Fachbereich Chemische und Pharmazeutische Wissenschaften, Johann Wolfgang Goethe-Universität, Frankfurt/Main, Germany

# The history of electrically-assisted transdermal drug delivery ("iontophoresis")

A. HELMSTÄDTER

***Dedicated to Prof. Dr. Dr. h.c. P. Pflegel, Greifswald, on the occasion of his 65th birthday***

The first proposals for the use of electric current in drug delivery date from the mid 18th century. Serious progress was made in the 19th century notably by Benjamin Ward Richardson (1828–1896), Hermann Munk (1839–1912), William James Morton (1846–1920), Stéphane Leduc (1853–1939) and Fritz Frankenhäuser (born 1868). Administration of metal ions as well as alkaloids was tried at that time. Until the early 20th century, current mediated drug delivery was known as "cataphoresis"; Frankenhäuser is said to have introduced the term "iontophoresis" before 1908. Recently, researchers talk about "electrically-assisted transdermal drug delivery". The technique was never widely adopted but always proved useful to some extent in solving particular drug delivery problems. At the dawn of the 21st century, attempts are being made to achieve iontophoretic delivery of peptides and proteins.

## 1. Introduction

Just before Luigi Galvani's (1737–1798) famous experiments on frog legs and the discovery of the so called "galvanism", it was suggested that electricity could be used for therapeutic purposes. Johann Gottlob Krueger (1715–1759), professor of philosophy and medicine in Halle suggested in 1743 that electricity should be useful in medicine, as it was obviously not useful for theology or jurisprudence and all things had to be useful for something [1]. Although electric shocks derived from electric fish had already been used for therapeutic purposes in antiquity, this episode is commonly said to be the cornerstone of the modern history of electrotherapy [2]. Besides the direct application of electric current by different apparatus and techniques, the concept of transmitting therapeutic substances through the skin is part of that history. This form of drug administration, which we usually call iontophoresis, has a history almost as old as that of modern electrotherapy in general. Although there have been some publications on various aspects of the subject [3–6], the history of iontophoretic drug delivery will be reviewed from an international point of view.

## 2. The early stages

The first suggestions for the use of electricity for drug transport to be reported in the literature date from the mid-18th century and not all of them seem to be reliable. In a publication dated 1747 [7], the Italian librarian Giovanni Francesco Pivati (1689–1764) reported that the smell of Peruvian balsam hermetically sealed in a glass cylinder became apparent in the room after applying electrical current and could even be transmitted to another room by a wire [8]. This experiment bas based on the observation that the odour of flowers could be recognized more intensively by electrifying the vase and allowing sparks to enter the observer's nostril [9]. Pivati furthermore reported that a patient holding the sealed, electrified glass cylinder containing Peruvian balsam in his hands massively exhaled the typical smell of the balsam hours later. Similar observations were made with the spread of the smell of sulphur or with mercury in the cylinder which caused the typical symptom of mercury intoxication, excessive salivation.

The Turin anatomist Giovanni Battista Bianchi (1681–1761) observed that purgatives held in the hand of a person during electrification had the same laxative effect as when administered orally. A third Italian, Guiseppe Veratti (1707–1793) and the German physicist Winkler, who reported on the subject in March 1748 in a Royal Society Meeting in London, expressly confirmed the reports [2, 8, 9].

However, the results could never be verified by other scientists. The scientific opinion leader in terms of electricity at that time, Jean-Antoine ("Abbé") Nollet (1700–1770) travelled to Italy in order to prove the claims. Bianchi as well as Pivati failed to convince the expert as did others formerly enthusiastic about the proposed method of drug delivery. When Nollet arrived, Pivati could only regret that his machine had meanwhile become broken.

Willi [6] refers to some other early proposals for what we call iontophoresis made by Abbé Mangin in 1752 [10]. He suggested the use of a dressing instead of the hand-held glass cylinder and recommended the use of electricity to enhance the effects of an antidote against snake bites. According to Willi [6], Mangin's work is not mentioned by Joseph Priestley (1733–1804) who dismissed the possibility of electrical drug transmission in a book dated 1769.

## 3. 19th Century developments

After Alessandro Volta found a simple method of producing a continuous flow of current (the Voltaic pile) in 1800, attempts to transmit chemical entities through membranes were continued. Most authors highlight the experiments done by the French physician Bernard Raymond Fabré-Palaprat (1773–1838) in 1833 [4, 9, 11–13]. In a meeting of the Medical Society of Paris he reported the following experiment [14]: A compress soaked with potassium iodide solution was fixed on one arm and connected to the negative pole of a Voltaic pile. Another compress, fixed on the other arm, had been moistened with starch solution and connected to the positive pole of the battery. A few minutes after the current flow had started, the colour of the starch solution turned blue. Fabré-Palaprat interpreted this observation as proof for the transport of iodine through the human body by application of electric current,

but several authors remained sceptical. For example, the American neurologist William James Morton (1846–1920) reported in his comprehensive book on the subject edited in 1898 [11] that he had not been able to successfully repeat the experiment. Similar attempts reported by the German authors Klenke as well as C. H. and H. Hassenstein in 1846 and 1853, respectively, also failed to convince the medical profession [4, 9]. So did the German physician Theodor Clemens who also proposed the transdermal transport of iodine [6] as did the Austrian physician Carl Beer. He observed the current mediated transport of iodine ions through a slice of beef *in vitro*, and reported the successful treatment of crop-patients using iodine iontophoresis [15]. It seems to be almost impossible to judge these experiments in retrospect, particularly as the composition and properties of the iodine solutions used are unclear and may have had substantial influence [6].

Nevertheless, in the middle of the nineteenth century, interest in iontophoretic drug delivery increased and led to applications in anaesthesia and (dental) surgery, in particular proposed by Benjamin Ward Richardson (1828–1896), sometimes called "father of dental iontophoresis". He connected a solution containing aconitine and chloroform with an anode and closed the electric circuit by placing an cathode anywhere at the body surface. This procedure showed a clear advantage over application of an unelectrified solution. In his landmark publication dated 1858, he called the principle "voltaic narcotism" [6, 16]. Colwell reports some more experiments done by Richardson on animals and man the same year in order to improve the analgesic and local anaesthetic effect of drugs like morphine by applying electrical current [17]. Richardson used a mixture of 3 drachms of tincture of aconite, 1 drachm of aconite extract and 3 drachms of chloroform [17, 18]. The method, however, was soon abandoned due to strong opposition within the medical community and the successful developments of general anaesthesia at that time.

In the 1870s, the German Hermann Munk (1839–1912) extensively investigated the current mediated transport of substances like copper sulphate through porous material like boiled albumen, chalk, clotted bovine blood, crystallized sulphur, potato slices or fired clay [19]. During these investigations, he thought about the possibility of penetrating animal or human skin, which is, to some extent, a porous membrane similar to those investigated, with therapeutic agents. To prove this theory, he tried to introduce strychnine hydrochloride into rabbits and potassium iodide as well as quinine sulphate into himself by means of electricity. After 20–25 min exposure to an electrified strychnine solution, spontaneous cramps were seen in the rabbits. Their intensity increased in parallel to the intensity of the current applied. The successful introduction of quinine into the experimenter's body using electrodes applied on both sides of one arm could be proven by detection of this alkaloid in urine. Analogously, iodine could be detected by starch solution in Munk's urine 30 min after applying potassium iodine electrodes. The skin of the rabbits and the man remained unchanged. Munk argues that this method of drug administration works well but mainly for substances active in very small concentrations as the amount of liquid moving into the body is very limited [20].

Later, there have been several attempts to improve the local anaesthetic action of various drugs, particularly cocaine and chloroform, by applying electricity [4, 20], a subject under scientific debate from 1886 to the turn of the century (Table 1). Based on results published by F. McGraw in 1889 and William Morton [11], electrically mediated cocaine anaesthesia in particular became more and more common in dentistry. Morton recommended the use of a solution of cocaine in guaiacol (e.g. 6 grains in 1 drachm), a procedure soon adopted by dentists worldwide [22, 23] So called "cataphoresis outfits" for dentists became commercially available [24]. Pharmacists prepared medicated cataphoretic disks containing the substances in advance; Morton also invented a plaster made from gelatin, carbon and medicine in a measured dosage. When moistened, the plaster could be applied to the desired point and attached to an electrode. Additionally he constructed several technical aids, for example rings or bandages to cause anaemia in the treated tissue area or electrodes containing a reservoir of drug solution [23].

**Table 1: Attempts at iontophoretic drug delivery between 1880 and 1900 as reported by Morton [11] and Levandowski [25]**

| Scientist | Year of report | Drug(s) in use |
|---|---|---|
| Erb | 1884 | (various) |
| Wagner | 1886 | Cocaine |
| Boccalari/Manzieri | 1888 | Strychnine, atropine, quinine, potassium iodide |
| Lauret | 1885 | (various) |
| Adamkiewicz | 1886 | Chloroform |
| Lombroso/Matteini | 1886 | Chloroform |
| Corning | 1886 | Cocaine |
| Peterson | 1888/1889 | Cocaine |
| Lawrence/Harris | | ? |
| McGraw | 1888 | Cocaine |
| Cagney | 1889 | Potassium iodide |
| Edison | 1890 | Lithium salts |
| Imbert de la Touche | 1891 | Lithium salts |
| Gärtner/Ehrmann | before 1892 | Mercury salts |
| Westlake | 1892 | Cocaine/carbolic acid, pyrozone |
| Grosheintz | 1896 | ? |

In the nineteenth century, there were not only attempts to introduce chemical substances into the human body but also to extract them by means of electrical current. In this context, several authors tell the legend of an electro-plater in Havana, Cuba, in the 1850s. He accidentally immersed his ulcer affected hand in a bath prepared for electro-plating and saw the negative wire becoming covered with a metallic coating while the ulcer at his hand started to heal. It was concluded that metal had been extracted by the electric current from the plater's body which led to electrode covering as well as to the ulcers healing. In the following years, the "electro-chemical bath" was invented based on the proposed principle to extract mercury, gold or silver ions from the body of patients suffering from intoxications, gout, neuralgia, paralysis, malaria, kidney diseases etc. [26–28].

## 4. Theories and terminology

Discussing the mechanisms of the transport of uncharged substances through intact skin, early authors claimed that liquid and substances were mechanically transported along with the flow of current ("just as a stream of water carries sediment with it" [29]). This hypothesis was known as "cataphoresis" [30, 31], a term which was particularly used for electrically mediated drug delivery in the nine-

teenth century. We now prefer to call this phenomenon electro(end)osmosis. William Morton stated in 1898 that "a great variety of terms have been invented to express special views of the general facts. We hear of 'osmosis', 'electric osmosis', 'anodal diffusion', 'metallic electrolysis', 'anaphoresis', 'interstitial electrolysis', 'electric transfer of particles and fluids' and 'electric transportation'. In place of these terms we will use those forming the title of this book, 'cataphoresis' or 'electric medicamental diffusion', the latter terminology expressing [...] that electricity does diffuse liquids and substances throughout other liquids and substances, and through soft and hard living tissues [...]" [32].

The phenomenon of electroosmosis is said to be first described by Emil de Bois-Reymond (1818–1896). In an 1860 publication he appears to have used the term "Kataphorese" as did Hermann Munk the same year [33]. It is therefore at best true only for the United States that in 1889 Newman Lawrence and A. Harris "separately and conjointly described the cataphoric method of medication, inventing the term "cataphoric medication" to describe it [34].

Around the turn of the century it became more and more obvious that substances are also, indeed preferentially, transmitted as dissociated, charged ions, i.e. after electrolysis. Positively charged ions, for example, will move away from a cathode at the skin and consequently be transported into body tissues. This phenomenon was intensively studied by Fritz Frankenhäuser (born 1868) who invented the term "iontophoresis" earlier than 1908 [35, 36]. The German veterinarian Wilhelm Schmidt (born 1883) concluded in his 1909 MD thesis that it is possible to introduce drug solutions containing strychnine or cocaine transdermally into animals and that both the cataphoretic as well as the electrolytic power of current play a role [35]. Nowadays, the phenomenon we discuss here, is commonly known as iontophoretic drug delivery regardless of its electroosmotic aspects. A recent definition says: "Iontophoresis or ion transfer is the noninvasive introduction of topically applied free ions into the skin using direct current" [38]. The most recently introduced term "electrically-assisted transdermal drug delivery (EATDD)" [39] does not depend on mechanistic considerations and includes molecule transport by way of iontophoresis, electroosmosis and electroporation.

## 5. 20th century developments

Although Hermann Munk and others had already succeeded in the iontophoretic delivery of strychnine salts to rabbits almost 30 years before, the French physician Stéphane Armand Nicholas Leduc (1853–1939) became famous for the following experiment done in the first years of the 20th century and described several times in different languages [40–42]: Two rabbits were placed in series in galvanic circuit; the current enters the first rabbit through a positive electrode soaked in strychnine sulphate solution and leaves via a negative electrode soaked in saline. It then enters a second rabbit via a positive saline electrode and leaves through an anode soaked with strychnine sulphate (Fig. 1). The first rabbit soon developed cramps and died whereas the other remained totally unaffected. The reason is that the positively charged strychnine ion is attracted to the negative pole in both rabbits. Leduc [41] also reported that potassium permanganate can be iontophoretically transported through intact human skin. The skin under a permanganate soaked cathode developed

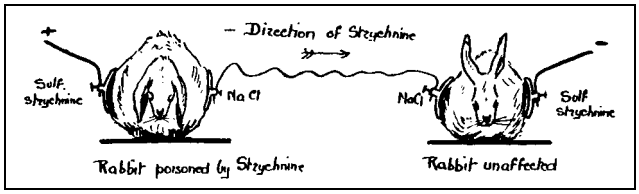


Fig. 1: Experimental setup according to Leduc [3]. For details see text; please note the rabbits' ears

brown coloured spots derived from manganate now located subcutaneously in its reduced, brown coloured form. Similar experiments with "finely-powdered lamp-black or graphite incorporated with some salicylate of soda" had been earlier described by Morton [43].

The technique of iontophoretic drug delivery now found its place in electrotherapy and it is continually described in textbooks on the subject [44, 45]. One of the most important electrotherapists of the first half of the 20th century, Elkin Percy Cumberbatch (1880–1939), summarized the techniques known at the end of the 1930s and states that after Leduc's publications, "the list of ions gradually lengthened as time went on" [46]. The most important ones and their indications are listed in Table 2. Cumberbatch clearly saw the limitations of the method, principally the shallow depth ions are able to reach in tissues. Therefore, any claims of systemic rather than local therapeutic action were in doubt. He also proposed electrodes for the application of ionic medication to particular organs (Fig. 2).

In the 1930s iontophoresis was starting to be used in the treatment of hyperhidrosis [47] which is – according to Chien and Banga [5] – a popular indication up to the present day. However, even the opposite was possible, the iontophoretic delivery of pilocarpine to induce sweating in the diagnosis of cystic fibrosis [48]. The therapeutic use of the method in the two decades after World War II was reviewed by Harris in 1967 [49]. From the "enormous list of conditions for which the treatment may be used" he concentrated on those indications, where iontophoresis had shown any kind of advantage over other treatment methods, but complained of the lack of an adequate number of controlled trials. The agents administered did not significantly differ from those used in the first half of the 20th century. They include heavy metal ions like copper, zinc, silver and tin for the treatment of rheumatic arthritis and similar complaints, as well as for their antimicrobial properties. Copper iontophoresis was additionally used in gynaecology for the treatment of chronic cervicitis; zinc or tin was tried in chronic otitis media and vasomotor or allergic rhinitis. Vasodilatators (histamine, mecholyl) were used in the iontophoretic treatment of arthritis, vascular diseases, pelvic inflammation and varicose ulcers. Vaso-

**Table 2: Iontophoretic treatment at the end of the 1930s according to Cumberbatch [46]**

| Ions used | Indication |
|---|---|
| Zinc | Wound care, hay fever |
| Copper | Substitute for zinc |
| Silver | Pain relief in neuritis and neuralgia |
| Chlorine/Iodine | Softening of scar tissue |
| Mercury | Syphilitic ulcers |
| Magnesium | Warts |
| Lithium | "Gouty arthritis" |
| Cocaine | Anaesthesia |
| Adrenalin | Vasoconstriction |
| Quinine | Neuritis, neuralgia |
| Histamine | Rheumatic diseases |

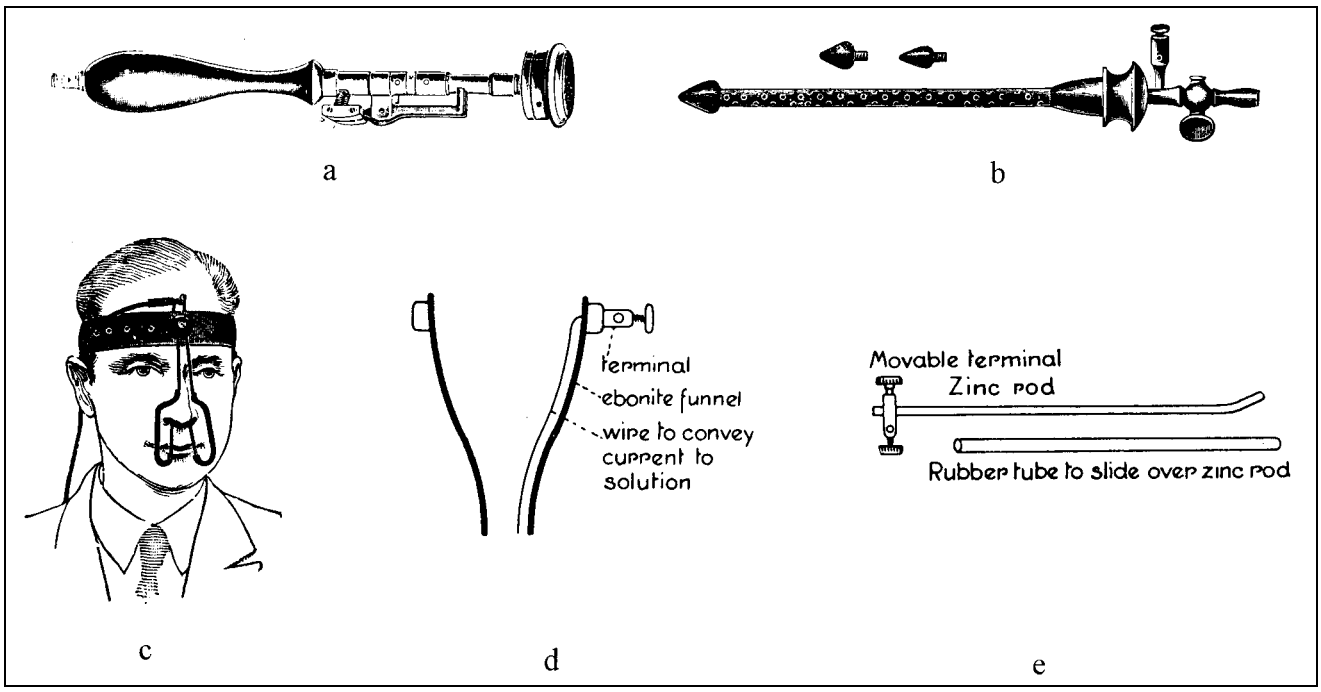


Fig. 2: Different types of electrodes for iontophoretic drug delivery. a: diffusion electrode according to Adamkiewicz [72]; b: electrode for urethral iontontophoresis [72]; c: electrode according to Franklyn for treating hay fever by zinc ionization [45]; d: vulcanite funnel electrode for ionization of the mucous membrane of the middle ear [44]; e: zinc rod electrode used for ionization of the mucous membrane of canal or cervix uteri [44]

constrictors like adrenaline and epinephrine have been tried in intermittent claudication and asthma, respectively. Local anaesthetics were still in use, particularly to therapeutically influence trigeminal neuralgia. Developments of the 1950s include the iontophoretic delivery of hyaluronidase in slceroderma [50] or lymphedema [51], and citrate iontophoresis in rheumatic arthritis [52].

As can be seen from the Medline database, the technique of iontophoresis was still being discussed in the last decades of the 20th century. From 1970 to 1999, between 40 and 80 scientific papers on the subject were published each year. The most recent developments are reviewed by several research groups [39, 54, 55]. Those refer to rather traditional therapeutic fields like dermatology [48, 53] including hyperhidrosis [56–58], opthamology [59] or pain relief [60–62], but focus more and more on future applications like delivery of peptides and proteins [63–65] or non-invasive glucose level measurement [66, 67]. From a technological point of view, studies have been done on the combination of chemical penetration enhancers with electric current [68, 69]. The iontophoretic delivery of vincristine in trigeminal neuralgia has recently been studied [70].

## 6. Discussion

The idea of transmitting therapeutic agents by means of electrical current has a history of more than 250 years. However, too much emphasis should not be placed on early reports. A breakthrough was seen in the mid 19th century. Two scientists considerably influenced development: Hermann Munk (1839–1912) in Germany and – two decades later – William James Morton (1846–1920) in Great Britain. The former reported the successful transdermal delivery of strychnine by use of electric current, the latter popularised the term "cataphoresis". Referring to another physical theory, Fritz Frankenhäuser (born 1868) started to mention "iontophoresis" around the year 1908. The contributions of these German scientists have been completely neglected in two recently published English language historical reviews [4, 5], which underlines the need for a truly international point of view in pharmaceutical history.

During almost two centuries, the method has always had its protagonists and the main fields of interest have been local anaesthesia in surgery and dentistry and painful inflammatory diseases. It seems, however, that in many cases the method has only been used until other, more successful therapies were developed but has then found new particular indications. Although the method was never widely adopted, it continuously proved to have some usefulness in solving problems of drug delivery. In general, the development of the hypodermic syringe has limited the use of iontophoretic drug delivery. The advantages of general anaesthesia exceeded that of iontophoretic delivery as did those of potent anti-inflammatory drugs in the case of rheumatic arthritis. Besides local anaesthesia, the sterilization of root canals and apical lesions was the most important use in dentistry. This indication was abandoned in the 1950s when instruments for mechanically cleaning root canals became available [71]. However, the technique is still under debate even at the beginning of the 21st century. For example, it is now being investigated for the transdermal application of peptides and proteins and will probably be used until better techniques are one day available.

The history of this kind of drug delivery further points attention to the fact that terminology may shift time by time and may not always define exactly what is meant. Sensu stricto, the terms cataphoresis and iontophoresis refer to particular mechanistic imaginations. The predominant pathway of drug substances through intact skin, iontophoresis, is now commonly used to define the drug delivery method in general. However, a term like "electrically-assisted transdermal drug delivery" [39] should be preferred, as it does not refer to a particular transport mechanism.

Acknowledgements: This study was generously supported by a grant the author received from The Bakken Research Foundation, Minneapolis, USA. In particular, the author has to thank the The Bakkens librarian, Mrs. Elisabeth

Ihrig, for support. Additionally, the author would like to thank Dr. Michael Mönnich, Karlsruhe, for his help in interpreting the Italian work of Pivati.

**Notes and References**


1 Krueger, J. G.: Zuschrift an seine Zuhörer worinnen er Ihnen seine Gedancken von der Electricität mittheilet und ihnen zugleich seine kuenftige Lectionen bekant macht. Halle 1744.
2 Licht, S.; in: Licht, S.: Therapeutic electricity and ultraviolet radiation, p. 1, New Haven 1967
3 Rowbottom, M.; Susskind, C.: Electricity and Medicine. History of their interaction, p. 177, San Francisco, 1984
4 Haller, J. S.: N. Y. State J. Med. **85**, 257 (1985)
5 Chien, Y. W.; Banga, A. K.: J. Pharm. Sci. **78**, 353 (1989)
6 Willi, J.: Die Geschichte der Iontophorese in der konservativen Zahnheilkunde und ihre Bedeutung für die Entwicklung der modernen Endodontie. Diss. med. dent. Univ. Zürich 1990
7 Pivati, G. F.: Della Elettricita medica lettera, p. 31, Lucca 1747
8 Rowbottom/Susskind [3], p. 18
9 Colwell, H. A.: An essay on the history of electrotherapy, p. 21, London 1922. In their work „Chemisch-elektrische Heilmethode", Leipzig 1853, p. 4–5, C.H. and H: Hassenstein report on highly successful attempts to deliver drugs by means of a home made electrical apparatus. However, they refused to give any details and the drugs used are unknown.
10 Mangin, Abbé: Histoire générale et particulière de l'électricité. Paris 1752
11 Morton, W. J.: "Cataphoresis" or electrical medicamental diffusion as applied in medicine, surgery and dentistry, p.12, London 1898
12 Althaus, J.: A treatise on medical electricity theoretical and practical and its use in the treatment of paralysis, neuralgia, and other diseases, p. 654, Philadelphia 1870
13 Meyer, M.: Die Electrizität in ihrer Anwendung auf practische Medicin, 3. Aufl., p. 26, Berlin 1868
14 Archive Générales de Médecine, II me série, Tome II, p. 126, Paris 1833
15 Beer, C.: Oesterr. Zschr. Prakt. Heilk. **15**, 900 (1869)
16 Richardson, B. W.: Brit. J. Dent. Sci. **2**, 407 (1858/1859)
17 Colwell [9], p. 107
18 Morton [11], p. 14
19 Munk, H.: Arch. Anatom. Physiol. Wiss. Med. 241 (1873)
20 Munk, H.: Arch. Anatom. Physiol. Wiss. Med. 505 (1873)
21 Buxbaum, A. I. F.: Cincinnati Lancet-clinic **37**, 539 (1896)
22 Schmidt, W.: Die Kataphorese unter dem Einflusse gemessener Stromstärke, p. 33, Borna–Leipzig 1909 (zugl. Diss. Bern)
23 Morton [11], p. 47 ff.
24 Willi [6], p. 26
25 Lewandowski, R.: Elektrodiagnostik und Elektrotherapie, p. 447, Wien 1892
26 Morton [11], p. 21
27 Althaus [12], p. 656
28 Lewandowski, R.: Die Elektrotechnik in der praktischen Heilkunde, p. 314, Wien 1883
29 Haller [4], p. 260
30 Frankenhäuser, F.: Die physiologischen Grundlagen und die Technik der Elektrotherapie. Physikalische Therapie in Einzeldarstellungen, 7. Heft, p. 35, Stuttgart 1906
31 Schmidt [22], p. 9
32 Morton [11], p. 8
33 Schmidt [22], p. 5
34 Morton [11], p. 19
35 Willi [6], p. 8
36 Frankenhäuser, F.: Ergebn. Inn. Med. Kinderheilk. **2**, 442 (1908)
37 Schmidt [22], p. 89
38 Gersh, M. R.: Electrotherapy in Rehabilitation, p. 337, Philadelphia 1992
39 Riviere, J. E.; Heit, M. C.: Pharm. Res. **14**, 687 (1997)
40 Leduc, S.: Introduction électrique des ions dans l'organism vivant, Paris 1901
41 Leduc, S.: Die Ionen- oder elektrolytische Therapie. Leipzig 1905
42 Leduc, S.: Electric ions and their use in medicine. Liverpool 1908
43 Morton [11], p. 37
44 Cumberbatch, E. P.: Essentials of Medical Electricity. 8. ed. London 1939 (former editions: 1. ed. 1905, 2. ed. 1909, 3. ed. 1916, 4. ed. 1918, 5. ed. 1924; 6. ed. 1929, 7. ed. 1933)
45 Dyson, J. N.: The practice of ionization. London 1936
46 Cumberbatch [44], 8. ed, p. 141
47 Ichihashi, T.: J. Orient. Med. **25**, 101 (1936)
48 Sloan, J. B.; Soltani, K.: J. Am. Acad. Dermatol. **15**, 671 (1986)
49 Harris, R.; in: Licht [2], p. 156
50 Popkin, R. J.: J. Invest. Dermatol. **16**, 97 (1951)
51 Schwartz, M. S.: Arch. Int. Med. **96**, 662 (1955)
52 Coyer, A. B.: Ann. Phys. Med. **2**, 16 (1954)
53 Kassan, D. G.; Lynch, A. M.; Stiller, M. J.: J. Am. Acad. Dermatol. **34**, 657 (1996)
54 Merino, V.; Kalia, Y. N.; Guy, R. H.: Trends Biotechnol. **15**, 288 (1997)
55 Guy, R. H.: J. Pharm. Pharmacol. **50**, 371 (1998)
56 Stolman, L. P.: Dermatol. Clin. **16**, 863 (1998)
57 Hashmonai, M.; Kopelman, D.; Assalia, A.: Surg. Today **30**, 211 (2000)
58 Swineheart, J. M.: Dermatol. Surg. **26**, 392 (2000)
59 Sasaki, H.; Yamamura, K.; Mukai, T.; Nishida, K.; Nakamura, J.; Nakashima, M.; Ichikawa, M.: Crit. Rev. Ther. Drug Carrier Syst. **16**, 85 (1999)
60 Rosenstein, E. D.: Rheum. Dis. Clin. North Am. **25**, 899 (1999)
61 Alexander-Williams, J. M.; Rowbotham, D. J.: Br. J. Anaesth. **81**, 3 (1998)
62 Sung, F. C.; Fang, J. Y., Hu, O. Y.: J. Control. Release **67**, 1 (2000)
63 Pillai, O.; Nair, V.; Poduri, R.; Pachangula, R.: Methods Find. Exp. Clin. Pharmacol. **21**, 229 (1999)
64 Chang, S. L.; Hofmann, G. A.; Zhang, L.; Deftos, L. J.; Banga, A. K.: Int. J. Pharm. **200**, 107 (2000)
65 Chang, S. L.; Hofmann, G. A.; Zhang, L.; Deftos, L. J.; Banga, A. K.: J. Control. Release **66**, 127 (2000)
66 Gibbons, G. R.; Newton, W.: J. Fam. Pract. **49**, 110 (2000)
67 Potts, R. O.: J. Annu. Diabetol. Hotel Dieu 67 (2000)
68 Gao, J. Q.; Hu, Q. H.; Liang, W. Q.: Pharmazie **55**, 467 (2000)
69 Kanikkannan, N.; Kandimalla, K.; Lamba, S. S.; Singh, M.: Curr. Med. Chem. **7**, 593 (2000)
70 Albrecht, I.: Diss. Univ. Leipzig 1994
71 Willi [6], p. 126
72 Krause, F. (Elektromedizinische Werke), Preisliste Berlin 1905


Received February 14, 2001
Accepted March 20, 2001

Dr. Axel Helmstädter
Theodor-Heuss-Str. 30b
D-63303 Dreieich
helmstaedter@em.uni-frankfurt.de