

Milestones... in Investigative Pathology

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Ueber die pathologischen Gerinnungsvorgänge

About the Pathologic Coagulation Functions



Dr. Carl Weigert

The first time you touch a van de Graaff generator, you're sure you're going to die. Anything that can arc and make your hair stand on end can't be good for you. Then you're taught that those millions of volts are not what kill you, it's the amps, and van de Graaff generators don't make enough amps to hurt you. You're probably wondering where this is heading, but the analogy is that in ischemic heart disease, it's not the pressure gradient (volts) that saves you, it's the coronary artery blood flow (amps).

Those pristine coronary arteries of your youth have transmogrified over years of dedicated service into strictured, lipid-laden, thrombosis-prone vessels that reduce coronary artery blood flow. Stenotic narrowing reduces blood flow more than common sense understanding would estimate. Yes, the vessel radius and blood flow are directly related, but not linearly as with the pressure gradient, instead to the fourth power of the vessel radius (Poiseuille, 1840). So, narrowing a coronary artery to 1/2 of its usual radius leads to reduction of blood flow to 1/16 of expected. Turbulence can develop, and could affect plaque surface stability. Therefore, atheromas in the coronaries have a marked effect on usual pulsatile laminar flow. No wonder your interventional cardiologist wants to sell you a shiny mesh stent to dilate your stenotic foci - if you double the diameter at the stenosis, you raise blood flow 16-fold. Our colleagues in Anesthesiology think this way when choosing calibers of endotracheal tubes and catheters. We Pathologists think this way because we have seen the coronary artery stenoses in association with sudden cardiac deaths from fresh myocardial infarcts (MIs), and in association with pump failure from old MIs. But it wasn't always so.

The anatomists of the Renaissance (Vesalius (Fabrica, 1543) and his students (Fallopium et al.)) began accurate, thorough documentation of normal human anatomy. In the 18th century, Dr. Morgagni focused and published on pathologic anatomy, and as such is the father of modern anatomic pathology. His detailed case reports of gross post-mortem findings, *The sites and causes of diseases investigated by anatomy* (1761, when he was 80, so get to it), positioned the rest of us to see cause and effect relationships between diseased organs/cells and the patient's signs/symptoms. The concept of disease could then evolve from that of a limited set of symptoms and signs to a vertical thought process that integrated anatomic/physiologic etiology, pathogenesis, and distortion of normal function. Signs and symptoms were a consequence of the disease process, not themselves the disease. Dr. Morgagni's descriptions of pathologic anatomy led his intellectual offspring (including us) to see disease through this etiology-pathogenesis-altered function lens. For example, he described cardiac

mural fibrosis ("the fleshy fibres of the heart themselves sometimes degenerate into a tendinous hardness"), but would leave it to future generations to sort this out microscopically and conceptually.

Dr. Edward Jenner (of cowpox vaccine fame) recognized coronary artery mural calcifications and intimal thickening in autopsy patients with a history of angina, and postulated in letters to Dr. Heberden in the 1780s that angina pectoris could be due solely to coronary artery narrowing. Dr. Parry's clinical review of angina pectoris in 1799 credited Jenner for this coronary stenosis-angina association. However, invention of the stethoscope (Laennec, 1816) focused clinical attention on the sounds of valves and pump failure, and invention of the electrocardiogram (ECG) by Einthoven in 1895 focused clinical attention on electrical arrhythmias, such that cardiologists did not seriously revisit the correlation of coronary artery occlusion, angina pectoris, and myocardial infarction until reviewed by Dr. Jas. Herrick in 1912. As late as 1907, a review of the works of our current Milestones honoree, Dr. Carl Weigert, mentioned his contributions to histopathology (e.g. myelin and elastin stains) without any reference to his 1880 description of coronary artery disease in association with myocardial infarction and mural fibrosis. We could argue that they ignored the concept because nothing could be done about ischemic heart disease at that time, but vasodilators like amyl nitrite and nitroglycerine were used from the 1870s on, and would have supported Dr. Weigert's hypothesis regarding pathogenesis of myocardial infarction and mural fibrosis. Perhaps they were distracted by the latest diagnostic technologies, or had not been taught how to think in terms of etiology-pathogenesis-altered function, or both.

Dr. Carl Weigert was a careful student of pathologic anatomy who started out as a treating clinician in the military in 1868. His interests turned to microscopic anatomy and histochemistry in the 1870s, when specific stains for classes of macromolecules, cell types, and microorganisms were hot topics. He was folded into the specialty of Pathology and mentored by Dr. Cohnheim at Leipzig after 1874, moving to Frankfurt after Dr. Cohnheim's death in 1884 to work with Elinger and Ehrlich. Dr. Weigert pursued the concept that coagulative necrosis was frequently the trigger for a proliferative/repairative host response. In the case of heart disease, he postulated that coronary artery occlusion led to coagulative necrosis of cardiac muscle, which in turn led to mural scarring in survivors. The title paper, written in German, is discussed in the English literature (Steven, 1887), as follows:

"In the writings of Professor Weigert and Dr. Huber, I have met for the first time with what appears to me to be an accurate and tenable explanation of the relationship existing between obstruction of the coronary arteries and the formation of fibrous patches in the walls of the heart.has shown that, where the circulation is slowly interfered with by sclerosis of the arteries, atrophy, with destruction of the muscular fibres, takes place without injury to the connective tissue. The shrunken fibres are thus set off by the stringy connective tissue..... If, however, the arrest of the circulation is more sudden in its onset, then yellow dry masses similar to coagulated fibrin make their appearance.....the muscular fibres and the connective tissue show no nuclei - a necrosis has occurred.the condition of the coronary arteries

Continued on page 11 - Milestones in Investigative Pathology

Milestones in Investigative Pathology

Continued from page 10

must be regarded as one of the most important etiological elements in the production of the morbid changes (cardiac mural fibrosis) at present under consideration.”

We can now expand Dr. Weigert's working hypothesis to say that elevated serum cholesterol contributes to atheromatous plaque formation (Anitschkow/Anitschkow, 1913) via increased serum low density lipoprotein (LDL) (Gofman, 1950), and that unstable plaque rupture leads to arterial thrombosis (rev. Falk, 1995), with subsequent symptoms and signs of myocardial ischemia and possible infarction.

Because of Dr. Weigert and his articulation of this model for pathogenesis of ischemic heart disease, we can now reduce the rate of development of arterial plaque by lowering our cholesterol/LDLs with statins, we can further reduce our risk of coronary arterial luminal thrombosis with aspirin and Plavix, and we can improve our coronary artery blood flow by stenting focal stenoses. The net result is that the progression of atheroma formation is slowed, fewer unstable plaques mean fewer ruptures to trigger thrombosis, and coronary artery blood flow in stented vessels can again approach laminar flow. And even your broker can't match Poiseuille's return on investment – a 16-fold increase in coronary artery blood flow in return for a 2-fold increase in vessel diameter.

Because after all, it's not the volts that kill you, it's the amps.

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