The Interest in the Pathology and Pathophysiology of Vascular Lesions

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Abstract: This chapter presents the historical and progressive interest in cerebrovascular lesions which began in the 17th century. Despite its frequent occurrence, knowledge of the natural history of cerebrovascular disease was surprisingly scanty until 18th century. The history of cerebrovascular lesions covers several centuries, although the observations influencing current practice have been analyzed only since the 20th century. This chapter is a review of the contributions of the principal physicians, pathologists, anatomists, anthropologists, philosophers, pathoanatomists, neuropathologists and neurologists to the present knowledge of the pathology and pathophysiology of cerebrovascular lesions. The period from the 16th to the 20th century has been analyzed; the pathophysiology of cerebrovascular lesions has been divided according to etiological classification. The greatest contributions to knowledge are due to Felix Platter (1536–1614), Johann Jakob Wepfer (1620–1695), Giovanni Battista Morgagni (1682–1771), Jean André Rochoux (1787–1852), Léon Rostan (1790–1866), Karl von Rokitansky (1804–1878), Charles Louis Maxime Durand-Fardel (1815–1899), Rudolf Ludwig Virchow (1821–1902), Jean-Martin Charcot (1825–1893), Joseph Jules Déjerine (1849–1917), Pierre Marie (1853–1940), Charles Foix (1882–1927), Charles Miller-Fisher (1913–2012). At the end of the 19th century, the development of clinical–anatomic correlation studies of cerebrovascular lesions was considered a brain condition worthy of specific research and future knowledge.

1. Introduction

Progressive interest in the pathology and pathophysiology of cerebrovascular lesions (CVLs) began in the 17th and 18th centuries, mainly through autopsy findings, though cerebrovascular disease (CVD) remained unknown to many physicians in the 18th century.

The development of knowledge of CVD, was sluggish until the first half of the 19th century when the vascular nature of CVD was widely identified and accepted [1,2]. With the beginning of the 19th, CVD was defined for the first time as a result of a CVL (ischemic or/and hemorrhagic).

Morphological lesions alone defined the decisive criterion to indicate a CVD; the symptoms were then considered solely as "indicatory signs" and "pathological anatomy" established the key basis for all CVD knowledge [3]. The 20th century represented a revolution in CVL knowledge.

Interest in CVLs among pathologists, anthropologists, philosophers, physicians, neuropathologists, and neurologists was promoted by the development of clinical–topographical correlation studies carried out by Joseph Jules Déjerine

(1849–1917) and Pierre Marie (1853–1940), followed by Charles Foix (1882–1927), the forerunner of modern clinical CVD research.

2. History of Cerebrovascular Lesions

The first mention to the nervous system is discovered in the Edwin Smith Surgical Papyrus dating from 3500 BC, with the first reference to "brain" [4].

A sound knowledge of ancient doctrines regarding health and disease is necessary to comprehend Greco-Roman medical texts dealing with CVD.

In the Middle Ages, from 500 AD to 1500, the focus was on miraculous healing and the concept of medicine was aligned with religious practices thus not creating much scientific interest. This could justify why anatomopathological awareness of CVLs lagged so far behind morphological anatomy.

In the 14th century, the first anatomical analyses of human bodies were carried out; in the middle of the 15th century, larger numbers of post-mortem examination were executed, resulting in improved knowledge of brain anatomy and cerebral vessels.

Subsequently, in the 16th century, through the verification of the first autopsies it was possible to document the anatomical lesions linked to some diseases. This marked the birth of pathological anatomy [2].

2.1. CVL History in the 17th Century

In 1602, following the death of one of his CVD patients, Felix Platter (1536–1614), performed a brain autopsy. He summarized his findings in this way "a phlegmatic humour is obstructing the inner passages of the brain" [5].

This sentence allows us to highlight two fundamental aspects of the historical study of diseases: (i) in the past as in the present, every scientific observation is theory-based; (ii) clearly it is extremely difficult to counteract traditional beliefs. Platter had supported Galen's belief that phlegm in the cerebral ventricles caused apoplexy, and indeed the brain post-mortem confirmed the presence of phlegm in the cerebral cavities.

Johann Jakob Wepfer (1620–1695), one of the most renowned authors of his time, wrote numerous medical monographs during the 17th century in which CVD was defined only as a set of various symptoms. He made an accurate description of the anatomy of cerebral vessels with anterior arterial, many years before Willis. He was one of the first physician to compare the neurological manifestations with the results of the brain autopsy and hypothesized a possible correlation, thus paving the way for the subsequent anatomo-clinical method.

In the 17th century, accurate descriptions of the cerebral vessels and the first detailed analyses of the consequences of occlusion began to appear.

The humoral theory met its end in 1628 when William Harvey (1578–1657) described vascular circulation in the treatise "Exercitatio anatomica de motu cordis et sanguinis in animalibus" or, as it came to be known, "De motu cordis". He was

intrigued by humoral circulation in the human body. At that time, it was widely believed that the liver converted food into blood which the body employed as fuel.

Up until the 1600s, it was thought that there were two distinct blood systems in the body. In the former, purple (nutritional) blood circulated through the veins to distribute nourishment from the liver to the rest of the body. In the second, scarlet (life-giving or vital) blood circulated through the arteries to deliver a life-giving principle from the lungs. At that time, the presence of oxygen in the blood was not known and it was thought that the circulation of the blood occurred around the body and consumed as it was produced. Circulation through the capillaries, small arteries and veins were unknown at the time and their presence was only discovered thanks to the microscope at the end of the 17th century.

By comparing clinical features with autopsy, Giovanni Battista Morgagni (1682–1771), an Italian anatomist, laid the foundations of clinical anatomic studies in CVD [6]. He promoted the anatomo-clinical approach in medicine which thus became the anatomical means to identify the origin and etiology of any disease. He also maintained the ancient apoplexy classification between "sanguineous" (hemorrhagic) vs. "serous" (no hemorrhagic) [7]. Furthermore, he subdivided hemorrhagic lesion in blood CVL (intracerebral hemorrhage) and water CVL (bleeding into the right ventricle) through the dissection of the brain analyzed.

2.2. CVL History in the 18th Century

Between the 17th and 18th centuries, evolving concepts of brain "softening" and "apoplexia" were consolidated [2]. Jean André Rochoux (1787–1852) claimed in 1814 that apoplexy was always the result of bleeding [8]. Apoplexy was described as "a sudden but mostly general, rather than focal, disorder of the brain".

In the period from 1820 to 1823, "spontaneous cerebral softening" is a different find from encephalitis and apoplexy was first defined by Léon Luis Rostan (1790–1866), a French pathologist, physicist and a representative of the anatomico-clinical School of Paris. The main finding of Rostan reported in his studies regarding CVD was his definition of "cerebral softening" (encephalomalacia), fundamental in the knowledge of CVLs. He no longer used CVD as a general term, regarding it as synonymous with hemorrhagic CVL.

He reported pathologic and clinical features of brain softening, which differed from apoplexy. In contrast to apoplexy, from which he had seen recovery, he declared softening to be fatal. He equated it with senile gangrene and retained that it was related to the "ossification" of cerebral arteries.

2.3. CVL History in the 19th Century

The definition of brain "softening" was opposed by authors such as François Joseph Victor Broussais (1772–1832) (from Lallemand, 1830 to Calmeil, 1859), who considered the brain softenings such as the result of "inflammation", hence the name encephalitis.

Conversely, Léon Rostan's proposals were accepted and elaborated by the Englishman Carswell (1835), the Scot Abercrombie (1836), and the Frenchman Andral (1827, 1840). While Léon Rostan had underlined a connection between an arterial condition (ossification) and parenchymatous lesions in his "Recherches sur les ramollissements du cerveau" (1823) he did not associate them with vessel blockage.

In 1856, this new concept was refused until the description of thromboembolism by the German Rudolf Ludwig Virchow (1821–1902), pathologist, statesman and anthropologist [2–9], and the studies of Adrien Proust (1862), Vincent Laborde (1866), Jean Louis Prévost and Jules Cotard in France (1865).

By the beginning of the 19th century, the clinical–anatomic method had spread from Italy to other countries but only at the end of the 19th century did authors begin to emphasize the relationship between arterial vascularization, brain lesions, and corresponding clinical features.

Jean-Martin Charcot (1825–1893) taught anatomic pathology before being nominated to the world's first chair of neurology. In 1862, Charcot and his friend Edmé Félix Alfred Vulpian (1826–1887) became directors of clinics at La Salpêtrière. The work of Charcot is widely recognized for its impact on neurology and psychology, but his contribution to vascular neurology remained small.

Between 1850 and 1900, the most common topics of study and interest were tabes and hysteria. A good example of the persisting relative disinterest in CVD by one of the most famous neurologists of this period is provided by Joseph Babinski (1857–1932). Only one paper focused on CVD, while the three others dealt with signs associated with hemiplegia. The critical trigger of the interest in CVD at this time was the description of specific brainstem syndromes. However, the underlying lesions were only rarely vascular, but were frequently tuberculomas, tumors, or abscesses. These reports stimulated prominent neurologists to study CVD cases from the angle of clinical–topographic correlations.

The turn of the 19th and 20th centuries saw the birth of the early generation of "vascular neurologists." Among them the Frenchman Charles Foix was particularly active. In the field of neurology, an interest in CVD as a distinct clinical entity took place at that time.

Foix is considered to be the first vascular neurologist for his work on the patterns of brain infarction in cerebral artery subdivision [10,11]. His work took a typical clinical–anatomic approach in an attempt to establish fine correlations between localization of parenchymal lesions and consequent clinical dysfunction.

The gradual evolution of knowledge during the 19th century was the result of work by isolated physicians or great names in pathology.

2.4. CVL Revolution in the 20th Century

After Charles Foix, interest in CVD gradually, though slowly, increased during the 20th century, especially in the1940s and 1950s, with the advent of new diagnostic

methods. Later work involved an increasing combination of morphological and physiopathological aspects followed by neuroimaging data.

In the 1960s, the Canadian Charles Miller Fisher (1913–2012) highlighted that a thromboembolic mechanism underlies the majority of ischemic CVLs and that the origin of thrombus derives from the heart or from a proximal arterial lesion [12]. He described the association of the lacunar lesion with specific neurological manifestations allowing the diagnosis of this type of CVD, very common in the decades before these ischemic lesions became visible on brain imaging studies.

The history of 20th century medicine relative to CVD/CVLs is fundamentally the result of the technical development in diagnostics [13].

3. Pathology of Cerebrovascular Lesions

CVLs result from the impaired function of the central nervous system vessels, divided into hemorrhagic, ischemic, or mixed. CVLs usually occur with sudden onset due to bursting of the cerebral arteries (hemorrhagic lesion) or/and occlusion by a thrombus or other particles (ischemic lesion); this results in focal brain dysfunction.

Critical advances in the study of CVLs came from pathologists such as Karl von Rokitansky (1804–1878) and Rudolf Ludwig Virchow.

In the 19th century, CVD became established as a scientific concept, and so medicine was included in the natural sciences. Working in Vienna, Karl von Rokitansky used post-mortem examination to document observations which aided future clinical diagnoses. The pathoanatomist Karl von Rokitansky, together with Joseph Škoda (1805–1881), developed the II. Viennese School, known as the "young Viennese School". The first volume of Rokitansky's "Compendium of General Pathological Anatomy" was published in Berlin in 1846, where a group of dedicated young physicians was particularly interested in "thinking cellularly" [14].

Arterial thrombosis and embolism were described by Rudolf Virchow who observed the interaction among blood and the arterial inner wall [9], and the results of interruption of blood flow to a parenchyma. He was also the first to use the term "ischemia".

He revived the term "arteriosclerosis" for the development of a thrombosis on the arterial wall, which had initially been employed by Jean Georges Chrétien Frédéric Martin Lobstein (1777–1835) in 1829, and furthermore demonstrated that portions of a thrombosis could detach from the wall and be carried in circulation as an "embolus" (also his term) [15].

Rudolf Virchow observed thrombosis secondary to arteriosclerosis, and local embolism caused by clots from the heart in patients with lower limb gangrene [16]. He extrapolated that a similar event in the brain could lead to cerebral softening. In 1856, he reported carotid thrombosis with ipsilateral blindness. Rudolf Virchow considered "arteriosclerosis" as "simple fat metamorphosis," and a frequent change in the blood vessel walls. Through Virchow's investigations, inflammation was

universally considered as the principal etiological cause of arteriosclerosis, and this has been confirmed recently.

Virchow's studies were pursued by Julius Cohnheim (1839–1884), one of his students. When "cerebral vascular lesion" is used as an academic alternative for "stroke", the reference is to Cohnheim's theory derived from his experiments of arterial injection of wax globules embolizing in a frog's tongue. These observations suggested that arterial blockage and reduced blood flow to brain areas caused softenings, and that this confirmed Cohnheim's proposal that the lesions were infarctions [17]. Such embolization produced either no injury or two types of lesions, which for almost a century have been defined as "ischemic necrosis" and "hemorrhagic infarct" [17].

A great advance in the 1840s was due to Karl von Rokitansky who insisted on the association of hemorrhagic apoplexy with heart disease [18]. Various "apoplexies" were thought to be due to right ventricle congestion or dilatation. Hemorrhage may have been associated with left ventricle hypertrophy and, therefore, to an increased "impulse". Arterial hypertension had not been taken seriously at that time. What is more, fragile arterial walls were thought to provide to hemorrhagic lesion, either singly or together with these two aspects. Finally, it was believed that an "anomalous condition of the blood" existed, which corresponded to "arteriosclerosis". Von Rokitansky believed that artery "ossification" derived from "the accumulation of an inner membrane upon the vessel by deposition from arterial blood," and that the vessel wall absorbed a chemical substance in the blood, leading to fatty streaks [19].

4. Pathophysiology of Cerebrovascular Lesions

The pathophysiology of ischemic/hemorrhagic CVL results in oxygen-depleted focal cerebral nerve cells. The corresponding vascular territory is functionally disturbed and dies if circulation is not immediately reperfused. The pathogenesis of ischemic CVLs is multifactorial and the inflammatory process is a key component in CVL pathogenesis [20].

4.1. CVLs Pathophysiology from the 19th to 20th Centuries

The term apoplexy occurs in Hippocrates' aphorism "Unusual bouts of numbness and anesthesia are signs of impending apoplexy".

Apoplexy was described as a sudden and generalized brain disorder. Apoplexy pathogenesis was defined by means of the humoral theory—that is, the balance between the four humors, blood, phlegm, black and yellow bile. It was frequently thought to be caused by a cluster of black bile within the cerebral arterial vessels, thus blocking the passage of spirits animated from the ventricles, with anatomy playing almost no role [21]. In ancient times, medicine was closely linked to religion, without arousing much scientific interest.

During the Renaissance, Leonardo da Vinci (1452–1519), one of the best known and most famous anatomists, reported and illustrated the great neck vessels.

Indeed, Leonardo realized that neck compression (strangulation) led to rapid loss of consciousness and, if continued for more than some minutes, resulted in death from cerebral blood vessel compression [22].

From the end of the 19th century onwards, the scientific knowledge of medicine represents a branch of knowledge linked to the natural sciences. In this period, the possible correlation between cerebrovascular–anatomical lesions and some neurological manifestations or specific diseases are researched, and the diagnosis of electrophysiological and imaging techniques are improved.

In 1905, Hans Chiari (1851–1916), and some years later, Hunt, Moniz, and Hultquist, among others, recognized the possible correlation of carotid artery disease and CVD. Hans Chiari, working in Prague, observed thrombus superimposed upon ulcerated carotid artery atherosclerotic plaques in 7 out of 400 patients in consecutive autopsies [23]. There were four cases of cerebral embolism, and so Chiari hypothesized that embolic material could become detached from carotid artery plaques and determine brain damage such as CVD. Chiari was the first to correlate carotid occlusive disease with neurological symptoms.

In 1914, James Ramsay Hunt (1872–1937) described the clinical characteristics of 20 hemiplegia patients but without supplying autopsy data. Once again, he stressed the importance of extracranial artery blockage in CVD. Hunt realized that partial and complete innominate and carotid artery occlusions could be the vascular cause of cerebral syndromes; therefore, he used the expression "cerebral intermittent claudication". Furthermore, he emphasized "the occurrence of unilateral vascular changes, pallor or atrophy of the optic disk with contralateral hemiplegia" in carotid artery obstruction and proposed that "the cerebral lesions in most CVD victims could be the effect and not the cause" [24,25].

At the end of the 19th and early-20th centuries, the relationship between arterial encephalic vascularization and CVLs began to be understood [26]. Between the 1920s and 1970s, the pathophysiological knowledge of CVLs improved thanks to work by the Frenchman Charles Foix and the Canadian Charles Miller-Fisher [27].

In the same period, attention began to be focused on how the brain works, including its vascularization. Charles Foix is remembered for his CVD studies, with particular regard to posterior circulation disease. He paid particular attention to clinical–anatomical correlation, trying to find a relationship between CVL and clinical signs [28].

Foix's work dealt with an analysis of the anatomical regions and vascular structures of each branch, providing a description of the softening distribution and relative accompanying neurological manifestations.

In 1895, the revolutionary discovery of X-rays by Wilhelm Roentgen (1845–1923) contributed to a deepened knowledge of CVD and CVLs [29]. Wilhelm Roentgen assigned the name of his discovery X-rays, since the nature of these rays was unknown. Subsequently, one of his pupils, Max von Laue (1879–1960), demonstrated

that they had the same electromagnetic nature as light, but differed only in the higher frequency of their vibration.

X-ray techniques continued to improve, and on 7th July 1927, the Portuguese Antonio Egas Moniz (1874–1955) described the first use of sodium iodide as a contrast medium in cerebral angiography at the Societé de Neurologie in Paris [30]. This breakthrough in CVD knowledge allows us to identify the affected vessel prior to surgical procedure [31].

Raymond Adams (1911–2008) and Charles Kubik (1891–1982) annotated the clinical findings and showed both the location of arterial occlusions and the resulting brain and cerebellar lesions [32]. They indicated morphological distinctions between thrombosis and embolism: "Thrombosis of the basilar artery could usually be recognized at a glance. The thrombosed portion of the vessel was distended, firm, and rigid and the thrombus could not be displaced by pressure. In embolism, the embolus was usually lodged in the distal portion of the basilar artery" [33].

Subsequently, Miller Fisher analyzed the artery pathology underlying lacunar lesions, cerebral hemorrhages, and carotid artery occlusions. In one of his works, Fisher highlighted the correlation between carotid artery occlusion in the neck and CVD diagnosis [34]. Further lacunar CVD studies and associated neurological diseases have allowed for the clinical diagnosis of these frequent and common ischemic CVLs decades before lesions were revealed by neuroimaging studies, thereby facilitating treatment [35,36].

Between the 19th and 20th centuries the pathophysiology of CVLs resulted from (i) experimental laboratory models; (ii) animal models of ischemic CVD; (iii) brain autopsies and anatomical preparations; (iv) electroencephalographic examinations; (v) X-ray techniques. Correlations between vascular and clinical anatomy became increasingly important. Animal models played a role in developing improved CVD prevention and treatment through the investigation of the pathophysiology of different CVD subtypes and by testing promising treatments before human trials began.

The pathophysiological basis of CVLs remained unclear until the 1960s, when Charles Miller Fisher carried out several autopsy studies on CVD patient brains. He described CVL pathological features in different nervous system areas such as thalamic and cerebellar hemorrhage lesion, lateral medullary infarction, and inflammatory CVLs. He found that the vessels exhibiting segmental arteriolar disorganization correlated with vessel enlargement, hemorrhage, and fibrinoid deposition.

This phenomenon has been termed "lipohyalinosis" to characterize the microvascular mechanism that generates small subcortical infarcts without a convincing embolic source. Notable progress has been made in understanding lipoyalinosis and lacunar stroke since Fisher's early studies.

Herein, we review the phenomenon of lipohyalinosis in relation to early concepts of cerebral small vessel disease [37]. Specific cerebral ischemia evolves

through a phase of acute encephalomalacia, where alternating cellular swelling and shrinkage determines morphologic change. Leukocytic inflammation follows for three to four days after arterial occlusion and then after about the 10th day of resolution begins [38].

At the end of the 20th century, CVD animal models contributed to improved knowledge of different CVL pathophysiology, despite important differences between rodent and human cerebrovascular anatomy (brain dimensions, perforating artery length and structure, and gray to white matter ratio) [39].

4.2. Introducing Etiological Classification

By the beginning of the 19th century, the terms thrombosis, embolism, arteriosclerosis, and lacune to indicate CVL etiology were introduced, but atherosclerosis carotid disease was recognized later.

4.2.1. Thrombosis, Embolism Infarction and Arteriosclerosis

Thrombosis and embolism were first recognized by Rudolf Virchow to describe the relevant interaction between blood and arterial damage [9]. Virchow documented the consequences of blocking blood flow to a parenchymal or tissue and named this process "ischemia" (Schiller, 1970; Nuland, 1993; Reese, 1998).

At the beginning of the 19th century research began to concentrate on vascular alterations. In 1829, Jean Lobstein proposed the term "arteriosclerosis" in his unfinished four-volume treatise "Traité d'Anatomie Pathologique" [40].

In the middle of the 19th century, cellular inflammatory changes in atherosclerotic vessel walls were described by Rudolf Virchow and Karl von Rokitansky who represented two opposing schools of thought [41,42].

By 1848, Rudolf Virchow had shown that "thrombosis", his term, was due to masses in the blood vessels (Virchow, 1856; Pearce, 2002). He identified three principal predisposing factors for venous thrombosis, now known as Virchow's triad (irregularity of the vessel wall lumen, reduced blood flow, and hyper-coagulability).

Virchow reintroduced the definition "arteriosclerosis", initially used by Lobstein in 1829, to indicate that portions of a thrombosis could separate and form an "embolus" (also his term) [2]. Virchow noted thrombosis secondary to arteriosclerosis, and local embolism caused by clots from the heart in patients with lower limb gangrene. He considered "arteriosclerosis" as "simple fat metamorphosis," and that it was one of the most common changes in blood vessels.

Through Virchow's investigations, inflammation was widely recognized as the principal etiological cause of arteriosclerosis, which has been confirmed in recent decades.

4.2.2. Lacunar Infarction

Introduced initially in 1838 by Amédée Dechambre (1812–1886), the term "lacune" referred to a small cavity that remains after a small CVD [43]. This term

is an uncommon example of an introduction of a French term which has remained unchanged in English. It derives from the Latin lacuna and it refers to an "empty space." In 1843, Charles Louis Maxime Durand-Fardel (1815–1899) described in more detail the finding of "lacunes" such as small healed brain attacks [44].

Durand-Fardel defined a lacune as a small cavity in the brain "without any change in consistency or color from which it was possible to remove a little cellular tissue containing very small vessels with a thin forceps". His objective was to distinguish "lacuna" from hemorrhage and large infarct. The issue as to whether lacunes were residual from a hemorrhage or an infarct led to a vehement argument between Rochoux and Durand-Fardel in 1844. Further advances on lacunes were not obtained during the next 50 years.

Pierre Marie, a devoted pupil of Jean-Marin Charcot, who became his third successor to the chair of Clinique des Maladies du Système Nerveux at La Salpêtrière, published his paper "Des foyer lacunaires de désintégration et les différents autres états cavitaires du cerveau" in 1901, in which he concluded that lacunes were small softenings caused by atherosclerosis, and were different from état criblé and "état vermoulu". He also declared that some lacunes which contained a patent blood vessel were due to a perivascular space dilation and ruined the contiguous brain parenchyma by "destructive vaginalitis".

When the term lacune was first described, its underlying pathophysiology was unclear. In the 1960s, Charles Miller-Fisher [35] performed autopsy studies that showed that vessels supplying lacunes displayed segmental arteriolar disorganization. He reintroduced Durand-Fardel's term for lacune as "small, deep cerebral infarct". Since then, there have been few attempts to render this pathological description consistent with modern mechanisms of cerebral small vessel disease [45].

4.2.3. Atherosclerotis Carotid Disease

Atherosclerosis has not recently developed in the last few centuries. It was present as degenerative modifications in the arterial walls of Egyptian mummies [46,47]. Ancient Egyptian atherosclerosis morphology does not differ from the phenomenon seen today in vascular surgery and pathoanatomic specimens.

Adolf Kussmaul (1822–1902) in 1872 and Franz Penzoldt (1849–1927) in 1881 reported thrombosis of carotid artery in the neck in patients with ipsilateral eye blindness and contralateral hemiplegia [48,49]. In 1875, William Richard Gowers (1845–1915) reported a patient with blindness and contralateral hemiplegia and mitral stenosis [50]. In the patient's autopsy findings, emboli were found in the central and retinal cerebral arteries, originating from clots in the auricular appendages. For more than a century, the cerebral embolic genesis was related to the heart and only since 1960 has it been considered the embolic source from the extracranial arterial.

Similarly, the term cerebral thrombosis remained well-entrenched as a synonym for cerebral infarction without cardiac embolism. It was generally assumed that

arterial disease involved intracranial vessels, although in 1905 Hans Chiari [23] had emphasized the association of extracranial carotid disease with CVD.

In 1910, the German chemist Windaus demonstrated that atherosclerotic plaques were made up of calcified connective tissue and cholesterol [51]. Soon after, Nikolai Anitschkow and Semen Chaltow managed to induce atherosclerosis in rabbits by feeding them a cholesterol-rich diet, thus definitely identifying a classical risk factor for progression of atherosclerotic mechanisms [52].

The pathogenetic mechanism of atherosclerosis remained unclear and classical analyses did not attribute great importance to inflammatory–immunological processes as possible pathogenetic factors [53]. The inflammatory process has been identified as playing a fundamental part in atherogenesis.

5. Perspectives for the 21st Century

Multiple biological systems are involved in CVL pathogenesis, and future research should aim to pinpoint potential interactions among all these mechanisms in order to develop therapies for the prevention of CVD. The increase in CVL pathogenetic knowledge derives from (i) anatomopathological studies of fatal head injuries; (ii) neuroprotection laboratory and animal experiments; (iii) cerebral angiography studies; (iv) static or functional neuroimaging and related imaging techniques.

Current knowledge of CVL pathophysiological mechanisms is derived from the critical activity of the 19th century physicians who managed to confute all the deceptive and constricting beliefs that had existed for many centuries.

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