman of the People's Education Commission. With the success of the Bolsheviks after the 1917 Revolution he found himself on the wrong side of the authorities and was jailed briefly before managing to escape the country to London. He appears to

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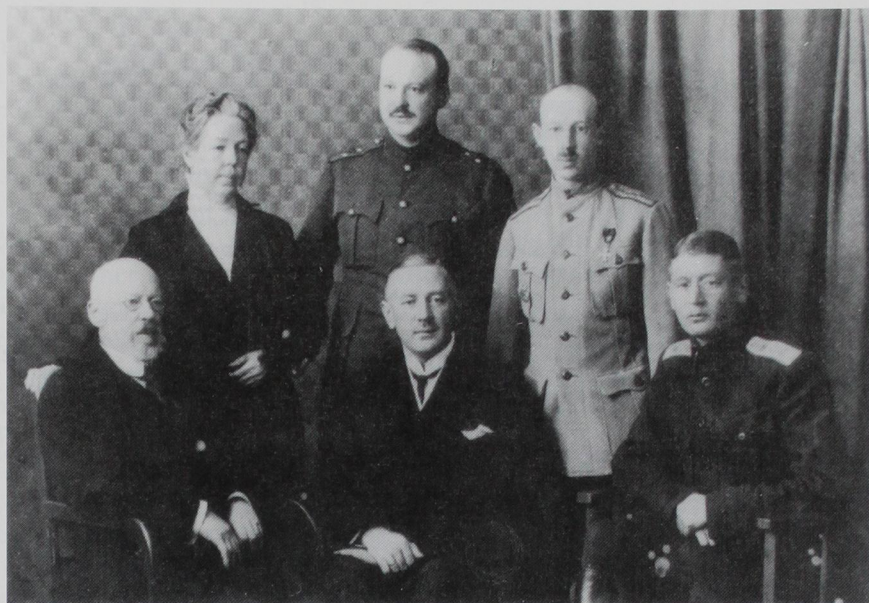
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Fig. 1. The von Anrep family, St. Petersburg, circa 1917. Left to right, seated: Vassily; Volodya and Erast (stepsons); standing: Prascovia; Boris; Gleb. Reproduced with permission.⁹



have drifted between his sons' bases in London and Paris during the next 10 years, dying in Paris in 1927 (I. Anrep, personal communication, 1997).⁷

von Anrep and Cocaine

His First Paper

Anrep studied a number of different areas of medical science, including tuberculin, ptomaines (amines resulting from putrefaction), and food poisoning, but is best known for his work on cocaine.⁵ Then, as now, it was common for young scientists to spend time studying abroad; why Anrep went to Würzburg, as opposed to anywhere else, is unclear, other than the high profile that Würzburg had at the time (Kolliker, Bezold, and von Bergmann were there during this period and Virchow had left just 22 years earlier). Rossbach, Anrep's supervisor, had an interest in alkaloids and presumably cocaine was one of many substances investigated in his laboratory.⁸ Anrep systematically investigated its effects on different tissues in frogs and different mammals, describing the stimulating effect when cocaine was administered systemically and the depressant effect at high doses, with death apparently resulting from respiratory arrest. Although Moréno¹⁰ and Bennett¹¹ had previously investigated the effects of cocaine in animals and Moréno had described the blocking action of cocaine when injected near the sciatic nerve in frogs and sug-

gested its use as a local anesthetic,¹⁰ Anrep's study was much more detailed and comprehensive, going through all the body's systems methodically in different species. He was the first to inject cocaine subcutaneously into humans (himself), and the first to report the anesthetic effect produced by the injection (he described the feeling of warmth and numbness, which persisted for 25–30 minutes). He also confirmed the numbing effect when cocaine was placed on the tongue. Anrep suggested that these properties could have very important applications in allowing surgery and treating painful conditions, concluding that he had been too busy to explore them thus far.

The Introduction of Cocaine

The early history of cocaine has been well described previously.^{3,10} The coca plant had been cultivated and its leaves chewed since ancient times in South America. The active component, an alkaloid named erythroxyline, was isolated in 1855, and this was purified in 1860 to obtain cocaine, which was subsequently synthesized.^{3,12} During this period, the introduction of the syringe and hypodermic needle led to many attempts to produce local anesthesia for surgery, using such agents as morphine, chloroform, water, and hypertonic salt solutions.³ Anrep's first paper therefore came at a perfect time and would surely have led to wider use of cocaine had he been a surgeon and published it in a mainstream surgical journal. In fact, it took another scientist, Sigmund Freud,

№ 46.

Четверг, 15-го ноября 1884 года.

Томъ V.

Врачъ... (text continues in small print, partially illegible)

ВРАЧЪ

ЕЖЕНЕДЕЛЬНАЯ МЕДИЦИНСКАЯ ГАЗЕТА, ПОСВЯЩЕННАЯ ВСЕМЪ ОТРАСЛЯМЪ МЕДИЦИНЫ, ОБЩЕСТВЕННОЙ И ЧАСТНОЙ ГИГЬЕНЪ И ВСЕМЪ ВОПРОСАМЪ ВРАЧЕБНАГО БЫТА.

Подъ редакціей профессора В. А. ЯНОВСКИНА.

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СЛѢД. КОКАИНЪ. КАКЪ СРЕДСТВО МѢСТНО АНЕСТЕЗИРУЮЩЕЕ.

В. Е. Анрепа.

Сколько мнѣ повѣствовъ, я первый указалъ на мѣстно анестезирующее свойство кокаина. Въ моей работѣ о анатомическомъ свойствѣ кокаина, напечатанной еще въ 1879 г., въ числѣ показаній въ терапевтическому приложенію этого вещества, я поставилъ на первомъ мѣстѣ мѣстную анестезію.¹ До самаго послѣдняго времени, однако, не было ни одной попытки подобнаго приложенія кокаина: такъ пріятно было мнѣ астритъ подобнаго подвѣрженію основательности моего предложенія воспользоваться этимъ свойствомъ кокаина съ терапевтическими цѣлями. Почти одновременно Koller, Jellinek и П. П. Качауровъ заявляютъ объ анестезирующемъ дѣйствіи кокаина. Наблюденія послѣднихъ свидѣтельствуютъ, что вызываемая при мѣстномъ употребленіи кокаина анестезія настолько полна, что позволяетъ производить безболѣзненно такіе операціи, какъ вышннее глазное яблоко.

Впрыскиваніе подъ кожу такихъ незначительныхъ количествъ кокаина, какъ 1—5 mgr., вызываетъ полную потерю чувствительности кожи вокругъ мѣста впрыскиванія: проколъ кожи булавкой не ощущается, прижатіе тѣлешей спичкой не вызываетъ боли.

Смазываніе слизистыхъ оболочекъ растворомъ кокаина или же внутреннее употребленіе его, въ пріемахъ средней величины, обуславливаетъ сухость этихъ оболочекъ, резко уменьшая ихъ отдѣленіе. Точно также уменьшается отдѣленіе желудочнаго сока, слюны и слезы; падаетъ замѣтно уменьшается и отдѣленіе пота (у члвчоточныхъ).

Налю замѣтить, что анестезирующее дѣйствіе кокаина всегда лишь кратковременно, т. е. смотря по приему, продолжается не долѣе 10—20 минутъ, по оно можетъ быть произвольно продолжено, если впрыскиванія, смазыванія и т. д. будутъ повторяться.

Что касается до мѣстнаго употребленія кокаина у больныхъ, то я могу убѣдительно въ пользу его въ слѣдующихъ случаяхъ:

При остромъ третичномъ, сопровождающемся сильной болью при мочеиспусканіи. Впрыскиванія въ уретру 5—10,0 грм. 0.4%—0.9% воднаго раствора сѣроукс- лодована вполне устраняетъ болевые ощущенія при

Fig. 2. Anrep's second paper published in the Russian journal *Vrach*. The date at the top reads "Thursday, November 15th, 1884." The reference to Koller, Jellinek, and Katsaurov can be seen in the left hand column.

to recognize the potential of cocaine and act on Anrep's suggestion. He obtained cocaine and gave it for independent testing to two young ophthalmologists, Carl Koller and J. Königstein. Koller's now-famous paper was presented to the German Ophthalmological Society in Heidelberg on September 15, 1884; he noted in his report that he was familiar with Anrep's experiments and started by confirming Anrep's results in animals before applying cocaine to the human eye.¹ Two weeks later, Jellinek¹³ reported similar anesthetic and analgesic effects when cocaine solution was applied to the mucous membrane of the pharynx and larynx. During the next 2 months, several other workers published reports of the use of topical cocaine for anesthetizing the ears, nose, mouth, trachea, rectum, and genital tract.¹² On November 15, Anrep published his largely unnoticed second paper: his account of use of cocaine for various painful disorders and the first conduction nerve blocks (intercostal nerve).⁶ On the same day, Hepburn¹⁴ published his observations regarding the numbing effect of cocaine after hypodermic injection—observations antedated by Anrep by 4 years.⁵ Other reports followed throughout November 1884¹²; on December 6, Hall¹⁵ announced his

and Halsted's experiences in producing nerve blockade with cocaine (ulnar nerve, musculocutaneous nerve of the leg, anterosuperior dental nerve, inferior dental nerve, and lingual nerve) in a letter dated November 26. Multiple reports of the use of cocaine followed, mostly involving topical application, infiltration, or both.

His Second Paper

Anrep published an account of his clinical work with cocaine in the Russian journal *Vrach* ("Physician").⁶ The date of publication is Thursday, November 15, 1884, some 3 weeks before Hall's report¹⁵ (fig. 2). (Because of the historical importance of this paper, we reproduce it in its entirety [see Appendix].)

Anrep's second paper raises a number of questions. First, why did he publish it in Russian when the major scientific language of the day was German, especially because his previous paper was published in German? We are unaware of any reference to this paper in the contemporaneous literature and, given the level of interest in cocaine at the time, can only conclude that the reason for this was the language and journal chosen. It is likely that Anrep's paper was available in America, be-

cause it is listed in the Index-Catalogue of the surgeon-general's office in Washington¹⁶ and volume 5 of *Vrach* is listed in the US Union List of Serials as being issued to nine other major American academic libraries.¹⁷ Presumably unread in its original Russian form, it is unlikely to have been abstracted in English because none of the abstracting journals of the time include reports of Russian articles (C. Ruggere, personal communication, 1998). One can only assume that Anrep was either unaware of the limited access of the medical community to Russian articles or merely did not attach adequate importance to his work.

Second, why did he wait for 4 years after his first paper before describing his clinical studies? Anrep finished his first paper by claiming he had been too busy to investigate the properties of cocaine fully and started his second paper by repeating the claim. One cannot deny the demands made by his medicopolitical career, particularly given the events happening in Russia at the time, but if he truly had glimpsed the potential of cocaine, it is hard to see how he could have let this lie. At the very least, one might have expected letters to journals and prominent surgeons publicizing his discovery. Moreover, Anrep did not report any clinical experience of the use of cocaine for surgery, despite his acknowledgement of its place as a local anesthetic in general. Furthermore, Anrep appears to have stopped his medical experimental work completely from the time of his second paper; certainly we have no record of any further publications regarding cocaine or any other medical topic after his second paper (Y. Golikov, personal communication, 1997).

Conclusion

On the face of it, there are similarities between Anrep and the introduction of regional anesthesia and Crawford Long and the introduction of ether general anesthesia.¹⁸ Although there is good evidence that both had been using their respective technique earlier than the widely acknowledged "fathers," each have been overshadowed by others. In the case of Long, he merely failed to come forward until ether had been publi-

cized.¹⁸ Anrep, conversely, missed the opportunity to introduce the world to a great discovery *twice*: having suggested the use of cocaine for surgery, he failed to explore it, and having used cocaine clinically, he then failed to publicize it. As it is, the early pioneers generally acknowledged Anrep's contribution (but only with reference to his first paper),^{19,20} whereas more recent authors tend not to mention his input at all.² Given the variety and number of nerve blocks described by Hall,¹⁵ he and Halsted had probably been experimenting with cocaine in this manner soon after Koller's landmark report. However, there is no suggestion that Halsted and Hall had been using cocaine before the Heidelberg Congress on September 15, 1884, whereas it is more than likely that Anrep had been doing so for some considerable time before this historic date, given his two papers regarding the subject.^{5,6} We believe that although Halsted, Hall, and others should of course be credited with the enormous impact of their achievements in developing and publicizing regional anesthesia, Anrep deserves some credit for his pioneering work, even if it represents something of a missed opportunity.

Appendix—Translation of Anrep's 1884 paper⁶

As far as I know, I was the first to point out the local anesthetic property of cocaine in my work on the physiologic properties of cocaine, printed as far back as 1879, and among indications for therapeutic use of this substance I pointed in the first place to local anesthesia. However, until very recently there were no attempts for such applications of cocaine; that is why I am so pleased to find full confirmation of the soundness of my suggestion to utilize this property of cocaine for therapeutic purposes. Almost simultaneously Koller, Jellinek and Katsaurov[‡] announce the anesthetic action of cocaine. The findings of the latter suggest that the anesthesia produced by local application of cocaine is so complete that it can allow operations, such as enucleation of the eyeball to be painlessly conducted.

During the last several years I have prescribed cocaine more than once for either external or internal use. However, since my observations had the features of casual observations and were not carried out under clinical conditions, I did not report them. But now, when the anesthetic property of cocaine is the "vogue of the day," I consider it appropriate to announce briefly the results of those observations. Now I can supplement my already published studies on cocaine with the following.

Submerging one of the paws of a frog into a cocaine salt solution (0.2–0.05%) [*sic*] and the other paw into a sodium chloride solution (0.4%) or into boiled water, we can be convinced only 10–20 minutes later by the rather distinct anesthesia of the sensory nerve endings of the paw submerged in cocaine solution. Tactile and temperature stimuli produce significantly weaker effect [on that paw] than produced on the other paw and even no effect at all. Application of [cocaine] solution of different strength to the tongue always produces weaken-

‡ I. P. Katsaurov, Russian ophthalmologist, having read of Koller's demonstration, published his account shortly before Anrep's second paper: Katsaurov IP. About the anesthetic influence of Cocaine on eyes. *Vrach* 1884; 5(43):733–6. Of interest is the fact that, despite being a compatriot of Anrep, Katsaurov makes no mention of Anrep's work—we have no explanation of why this might have been.

ing or complete loss of gustation for sweet and sour; pinprick on the mucosa feels only like a light touch. Subcutaneous injection of such minuscule amounts of cocaine as 1–5 mg results in complete sensory loss in the skin around the injection: puncturing the skin with a pin is not felt and burn with a match does not produce pain. Lubrication of mucous membranes with cocaine as well as its internal use causes dryness of these membranes, diminishing distinctly their secretion. Gastric secretion and secretion of saliva and tears decrease in exactly the same fashion; it seems that sweating also decreases noticeably (in people suffering from tuberculosis).

We have to point out that the anesthetic influence of cocaine is always short-lived, i.e., counting from the time of administration, lasts no longer than 10–20 minutes. However, it could be prolonged arbitrarily if injection, lubrication, etc., would be repeated. In acute urethritis presenting with severe pain on micturition urethral injection of 8–10 g 0.4%–0.9% aqueous solution of cocaine hydrochloride completely eliminated the pain with the next urination, and also transiently alleviated the frequency. Such injections when repeated in 4–5 hours did not affect negatively the course of the urethritis, and even seemed to speed up healing.

Cocaine has a very distinct anesthetic effect in photophobia. I have had only two observations, yet both of them very convincing (photophobia in iritis and keratitis phlyctenosa). After application to the eye of several drops of maximally saturated solution of cocaine salt the patients could look at light for some time without any discomfort. This effect lasts several minutes and starts to dissipate afterwards. Since the application of eye drops in such cases is rather difficult and associated with pain, and because of the abundant tear secretion which makes it less expedient, and also because saturated solutions are used that always have somewhat acidic pH, it is much more convenient to use "eye-baths" with weak solutions (0.2–0.1%) [sic]. Apart from its analgesic effect, cocaine also has two other very important properties: it dilates the pupils and decreases the secretion of tears. The application of cocaine could be continued without any fear over a long period of time; no side effects are noted. The mydriasis after cocaine application is almost as complete as the one after atropine, but it is not as long-lasting; actually, it could be maintained for days, which might make it suitable for diagnostic use when examining the eye with an ophthalmoscope.

In one case of acute pleuritis presenting with severe sharp shooting pain, I injected cocaine solution (0.025 g) into one of the intercostal spaces on the affected side: in less than 10 minutes the pain subsided completely, the patient could take a deep breath. The effect lasted for more than two hours. It was exactly in the same fashion that the excruciating pain caused by intercostal neuralgia disappeared after injection of the same amount of cocaine in the corresponding intercostal spaces. The patient was given eight series of injections over five days with no change in the course of the disease which was eventually successfully treated by punctate burns with Pacquelin's thermocauter, yet the temporary relief [from the injections] was the best we could hope for in the meantime.

In three cases cocaine was used by me for treatment of painful ulcers. Application of cocaine ointment or powder mixed with inert substances, yielded completely satisfactory results. Application of cocaine powder over exudative eczema of the scrotum associated with severe pruritus, completely relieved the itching for more than three hours. The same effect was achieved with cocaine solution compresses. Finally, having in mind that cocaine distinctly decreases different secretions, I tried lubricating with cocaine solution the nasal

mucosa in cases of acute rhinitis. The only consequence was a short-lasting decrease of secretions, but there seemed to be no noticeable change in the course of the disease.

Thus, we can see that the range of the indication for cocaine as a local anesthetic is rather wide. I convinced myself in this property of cocaine five years ago in my animal experiments, yet I was far from the thought that the anesthesia produced by cocaine could be as complete as to allow carrying out painful operations such as eye enucleation. I am convinced that in some cases cocaine will limit the use of morphine, having some advantages with its local anesthetic properties. First, cocaine belongs to the group of the alkaloids with weak systemic effect; second, tolerance does not build, that would require increase of the dose; finally, it does not lead to signs of chronic intoxication. Its use for diagnostic purposes in the examination of the eyes, larynx and the genitalia, are, of course, preferred to the administration of atropine, morphine and potassium bromide, and also to chloroform, because the effects of cocaine are quickly transient, not associated with any side effects or sequelae, and are always quicker and more reliable than these of potassium bromide. Maybe now, when cocaine became the "vogue of the day," attention would be paid to many of its other very important properties. But we can talk about that next time.

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References

1. Koller C: Ueber die verwendung des Cocain zur anästhesirung am auge. *Wien Med Wochenschr* 1884; 34:1276–8, 1309–11
2. Rushman GB, Davies NJH, Atkinson RS: Regional techniques, A Short History of Anaesthesia. Oxford, Butterworth-Heinemann, 1996, pp 140–1
3. Fink BR: Leaves and needles: The introduction of surgical local anesthesia. *ANESTHESIOLOGY* 1985; 63:77–83
4. Olch PD: Willam S. Halsted and local anesthesia: Contributions and complications. *ANESTHESIOLOGY* 1975; 42:479–86
5. von Anrep B: Ueber die physiologische Wirkung des Cocain. *Pflügers Archives ges. Physiology* 1880; 12:38–77
6. Anrep VK: Kokain kak sredstvo mestno anestezirovushchee [Cocaine as a means of local anesthesia]. *Vrach* 1884; 5(46):773–4
7. Genealogisches Handbuch des Adels 32; Briefadelige Häuser B VI. Limburg a.d. Lahn, CA Starke Verlag, 1964, pp 1–21
8. Henschler D: Zur Entwicklung von Pharmakologie und Toxikologie, Vierhundert jahre Universität Würzburg. Eine festschrift. Edited by Baumgart P. Neudtadt an der Aisch, Verlag Degener & Co., 1982, pp 1032–4
9. Yentis SM: Minds and hearts: Themes in the life of Gleb von Anrep. *J R Soc Med* 1998; 91:209–12
10. Moréno Y Maiz T: Recherches chimiques et physiologiques sur l'érythroxylum coca du Pérou et la cocaïne. Paris, Louis Leclerc, 1868, pp 70–1
11. Bennett A: An experimental inquiry into the physiological actions of theine, caffeine, guaranine, cocaine and theobromine. *Edinburgh Med J* 1873; 19:323–41

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12. Matas R: Local and regional anesthesia: A retrospect and prospect. *Am J Surg* 1934; 25:189-96, 362-79
13. Jellinek E: *Wien Med Wochenschr* 1884; 39:1175
14. Hepburn NJ: Some notes on hydrochloride of cocaine. *Med Rec* 1884; 26:534
15. Hall RJ: Hydrochlorate of cocaine. *N Y Med J* 1884; 40:643-4
16. Index-Catalogue of the Library of the Surgeon-General's Office, United States Army. Ser. 2, III. Washington DC, Government Printing Office, 1898, p 706
17. Union List of Serials in Libraries of the United States and Canada, Vol. 5 (S-Z). Edited by Titus EB. HW Wilson, 1965, p 4432
18. Long CW: An account of the first use of sulphuric ether by inhalation as an anaesthetic in surgical operations. *South Med Surg J* 1849; 5:705-13
19. Knapp H: Cocaine and Its Use in Ophthalmic and General Surgery. New York, Putnam, 1885, pp 1-8
20. Braun H: Local anesthetic agents, Local Anesthesia: Its Scientific Basis and Practical Use. Philadelphia, Lea & Febiger, 1914, p 75