Abstract

The role of the venous circulation has long been underestimated in clinical practice and research into neurological diseases. In this review, we present an overview of the evidence that venous abnormalities can play a key role in the development and manifestation of some neurodegenerative diseases. We review the history behind the role of veins in: multiple sclerosis (MS); the links of chronic venous hypertension to normal pressure hydrocephalus; the relationship of venous disease to developmental anomalies, reduced perfusion and ischemia; leukoaraiosis; jugular reflux; the link between spinal damage and venous abnormalities; and finally flow abnormalities in MS.
The Role Of Venous Abnormalities in Neurological Disease

I. Introduction

II. An historical perspective

III. Reduced perfusion, ischemia and hypoxia in MS
   a. Reduced perfusions
   b. Chronic versus acute
   c. Ischemia
   d. Treatment of ischemia, clotting and arterial spasms

IV. Architecture of the periventricular veins

V. Cerebral hydrodynamics and venous hypertension

VI. The role of venous abnormalities in other diseases
   a. Jugular venous reflux associations
   b. Optical problems in MS
   c. Transverse myelitis
   d. Vascular damage to nerves
   e. Developmental venous anomalies
   f. Idiopathic intracranial hypertension
   g. Supratentorial craniotomies
   h. Hydrocephalus, cerebrospinal fluid flow, arteriovenous flow: linking it all together
   i. Cranial and spinal damage congenital or otherwise and its effect on venous and CSF flow
   j. Leukoariaiosis

VII. The role of drugs in treating vascular problems

VIII. Truncular venous malformations

IX. Venous stenoses and their relationship to poor flow
   a. Venous stenosis
b. Vascular immunology

c. The role of the caval system in venous hypertension

d. The re-introduction of CCSVI specifically for multiple sclerosis

e. The introduction of cerebral thoracic neuro-vascular syndrome (CTNVS)

X. The use of MR as a pre-treatment guide to treating CCSVI in multiple sclerosis

XI. Future Directions and Conclusions
I. Introduction

At a workshop in Bologna, Italy in 2009, Prof. Paolo Zamboni presented the first evidence of a venous vascular problem that appeared to be prominent in patients with multiple sclerosis (MS). His data showed that there were major extracranial venous abnormalities that led to abnormal flow characteristics in MS patients. Although he did not claim these were “the” etiology of MS, he did observe that they may well exacerbate the disease and that, if treated, the patient may gain some benefit. Zamboni referred to the resulting problem as: chronic cerebrospinal venous insufficiency or CCSVI 1. In this review, we would like to bring to bear some of the previous research into the role of the venous vasculature in both multiple sclerosis, venous occlusive disease 2, and a variety of other diseases or syndromes that are now associated with venous problems and that may shed some light onto the relationship between abnormal fluid dynamics, the resulting abnormal hemodynamics, and the usual immunologically driven hypotheses behind MS as an inflammatory demyelinating disease.

II. An historical perspective

According to Putnam 3, who discussed vascular abnormalities in MS in 1937, the first observations related to abnormal vasculature or effects related to the vasculature appeared in Cruveilhier 4 in 1839, more than 170 years ago. Rindfleisch 5 noted in 1863 an engorged vessel in the center of a plaque, and in the same year, Charcot 6 described vascular obstruction in MS. These observations would be noted again and again over the next 135 years. Putnam appeared convinced that the etiology of MS lay in the venous system. To test his hypothesis, he proceeded to study the effects of obstructed venous flow in the cerebral veins of dogs. These animals developed a number of abnormalities—many of them similar to encephalitis or multiple sclerosis. His precocious comment at the end of his paper was as follows 7: "The later stages (up to ten months) of the lesions consist of plaques of demyelination with practically complete preservation of the axis-cylinders and with dense fibrous gliosis confined to the white matter." And he continues with:

“The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques.”
There are more intriguing connections as one reviews the literature of the 20th century. On occasion, Putnam observed clotting and perivascular hemorrhage in encephalomyelitis. He continued to believe that venous clotting was a problem for the rest of his professional life. As a result of this venous clotting, an increase in capillary density also seems to develop, and this may be consistent with the iron build up seen in MS lesions and the basal ganglia of MS patients. A possible hypothesis for what happens could be: 1) the obstructed flow leads to endothelial damage and iron build up; 2) the need to increase the outflow capacity in the venous system; 3) venous capillaries are recruited to become veins and 4) these in turn are also damaged leading to further iron deposition. If this hypothesis is true, then the iron buildup should take place backward along the venous drainage system, which appears to be the case (Figure 1).

The story continues with a reference to Borst, who founded a theory on the occurrence of vascular obstruction, in which he mentions the process of significant vessel narrowing to the point of complete obliteration, hyaline transformation, etc. This loss of vasculature has been reported using susceptibility weighted imaging (SWI) by Ge et al. in 2009. Perivascular hemorrhages were also frequently described by many authors. Borst also mentions the presence of pigments. Others describe the combination of all three: congestion, perivascular hemorrhage and pigments (possibly hemosiderin or iron-related) in encephalitis post-measles. Many noticed venous engorgement and one study showed that thrombi were visualized in nine of seventeen MS cases and in all three encephalomyelitis cases. Others tried to validate Putnam’s work with variable success. Dow and Berglund studied 5 cases and found thrombus also but could not validate that this was caused by the thromboplastic substances used in the cadaver studies. They did note that of the 40 out of 60 MS lesions seen with vessels, 9 showed small vein thrombosis whereas only a few of the normal veins sampled showed thrombosis (6 out of 25). They note that in 3 of the 9 cases the thrombosis was outside the vein. They also suggest that extracts of brain tissue act as potent thromboplastic substances. Today, one might ask if this hemosiderin and/or thrombosis could correspond, for example, to cases where we see iron deposition with SWI in brain lesions (Figure 3).
Three interesting papers point toward other features associated with venous congestion, small thrombi and iron deposition. In the first two, children with early cerebral infarction and children following severe ischemic-anoxic events showed increases in iron content in the basal ganglia, thalami and white matter. Iron deposition was also associated with periventricular gliosis. In fact, desferrioximine (an iron chelator) has been used to minimize the damage for patients undergoing cardiac resuscitation. These findings also may be consistent with the fact that some MS lesions may show iron buildup in ring-like structures and/or in the midline, possibly associated with a central vein (Figure 4). The putative hypothesis of iron in the ring-like structures has not been substantiated. It could in fact represent paramagnetic changes associated with gliosis or some form of molecular change or tissue breakdown in that region. One might conject that these areas of highest putative iron content or tissue susceptibility change may represent ischemic tissue of lesions and that they may correspond to the lowest blood volume. An interesting pediatric case of venous congestion shown with SWI and similar in appearance to a developmental venous anomaly (DVA) shows that SWI may be able to detect small thrombosed veins. In this particular case, the child was treated and recovered; evidence of the problem on imaging disappeared at two months.

Could it be that iron regulation is disrupted in ischemic-anoxic insult in MS lesions? A very recent paper by Zamboni talks about the increases in iron seen in chronic venous disease for patients who are carriers of the C282Y and H63D mutations in the HFE gene. Evidently in these people, the intracellular iron deposits of mutated macrophages have less stability than those of the wild type. The diapedesis of red blood cells and the ensuing extracellular hemolysis leads to the release of free iron, which may act as an inflammatory agent. The predominant cells migrating into the extracellular matrix are then T-cells and macrophages. If these macrophages are not functioning properly or the form of ferritin created is corrupted and the iron is prematurely released, free iron may well play a strong role in generating further free radicals.

Almost from the beginning of in vitro studies of MS brains, the presence of inflamed veins was noted. Rindfleisch states:
"If one looks carefully at freshly altered parts of the white matter ... one perceives already with the naked eye a red point or line in the middle of each individual focus ... the lumen of a small vessel engorged with blood. All this leads us to search for the primary cause of the disease in an alteration of the individual vessels and their ramifications. All vessels running inside the foci, but also those which traverse the immediately surrounding but still intact parenchyma, are in a state characteristic of chronic inflammation."

According to F. A. Schelling's tome on the role of the vasculature in MS and lesion genesis 25, there are a number of crucial observations from which we quote two here. The first relates to the mechanical nature of the problem and the fact that the vascular damage follows a path opposed to the flow. In turn, he quotes Carswell as saying: "In inflammation, the local congestion commences in the capillaries, afterwards extends to the small veins, but never to large branches; in mechanical congestion (by venous flow inversion) the blood accumulates first in the venous trunks, which are always conspicuous, and afterwards in the branches and capillaries 26." Further evidence of this mechanical effect comes from observations of I.V. Allen, who noticed the wide vascular beds around veins and the central widening of the venous tree indicative of intermittent increases in cerebral pressure 27. It is also worth looking into Fog's work. He summarizes his results from a series of cadaver brain studies as "30 plaques showed that they definitely followed the course of the veins, so that course and dimensions of the veins determine the shape, course and dimension of the plaques 28." He also closes with the comment:

"Consequently, multiple sclerosis, pathologico-anatomically, must be considered a periphlebitis, as proved by the author in 1948 in the case of plaques of the spinal cord 29."

There is still more early evidence of venous association with similar diseases. Consider the comments by Schlesinger 30 who notes in his work on the Galenic system: Meyer and Cook 31 noted that the peculiar network-like localization of hypermyelinaized scars in cases of status marmoratus may be due to veins; Pette 32 noted that in post-vaccinal encephalitis and in encephalitis following measles that characteristic lesions are situated around veins, and finally Schlesinger himself saw extravasations following the distribution and shape of
plaques in advanced cases of multiple sclerosis after injection of cadaver brain with hot carmine-gelatin solution (more discussion on his work appears under architecture of the periventricular veins).

As for vascular insufficiency, Putnam discusses this in his 1953 paper entitled, "Cerebral vascular insufficiency 33." Although this paper is about arterial insufficiency, Putnam shows that the effects of hypotension can cause significant neurological problems when it leads to a deficit of blood flow to the brain in the presence of already compromised (narrowed) vessels.

Another key issue is the role of vitamin D in multiple sclerosis. Perhaps vitamin D plays a role in the health of the endothelium or cardiovascular health in general. A recent paper by Cecik and Stein 34 states: "Vitamin D deficiency has been associated with many systemic disorders, including infectious, inflammatory, and autoimmune conditions, cardiovascular disease, hypertension and atherosclerosis, neuromuscular function, cancer, neurodegenerative diseases, and neuropsychological and functional outcomes in the elderly population."

Further, Nemerovski, et al. 35 in a review of much literature on the topic state that "vitamin D deficiency was implicated in several types of vascular disease including peripheral artery disease, atherosclerosis, myocardial infarction and ischemic stroke." They also state that vitamin D deficiency has been associated with increased hypertension. Another recent paper suggests that vitamin D is one of the major risk factors associated with MS as are Epstein-Barr virus and smoking 36. This author states that vitamin D could play an anti-inflammatory and immunomodulatory role and that it prevents the induction of experimental autoimmune encephalomyelitis (EAE) if administered before triggering of the disease and noticeably improves clinical outcomes.

Recently, it has been demonstrated that there is reduced perfusion and even loss of small medullary vein visibility in multiple sclerosis 15. The idea of reduced perfusion emanates from the work of Putnam, as described earlier. A paper by Juurlink has a nice discussion of the role of hypoperfusion in MS 37. He comments that the reduced perfusion can be detrimental to oligodendrocytes, preferentially affect white matter, cause demyelination, and lead to microglial activity. He notes that these can be most marked in the optic nerve and tract. He then states: "There is now ample evidence that ischemic insults of sufficient severity can cause upregulation of cell adhesion molecules onto the endothelial cells, thus allowing infiltration of leukocytes into
the brain parenchyma, resulting in an inflammatory lesion.” He goes on to point out that hypertension of genetically susceptible lesions (recall that reduced vitamin D can lead to increased hypertension) leads to vascular damage which in turn leads to ischemia. In a review of the role of venous reflux, Simka\textsuperscript{38} presented a similar opinion and stated: “It is hypothesized that pathological refluxing venous flow in the cerebral and spinal veins increases the expression of adhesion molecules, particularly intercellular adhesion molecule (ICAM-1), by the cerebrovascular endothelium.”

It has been long thought that iron misregulation is associated with neurodegenerative disease\textsuperscript{39}. There is an extensive recent review of iron in neurodegenerative diseases by Kell\textsuperscript{40}. Although the role of iron in these diseases will require much more detailed experimentation\textsuperscript{40}, there is certainly some evidence for it in specific diseases such as neuroferritinopathy, aceruloplasminemia and hemochromatosis, for example. In the latter case, Thomas and Jankovic\textsuperscript{41} state, "The presence of central nervous system superficial siderosis and central nervous system vasculitis, in association with systemic hemosiderosis, may be the neurological manifestation of hemochromatosis." (In hemochromatosis, iron levels are sometimes reduced with either chelation or with phlebotomy). They go on to note that iron elevation follows dopaminergic cell death. On a different, but related note, there is some suggestion that the amount of stored iron might also play a role in risks of white matter damage post-injury\textsuperscript{41}. Sullivan suggests that there is evidence that oxidative DNA damage as measured by 80HdG correlates with the amount of stored iron. A very interesting paper by Patt et al.\textsuperscript{42} and another by Grant, et al.\textsuperscript{43} suggest that reduced iron levels are associated with reduced damage to the brain. The former reports that "Gerbils fed a low iron diet for 8 weeks had decreased brain and serum iron levels, less neurological deficits and decreased brain edema after temporary unilateral carotid ligation (ischemia) and then reperfusion than gerbils fed a control standard of iron diet." The latter reports that EAE did not develop in low-iron mice. They also suggest that: "The mechanism of EAE inhibition in iron-deficient mice likely involves the delivery and metabolism of iron for optimal CD4+ T-cell development." In their paper, they also comment that iron supplementation has been shown to increase progression and mortality in HIV-infected people and that iron chelation in mice with EAE also reduced the clinical severity of the symptoms. Clearly, iron plays some role in
neurological processes that lead to neurodegenerative effects. But white matter is not the only tissue affected in MS. Derfuss et al. 44 have observed inflammation of gray matter blood vessels after transferring TAG-1-specific T cells into rats, a finding absent in classic models of EAE. When combined with a two-hit model using antibodies against myelin, they observed widespread demyelination in both white matter and gray matter. Rudick and Trapp 45 point out that there are three patterns of lesions: 1) lesions involving both gray matter and white matter; 2) lesions involving perivascular areas of cortical demyelination; and 3) lesions involving bands of cortical demyelination below the pial surface. All this suggests that there could be a proclivity to MS if there are multiple hits to the system, i.e., CCSVI, reduced vitamin D, iron misregulation and perhaps other related processes such as disrupted CSF flow that would exacerbate an already present problem to the level that tissue damage becomes inevitable. As more of a historical note, in the 1930s, it was believed that MS may have been caused by acute insult to the nerve tissue, usually in the form of toxemia, incident to an infectious disease or metal poisoning 46.

III. Reduced perfusion, ischemia and hypoxia in MS

i) Reduced perfusion

Following up on the earlier discussion of Juurlink’s paper 37, there is more evidence pointing toward reduced perfusion in MS patients. Back in the 1980s, Swank, et al. 47 found that past the age of 40, MS patients had markedly reduced blood flow compared to normal subjects. Using MRI, there has been a thrust in the last ten years to study perfusion in MS. The work of Meng Law and others shows that there is reduced perfusion as a function of severity of disease. Law et al. 48 reported a significant decrease of cerebral blood flow (CBF) and a prolongation of mean transit time (MTT) in the normal-appearing white matter (NAWM) at the level of the lateral ventricles in MS patients. This agrees with a study conducted by Ge, et al. 49 whose data has demonstrated reduced perfusion with significantly prolonged MTT in lesions and in NAWM in patients compared with normal white matter in controls. Moreover, other studies showed significant decreases in CBF and cerebral blood volume (CBV) in all NAWM regions in MS patients compared to controls 50, 51. Conversely, elevation of CBF and CBV has been reported in NAWM of MS patients several weeks before focal leakage of
the blood brain barrier (BBB) and plaque formation \(^{48}\), and in NAWM regions adjacent to areas of decreased gray matter in MS \(^{52}\). Not only in the white matter but also in gray matter, altered cerebral perfusion has been reported. In a study conducted by Yamada et al. \(^{53}\), measurements of relative CBF (rCBF), relative CBV (rCBV) and MTT were obtained at the globus pallidus, putamen, caudate nucleus, thalamus, and cerebral cortex of temporal, frontal, and occipital lobes using a gradient echo approach and a spin echo approach. The globus pallidus showed significantly lower values of relative CBF and relative CBV compared with other parts of the gray matter. In this paper, the authors concluded that GM hypoperfusion in MS is likely to be secondary to white matter injury and tissue loss. Cerebral NAWM perfusion is decreased since the earliest stages of the disease whereas sub-cortical normal-appearing gray matter perfusion develops as the disease progresses. In a study conducted by Varga et al. \(^{51}\), MTT, CBV, and CBF were calculated in the thalamus and the putamen bilaterally. Significant decreases were found between MS patients and controls with respect to CBF in the putamen but not in the thalamus. The correlation between altered flow and disease progression has been also studied. Inglese et al. \(^{54}\) investigated the decrease in cerebral blood flow in the deep gray matter of patients with MS and its correlation with fatigue severity. Patients with primary-progressive MS have been shown to have lower average cerebral blood flow than patients with relapsing-remitting MS (RR-MS). With respect to cerebral blood volume, there was a significant difference between patients with primary-progressive MS and controls and between the two groups of patients but not between patients with relapsing-remitting MS and controls. In addition, Rashid, et al. \(^{52}\), using arterial spin labeling, observed hypoperfusion in several cortical areas of patients with relapsing and progressive MS. In summary, regions of lower perfusion predominantly in GM were observed in the primary and secondary progressive cohorts, particularly in the thalamus \(^{51,52,54}\). Finally, some interesting comments in a paper by Barnett and Sutton \(^{55}\) points toward a link between the different lesions observed in MS both pathologically and with SWI (18) that may link susceptibility changes and putative iron content with lesion type. They specifically state that out of the different patterns of MS lesions there are two relevant patterns of lesions \(^{56}\): pattern two which are perivenous in location, associated with degenerating and remyelinating shadow plaques; and pattern three, non-vascular centered plaques associated with
oligodendrocyte apoptosis at the active plaque edge. Some patients might show only one type preferentially showing the pathologic heterogeneity of the disease. They also note that tissue preconditioning \textsuperscript{57} may explain concentric layering of damaged and preserved myelin in Balo’s MS. But most interesting is the comment that the these may be expanding rings with the edge containing preserved myelin but that in this edge region there is intense expression of hypoxia-like tissue damage (D-110 epitope), regulators in the hypoxic pre-conditioning (HIF-1a) and stress proteins which afford protection against hypoxic injury (heat shock protein 70).

Using ultrahigh-field (7 Tesla) MR imaging, Ge et al \textsuperscript{58} identified subtle venous wall signal changes in small MS lesions, which they interpreted as early-stage vascular changes. These changes may be the result of early ischemic injury leading to increased demyelination, without any apparent BBB breakdown. Further evidence supporting the hypothesis that focal inflammatory BBB leakage may not be the initiating event in MS plaque formation, comes from Werring et al \textsuperscript{59} who used MR diffusion imaging to measure water molecule random motion in the NAWM of MS patients. They found that the formation of lesions was preceded by subtle progressive alterations in tissue integrity beyond the resolution of conventional MRI. Collectively, the findings of these researchers reinforce the opinion that profound microvascular changes are associated with the progression of MS; vascular changes that may be precipitated by hemodynamic changes in the extracranial venous pathways.

In a study investigating the impact of CBF in elderly individuals on hyperintense regions in MRI images, ten Dam et al \textsuperscript{60} observed that a decline in total CBF was associated with an increase in the volume of periventricular hyperintensities. They observed that periventricular white matter hyperintensities were typically located symmetrically in both cerebral hemispheres and concluded that this was suggestive of diffuse perfusion disturbance. They postulated that fluctuations in CBF might result in ischemia, which could lead to breakdown of the BBB or perivenous collagenosis, resulting in damage to the periventricular white matter. This finding is consistent with those of Moody et al \textsuperscript{61, 62} and suggests that microvascular changes leading to altered hemodynamics may be associated with damage to the NAWM in the periventricular region. While relatively little work has been done on the role of hypoxia in MS, there is increasing evidence to suggest that a hypoxia-
like metabolic injury is a pathogenetic component in the formation of MS lesions. Wakefield et al found morphological changes in the venous endothelia which progressed to occlusive vascular inflammation. They proposed that these changes were the precursor to lesion formation and suggested that demyelination may have an ischemic basis in MS. Using an in vivo rat model, Lochhead et al demonstrated that hypoxia followed by re-oxygenation altered the conformation of the occludin in the tight junctions between the endothelial cells, resulting in increased permeability of the BBB, confirming the earlier findings by the same team. The earliest detectable event in the development of white matter lesions is thought to be an increase in the permeability of the BBB followed by inflammation and demyelination. Several researchers have implicated tight junction abnormalities with increased BBB permeability and lesion formation in MS.

### ii) Chronic versus acute

A study of seven patients with RR-MS revealed decreased relative CBV in chronic lesions and further reduced relative CBV in one acute lesion in white matter compared with that in gray matter. Haselhorst et al examined 25 patients with MS and found that acute lesions had significantly higher relative CBV than NAWM and that chronic plaques had significantly lower relative CBV than NAWM. Inflammatory activity can cause compensative vasodilatation and result in increased CBF and CBV, which is found in enhancing lesions (Figure 5). On the other hand, any evidence of increased perfusion in some chronic non-enhancing lesions can be explained by lesion reactivity with new vascular inflammatory changes.

### iii) Ischemia

If ischemia is indeed prevalent and caused by reduced perfusion, it may be one of the sources of endothelial activation, T-cell trafficking and VEGF up-regulation. This is in fact the case in transplant associated reversible encephalopathy suggesting that hypoxemia induces vasogenic edema. It is possible that the reduced flow is due to primary or secondary vasculopathy. In children, this vasculopathy may be responsible for both destructive and reversible lesions seen in influenza associated encephalopathy and encephalitis. There is evidence also in children that iron build up is directly associated with severe ischemic-anoxia insults. The watershed for the
periventricular vessels is more susceptible in children than the cortex. Whether ischemia-anoxia leads to ventricular leukomalacia or cortical infarction, there is a net accumulation of iron. Under these circumstances, it is possible that the usual iron transport does not occur and iron builds up in the basal ganglia and thalamus (see for example the Figure 1). Iron has been seen in ferruginated neurons in autopsy. Evidence also exists of iron build up following anoxic-ischemic events in adults.

iv) Treatment of ischemia and arterial spasms

The concept of ischemia is not new in the study of MS. Those paying attention to Putnam’s vascular hypothesis were looking at ischemia as being caused by vascular spasms or constriction of blood vessels. Putnam himself was so convinced that there was micro-clotting or thrombus that he used anti-clotting agents for his patients for much of the remainder of his career. To deal with this in the 1930s a number of people attempted to reduce the body’s ability to create these spasms by performing a sympathectomy or ganglionectomy. These were not trivial operations with high risk of hemorrhage and death but they succeeded in reversing some severe symptoms of some patients including fatigue. Cervicodorsal sympathectomy involved removing the inferior cervical and the first thoracic ganglion by the posterior approach. If MS were caused by an insult to nerve tissue, Wetherell comments: “it is reasonable to assume that one set of sympathetic nerve fibers may be more liable to insult than another.” And he then notes: “This, of course, is known to be a fact when the system is considered in the light of such diseases as hyperthyroidism and Raynaud’s and Hirschsprung’s disease. The somatic nerve system may also be attacked in part, for example, the radial nerve in cases of lead poisoning.” These observations he makes are similar to what has been seen in some cases of balloon angioplasty in treating CCSVI in MS patients, and that is an immediate amelioration of some of the physical disabilities. Royle, who appears to have had the most early experience with sympathectomy, points out that this operation tends to improve the brain’s circulation by dilating the arterioles and venules. He notes that tone is reduced, and conjectures that this is brought about by reducing spasm or constrictions of the blood vessels in the brain. Between 1923 and 1931 he had performed more than 600 such operations. These sympathetic ramisections could be performed to focus on a given part of the body or brain (one side versus the other for example). He demonstrated that, with this surgery, some
forms of tremor and rigidity are alleviated, spastic hemiplegia, spastic paraplegia, trigeminal neuralgia, Raynaud’s disease, Buerger’s disease and a variety of other conditions likely related to cerebral vascular supply.

IV. Architecture of the periventricular veins

While patients with MS experience a wide range of clinical outcomes, the disease tends to be characterized by the formation of lesions, so called ‘Dawson’s fingers’ \(^{79}\), in the periventricular region. These thin linear lesions invariably orientate themselves along the axis of central veins that drain into the subependymal veins. This observation raises intriguing questions as to why periventricular lesions should be such a consistent feature \(^{80}\) of a disease that has otherwise a particularly diverse pathophysiology. What is so peculiar about the periventricular region that makes it uniquely susceptible to the formation of these characteristic lesions? Furthermore, given that both hemispheres of the cerebrum are frequently affected, what is the common vector that affects similar changes in both halves of the brain? While definitive answers to these questions have so far eluded the clinical community, there is evidence to suggest that the architecture of the periventricular venous system, itself, may contribute to the formation of lesions. Perhaps the strongest evidence in support this opinion comes from Schlesinger \(^{30}\) who, in 1939, forced hot carmine-gelatine solution, under high pressure, into the vein of Galen in human brains. He found that extravasations were produced, chiefly in the region of the angle of the lateral ventricle, which “closely resembled the distribution and shape of plaques in advanced cases of multiple sclerosis”.

From this observation Schlesinger concluded; “it seems possible that the plaques may only be found in this area of the ventricular wall because they have a definite topographical relationship to the veins which are crowded together in the region of the lateral ventricular angle.”

The characteristic periventricular lesions that are associated with MS are not limited to one side of the brain. This suggests that there may be a common source involved in their formation which acts on both hemispheres. Evidence supporting this view comes from Werring et al \(^{59}\) who observed that, in MS patients, increases in the average apparent diffusion coefficient (ADC) associated with lesion formation in one half of the cerebrum, were
mirrored by similar increases in matched normally appearing white matter (NAWM) regions of the contralateral hemisphere. While no common vector was identified, these findings suggest that similar pathophysiological processes occur simultaneously in both hemispheres of the brain, and that factors, which are not directly related to the focal lesions, might be at work. Unpublished work by Haacke using perfusion weighted imaging shows that most MS lesions have the same temporal response to contrast agent concentration changes which are distinctly different from the surrounding white matter. This connectivity suggests a common vascular relationship between MS lesions.

These findings are not at odds with the actual vascular watershed affecting MS. Unlike the superficial veins, which drain directly into the sagittal sinus, those in the periventricular region drain into the straight sinus via the vein of Galen. This creates a ‘bottleneck’ through which the blood from the subependymal veins must pass. Any phenomenon that affects the flow of blood through the vein of Galen, will therefore impact directly on the subependymal veins in both hemispheres of the cerebrum – something which Schlesinger demonstrated in his experiments. Consequently, any venous abnormalities, be they intracranial or extracranial, that adversely influence hemodynamic behavior in the straight sinus are likely to have a profound effect on the blood flow in the periventricular veins in both hemispheres of the brain. Indeed, altered hemodynamic behavior in the periventricular veins may not be a consequence of local circulatory disturbances, but instead might arise from extracranial venous blockages located far away from any plaques.

In the brain, the superficial venous system is protected by a sphincter mechanism that regulates flow from the cortical bridging veins to the sagittal sinus. This protects these veins against increased pressure in the sinuses. The deep venous system, however, appears to lack a similar mechanism and therefore may be more susceptible to changes in pressure in the sinuses than its superficial counterpart. While Dagain et al observed anatomical features at the junction of the vein of Galen and the straight sinus, which they surmised might have a regulatory function, this has not been proven. Indeed, the fact that Stolz et al found the pulsatility characteristics of the straight sinus to be almost identical to those of the vein of Galen, suggests that no damping
mechanism exists between the two. Therefore, the periventricular veins are in effect ‘hard wired’ to the straight sinus. Consequently, any change in pressure in the venous sinuses is likely to have a greater impact on the periventricular veins in comparison with the cortical veins.

The veins in the periventricular region appear to be prone to morphological changes. Moody et al. 61 investigating cerebral microvascular alterations in the elderly, found the periventricular veins on the efferent side of the cerebral microvessels to be particularly susceptible to luminal narrowing caused by noninflammatory mural thickening characterized by the proliferation of collagen fibers. They termed this phenomenon “periventricular venous collagenosis” (PVC) and found that thickening of the mural wall progressed with age, was strongly associated with leukoaraiosis, and frequently resulted in stenosis of the periventricular veins. 62 They hypothesized that stenosis, caused by PVC, in the transcerebral veins flowing into the subependymal veins would reduce blood flow to the periventricular region and may result in the shunting of blood away from the internal cerebral veins. 61 Corroborating evidence supporting this opinion comes from Schlesinger 30, who demonstrated that occlusion of the vein of Galen resulted in collateral flow higher up, with venous blood flowing away from the periventricular region towards the cortical region. Leukoaraiosis is generally associated with the periventricular region; a region in which the perfusion pressure is relatively low and the white matter is particularly sensitive to fluctuations in total cerebral blood flow (CBF) 60. Any narrowing of the lumen in the periventricular veins increases their hydraulic resistance and might cause shunting of blood away from these vessels, with the result that the surrounding tissue would experience hypoxic stress. Patients with leukoaraiosis have been found to have significantly decreased blood flow in the deep white matter 87 and it is thought that ischemia, resulting from poor perfusion, is a major contributing factor in the etiology of this condition 61, 62, 88.

Santucci et al. 89 investigating the occurrence of brain parenchymal signal-intensity changes within the drainage territory of developmental venous anomalies (DVAs), found that MRI signal-intensity abnormalities were associated with some DVAs. In particular, they found that signal intensity abnormalities were more likely to be associated with DVAs in the periventricular region rather than the juxta-cortical and sub-cortical regions. San Millán Ruiz et al. 90 observed similar results and concluded that brain parenchymal abnormalities were
frequently associated with DVAs. Several parallels can be traced between PVC and developmental venous anomalies (DVAs), suggesting that the two conditions have similar pathophysiological pathways \(^{86}\). DVAs are characterized by a venous confluence in which a single collecting vessel drains an abnormally large venous territory, resulting in a relative volume overload. This anatomic configuration, as San Millán Ruíz et al pointed out, is similar to that encountered in the periventricular region, where many transcerebral veins drain into the subependymal veins. In addition, DVAs have been shown to have thickened walls \(^{90}\), similar to that found in PVC. Indeed, San Millán Ruíz et al observed stenosis of the collecting vein in 13.1% of the patients in their study. Stenosis of this kind invariably increases the hydrodynamic resistance of the vein so that the up-stream pressure is greatly increased, as was demonstrated by Dillon \(^{91}\) who measured a 15-mm-Hg pressure gradient across a stenosis of the collecting vein of a DVA in one patient. (For more discussion of the role of abnormal venous flow in DVA see also the section on the role of venous abnormalities in other diseases.)

V. Cerebral hydrodynamics and venous hypertension

While the full implications of Zamboni et al’s work \(^{1,80,92,93}\) are as yet not known, their findings suggest that the venous hemodynamics in many MS patients are radically different from those of healthy individuals, something which has been subsequently corroborated by other researchers \(^{94,95}\). Collectively, these findings suggest that cerebral venous hypertension might be a feature of MS. For any given vessel, the relationship between blood flow rate, \(Q\), and hydraulic resistance, \(R\), is given by \(Q = \Delta P/R\) where \(\Delta P\) represents the pressure drop between the two ends of the blood vessel. Any stenosis in the extracranial venous system will inevitably increase the hydraulic resistance of the venous pathways back to the heart \(^{96}\) and may cause alternative collateral routes to open up – something that Zamboni et al observed \(^{1}\). If the resistance of the extracranial venous pathway is increased, then in order to ensure that the total blood flow through the system is maintained at a constant level, it is necessary to increase the pressure drop across the extracranial venous system \(^{96}\). Without such an increase in pressure, the flow rate would naturally decrease as the resistance of the system increased (which is in fact seen as MS progresses in its severity \(^{54}\)). Consequently, an extracranial stenosis would tend to
lead to venous hypertension up-stream of the point where luminal narrowing occurs. Evidence supporting this opinion comes from Zamboni et al.\textsuperscript{97} who performed transluminal angioplasty on sixty-five MS patients in order to open up blocked extracranial venous pathways. They found that the therapy reduced the pressure in the azygous vein and internal jugular veins of the patients by an average of 2.2 mm Hg, an indication that prior to the operation venous hypertension had been present. Further evidence supporting a relationship between extracranial stenosis and hypertension in the periventricular veins comes from Mayhan and Heistad\textsuperscript{98} who found that occlusion of the superior vena cava in rats produced a dramatic increase in the cerebral venous pressure ($30 \pm 3$ mm Hg) compared with controls ($7 \pm 1$ mm Hg). This increase was similar in magnitude to that produced in the cerebral veins ($28 \pm 2$ mm Hg) when acute arterial hypertension was induced. Interestingly, they concluded that occlusion of the superior vena cava resulted in blood pressures that were capable of breaching the cerebral venous BBB. While the extent to which venous hypertension might be involved breaching the BBB in MS is not known, it has been hypothesized that raising transmural pressure might result in separation of endothelial tight junctions in the cerebral veins\textsuperscript{99}. (See also the discussion on supratentorial craniotomies in the next section on the role of venous abnormalities in other diseases.) It is therefore reasonable to believe that the venous stenosis reported by Zamboni et al.\textsuperscript{1} and others\textsuperscript{94,95} might result in reduced CBF in MS patients. If the CBF in a given location falls low enough, then there is increased risk of hypoxic stress and ischemic injury\textsuperscript{61,62,88}. (See the section on reduced perfusion for further discussion of reduced perfusion and ischemic effects seen in MS subjects).

Further evidence supporting the opinion that venous hypertension may be a feature of MS comes from Zamboni et al.\textsuperscript{100} who found the pulsatile characteristics of CSF flow to be altered in MS patients, with the result that the bulk flow of this fluid was greatly reduced. Given that CSF only flows from the choroid plexus to the superior sagittal sinus (SSS) and other venous pathways because of a positive pressure gradient\textsuperscript{101}, the presence of a greatly reduced CSF flow in these patients suggests that venous hypertension may be occurring. If hypertension is present in the SSS, then this would inevitably lower the pressure drop through the cortical veins, resulting in reduced blood flow through these vessels. If this reduction in flow were large enough, then this might induce
hypoxic stress in these vessels resulting in morphological changes to the BBB\textsuperscript{66}. This may explain, in part, why the cortical lesions associated with MS are often perivenous in nature\textsuperscript{102}.

When considering the issue of cerebral hydrodynamics, one inherent problem is the difficulty in characterizing and quantifying intracranial blood flow using existing imaging techniques. This is particularly the case when quantification of blood flow in the upright position is required. Perhaps one approach that might help to overcome this problem, and which might shed new light on the role of the venous system in MS is to construct mathematical fluid dynamic models to evaluate intra- and extracranial blood flows. One such example is the paper of Gisolf et al\textsuperscript{103} that discusses the effect of posture and central venous pressure on the distribution of the venous outflow in the internal jugular veins and vertebral plexus. They successfully show that the flow is dominated in the supine position by the jugulars but when standing is mainly through the vertebral system, something confirmed by Valdueza et al\textsuperscript{104}. If such modeling becomes viable, then one could imagine using MRI as a means to map out not only the major vascular components of the venous system, but also their blood flows as a function of the cardiac cycle as well, and then model the expected effects for a given individual. This could be done pre and post treatment as well to try and understand the role of increased resistance due to collateral flow necessitated by an incomplete or somewhat abnormal venous drainage system.

The constraints of the Monro-Kellie doctrine result in a complex hydrodynamic mechanism, which compensates for transient increases in cerebral blood volume by pushing CSF out of the skull\textsuperscript{105}. This is achieved through a sophisticated windkessel mechanism, which utilizes the CSF to dampen the arterial pulse and ensure the smooth flow of blood through the cerebral capillary bed\textsuperscript{106}. The energy from the arterial pulse is transferred to the CSF, which pulses backwards and forwards across the foramen magnum. While the blood flow through the cerebral capillary bed is normally smooth and free from a pulse, by the time it reaches the venous sinuses it once again exhibits pulsatile characteristics\textsuperscript{107, 108}. This suggests that energy transferred from the arterial pulse to the CSF is in turn transferred back to the venous flow. While the physiological mechanism by which this occurs is not fully understood, it is thought that because the CFS drains directly into the SSS via arachnoid granulations, any pulse in the CSF will be transferred to the venous fluid in the sinus.
The cortical bridging veins that traverse the subarachnoid space (SAS) are characterized by a sphincter, which regulates the blood flow into the SSS from these veins. The constriction caused by this sphincter results in an increase in the transmural pressure of the bridging veins causing them to engorge and ‘puff’ out, before periodically discharging into the SSS. Thus, these sphincters create Starling resistors in the bridging veins whose characteristics are wholly governed by the respective venous and CSF pressures. Under normal circumstances this Starling resistor interacts with the CSF pulse to create a coupled resonance circuit which ensures the correct flow of blood into the SSS. However, Bateman showed in a patient with leukoaraiosis, that when the pulses in the veins and CSF lose syncopation, a complicated pulse-wave is reflected back towards the cortical veins, something which would increase the shear forces on the endothelia and might result in transient increases in intracranial pressure (ICP). Given that the CSF pulse appears to be altered in MS patients, there is good reason to believe that this will impact on the pulsatile characteristics of the cortical veins, and while the physiological implications of this are unknown, it can be postulated that the resultant altered hemodynamics might contribute to perivenous lesion formation in the cortical region.

VI. The role of venous abnormalities in other diseases

i) Jugular venous reflux associations

There is a very timely review of the importance of jugular venous reflux. In this paper, the authors note that without a competent jugular valve, and prolonged venous reflux, the subject may develop venous hypertension or occlusion. What represents too much reflux? This is unclear, but reflux occurring for 50% of the cardiac cycle (one of Zamboni’s conditions) is suggestive of a physiological problem. Several disorders are now associated with internal jugular vein (IJV) incompetence, including: transient global ischemia; transient blindness; cough headache; and primary exertional headache. Many other conditions can also generate some level of this elevated venous pressure, such as congestive heart disease, tricuspid valve regurgitation, primary pulmonary hypertension and chronic obstructive pulmonary disease. Valves can also tend to break down with age. In veins without valves, simply reversing the pressure gradient can produce reflux. This condition “might impede cerebral venous outflow and induce neurologic dysfunction,” according to Chung and
These conditions can occur during Valsalva-like activities such as coughing, heavy lifting, and other strenuous activities. In another paper on transient monocular blindness (TMB), Chung\textsuperscript{116} points out that 74\% of these patients had JVR compared to 20 to 40\% of normals. They noticed that there was a dilation of the venules in these patients but not at all in normals. When a VM was performed normals also showed venous dilation. So the evidence appears to suggest that JVR affects ocular venous drainage.

\textit{ii) Optical problems in MS}

Optical neuritis is often one of the conditions resulting from MS. A logical question to ask is: “What role does the venous system play in depicting the damage done in the optical system for people with multiple sclerosis?” The answer may lie in detecting sheathing and hemorrhage in veins in the retina (periphlebitis retinae). In a study of retinal blood vessels and their integrity, Lightman et al\textsuperscript{117} show that 3.5 years after initial onset of acute idiopathic optic neuritis 8/14 patients who had vascular abnormalities in a first episode of optic neuritis went on to develop MS while only 5/32 without vascular abnormalities went on to get MS. They quote the relative risk for MS once you have had evidence of optic neuritis as 14.4. The overall incidence of patients with optic neuritis going on to be diagnosed as clinically definite was 13/46 or 28\%. Therefore, they propose that the presence of these vascular abnormalities may have predictive value. They go a step further and after noting that there are continuous endothelial tight junctions in both the brain and retina and both have selective permeability to a variety of molecules: “We therefore suggest that the sheathing of retinal vessels that we observed ophthalmoscopically is the visible clinical sign of the perivascular lymphocytic infiltration and accompanying edema which characterizes the lesions of MS.” Finally, they come to the logical conclusion that: “The occurrence of perivenular abnormalities in a region free of myelin and oligodendrocytes provides evidence that the vascular changes in MS can occur independently of contiguous demyelination and may be the primary event in the formation of a new lesion.” In another paper\textsuperscript{118}, Engell et al showed that probable MS patients (based on periphlebitis retinae, oligoclonal banding and MRI data) may have already suffered from clinically silent disease in the retina. Despite these findings, no correlation has been found with clinical symptoms as of yet or with lesions seen using MRI\textsuperscript{119}. Another paper related to retinal vein occlusion in dural carotid-cavernous
fistula suggests that the progression from venous stasis retinopathy to central retinal vein occlusion is caused by an elevation in pressure of the cavernous sinus. All in all, this data again points to the fact that a disruption in the venous system can have major consequences to those areas affected by the associated draining veins. Periphlebitis that is seen in the eyes of MS patients may not be directly associated with optic neuritis and impaired vision\textsuperscript{118}. If this were the case, one may expect an inflammation of at least one layer of the eye, which is not seen. On the contrary, vision impairment is primarily due to loss of axons in the optic nerve, mainly, small axons – therefore color vision is affected first. Also, there is a substantial loss of ganglion cells in the retina, but this is rather not caused by a process within retina, but due to the Wallerian degeneration (backward atrophy) of those neurons. Interestingly, optical coherence tomography (OCT) signs of injury to optic nerves in MS patients (also CCSVI, as we have found) are very similar to glaucomatous injury\textsuperscript{120}. Glaucoma is thought to result from ischemia of optic nerves, could it be related to CCSVI as well? Also is glaucoma related to normal pressure hydrocephalus?

\textit{iii) Transverse myelitis}

And finally, transverse myelitis has been considered related to multiple sclerosis. The many pressure changes that can occur similar to a Valsalva maneuver can also occur in everyday life to some extent or another depending on the exercise. But provocative statements have been made as long ago as the 1950s\textsuperscript{121}. Transverse myelitis is not common in the general population, but has been seen “often enough in miners, fliers and divers to suggest some occupational correlation. These three groups subject themselves to the Valsalva maneuver or something closely related”\textsuperscript{121}. At that time no mechanism for this had been postulated, but could it be that these individuals also suffer from some venous abnormalities either congenitally or brought on by these demanding activities? Could CCSVI be part of what they suffer from?

\textit{iv) Vascular damage to nerves}

The role of the vascular supply to the nerves remains a critical question to understanding why CCSVI may impact motor function and why some people appear to recover this motor function after balloon angioplasty.
Anderweg \textsuperscript{122} also has a potent discussion of the role of increased pressure and the plexiform networks. Specifically, he states: “In 1940, Batson \textsuperscript{123} explained paradoxical metastases toward vertebrae and brain as the result of reversal of flow in the internal vertebral plexuses during moments of pressure elevation in the thoracoabdominal cavity. In 1944 \textsuperscript{124}, he also described the vertebral vein system as a pathway of collateral outflow from the brain when the jugular veins or the superior vena cava are occluded. He stated that: The so-called sinuses on the skull base, such as the basilar, the cavernous, etc., are really plexiform networks which communicate with similar meshworks within the bones of the skull base, and the pterygoid plexus of either side, below the skull, and the veins of the orbit. Every nerve and arterial foramen in the skull base transmits some veins in this network.” Although it should be clear that most tissues will be affected by a loss of blood flow, the real question is to what extent can reductions in blood flow affect the nerves? There is already some evidence that neuropathic patients suffer from severe endoneural hypoxia. A paper by Cameron et al \textsuperscript{125} has demonstrated that the vascular supply to the vaso nervorum appears to couple to nerve function by causing a reduction of conduction velocity (CV). They showed that normal rats overloaded with glucose developed reduced flow and reduced CV. When the rats recovered from being hyperglycemic, they recovered normal CVs. They also showed that two month diabetic rats treated with guanethidine showed an increase in flow and a concomitant increase in CV. This link with nerve flow might explain the recovery of motor function immediately following balloon angioplasty in some patients.

\textit{v) Developmental venous anomalies}

The role of the venous system in neurological problems already has some history. In the material to follow we will see that there are a number of diseases where we already understand some aspects of disrupted flow in the venous system. For example, venous hypertension is thought to play a role in developmental venous anomalies and may be a cause of intracranial vascular malformations \textsuperscript{126}. Increased evidence suggests that the primary pathogenetic factor in the development of dural arteriovenous malformations (DAVMs) is venous hypertension related to either thrombotic or non-thrombotic reduction of venous outflow \textsuperscript{127-130}. (One needs to recall that AVM is mostly considered a truncular venous malformation from defective development during various stages
of embryogenesis. Conditions in animal models are usually of the fistula type.) Several events that increase venous pressure (such as developmental anomalies of the venous system, venous thrombosis, and head trauma or transcranial surgery) may serve as a trigger. Further, cessation of venous hypertension by complete recanalization of the thrombosed sinus may lead to improvements in the patient’s condition. On the other hand, progressive thrombosis or occlusion of venous hypertension leads to an aggressive clinical course. Some authors suggest that AVMs in deep locations, such as the basal ganglia, or in the periventricular or intraventricular space, have an increased risk of bleeding. This may occur due to the fact that the veins of central drainage have one final common pathway (the vein of Galen and the straight sinus), compared to the superficial veins, which have more connections and are probably more flexible in terms of adapting to changes in flow patterns.

The clinical presentation of DAVMs has been classified as either benign or aggressive. They are considered benign if they produce only ocular symptoms, pulsatile tinnitus, bruit, and/or local cranial deficits. Most of the symptoms are related to venous overload of the primary draining veins, mainly the superior ophthalmic vein and the inferior petrosal sinus. A more aggressive natural history and more severe clinical presentation are associated with retrograde venous drainage and venous drainage into leptomeningeal veins. Some studies show that some DAVMs may disappear without treatment. Spontaneous closure of cavernous sinus DAVM is frequently preceded by transient worsening of symptoms, including retinal hemorrhages and reduced vision. Central retinal thrombosis has been implicated as the underlying cause. A significant change in symptoms (including improvements, such as cessation of tinnitus) may indicate spontaneous closure of cavernous sinus DAVM.

Classification systems for retrograde venous drainage have been proposed by Djindjan et al. and Cognard, et al. In their analysis, Cognard, et al. found that hemorrhage, as the most severe complication, was related strictly to cortical venous drainage and was found in 40% of veins draining exclusively into cortical veins, and in 66% of veins draining into a cortical vein with venous ectasia. The significant difference between these two
types of veins demonstrates that venous ectasia is associated with particularly high risk of hemorrhage, due to vessel wall degeneration that has been found in these venous pouches. Borden created a simplified classification system combining the previous two. Venous ectasia is one form of truncular VM with abnormal venous structure which is generally more vulnerable to thrombosis than rupturing or bleeding.

Leptomeningeal venous drainage, venous dilatations and galenic drainage have been found to significantly correlate with aggressive symptoms. Analysis of the venous drainage pattern demonstrated that high incidence of aggressive symptoms in certain locations was related to the typical venous anatomy in each location rather than to the location itself. Studies done by Davies, et al. support the concept that the type of venous drainage not only determines the first clinical presentation but also reliably predicts the natural history of the AVMs.

vi) Idiopathic intracranial hypertension

Of significance to MS patients undergoing treatment are studies of idiopathic intracranial hypertension. In a group of MS patients, it has been shown using 3D MR venography (MRV) that on the order of 90% of these patients have sinovenous stenoses. It is possible that this too is one form of truncular venous malformation. The treatment for stenoses in the transverse and sigmoid sinuses varies, but it is possible to open these vessels up again. It is not understood if the hypertension causes these stenoses or vice-versa. Higgins, et al. postulates that benign intracranial hypertension “appears to be the result of focal venous sinus lesions, causing partial or complete obstruction to cranial venous outflow.” This particular patient was treated with a stent, with subsequent improvement of symptoms and a reduction in pressure gradients. Higgins et al go on to say that absent or hypoplastic lateral sinuses barely excite comment on MRV. But if the underlying cause of hypertension is venous outflow obstruction, “then removal or bypass of the obstruction should be the aim.” They finally comment that such venous effects have probably been considerably underestimated in the past and need to be carefully researched. In any case, treating the stenoses tends to relieve the symptoms. Today patients with intracranial hypertension can be treated with a lumbar puncture and the drainage of some amount
of CSF. (It is interesting to note that in 1935, Dr. Temple Fay of Philadelphia noted that he treated two patients with spinal drainage and both improved. One had been bed fast and recovered enough to return to work without the use of a cane).

A more recent example where there was compression of the jugular bulb from a tumor was also treated with first balloons and then stenting both leading to improvement of the patient’s condition. There are a variety of different methods used to image these abnormalities (including computer tomography angiography (CTA), but MRV appears to be the safest and provides sufficient information to make the diagnosis. However, stenting on the arterial side can have severe complications and this treatment for the venous side remains unproven and will require careful study. One study discusses the treatment of 4 individuals in whom CSF shunting was not sufficient and the patients required the use of stents in the transverse sinuses. They observed that a fat deposit in one case and a large arachnoid granulation in another caused part of the problem. They specifically used venous stents, so it should be noted that venous stents are not new.

In a recent review by Rangwala and Liu, they note that increased attention has focused on venous sinus pressure and decreased SF absorption. Others argue that reduced venous sinus pulsatility may be a marker for IIH secondarily to raised venous pressure. There is increasing prevalence in adolescence. There is a feeling that onset of puberty is associated with less favourable outcomes. Could this be a more serious form of CCSVI? Although younger children with IIH are male, the older ones are mostly female. There is also some evidence that it is associated with obesity although this is still unclear. Although there are many symptoms, some similar to MS, two of interest to this discussion are pappiledema, preferring a knee-chest position, headaches that are worse lying down (when blood flow should be flowing through the jugular veins but as we know with CCSVI may be hampered). It is also noted that those presenting with vison loss and neurological signs have poorer long-term outcomes. Children with IIH have been reported to have Vitamin A and D deficiencies. Children receiving growth hormone can develop IIH. Growth hormone increases CSF production.
A reasonable question to ask is: “Do people with IIH go on to develop MS?” Or “Do some MS patients also have IIH?” One group reports on 3 cases with MS and IIP. They do raise the question about IIP being caused by MS and why there is not more IIP observed in MS. However, they make the following observation: “the Russian literature refers to cerebrospinal fluid hypertension in the setting of MS exacerbation as if it were a commonly accepted association.” In the Russian study 40 young men and women aged 22 to 44 years old were all found to have raised intracranial pressure (220-380mm of water). In 33 of these patients, there was a widening of the third ventricle. At our own site we have imaged just one IIP case in the last few months using the CCSVI imaging protocol. In a young teenage boy, a normal looking left internal jugular vein was seen on a time resolved MR angiogram but a flow quantification analysis revealed that there was no flow in this vessel. This patient has been treated successfully with a lumbar puncture to drain CSF which provided temporary relief. However, he continues to have problems. Although his referring physician insisted he did not have MS, we did find one clear white matter lesion. This is a young teenage boy (Figure 6) who may also have suffered from some trauma associated with sports activities.

vii) Supratentorial craniotomies

Although perhaps not so common, the role of upper level compression of the IJV by the transverse process of the atlas is hard not to consider as it may play some role in our future understanding of the venous vascular problems in MS. In a study of 36 supratentorial craniotomies, Seoane et al showed that obstruction of the IJV is a cause of venous hypertension and resulted in cerebellar hemorrhage. They note that obstructing the dominant vein markedly increases venous hypertension. So could it be that MS patients with one dominant vein tend to cause hypertension intermittently depending on the physical actions they take during sleep by compressing the one major source of drainage. They note that the interruption of flow in this case can lead to tinnitus and cervical venous hum. Rotation can also lead to compression against the transverse process since the IJV is fixed in position at the jugular foramen. Interestingly they note that when the flow carried by the dominant to sub-dominant transverse sinuses was 3:1 or less that such compressions had less chance to cause such hypertension during the prolonged periods of supratentorial craniotomy surgery.
viii) *Hydrocephalus, cerebrospinal fluid flow, arteriovenous flow: linking it all together*

Cerebrospinal fluid (CSF) plays a critical role in the regulation of cerebral volume in response to the incoming arterial flow and outgoing venous flow. There is much that can be investigated in CSF flow dynamics involving the ventricular, cranial subarchnoid and spinal subarachnoid compartments. With 70% of the brain’s blood being venous in nature, the veins also provide some degree of compliance to the system. Greitz reported evidence of compression of the veins in patients with communicating hydrocephalus (CH). This sounds similar to the loss of visibility of medullary veins seen with SWI in more severe MS cases. Hirabuki showed reduced flow in the superior sagittal sinus causes hydrocephalus in some patients. The work of Baledent et al also showed that there was a shorter delay to venous peak flow indicating a loss of compliance and that the arteriovenous flow as a function of the cardiac cycle showed a biphasic behavior in normal controls and a tri-phasic behavior in CH patients. In studies on kittens, Da Silva et al showed that there was a reduced CBF after just one week after the onset of kaolin-induced hydrocephalus. But the most intriguing result was a case seen by Baledent et al that showed bilateral jugular vein stenosis. The question then is whether or not the venous obstructions led to CH or whether the CH led to venous collapse. This is a similar argument to that in intracranial hypertension. But it is becoming clearer that these systems are strongly linked and the presence of CCSVI in these cases is buried in the literature predating the Zamboni hypotheses. As a clear example of this, consider the following case study where there was a bilateral blockage of the internal jugular veins and a dilated of the epidural veins blocking the CSF flow. This patient had hydrocephalus and myelopathy. As the authors note that the patient underwent a sigmoid sinus-to-internal jugular vein bypass with a saphenous vein interposition graft and found that the obstruction accounted for both the hydrocephalus and the myelopathy. They go on to state: “The exact pathophysiology of our patient’s myelopathy is not entirely clear. It is tempting to hypothesize that the bilateral occlusion of the internal jugular vein caused the blood to be shunted progressively through the epidural venous plexus. However, venous hypertension, direct compression of the spinal cord, or both could have caused the myelopathy.”
But CSF flow in 20 patients with NPH and CH compared to 10 normals is not so simple. The work of Giang et al.\textsuperscript{165} suggests that there are two types of these patients, a slow component flow type for NPH and a fast type for NPH and CH. In the former they measured peak velocities in the aqueduct of Sylvius to be 1.92 +/- 1.11 cm/s and in the latter 10.52 +/- 0.23 cm/s. Normal peak speeds were 4.92 +/- 0.28 cm/s. These patients all had ventriculomegaly and the triad of symptoms of dementia, gait disturbance and urinary incontinence.

There have been some efforts recently linking venous flow insufficiency to hydrocephalus\textsuperscript{166}. Williams notes that “reduced volumes of arterial blood will enter the system if venous flow is interrupted.” In hydrocephalus, the speed and origin of the venous insufficiency will influence the morphology of each case, particularly with respect to ventricle size. When pressure increases rapidly, edema, compression of CSF spaces and cerebral ischemia will follow. Ischemia will be a feature of all instances of pathologically raised central nervous system pressure. Situations that increase pressure will reduce venous volume and increasing venous pressure. Venous flow may be sufficiently reduced to affect both CSF absorption and arterial supply. These lead to CSF accumulation (since CSF is carried out of the brain also by veins) and ischemia. It is well known that removing CSF improves cerebral venous and arterial flow\textsuperscript{167}. Could those people with limited vertebral plexus, vertebral veins and deep cervical veins be suffering the same form of venous insufficiency?

One paper that links ventriculomegaly, hydrocephalus, increased intracranial venous hypertension and jugular constrictions or stenoses in several clearly documented cases in children with achondroplasia\textsuperscript{168}. This work studied five children with ventriculomegaly and monitored intravascular pressure (IVP). The IVP was elevated in all cases and the resorption of CSF into the sagittal sinus was slow in all cases. Jugular venograms with pressure monitoring were acquired in four cases. These studies confirmed a narrowing in the jugular foramen in all patients with a significant pressure gradient varying from 3 to 10 mm Hg from the sigmoid sinus to foramen. These pressure gradients were independent of head position. A second gradient was found in two patients in the level of the upper thoracic aperture from 6 to 14 mm Hg. Identical procedures in a control group showed no pressure gradients by the foramen and only 2 to 5 mm Hg by the thoracic aperture. The lack of obstruction but
the presence of decreased absorption of CSF is suggestive of venous sinus hypertension. Although this association is still somewhat contentious, Steinbok et al note that: “Bering and Salibi\textsuperscript{169} were able to cause hydrocephalus in 74% of dogs by occluding the internal and external jugular veins and the condyloid foramina at the base of the skull.” They also point out that there are numerous references showing that hydrocephalus is associated with intracranial venous occlusion, jugular venous obstruction, superior vena cava hypertension and superior vena cava occlusion. More specifically the work by Wu et al\textsuperscript{170} shows that hydrocephalus is reversible when related to jugular stenosis. As to the question of which comes first, hypertension or venous hypertension, the work of Sainte-Rose et al\textsuperscript{171} is perhaps the most definitive study showing that after shunting sagittal sinus and jugular vein pressures equalize except in the cases where narrowing of the sigmoid sinus obstruction. Clearly these findings begin to tie together much of the association of venous drainage problems with direct effects (in this case major effects) in the CSF. Perhaps the less severe the venous narrowings and stenosis the slower or more chronic the effects would be as proposed by Zamboni with chronic cerebral spinal venous insufficiency.

**ix) Cranial and spinal damage congenital or otherwise and its affect on venous blood flow or CSF flow**

Flanagan\textsuperscript{172} has focused on the role of the spine and CSF flow in proposing the importance of physical and mechanical abnormalities that can affect CSF flow and hence modify cerebral fluid dynamics and lead to tissue damage. He notes that the suboccipital cavernous sinus, marginal sinus and other venous plexuses play a key role in maintaining blood flow and a balanced CSF response. He states: “In brief, the accessory drainage system of the brain plays an important role in upright posture in that it affects cerebral perfusion pressure and brain blood flow; brain blood flow via the myogenic autoregulatory reflex mechanism; brain cooling; the CSF pressure gradient and passive production of CSF and lastly, brain flotation and support.” Since these veins pass through openings in the base of the skull, they are most susceptible to compression from certain conditions of the skull and spine, especially the upper cervical spine. For example, the optic nerve can be compressed by the weight of the brain due to collapse of the inter-chiasmatic cistern on the floor of the middle fossa. Compression of the vertebral veins can prevent blood supply back to the cord. Compression of the jugulars by the transverse
processes can cause poor jugular flow. Absent accessory outlets and intracranial anomalies can decrease drainage capacity. This may predispose patients to venous hypertension similar to the case when tight iridocorneal angles predispose patients to venous hypertension and glaucoma. All of these may occur naturally or they may be induced by traumatic events as well. Poser has suggested that trauma to the spine can lead to exacerbations of MS and that repair of herniated discs causing cord compression can alleviate symptoms. Thus one might postulate that inherited or acquired disorders of the spine could lead to chronic venous hypertension ischemia and oxidative stress. On the other hand blockages of the CSF could cause similar venous problems through the development of chronic normal pressure hydrocephalus. These changes may not be visible in major veins but may be caused in part from poorly developed venous vertebral plexi, increased pressure and poor flow to the cord. If at the same time there are major stenoses to the internal jugular veins this could also impact the brain. The low prevalence of MS in the Asiatic population may also be related to their cranial structural differences between Caucasians. Generally spondylosis can have associated with it not only compression of nerves and cord and degeneration of the discs but also an effect on the vertebral vascular system. In a paper by Brain and Wilkinson, they show the presence of spondylosis in a series of 17 patients with MS. Problems were often found near C5/C6/C7 which may have involved nerve compression, spurs (osteophytes), disk degeneration, sclerosis, filling defects (after cervical myelogram) and narrowing of the intervertebral foramen. They go on to note that those with cervical spondylosis and MS appear to have relapses post trauma and they raise the question, “Could this be due to vascular damage to the vertebral plexus and cord?”

Flanagan also suggests that scoliosis can cause functional stenosis and compression of the VVP (vertebral venous plexus) against the inside curve of the spine and subsequent venous hypertension. It can also cause deformation of the thoracic outlet neurovascular tunnels. It is possible that Chiari malformations due to a decrease in CSF volume can cause the brain to sink sufficiently toward the base of the skull to compress the dural sinuses. The aging dura mater can also cause weakness in the dural sinuses making them more susceptible to compression. Furthermore, the occipital marginal sinuses and accessory vertebral venous outlets are much
smaller in size than the transverse and sigmoid sinuses making them more susceptible to compression. Cervical kyphosis can disturb and distort the normal relationship of the brainstem within the vault and neural canal causing functional Chiari type malformations. Thus venous hypertension is transmitted to blood and CSF in the subarachnoid space, which is transmitted to the cord without evidence of defacement or compression. In this regard, venous pressure in the iridocorneal angle is transmitted to the optic nerve without deformation of the iridocorneal angle or the optic nerves. The long tracts of the cord are the first to feel the pressure caused by venous hypertension in the VVP. Signs of bilateral weakness suggest increased pressure on the cord. Finally, the valveless craniofacial veins, cavernous sinus, and suboccipital cavernous sinus are vital to brain cooling. With poor venous drainage, MS patients most likely have reduced brain cooling which may further compromise the state of health of the brain tissue.  

Part of the problem associated with venous stasis in spinal damage can be understood from a paper on lumbar spine problems associated with congestive heart failure, night pain and increases in venous volume and pressure in the paravertebral plexus of Batson. These authors note that diminished right heart compliance and/or primary pulmonary hypertension can cause a partial lumbar spine stenosis to become complete. The increased pressure in the right atrium creates a venous back pressure that is transmitted to the relatively valveless vertebral plexus producing an distension of the epidural venous plexus. Most interestingly, they note that the supine position itself predisposes to an increased paravertebral plexus venous volume. This can be due to both atrial pressure increases and intra-abdominal pressure increases. They note that pulmonary blood volumes can change from 400mL in the upright position to 700mL in the supine position. These increased pressures lead to chronic overstretching of the venous plexus and induce a creep or plastic-like deformation in the collagen of the vessels. They note that permanent bulbous dilations may occur and at surgery distended pedicular venous varicosities adjacent to an inflamed spinal root can be seen. Of interest to much of the venous discussion in this review is their comment that “Sudden surges in pressure produced by episodic Valsalva maneuvers can be transmitted undamped by this comparative lack of segmentation, producing a decompensating “water-hammer” effect on the venous walls.” They go on to note the potential of creating a local anoxic effect and possibly
stagnant neuroischemia. This rather independent assessment of the role of veins begins to sound very similar to the mechanical considerations described by Schelling \cite{25} and draws attention to the importance of the venous system and proper blood flow whether it be in the spine or in the brain.

Finally, another known problem with MS patients relates to their dental health. Williams et al\cite{166} noticed a mean bilateral displacement of the temporal bones in the skull with only 100lb of force. Biting at 100lbs for 5 seconds resulted in displacement of 0.27mm (peak 0.8mm) in normals and 1.71mm (peak 3.6mm) in MS patients. Increased suture mobility from teeth clenching could result in pressure changes inside the cranium that could influence CSF flow, blood flow and brain tissue in general. Night-time clenching can exceed 600lbs of force at the tooth surfaces. These periodic episodes of bruxism related skull distortions may lead to short bursts of increased ICP which, over time, may lead to demyelination around periventricular veins. If bruxism causes changes in venous flow or pressure spikes, this could explain valve deterioration, luminal fibrosis and collagen buildup in the extracranial venous system. Williams also noticed that the sutures in MS patients are abnormal similar to the findings of Flanagan\cite{172}.

\textit{x) Leukoaraiosis}

Leukoaraiosis is a radiological finding characterized by white matter hyperintensities in the periventricular region on T2-weighted MRI scans\cite{177}. Severe leukoaraiosis is associated with spongiosis, gliosis, and demyelination\cite{62}. Its clinical symptoms are diverse, with some individuals being asymptomatic, while others may develop gait disturbance\cite{178}, cognitive impairment\cite{179}, vascular dementia\cite{180,181}, and enhanced risk for stroke\cite{182}. While the pathogenesis of leukoaraiosis is not fully understood, it is thought that the condition is associated with chronic cerebral ischemia\cite{183}. In particular, the condition is characterized by non-inflammatory collagenosis of the periventricular veins\cite{61,62}, resulting in thickening of the vessel walls and narrowing, or even occlusion, of the lumen\cite{62}. Commenting on the physical location of this phenomenon, Moody et al\cite{62} state that periventricular venous collagenosis (PVC) is “most intense and appear(s) to originate in the tissue adjacent to the lateral angle of the lateral ventricles. In the most severe cases, venous wall thickening (is) also observed in
vessels of the middle and superficial portions of the deep white matter although to a less severe extent than in the periventricular region.” Moody et al 62 found a strong association between the probability of severe leukoaraiosis and vein wall thickness, suggesting that altered venous hemodynamics are implicated in the pathophysiology of the disease.

Given that the perfusion pressure in the periventricular region is generally very low 60, it has been postulated that stenosis due to PVC will result in reduced blood flow through the periventricular veins, with possible shunting of blood away from this region via the transcerebral medullary veins 61. Indeed, O’Sullivan et al 184 found CBF in leukoaraiosis patients to be reduced in the deep white matter of the periventricular region compared with healthy controls. Other researchers 87, 185 have also found reduced CBF in the white matter to be associated with leukoaraiosis. If low enough, reduced blood flow in the periventricular region will result in hypoxic stress and ischaemic damage 62, and this is something which, it has been postulated 60, 186, might lead to breakdown of the BBB or even perivenous collagenosis. This hypothesis appears to be supported by the work of Lochhead et al 66, who found hypoxia followed by re-oxygenation to cause increased permeability of the BBB in rats. Further evidence implicating ischaemia in cerebral vascular loss in individuals with leukoaraiosis comes from Brown et al 88, 186. Though staining of afferent vessels (arterioles and capillaries, but not veins or venules), they found the vascular density in leukoaraiosis lesions to be on average 20% lower than that in the deep white matter of normal subjects 88. While this is perhaps not such a surprising finding, given the reduced metabolic requirement of lesions, they also found the vessel density in the superficial normally appearing white matter of individuals with leukoaraiosis to be significantly lower than that in controls, suggesting the phenomenon to be widespread rather than just affecting the lesions. The fact that significant loss of vessels in the normally appearing white matter in leukoaraiosis subjects was not associated with histologically detectable abnormalities, indicates that vessel loss precedes parenchymal cell loss, and not the other way round, as some commentators have suggested 187. Brown et al 186 postulated that ischaemic damage caused by flow stasis in capillaries, results in atrophy of these vessels and ultimately vascular loss. Although Brown et al 88, 186 only considered arterioles and capillaries, loss of these vessels must inevitably have resulted in a reduction in the venous vasculature in
leukoaraiosis subjects. While cerebral venous atrophy has not been specifically studied in the context of leukoaraiosis, several researchers have observed loss of venous vascular visibility in susceptibility-weighted MRI scans of patients with MS\textsuperscript{15,188}.

The degree of pulsatility experienced in the cerebral vascular bed is controlled by a windkessel mechanism, which transfers energy from the arterial flow to the CSF as the blood enters the brain\textsuperscript{106}. The efficacy of this mechanism is, in part, governed by vascular compliance; if compliance is high, then flow through the cerebral vascular bed is smooth. If however, compliance is low, then increased pulsatile energy will be transferred to the arterioles and capillaries, and ultimately to the veins. It is therefore perhaps not surprising that individuals with vascular dementia, a condition strongly associated with leukoaraiosis\textsuperscript{180,181}, exhibit greatly increased pulsatility in the blood flow through the straight sinus\textsuperscript{106}. However, the same phenomenon is also observed in individuals with leukoaraiosis\textsuperscript{107}, suggesting that the two conditions share similar vascular characteristics. The fact that pulsatility of the flow through the straight sinus is greatly increased in leukoaraiosis subjects implies that the flow through the transmedullary and periventricular veins will also be strongly pulsatile. Consequently, the abnormal shear forces associated with this pulsatile flow might result in damage to the venous endothelia\textsuperscript{189}, thus precipitating collagenosis\textsuperscript{186}.

VII. The role of drugs in treating vascular problems

Perhaps the recent results on CCSVI can actually serve to draw our attention to those aspects of current drug treatment that may be affecting the vasculature in a positive way when the drugs work. Our focus in this section is on the role of cerebral endothelial cells (CECs) in the pathogenesis of MS\textsuperscript{190}. The blood-brain barrier (BBB) is an impermeable barrier to most of the circulating substances in the blood. It is already assumed by some researchers in MS that the disease is characterized not only by demyelination but also the presence of perivenular activated leukocytes.

Although the following discussion is understood to be a potential pathway to the chemistry of the neurodegenerative process, there is no initiation or known antigen that starts the process. The current belief is
that CD4+ T cells become activated toward myelin-specific proteins and trigger a massive inflammatory cascade that eventually leads to transendothelial migration of activated leukocytes and macrophages from the vascular space into the brain. CECs themselves may act as antigen presenting cells (APCs), presenting antigens to activated leukocytes and acting as human lymphocyte activation (HLA) class II molecules. It is then believed that CD4+ T cells, B cells and macrophages enter the CNS through the disrupted BBB. The initial capturing of the leukocytes into the endothelium involves a rolling of the leukocytes along the underlying endothelial layer. Capture and rolling appear to be necessary for firm adhesion of the leukocyte to the underlying endothelium. This process involves the expression of integrins which bind to their ligand on the endothelial cell (VCAM-1 = vascular adhesion molecule -1). Platelet endothelial cell adhesion molecule-1 (1/PECAM-1) is involved in the regulation of extravasation of activated leukocytes. Elevated levels are seen in MS patients.

Simka 191 gives the following summary from von Andrian 192: “Actually, transmigration of a leukocyte through the endothelial barrier is an active and orchestrated phenomenon. A simple increased expression of one element (an integrin, for example) is not enough. In brief: “Migration of a leukocyte to the pericapillary space consists of at least three consecutive steps. Each of them is executed by a specialised set of signalling proteins. These steps are: 1) tethering and rolling which are mediated by selectins and addressins; 2). exposure to chemotactic stimulus, which is dependent on chemokines and G-protein-coupled receptors; and 3) firm adhesion of a leukocyte to the endothelium, which is mediated by activated integrins and their counterparts. Adhesion of a leukocyte to the endothelium is followed by its transmigration through an endothelial barrier to the perivascular interstitium.

Also, serum pro-inflammatory cytokines are elevated before clinical exacerbations of MS and these affect CECs and alter CNS endothelium barrier function 193. Elevated serum levels have been seen in MS patients. Matrix metalloproteinases (MMPs) also lead to disintegration of the BBB and convert inactive endothelin in to endothelin-1. MMP-9 levels are elevated in MS 194 and appear to correlate with the degree of BBB disruption (documented by the presence of contrast-enhancing lesions). Interferon may help reduce these BBB disruptions.
Specifically, IFN-b (Betaseron, Rebif, and Avonex) adhesion to cell surface receptors may help stabilize CECs by blocking the release of endothelial microparticles (EMP) and transendothelial migration of monocyte-EMP complexes and maintaining expression of junctional proteins.

Drugs may help alleviate or ameliorate the problems with the vascular system when other forms of treatment are not possible or not available. The long history of immunological studies and vascular studies might well be brought together under a future single umbrella of “vascular immunology”.

VIII. Truncular venous malformations

Venous abnormalities might best be viewed from an embryological background when trying to understand the presence of truncular venous malformations. The development of the venous system begins in the early stages of the fetus and has a well-known developmental etiology. A well-known example of abnormal venous development occurs in the case of primary Budd-Chiari syndrome, which can lead to severe portal hypertension. For jugular veins, development occurs as the neck lengthens and its drainage level shifts toward the cephalad part of the pre-cardinal vein which later develops into the internal jugular vein. This makes one wonder what happens to the venous development in the final growth spurts from pre-puberty to manhood during the teenage years often before the first manifestations of the disease occur in adults. An interesting paper reviewing the adult collateral venous flow from the brain points out how well studied the venous system was back into the early 1800s. This well written and at times ribbing paper when it comes to our current lack of focus on the venous system and loss of venous knowledge in a sense. Anderweg points out a few interesting findings: individuals who had bilateral jugular resection had elevated cerebrospinal fluid pressure with compression of the muscle bed in the neck. He suggests that disturbances of cerebral venous outflow as a whole can lead to ventricular enlargement and increase cerebrospinal pressures and “insufficient deep venous flow also causes periventricular atrophy”. This begins to sound like the more recent papers on disrupted perfusion seen with MRI and a loss of small vein visibility as seen with SWI. He also points out that elevated pressures may lead to collapse of the sigmoid sinuses due to increased superior sagittal sinus pressure. Some
discussion of the role of cerebral blood flow in hydrocephalus patients and their cognitive condition refers to the need to improve flow in the white matter of children with this disease (see also ref 111). Finally, he closes by noting that critical discussions are needed not just on new theories but on old interpretations that are based solely on multiple referenced papers that still remain to be proven or are taken as gospel without having met the full modern day barrage of investigations. He then says: “Strict demands must be made not only on new interpretations, but also on old ones, which is much more difficult because of habit and loyalty.” Finally, he notes the powerful new imaging tools such as computed tomography and magnetic resonance imaging and closes with: “Great opportunities have opened up for the acquisition of new insights.” That is particularly true when it comes to the study of the role of the venous vasculature in multiple sclerosis.

IX. Intracranial and extracranial venous stenoses and chronic venous hypertension

i) Venous stenosis

Moody et al. 61, 62 observed periventricular venous collagenosis in patients with leukoaraiosis, resulting in noninflammatory thickening of the venous wall. From this they concluded, “stenosis or occlusion of deep cerebral veins may promote development of leukoaraiosis”. While luminal narrowing of the periventricular veins has not been reported in MS patients, Putnam and Adler 197 observed that the periventricular lesions associated with MS result in gross distention of the transcerebral veins up-stream of the lesion. This indicates that venous stenosis may be occurring and that the hydrodynamic resistance of the veins adjacent to the plaque may be greatly increased. The fact that stimuli which produce vasodilatation of the extraneural vascular bed, such as hot baths, exercise, and alcohol frequently provoke adverse symptoms in MS patients 48, 65, also suggests that luminal narrowing may be present in the periventricular veins in individuals with MS. Venous pooling in the lower limbs, when upright, can, in deconditioned individuals such as MS patients, greatly reduce the cerebral blood pressure 198 and this will inevitably reduce the perfusion pressure pushing the blood through the periventricular veins. Given that the perfusion pressure in the periventricular region is relatively low and particularly sensitive to fluctuations in total CBF 60, any stenosis in these veins would reduce the blood flow in
this location and under conditions of extracranial venous dilation might encourage shunting of the blood away from this region, resulting in hypoxic stress.

For more major veins, the question remains open as to what causes these stenoses. It could be that once there is a congenital problem that causes collateral flow to develop or especially in those cases where it is difficult for collateral flow to develop, that there is a change in wall shear stress (WSS). WSS represents the dragging force exerted by the flow on the endothelium. This could be a potential exacerbating factor in further stenosis development or in the widening of the jugular veins often seen near the confluence with the subclavian and brachiocephalic veins. Narrowing and restenoses may occur with hemodialysis patients at the vein to graft anastomosis. A recent paper using a pig model has shown increases in WSS subsequent to the placement of a hemodialysis graft. They found neointimal thickening, increases in wall shear stress, VEGF-A and pro-MMP-9 followed by increases in pro-MMP-2, active MMP-2, VEGFR-1, VEGFR-2 and TIMP-1. VEGF-A is important in vascular remodeling. The contention here is that an imbalance of MMP activity over TIMPs promotes the migration and proliferation of smooth muscle cells which leads to intimal hyperplasia. Other hemodynamic factors can also initiate intimal hyperplasia such as turbulent flow, eddy currents, and vessel hypoxia. Similar problems near stents might also be expected when blood flow characteristics are significantly modified. Interestingly, they then state: “It has been shown in animal models of atherosclerosis and restenosis after angioplasty that inhibition of VEGF-A will decrease restenosis.” They later state that an overexpression of TIMP-1 can also lead to a decrease in stenosis formation.

**ii) Vascular immunology**

Bergan’s animal work on chronic venous disease is perhaps the closest to the earlier work of Putnam in evaluating role of venous obstruction. Occlusion of a mesenteric vein at least 350μm long and 35 to 70μm in diameter was performed in a rat. The number of leukocytes migrating across the vessel wall increased progressively during occlusion. Multiple microhemorrhages occurred upstream of the occlusion (usually 20 to 30μm but some as large as 200μm in diameter) It is well-known in carotid atherosclerosis that normal flow and
The role of the caval system in venous hypertension

The team of Aboulker et al.\textsuperscript{203-206} studied the vertebral plexus network using a phlebology technique as early as 1971. Between 1971 and 1977, they studied 176 patients with myelopathies with an eye toward the potential role of venous hypertension and abnormal venous behavior of the vena cava system and its major trunks and feeding veins. They found that the most frequently occurring events from highest to lowest were as follows: stenosis of the left iliac; obstruction of the left renal vein; anomalies of the azygous vein; compression of the brachiocephalic vein; atresia of the internal jugular veins; compression of the vena cava. In 38% of the cases...
they found 3 or more anomalies. These venous problems may have been from stenoses or from external compression. When major vessels were re-opened some of these people with motor problems (such as development of quadriplegia) recovered and the progression of the problems not only stopped but was reversed. Their work may well be considered to be the major clinical precursor to the work of Zamboni and that work which first suggests the major role played by venous hypertension throughout the vena caval drainage system. This approach was quite new at the time and required special consents by the families. These venous treatments were undertaken when no other causes for the problems could be found. They discuss potential dangers such as pulmonary emboli and other problems. Of these studies, it is interesting to note that there were 17 of 50 operations that showed improvement for the patient, 17 were transitory, and 16 failed to show improvement. Interestingly, they also use the expression “une libération poussée de la veine cave” (see bottom right of page 1012 in ref. 206). The choice of the phrase liberation procedure that has become the bane of CCSVI has its roots in opening the flow not in freeing the subject from disease.

**iv) The re-introduction of CCSVI specifically for multiple sclerosis**

As demonstrated above, historically, various researchers have implicated the intracranial venous system in the etiology of MS, but it was not until Zamboni formulated the concept of CCSVI ¹ that abnormalities in the extracranial venous system became associated with multiple sclerosis specifically. In 2009, Zamboni et al ¹ published a ground-breaking study involving 65 MS patients and 235 controls in which they found anomalies in the venous pathways from the brain to the heart to be strongly associated with MS. These abnormalities were characterized by the following five criteria, which were measured using color-Doppler sonography. Zamboni defined CCSVI as being present when two or more of these criteria were observed in any given subject ¹⁰⁰.

1. Reflux constantly present in the internal jugular veins (IJVs) and/or vertebral veins (VVs) with the head at 0° and +90° (46/65 for MS patients and 0/235 for controls).

2. Reflux in the deep cerebral veins (40/65 for MS patients and 0/235 for controls). High resolution B-mode evidence of proximal IJV stenosis (24/65 for MS patients and 1/235 for controls). Flow not
Doppler detectable in the IJVs and/or VVs despite numerous deep inspirations with the head at $0^\circ$ and $+90^\circ$ (34/65 for MS patients and 7/235 for controls). Negative change in cross-sectional area (CSA) in the IJVs when head moves from $0^\circ$ and $+90^\circ$ (36/65 for MS patients and 25/235 for controls).

In this study, Zamboni et al also undertook selective venography and this revealed extensive stenotic patterns to be associated with MS, with 59 out of the 65 MS patients exhibiting either unilateral or bilateral stenosis of the IJVs, and 56 out of 65 affected by stenosis of the azygous vein. In a related study, Zamboni et al observed that in MS patients the CSA of the IJVs did not appreciably enlarge when subjects were supine in comparison with sitting. Given that in healthy individuals the CSA of the IJVs when supine is approximately six times that when sitting, this suggests impairment of the flow through these veins in the MS patients and extensive collateral rerouting of the blood through other venous pathways when in the supine position; something that is indicative of extracranial stenosis. Indeed, through venography, Zamboni et al have been able to demonstrate extensive collateral rerouting of venous blood back to the heart due to the presence of extracranial stenosis in MS patients.

v) The introduction of cerebral thoracic neuro-vascular syndrome (CTNVS)

Throughout this review, the focus has been on the venous system. However, it is hard not to also reconsider the arterial system as a player here as well. The earlier discussion of sympathectomies leading to less cerebral vascular constriction and dilation of both arterioles and venules opens the door to a role for insufficient arterial supply in some cases that might compound the presence of CCSVI. Along these lines, work of Noda et al as early as 1982 focused on the concept of treating thoracic outlet syndrome. The authors performed a bilateral scalenotomy in a patient suffering from thoracic outlet syndrome with ipsilateralparalysis and Parkinson’s disease in 1983 with some success. This first effort led the authors to pursue this technology over the next 20 years culminating in experience with 1600 patients. They claim that compression of the arterial system, specifically the internal carotid arteries, vertebral arteries around C6/C7 and the subclavian can lead to such
symptoms as Parkinson’s disease, Alzheimer’s disease, and multiple sclerosis. They comment that in 12 of 17 MS cases operated on showed improvement. It behooves us then to ask: “How much of the neurological disease we view today might be caused by neurovascular and extracranially initiated neurovascular disease?”

X. The use of MR as a pre-treatment guide to treating CCSVI in multiple sclerosis

Zamboni used Doppler ultrasound as a means to diagnose CCSVI. However, ultrasound is an operator dependent methodology that, for the most part, does not provide full 3D coverage of the brain, neck and upper chest. Magnetic resonance imaging (MRI) on the other hand is capable of both 3D anatomical and 2D cross sectional flow measurements in an operator independent fashion. MRI is already used by neurologists to study the presence of lesions and iron in the brain and it is not difficult to extend the scanning procedure to include functional information as well. From a vascular perspective, MRI offers a non-ionizing means by which to collect high resolution 3D information about arteries and veins in the brain and neck and major vessels above the heart with a resolution on the order of 1mm³. Further, it offers a means to quantify flow in a given slice in minutes and estimate the cardiac input/output to the entire brain from all major vessels. Using susceptibility weighted imaging (SWI), one can monitor the small veins in the brain and estimate the iron content in the basal ganglia and thalamus. Armed with these data, it becomes possible to monitor the brain and its function before and after treatment. Therefore, these measurements may provide a strong tool for treatment planning and an objective tool to study if the patient has improved flow pre and post treatment.

In the first part of this review, several MR images were shown to address issues such as iron content, reduced perfusion and vascular abnormalities, for example. In this section, we present evidence that there are a variety of venous abnormalities that can occur in MS patients (Figure 7). A priori knowledge of this 3D vascular structure can prove to be essential to determine what plan of action should be followed for endovascular treatment. In some cases, it may be so complicated that no treatment may be possible. For example, consider the example in Figure 8, where there appears to be no collateral vein development in the deep vertebral system or in Figure 9 where the deep cervical veins play the role of the jugular veins. As the venous system is quite varied,
having the most information pre-treatment is an important consideration both for the interventionalist and for the neurologist as well; the former for treatment planning and the latter to follow objectively any results that may ensue because of the treatment itself.

As demonstrated above, MRI offers a powerful means to non-invasively identify both functional and structural abnormalities in MS patients. Since MS patients are being treated by the 1000s annually now, it is critical to discuss the role of imaging pre and post treatment. Although ultrasound provides a wonderful inexpensive tool to study real time blood flow, it does not offer the critical 3D structural data available from MRI or the complete cross sectional flow information. One also has to bear in mind that the geometry of the venous system is unique in every person. Therefore, MRI is critical for the following reasons:

- it provides key neurological information for the patient and the neurologist following the patient such as the presence or absence of lesions which are markers for the state of the disease;
- it provides a means to monitor iron content in MS lesions, in basal ganglia and in the thalamus;
- it can visualize arteries and veins in the head, neck, spine and aortic arch which are key elements in treatment planning for the interventionalists;
- it provides a means to measure blood flow in each major vessel everywhere in the body;
- it can provide quantitative information on perfusion to brain tissue;
- it can be compared to either ultrasound or angiography both qualitatively and quantitatively;
- it may offer a means in the future by which to categorize those patients who respond best to angioplasty;
- and the data serve as a control prior to treatment for patient follow-up or in case restenosis occurs.

The advantage of MR data is that it is objective and quantifiable. MR has the capability to address a broad range of physical phenomena including but not limited to measuring: iron content; lesion load; vascular anatomy; quantitative flow of vessels and CSF; perfusion to tissue; functional brain imaging; oxygen saturation; diffusion of water through tissue; and metabolite concentrations. All of these methodologies have the potential to investigate the effects of MS on the human brain. We give some rationale for the use of each method in bullet form below:
• **iron content:** iron likely serves as a biomarker for tissue damage (and perhaps endothelial damage)

• **lesion load:** this is a direct measure of affected tissue usually in white matter but also in gray matter

• **vascular anatomy:** 3D MR angiography is a powerful means to review all major vessels in the body

• **quantitative flow of vessels and CSF:** flow characteristics are critical to understanding what is normal on both the venous and arterial sides as well as for the CSF

• **perfusion to tissue:** PWI in MRI is used to monitor flow to the tissue and can be used to measure CBV, CBF and MTT but not oxygen saturation

• **functional brain imaging:** also known as BOLD, fMRI is commonly used to study brain function in areas such as cognitive, motor and visual activity in the brain by monitoring the MR signal in time which is indirectly monitoring changes in oxygen saturation

• **oxygen saturation:** MR is actually sensitive to the de-oxyhemoglobin in venous blood and as such new techniques are being developed to allow for direct oxygen saturation measurements in major veins in the body

• **diffusion of water through tissue:** both DWI and DTI offer an indirect look at how water diffuses through tissue and can be a sensitive measure of when cytotoxic or vasogenic edema occur of injury to the tissue

• **metabolite concentrations:** MR spectroscopy is used as a means to map out NAA, Cho and Cre and monitor tissue bio-chemical function.

Much of the data collected with MR is 3D in nature. As such, it is in principle relatively simple to perform image rotations for 3D display purposes (see for example [www.ms-mri.com](http://www.ms-mri.com) for some examples of venous vasculature in MS). Also, 3D data is amenable to not only rotations but also scaling and with these two features, multi-modal comparisons with ultrasound and angiography are viable today. Finally, given the non-invasive and non-ionizing nature of MRI, patients can be scanned multiple times without fear of damaging cells in the tissue.
XI. Conclusions and Future Directions

The venous system has long taken second place to the study of the arterial system. But a careful look back into
the early understanding of the origins of cardiac circulation by William Harvey will reveal that the study of
veins was the catalyst that led us to breakthroughs in understanding the cardiovascular system. In this particular
instance, Harvey made the observation that the valves in the veins led to unidirectional flow and hence blood
must travel in a circle. His subsequent experiments to prove this introduced the world to the notion of blood
being pumped throughout the body and at the same time introduced the entire world to the concept of
hypothesis driven research. As Brecher notes in his review of the history of venous research \(^\text{210}\), this one major
breakthrough may well have been “the greatest piece of venous research ever done.” Today we are
rediscovering the role of the veins in numerous diseases, with the current breakthrough being the presence and
association of abnormal venous flow in multiple sclerosis \(^1\).

In this review, we have demonstrated that abnormal venous flow is associated, in part, with the following
diseases: idiopathic intracranial hypertension, hydrocephalus, encephalomyelitis, intracranial vascular
formations, nerve function, transient global ischemia, cough headache, primary exertional headache,
hydrocephalus, transient blindness and optic neuritis. We have shown there is evidence that with more severe
venous insufficiency venous blood volume reduces. This coupled with a mild form of hydrocephalus may be
enough to explain the findings in MR of: reduced arterial flow and hence reduced perfusion to the brain; the
subsequent chronic ischemia that would naturally follow; the iron build up when this ischemia is more severe;
and many of the symptoms seen with MS patients. Why is multiple sclerosis such a variable disease? Let’s
consider perhaps the role of a single jugular vein carrying the major flow out of the brain. If during sleep or
exercise flow in this vein is affected on a regular basis, this is bound to have a chronic effect on perfusion to the
brain, similar to the same reason why one finds reflux in transient global amnesia and transient optical
problems. With the evidence of severe problems in compressing dominant veins in supratentorial craniotomies,
such as venous hypertension, cerebellar hemorrhage, tinnitus and cervical venous hum, could not constant
venous hypertension lead to the same effects especially if exacerbated by specific physical events that put strain on the vascular system such as giving birth to a child for women with MS or for especially demanding physical exertions that have severe forms of Valsalva manoeuvres?

Despite the fact that the finger is pointing toward the venous system as one of the culprits in multiple sclerosis much research remains to be done. Specifically, a careful mapping of the actual hemodynamics and fluid dynamics of the vascular and CSF systems will be required in normal controls and MS patients. Following patients pre and post-treatment to validate changes in both systems may help unravel the importance of each. Both human and animal studies should be done. The advantage of having a specific hypothesis such as this is that one can begin to design new experiments to test these hypotheses. One can redirect genetic efforts to look for genes associated with vascular development and growth; for the role of flow in immunological response; for new methods to monitor the brain’s hemodynamics; the role of the damage to the cranio-cervical spine and the effect this has on CSF and blood flow; for characteristics that define when the risk of disease from CCSVI is highest; and for new treatments that attack one of the major sources associated with multiple sclerosis. The search for a clear understanding of the role of CCSVI in neurological diseases is just beginning. Whether the vascular issue is understood or not yet, it is important to be open minded and as said by Dr. George B. Hassin of Chicago in 1935 when reviewing the extreme work of sympathectomies (46):

“However, multiple sclerosis is such a distressing, hopeless condition that any therapeutic measure that appears promising should be given careful consideration, regardless of the difference of opinion as to the pathophysiologic features of this disease.”
References


13. Haacke E. Evidence of an increase in basal ganglia and thalamic iron content in multiple sclerosis and its vascular implications: An initial analysis with susceptibility weighted imaging. *International Angiology* 2010;29:147-157


17. Wohlwill F. Ueber encephalomyelitis. *Neuro and Psychiat* 1928;112:20


29. Fog T. Rygmarvens patologiske anatomi. *Munkgaards, Copenhagen* 1948
31. Meyer A, Cook IC. *Brain* 1936;59:100
32. Pette H. *Ges Deutsch Nervenarzte* 1931;135:95
33. Corday E, Rothenberg SF, Putnam TJ. Cerebral vascular insufficiency; an explanation of some types of localized cerebral encephalopathy. *AMA Arch Neurol Psychiatry* 1953;69:551-570
34. Cekic M, Stein DG. Traumatic brain injury and aging: is a combination of progesterone and vitamin D hormone a simple solution to a complex problem? *Neurotherapeutics* 2010;7:81-90


Royle N. Alteration of the circulation of the brain by surgical means in diseases of the central nervous system. *British Medical Journal* 1932;3727:1063-1068

Royle N. The clinical results following the operation of sympathetic ramisection. *Canadian Med Assoc Journal* 1931;24:229-234


Simka M, Zaniewski M. Reinterpreting the magnetic resonance signs of hemodynamic impairment in the brains of multiple sclerosis patients from the perspective of a recent discovery of outflow block in the extracranial veins. *J Neurosci Res* 2010;88:1841-1845


Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. *Int Angiol* 2010;29:115-120


Beggs CB. Multiple sclerosis appears to be associated with cerebral venous abnormalities. *Ann Neurrol* 2010
110. Harvey W. Cardiac Classics. CV Mosby, St Louis 1941:19
121. Batson OV. The Valsalva maneuver and the vertebral vein system. Angiology 1960;11:443-447
123. Batson OV. The Function of the Vertebral Veins and Their Role in the Spread of Metastases. *Ann Surg* 1940;112:138-149


126. Forsting M. Intracranial vascular malformations and aneurysms. From diagnostic work-up to endovascular therapy. *Springer* 2003


151. Corbett JJ, Digre K. Idiopathic intracranial hypertension: an answer to, "the chicken or the egg?". *Neurology* 2002;58:5-6
160. Seoane E, Rhoton AL, Jr. Compression of the internal jugular vein by the transverse process of the atlas as the cause of cerebellar hemorrhage after supratentorial craniotomy. *Surg Neurol* 1999;51:500-505
169. Bering EA, Jr., Salibi B. Production of hydrocephalus by increased cephalic-venous pressure. *AMA Arch Neurol Psychiatry* 1959;81:693-698


172. Flanagan M. *The downside of upright posture: the anatomical causes of alzheimer's, parkinson's, and multiple sclerosis*. Minneapolis, MN: Two Harbors Press; 2010


180. van Gijn J. Leukoaraiosis and vascular dementia. *Neurology* 1998;51:S3-8


191. Simka M. Private Communication.


207. Beggs C. Multiple sclerosis appears to be associated with cerebral venous abnormalities. *Ann Neurol*;68:560-561


Figure 1: These images show potential iron build up backward along the venous system. (a) SWI phase image showing iron buildup at the head of the caudate nucleus and posterior aspect of the putamen. (b) SWI phase image showing lack of iron build up. (c) SWI processed image mipped over 4 slices showing abnormal iron build up in the globus pallidi.
Figure 2: Axial SWI mIP images showing (a) sparse cerebral venous vasculature compared to (b) normal appearing thalamostriate veins.
**Figure 3:** Iron rings seen in MS lesions using SWI filtered phase images. (a, c) FLAIR images showing white matter lesions in an MS patient. (b) SWI filtered phase images showing putative ring like iron deposits around the lesion (white arrow in SWI phase and black arrow in FLAIR). (d) SWI phase image showing iron deposition inside the MS lesion (white arrow in SWI phase and black arrow in FLAIR).
Figure 4: Veins are shown in the center of lesions indicating lesion-vessel connectivity and the venocentric property of MS lesions. (a,d): Phase image; (b, e): SWI image; (c, f): FLAIR image. (a-c): A periventricular vein is shown draining in-plane through an MS lesion (white arrows). (d-f): A periventricular vein is shown draining through-plane, in the center of an MS lesion (black arrows).
Figure 5: FLAIR images (a,c) and cerebral blood volume (CBV) maps from perfusion weighted imaging (b,d). Arrows in a and b point to a chronic lesion - seen on FLAIR (a) and showing reduced CBV (b). Arrows in c and d point to an acute lesion - seen on FLAIR (c) and showing increased CBV. The reduced CBV seen in b presents strong evidence that this lesion is in a chronic state: i.e., the blood supply to the tissue has decreased. On the other hand, the increased CBV visualized in d show that this acute lesion (black arrow in c) has an apparent increase in its blood supply.
Figure 6: A detailed quantitative set of flow plots for an idiopathic intracranial hypertension case. The integrated flow (a) and volume flow rate (b) are shown throughout the cardiac cycle. The right internal jugular vein-blue arrows (with a flow of 5.76ml/cdc, where cdc refers to the time for one complete cardiac cycle) dominates the flow and the left IJV-red arrows (with a flow of 0.26ml/cdc) has been replaced by an enlarged left anterior jugular vein-yellow arrows (with a flow of 1.38ml/cdc) as far as the next major source of outflow is concerned. Total arterial and venous flows are given in the upper left corner of the figure. (c) 2D Time of Flight of the head and neck with flow localization line showed. The internal jugular veins (blue arrow-right internal jugular veins and red arrow-left internal jugular vein) show stenosis at lower neck level; the left anterior jugular vein (yellow arrow) has a large diameter.
Figure 7: Structural abnormalities in CCSVI. (a) An example of a severe stenosis: A coronal view of the 3D MRAV (0.58x0.58x2mm³, TR=3.32msec, TE=1.26msec, FA=25°) data where the arterial phase is subtracted from the early venous phase. The left internal jugular vein (LIJV) shows long narrowed caliber at all neck levels (white arrows in a). (b) An example of bilateral truncular venous malformation (white arrows). (c) A complicated case with a severe RIJV stenosis that connects to the vertebral plexuses (long white arrow). This also has a truncular venous malformation (short arrow) and would have been hard to determine without further catheter investigation and injections. The 3D MRA provides important pre-treatment planning in this example.
Figure 8: Coronal views of 3D MRAV (0.58x0.58x2mm³, TR=3.32msec, TE=1.26msec, FA=25°) where the arterial phase is subtracted from the early venous phase. Image (a) was mipped over 72 slices; image (b) over 20 slices and image (c) over 15 slices. A lack of vertebral plexuses, vertebral veins and deep cervical veins is noted.
**Figure 9:** Coronal views of 3D MRAV (0.58x0.58x2mm³, TR=3.3msec, TE=1.23msec, FA=25°) where the arterial phase is subtracted from the early venous phase. Image (a) was mipped over 72 slices; image (b) over 21 slices and image (c) over 24 slices. The images show very well developed vertebral veins (white arrows in b), vertebral plexuses (top white arrows in a, b) and deep cervical veins (grey arrows in c).