On the Historical Succession of Vessel-Based Therapies in the Treatment of Multiple Sclerosis

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Abstract

Since 2009, the (CCSVI) model of multiple sclerosis has drawn much attention, and the associated surgical ‘venoplasty’ interventions have often been advertised as a novel idea. In fact, it is a new incarnation of various vessel-based therapies attempted for multiple sclerosis in the past, dating back to the 1930s, when Tracy Jackson Putnam (1894–1975) attempted pharmacological anticoagulation. This was followed in the 1940s by Richard M. Brickner’s (1896–1959) studies of vasodilatory drugs, which further inspired trials of sympathectomy and ganglionectomy. In the 1950s, Ilya Mark Scheinker (1902–1954) studied vasopressor therapy, while Roy Laver Swank (1909–2008) investigated the effects of a low saturated fat diet in his patients. This paper discusses the longer history of these therapeutic endeavours and the aetiological theories that inspired them.

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Introduction

Multiple sclerosis (MS) is a chronic, debilitating, incurable demyelinating disease of the central nervous system (CNS), affecting close to 2.5 million people worldwide [1]. MS is currently conceived as resulting from an autoimmune mechanism, but various potentially interacting genetic, environmental, nutritional, and infectious factors have been implicated in its aetiology [2, 3]. In 2009, Italian vascular surgeon Paolo Zamboni (b. 1957) drew the attention of the research world and the international media, when proposing that MS was caused by blockages in the jugular and azygos veins [4]. Zamboni and his team presented evidence from an unblinded study of venous abnormalities in MS patients, diagnosed by ultrasound venography, which were apparently absent in control individuals, and hypothesized that the consequent abnormal flow promotes inflammation at the blood-brain barrier, leading to CNS demyelination and neurodegeneration [5]. This pathophysiological theory of chronic cerebrospinal venous insufficiency (CCSVI) and the ‘venoplasty’ procedures (using angioplasty techniques to open up veins) inspired by it [6], were praised by many in the media and lay organizations as revolutionary breakthroughs [7]. In the medical literature, however,

Zamboni's publications led to highly polarized commentaries. Several independent clinical imaging studies presented conflicting results ranging from pointed critiques of CCSVI's existence to suggestions that venous flow abnormalities may be more common in MS patients [8–12].

Much of the ongoing discussion features the idea that the CCSVI theory-based vascular interventions represent a completely novel concept. However, a close historical examination of the medical literature reveals that treatments based on hypothesized vascular aetiologies of MS had been investigated in numerous ways as far back as the 1930s. In fact, a potential vascular aetiology for MS had been hypothesized already in the late 19th century by Georg Eduard von Rindfleisch (1836–1908), a student of Rudolph Carl Virchow (1821–1902). In 1863, Rindfleisch noted the consistent location of a blood vessel in the centre of MS plaques with perivascular inflammatory infiltrations and fatty neuroglial changes, which he postulated may be originating from changes in the individual blood vessels [13].

Only a small minority of authors have briefly alluded to these historical publications [14, 15], such as American public health scholar Colin Talley (b. 1963) who suggested that this enthusiasm towards vascular therapies fed into the familiar concept of blood manipulation in disease treatment:

Whether it was Tracy Jackson Putnam's blood thinning, or the increased blood flow from vasodilators, or the prevention of blood sludging through Roy Laver Swank's low-fat diet, these strategies made sense, not only in the then current theories of pathogenesis but also because of the powerful roots of these practices in the ancient traditional panoply of Western healing [16].

Nonetheless, a comprehensive academic and critical assessment of these investigations remains to be undertaken, which would be key to providing a firm basis in the enduring dialogue on the multi-factorial aetiology of this complex disease. Using journal articles and reviews, this paper discusses the history of vessel-based therapeutic endeavours in clinical and pathological MS research.

Pharmacological Anticoagulation

In the early 1930s, experiments by Tracy Jackson Putnam (1894–1975) – co-discoverer of the anti-epileptic activity of Dilantin [17] – suggested that symptoms similar to MS could be produced through modifications of the blood supply to the brain [18, 19]. Putnam's investi-

gations were motivated by cases of acute demyelination, termed disseminated encephalomyelitis [20], and reported as the effects of acute infections like vaccinia and measles, and experimentally produced in dogs using tetanus toxin [21], *Aspergillus* spores [22], and carbon monoxide poisoning [23]. In 1931, Putnam's group conducted a series of experiments that attempted to obtain demyelination phenomena by injecting emboli such as a cod-liver oil emulsion into the carotid arteries of cats and dogs [24]. Putnam hypothesized that the 'viscous, cohesive globules would obstruct long stretches of rather large vessels, as do the thrombi in the degenerated areas after carbon monoxide poisoning' [24]. He found that his oil-based emboli could experimentally elicit perivascular infiltrations and demyelination in the animals, which he interpreted as resembling MS pathologies. Noting that many of his arterial emboli had given unsatisfactory imitations of encephalomyelitis, forming areas of tissue destruction and cysts, Putnam developed the following conviction:

If vascular obstruction is the cause of destruction of myelin and proliferation of glia without destruction of the axis cylinders, it must be an obstruction chiefly on the venous side of the capillary bed [25].

To test this hypothesis, he injected an oil-based mass into the longitudinal sinus of 14 dogs such that it would run upstream into the cerebral veins and obstruct them (fig. 1). In 10 animals euthanized over the course of several months, Putnam observed what he assumed to be the successive stages of development of a characteristic lesion – perivascular infiltration, then demyelination with preservation of axis cylinders, and localized glial proliferation. While Putnam acknowledged that the results were not as pronounced as those he had previously seen using tetanus toxin [26] – particularly in that the plaques were not disseminated through the spinal cord, nor showed complete demyelination or sharp borders – he interpreted his results as a chain of pathological events preceding plaque formation and resulting from circulatory disturbance.

Putnam highlighted the histological association of disseminated encephalomyelitis with cerebral small-vessel thrombi [27], and phenomenological similarities between acute disseminated encephalomyelitis and MS [28]. He postulated that encephalomyelitis may be the acute stage in the pathological development towards chronic relapsing MS [29]. He studied tissue samples from cases of MS and encephalomyelitis from various laboratories, finding

Fig. 1. A diagram of the experimental procedure, the injection of oil (shown in solid black) into the longitudinal sinus of a dog between the ligatures. The oil is forced against the bloodstream into the pial and then into the cerebral veins. Perhaps owing to the richer collateral circulation in the cortex, a lesion is produced only in the white matter. Only the venous channels are shown. From Putnam's *Studies in Multiple Sclerosis*. Arch Neurol Psychiatry, 1935.

that visible plaques tended to surround gnarled, tortuous, and engorged veins, while areas of fresh degeneration often appeared in proximity to venous thrombi (fig. 2) [30, 31]. He also noted the frequent presence of fibrous plugs and endothelial cells which occluded vessels, as well as iron-containing pigment in the vessels' penumbras. Focussing more on the occlusive changes in the vessels than the engorgement seen in acute lesions, Putnam argued that his findings reflected a primary thrombotic aetiology for MS based on hypercoagulability:

There is no indication that the primary cause of the thrombosis exists in the wall of the vessel. It appears that it should exist therefore in the circulating blood [31].

Following the development of the quantitative prothrombin time test as a measure of the extrinsic coagulation pathway by the American physician and chemist Armand James Quick (1894–1978) in 1935 [32], coagulation studies were also attempted in MS patients, although without conclusive analyses [33, 34]. Nonetheless, after 1939, with the availability of anticoagulants,

Putnam used a variety of these drugs to study his conception of MS as being caused by vascular occlusion due to hypercoagulability.

However, when German neurologist Hans Reese (1891–1973) treated 28 patients with Dicoumerol (Synparin), he found only a subjective improvement and no objective changes in disease status [35]. Putnam countered that Reese's doses had been too low, enabling fluctuations in the prothrombin level, and permitting attacks to occur when the level was low. Putnam himself reported 74 cases of MS that had been treated with Dicoumerol [36, 37] and discussed them at the 1948 conference of the Association for Research in Nervous and Mental Disease in New York [38]. Although 31 patients dropped out of the study, Putnam observed that patients with more acute relapses appeared to benefit from treatment, whereas those with progressive MS either remained static or continued to deteriorate. Putnam provided an extensive statistical study of 3,797 attacks in 810 patients over an average follow-up period of 9.7 years that appeared to confirm the effectiveness of Dicoumerol in preventing attacks in relapsing cases. Notwithstanding,

Fig. 2. Representation of a typical MS plaque originally reconstructed as a glass-plate model, in the form of a line drawing. Blood vessels are represented as hollow tubes, except where the thrombus occurs, which is represented in black with white shading. Dense old plaques are shown in punctate stippling, with the convention that larger dots represent more superficial plates of glass. Fresh areas of degeneration (without fibrous gliosis) are shown by annular stippling, heavier rings marking the more superficial layers. Notice that the freshest plaque appears about a vein between a fresh thrombus and a dense, congested old plaque. From Putnam and Adler's 'Vascular architecture of the lesions of multiple sclerosis'. *Arch Neurol Psychiatry*, 1937.

patients with relapsing MS would already be more likely to experience symptom-relieving periods of remission as per the natural history of their disease, and attacks would be expected to decrease over time. Chicago-based neurologist George A. Schumacher (1912–2008) astutely noted that the average interval between attacks prior to treatment was longer than the average period of observation for each patient [39]. Other authors highlighted the danger of spontaneous haemorrhage posed by anticoagulation, warning that this outweighed any therapeutic benefits [40].

In 1953, a review of the course of 105 attacks of MS in 60 patients, 35 of whom were treated with anticoagulants, was published by Danish neurologist Paul Thygesen (1914–1999) in Copenhagen, with a simultaneous study by Torben Fog (1912–1987) [41]. The patients had been treated with Dicoumerol for an average of 11 months, and

the reviews found that therapy altered neither the number of attacks nor the course of the disease. Whereas Putnam did not publicly waver in his endorsement of anticoagulation as a useful therapy of MS until his death, Colin Talley noted that Putnam's use of Dicoumarin in his own practice became more cautious upon completion of these trials [16].

Vasodilatory Drug Therapy

The American neurologist Richard M. Brickner (1896–1959), who reviewed Putnam's work as well as other efforts at experimental demyelination [42], noted an inherent problem in the approach of inducing changes in animals by using materials of non-human origin:

It can indeed be said that pictures resembling multiple sclerosis have been produced in animals, but the disease itself has not. This will be accomplished only when patchy demyelination has been caused by the injection into animals of material obtained from human patients [42].

Therefore, Brickner [43] began working with blood samples from MS patients in 1929, looking for evidence of a lipolytic agent that might be affecting nerve myelination. He immersed spinal cord segments from rats in vitro in the plasma of MS patients and healthy controls for 24 h, observing that blood from MS patients had a demyelinating action. His observations were confirmed by internist Arthur Weil (1887–1969) at Yale University [44]. To further study this apparent demyelinating action, Brickner [45, 46] and his team conducted several experiments mixing serum from MS patients and controls in vitro with lipid lecithin and certain esters, while measuring the degree to which the lipid was broken down by the serum after a 24-hour incubation. Although it emerged that there was a constant difference in lipid breakdown between MS serum samples and controls, the results were not sufficiently clear to reliably identify a given case as MS. Nonetheless, Brickner attempted to integrate his own findings with Putnam's animal experiments by postulating that the apparent lipolytic material was modifying erythrocytes to precipitate coagulation:

It is not impossible that the lipolytic material with which Arthur Weil, Lathan Crandall (1850–1923), Ian Cherry (1905–1995) and I have been working is active not only on the myelin sheath but also on the erythrocytes. Conceivably, such erythrocytic alteration could lead to the formation of Putnam's thrombi [42].

Brickner's endorsement of a vascular aetiology for MS was strengthened by his investigations in the 1930s that reported a prompt reduction within minutes of neurological deficits in MS patients due to the action of vasodilative drugs. These substances included amyl nitrite, carbon dioxide, histamine diphosphate and hydergine, and all possessed the capacity to increase cerebral perfusion [47–53]. Brickner's preliminary findings were confirmed by others [54–56], while the phenomenon became termed pharmacological reduction of abnormality (PRA) within minutes. PRA was seen as further evidence of vascular insufficiency in the aetiology of MS, with Brickner remarking:

The hypothesis underlying these studies is that the effects of the drugs are associated with their vasodilating or sympathicolytic effects, or both [57].

In 1958, Brickner published a statistical study on PRA consisting of 4,458 observations in 116 patients with MS, for 311 diverse symptoms [57]. Brickner graded each patient's symptoms from 1 (within normal limits) to 5 (most severe abnormality). Each patient was asked to rest prone for 20 min to account for any effects of rest on the symptoms, and then the test drug was administered. Following this, the symptom would be re-graded periodically for an hour. The PRA phenomenon was considered as established if symptom improvement occurred (of at least one grade) and could be duplicated or objectively measured.

Onset of PRA, if it occurred, was typically visible between a few minutes and 1 h. Brickner's statistical analysis further suggested that the shorter the prior duration of a symptom had been, the more likely became the induction of PRA by one or more of the administered drugs. The phenomenon endured up to several days given a shorter prior symptom duration, as compared to only a few hours with longer prior durations. 57 symptoms in 36 patients also showed a remarkable persistence of PRA within four cycles of drug administrations, often showing a stepwise improvement with each administration. Recognizing that the natural history of relapse and remission in MS was a key confounding element in the study of therapeutic effects, Brickner compared his data with the incidence of spontaneous remissions in MS, as reported by the American neurologist John F. Kurtzke (b. 1926) [58] and noted that PRA occurred far more frequently than remissions. Brickner also noted that the most pronounced therapeutic effect was with prior duration ranges of 1 month to 1 year, whereas remissions could also account for improvements of symptoms with shorter prior durations. He argued that the promptness of onset of PRA suggested that it was unlikely to reflect spontaneous remissions, and that its experimental reproducibility ruled out a mere psychogenic effect of medication administration.

Along the same lines, Brickner [57] and his colleagues also studied the procainization of the stellate ganglion and the cervical sympathetic nerves. Some symptoms, ascribed to MS plaques, showed striking improvement when undergoing this procedure, which began with the onset of sympathetic paralysis. While Brickner's findings were intriguing and he began using vasodilators to treat MS [59], along with several contemporary neurologists, the validity of his methods did not go uncontested. In discussing therapeutic attempts in MS, Glasgow neurologist Archibald Douglas McAlpine (1890–1981) and his colleagues noted that there had

been no adequate control group in Brickner's trials and that these insufficiently accounted for the variability in relapse durations in MS [60].

Vasopressor Drug Therapy

In 1943, Russian neurologist Ilya Mark Scheinker (1902–1954) studied the histopathology of acute lesions of MS in 4 cases, and concluded that pronounced congestion and thrombosis of the small veins was one of their most characteristic microscopic features [61, 62]. Scheinker [63] presented 2 cases illustrating the morphology of vasoparalysis in the CNS – distension and engorgement of veins and capillaries associated with stasis in the bloodstream – which he viewed as a vessel reaction to acute neuronal damage due to vascular traumas or intoxication. Scheinker [64] presented a study of 250 MS patients of whom 61.6% reported increased fatigue of their skeletal muscles, and 53.6% showed evidence of low blood pressure during repeated measurements. He argued that these findings were “in harmony” with the precipitation of onset or exacerbation of MS by acute infections and injuries, frequently associated with lowered arterial blood pressure, and the frequent association of early CNS lesions with instances of vasoparalysis [65]. Scheinker also saw these results as being in keeping with the abnormally low cerebral blood flow that some authors had previously identified in MS patients [66], and with Putnam's observations of venous thrombi within some MS lesions. He integrated these observations into the following hypothesis:

Multiple sclerosis lesions develop as the result of recurrent episodes of focal disturbance of nutrition by vasoparalytic reactions of the small veins and capillaries of the central nervous system [64].

In the same paper, Scheinker proposed various treatments aimed at the elevation of blood pressure and stimulation of cerebral circulation to counteract the vasoparalytic phenomena that he hypothesized were causing stasis, sludging, and eventually thrombosis of the small vessels in MS. These treatments included daily administration of vasopressor drugs – such as pavidin hydrobromide, desoxyn hydrochloride, and ephedrine sulfate – with the dosage adequacy being monitored by repeated blood pressure readings. Scheinker also recommended calcium and vitamin B supplementation to alleviate assumed focal nutritional disturbances through vascular

alterations, as well as muscle ‘re-education’ by applying exercises along with psychotherapy. He further presented an evaluation of the therapeutic results in 237 MS cases based on a follow-up period of 1–4 years, wherein 157 patients (66.3%) showed either complete or partial recovery, while 57 patients improved only slightly without evidence of neurological changes and 24 were complete failures. In the positive cases, the degree of improvement was reported to be closely related to increases in arterial blood pressure and flow. Scheinker argued that since only 96 of his patients seemed to display remissible phenomena, and of the other 141 showing evidence of progression 85 showed complete or partial recovery, his findings were less likely to reflect only spontaneous remissions. However, the absence of a control group meant that remissions could not be adequately accounted for. Scheinker acknowledged this major limitation:

Because of the frequent incidence of spontaneous remissions inherent in the nature of the disease, any and every beneficial result – or, rather, tendency to improvement or alleviation – must be appraised, not without a just proportion of skepticism [64].

Other therapies applied by Scheinker [67] to alleviate putative states of vasoparalysis included caffeine, alcohol, and adrenal cortex extract, yet the broader interest in his treatments waned, in part due to the poor evidence and documentation level in many of his case reports [14].

The Swank Diet

In 1950, the American neurologist Roy Laver Swank (1908–2008) proposed dietary factors as aetiological contributors to MS, a view which he related to the effect of high fat intake on vascular flow mechanisms [68]. He assessed the incidence of MS between 1935 and 1948 in 18 counties in Norway and found considerable variation between farming-dairying areas and fishing districts, as well as between inland and coastal areas. He then assessed the preferred diets in these areas through 7-day recordings of food intake, and was convinced that there existed a strong association between MS risks and butter fat (increased risk) and fish consumption (decreased risk) [69]. Presuming that high dairy-related fat contributed to MS risk through impaired vascular flows in the individuals, Swank advocated for consumption of a low animal fat diet as a means of altering blood lipids and coagulation [70], and demonstrated the positive influences

of such a diet on the lipid levels in MS patients [71]. This special diet became known as the Swank Diet, and in his 1987 Multiple Sclerosis Diet Book, Swank further elaborated on his conception of the aetiology of MS, closely allied with Putnam's and Brickner's foregoing theories:

...the frequent location of the pathological lesions ...in the brain and spinal cord surrounding small venous channels, suggest that the small blood vessels (microcirculation), which includes the arterioles, capillaries and venules, play a role in the genesis of this disease [72].

Swank argued that a diet high in saturated fat would lead to these small vessel obstructions, and the consequent decrease in blood flow would contribute to the development and progression of MS:

A search for a mechanism that could cause both an interference with, and slowing down of, the cerebral... blood flow, and breakdown of the blood-brain barrier in the central nervous system, leads to a consideration of the circulatory changes that have been observed in a number of species, including man, following large saturated fat meals [72].

Over a period of 50 years, during which he published several papers on the subject, Swank reported less progression of symptoms in MS patients who followed his dietary suggestions, when compared with foregoing published reports that served as historical controls [73–78]. In 1990, Swank discussed the results of his follow-up in 144 MS patients prescribed a low-fat diet for 34 years, classifying them into 'good dieters' (72 individuals) – who complied well with the diet and consumed no more than 20 g of fat per day – and 'poor dieters' (72 individuals), who consumed more than this amount daily [79]. Swank reported that for each category of neurological disability based on Kurtzke's Expanded Disability Status Scale (minimum, moderate, and severe), the 'good dieters' showed significantly less deterioration and much lower death rates than the 'poor dieters'. In analysing his findings, he inferred that in addition to strict adherence to the diet, implementing the treatment in cases with minimum disability predicted the best results:

Our findings indicate that a diet of ≤ 20 g saturated fat daily was best able to keep patients with MS ambulant and working when it was started before the patients' normal abilities and activities were restricted – under these circumstances about 95% of MS patients remained only mildly disabled for approximately 30 years. Adherence to the diet is important. Defaulting from the diet even after 5–10 years was, in almost all cases, followed by reactivation of the disease [79].

However, the fact that the treatment outcomes in Swank's patients were not compared with a randomized control group, led to continuous criticisms in the neurological community regarding the validity of his findings [80]. In addition, the absence of any blinding in the follow-up assessments even in the decades after such practice became the norm, did not help alleviate criticism of the diet's purported efficacy [81]. While Swank sought primarily to decrease saturated-fat intake in MS patients, other researchers sought also to increase unsaturated-fat levels in these patients, culminating in three double-blind randomized clinical trials of linoleic acid supplementation in the 1970s [82–84]. However, the results of these trials were not convincing for any impact on clinical deterioration or relapse frequency, although a combined meta-analysis consisting of neurological assessments over 2.5 years for 87 treated and 85 control patients, found a slower progression of disability and less severe and/or shorter relapses in the mildly disabled patients [85].

Surgical Interventions

In addition to dietary and pharmacological interventions, surgical procedures were also historically attempted in MS patients, aiming to modify the vessels, which by far preceded Zamboni's 'venoplasty' procedures [4]. These procedures were motivated by Brickner's use of sympathicolytic vasodilatory drugs and the emphasis placed on vascular factors by Putnam and his supporters. In an effort to improve the circulation to the brain, a series of patients were subjected to sympathectomy and ganglionectomy in the 1930s [86, 87], and a detailed report was subsequently published in 1938 on 10 patients, 6–14 months after they had received bilateral surgeries [88]. Given that the vascularization of the brain and spinal cord depends primarily on the carotid and vertebral arteries, which are innervated by the sympathetic nervous system, any vascular spasm could theoretically be alleviated through the surgical removal of these nerves. When comparing the intensity of MS symptoms before and after the procedures, the researchers reported only positive improvements. A detailed single patient description was provided in this paper, which reported a marked deterioration in this individual over about a decade prior to undergoing the procedure, after which he apparently showed an arrest in the progression of his symptoms and re-establishment of some lost functions [88]. Needless to say, these

invasive surgical interventions were not without serious complications. Two fatalities occurred – one embolism and one haemorrhage post-operatively. Owing to the absence of sympathetic stimulation from the stellate ganglion's cardiac accelerator fibres, the heart was unable to respond with acceleration to muscular effort, such that the patients risked profound weakness or collapse with exertion. Transient incontinence over 48 h was also seen in one-third of cases [88]. Although no controls were used, the physicians seemed confident that the changes were not due to spontaneous improvement in the natural course of the disease:

It would be premature to draw final conclusions regarding the ultimate possibilities of this treatment. Nonetheless, we feel encouraged because in the majority of cases a remarkable degree of amelioration has taken place. It is not possible to attribute all the improvement to spontaneous changes in the course of the disease. All of the patients were in an advancing stage of the disease [88].

Interest in vascular surgical interventions in MS began to emerge again in the 1970s when the Algerian-French neurosurgeon José Aboulker (1920–2009) and his colleagues in Paris began to treat paraplegic and quadriplegic patients surgically by trying to relieve functional 'venous obstructions' [89]. During this period, Aboulker and his team documented various abnormalities – stenoses, compressions and thromboses – in the major pathways of the caval and azygos venous system in hundreds of patients with neurological abnormalities, by means of a newly developed cavospinal phlebographic surgical procedure [90]. They inferred that these abnormalities were causing chronic venous stasis in the intraspinal venous plexuses, leading to increased intravascular pressure and consequent myelopathic syndromes [91].

Aboulker's procedures since the 1970s were further referred to by Paolo Zamboni and colleagues about three decades later [5], and they have also recently received considerable attention in patient forums as prior evidence supporting the CCSVI theory [92]. Nonetheless, from a historiographical perspective it is critical to note that the neurosurgical work of Aboulker's group in Paris had only little to do with MS, since the relevant patients did not have clinical MS diagnoses. In fact, the patient pool had been classified as myelopathies of unknown origin or 'unexplained paraplegias and tetraplegias' [90], and the individual pathologies were exclusively seen in the spinal cord and related directly to the venous abnormalities found, in contrast to the disseminated disease pattern seen in MS.

Discussion

This historical paper has provided an explorative account of therapeutic investigations based on hypothesized vascular aetiologies for MS since the 1930s. In the contemporary international research literature of the 20th century, we have identified various forms of precursor theories and treatments that have targeted the cerebral and spinal blood vessels for their aetiological role in the disease. These interventions ranged from lifestyle modification such as the Swank Diet, to pharmacological attempts as in Putnam's anticoagulant therapy, Brickner's vasodilators, or Scheinker's vasopressors along with surgical therapies like sympathectomy and ganglionectomy.

In examining the pathological theories which motivated the successive historical therapies, one finds a common thread of concerns focused on understanding and influencing vascular blood flow. However, there was also a considerable heterogeneity in how contemporary researchers envisioned the development of abnormalities in MS, which in turn gave rise to varied therapeutic approaches. Putnam's experimentation with artificial venous emboli in animals, for example, influenced him to view venous thrombi as contributing to vascular congestion in MS and thereby contributing to the development of inflammatory demyelination. Consequently, his therapeutic attempt remained focussed on anticoagulation to counter the assumed hypercoagulability. Conversely, Brickner's observations of lipolytic activity in the blood apparently triggering demyelination in MS patients led him to assume that thrombi were involved in the pathogenesis of MS by way of curious modifications in erythrocytic activity through the lipolytic agent. Brickner's therapeutic focus was not directed towards either the thrombi or this apparent lipase, but was instead motivated by the interesting phenomenon of PRA seen in vasodilatory and sympathicolytic drug activity. In principle, vasodilators would help relieve any congestion in the vessels and promote greater blood flow. Brickner's work in turn, motivated surgeons to attempt operative procedures of sympathectomy and ganglionectomy in MS with the physiological hope to reperfuse damaged nervous tissue by relieving any vasospasm impeding flow.

Scheinker likewise agreed with Putnam in regarding venous thrombi as aetiologically relevant in the disease causation of MS, based on his own pathological and experimental studies. In this regard, Scheinker's use of vasopressors – which clamped down on the vessels instead

of opening them up – seems counter-intuitive from a modern perspective, when considering the goal of improving vascular flow, and diametrically opposed to Brickner's vasodilatory therapies. However, in hindsight, Scheinker's approach was ultimately driven by his observations of instances of vasoparalysis in certain CNS lesions and low blood pressure readings in the majority of his MS patients. This led him to use vasopressor drugs to elevate the blood pressure and prevent stasis, which he interpreted as causing thrombus formation. On the other hand, while Swank also agreed that small-vessel obstructions could contribute to the pathogenesis of MS, his epidemiological studies of different diet patterns and MS incidence distribution led him to understand that vascular obstruction phenomena essentially arose from atherosclerotic disease, propagated by high dietary fat intake.

When examining the work of these MS researchers, there are several key influences and biases that become apparent. In pursuing his theory of cerebral venous thrombosis in MS, Putnam, for example, did not analyse key contradictory findings in his pathological studies further, such as the engorgement or proliferation of the blood vessels in the absence of any lesion-associated thrombosis. Conversely, he was eager to accept the encephalomyelitic lesions that he produced experimentally in his animal subjects as representative of the pathological features of MS. This is even more interesting, because of his own admission that the changes were not clearly representative of well-demarcated demyelinating and disseminated lesions. Furthermore, Brickner overzealously connected his findings about lipolytic activity in the blood of MS patients with Putnam's thrombi. When promoting this view, however, he had only scarce experimental or observational evidence of the relationship between lipolytic agents in the serum of MS patients and the incidence of venous thrombi. Scheinker, in addition, leapt to comparing low blood pressure readings in many of his MS patients with cases of stasis and vasoparalysis that he had studied in patients with cerebral oedema and venous trauma. Finally, although Swank did find an interesting association between high dietary fat intake and MS incidence in the Norwegian population, he could not provide further experimental or clinical evidence which would have suggested that atherosclerotic disease was pathologically tied to the development of MS.

Moreover, the jump from clinical association to pathological causation made by each of these researchers was substantial, while the only studies attempting

to bring the diverse forms of causation-related evidence (clinical, pathological, and experimental) together, were those performed by Putnam and his associates, even though many contemporary neurologists regarded their outcomes as unconvincing [24]. Brickner and Swank attempted to compare their data to historical controls in the form of previously published data, yet most other researchers had not attempted this in their approaches. The key exceptions where adequate control groups were utilized are notable for their largely negative results, such as the double-blind trials of linoleic acid supplementation in the 1970s or Thygesen's 1953 review of anticoagulant use in MS, which included 25 control patients and demonstrated that therapy had no significant impact on the relapse risk or disease course.

Thus, the current CCSVI-based venoplasty procedures are clearly not the first therapeutic attempts – or even the first surgical ones – to manipulate the cerebral and spinal blood vessels in MS patients. Given the wealth of therapeutic endeavours that populate the historical medical literature, it is easy for modern medical researchers to overlook the details and outcomes of prior ventures similar to their own. Yet undertaking such a historical review is of critical importance before a supposedly innovative theory or treatment for a long-known disease like MS is presented as novel, to prevent medical history from simply repeating itself, at the risk of considerable cost or harm to patients. Admittedly, the venoplasty procedures appear unique in their attempt to surgically relieve venous congestion in these patients, since the venous surgeries attempted by Aboulker and others did not really target MS. Nevertheless, with regards to the trade-off between debatable potential benefits and serious surgical risks presented by CCSVI-based interventions, the trials of sympathectomy and ganglionectomy discussed in this paper serve as excellent mirrors to Zamboni's venous procedures.

Ultimately, the highly politicized and sensationalist debate surrounding the CCSVI theory today and the overly enthusiastic procedures resulting from it, have cast a much more relevant and enduring question to the sidelines, namely as to what aetiological role, if any, the vessels really play in the pathogenesis of MS? From a history of medicine perspective, compiling the evidence from the assorted prior investigations on this subject – as this paper has attempted with a focus on treatment approaches – can serve as an important first step to help refine current discussions concerning the relevance of vascular pathology in MS.

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