

Constantin von Monakow (1853–1930) and Lina Stern (1878–1968)

Early explorations of the plexus choroideus and the blood-brain-barrier

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Summary

The physiologist Lina Stern (1878–1968), from Baltic origin, and the neuroscientist Constantin von Monakow (1853–1930), from Russian origin, are the protagonists of this article. Lina Stern studied medicine and initiated research work at the Physiology Institute in Geneva. Her research career was quite unique and led, unusually soon, to a professorship. Monakow was professor and head at the Brain-Anatomy Institute of the University of Zurich. Late in his career, he was among the first to work on the problem of the Blood-Brain-Barrier. In 1915, he hypothesised that the brain needs to be protected by the plexus choroideus and the “Glia-Schirm”. Monakow observed severe degeneration of the plexus at autopsy, suggesting that the barrier had lost its protection. The publication was not well received, probably because the microphotographs were of doubtful quality and difficult to interpret.

At the Institute of Physiology in Geneva, Lina Stern used a physiological approach of testing substances in terms of barrier penetration. Her team discovered some substances which had the capacity to be transported through membranes of the brain. She coined the term “Blood-Brain-Barrier” (BBB) and soon obtained a high international profile. In 1925, she accepted an offer to continue her research in Moscow. Her career continued most successfully as the only female Academician. However, late in the Stalin era, she suffered in prison and was exiled to Kasakstan. She died in 1968.

Introduction and a short overview of Monakow’s career

Constantin von Monakow (1853–1930), of Russian origin, spent most of his life in Zurich (Gubser and Ackerknecht, 1970). He was an early pioneer in brain research, who studied the organisation of nuclei with interconnecting pathways and relays in animal and human brains. As a medical student in Zurich, Monakow was already motivated by some of his professors who wrote and lectured on the human brain: Wilhelm Griesinger (1817–1868), Bernhard Aloys von Gudden (1824–1886), Eduard Hitzig (1838–1907) and Auguste Forel (1848–1931). Monakow soon decided to study the construction of the brain! As an advanced student, he took the opportunity to work for a

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short period in psychiatry, headed by Gudden who inspired him particularly in the art of neuroanatomy. As a young assistant, Monakow started his medical duties at the psychiatric asylum in Pirminsberg, remote from Zurich above Bad Ragaz. In spite of his heavy clinical load, without any support from the director, Monakow planned and followed up the neuroanatomical work along with the technique he had learned from Gudden (1870). By chance, Monakow discovered a never-used, disposed of “Gudden-microtome”: a marvellous opportunity for Monakow! Ready to initiate his research, his goal was to understand the connections of neural pathways and systems, mostly in lower animals. Monakow followed Gudden’s procedure of *retrograde and trans-synaptic anterograde degeneration* (Akert, 1996). Later, Monakow also studied the *anterograde fibre degeneration of Waller* by means of the Marchi method. He started to study the ascending (visual) and descending (motor) pathways of the brain in rabbits, by means of selected lesions of nuclei or fibre tracts. Patients who died from brain-lesions were studied at autopsy. His first publications and presentations were well received. As a young assistant, Monakow quickly became a self-made neuroscientist, building up his European profile.

At the age of 27, Monakow was promoted to “Privat-Dozent” at the University of Zurich, giving few lectures but, as usual, he received no financial reward from the University. He had to work hard to support his family, that is to say, to continue his (also non-neurological) medical duties and research in Zurich. In 1894, the state of Zurich promoted Monakow to Professor “extraordinarius” and Director of the “*Neurologische Poliklinik*”. In 1910, the “*Hirnanatomisches Institut*” was also becoming under the rule of the state of Zurich. In 1913, the two sections were finally relocated together under one roof, near the main building of the University. Slowly, Monakow assembled a group of technical and scientific personnel. More scientists came for short or long periods to Zurich for research, from Europe, the USA and Japan. The published works (mostly in German) were well received, and also were rarely criticised. Monakow is best known for the two books “*Gehirnpathologie*” (1897/1905) and “*Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde*” (1914).

This short introduction about Monakow’s early period is meant to present the outstanding, self-made scientist who built up a small, but effective “Neuro-Center” in Zurich. More detailed descriptions can be found in Akert (1995), Koehler et al. (1995), Finger et al. (2004) and Wiesendanger (2006).

A turning point in Monakow's life

Monakow wrote his reflections about his most interesting scientific life over many years, which was edited much later as a book: *Vita mea* (edited by Gubser and Ackerknecht, 1970). Although he was satisfied with his work and internationally recognised, the outbreak of WW1 in 1914 was a sad turning point for Monakow. He describes his pessimism about the catastrophe of WW1 with its destruction of civilisation and culture. It was also the end of the international *Brain Commission* (the first attempt to foster international links about brain research). The goal had been to help each other in exchanging scientific knowledge, books and histological preparations for example. However, due to the war, cooperation, meetings and exchange with younger scientists was sadly finished. Monakow modified his work, and was now mostly thinking and writing. He thought about higher functions of the human brain, particularly of psychiatric diseases. He also studied eagerly and wrote to himself about the brain and philosophy.

One of the objectives of the *Brain Commission* had been to create, as an international effort, a giant histological atlas of the human brain. Unfortunately, only a small piece of that project was accomplished: an *Atlas of the Human Medulla Oblongata* by the Japanese scientist Fuse and Monakow. This atlas played a crucial role, triggering the idea of the plexus choroideus protecting the brain.

“Biologische Psychiatrie” – and functions of the brain (Monakow, 1925)

The German Walter Griesinger (1817–1868), came to the young University of Zurich for a few years during the 1860s as a Professor of Medicine and Psychiatry. He had published a remarkable book on pathology and therapy in psychiatry (1861). On page 1, he starts with the bold statement that “... *psychiatric diseases are diseases of the brain*”. Monakow had read the book as a medical student and was highly impressed by it, also considering that schizophrenia may be an organic disease. Monakow (1925) thus followed the line of Griesinger and introduced the term “*Biologische Psychiatrie*”. Interestingly, this term was later introduced in the USA by the famous Swiss-American psychiatrist, Adolf Meyer (previously under the Direction of Auguste Forel and Eugen Bleuler).

In the summer of 1915, Monakow travelled alone to the French-speaking pre-alps of Switzerland. He stayed for five weeks in the small hotel of *Chesièrè*, above the Rhône valley. Monakow, at that time aged 61 years old, wrote about *Biological Psychiatry, Phenomenology, Biology and Psychology, Biological Conscience (= Syneidesis), Truth, Error and Lie, Religion and Nervous System*. Later, some of these essays (the “*Chesièrè papers*”) were edited as a book by Maria Waser (1933). Monakow continued his trip to Geneva where he stayed for three weeks, visiting some colleagues at the University: the neurologist Paul Ladame (1842–1919), the psychologist Edouard Claparède (1871–1940) and the physiologist Lina Stern (1878–1968). In 1915, Monakow already talked about an “*ekto-mesodermale Barriere*” and about the “*plexus choro-*

Figure 1

Constantin von Monakow
(1853–1930).



Lina Stern
(1878–1968).



deus” (in *vita mea*, p. 263–264). It is very likely that Monakow had, at physiology meetings, already met, or heard about, the physiologist Lina Stern.

The physiologist Lina Stern (1878–1968) in Geneva and her first experimentation into membrane permeabilities

Lina Stern was born in Libau in Kurland (later joined to Russia with the name Libawa, developing into an important Russian harbour). She travelled from Libau to study medicine in Geneva, after being prevented from studying medicine in Russia. She was a brilliant student, particularly attracted to physiology and biochemistry. As a student, she was already allowed to participate in experimental research in the laboratory under the guidance of the Professor Jean-Louis Prevost (1838–1927), whom she much admired for his scientific and cultural “*esprit*”. Lina Stern passed the final examination with distinction and was awarded a prize for her doctoral dissertation in 1904. She then continued to work in physiology, collaborating with the assistant (and later professor) Federico Battelli (1867–1941). Already in 1905, Lina Stern was awarded the title of “*privat-docent*”. The two undertook a series of intensive experiments on the oxidative cycle. Their experiments were fore-runners of the famous “*Krebs cycle*”. At the Nobel ceremony, Krebs congratulated the team in Geneva for their work.

Figure 2

Jean-Louis Prevost
(1838–1927).

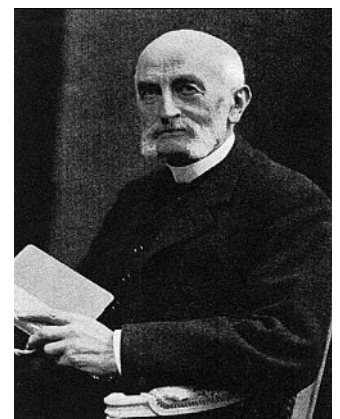
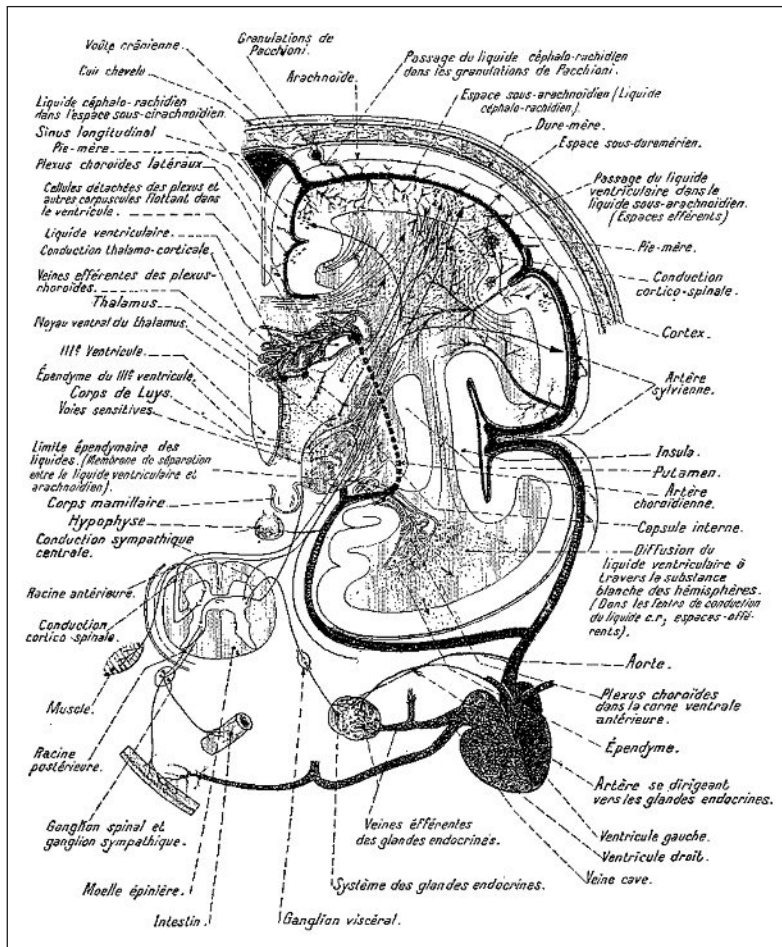


Figure 3 The anatomical blood-brain-barrier.



nerveux central chez les différentes espèces animales". Stern and Rothlin (1918) published their first full paper on the physiological barrier in the Schweizer Archiv für Neurologie und Psychiatrie, launched by Monakow during WW1 in 1917. In the following year, Monakow and Kitabayashi (1919) published their paper on the pathological "barrier"; it was purely a histopathological investigation of the plexus choroideus, whereas the Geneva team worked with an experimental physiological approach.

A hypothetical link between a degenerating plexus choroideus and schizophrenia

Back in Zurich, Monakow vividly admired the finished histological atlas of the Human medulla oblongata (p. 264, Vita mea). A senior researcher from Japan, Gennosuke Fuse (1880–1946), had worked for two years, during WW I, on this atlas at the Brain-Anatomy Institute in Zurich (Fuse and Monakow, 1916).

Monakow was particularly interested in the histological preparations, from embryonic phases (7 mm) up to the newborn foetus, in order to familiarise himself particularly with the structure of the *plexus choroideus*. For the first time, one could read Monakow's interest about the ill-known function of the plexus choroideus and the ependyma: he posed the question regarding whether the function of the plexus choroideus might protect the cerebral cortex. If so, an ineffective plexus may lead to either insufficient or lacking protection of the cortex. In short: do psychotic patients suffer from a degenerating plexus choroideus? At this time, Monakow decided to study the development and morphology of the plexus choroideus, as well as the ependyma of the human foetus.

Monakow soon began to investigate the plexus of a brain from a recently deceased patient who had suffered from severe schizophrenia. The brain was sent to him from a psychiatric clinic. In *Vita mea* (p. 265), Monakow mentions this first preliminary and purely microscopic investigation of the plexus choroideus. He found variable degeneration in the plexus morphology, but realised that only a series of severe alterations may give an answer. He wanted to organise this project together with the Japanese researcher Kitabayashi, realising that this project would be enormous. From this time on, Monakow was much involved with a bold hypothesis: 1) is the histology of the plexus normal or are there signs of degeneration? and 2) is any degeneration of the plexus related to cortical dysfunction?

In 1919, the first article by Monakow and Kitabayashi on the plexus choroideus was published in the *Schweiz Arch Neurol Psychiat.* The article was obviously written by Monakow, with a lengthy, general introduction about membranes, glands and their role in affective disorders, also including histology photographs of their findings. Kitabayashi returned to Japan in 1920, from where he wrote a second article on his own about the post-mortem plexus in various cases of degenerative brain diseases. The pathology included 13 micro-photos with descriptive terms, such as "*Kolloid Schollen*", "*Gequollene Zottenköpfchen*" and "*Ependym selten intact*". In 1922, Monakow sent another article on the plexus

Figure 4 Oblongata Atlas.



choroideus for the *Festschrift*, in honor of Ramon y Cajal (1852–1934), who celebrated his 70th birthday.

Another pupil of Monakow, Allende-Navarro (1925) also published on the “*Barrière ecto-mésodermique*”, but mainly included hypothetical points, rather than facts. Finally, Monakow and Mourgue (1928) published a book containing 416 pages: “*Introduction biologique à l’étude de la neurologie et de la psychopathologie*”. In the last two extensive chapters, the issue of the plexus choroideus was again discussed in terms of its degeneration and of the link with psychotic diseases. The above book (in French) deals with recent aspects of that time, including neurology, neuropsychology and neuropathology. It has also a philosophical touch as Mourgue was a pupil of the philosopher Bergson. The pathology of the plexus was again illustrated with histological micrographs (although not comparable with today’s standard). It is not surprising that the (loosely described) results were not well accepted. Negative opinions were mentioned, such as for example “... *ich glaube sagen zu dürfen, dass ich die Befunde Monakow’s und seiner Schüler nicht bestätigen kann*”. The answer from the authors was that the amount of degeneration may determine the degree of dysfunction of the barrier (“*l’électivité de ces grosses lésions cellulaires paraît être en rapport avec la gravité de l’atteinte de la barrière choroïdo-épendymaire à cet endroit*”). On page 372 of the book (with Mourgue), the authors mentioned that “... *Morokowa, in the laboratory of F.W. Mott at the Maudsley Hospital in London, could confirm the results of Monakow and Kitabayashi*”. However, among the 25 cases mentioned by Mott, there was also a large spectrum of neuropathological findings. Up to the present day, the role of a defective blood-brain-barrier in schizophrenic patients has not been confirmed. However, today’s research on schizophrenia is intensively pursued at a molecular and genetic level.

In 1923, Monakow celebrated his 70th birthday, with colleagues and friends coming together from many countries and he received letters “... *von der ganzen Welt*”. Monakow gave a 2 hour lecture about “*Fünfzig Jahre Neurologie*” (published in 1925 by Orell Füssli, Zürich). He summarised the development of the Institute, from the very small “one-man show” to a considerable number of collaborators from many countries, an increase in space, a large number of instruments gained and a neurological policlinic (the first in Switzerland). Monakow’s *Festschrift* is remarkable and occupies two volumes of the *Swiss Arch Neurol Psychiat*. A number of articles deal with the permeabilities of membranes by Paul Monakow (internist and son of Constantin von Monakow), Goldmann, Zangger, Lina Stern and Kitabayashi. Many friends in neurology and neurosciences from Amsterdam, Paris, Madrid, USA, Japan and Russia (Bechterev) brought or sent their contributions for the *Festschrift*.

Lina Stern (1878–1968) and the discovery of the “Blood-Brain-Barrier”

Since the meeting with Monakow in 1915, Lina Stern thought about experiments on the “*barrière hémato-encéphalique*” (the term she used in an abstract of the *Comptes rendus* of the *Société de Biologie et Médecine*). She, to-

gether with Rothlin, published the first full paper on the barrier (Effets de l’action directe du curare sur les différentes parties du cervelet) in the *Schweiz Arch Neurol Psychiat* (Stern, 1918). They developed an ingenious way to place, via an extremely fine “arrow” (loaded with 1 mg curare), directly into the fluid space of the 4th ventricle of the animal. After some time, the animal started to perform uncontrolled movements, indicating that the curare excites the cerebellar neurones of the deep cerebellar nuclei by slow diffusion from the ventricular fluid, through the membrane of the leptomeninges to the deep cerebellar nuclei: therefore curare had been transported from the fluid space, through the membrane to the cerebellar neural tissue.

Lina Stern (1921, 1922 and 1923) undertook massive experimental work on the now central issue of a selective passage of biological substances through the “*barrière hémato-encéphalique*”, corresponding to the common term “*blood-brain-barrier*” or the “*BBB*”. In 1921, Lina Stern also wrote an overview of her work on the BBB in the *Schweiz Arch Neurol Psychiat*. At the end of the review, she emphasised the selectivity of the barrier. This point was extremely important for her future extrapolation for medical applications. Monakow (1921) added a 2-page appendix about the circulation of the spinal fluid, also including a figure with the schema of this system.

From her rich harvest, Lina Stern (1923) published a general synthesis of her work: “*La barrière hémato-encéphalique dans les conditions normales et pathologiques*”; this was the paper she contributed for the *Festschrift* at Monakow’s 70th birthday. At the end of her paper, Lina Stern points kindly to the role of the plexus degeneration in schizophrenia, as argued by Monakow and Kitabayashi. It means “*a loss of the plexus shield*”.

Epilogue

Lina Stern was brilliant, already as a student, as an assistant and as a young Professor of Physiology in Geneva. She was socially well integrated and achieved two important scientific results: first, the biological oxidation cycles (together with Batelli), second, the discovery of the blood-brain-barrier. In the second half of the 1920s, many Russians of the University community in Geneva, including personal friends of Lina Stern, returned to the young Soviet Union. When Lina Stern received an offer to build up a physiological-biochemical institution at the Moscow University, she decided to accept the offer and her work in the Soviet Union started in 1925. Lina Stern maintained the links with the Physiology Institute in Geneva and visited Switzerland several times before the outbreak of WW2. For example, she gave a talk about the BBB at the Swiss Society of Natural Sciences, essentially an exposé of the results she had obtained from the last experiments that led to the Doctoral Thesis of Baatard in Geneva. The shortened paper from the thesis was published in the *Swiss Medical Journal* (Stern, 1929). She also entertained a correspondence with Monakow.

The story of her new life began well: as a director she provided the whole Institute with all the equipment she needed; she recruited a large number of staff and co-

workers, pursuing her brilliant career as has been told in several papers (Jaenicke, 2002; Dreifuss, 2005; Vein, 2008). Before WW2, she was travelling frequently in Europe, including Switzerland. She was scheduled to visit Monakow again in the fall of 1930, but this did not happen. Monakow, who maintained strong ties with her, died shortly before her expected visit to Geneva and Zurich in November of 1930. The two scientists had been close friends, both from Russian origin, and both very interested in the newly emerging BBB. Yet, Monakow's anatomical approach failed. Lina Stern, physiologically-minded, was obviously the winner. However, after nearly 100 years since Monakow's concept, the key to the pathogenesis of schizophrenia is lacking and still poses many questions.

Lina Stern, well settled in Moscow, received the prestigious Stalin-prize and was elected, in 1938, for full membership at the Academy of Sciences of the Soviet Union. At the University, advanced scientists, young researchers and students were working, initially in the laboratories of the Medical Faculty. Generous laboratories and rooms were offered to Lina Stern as a Director. She was the only, full female member of the Academy. She maintained her correspondence with Constantin von Monakow until his death in 1930.

The war period in the Soviet Union was hard. In April 1941, the Swiss physiologist, Walter Rudolf Hess (1881–1973), corresponded with Lina Stern (letters from both are at the Zurich Institute of Medical History). She alluded to some health problems and to the bitter war, especially in the winter of 1941, provoking great hardships among the population. The Soviet government created five "antifascist committees", one of them being the Jewish Anti-Fascist Committee (JAFC) which included Lina Stern as the only woman. The committees travelled to the USA and received considerable financial support. Unfortunately, after 1949, the JAFC came more and more under accusations during Stalin's reign (Vein, 2008). In 1948, they had to pay for almost four long years of crude confinement at the Lubjanka prison in Moscow. In 1952, Lina Stern was then, for almost one year, exiled to the city of Dzhambul in Kazakhstan, while all other members of the committee were executed through Stalin's order. Under the rule of Chruschtshev, Lina Stern could return to Moscow and she was re-instated as a member of the Academy with the possibility to take up some limited research (Rubenstein, 2001).

Lina Stern, not forgotten in Switzerland, received the distinction of a *Doctor honoris causa* from the University of Geneva in 1960. She died in 1968, shortly before her 90th birthday. In 1978, a special conference was organised in honour of her rich and important heritage.

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