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Quinckes' pioneering 19th centuries CSF studies may inform 21th centuries research

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We decided it was timely to translate Quincke's work published in 1872 on cerebrospinal fluid (CSF) flow and outflow pathways from German to English (see this issue of *Neurology, Psychiatry and Brain Research*, Bechter et al.) because when perusing the literature on CSF and CSF flow dynamics, we were surprised that Quincke's seminal work appears to be largely overlooked. In his pioneering experiments, Quincke used fine cinnabar granules as an intrathecal contrast dye to observe CSF transport and outflow pathways over time.[1] Interestingly, Quincke characterized CSF transport – as represented by cinnabar deposits observed in the central nervous system (CNS) post-mortem – after days, weeks, and even months (of CSF circulation) in freely moving animals.[1] The implementation of freely moving animals is a unique aspect of these studies because Quincke was the first (to our knowledge) to ponder the impact of psychomotor activity on CSF transport which is now often disregarded since most experimenters use anesthetized and/or immobilized animals. In the studies from 1872, Quincke confirmed that CSF moved (and transported particulate matter) from the lumbar intrathecal sac towards the brain as well as along peripheral and cranial nerves.[1] We repeated Quinke's cinnabar experiments using a rodent model, shorter CSF circulation times and modern imaging methodology; and largely confirmed the previously characterized CSF outflow patterns, thus attesting to the high quality of Quincke studies performed in the 19th century.[2]

It is interesting to read and reflect on Quincke's findings from 1872 in the light of today's research revealing other intriguing aspects and diverse functions of cerebrospinal fluid (CSF) transport,[3–11] as well as the choroid plexus.[12–15] For example, one of the reasons as to why Quincke did not observe cinnabar inside the parenchyma of brain, spinal cord or peripheral nerves was probably because the cinnabar granules were relatively big (>1 μm); and therefore, would not be expected to pass from the intrathecal CSF compartment into the narrow Virckow–Robin spaces along the penetrating CNS arteries. The importance of the molecular weight (MW) of a given solute used to characterize CSF transport was recently described in detail in a study using fluorescently tagged tracers of different MW administered into CSF in combination with optical imaging[9]; and in another study using paramagnetic tracers and contrast-enhanced MRI.[16] Specifically, in the study by Iliff et al.,[9] molecules with a MW of 2000 kDa were unable to pass through the narrow 28-nm gaps between the glial end-feet. Further, the acquaporin-4 (AQP4) water channels present on the glial end-feet was proven to be essential for convective CSF transport of solutes and efficient `detoxification' associated with the brain-wide process of CSF-ISF exchange now

referred to as the `glymphatic pathway'.[9,17] As such, the continuous sweeping bulk flow of CSF through the `glymphatic pathway' comprise: (1) para-arterial CSF transport facilitated by arterial pulsatility,[10] (2) CSF-ISF exchange facilitated by AQP4 water channels and (3) exit of the CSF-ISF mix along para-venous spaces and ultimately lymph vessels on the neck. Importantly, the glymphatic pathway has recently been shown to transport soluble amyloid-β and tau out of the brain.[9,18]

With all of the novel work on CSF-ISF exchange and its apparent importance for brain detoxification, especially during sleep states,[19] it is logical to also discuss `glymphatic' transport in relation to the older concept of `volume transmission' introduced by Fuxe et al.[20] Fuxe et al. proposed in his seminal paper the ``existence in the CNS of two types of electrochemical transmission, namely the wiring transmission (WT) and the volume transmission (VT)".[20,21] The WT was the classical type, which relied on direct neuronal connections, and the VT was a `humoral' type of transmission which operated via the interstitial fluid (Ref). In fact, Fuxe referred to the ISF of the brain as a `collection of several interconnected micro-environment(s)'.[20] Interestingly, Fuxe predicted that the VT mechanism would be slower than WT; which is certainly in agreement with tracer movement (min) we observe in glymphatics studies and which Quincke also observed in his studies using cinnabar.[1] From the point of view of VT, CSF which is known to contain a wide range of signaling molecules including neuropeptides, transmitters, microparticles, proteolytic inhibition and inflammatory cells,[22,23] clearly serves many different functions besides `waste removal' which is linked to the ability to relatively rapidly transport substances from one place to another. These many diverse functions are now slowly unveiled and will continue to enhance our understanding CSF dynamics during normal and pathological conditions. The diverse roles of CSF are reflected in the growing diagnostic value of CSF analysis in a wide range of brain disorders, in particular, neuroinflammatory disorders.

At the time Quincke performed his study, it was not known that CSF was produced in the choroid plexus. Today it is clear that the choroid plexus produces CSF, in addition to functioning as the blood-CSF barrier.[24–26] Recently, Baruch and colleagues demonstrated that the choroid plexus also serves as a neuroimmunological inductor in the aging brain.[12] Specifically, in the aging brain, the choroid plexus is characterized by type I interferon (IFN-1), signaling which is not present in the young brain; and IFN-1 signaling adversely influences cognitive function and neurogenesis, at least in rodents.[12]

Thanks to Quincke, who introduced lumbar puncture into medicine in 1891[27]; therapeutic approaches to both control and manipulate the CSF-ISF fluid milieu continues to be developed, further refined and applied in many clinical disciplines. The most familiar clinical manipulation of CSF content is associated with regional anesthesia and pain management by means of intrathecal administration of local anesthetics, opioids and other synthetic analgesics.[28–33] Of note, pharmacokinetics and pharmacodynamics of intrathecal drug administration is still incompletely understood (and in some instances relatively unpredictable) probably due to the complexity of CSF flow dynamics and outflow pathways eluded to in Quincke's studies, as well as many other more recent CSF studies.[34,35] For example, a very new discovery pertains to the real time demonstration in the live human

brain (by MRI) that CSF circulation (at least in the ventricular spaces) is regulated by inspiratory force and much less by cardiac pulsation.[11]

Other more rare and invasive clinical procedures pertaining to CSF include CSF filtration,[36–39] designed to modulate the intrathecal immune response in neuroinflammatory disorders like Guillain–Barré syndrome.[39] CSF filtration has also been used successfully in therapy resistant depression and schizophrenia.[40,41] The relative success of using CSF filtration in treatment of psychiatric disease, neuroinflammatory disorders and chronic pain syndromes is based on the concept that CSF carries and transport antigens, not only centrally, but also along cranial and peripheral nerves; and the antigens triggers an immune response clinically expressed as mild `encephalitis' or pain and/or may be involved in pathophysiology by peripheral nerve-CSF signaling interactions.[42,43] The outflow pathways of CSF that are implicated in mediating the immunological CSN disease process are perfectly described in Quincke's study.[1] Quinke characterizes in detail the CSF outflow (via cinnabar deposits) along cranial nerves, intercostal nerves, lumbar and sacral nerves. The clinical potential importance of the CSF outflow pathway for mediating disease has been highlighted and conceptualized in the `peripheral CSF outflow pathway' (PCOP) hypothesis,[42] which links the CSF outflow pathways along peripheral and cranial nerves directly to the ``outside'' via the lymphatic system.

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