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Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347:284-7.

Books and Monographs

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Homepage/Web site

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EDITORIAL

Theories and experiments in medical research

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Theoretical medical research is often considered marginal, in comparison with the universally accepted experimental research.

Medical journals as well as many meeting organizations, with the exception of specialized theoretical journals, nowadays prefer scientific contributes, which fit the pre-requisite of the well-known IMRaD[1] sequence: introduction, aims, materials and methods, results, discussion and conclusion. Theoretical research and model design generally do not comply with this strict scheme, asking instead for more relaxed constraints.

The current issue of JTAVR guests 3 papers, which are just free-format examples of theoretical frames, able to explain several pathophysiological events in the venous system.

The 1st (C Franceschi) deals with the problem of the 0-point in pressure measurements, underlining the role of collapsible veins in physiology, laboratory sets and daily clinics. Indeed, the central venous pressure is usually monitored in intensive care units (ICUs), almost everywhere in the world, as well as it is part of many invasive hemodynamic research protocols.

The 2nd (F Passariello) formulates the hypothesis that the venous collateral circulation, in addition to its beneficial effect by-passing a venous occlusion, has also a detrimental effect on the tissues it passes through, owing to the transport of catabolites and carbon dioxide.

The 3rd (F Schelling) is the first paper ever published (1982) on the venous origin of multiple sclerosis and appears here as an authorized reprint, together with several notes. Looking at the wide resonance of this paper, made by a great deal of theoretical an experimental research works and hints to therapy, we understand something more about the role of theories as suggestions to research.

Generally theories must explain already accepted experimental results, but their main value is related to their ability to suggest new experimental research work, in order to corroborate or falsify their forecasts.

Franceschi provides new theoretical frame and tests it with a do-it-yourself set, built in the kitchen and described in a movie, which faces many cliché prejudices and asking for a deeper understanding of the concept of pressure.

Passariello asks for deeper studies on venous collateral circulation and for an analysis of the relationship between clinical severity and quantitative/categorized intensity of collaterality.

Schelling would greatly appreciate measurements of venous pressure impact on brain and spinal cord structures, especially during rapid body movements and taking into account physical constraints which limit the movement, mainly in the spinal cord.

Note that all these three papers can be related to venous research in multiple sclerosis, thus suggesting how to proceed in order to get new meaningful results.

This short "excursus" in theoretical research, well matching the aims of the Journal, shows how a structured (but not too strict) standard scheme is needed for a correct approach to hypotheses in research work.

Fausto Passariello

Editor in Chief

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NON-ANIMAL EXPERIMENTS REVIEW

Both for Ethics and Health. Non-Animal Technologies: an achievable goal

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Abstract The international debate on animal testing, its improvement through the well known "3Rs" methodology, and the possibility of its replacement with the emergent NATs (Non-Animal Technologies) brought into the new millennium a turn. Nations as U.S.A. and U.K., and partly international bodies as the EU. seem be doing a renewed effort to diminish and possibly replace animal testing with more reliable and less invasive techniques, to which also the giants of the chemical and pharmaceutical industry seem very interested.

Keywords Animal Testing, Non-animal Technologies (NATs), Toxicogenomics, 3Rs, Ethics.

During the 20th century, animals were used in a large range of scientific areas: basic biological, medical and veterinary research, pharmacology and dentistry, environmental monitoring and toxicology, testing of ballistic, chemical, nuclear and biological weapons, as well as in neuroscience and experimental psychology.

However, the international debate on animal testing, its "improvement" (the well known "3Rs")[i] [1] , and its replacement with the emergent NATs (Non Animal Technologies) brought a turn into the new millennium. A change of strategies which consist of a renewed effort to diminish and possibly completely replace animal testing with more reliable and less invasive techniques, and which regards both the control bodies and research institutions of nations as U.S.A. and U.K., or supranational organizations as the European Union, and the giants of the chemical, agrochemical, pharmaceutical, medical and veterinary industry.

What the reasons of this change? At least three motives emerge from the on-going debate:

- the undeniable evidence of the poor predictive value of animal experimentation in crucial fields as toxicology and pharmacology (according to PubMed and the U.S. Food and Drug Administration, 92% of the drugs harmless in non-human animals are then discarded during the mandatory clinical trials in humans);
- the damage to health caused by it (the most well-known and severe case was that of Talidomide, a tranquilizer for pregnant women that, harmless in animal tests, turned out to be teratogenic to our species, but was withdrawn only when more than 10,000 phocomelics babies were born);
- the advent of in vitro cellular technologies and in silico (computational) methods, which turned out to be more reliable, economical and faster than animal testing.

An important step in this turn took place in 2007, with the publication of the results of the study *Toxicity Testing in the 21st Century: a Vision and a Strategy*, commissioned by the U.S. Environmental Protection Agency (EPA) in order to promote an innovative approach to toxicity testing, and edited by the staff of Committee on Toxicity Testing and Assessment of Environmental Agents of the National Research Council (NRC), which "includes experts in developmental toxicology, reproductive toxicology,

neurotoxicology, immunology, pediatrics and neonatology, epidemiology, biostatistics, *in vitro* methods and models, molecular biology, pharmacology, physiologically based pharmacokinetic and pharmacodynamic models, genetics, toxicogenomics, cancer hazard assessment, and risk assessment" (Krewski *et al*. 2010)[ii] [2].

What the EPA asked to the NRC was a strategy which, over the next few decades, could be able to turn the research in toxicology from the current expensive and lengthy in vivo testing to in vitro and in silico technologies in which the "assays will be conducted primarily with cells or cell lines, optimally with human cells or cell lines, and as time passes, the need for traditional apical animal tests will be greatly reduced and optimally eliminated"[iii] (*Ivi*).

Which the results? According to the authors, thanks to the introduction of toxicogenomics (or cellular toxicology), based on the analysis of the reactions of genes contained in human cells or cell lines tested to the chemicals, a "*revolution is taking place in biology. At its centre is the progress being made in the elucidation of cellular-response networks. Those networks are interconnected pathways composed of complex biochemical interactions of genes, proteins, and small molecules that maintain normal cellular function, control communication between cells, and allow cells to adapt to changes in their environment. A familiar cellular-response network is signalling by estrogens in which initial exposure results in enhanced cell proliferation and growth of specific tissues or in proliferation of estrogen-sensitive cells in culture […]. In that type of network, initial interactions between a signalling molecule and various cellular receptors result in a cascade of early, midterm, and late responses to achieve a coordinated response that orchestrates normal physiologic functions* ". (*Ivi*)

What do the authors forecast about the future of animal and non-animal testing? The committee envisions a future in which, if a sufficient effort will be made, tests based on human cell systems will be able to replace, completely or almost totally, testing in animals.

After the first publication of this study in the US followed a series of experiments with the new Comp.Tox (Computational Toxicology), based on the use of "robots" that allow an assessment of the toxicity of chemicals at high speed. "*The program, initially started at EPA as Tox.Cast to assess 1,000 chemicals (and known as* ***Tox21*** *in its expanded form), employs a robot to speed chemical screening" which "wells replace the old standby of toxicology-animal testing. In addition to being slow and controversial, animal tests do not reveal how a chemical might impact humans, nor do they deliver any insight into the mechanisms by which a given chemical produced toxic outcomes. Simply by running the robotic tests, the EPA and its partner agencies will generate more information on chemical toxicity in the next few years than has been created in the past century*"(Biello 2011)[3]. One of the most ambitious studies in the field is the Human Toxome Project which will comprehensively map the pathways of endocrine disruption (ED), as a first step towards mapping the whole human toxome.

If the new strategy outlined by the US EPA and NRC suggests a transition to end animal testing in more or less long times, but in fact still proposes procedures that include it, while reducing its use, the UK seems more clearly geared towards achieving this goal in just over a decade: by 2030.

A significant testimony to this effort is the study "A non-animal technologies roadmap for the UK. Advancing predictive biology", published in November 2015 and drawn up by the governmental agency Innovate UK, the National Centre for the Replacement Refinement and Reduction of Animals in Research, the Biotechnology and Biological Sciences Research Council, the Defence, Science and Technology Laboratory, the Engineering and Physical Sciences Research Council and the Medical Research Council. It provides that, over the next thirteen / fourteen years, non-animal technologies (NATs) could potentially replace the use of animals, and intended "to guide the efforts of all those working in this area" (NC3Rs 2015, p. 2)[4].

The study underscores in particular the enormous potential of development of this market sector and the huge amount of investment it already attracts. According to the authors, the "global market for cell based assays in drug discovery, safety, and toxicology will reach $21.6 billion by 2018. The estimated global market for induced pluripotent stem cells is expected to reach $2.9 billion in 2018, and the 3D cell culture market is expected to grow to about $2.2 billion in 2019" (*Ibidem*, p. 4).

According to other estimates, published in BBC Research's 2014, "the only in vitro toxic test market was in 2012 $ 4.9 billion and will reach nearly 9.9 billion in 2017, with a compound annual growth rate of 14.7% for the five-year period 2012-2017" (translated from the Italian text) (Lucchini 2016)[5]. And these are figures that refer to the global market for in vitro tests but only in the field of toxicology, which should be added, for a realistic calculation, to "the value of what even the Kits and methods applied to research", as suggests G. Dal Negro, World-wide Director 3Rs at GlaxoSmithKline, interviewed in 2016 by C. Lucchini (*Ivi*).

But, what about the European Union? Here we find a strange situation: on one side, EU, adopting in 2004 the REACH (Registration, Evaluation and Authorization of Chemicals), a regulation designed to improve the protection of human health and environment from harmful chemicals, promoting methods alternative to animal testing,

anticipated and inspired the American and English turn. On the other hand, some innovative guidelines suggested by REACH, according to which all chemicals placed on the market should be tested for their side effects on humans and the environment with the methods of emerging toxicogenomics (and with costs incurred by manufacturing industries), have had so far limited application and disappointing practical effects.

This is due to delays in the application of the new rules, insufficient investment, and the several exceptions to the constraints imposed on the use of animals in experiments, which REACH actually allows. It is in fact a document that promotes "alternative" methods to animal experimentation, meaning by this formula, not necessarily and not merely replacing techniques which do not imply animal testing, but also methods that, following the principle of the 3Rs, decrease the number of animals employed or the suffering endured by them.

Not by chance, according to the Seventh Report on the Statistics on the number of animals used for experimental and other scientific purposes in the EU Member States, the results were so far relatively modest: in Europe the number of animals used for "scientific purposes" have gone from 12 million subjects used in laboratories by industry, universities and research centres in 2008, to 11.5 million in 2011. And only since 11 March 2013, in application of the Directive 2010/63/EU, it has entered into force in EU the ban on the marketing of cosmetics tested on animals.

What is, in the end, the situation in Italy?

Early in 2014, at request of the Environment Commissioner J. Potocnik, Italy was denounced at the European Court of Justice for failing to transpose the already mentioned Directive 63/2010, that imposes to improve the principle of the 3Rs.

Italy replied approving on March 4, 2014 the Legislative Decree, no. 26 which, acknowledging the European Directive and in some ways even overtaking it, establishes inter alia that all research projects involving the use of vertebrate animals and certain invertebrates, such as Cephalopods, must be authorized by the Ministry of Health and carried out within authorized user establishments. But in February 2017 the application of the new legislation was set for a three-year period, for the research on abusers and xenografts.

Trying to take a snapshot of the current situation, we could say that in some areas, such as toxicology, pharmacology and environmental testing, new emergent NATs seem able to overcome and replace, in a few decades, the animal testing, with a political will that goes towards this and if different interests do not prevail. In vitro technologies and human cell cultures have proved to be more rigorous, faster and cheaper than animal testing in crucial fields as cancer-screening treatments, or drugs and environmental testing. In other areas, such as neurophysiology and the study of brain diseases or of the cardiovascular system, where it is more difficult to replace in vivo models with cell cultures or computerized simulations, given their enormous complexity, the goal seems farther and hard to reach but[iv] [6,7], also in this areas, some recent technical innovations have been very important. Very sophisticated non-invasive imaging methods such as the CT scan (computed tomography), the MRI (magnetic resonance imaging), the AMS (accelerator mass spectroscopy), the DTI (diffusion tensor imaging), or the MEG (magnetoencephalography) allow real-time measurements of associations between structure and function in humans with possible resolutions down to the single cells. In vitro models of the brain and of the blood-brain barrier (BBB) are today used for studies of neurotransmitter pathways, electrophysiological characteristics, morphological associations of human pathologies as Alzheimer's, Parkinson's, Huntington's diseases and epilepsy. They are today in use in cardiology computer models of the human heart which show the heart beat and heart reactions in 3D; the recent development of microfluidics, based both on in vitro and in silico technologies, even though it is far from the ambitious goal of a hypothetical Lab-on-a-Chip, capable of concentrating in a millimeter chip all the operations needed for scientific testing, certainly represents a breakthrough.

In summary, is there reason to hope that, in a not too distant future, animal testing can be completely overcome or reduced to very rare limit cases? My view is that to achieve such goals technological innovations are never enough. It will be necessary to spread among scientists and people a critical awareness of all the ethical and medical implications of animal experimentation; a strong social and cultural commitment will be needed by those who are already today sensitive to these issues.

Both for Ethics and Health.

Endnotes

[i] Introduced in 1959 by WMS Russell and RL Burch (Russell 1959), of the Universities Federation of Animal Welfare, the principle suggests three guidelines for the scientific experimentation:

- **Replace** the use of animals with alternative techniques, or avoid the use of animals altogether.
- **Reduce** the number of animals used to a minimum, to obtain information from fewer animals or more information from the same number of animals.
- **Refine** the way experiments are carried out, to make sure animals suffer as little as possible. This includes better housing and improvements to procedures which minimize pain and suffering and/or improve animal welfare.

[ii] See the part titled: "The Committee's First Task and Key Points From its Interim Report" in the updated version of the essay (Krewski *et al.*2010).

[iii] See the part titled: "Component B: Toxicity Testing of Compounds and Metabolites".

[iv] For an introduction to the difficulties encountered by the project of a complete overcoming of animal testing, see Di Porzio (2012); Mario Negri Institute (2013).

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Theoretical Analysis of the Vascular System and its Relation to Adrian Bejan's constructal Theory

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Abstract Basically, the main function of the cardiovascular system is to provide oxygen and other nutriments to the tissues, achieved by the pumping action of the heart and the subsequent blood flow through the tree-like vasculature. Classically, in the physical and mathematical analysis of the relationship between form and function of vascular systems, form is given first. The constructal theory, first proposed by Adrian Bejan in 1996, is a thermodynamic principle according to which flow systems, such as watersheds and vascular networks, evolve so that they gain more global performance over time. There are two major points about the constructal theory. The first one is that it provides a unifying concept of form and function, in which the configuration is not postulated, but is to be discovered. The second one is that it is presented as a unifying physical concept of evolution of organic and inorganic flow systems. By comparing non-living (watersheds) and living (vasculature) systems, we show that the processes of morphological "change upon time" in watersheds and those of developmental morphogenesis and evolutionary modifications through generations in a population are not equivalent. Mechanistic explanations in biology include physico-mathematical models but, from the biological point of view, the epistemic value of the constructal law is not its unifying power by subsumption of biological processes under a general nomological principle, but, to the contrary, to provide an idealized physico-mathematical model of living systems that is embedded in general mechanistic explanatory frameworks of biological processes such as development and evolution.

Keywords network, self-organization, causality, evolution, morphogenesis

Introduction

Form and function of vascular networks

The cardiovascular system is a canonical example of ascription of a biological function. Since William Harvey's book publication in 1628[1], in which he evidenced the existence of the circulation of the blood in the vessels, the structure and the functional properties of the vasculature has been extensively studied. Basically, the function of the cardiovascular system is to ensure fast transport of matter and energy, and, in particular, to provide oxygen and other nutriments to the tissues, achieved by the pumping action of the heart and the subsequent blood flow through the vasculature. Oxygen delivery to the tissues occurs via two combined mechanisms, oxygen transport via blood convection throughout the arterial, capillary and venous

networks[i], and oxygen diffusion through the capillary walls to the mitochondria within the cells, where oxygen is used by the aerobic process of energy production[2, 3]. According to its function, as identified by biologists, the functional efficency of the vasculature, i.e., the properties of the system that determine the flow rate of oxygen delivered to the tissues, has been analyzed in physical terms: fluid mechanics and the physical properties of the blood, solid mechanics and the properties of vessel walls, laws of diffusion, allometry, etc. Physiological textbooks have usually a summary of the basic physics of circulation[3], and specialized textbooks are dedicated to the biomechanics of the circulation[4, 5].

Functional analysis of vascular networks based on their physical properties should also consider their structures. Taken altogether, the total length of the vessel segments in a human body is around 100 000 km. These segments and their connections form a highly hierarchical structure, similar to that of a tree and its branches. The morphological analogy between the branched organization of blood vessels and trees had been noticed by early physiologists such as Jean Fernel, even prior to the discovery of blood circulation by William Harvey[6, 7]. Despite the differences between a tree and a vascular network, and the interindividual variations in their detailed geometry, all these structures share a common kind of pattern, based on the fact that they are multiscale branched structures. These patterns can be found not only in living systems such as vasculatures, bronchial arborescences, trees and branches, but also in non-living systems such as river basins.

Beyond angiology, the anatomical description of the vessels, several mathematical concepts and tools have been used to grasp the apparent complexity and variability of the vascular networks and to provide a quantitative characterization of their patterns. The Strahler number, which is a numerical measure of the branching pattern of a mathematical tree, has been used to provide a rank-ordered topology of the vasculature. Interestingly, this mathematical tool was first developed in hydrology for the analysis of river networks[8], and later used for the analysis of biological hierarchical patterns such as respiratory and vascular systems[9-13]. The emergence of fractal geometry has also provided a mathematical concept initially applied to non-living systems but quickly extended toward life sciences[14, 15]. Actually, biological structures are not pure fractals, but, in a given range, may exhibit fractal properties, i.e., exhibit the same design at different scales. Whether a given network has fractal characteristics should not be taken *a priori*, but as a hypothesis that requires empirical validation. An abundant literature has been devoted to the fractal properties of biological features (see, for a review, Losa[15]), among them the pattern of the vascular network[10, 13, 16, 17], which have been described as a combination of scale-invariant and scale-specific patterns17. What it is important to notice is that these kinds of structural analysis of vascular networks are grounded on physico-mathematical concepts and tools.

The combination of these mathematical descriptions of the pattern of the circulatory system with the biomechanics of the circulation have been done to provide physical interpretations of the functional capacity of the vascular system (see for example[13, 18, 19]. Two interesting remarks can be done about this way to analyze the vascular system. First, the mathematical and physical methodology and concepts used for such an analysis are not specific to biological systems. In particular, it seems that it exists a deep analogy, both in pattern and functionality, between non-living systems, like hydrologic basins, and living ones, like vascular networks, throughout which flows a fluid. For example, the Strahler order had been initially developed for the analysis of watershed morphology, and applied later to airway and vascular networks. Comparison of the functional properties of irrigation fields and blood circulation is done by physicists themselves:

"There are infinite variations in the detailed geometry of microvascular beds, just as there are infinite varieties of irrigation fields in agriculture." […] *"To help visualize the difference between [glomerulus, sinusoid and sinus network] models, analogous agricultural irrigations are sketched on the side."*[5]

Second, in the combination of form and function, the pattern of the structure is given first, and not understood as the consequence of the flow of the fluid throughout the system, as illustrated by the methodology explained by Fung:

"As usual, we shall start with anatomy, then proceed to the mechanical properties of the tissues, and finally, to system dynamics. The importance of the subject is unquestionable because the whole purpose of the heart and arteries is to carry blood to the capillaries to nourish the cells of the body."[5]

The constructal theory

The constructal theory, first proposed by Adrian Bejan in 1996, is a thermodynamic principle according to which flow system, such as watersheds and vascular networks, evolve so that they gain more global performance over time[20-22]. Based on the principle of global optimization, i.e., minimization of the entropy generation, of local constraints, the principle of the constructal theory is, according to its author, as follows[21]:

"*Constructal theory is the view that the generation of flow configuration is a universal phenomenon of all physics.* […] *This law is about the necessity of design to occur.*"

According to Bejan, the constructal law is the last of the three laws of thermodynamics, to each of which he attributes a self-standing tendency in nature: energy conservation for the first one, irreversibility for the second one, and evolution for the third one the so-called constructal law, which he himself summarizes[23]:

"*For a finite-size flow system to persist in time (to live) it must evolve freely such that it provides greater access to its currents.*"

There are two major points about the constructal theory. The first one is that it provides a unifying concept of form and function. Contrary to Fung's methodology, form is not given first[23]:

"*We did not postulate the configuration: in fact, in the physics of evolution the configuration is unknown* […] *In the physics of evolution, the boundaries (the drawings) are to be discovered*".

The constructal law hence predicts the evolution upon time of the pattern of a flow system to the least imperfection, i.e., the design of the system that provides minimal global resistance to the flow. The emergence of some morphological characteristics, such as the fractal structure of watershed, vessel networks, airway tree is, according to the constructal theory, the thermodynamical consequence of flow.

"*Organization of the real (system) scale appears to be a collage of the same design from smaller scales. This is an appearance, but its basis is physics, and it has nothing to do with fractal geometry. It has everything to do with flow and the free morphing of architecture toward greater access*".[23]

The constructal theory has been applied to a variety of systems, including biological flow systems like the Mammalian bronchoalveolar lung[24] and several Mammalian circulatory networks[ii][25-27]. Recently, based on the constructual law applied to vascular systems, an evolution parameter E_V, defined as the ratio of the global flow conductance of the evolving configuration on the global conductance of the configuration with least imperfection, has been proposed to quantity the evolutionary value of the network configuration with regard to the configuration of least imperfection, as predicted by the constructal law[27].

The second important point of the constructal theory is that it is presented as a unifying physical concept of organic and inorganic flow systems. As an example, the first line of an article written by Bejan[21] is:

"Why are lungs and river basins 'vascular'?"

According to the constructal theory, the reason is that the type of stress that the water flow exerts on the river bed is similar to the type of stress that the blood flow or the air flow exerts on the vascular network and the bronchial network, respectively[24, 27, 28]. The same laws determine the systems of inanimate and animate flows. Watersheds, lungs and blood vessels exhibit similar patterns because there are submitted to the same physical principle of flow optimization.

"*We show that the emergence of scaling laws in inanimate (geophysical) flow systems is the same phenomenon as the emergence of allometric laws in animate (biological) flow systems.*"[21]

According to Adrian Bejan, the constructal law not only provides explanations about the relationship between form and functionality in biological and non-biological systems, but it unifies life and non-biological processes under the same nomological principle. Under the constructal law, life and evolution are physics[23].

The explanatory value of the constructal theory

We do not question the epistemological status of the constructal law in physics, compared to the first and second principles of thermodynamics, nor the validity of the generalization of the constructal law to universal properties, as Bejan himself claims:

"*In conclusion, the constructal law is the law of physics of life and evolution everywhere, animate and inanimate, and at all scales, from vascular tissues to celestial bodies.*"[23]

We will limit our discussion to the epistemic significance of the constructal law with regard to vascular tissues. For this purpose, we will compare the application of the constructal theory to watersheds versus vascular networks. The reason of such a comparison is that, as noticed previously, the analogy between circulatory systems and watersheds has already been done, and that Adrian Bejan and other partisans of the constructal theory have also applied it to both types of systems, as an example of its unifying power.

If we take the examples of the hydrological and vascular networks, the constructal theory says that the similarities in the structure of these networks are explained by the fact that their construction responds to the same type of constraints that lead to the overall optimization

of the system[24, 27, 28]. In these two cases, the system of constraints seems to shape the network dynamically. Indeed, the hydrological network is gradually formed, as the bronchial network and the vascular network are built during development. However, there is a fundamental difference between the physical principles common to the two classes of networks that explain their structure (global optimization of local constraints), and the mechanisms that build hydrological networks and vasculo-bronchial networks. In the case of the geophysical network of a hydrological system, the system of constraints explaining the functioning of the hydrological network - the form of the network and the characteristics of the flow of water flowing through it - is at the same time the efficient cause of the occurrence of this network. There is therefore an explanatory completeness of the system constituted by the hydrological network and the flow of water which traverses it. The set of constraints formalized within the framework of the constructal theory explains the existence and the evolving structure of this network. It can be said that the system of constraints "creates" the hydrological network. From an experimental point of view, the constructal study of such a network was based not only on the analysis of natural hydrological networks but on networks created in the laboratory by an artificial rain[21]. On the other hand, in the case of biological networks such as vascular and bronchial networks, this same system of constraints, although it explains the functioning of these networks, is not the efficient cause of their existence. The constructal theory can explain the structure of this network, but it does not explain the existence of lungs and, experimentally, the authors did not create a lung in the laboratory by applying a continuous flow of air over an amorphous tissue[24]. In this case, therefore, there is an explanatory incompleteness of the biological circulatory and pulmonary networks (In our comparison of watersheds versus biological networks, we take the example of the lung because the same author has applied the constructal law to river basins[24, 28], but the argument is similar with vascular networks.)

In a non-living hydrologic system, its evolution, i.e., morphologic change upon time, is due to the dissipation of the energy of the water flow. In biology, evolution of a biological system means something else. Actually, there is an ambiguity in the meaning of evolution and its equivalence between living and non-living systems. In "*Life and evolution as physics*", A. Bejan discusses the meaning of evolution from its Latin etymology[23]. However, the meaning of evolution in life science should be inferred from the history of this word and its use in biology. In biology, "evolution" can have two different meanings (i) developmental morphogenesis of an organism, which is its first signification, and (ii) change over generations, its current meaning. Actually, in the middle of the nineteenth century, when Darwin published his book on the origin of species, the term "evolution" did not refer to transformationist theories like Darwin's, but to some kind of developmental process. Darwin himself did not use the word "evolution" in the current meaning of the word in evolutionary biology until the last edition of his book[29, 30].

If the change upon time of the form of a river basin is equivalent to that of a biological system (for example a bronchoalveolar lung), there is hence an ambiguity in the correspondence: does it correspond to the developmental process of lung morphogenesis in a Mammalian fetus, or the evolutionary process of the emergence of a bronchoalveolar lung from a saccular one?[31] Additionally, phylogenetic evolution is not the progressive transmutation of one pattern into another but, in most of the cases, a branched process during which the initial pattern persists. Actually, Vertebrate animals with saccular lungs still exist, and, moreover, the Mammalian bronchoalveolar lung is not the only structure that has evolved from the primitive saccular one. Birds have tubular lungs which structure is different from both the bronchoalveolar lung and the saccular one.

The difference in the thermodynamic aspects of living and non-living systems can further be explained in regard to the organization of biological vascular systems. The fact that living entities share a specific kind of self-organization, distinct from physical self-organization, has been discussed by philosophers and scientists since I. Kant[32] and C. Bernard[33] to now [34-38]. Due to this organizational singularity, the processes of morphological "change upon time" in watersheds and those of developmental morphogenesis and evolutionary modifications through generations in a population are not thermodynamically equivalent.

Bejan may agree that biological and non-biological systems differ in the causal processes responsible for their respective "change upon time". But, according to Bejan, the explanatory power of the constructal theory is grounded on the epistemological principle that the aim of science is to seek for unification, not for mechanistic explanation.

"*The unifying power of the physics of life and evolution is the whole point - the usefulness - of science itself. This quote from Henri Poincaré says it best: the true and only goal of science is to reveal unity rather than mechanism*".[23]

However, this epistemological claim regarding the aim of science cannot be generally considered relevant, at least in biological sciences[39]. It may be true that the goal of physics is to subsume each particular case to a general principle (the quest for unity). In this meaning, explanation is the deduction of a particular case from a general law. But this nomological-deductive model of explanation, developed by Hempel[40], has been shown to

fail to account for scientific practice in life science. Causal mechanisms[41], not unity, are the usefulness of biological sciences[iii]. This does not deny any explanatory value of physical principles like the constructal law. Although the constructal theory cannot explain the existence of lungs or vascular systems, there is no doubt that the structures are optimized due to physical constraints[iv]. In order to minimize the energy dissipation, the systems must be conventional self-similar fractal[42]. A non-optimized vascular network would be very costly, and the first attempt to link the geometry of blood vessels with the energy costs was made by Murray in 1926[34]. To this purpose for the blood flow the Poiseuille's laws were applied whereas the cost was considered as dissipation added to the metabolic rate of energy consumption in blood. This leads to Murray's law that states that minimal dissipation in a bifurcation is reached if the cube of the radius of the mother branch is equal to the sum of the cube of the radii of the daughter branches. In this context the Bejan's constructal theory can be seen as a generalization of these previous approaches[43].

Mechanistic explanations in biology include physico-mathematical models[39]. However, from the biological point of view, the epistemic value of the constructal law is not its unifying power by subsumption of biological processes under a general nomological principle, but, to the contrary, to provide an idealized physico-mathematical model of living systems that is embedded in a more general mechanistic explanatory framework. Several explanatory frameworks can be built to respond to specific biological problems (i.e., developmental biology, evolutionary biology, physiopathology), and the explanatory significance of the constructal law will depend on the inclusive explanatory power of the overall framework.

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Endnotes

[i] In such an organization, the so-called "closed" vascular system, found in humans and numerous other Metazoans, the vasculature is a closed circuitry composed of arteries, capillaries and veins, isolated from the interstitial medium by the endothelial barrier. However, other Metazoans have an "open" vascular system, in which the circuitry is not closed. The arterial network opens in internal cavities that constitute the so-called *haemocoel* that bathes the internal tissues. We will limit our discussion to the closed circulatory systems.

[ii] We precise "*Mammalian*" because other taxons may have different types of lungs and circulatory systems, that have not been analyzed by these publications.

[iii] "*Mechanism*" may have different meanings in philosophy and the different scientific disciplines, including different meanings in biology, as analyzed by Nicholson[41]. We use it here in the meaning of "the causal explanation of a particular phenomenon (causal mechanism)".

[iv] This does not mean that the notion of optimization based on physical constraints is equivalent to evolutionary optimization, which includes other criteria, such as robustness.

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IRON PATHOPHYSIOLOGY REVIEW

The role of free iron in cardiovascular diseases - Part I

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Abstract An unavoidable consequence of the aerobic mechanism is the production of super-oxides and peroxides known as *"Reactive Oxygen Species" (ROSs)*. These substances can trigger a number of biological reactions not particularly dangerous at physiological concentration. However, in presence of iron such reactions greatly enhance the radicals production and, in particular, determine the release of strongly reactive and toxic radicals as the hydroxyl radical ($OH^{\cdot}$). Many chronic inflammatory conditions share this underlying disequilibrium of the iron induced radical-antiradical balance. Aim of the present review is to enlighten the role of the free or weakly chelated portion of iron in vascular and cardiac diseases.

Keywords Reactive Oxygen Species, Unchelated iron, Free Radicals, Cardiovascular diseases, Iron-mediated reactions

Introduction

The large number of works recently appeared in the literature report on the crucial role of the iron in different pathologies such as the cardiovascular diseases, the atherogenesis, the advanced dystrophic-ulcerative stages of the chronic venous disease, the diabetes mellitus, the chronic neurodegenerative illness, etc. Actually, underlying these different pathologies seem to exist a common denominator, that is the continuous iron-induced production of very toxic free radicals such as the hydroxyl radical ($OH^{\cdot}$)[1]. A portion of iron exists that is non effectively chelated by the physiological ligand carriers (transferrin, ferritin, albumin, lactoferrin, etc.). This iron portion is able to silently but continuously initiate a progressive and worsening biological damage, together with the decay of the biological function and of the organs. The biochemical complexity of reactions induced by the highly toxic radicals (hydroxyl, $OH^{\cdot}$, etc.) provides an explanation of the often conflicting effects of the so called "substances with antiradical activity", that from defenders become attackers when, due to different reasons, non-chelated iron is present. The hydroxyl radical $OH^{\cdot}$ is normally a byproduct of water hydrolysis due to radiations or by the Fenton reaction starting from the hydrogen peroxide (with the ferrous ion Fe^{++} as catalyst). It is the more reactive ROS and is also produced by the leukocyte starting from the hydrogen peroxide in order to destroy pathogenic agents though, in case of excess, it causes damages to the plasmatic membrane, to proteins and to nucleic acids. The hydroxyl radical is inactivated and then disposed of through conversion into H_2O by glutathione peroxidase. Therefore, the chelation of iron and, possibly, of other metallic ions such as copper etc. by natural or syntetic chelant agents could play a critical role in the safeguarding of the biological functions of organ and apparatus. Understanding the mechanisms of unbound iron has a basic relevance in the differentiation of anti-phlogistic

and pro-phlogistic processes. These "escape reactions" on which the unbound iron initiate the production of the hydroxyl radical are hard to counter since they work at the same time on different biological targets. Some molecules (statins, erythropoietin, etc.), usually not associated to antiphlogistic effects, actually reveal useful to fight such mechanisms. The role of scarcely chelated iron is pretty underestimated while it could help in the understanding of the different oxidative reactions creating a chronic biological damage and could permit the tuning of new therapeutic strategies.

Iron-related physiological processes

In the respiratory chain, during the conversion of oxygen in respiratory water a variable portion of reduced oxygen (about 2-4%) is produced in the form of hydrogen peroxide and superoxide (H_2O_2, $O_2^{-\cdot}$), the superoxide dismutases (SOD) and the catalase (CAT) control the process[1,2]:

$$O_2 + 4H^+ + 4e^- <--> 2H_2O$$

Of course these redox reactions are implemented during hypoxia, ischemia or perfusion, due to the lack of the terminal electrons acceptor (oxygen). Similarly, the production of reduced forms of O_2 can also be realized in vivo by means of the direct action of different enzymes such as oxygenase, oxidase and peroxidase. For example, in ischemia-perfusion conditions, the activation of the xanthine-oxidase occurs as consequence of the accumulation of calcium in the cytosol that, in turn, initiates a number of Ca-dependent enzymatic activities (phospholipase, protease, endonuclease, etc.) like the calpain, a protease that irreversibly cuts the xanthine-dehydrogenase and trasforming it into the xanthine-oxidase isoform. This latter, then, oxidise the hypoxanthine to uric acid using oxygen as substrate and producing superoxide anion and hydrogen peroxide ($O_2^{-\cdot}$, H_2O_2), source of oxidative stress[3,4]. Though cell has many antioxidative mechanisms, these oxygen species play a major role, as they are very reactive and are able to react with other species generating a cascade of other toxic radicals such as hydroxyl radicals[5-7]. The reactions with those particular "metallic ligands" like iron received less attention than the general role of ROS "(Reactive Oxigen Specie)[8,9]. They are common to many biological functions and, once set off, these reactions can lead to progressive functions alterations and eventually to diseases, in particular to progressive chronic degenerative forms.

Superoxide (O_2^-) and peroxide (H_2O_2) are incomplete reduction forms of oxygen. The reaction catalyzed by SOD equilibrates superoxide and peroxide[10]:

$$2O_2^{-\cdot} + 2H^+ --> H_2O_2 + O_2$$

while the catalysis determines:

$$H_2O_2 --> H_2O + ½O_2$$

The most relevant reaction of hydrogen peroxide with Fe^{++} is known as Fenton reaction. It leads to the formation of highly toxic hydroxyl radicals ($OH^{\cdot}$):

$$Fe^{++} + H_2O_2 --> Fe^{+++} + OH^- + OH^{\cdot}$$

Superoxide (O_2^-) can also react with Fe^{+++} by the Haber-Weiss reaction to produce Fe^{++} and leading, in this way, to a redox cycle:

$$O_2^{-\cdot} + Fe^{+++} --> O_2 + Fe^{++}$$

In the same way as they work with hydrogen peroxide, radical reaction can also develop with lipidic hyperoxide (ROOH). By means of the O-O bond rupture, alkoxy groups ($RO^{\cdot}$) are produced, that are the initiators of lipidic peroxidation while, interacting with polyunsaturates fats, they form the peroxyl groups $ROO^{\cdot}$, that are the actual chain amplifiers of the lipidic peroxidation[11]. The oxidative stress leads to considerable damages to DNA[12] and to the proteins[13,14] or carbohydrates denaturing, with the formation of unsoluble structures known as lipofuscins[15]. The action of non-bioavailable, that is, poorly chelated iron, that on the other hand works as oxidative reactions catalyst, is an often underestimated aspect in biology, For this reason it is possible to observe a situation in which there is, at the same time, iron-deficiency anaemia together with a great abundance of unbound iron acting as catalyst of oxidative reactions. Moreover the unchelated, and then biologically unavailable, iron is able to initiate, interacting with nitrogen, a nitrogen oxidative stress with formation of phlogistic carriers such as nitrogen peroxides (reaction of NO with superoxide)[16] or S-nitrosothiols[17]. In the hemoglobin the Fe^{+++} ferric ion binds the oxygen giving rise to Fe^{++} ferrous ion. This oxidation takes place in the lungs, then the ferrous ion reduces again to ferric ion Fe^{++}releasing O_2. This oxidation-reduction reaction occurs both for the weakness of the bound and for the presence of CO2 in tissues, that reduces the affinity among hemoglobin and O_2 (pH variation). The reaction of ferrous iron Fe^{++} with the oxygen in natural aerobiotic conditions produces ferric Fe^{+++} that is less soluble and toxic, for in their evolution bacteria and fungi overcame the problem creating siderophores, which are able to capture ferric Fe^{++} ions and make it available to enter intgo the plasmatic

membrane[18]. The Siderophores possess such a hexatoothed chelation structure (the deferoxamine, that is produced by the Streptomyces pilosus and is highly specific to Fe^{++} $^{+}$) and then are able to use ferric iron, of fundamental importance for growth and virulence of these bacteries[19,20]. More than 500 different types of microbic siderophores have been described. On the other hand, they have not been found in humans; however, as pointed out by Kaplan[21], the presence of siderophores in mammals improved our knowledge of human ferrokinetics.

The discovery in 2000 of hepcidin[22], an hormone produced by the liver, marked a major turning point in the understanding of the tissues ferric release and overload mechanisms as well as its role in the phlogistic processes. In fact, hepcidin is overexpressed in inflammation and has a role in the instability of atherosclerotic plaque, and it is considered an early marker of phlogosis[23,24].

It is worth to remark another relevant discovery. The NGAL (lipocalin-2 or siderocalin) is a negative iron regulator having the function of a real siderophore whose role in renal diseases has been observed much earlier than creatinine[25]. The lipocalins are a heterogeneous group of small ligand proteins[26]. It is worth to stress the correlation among lipocalins and the metalloprotease activation (MMPS), since NGALs act as allosteric activators of MMPS[27,28]. A different source of oxidative stress is the erythrocyte degradation that release free hemoglobin (Hb-free), with endothelial damage and free iron production[29], so that the formation of biliverdin in the ecchymosis absorption would have a powerful antioxidative role.

The EME-oxigenase is an enzyme in the class of oxidoreductase, that catalyzes the following reaction:

eme + 3 AH_2 + 3 O_2 <--> biliverdine + Fe^{++} + CO + 3 A + 3 H_2O

"A" being the A ring of the hemoglobin tetrapyrrole group, with the possibility of making available Fe^{++} as catalyst of oxidative stress[30]. In physiologic conditions in a mid adult man of 70 Kg weight, 1-2x10^8 red cells are destroyed per hour, corresponding to about 6.0 grams of hemoglobin per day. Since from 1 g of hemoglobin are derived about 35 mg of bilirubin, this means that about 210 mg of bilirubin are produced per day.

Cardiovascular diseases involving iron

Arterial hypertension is considered one of the main cardiovascular risk factors, and it i known its ROS-iron mediated phlogistic genesis[31-33]. The ferritin rate has been correlated to the risk of developing arterial hypertension in mid adult men[34] and to diabetes[35]. Concerning the type 2 diabetes a large number of evidences exist that stress the role of the ROS generating unbound iron in the disease onset. It is known for sure that the ROS play a role in the insuline resistance[36-39]. The iron excess is a proven feature of gestational diabetes[40] and of the diabetes during hemochromatosis[41], and the oxidative stress is involved in the mitochondrial damage and in the different diabetes complications[42]. Some of the anti diabetes drugs like glitazones and thiazolidinediones (pioglitazone and rosiglitazone) that improve the insuline resistance work as reducers of the iron-induced ROS production[43,44]. The iron could also be related, via the oxidative stress, to the level of visfatin produced by visceral adipocytes through an increase of hepcidin and the levels of lipocalin 2 (NGAL or siderocalin) are strictly associated with the diabetes onset[45,46], while low iron levels improve the receptor sensitivity of insulin[47].

High values of iron can promote the onset of cataracts[48] and a role of iron has been recognized in hepatic steatosis and in the nonalcoholic steatohepatitis (NASH) syndromes[39], while high values of serum ferritin are correlated to metabolic syndrome which is in turn related to diabetes[49-51]. In 1981 J. Sullivan[52] showed the cardiovascular protective action of a low level of body iron in women during the fertile era of menstrual cycle, and in 2005 the same author pointed out the relation between the quantity of iron in the deposit and the alteration of vascular reactivity[53]. The role of iperhomocysteinemia as vascular toxic factor is well recognized, while the observation that the mere supply of folates and of group B vitamins in presence of high values of ferritin is poorly effective in the regulation of the endothelial reactivity is less known[54,55].

The relationships between iron and ischemic cardiac disease or the myocardial infarction have been reported in a number of papers in literature, and recently the correlation of high ferritin level and STEMI infarction (ST Elevation Myocardial Infarction) has been pointed out[56-60]. The ROS are surely involved in the cardiac insufficiency[61,62]. In fact, the xanthine-oxidase oxidizes the hypoxanthine to uric acid using oxygen as substrate and producing superoxide and peroxide anions ($O_2^{-\cdot}$, H_2O_2), source of oxidative stress further enhanced in presence of unchelated iron and in condition of ischemia-perfusion[3,4].

Endnotes

[i] According to the International Union of Pure and Applied Chemistry (IUPAC) the point high on the right represents radicalic species.

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Paradoxical ankle venous pressure in standing and walking compared to the venous blood column height

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Abstract The mechanism responsible for the pressure at the foot in standing still lower than expected by the height of the venous blood column, is controversial. It can be theoretically explained by the hydrostatic laws if we consider the vacuum pressure in the head and thoracic veins and the continuity of the blood column from the feet up to the top of the head without including the dynamic flow which is, according to Bernouilli equation, independent of height, even in vivo conditions. The additional lowering of the pressure when walking is due to the discontinuity of the blood column achieved by the dynamic closure of the valves alternatively proximally and distally to the muscular pumps of the legs. A theoretical model is proposed, illustrated by a video plain experimentation.

Keywords venous pressure, hydrostatic pressure, air embolism.

Introduction

A recent paper[1] deals with the discrepancy between the measured venous pressure at the ankle and the expected hydrostatic value. The ankle venous pressure when standing still and during ambulation is lower than expected by the height of the venous blood column from the foot up to the top of the head. According to an experimental model and to basic physical arguments, the Authors conclude: "*Persistent negative pressure in systemic chest veins probably does not occur. The reason for the discrepant foot venous pressure is likely to be a result of dynamic flow and not negative pressure in chest veins. External positive pressure results in slowing of velocity but the transmural pressure remains largely unchanged.*"[1]

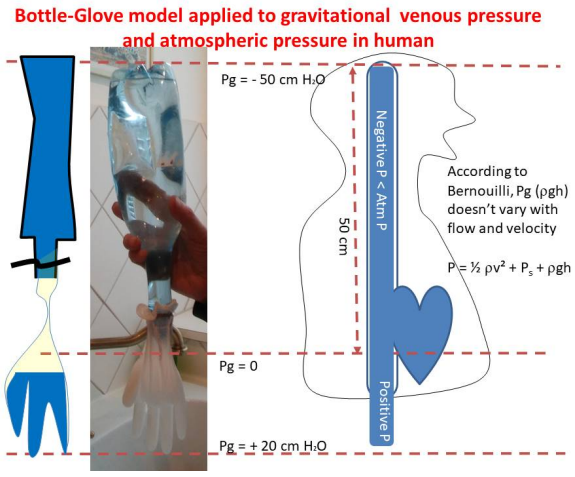

Fig. 1: Additional experimental data about venous pressure can be found in an online video[2] *at the address https://www.youtube.com/watch?v=Udsg8hIzPu8. P_g - Gravitational Hydrostatic pressure, P - total pressure, ρ - density, v - velocity, P_S - static pressure, g - acceleration of gravity, h height.*

A different model, based on other parameters can be proposed. It relies on the transmission of the atmospheric pressure to the venous hydrostatic pressure according to the rigidity of the surrounding tissues, irrespective of flow kinetics. In this paper a theoretical model is proposed in

favor of a hydrostatic mechanism, while several related experimental data are available in a video[2]. (Fig 1)

1-Physics background

11-Pressure definitions

111-Bernouilli equation

In physiology, blood is usually approximately considered as Newtonian, thus according to the Bernouilli law:

$$P_t = P_S + ½\ \rho v^2 + \rho gh = P_S + P_{dyn} + P_g = Konst.$$

where:

- P_t = Total pressure at a point on a streamline = total energy density;
- P_S = static pressure at a point on a streamline = Energy density due to the work of the forces of pressure;
- ρ = density of the fluid at all points in the fluid;
- v = fluid flow speed at a point on a streamline;
- g = acceleration of gravity ;
- h is the elevation of the point above a reference plane, with the positive h (direction pointing upward) so in the direction opposite to the gravitational acceleration;
- $P_{dyn} = ½\ \rho v^2$ = dynamic pressure at a point on a streamline = kinetic energy density;
- $P_g = \rho gh$ = Gravitational Hydrostatic pressure = density of potential energy of gravity.

$P_{dyn} + P_S$ = Konst. because they convert one into the other, while P_g does not vary with P_{dyn} nor P_S but only with ρ, g and h. **So P_g does not change with flow velocity**.

P_g and ($P_S + P_{dyn}$) are independent while P_{dyn} and P_S are linked by a constant and convert one into the other according to the velocity rate.

112-Absolute pressure

Absolute pressure = total pressure at a point in a fluid equaling the sum of the gauge and the atmospheric pressure. $P_{abs} = P_{atm} + P_{gauge}$.

1121-Atmospheric pressure

P_{atm} = atmospheric pressure = 10.33 meters of water = 760 mmHg at the sea level.

1122- Gauge pressure

Gauge pressure = Stagnation pressure (standard and usual pressure measurement reference) measured in open air, so $P_{gauge} = P_{abs} - P_{atm}$. When negative (vacuum P_{gauge} pressure), P_{gauge} does not mean a reversal direction of pressure, but only values lower than P_{atm}. The vacuum P_{gauge} pressure varies from Zero to -760 mmHg or 10.33 mH_2O. So P_t expressed in Gauge pressure is equal to $P_{abs} - P_{atm}$.

1123-Vacuum pressure

Vacuum pressure = $P_{atm} - P_{abs}$. When a one-end of a closed rigid tube (> 10.33 m long) full of water is immersed vertically by its open end in a tank filled with water (at the sea level where P_{atm} is maximum, i.e. 760 mmHg of absolute pressure (P_{abs}), the gauge pressure (P_{gauge}) inside the tube turns negative (vacuum pressure) and decreases upwards from 0 to -10.33 mH_2O i.e. -760 mm Hg . In other terms, the water is pushed up to a 10.33 m high column by the equivalent air weight (almost 10000 m of air) into a rigid container shielded against P_{atm}. ($P_{abs} = P_{atm} + P_{gauge}$) (Fig 2)

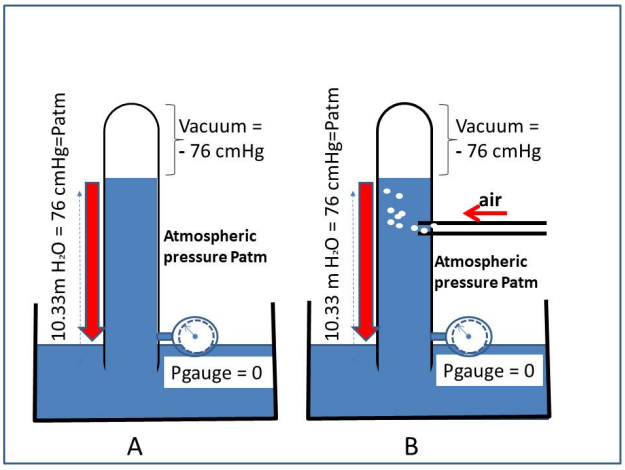

Fig. 2: A) When a one end of a closed rigid tube (> 10 meters long) full of water is immersed vertically by its open end in a tank filled with water (at the sea level where the atmospheric pressure (P_{atm}) is maximum, the gauge pressure (P_{gauge}) inside the tube turns negative (vacuum pressure) and decreases upwards from 0 to -10.33 mH_2O, i.e. -76 cmHg up to zero absolute pressure (P_{abs}). B) Air suction by the negative pressure in the tube.

1124-Transmural Pressure

Transmural Pressure (TMP) results from the difference of two opposite pressures against a tube wall. TMP = $L_p - E_p$, where L_p = Inner wall pressure or Lateral

Pressure and E_p = External wall pressure of the tube. In addition, $L_p = P_s + \rho gh$. What happens to a tube full of fluid submitted to P_{atm}? If its TMP is negative ($L_p - P_{atm} < 0$, negative TMP) a collapsible tube collapses while the rigid one does not. In both cases, if we push a needle through its wall, the pressure difference will suck the air into the tube. Two distinct conditions can provide negative L_p.

- The first one occurs when the tube is closed (Fig 3B);
- The second one when, in an open or closed tube, according to the Venturi effect, the velocity is high and the fluid column height h is negligible and the hydrostatic energy density term (ρgh) can be omitted.

The Venturi effect relates to the Bernouilli law $P_t = P_s + ½ \rho v^2 + \rho gh$, when it is applied in horizontal condition. Thus, $P_t = P_s + ½ \rho v^2$ where L_p depends only on P_s, which decreases inversely proportional to the square of velocity. (Fig 3)

12-Statics

Physical relationship between venous pressure, atmospheric pressure, vacuum pressure, gauge pressure.

121- Static pressures in open tubes and containers submitted to the gravity forces and atmospheric pressure

The P_{gauge} of static fluids inside an upper end open vertical tube submitted to the atmospheric pressure P_{atm} obeys the hydrostatic law $P_t = \rho gh = P_g$ = Gravitational Hydrostatic pressure = density of potential energy of gravity. (Fig 4)

13- Dynamics

Physical relationship between venous pressure, atmospheric pressure, vacuum pressure, gauge pressure: The previous model is static. It becomes dynamic instead, if a pump is inserted into the circuit, the water being submitted by the pump to a Pressure = $½ \rho v^2 + P_s$= Konst. As it can be seen, the Zero P_{gauge} is just at the junction of the rigid tube and the collapsible bag. The bag volume varies according to the TMP and its compliance, following the Hook's law. $TMP = L_p - E_p = (P_g + P_s) - (P_{atm} + K)$ where K is any additional external pressure. If the fluid moves, P_g does not change but P_{gauge} will be higher because increased by $P_{dyn} + P_s$ so that $P_t = P_s + ½ \rho v^2 + \rho gh = P_g + P_{dyn} + P_s$. (Fig 5)

If the upper open end of the tube is closed, then P_{gauge} does not change if it connects to symmetric but still open tube. (Fig 6)

If the tube is no more submitted to the atmospheric pressure, then a negative pressure occurs inside the system. (Fig 7)

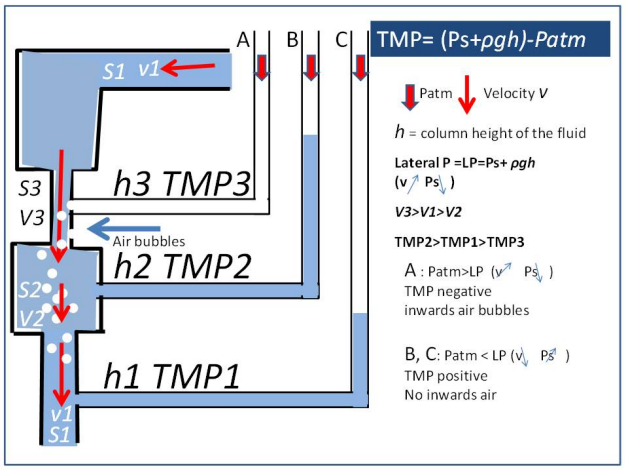

Fig. 3: Pitot tubes and Venturi effect showing the transmural pressure (TMP) according to the flow velocity (v) and the height (h) of the overlying fluid column. Lateral pressure (L_p) decreases because the static pressure (P_s) decreases proportionally to the squared velocity. Thus a very high velocity can cause a negative TMP and let the air enter into the tube, but only where h is negligible (h3). P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity.

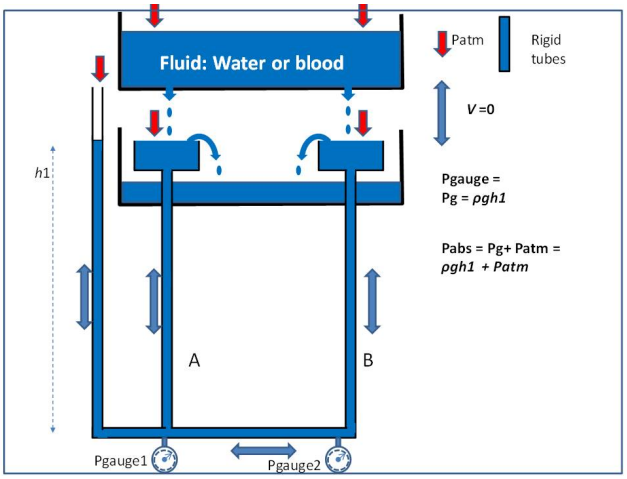

Fig. 4: $P_{gauge}1 = P_{gauge}2$ and varies only according to P_g i.e to the height h1 of the column A and B because ρg is constant and does not depend on the fluid velocity when v=0. P_g - Gravitational Hydrostatic pressure, P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity.

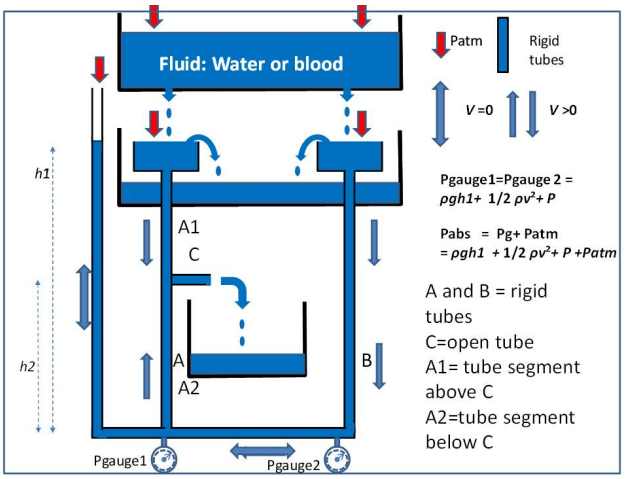

Fig. 5: $P_{gauge}1$ is still = $P_{gauge}2$ and varies not only according to P_g i.e. to the height h1 of the column A and B but also to the fluid velocity (v) when v>0. Thus P_{gauge} is >P_g. P_g - Gravitational Hydrostatic pressure, P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity.

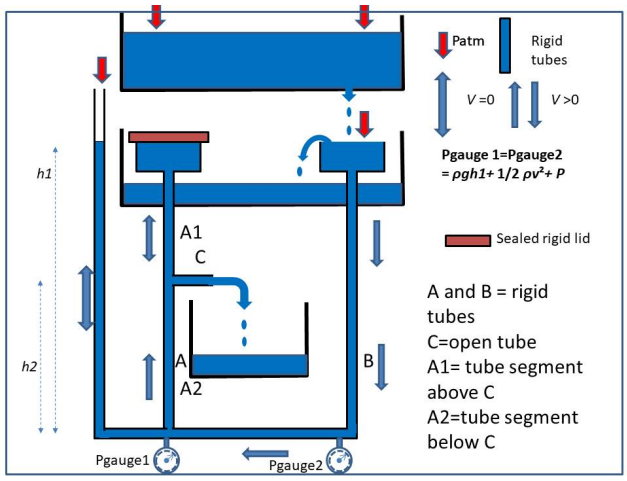

Fig. 6: Despite a sealed rigid lid above C (column A1), $P_{gauge}1$ is still = $P_{gauge}2$ =ρgh1 + P_{dyn} +P_S , transmitted by the column B. P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity.

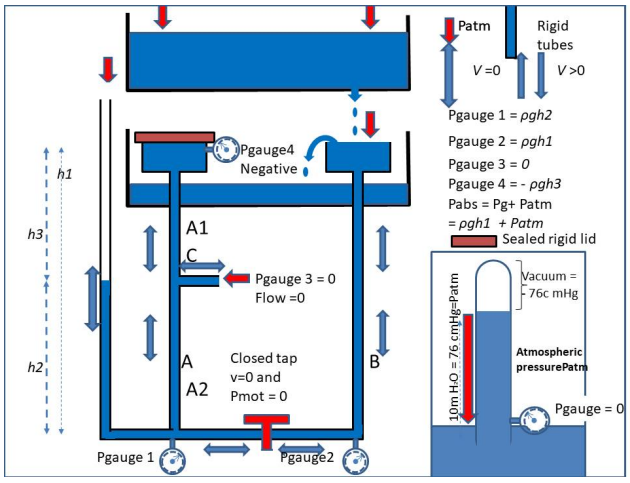

Fig. 7: If the flow between column A and column B is blocked, $P_{gauge}2$ = ρgh1 while $P_{gauge}1$ = ρgh2, i.e < $P_{gauge}2$. At the same time, the outwards flow is stopped at C ($P_{gauge}3$ = 0) and the $P_{gauge}4$ at the top A1 is negative = -ρgh3. A and B = rigid tubes, C = open tube, A1 = tube segment above C, A2 = tube segment below C. P_g - Gravitational Hydrostatic pressure, P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity. v - velocity.

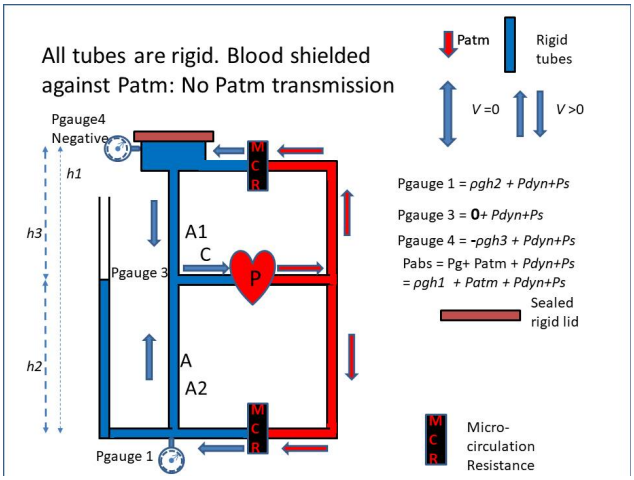

Fig. 8: If A and C rigid tubes are connected to a pump in a closed circuit, Pauge3 =0 because the circuit is shielded against the atmospheric pressure P_{atm}. A and B = rigid tubes, C=open tube, A1= tube segment above C, A2=tube segment below C. P_g - Gravitational Hydrostatic pressure, P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity. v - velocity. MCR - micro-circulatory resistance.

If the rigid tube is connected to a pump, in closed circuit, then, the negative P_{gauge} does not change except the additional pressure P_S + ½ ρv^2 provided by the pump. (Fig 8)

If the open end of the tube is connected to a collapsible bag and then verticalized in open air, water will remain in the rigid tube, because it is shielded against TMP. On the contrary, the bag collapses because P_{atm} can press it and closes the open end of the rigid tube. If the lower segment of the tube is replaced with a collapsible bag, its inner P_{gauge} is positive in proportion to the height of the water it contains, while it remains negative in the upper rigid tube. (Fig 9)

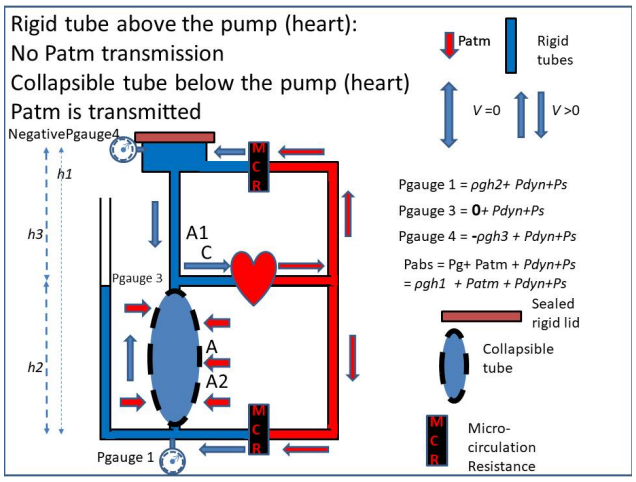

Fig. 9: If A and C rigid tubes are connected to a pump in a closed circuit, Pauge3=0 because the circuit is shielded against the atmospheric pressure P_{atm}. But if the tube segment is replaced with a smooth container, the atmospheric pressure is transmitted to it and $_{gauge}1$ = ρgh2 + P_{dyn} + P_S, $P_{gauge}3$ = 0 and $P_{gauge}4$ = - ρgh3 + P_{dyn} + P_S. A and B = rigid tubes, C=open tube, A1 = tube segment above C, A2 = tube segment below C. P_g - Gravitational Hydrostatic pressure, P_{atm} - atmospheric pressure, ρ - density, g - acceleration of gravity. v - velocity. MCR - micro-circulatory resistance, P_{dyn} - dynamic pressure, P_S - static pressure.

2- Can this theoretical physical model be applied to the venous system?

21- Positive and negative venous pressure in standing still

We presume that the skull, the cervical spine and the rib cage can be roughly assimilated to a rigid tube as also the abdomen and the lower limbs to a collapsible bag. This gives the Zero P_{gauge} at the xyphoid. The pressure at the foot in standing still:

- Foot-xyphoid distance = 115 cm in a 180 cm tall individual);
- P_g = 115 cmH_2O = 85 mmHg;
- P_{gauge} = 85 mmHg + Pdyn (Pdyn + P_S);
- P_{mot} = 95 mmHg;

where P_{mot} is the driving pressure provided by the heart, i.e. the residual pressure. NB! P_{gauge} at the foot, in recumbent position, is worth only P_{mot} = 10-15 mmHg, because h is around Zero and P_g is negligible. The height of the rigid portion above the xyphoid is 65 cm. P_{gauge} at the top of the skull is -65 cmH_2O + 20 cmH_2O (residual pressure) = - 45 cmH_2O = - 48 + 15 mmHG = -33 mmHG. At the heart level: P_{gauge} varies around Zero according to the heart rate and to the breath phases. These values match with literature data. It is obvious that these values and their causes remain variable according to the stiffness of rigid and collapsible portions of the body, below and above the xyphoid. Particularly, the jugular veins at the neck, that are less protected against the P_{atm} pressure but nevertheless let the blood flow according to the waterfall effect, while the vertebral flow is well shielded by the surrounding osseous tissues. The ascending and descending flows towards the heart are caused by the residual pressure around 10mmHg (result of the push of the arterial pressure through the variable micro circulation). (Fig 10)

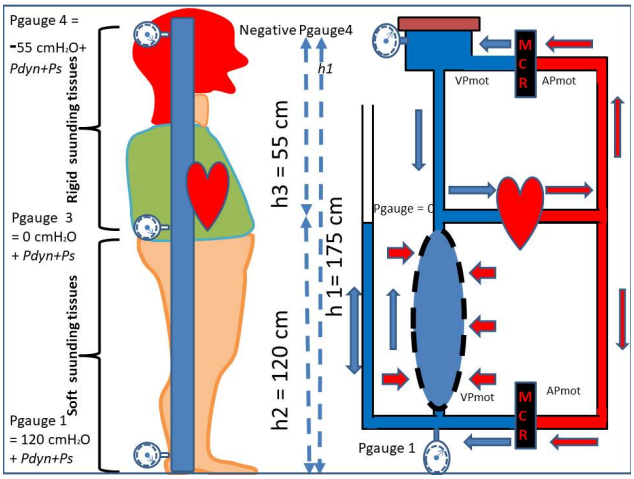

Fig. 10: Comparison between the physical model and the physiology. Head and chest can be assimilated to a rigid shield against the atmospheric pressure (P_{atm}) while the belly and the lower limbs considered as soft bags. MCR - micro-circulatory resistance, P_{dyn} - dynamic pressure, P_S - static pressure, AP_{mot} - arterial pressure, VP_{mot} - venous residual pressure.

22-Air embolism relation to TMP and/or Venturi effect

What causes the air embolism in case of puncture of the jugular vein in standing or sitting position ? If

the Venturi effect may be partly responsible, the negative Intravenous Pressure is a much more relevant cause. Any puncture of the rigid tube will make air enter because TMP is negative (P_{gauge} inferior to P_{atm}). The Venturi effect occurs in addition when the flow velocity is high enough and the column height very short (negligible ρgh or negative in closed tube).

23-Dynamic fractioning of the Gravitational pressure

The pressure at the foot level drops dramatically in normal individuals from 90 mmHg in standing still to 30 mmHg when walking. The reason is necessarily a segmentation of the blood column according to Bernouilli equation. Indeed the more the valves are incompetent, the less the pressure drops. In prolonged standing at rest the venous valves of the lower limbs are not closed, so the blood column is not segmented and transmits its full weight and pressure to the foot. During walking, the P_{gauge} drops down to 30 mmHg. The only way to reduce it, is lowering P_g by a segmentation of the hydrostatic column, achieved by the alternate closing of valves below and above the muscular pump of the calf. This phenomenon is called Dynamic Fragmentation of the Gravitational Pressure. (DFGP) (Fig 11) The evidence is provided by an impaired reduction of pressure during the walk when valves are incompetent.

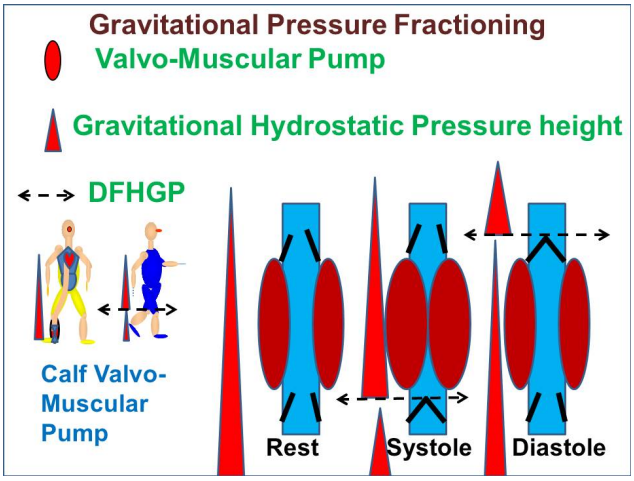

Fig. 11: Dynamic Fractioning of Hydrostatic Gravitational Pressure (DFHGP). Valves keep open at rest and the pressure at the ankle is maximum (90 mmHg). When walking, the pressure drops down to 30 mmHg, because during the systole, the valves close distally to the pump and fractionate the blood column height distally; during the diastole instead, the proximal valves close and fractionate the blood column height proximally.

Conclusion

The pressure discrepancy at the foot in standing still may be explained by hydrostatic laws according to on one hand the vacuum pressure in the head and on the other hand the continuity of the blood column up to the top of the head without any interference with the dynamic flow which remains independent, according to Bernouilli equation. The additional pressure loss during walking is due to the discontinuity of the blood column, achieved by the dynamic closure of the valves alternatively proximally and distally to the muscle pumps of the legs.

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COLLATERAL CIRCULATION MODELS

The hypothesis of the toxic effects of the venous collateral circulation

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Abstract Comparing the arterial and venous collateral circulation interesting symmetries are detected as well as important differences. Venous compensating pathways are essentially intra-parenchymal and convey dirty as deoxygenated blood. The hypothesis of the toxic effects of the venous collateral circulation is formulated, i.e. the greater the volume of compensation, the greater the toxic damage. Two scenarios are previewed as possible targets, i.e. the postthrombotic syndrome (PTS) and the chronic cerebrovascular insufficiency (CCSVI).

Keywords Blood collateral circulation, postthrombotic syndrome, MS,CCSVI.

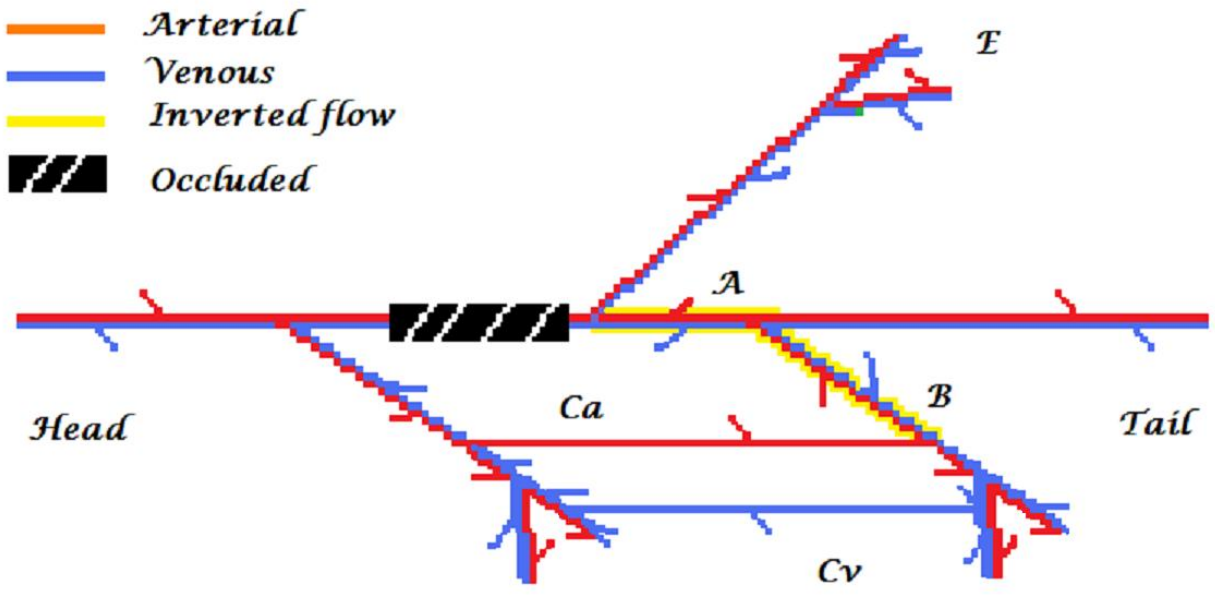

Figure 1 - Collateral circulation by-passing an obstruction in an arterial and venous schematic example. Half arrows point to the direction of flow, red for arteries, blue for veins. Yellow for inverted flow. Black for occlusion. A, inverted main trunk. B, inverted collateral path. E, excluded region. Ca, arterial anastomosis. Cv, venous anastomosis.

Collateral circulation in arteries and veins

	Arterial	Venous
Collateral circulation	Transport vessels	Even small peripheral veins
Speed	High	Low
Main trunk inversion		Valve incompetence, if any
Profile	Blunt	Parabolic
Blood	Clean and Oxygenated	Dirty and Deoxygenate
Wall	Stiffer	Collapsible
Shear rate	High	Low

Table 1 - Morphological and hemodynamic differences in post-thrombotic collateral circulation in the lower limbs.

An interesting discussion on the venous collateral circulation was held on Vasculab in July 2013[1]. The following lines report a theory which was formulated about.

Compensating vessels in the venous system follow essentially different patterns than in the arterial system. (Fig. 1)

Arteries

a. The arterial tree (red) is designed with a complete occlusion and a collateral circulation which jumps the occlusion, where flow runs from the Head to the Tail of the picture. (e.g. occlusion of the femoral artery, compensated through the deep femoral artery and a Hunter arterial perforator)

b. There must be a previous natural or newly formed arterial anastomosis (Ca) between the 2 main components of the compensating path.

c. In addition, the (B) component is inverted, in comparison with the physiological flow and the same occurs for the main trunk (A), as it carries a feeding flow towards an excluded region (E). Inverted arteries are contoured by a yellow colour.

Veins

a. The same picture can serve to represent the venous tree (blue) with a complete occlusion and a collateral circulation which jumps the occlusion, where now flow runs from the Tail to the Head of the picture. (e.g. occlusion of the femoral vein, compensated through the deep femoral vein and a Hunter venous perforator)

b. There must be a previous natural or newly formed venous anastomosis (Cv) between the 2 main components of the compensating path.

c. In addition, the (B) component is inverted, in comparison with the physiological flow and the same occurs for the main trunk (A), as it carries a drainage flow coming from an excluded region (E). Inverted veins are contoured by a yellow colour.

In the depicted structure there is an important symmetry in structure and function, which depends on the designed scheme and the direction of flow.

However this symmetry is abandoned as soon as we introduce some specific venous structures.

The A venous tract can contain valves, thus the inverted flow can occur only if the valve is destroyed of forced to be incompetent. This is of course achieved by the hypertension caused by an impaired venous outflow.

In addition, a lot of differences can be found and are reported in Table 1.

The main remarks are:

1) The Energy density (Energy per unit volume) is

$$\frac{E}{V} = p + \rho g h + \frac{1}{2}\rho v^2$$

In veins, the mean velocity is generally much smaller than in arteries, thus phenomena are governed by hydrostatics much more than hydrodynamics, i.e. the energy density is almost the same than in a static container.
Thus, whatever the stenosis/occlusion in the system, whatever the posture, as soon as the blood by-passes it, just downstream the obstacle the pressure is almost very near to the upstream value, i.e. the pressure difference is minimal.

2) An hypothesis can be proposed, that the venous collateral circulation is generally spread in more peripheral vessels than in arteries, **i.e. in veins, the collateral circulation can be intra-parenchymal**. The hypothesis is partially justified looking at the A segment in Fig. 1, which is caudal to the occlusion in the artery, cranial to the occlusion in the vein, in the same tree-like structure.

3) The venous collateral circulation conveys dirty and deoxygenated blood, just the contrary than in arteries. This does not include arterial-venous fistulas, where veins receive oxygenated blood.

- Tissues which are overcharged by collateral arteries receive oxygen and are fed by them.

- Tissues which are overcharged by collateral veins receive catabolites and carbon dioxide.

There is enough material to formulate the theory of the **Toxic Effects of the Venous Collateral Circulation**. (**TEVCC**)

Two scenarios are previewed as possible targets:

- the lower limb veins, where the effect is the same than in chronic venous insufficiency, when the closed shunts convey back dirty as deoxygenated blood. However, the most immediate recall is to the postthrombotic syndrome (PTS), with its huge and long lasting tissue damages;

- the venous cerebrospinal circulation in multiple sclerosis (MS) instead, where the clinical presentation is the chronic cerebrovascular insufficiency (CCSVI).

As regards CCSVI, the TEVCC hypothesis can be interestingly reformulated as follows:

Stenosis/occlusion in the venous cerebrospinal system causes a venous surcharge by collateral circulation inside the brain and the spinal cord system.

The hypothesis suggests that it could have an effect only when a valid collateral circulation has already developed.

The greater the volume of compensation, the greater the toxic damage.

Conclusions

As a consequence the pathology could be related not only to the severity of the stenosis/occlusion, but also to the exuberance of the collateral circulation with its toxic effects, i.e. to the **TEVCC**.

As regards MS, the hypothesis could be easily tested looking at the distribution in clinical severity of MS of the magnetic resonance arterial/venous flow mismatch (AVM), interpreted as the amount of outflow through small or collateral veins[2, 3].

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On a possible endogenous traumatization of brain, spinal cord, and nerve roots

The first paper (1982) on the venous origin of multiple sclerosis

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Abstract Translation and reprint of the paper "Möglichkeiten der endogenen traumatisation von gehirn, rückenmark und nervenwurzeln", by Franz Schelling, selfpublication Dornbirn (Austria) 1982.

Keywords Multiple sclerosis, Venous hypothesis, Cerebral reflux

(i) On the problem of venous reflux towards human brain and spinal cord

(A) Basic considerations

The occasional absence of the vein valves located at the inferior bulb of the internal jugular was already described 135 years ago (Gruber 1847).

In these veins, the valves alone withstand a reflux from the cava veins into the main venous drainages of the brain.

Intrathoracic pressure attains values which would drive up a blood column of a two and a half meters height e.g. during heavy coughing (Rollet 1877, Comroe, Gerlach, Bodenstab 1968), meeting slightly negative values in the superior sagittal sinus of persons standing erect (Ganong, Auerswald 1974).

This raises the question: What happens, once such central venous excess pressures are pushing back into particular venous draining systems of the central nervous system?

Venous pressure waves proceed at a speed of 1 to 2.5 m per second, this in dependence of the vascular filling pressure (Knebel, Wick 1958). In the presence of venous reflux, intrathoracic excess pressures can thus involve cerebral veins in less than the tenth of a second. The concurrent damming up of venous blood in the other vascular drainages of the central nervous system raises cerebrospinal fluid pressures several tenth of seconds up to seconds later (Gilland 1962, Lakke 1975). In the intervening time the cerebral veins exposed to venous reflux are in part burdened by enormous peaks in their transmural pressure (Fig. 1). They will expand up to the point at which no cerebrospinal fluid is to be any longer displaced out of their neighborhood respectively until the pressure gradient to encompassing cerebrospinal fluid and vascular compartments has been leveled out. The mechanical resistance of the brain tissues (Aoyagi, Hayakawa, Masuzawa 1981) and even of the reinforced cones of the vascular entries into the pia mater (Schaltenbrand 1955) are not resistant to the forces which are to be exerted thereby.

From studies into the vascular architecture of the human brain (Pfeifer 1930) mainly a straightening of venous bows has to be anticipated. From Laplace's law the widening of larger venules has to be expected first: In the central nervous system they show, in relation to their diameter, particularly weak walls. The combination of these activities can't remain without consequences for the

surrounding structures, especially regarding the vulnerable units formed by oligodendroglia cells and myelin sheaths. This is evident from the riddling of the white matter about arteries which lost their normal pulsation-dampening form (Pfeifer 1930, Yates 1976). This irrespective of the virtually synchronous and even transmission of the arterial pulse on well pressure-adapted vascular tubes.

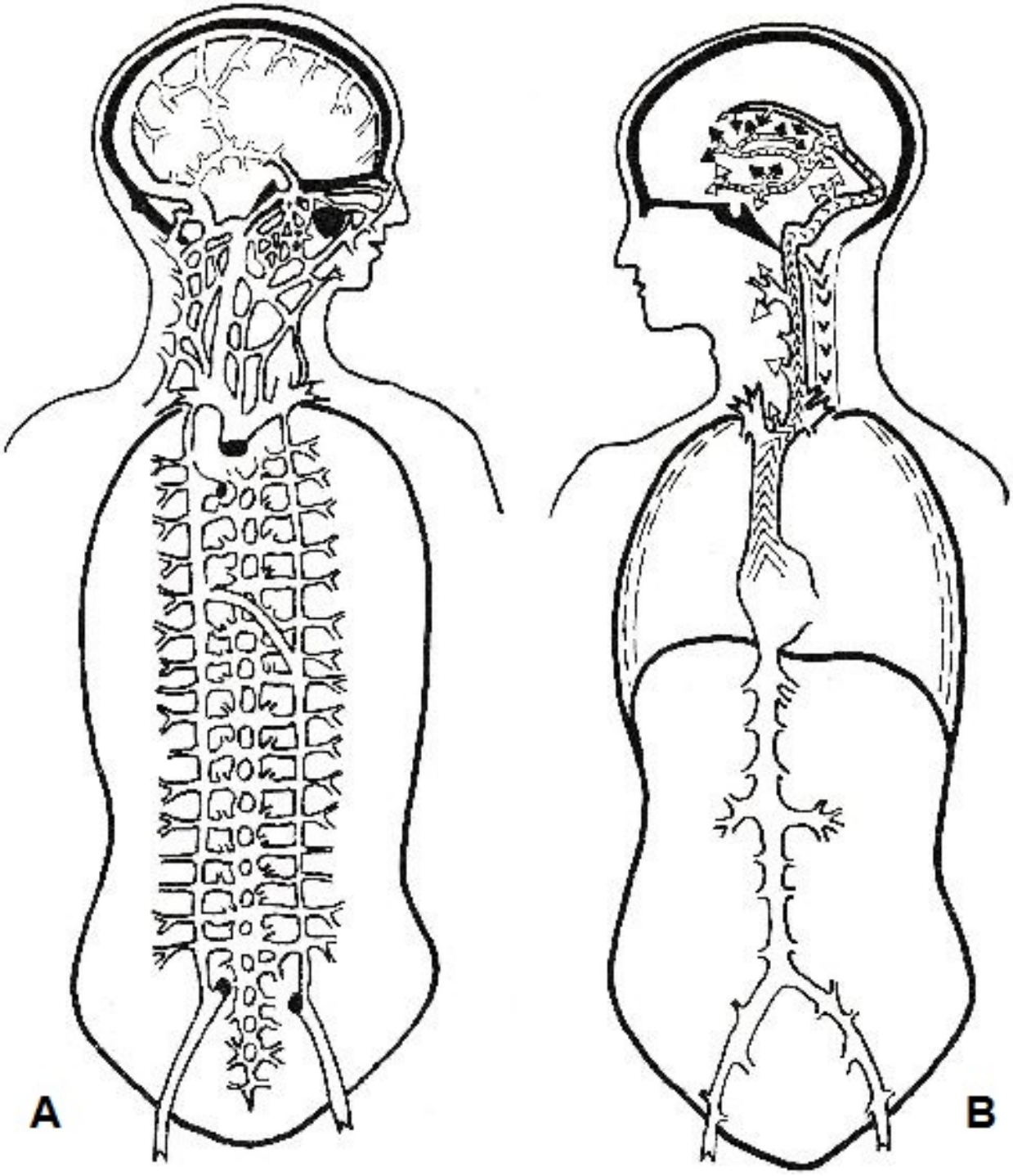

Fig. 1: Compare the pressure distribution in venous stasis (A) with the pressure distribution in a reflux via one internal jugular vein (B)

Over and above this a mechanical overstraining of nervous structures is also possible by the resulting fluctuations of cerebrospinal fluid causing higher pressure gradients between cerebral ventricles and intracranial

cisterns respectively such within the spinal subarachnoid space on the one hand, and such within spinal subarachnoid space and the sheath of the optic nerve on the other. The extremes of these pressure gradients have certainly a higher pathogenic relevance than the continuous work of the secretion of cerebrospinal fluid. And it is at narrow passages respectively on the optic disc that they will make themselves much more severely felt.

Reductions in the brain and spinal cord's leeway to movements will finally be as detrimental with movements due to fluctuations of blood and cerebrospinal fluid as they are with intraspinal displacements due to bodily movements (O'Connell 1946, Breig 1964).

(B) Special zones of attack of venous reflux and of fluctuations of cerebrospinal fluid

The mitigation of venous refluxes into one of the main pathways of the brain's venous drainage (the same applies to the effects of local pressure increases due to venous stasis) is the stronger, the better refluxes can be dissipated into extracranial vascular domains. The other way round: The venous refluxes' bearings on the nervous tissues will be the more intense, the more narrowly circumscribed the involved cerebral and spinal drainage systems are, and the faster they are reached. In respect of the main variations in the brain and spinal cord's venous drainage, the following directions of venous refluxes are to be indicated:

- (a) Refluxes into immediate tributary vessels of internal jugular veins, of the sigmoid sinus, the marginal sinus, the transverse sinus, respectively the inferior petrosal sinus on the right respectively left.
- (b) Refluxes into tributary vessels of the occipital sinus, straight sinus and inferior sagittal sinus, and/or the superior sagittal sinus. With complete septations of the confluence of sinuses and the straight sinus, the possibility of refluxes from one of the transverse sinuses into one of the internal cerebral veins appears particularly disquieting.
- (c) Refluxes into tributary vessels of the smaller dural sinuses of the middle cranial fossa and of the cavernous sinus. Owing to their high flow resistance against venous refluxes, and especially with stronger connections to the pterygoid plexus, no substantial expansions of the tributary vessels, entering mainly via the Sylvian fissure, are to be expected.
- (d) Venous backlashes into the epidural venous plexuses of the spinal canal. Commonly dissipated in a closely-meshed, often voluminous, widely spread plexus of veins, they might rarely result in circumscribed expansions of epidural convolutes of veins, and especially in direct refluxes into spinal radicular veins.

The central nervous system's grey portions (e.g. cortex and nuclei) are relatively well prepared to contain the changing venous pressures. This on account of their dense feltwork of neuronal, glial and, in part, also connective fibers, as well as the dense vascular networks of pia, cortex and nuclei.

What appears utmost at risk are, on the other hand, the delicate, soft structures of the white matter in particular in the neighborhood of large volumes of cerebrospinal fluid, being approached, as this is prominently the case, along the outer angle of the lateral ventricles and this at varying angles by variously curved medullary veins (Figs. 2 and 3).

Heavier fluctuations of cerebrospinal fluid result mainly from the divergence of the fluctuations of venous pressures and volumes in different drainage systems of cranial cavity and spinal canal. The critical factors, in this context, are the changing thoracic and abdominal respiratory pressures and the diversified inspiratory (vein collapses!) and expiratory conditions for the drainage of the different vascular compartments. Exaggerations of these fluctuations, namely on account of venous refluxes, potentially attack the intradural nervous structures by additional mechanisms (Fig. 4):

In displacing ventricular fluid, the expansions of the inner veins of the brain are capable of bulging weaker ventricular wall parts in direction of the cisterns. Pressing, for example, the floor of the third ventricle against the optic chiasm's posterior circumference.

With a low buffer capacity of the spinal dural sac respectively impediments to the displacement of cerebrospinal fluid in this direction, the optic disc can be damaged also by short-lasting, stronger ascents of the intracranial pressure over the intraocular pressure.

Intense cerebrospinal fluid shifts burden the adjacent surfaces with a propulsive force which attacks the anchorage points of the spinal cord and the nerve roots in an indirect way, this especially at narrow passages of the spinal canal.

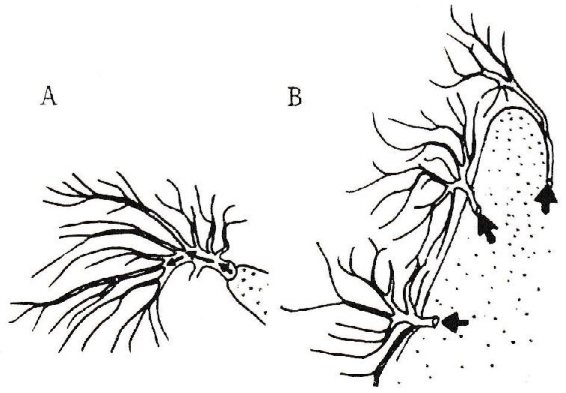

Fig. 2: The course of the medullary veins at the outer angle of the lateral ventricles (A sagittal, B axial view).

(In particular with higher CSF pressures) widenings and deformations of the spinal dural sac also strain the spinal cord via the insertions of its mooring ligaments, especially if the latter are already densely taught.

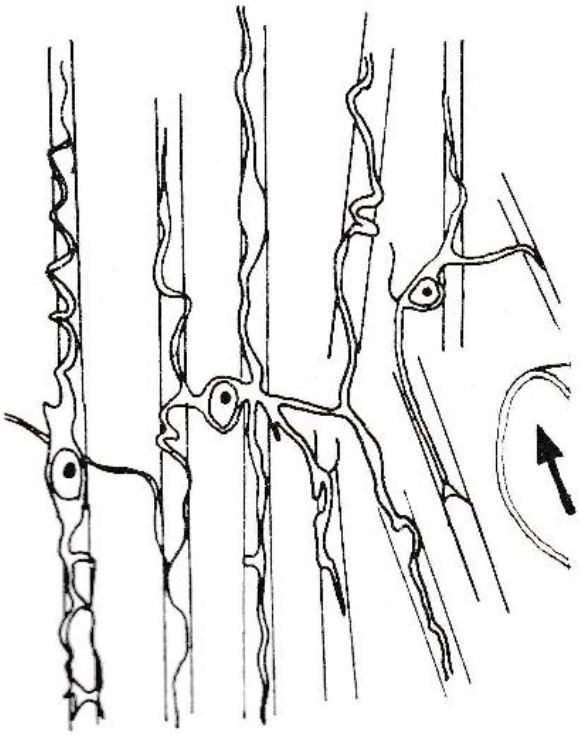

Fig. 3: Schematic drawing of the connection of oligodendrocytes and myelin sheaths.

Fig. 4: The structures which stabilise and the intradural spaces offering leeway to the movements of brain and spinal cord.

Stronger displacements of the brain via tentorial notch and foramen magnum require a more massive increase of the intracerebral blood volume as a whole, involving also the capillary vessels - and this in dependence of a corresponding compliance of the spinal dural sac. With a narrowed spinal canal respectively with meningeal scars the spinal cord can be superficially damaged while floating more intensely.

The venous refluxes respectively and the fluctuations of cerebrospinal fluid will be the more intense, the lower the intradural pressure they meet and the slower a pressure rise they effect.

An involvement of the indicated pathomechanisms in the pathology and clinical presentation of central nervous respectively radicular affections may be mainly suspected where cerebral veins and myelin structures are affected first, and where pressures and temperatures inside and outside the human organism impact on a disease's course in an extraordinarily strong intradural pressure.

(ii) Indications of [a missed kind of venous] endogenous traumatization of central nervous and radicular structures, as exemplified by multiple sclerosis

(A) Clues of pathological anatomy and histology

On character and nature of the given demyelinations:

Long and thin, in part branching bridges of cytoplasm connect the oligodendroglia cell to its up to fifty segments of myelin (Blackwood 1976, Ritter 1980): Fig. 3. Stronger distending and shearing forces which act on the nervous parenchyma are liable to destroy this trophic unit. This explains its mechanical vulnerability in traumatic injuries (Koenig, Dohrmann 1977), its selective damaging by more intense motions of cerebrospinal fluid (Bunge, Bunge, Ris 1960), and the prominence of myelin destructions in

decompression disease (Haymaker 1957). Including the specifically located patterns of demyelination observed in multiple sclerosis (Peters 1958). It also explains the initial destruction of not the superficial but the intermediate layer of myelin sheath in the latter disease (Poser, Ritter 1980).

Understanding the topography of lesions in multiple sclerosis:

Character and location of the sclerotic plaques reflect the picture of the damage which the vascular expansions of venous refluxes is expected to produce down to the smallest detail.

This circumstance applies first to the extension and severity of the finger-shaped demyelination invading the semioval center via larger venules (Dow, Berglund 1942, Fog 1950).

Lhermitte (1950) and Lumsden (1975) stressed as well: The sclerotic foci are not centered on capillary vessels, as seen in central nervous infection or in a visceral [Systemic] Lupus Erythematosus, but around larger venules. The straightening of venous bends possibly accounts for the spot-shaped focis' scattering.

The striking proclivity to thromboses affecting veins downstream of recent plaques (Rossolimo 1904, Putnam 1937, Dow, Berglund 1942, Prineas 1975) possibly relates to vein wall damages due to reflux. Leaky brain veins (Broman 1964) may also form the point of exit for the observed derangements in the system of coagulation (Prineas 1975, Brunetti et al. 1981, Prosiegel et al. 1982).

What argues for a production of the spinal foci of multiple sclerosis by displacements of the spinal cord in relation to its sheaths is the lesions' lack of a vessel relationship (Falkiewicz 1926), and, above all, the cervical cord lesions' arrangement according to the insertions of the denticulate ligaments (Oppenheimer 1978).

The indicated pathomechanism also offers a plausible explanation for the spinal demyelinations' accumulation in the reach of spondylotic narrowings of the vertebral channel (Brain, Wilkinson 1957).

It also has to be pointed out that also the nerve roots, but not the rest of the peripheral nerve lengths are affected by primary demyelinations (Zimmermann, Netzky 1950). Both, however, have the same antigenic structure of their own.

After all that has been said, it has to be expected that the fibrohyaline changes of primarily venules, later possibly also capillaries, described by LUMSDEN in 1975, might commonly involve only the brain.

(B) Epidemiological and clinical findings

The indefinite and protean clinical picture of multiple sclerosis complicates epidemiological studies enormously. It was nonetheless possible to trace diverse conditions that further the development of the disease.

A familiar clustering of the disease in conjunction with a raised disposition to a variety of different nervous and mental diseases is no longer to be denied (Curtius 1959, Myrianthopoulos 1975, Poser, Ritter 1980).

What is equally evident: Neither the duration nor the intensity of a contact with MS patients change the probability of acquiring the disease (Myrianthopoulos 1975, Poser, Ritter 1975).

Globally it is the more probable for people to acquire the disease, the farther from the equator they have grown up (Kurland 1975).

The varying statements on the male/female ratio of the patients with multiple sclerosis point overall to a somewhat more frequent affection of women.

The distribution curves on the patients' age at the manifestation of the disease show a high peak in the bodily most active years of live.

What diverges extraordinarily are the opinions on the causal relevance of the diverse circumstances that coincide more frequently with the beginning respectively with later exacerbations of the disease process (childbirth, traumata, exertions, mental turmoil, overheating etc.) (Behrend 1957).

Dramatic symptom changes induced over and over again to asserting they were of a psychogenic, neurotic or hysteric nature.

What prevented the precise registration of these latter peculiarities seems to have been, on the one hand, the inability of reducing the diverse circumstances which release the disease to a common denominator. It might have also been blocked by the impossibility to bridge the gap to the established pathogenetic conceptions concerning the essence of multiple sclerosis.

In view of the preceding indications, patients with multiple sclerosis might be conceived to have a genetically reduced mechanical resistance and tension of their vascular walls, which predisposes to the development of venous refluxes into the venous drainages of the central nervous system.

A compensatory widening of the brain's vascular pathways for increasing its perfusion in colder surroundings so as to maintain the brain's temperature, or to ensure the brain's sufficient supply with oxygen (e.g. with iron deficiencies related to menarche) might contribute to the understanding of the relation between the prevalence of multiple sclerosis and geographic latitude on the one hand,

and sexual factors on the other: The widening of veins is a factor which predisposes to valvular deficiencies and so to venous reflux.

Especially the typical relationships to the patients' age and the fact that exertions release bouts could be related to the occurrence of steeper and more massive ascents of the pressure gradient between central and intracranial veins.

What came to be explained, over and above this, is why weeks are passing before the first clinical manifestation of multiple sclerosis leaves its traces in the cerebrospinal fluid, but no inflammatory reactions (leucocytes, proteins, blood sedimentation rate) in the blood.

From this derives the necessity to examine the reflux conditions in the central nervous drainage systems in autopsies of persons who suffered from nervous and mental diseases, and in particular of multiple sclerosis. In this context also the circumstances underlying the aggravations and manifestations of multiple sclerosis ought to be clarified. As for the postulated pathomechanisms, the following questions attain clinical relevance in the attempt to discriminate the damages in which hemo- and cerebrospinal fluid dynamics may play a role:

How often, and with what a delay, is the beginning of the disease preceded by events in which the valves at the inferior bulb of the internal jugular veins can be damaged? After accidents and other mechanical impacts a delay of maximally days, with inflammatory processes affecting the venous periphery a delay of weeks, months, and even years seems imaginable.

How frequently and with what a delay (of maximally days) result conditions causing excessive rises in central venous pressures (coughing, childbirth, exertions and others) in relapses or a progression of the disease? Whenever possible, the degree of straining ought to be quantified.

How far are other factors favouring refluxes respectively raising their efficacy of relevance (e.g. heat, falling ambient pressures, bending over, lying down)?

How often do patients experience feelings of head/ top pressure respectively a tinnitus in being involved in circumstances which further refluxes?

How often are there affections of a thyroid gland relating to the pathways of a given reflux?

How often are there signs of a meningeal, radicular or pial irritation? (pains on nerve stretching? meningism? Lhermitte sign? how often is knocking at interlaminar spaces, spinous processes, cranium causing pains?)

How often are the warpings or more serious and complex distortions of the spine? How relate abnormal cerebrospinal fluid findings (cell counts, immunoglobulins, relation of albumin to globulins) to what has been given above?

Which neurological and mental problems affect the multiple sclerosis patients' kinship preferentially?

Clinical outlook

The addressed problems appear to have practical implications: Once the pathogenic significance of venous refluxes in direction of brain and spinal cord has been determined and is to be individually assessed, a few minimally invasive examinations (including radiographs and sonograms) would lead up to the concerned patients' plain and causal treatment which consists in the prevention of the refluxes' recurrence.

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Notes to the reprint

Notes of the Editor

This paper[1] was just the first one of a small series of articles and poster presentations by F Schelling which appeared in the '80s [2, 3], dealing with the hypothesis of the venous origin of multiple sclerosis (MS). We thank the Author for having agreed to make the huge job of translating it from German, thus giving our readers the opportunity of appreciating a forgotten work about the venous cerebral circulation.

Notes of the Author

This first attempt to deblur the thinking on venous refluxes into brain and spine had, and still has its shortcomings. First of all, because no data are available about the speed of ascent and eventual height of the pressure peaks which occur in the internal jugular veins. Besides this, because the effects of muscular and external impacts exterted on the internal jugular veins upstream of sporadic and functional occlusions have as yet not been duly taken into account.

The occurrence of a one-sided incompetence of the valve securing the upper end of the inferior bulb of right respectively left internal jugular vein won't be questioned by anyone. Nor it's being the only valve which guards the brain against excess pressures that emerge from below.

What seems not to be known as well are the ways in which refluxes spread pushing up via, or from, internal jugular veins. No better the fact that an absence of the confluence of sinuses, of each cranial venous outlet bypassing a principal one has repeatedly been observed.

Impressive anatomical findings of varicose dilations of posterior condylar emissary veins relating to such of the upper jugular bulb made in 1973 had pointed to the occurrence of voluminous refluxes passing from internal jugular into deep cervical veins. Less could be said about the excess pressures which the involved internal jugular veins' cerebral affluents are in such contexts burdened with.

In this context, observations of small veins connecting the upper end of the internal jugular directly with bulbar veins, and such of the exceptional feeding of an (rather the left) internal jugular vein via an isolated lateral and straight sinus primarily by the internal cerebral veins (or but one of them) are calling for special attention. They point to the fact that refluxes from an internal jugular vein will tend to have

their most disastrous effects in precociously or selectively burdening a narrowly circumscribed venous domain.

Curiously enough, both brain damages and lesion dynamics which appear to perfectly reflect the postulated events have been described under the heading of multiple sclerosis.

Since this paper was published, no piece of evidence came forth, no objection was raised, which might have invalidated its content.

To the contrary, more and more data accrued which confirmed its critical indications in the one or the other respect. This at a rate rendering it more and more demanding to keep track of them (e.g. central/lesional vein/vessel sign).

Long forced to retire, I can but wonder who might achieve the feat of pulling all these strands of evidence together and so become entitled to fulfill my dream: The carefully planned and executed prevention of injurious venous refluxes into brain and spine.

Acknowledgements

The willingness of doctor Fausto Passariello to present my original argumentation for widening the scope of MS research accordingly can hardly be appreciated highly enough.

It is thanks to Mrs. Alison Fisher (Scotland), Dr. Elcio Machado (Brasil), and Prof. Jaap Valk (Netherlands) that my early work has not fallen into oblivion. I owe the links to the references 2) and 3) below to them.

If I did make any headway at all, it is yet because Prof. Werner Platzer tutored me in anatomy, Prof. Gerhard Breitfellner gave his permission to perform retrograde venous injection studies in MS and control autopsies, Prof. Walter Rhomberg paved the way to my poster presentations - all of this in nearby Austria.

The motivation to carry on, however, came from my most seriously affected MS patients.

Gaining decisive support from a congenial Prof. Colin Adams (England) who best showed how MS destroys, actually bursts its lesion veins in the brain[4], and from admired Prof. Emil Beck (Austria) and kind Prof. Wilhelm Doerr (Germany) who acquainted me with parallel observations made after accidents[5].

A deeply grateful,

Franz Schelling, M.D.

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MEMORIAL

In memory of Prof. Sergio Mancini

G Botta[1]

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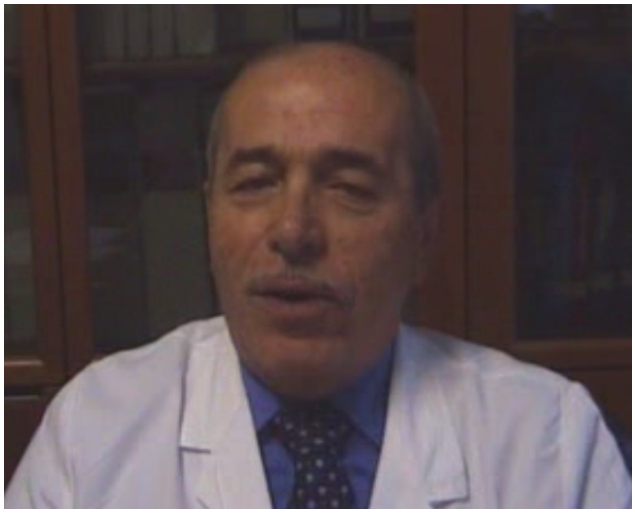

Figure 1 - Prof. Sergio Mancini

Sergio Mancini left us after a long illness in the night between 26 and 27 April, 2017.

He was born in Livorno on October 19, 1937.

After graduating at the high school Carducci of Milan, he matriculated to the Faculty of Medicine of the Naples University, where his family had moved for work.

Graduated in Medicine and Surgery at Naples University in March 1964, he came to Siena, where he began his academic career in the surgical school of Prof. Luigi Gallone.

Winner of a university chair of surgery, Sergio Mancini was called unanimously by the Faculty of Medicine and Surgery of the Siena University to cover the Chair of General Surgery from November 1, 1995.

Later he became Director of the Department of General Surgery at the Siena Hospital and also Director of the School of Specialization in General Surgery after the retirement of his teacher, Prof. Luciano Lorenzini. In this role he became at the end of the last century and the beginning of the present century one of the most authoritative representatives of the Siena Surgical School.

Master of Life and Science, man of great humanity and sensibility with strong charisma, he was a talented general surgeon and a great teacher, forming many students, some of whom later became academics and specialists in Phlebolymphology of the highest national reputation.

Both in chair and in life he has always shown a great and eclectic personality, transferring to the students, to the doctors of his group and to the patients an extraordinary authority, which has been the emblem of his professional image.

But his passion were the diseases of the veins and the lymphatic vessels, both in terms of care and research. In 1985 Sergio Mancini founded at the Siena University the Center of Phlebolymphology, that soon became one of the most important in the world, and he surrounded himself strategically with a group of young doctors, to whom he transmitted the passion for the care of patients suffering from diseases of the veins and lymphatic vessels.

Finally, over the three-year period 1997-1999, Prof. Sergio Mancini became President of the Italian Society of Phlebolymphology and in this role he contributed greatly as a founding member to the birth of the Italian College of Phlebology, which had to become in his intentions the common house of all Italian Phlebologists.

Known and much appreciated as specialist in the international context, he left many friends and colleagues in

various parts of the world, such as Argentina, Brazil, United States, France.

Dear professor, I do not know if You can still be interested in earthly things from the place where You are now, but if You can read these few lines, know that You left in me - Your beloved pupil as You often told me - an unbridgeable void and an indelible memory.

Giuseppe Botta

Director of Phlebological Unit of the Siena Hospital

MEMORIAL

In Memory of Prof. Leonardo Corcos

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Prof. Leonardo Corcos

Leonardo Corcos born on 3 September 1946 in Florence, Italy, died in a terrible motorcycle accident near Florence on 13 August 2017.

Leonardo received his degree in Medicine, University Firenze, 1970 and trained as a general, vascular surgeon and phlebologist.

We got to appreciate him how a talented and innovative medical researcher he was, as well as tenacious, meticulous and precise.

Experienced doctor and always attentive to the patient, he leaves in those who knew and enjoyed him a huge void and at the same time a lasting memory.

He was a trusted friend and secure with strong attachment to his family.

Active and dynamic man, he engaged in leisure in many other activities besides the profession: in particular we remember him as a great pianist and sailor.

Founder and Vice President of the Italian Society of Phlebo-lymphology, member of the Italian College of Phlebology and of the UIP, author of numerous scientific publications, he attended many conferences and loved teaching. He was an outstanding reviewer of manuscripts for a variety of medical Journals and always strove to help junior authors and researchers enhance their work.

Condolences to his family by everyone who knew him.

Giampiero Peruzzi, MD

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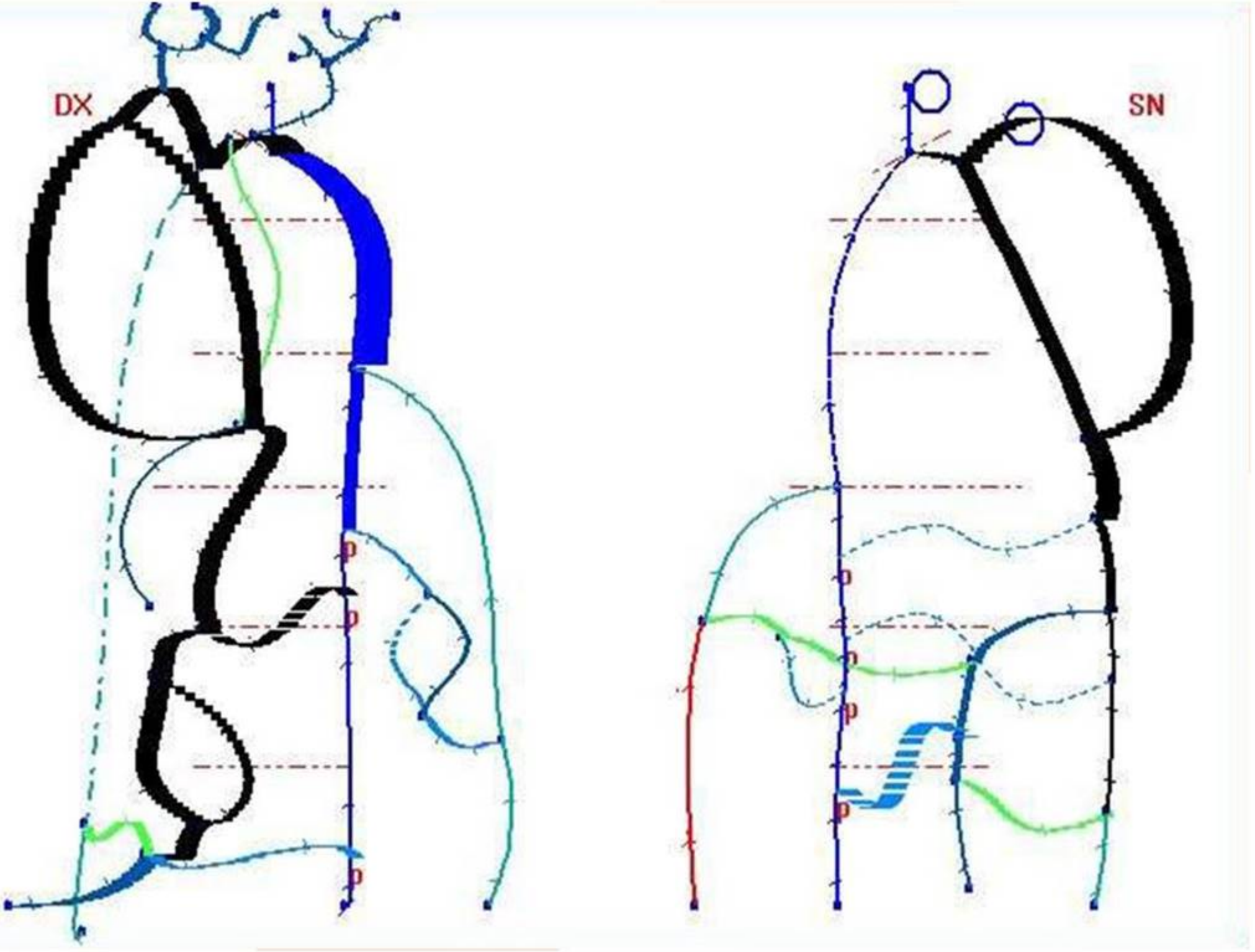
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