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History of Neurology

Arnold Netter (1855–1936) and infectious pathology of the nervous system[☆]

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ABSTRACT

Arnold Netter (1855–1936) was a paediatrician who clinically applied the progress that his Pasteurian contemporaries had made possible through their bacteriological discoveries. From a neurological point of view, he brought looking for Kernig's sign into mainstream use to confirm the clinical diagnosis of meningitis and made diagnostic lumbar puncture systematic. He was one of the first to cure meningococcal and pneumococcal meningitis, long before the era of antibiotics, using subtractive lumbar puncture and intraspinal serotherapy. Netter's attentive vigilance enabled him to recognise, from its onset, the first poliomyelitis epidemic of the 20th century which took place in the summer of 1909. He described the clinical and epidemiological characteristics, identifying the viral rather than microbial origin.

Netter detected the first cases of encephalitis lethargica in Paris in 1918. The disease had been described by Constantin von Economo (1876–1931) in Vienna the previous year. Netter spent fifteen years studying this new disease, which caused a pandemic a century ago. He filled in the clinical picture and used his understanding of cerebrospinal fluid and pathological anatomy to enhance knowledge and improve treatment of this neurological pathology.

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Arnold Netter (1855–1936) was a Parisian paediatrician very famous during the first thirty years of the 20th century, owing to his work on infectious diseases and hygiene (Fig. 1). In 1962, the city of Paris honoured him by naming an avenue after him in the 12th arrondissement, near the Trousseau Hospital where he had spent his entire career after 1895. Following a biographical overview, this paper will present his contributions to the infectious pathology of the nervous system, in particular his publications on bacterial meningitis and poliomyelitis, as well as encephalitis lethargica, a pandemic

that broke out in 1917 and ravaged the world at the same time as the so-called “Spanish” flu, just over a century ago.

1. A brilliant career

Juste Arnold Netter, the son of the physician Léon Netter (1816–1896) and Mathilde Seligmann (1827–1895), was born in Strasbourg on 20 September 1855. As an adolescent he watched the 1870 Franco-Prussian War unfold. After his

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Fig. 1 – Arnold Netter around 1900 (Collection OW).

native city was bombarded, his parents fled Prussian oppression and took refuge in Nancy where Netter finished his study of the humanities at secondary school. Then the entire family moved to Paris where they lived in a modest apartment on Rue du Château-d'eau (10th arrondissement). During this period, he found a friend for life in Antoine Béclère (1856–1939).

After ranking 31st on the entrance exam in December 1875 to become a non-resident medical student, he came in 13th in December 1877 in a class that included a number of future celebrities: Ernest Gaucher (1854–1918), Anatole Chauffard (1855–1932), Antoine Béclère, and Charles Féré (1852–1907). Finishing his military service at the end of 1878, he began as a resident in 1879 at Bicêtre Hospital, working with a student of Jean-Martin Charcot (1825–1893), Charles Bouchard (1837–1915). Then in 1880, at Lariboisière Hospital, he worked with Simon Duplay (1836–1924); in 1881 at Trousseau Hospital with Jules Bergeron (1817–1900); in 1882 at Enfants-Malades Hospital with Jacques-Joseph Grancher (1843–1907); at La Pitié Hospital in 1883 with Paul Brouardel (1837–1906); and finally with Sigismond Jaccoud (1830–1913) in 1884, for his additional year as a gold medal winner of the resident competition in 1882. The evaluations of his teachers are all comparable to Bergeron's assessment: "Extremely hard-working, very knowledgeable, a good clinician, performs his duties with exemplary zeal, all without ever once interrupting his personal research on the very important topic of probable agents in the transmission of contagious diseases" [1].

On 16 March 1883, with a jury presided by Brouardel, he defended his thesis: "*Diagnostic précoce d'une forme de tubercu-*

lisation pulmonaire à début pleurétique" (early diagnosis of a form of pulmonary tuberculation with pleuritic onset) [2]. Jaccoud kept him for an additional year, from 1886 to 1887, as chief resident; at the same time, he worked as head of the hygiene laboratory of the medical school. According to his student Robert Debré (1882–1978), it was during this time that "he fell under the intellectual charm of Édouard Brissaud" (1852–1909) [3]. He became a hospital physician in 1888 (first working for the Central Office before receiving a permanent assignment) and successfully passed the *agrégation* exam in 1889 (the first step toward a university career). After his introduction to research in Bouchard's laboratory, Brouardel and Adrien Proust (1834–1903) introduced him to hygiene and bacteriology, a young science that was developing rapidly. Spending much time at the conferences and in the laboratories of the Pasteur Institute during his residency, Netter would collaborate throughout his life with the Pasteurian Maurice Nicolle (1862–1932), brother of the Nobel prize-winner Charles Nicolle (1866–1936). It should be noted that Netter was a precursor of the discoveries in the area of typhus that led to Nicolle's prize [4].

With the aid of talented students like Debré, Netter performed numerous tasks, such as teaching, hospital care, and research in the fields of epidemiology, bacteriology, and hygiene, all while becoming an esteemed consultant with an international reputation. In 1889, he led an inspection delegation in Lebanon. He was named member of the "serum committee" in 1896 and member of the French High Council of Hygiene in 1898. In 1904, he was elected to the French Academy of Medicine, holding the chair previously occupied by Adrien Proust. Decorated with the French Legion of Honour medal in 1892, he became an Officer in 1912, a Commander in 1921, and a Grand Officer in 1928 [5].

Netter married Esther-Jeanne Lang (1870–1929) on 17 November 1890 with whom he would have two daughters and two sons. Henri-Charles (1895–1946) went on to become a physician and Léon (1897–1987) a lawyer.

He died on a Sunday morning, 1 March 1936, shortly after stepping down from the podium in the lecture hall at Hôtel-Dieu Hospital, where a conference on clinical medicine was being held. He had been defending the value of the fixation abscess, particularly in the treatment of encephalitis lethargica: "Despite the breathlessness he had grown accustomed to over the past year or two that nonetheless alarmed his friends, he attended the session and spoke with warmth and conviction, better than he usually did.. Our colleague Comby [6], who was sceptical about the fixation abscess, spoke after Netter, but he expressed his difference of opinion with such respect and kindness that Netter smiled at him with gratitude, despite being contradicted. His face was happy and peaceful. He seemed to fully savour this moment of grace. It was his last moment. He was suddenly seen to slump, having already left us" [7].

2. First and foremost an infectious disease specialist and a clinician: meningitis

The first description of pneumococcus in 1881 was that of Charles Talamon (1850–1929) at the Pasteur Institute, but it



Fig. 2 – Arnold Netter demonstrating how to look for Kernig's sign in a child (ref. 17–BIU Santé Paris).

was cultivated and named by the German Albert Fraenkel (1864-1938) in 1886 [8]. In 1887, Netter demonstrated that this microbe was responsible for lobar pneumonia, but also numerous forms of purulent pleurisy, peritonitis, and endocarditis. He also provided evidence of pneumococcal meningitis in the absence of simultaneous pneumonia, observing that “pneumococcus can be present in the mouth and undoubtedly in the nasal cavities of healthy subjects. In addition to the influence of cold weather, trauma in such cases

suffices to produce favourable conditions in the lung for the attraction and development of pneumococcus, as does coryza, delirium tremens caused by alcoholism, etc., which can lead to the spread of the microbe to the meninges” [9]. Having discovered the presence of pneumococcus in saliva, he intensified his research on the commensal flora of the mouth, showing that a healthy carrier may host multiple pathogens (streptococcus and Friedländer's bacillus, to use his terms) [10]. Also at this time, he studied the prophylactic measures to fight diphtheria, plague [11], and typhus [4].

At the 13 May 1898 session of the Medical Society of the Hospitals of Paris, Netter drew attention to the development of a meningitis epidemic in the capital that would soon spread to all major French cities [12]. Anton Weichselbaum (1845–1920) had described the cerebrospinal meningitis microbe in 1887: “diplococcus intracellularis meningitidis” [13]. During this epidemic, Netter demonstrated the diagnostic usefulness of looking for Kernig's sign and the bacteriological benefit of lumbar puncture, a technique proposed by Irenäus Quincke (1842-1922) of Kiel in 1895 [14,15]. In 1882, Vladimir Mikhailovich Kernig (1840-1917) of Saint Petersburg had discovered a clinical sign indicating meningeal inflammation: the inability of a seated subject to completely extend their knee [16] (Fig. 2). But most physicians were unfamiliar with this novel publication until Netter made it more widely known after 1898 [17]. Netter also highlighted the value of purpura for signalling the meningococcal origin of meningitis or septicaemic disease. He promoted repeated subtractive lumbar punctures and serotherapy using specific sera, prepared by Maurice Nicolle, thus saving the life of his own son. He grouped, updated, and condensed his numerous publications on this disease in a 1911 book, written in collaboration with Robert Debré [18].

Netter was a fervent champion of serotherapy, not only against meningitis but also diphtheria, plague, and tuberculosis [1]. For example, in 1904 he noted having already made



Fig. 3 – Medal by Georges-Henri Prud'homme (1873–1947) (Collection OW).

use of “prophylactic injections of diphtheria antitoxin” in more than 3000 cases, not only curatively but also “preventively within families” [4].

3. Paralysis and poliomyelitis

At the 12 November 1909 session of the Medical Society of the Hospitals of Paris, Netter pointed out “the unexpected frequency of poliomyelitis in France during the summer of 1909” [19]. After showing that cerebrospinal meningitis could lead to paralysis, he referred to the 1890 description of poliomyelitis by the Swedish Karl-Oscar Medin (1847–1927) [20]. The German Jacob von Heine (1800–1879) had distinguished between cases of infantile paralysis that were cerebral in origin, and those that were purely medullary, in two publications over a period of twenty years, published in 1840 [21] and in 1860 [22]. This led to the eponym of Heine-Medin disease, which was used for many years to refer to acute anterior poliomyelitis.

Wilhelm Knöpfelmacher (1866–1938) in Vienna was the first to demonstrate the transmissibility of poliomyelitis by intraperitoneal injection of a Rhesus macaque with the spinal cord hydrolysate from a deceased child, which triggered paralysis in the monkey on the seventh day. On the eleventh day, histological lesions were found in the monkey’s anterior horns that were identical to the child’s lesions [23]. Netter made these findings widely known, highlighting the distinction between poliomyelitis and cerebrospinal meningitis, both in terms of clinical progression and the latter’s microbial aetiology, noting “an organism belonging to the group of filtering viruses” for Heine-Medin disease [24].

Netter showed that epidemic poliomyelitis was identical to what had been called “infantile paralysis” until then, associating with poliomyelitis a number of mild forms that others had erroneously attributed to the after-effects of spontaneously resolving tuberculous meningitis. He also highlighted the importance of healthy carriers in the spread of the epidemic. Once again, Netter identified “immunising principles” in the serum of convalescents that he used for serotherapy at the initial acute phase of the disease [24] (Fig. 3).

In 1910, Netter had Jules Tinel (1879–1952) as a resident [25]. Tinel had married Louise-Marianne Giry-Wissembourg (1873–1914) on 1 June 1909. Giry-Wissembourg was the first French woman resident and fully completed her four years of residency. She spent her last year, in 1909, as Netter’s resident. In 1911, she defended a very remarkable thesis of more than 300 pages complete with numerous illustrations. Her subject matter was the 1909 poliomyelitis epidemic in Paris. She detailed all the observations gathered with Netter to which she added numerous novel histopathological descriptions [26].

4. Encephalitis lethargica

On 22 March 1918, Netter informed the Medical Society of the Hospitals of Paris that he had observed seven cases of a new disease he described using the name given by Constantin von Economo (1876–1931): “epidemic encephalitis lethargica”. Preceded by headaches and vomiting, a period of somnolence

characterised this new entity: “As soon as the patient is not otherwise occupied, they return to sleep. At a more marked stage, they lie inert in their bed, unable to execute the slightest movement. Every two to three days, they wake up to eat; otherwise, they must be spoon-fed or given a bottle while asleep. Their sleep can even become a true comatose state from which it is impossible to rouse them for feeding” [27]. This state lasted several weeks or months, with intervening episodes of delirium or convulsions; the clinical examination, however, did not reveal a meningeal syndrome. Paralysis occurred, first affecting cranial nerve pairs (III, V, VI, VII, IX) with ptosis, strabismus, external ophthalmoplegia of nuclear origin, nystagmus, facial palsy, etc. Fever was mild and fluctuated. Most cases benefited from a lumbar puncture revealing unpressurised clear liquid with normal albumin content but frequently with low glycochorrhachia. Progression could lead to total resolution in a few hours or, on the contrary, to sudden death by paralysis of the vital centres of the medulla oblongata [28]. Netter clearly distinguished this pathology from flu, poliomyelitis, and botulism [27,29].

From the first cases he treated, Netter made anatomopathological observations: “Cellular infiltration lesions especially marked around the vessels. The damage is primarily located in the medulla, pons, and basal ganglia of the brain” [27]. Netter noted that this encephalitis lethargica had already been observed in 1890 in Italy and Hungary and had been named “nona”. He also pointed out that the cases he had observed were similar to those described by von Economo in 1917, both from a clinical and an anatomopathological point of view. He confirmed the damage to the substantia nigra as Pierre Marie (1853–1940) and Konstantin Tretiakoff (1892–1958) had described it in 1918 [30], the year before Tretiakoff defended his magisterial thesis on the histopathology of Parkinson’s disease [31]. Netter’s reasoning led him to conclude, “This is an autonomous disease in which the specific agent does not yet seem to be determined” [27]. He proposed treating patients with intraspinal injections from subjects who had previously been infected and who had recovered.

Other cases were soon recorded in France by Anatole Chauffard (1855–1932) and his student Marthe Bernard (1890–?) [32], by the psychiatrist Henri Claude (1869–1945) [33], and by Paul Sainton (1868–1958) who, six months after Netter’s first account, published a general summary of the disease in *La Presse médicale* intended for practitioners in the field [34].

Netter’s publications on encephalitis multiplied for more than fifteen years. In 1921 [35], then in 1933 [36], he brought to light the persistence of the contaminating infectious agent in the salivary glands, a lasting cause of possible contagion. Contrary to von Economo, Netter never deduced from his observations any hypotheses about a structure inducing sleep in the diencephalon.

It should be noted that Netter only cited the publications of René Cruchet (1875–1959) [37,38] incidentally. Cruchet had always argued that his publication on 27 April 1917, written with François Moutier (1881–1961), a student of Pierre Marie and Albert Calmette (1863–1933) who was a bacteriologist at the Pasteur Institute, should have been recognised as the initial publication [1], seeing how it was published three weeks before that of von Economo, on 10 May 1917 [39]. It should also



Fig. 4 – Cartoon by Harry Whist (Album de l'Académie de Médecine, 1913, BIU santé Paris).

be noted that in recent books on encephalitis lethargica, the sections describing Netter's publications are much more detailed than those on Cruchet's work [40,41].

5. In conclusion

The very considerable body of work that Netter contributed can be divided into two categories: first, the bacteriological work applied to clinical medicine and pathology, and second, the work related to epidemiology and hygiene during the cholera, typhus, and plague epidemics that struck France in 1892 and 1893. He brought serotherapy against infectious diseases into widespread use, enabling unprecedented disease resolution, notably during infectious pathologies affecting the nervous system (Fig. 4).

Robert Debré concluded the eulogy in remembrance of his teacher this way: "Netter remained true to the characteristics of his native Alsace, from the melodic accent which made his words sing to the firm character which he exemplified" [3].

Statement of ethics

This work required no approval from an institutional review board and was prepared in accordance with the ethical guidelines of the journal.

Disclosure of interest

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REFERENCES

- [1] Netter A. Archives AP-HP, cote 774FOSS213. Hôpital Bicêtre 78 Rue du Général Leclerc, 94270 Le Kremlin-Bicêtre.
- [2] Netter A. Diagnostic précoce d'une forme de tuberculisation pulmonaire à début pleurétique. Thèse Paris n°155. A Davy; 1883.
- [3] Debré R. Nécrologie: Arnold Netter (1855-1936). La Presse médicale 1936;44:793-6.
- [4] Netter A. Exposé des titres et travaux scientifiques. Paris: Masson; 1904.
- [5] Archives nationales. Base Leonore cote LH/1982/36.
- [6] Jules Comby.(1853-1947).
- [7] Rist E. 25 portraits de médecins français (1900-1950). Paris: Masson; 1955.
- [8] Drings P, Thierfelder J, Weidemann B, Willig F, Albert Fraenkel Ehmman M. Ein Arztleben in Licht und Schatten 1864-1938. Landsberg: Ecomed Verlagsgesellschaft; 2004.
- [9] Netter A. De la méningite due au pneumocoque avec ou sans pneumonie. Archives générales de Médecine 1887;20:28-51 [série VII 19 257-277/435-468/série VII].
- [10] Netter A. Microbes pathogènes dans la bouche de sujets sains. Revue d'hygiène 1889;11:1-16.
- [11] Netter A. La peste et son microbe, sérothérapie et vaccination. Paris: G. Carré et C. Naud; 1900.
- [12] Netter A. Première communication sur une petite épidémie de méningite cérébro-spinale à Paris en 1898. Bulletins et mémoires de la Société médicale des Hôpitaux de Paris; 1898: 406-16 [sérieIII15].
- [13] Weichselbaum A. Über die Aetiologie der akuten Meningitis cerebrospinalis. Fortschritte der Medizin (München) 1887;5:573-620.
- [14] Quincke HI. Über Lumbarpunction. Berliner klinische Wochenschrift 1895;32:861/889-9.
- [15] Frederiks JA, Koehler PJ. The first lumbar puncture. J Hist Neurosci 1997;6:147-53. <http://dx.doi.org/10.1080/09647049709525699>.
- [16] Kernig VM. Über ein Krankheits Symptom der akuten Meningitis. St. Petersburg Medizinische Wochenschrift 1882;7:398.
- [17] Netter A. Importance du signe de Kernig pour les diagnostics des méningites, des méningites cérébro-spinales frustes. Bulletins et mémoires de la Société médicale des Hôpitaux de Paris; 1898: 639-47 [sérieIII15].
- [18] Netter A, Debré R. La méningite cérébro-spinale. Paris: Masson; 1911.
- [19] Netter A. Fréquence insolite des poliomyélites en France pendant l'été et l'automne 1909. In: Bulletins et Mémoires

- de la Société médicale des Hôpitaux de Paris. Paris: Masson; 1909: 33.
- [20] Medin O. En epidemi af infantil paralyse, Stockholm. Hygiea 1890;52:657-68.
- [21] von Heine J. Beobachtungen über Lähmungszustände der untern Extremitäten und deren Behandlung. FH. Köhler: Stuttgart; 1840.
- [22] von Heine J. Spinale Kinderlähmung. Stuttgart: Cotta; 1860.
- [23] Knöpfelmacher W. Experimentelle Übertragung der Poliomyelitis acuta auf Affen. Medizinische Klinik 1909;44:377-90.
- [24] Netter A, Lavaditi C. Action microbicide exercé par le sérum sanguin des malades atteints de paralysie infantile sur le virus de la poliomyélite aiguë. Comptes rendus hebdomadaires des Séances et Mémoires de la Société de Biologie 1910;68 [617-619/855-857].
- [25] Walusinski O. Jules Tinel (1879-1952): beyond the eponym, the man and his forgotten neurological contributions. Rev Neurol (Paris) 2017;173:364-73. <http://dx.doi.org/10.1016/j.neurol.2017.03.001>.
- [26] Tinel-Giry LM. La poliomyélite épidémique (maladie de Heine-Medin). Thèse Paris n°5. Al fred Leclerc; 1911.
- [27] Netter A. L'encéphalite léthargique épidémique. Bulletin de l'Académie de Médecine 1918;79:337-47 [série III].
- [28] Netter A. Sur quelques cas d'encéphalite léthargique observés récemment à Paris. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1918;42:384-5.
- [29] Netter A. L'encéphalite léthargique épidémique. Paris médical 1919;31:81-6.
- [30] Marie P, Trétiakoff K. Examen histologique des centres nerveux dans deux cas d'encéphalite léthargique. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1918;80:411-8.
- [31] Trétiakoff C. Contribution à l'étude de l'anatomie pathologique du Locus niger de Sæmmering, avec quelques déductions relatives à la pathogénie des troubles du tonus musculaire et de la maladie de Parkinson. Thèse Paris n°293. H. Jouve; 1919.
- [32] Chauffard A, Bernard M. Deux cas d'encéphalite léthargique. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1918;42:470-5.
- [33] Claude H. A propos de l'encéphalite léthargique. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1918;42:364-8.
- [34] Sainton P. L'encéphalite léthargique. La Presse médicale 1918;26:487-90.
- [35] Netter A, Césari E, Durand H. Altération des glandes salivaires dans l'encéphalite léthargique. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1921;45:721-4.
- [36] Netter A. Longue persistance du virus à l'état latent chez les sujets atteints d'encéphalite. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1933;49:61-71.
- [37] Walusinski O. René Cruchet (1875-1959), beyond encephalitis lethargica. Journal of the History of the Neurosciences 2022. <http://dx.doi.org/10.1080/0964704X.2021.1911913>.
- [38] Cruchet R, Moutier F, Calmette A. Quarante cas d'encéphalo-myélite subaiguë. Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris 1917;41:614-6 [série III].
- [39] von Economo C. Encephalitis lethargica. Wiener klinische Wochenschrift 1917;30:581-5.
- [40] Vilensky JA. Encephalitis lethargica, during and after the Epidemic. New York Oxford University Press; 2011.
- [41] Foley P. Encephalitis lethargica: the mind and brain virus. New York: Springer; 2018.