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THE RE-DISCOVERY OF DURAL (MENINGEAL) LYMPHATICS: AMNESIA OR AMBITION?

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ABSTRACT

In 2015 the discovery of meningeal (dural) lymphatics was announced to much fanfare. The journal Science *named this the second most important discovery of the year! Yet, they had actually been well described two and a quarter centuries earlier, in Italy, England and Holland. However, there was controversy about their existence because of the difficulties in studying them, also addressed two and a quarter centuries earlier. Their study had generated a very large literature and they were "textbook" knowledge. The reasons for this neglect are discussed emphasizing the current scientific milieu and the changing modes of evaluating scientists.*

Keywords: history of meningeal/dural lymphatics, glialymphatics, scientific ambition, pursuit of publications v.s. knowledge

In 2015 Aspelund et al (1) announced in *Nature* and Louveau, et al (2) announced in the *Journal of Experimental Medicine*, the discovery of meningeal lymphatics. The journal *Science* described this "discovery" as the second most important advance in the preceding year. However, meningeal lymphatics had first been described by Mascagni in 1787 (3). When Professors Földi, husband and wife and authors of the major textbook on lymphatics and Marlys Witte, past *president* of the International Society of Lymphology, wrote a letter pointing out this much earlier discovery and the intervening numerous studies of these lymphatics (4), *Science* declined to publish it in an issue of *Science* although they did post it online. An historical rebuttal had already appeared in the *Journal of Anatomy* (5). This neglect of a long-standing scientific literature (a "textbook" fact, beautifully illustrated in Földi and Földi, 2006, p. 38) (6) by many of the current investigators of what is now termed the "glialymphatics" needs explaining. The review of the neglect presents previously unnoted descriptions of meningeal lymphatics from more than two centuries ago, a brief review of the intervening history of studies of meningeal lymphatics, which has been well covered by others, and explores possible reasons for the neglect.

Abbreviated History of Dural Lymphatics

Authors of both the *Nature* and the *Journal of Experimental Medicine* articles acknowledged their failures to report previous discoveries of the dural lymphatics but in very different ways. Jonathan Kipnis, senior author of the paper in *Nature*, collaborated with others, including Jan van Gijn, a neurologist turned historian, in an article emphasizing Mascagni's discovery of dural lymphatics in 1787 (7). Only seven further publications are cited as other confirmations in the intervening 2 and a quarter centuries. There is no mention of the Földi's who have published extensively on the meningeal lymphatics (8-13) or their

textbook (6). On the other hand, Stephen Proulx, one of the authors of the *Journal of Experimental Medicine* article, has written a massive review of the historical and contemporary evidence for their existence, with 263 references, (many of them, however, to the cerebral-spinal fluid circulation, which is only part of the story) (14). His history also starts with Mascagni but provides several dozen further confirmations, including Földi's.

Besides Mascagni (3), William Cruikshank (15) in London was studying meningeal lymphatics (which he called "absorbents") towards the end of the 18th Century (15).

William Cumberland Cruikshank (1745-1800) was trained in Edinburgh but went to London and was an assistant of William Hunter (16). His most famous patient was Samuel Johnson. He was elected to the Royal Society in 1797. This volume of Cruikshank is the 2nd Ed. The first edition was in 1786 (16) which has not been available to examine to see if this description of meningeal lymphatics was first presented there.)

His discovery is almost certainly independent of Mascagni's (and may precede it) (16; he gives an apt description of the troubles encountered in the study of them in cadavers:

> The brain is viscus which so soon becomes putrid, that we cannot trust to the gradual extrication of vapor, as in other parts, for the discovering of these vessels, and they must also be so tender, as every part of the brain is, that they will hardly bear a column of quicksilver without presently bursting: – in firmer brains, and on some more fortunate occasion, it may prove otherwise – (15, p. 204).

He goes on to describe his findings in regards to meningeal lymphatics: There is the appearance of absorbents on the surface of the brain, between the tunica arachnoides and pia mater. Ruysch was first who observed this, he has given an engraving of them, inflated with air, and calls them vasa pseudo-lymphatica.

Frederik Ruysch (1638-1731) was a Dutch botanist and anatomist who first described lymphatic valves (17). He also correctly described the direction of lymphatic flow. He developed special preservative techniques (air or mercury sulfide and glycerol injection) that allowed him to find many semilunar lymphatic valves, the results of which were published in 1744 in the book Dilucidatio valvularum in vasis lymphaticis et lacteis (19).

> I have repeatedly injected them with quicksilver; but, as they appear to me too large, and to be destitute of valves, the great characteristic of absorbent vessels, and as I have not traced them to the glands, I have not yet determined what they are (19).

However, he goes on the conclude that the brain has absorbents, I am perfectly certain; for I have seen absorbent glands in the foramen caroticum [carotid foramen], which, from this situation, could not belong to any vessels but such as were coming down from the brain. The glands of the neck swell in some diseases of the brain (19).

A finding Proulx (14) attributes to Schwalbe (20).

Thus, Cruikshank had described meningeal lymphatics as had Mascagni but, because of the lack of valves, did not label them as such. His citation of Tuysch (1744) adds an even earlier Dutch example (15).

It is not that the many intervening studies of the dural lymphatics agreed as to whether they existed or how they functioned (7) particularly pick out Retzius's denial of their existence (1875) as inhibiting the acceptance of the discovery (7). Perhaps Retzius's negative view was more powerful in the German sphere of influence. During the first half of the 20th Century, the French were equivocal about their existence. The textbook *The Lymphatics* by Delamere, Poirier, and Cuneo, consisting of two parts, the first on the general lymphatics by Delamere and the second on the description in different parts of the body, denies their existence (21). "Fohmann, Mascagni, Fr. Arnold have, however, described and figured meningeal lymphatics.

They have clearly been deceived." On the other hand, the French anatomist Rouvière concedes that they may exist in 1932: "It is also possible, like the plate 27 of Mascagni appears to demonstrate, that the lymphatics issue from this network following the large blood vessels in order to leave the cranial and spinal cavities" (21, author's translation).

In the first half of the 20th century, at least in anglophone countries, it seems that the weight of the argument was in favor of the existence of the dura lymphatics. The studies of Weed (22,23) always mention lymphatic drainage of CSF but he does not credit this to lymphatics in the dura mater. In fact, his view was: This lymphatic absorption is wholly indirect; the fluid reaches the true lymphatic vessel only outside of the dura and of the cranium. The mechanism for this drainage is by way of perineural spaces around the spinal nerves to a slight extent but chiefly around certain of the cranial nerves-particularly the olfactory branches (24).

However, Weed describes a series of leptomeningeal channels with outer surfaces of low cuboidal mesothelium and the inner surface being the lining of the pia mater. It is the lack of valves that keeps him from considering these as lymphatic vessels. A better example is that by Drinker and Yoffey on the physiology of lymphatics accepting their existence (25). "Lymphatics, not impressive in number or size, leave the cranium with the blood vessels" (25). In the second half of the 20th century, the multiple studies of the Földis have already been mentioned. Another particularly convincing study in 1980's is that of Andres et al (26).

The reasons for these controversies were multiple. Most of the investigators were aware that dyes injected into the brain rapidly appeared in the cervical lymph nodes. Many of the arguments concerned the substances injected, the isotonicity, or lack of it, of the fluids, the pressures involved, the mode of detecting dyes, etc. – problems which Cruikshank had in part anticipated. It was Földi that showed (in the obverse of Cruikshank's description of cervical node swelling with some diseases of the brain) that ligating the cervical lymphatics resulted in cerebral edema and behavior changes (9).

Continued Neglect of this History by Current Researchers

Despite the "apologetic" historical articles, a lack of acknowledgments of highly relevant previous work continues. In a recent paper from the Washington University School of Medicine St. Louis (Kipnis's group), complete amnesia for the previous work occurs: "more recently, bona fide lymphatic vasculature has been identified in the dura mater" with mostly post 2014 references (27). Only 8 of the 53 references in the article are pre-2015 and, of these, only 4 relate to fluid flow. This thorough article beautifully demonstrates discontinuities where bridging veins cross the arachnoid barrier which they name "arachnoid cuff exit[s]". However, the large literature on other modes of exit is not discussed. Particularly lacking is Li et al (28) scanning electron microscopic finding of meningeal stomata providing lymph drainage-this paper was 1 of the 7 mentioned in historical "apology" (7), with Kipnis as one of the co-authors) had cited as important for the study of meningeal lymphatics in the years between Mascagni and present! Such stomata provide the pathway for lymphatic drainage of the plural, peritoneal, and peri-cardial cavities (30).

Why Was this History Neglected?

We are faced with a need to understand, the neglect of a large body of knowledge, readily accessed through online searches. Using Google Scholar and the search term "meningeal lymphatics" brings up only 4 displayed references prior to 2015 but add the phrase "functional aspects" it becomes many hundreds. If one uses PubMed, limiting the searches to pre-2015, "meningeal lymphatics" pulls up 1325 references of which 4 are to Földi's work. If one uses the term "dural lymphatics" there are only 46 prior to 2015 which, while not including Földi, et al work, do include specific references to dural lymphatics. Google Scholar has many more "hits" than

PubMed (about 10-fold) but displays a much smaller number while PubMed displays all the "hits" which could make finding the relevant ones harder.

In the first place, it is surprising that the reviewers of these articles for their respective journals did not point out the negligence. One must assume that the reviewers were molecular biologists with poor backgrounds in anatomy and physiology, and not physicians, or others, with wider biological backgrounds. Still, there is a necessity to understand why the authors themselves neglect to mention this background to their research which they certainly must have known because it is so easily found.

One aspect is the increased competitiveness of science. Fewer individuals are receiving a higher percentage of the available research money. For instance, although NIH funding rates were on the order of 20% of submitted grants 30 years ago, now it is more like 10-12%, varying greatly by institute. However, the funding rates reported by NIH are now based on reviewed grants and not total of grants received. Since about half of the grants are triaged out, the figures are really about half of what is reported. A study of Australian researchers revealed an average of 34 days effort per proposal (31). Many scientists report spending up to half of their time writing multiple grant applications (Personal conversations with multiple scientists at this and other institutions.) While the penalties for lying on applications is severe, neglecting relevant previous work is not hurtful to an application unless the grant reviewer, unlike the manuscript reviewer, is not ignorant of it. Thus, since there is a large emphasis on novelty for funding, neglecting past work has an advantage if you can get away with it.

Is it harmful not to acknowledge previous work? Not at all! If there is controversy, all the better, since it will lead to more citations and for scientists, citations are the "coin of the realm". It is hard to evaluate the individual contributions when there are many co-authors of a paper. Physicists frequently just list the authors alphabetically, which may be more than 100 for a paper from a place like the Large Hadron Collider. In some fields, the authors are listed in order of their perceived contribution. Currently, in biomedical research, "if you can't be first author, you want to be last, and if you can't be first or last, you want to be second or next to last". Thus, many universities, granting agencies, and scientists closely follow the individual's H (Hirsch) number (32). This is the largest number of authored or co-authored papers by the individual which have that number of citations.

There is much written about changing values in science. One change is in the importance of publications. Once upon a time; e.g. early years of the *Proceedings of the Royal Society, London*; a publication was Letter to report an observation or experiment in order to elicit comments, countering experiments or facts, other interpretations, etc. The publication was not the goal, new knowledge was the goal. Now the publication has become the goal.

Bruno Latour, an anthropologist embedded in the laboratory of future Nobel Laurate, Guillemin, studied the function of the lab objectively, a case study of Hagstom's (33) "Production of Culture I Science". He found that the purpose of the laboratory was to produce publications (34; it is relevant that the co-author, Steve Woolgar, is a philosopher of science. The title of the book is not "the construction of a publication" as would befit the conclusion, echoes that of Fleck's (35) "Construction and Development of a Scientific Fact"). Treating the laboratory as an ethnographer would a new society he/she entered, he found that the equipment, technicians, etc. were all dedicated to the purpose of generating publications – this was the "product" desired. He found that the postdoctoral fellows, graduate students, and the head of the lab spent a large proportion of their time writing, editing, talking about, and publishing them. The facts accumulated were only intermediaries to the publication.

A number of authors have discussed the changes in biomedical science that affect the role of the scientist (36,37). Perhaps the most relevant one concerning "forgetfulness" is the greatly increased competition among scientists. Freeman, (37) have compared to a tour-

nament where one or a few individuals win big prizes and the rest go without. Other major factors include the greatly expanded array of techniques used and the greatly increased amounts of data generated – all of which led to a need for collaboration as no one scientist can master all the techniques and methods of data processing (bioinformatics). A greater amount of technical training is required. and the scientist is less likely to have a broad knowledge of the liberal arts as well-a problem C. P. Snow brought attention to in 1959 (38). This includes a lack of knowledge of history in general and science in particular. Many of these changes are all part of the molecularization of biomedical research-a much discussed topic (39-41).

Perhaps these changes could be classified as "lymphology agnosticism", following Campbell et al's (42) "histology agnosticism". These authors followed the molecularization of oncology by involvement in many meetings of a tumor board and interviews with oncologists. In this case study, the replacement of classical anatomy and histology of tumors by the molecular characterization of tumor driving mutations was documented. The lack of historical perspective by these oncologists was not discussed but, perhaps, can be inferred. One can argue that the recent developments in glialymphatic research have similarly been the molecularization of the field with agnosticism for its earlier modes of study, i.e., the history of the field. While this analysis concerns "lymphology agnosticism", it is generally true of the hubris of many of the current "biomolecular" re-searchers. With the vast array of new techniques such as cell sorting, single cell transcriptions and localizations, many new visualization techniques including 2 photon and cryoelectron microscopy, etc., a past history of anatomy, histology, physiological measurements of fluid pressure and flow, etc., no longer seems relevant to them and can be denied.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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