Arteriosclerosis is an Inflammatory Process

The last decade has shown an increase in the relevance of inflammation and its mediators in vascular biology; thus, the role of inflammation during atherogenesis is now a matter of intense investigation. Basic science studies proved that elements belonging to both innate and adaptive immunity can be involved in the formation, progression and complication of atherosclerosis. This discussion document should be viewed as my personal approach to cardiovascular and other inflammatory diseases.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in modern societies, and age is the major risk factor for CVD. This effect of aging on CVD risk is primarily the result of pathophysiological changes to arteries that lead to vascular dysfunction and disease. Although the mechanisms are incompletely understood, one of the key pathological changes to arteries with age is the development of chronic, low-grade inflammation. (11)

Plasma levels of circulating inflammatory molecules, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been shown to be predictive of future cardiovascular disease (CVD), and drugs which modify their levels can reduce the risk of myocardial infarction and stroke. It has been shown that an inflammatory response can develop in the arteries of animal models of hypertension.

This phenomenon is characterized by the expression of cytokines (IL-6, IL-1, TNF-α), chemokines (MCP-1), adhesion molecules (ICAM-1, VCAM-1), and has been linked to NF-κB system activation. The NF-κB system regulates multiple aspects of the immune system and is a pivotal mediator of inflammatory responses. (10)

Mechanisms leading to this inflammatory response are not clarified and can include both mechanical stress of the arterial wall and pro-inflammatory effects of humoural (relating to the body fluids, especially with regard to immune responses involving antibodies in body fluids as distinct from cells) factors, such as Angiotensin II.

These studies thus showed that the presence of a chronic low-grade inflammatory status can anticipate the future development of hypertension. (5) These processes involve components of both innate and adaptive immune systems.

Hypertension

In hypertension there is increasing wall thickness and loss of elasticity with increasing pulse wave velocity. There is gradual fragmentation and loss of elastin fibres with accumulation of stiffer collagen fibres in the vessel walls, that occurs independent of the atherosclerotic process. Similarly, with increased homocysteine there is increasing vascular thickness, elastin fragmentation and arterial blood pressure.

Nitric oxide (NO) is a potential regulator of the vessel matrix, and so differential production of NO contributes to oxidative stress and increased oxidative damage by vascular remodelling. Increased NO activity is a key contributor to homocysteine-mediated collagen/ elastin switch and resulting decline in aortic compliance.

Increasing aortic stiffness has been recognized as being associated with coronary ischaemia, diabetes and hypertension and provides a marker for vascular damage and long-term cardiovascular risk. There is still speculation though whether the arterial stiffness is a cause or consequence of hypertension, and whether large or small vessels are damaged first. A similar question exists with homocysteine- is it the cart or the horse.

Accumulating evidence from basic science researchers and clinical studies showed that Angiotensin II (AngII), besides regulating the vascular tone, may exert some pro-inflammatory effects on the arterial wall. AngII attenuates the formation of Reactive Oxygen Species (ROS) such as superoxide anion with upregulation of inflammatory mediators that contribute to increased blood pressure and atherosclerosis.

The treatment of animal models of hypertension with Angiotensin-II Receptor Blockers (ARBs) reverses most of the detrimental effects of AngII on endothelial function and reduces the level of inflammatory

activation in the vessels. These basic science results were recently confirmed by clinical studies showing that treatment with ARBs can reduce the circulating levels of some inflammatory mediators, such as IL-6, TNF-α, MCP-1 and CRP.

Autonomic factors such as a hyperactive autonomic nervous system as well as local vessel injury, elevated serum uric acid are also part of the atherogenic process. The finding of “variable hypertension” or “white coat hypertension” should alert the treating clinician to the presence of autonomic instability, which is easily determined by heart rate variability studies done in conjunction with the normal 24 hour Holter monitor testing.

Atherosclerosis

Atherosclerosis is an inflammatory disease, similar to Rheumatoid Arthritis etc. The atherosclerotic plaque is characterized by the migration into tissue of blood-borne inflammatory cells, followed by interactions with vascular endothelial cells and connective tissue cells, leading to a chronic inflammatory response.

Endothelial dysfunction/activation is the earliest step- induced by numerous factors including cytokines, free radicals, lipids, bacterial or viral infection, or by haemodynamic forces. Activated endothelial cells upregulate adhesion molecule expression promoting recruitment of monocytes into the subendothelial space.

Recruited monocytes ingest modified lipid and become foam cells, hallmarks of early atherosclerosis, trapped in vessel wall. Progressive lipid accumulation and leucocyte recruitment leads to gradual formation of atheroma. As lesions progress smooth muscle cells proliferate and migrate into the intima where they deposit extracellular matrix components forming a fibrous cap over the lesion.. Rupture of unstable lesions causes thrombus formation which can cause a MI.

Innate immunity is first line of defence and is programmed to detect molecular motifs called pathogen-associated microbial patterns (PAMPs) via specialized receptors. TLRs are the most characterized pattern -recognition receptors (PPRs) so far. TLRs share the same cytoplasmic domain with IL-1 receptors so TLRs activate signalling pathways shared with IL-1.

TLRs and their ligands (an ion or molecule that binds to receptors) are critical in atherogenesis, so far TLR-2 and -4 activation has profound consequences. TLR-2 signalling appears to be a predominant event for activation of inflammation and matrix degradation. Low density lipoproteins and ROS induce cytokine production. [(6)]

At a cellular level, ageing can be determined by the length of telomeres, small segments of DNA that bind the DNA and are essential for maintaining DNA integrity during replication. As cells age, the telomeres become shorter. This vascular ageing is thought to be from oxidative stress, and the presence of reactive oxygen species (ROS) and oxidized low-density lipoprotein (LDL) below the intimal lining of the vessels. Also involved is modification of collagen, especially in diabetes.

These processes lead to aortic stiffening, dilatation and wall hypertrophy. If untreated, these changes augment the ageing process and can lead to cardiac remodelling and impaired ventricular and vascular function. These have been linked to damage to the brain microarchitecture, with white matter infarcts, small vessel disease and microvascular injury.

This arterial ageing is accelerated by hypertension, impaired glucose tolerance, diabetes, dyslipidaemia and smoking, along with other inflammatory and autonomic processes.

Preventing vascular ageing

Preventing vascular aging is complex and requires early intervention and management. Arteriosclerosis is all about increasing stiffness in the vessels, and results from reversible and irreversible components, and are responsible for the elevated blood pressure that continues with ageing, with increasing risk of cardiac, cerebrovascular and chronic renal disease. The majority of treatments target the consequences rather than the cause.

Regular aerobic exercise is associated with a reduced risk of CVD (and preservation of arterial function with aging in humans. It has been hypothesized that aerobic exercise exerts anti-inflammatory effects that could contribute to its vascular-protective influence. That regular exercise is associated with lower circulating concentrations of inflammatory proteins in some adults is consistent with this idea. (11)

Lesniewski et al demonstrated that regular aerobic exercise improves arterial inflammation with aging in mice studies and that the anti-inflammatory effects of aerobic exercise on aging arteries include normalization of IKK-NF-κB activation, proinflammatory cytokines, and adventitial-perivascular macrophage infiltration. These anti-inflammatory effects are associated with amelioration of age-associated vascular dysfunction via a combination of antioxidant and anti-inflammatory effects. (11)

Preventing vascular inflammation and repairing damaged tissue with ARBs

Angiotensin 11 is a powerful pro-inflammatory molecule linked to the generation of oxidative free radicals in vascular smooth muscle cells with damage to cellular DNA especially in the region of the telomeres. Treatment with an angiotensin receptor blocker (ARB) has been shown to reduce this damage thus preventing ageing effects, and is not a response to blood pressure lowering.

Studies showing that treatment with ARBs can reduce the circulating levels of some inflammatory mediators, such as IL-6, TNF-α, MCP-1 and CRP. Not all ARBs exert this response to the same degrees. Atacand, Micardis and Olmetec appear to have the strongest data, but there have been no direct head to head studies I am aware of. Beta-blockers appear also to suppress plasma renin activity and hence angiotensin 11.

ARBs (and ACE-1s) prevent age-related increases in heart weight and left ventricular enlargement while also reducing collagen and fibrosis in the aorta. This provides the rationale for targeting the renin-angiotensin mechanism to reduce vascular ageing. (1)

These results are so important in management of arteriosclerosis probably at any stage, so these medications (ARBs) probably should be first-line and statins employed when there is significant plaque. It is again the ARBs that have shown benefit in other areas of vascular damage such as dilatation of the ascending aorta.

Prolonged sitting and CV risk

Sedentary behaviour has been clearly demonstrated to increase cardiovascular risk considerably. In one study a single 3 hours period of sitting without moving around was sufficient to demonstrate change in vascular flow. Men riding in cars >10 hr a week or > 23 hrs/week of combined sedentary behaviour had 82% and 64% greater risk of dying from CV disease than those who had <4 hrs/week or <11 hrs/week respectively. Physical activity however was shown to reduce this risk. (2) Similar finding have been found in women in other studies- moderate intensity exercise for at least 30 minutes on most (preferably all) days of the week (e.g., brisk walking for three or more hours per week) could reduce the risk of coronary events in women by 30 to 40 percent. Increasing walking time or combining walking with vigorous exercise appears to be associated with even greater risk reductions.

This relationship is thought to be from chronic low-grade inflammation that affects the arteries resulting in hypertension and arteriosclerosis. In studies looking at the effect of ageing, again regular aerobic exercise was found to provide a reduced risk of CV disease and preservation of arterial function, and that this benefit is associated with lower circulating concentrations of inflammatory proteins. (3)

Recovery From Metabolic Syndrome Linked to Lower CV Risk

Kelly Young from NEJM Journal Watch writes: “Recovery from metabolic syndrome is associated with lower risk for major adverse cardiovascular events (MACE), finds an observational study in the *Annals of Internal Medicine*.(15)

Researchers studied roughly 9.5 million adults in Korea who had three or more health exams. During a median 3.5 years' follow-up, participants who had chronic metabolic syndrome had the highest MACE

rate (8.52 per 1000 person-years), followed by those who developed metabolic syndrome during the study (6.05 per 1000), those who recovered from metabolic syndrome (4.55 per 1000), and finally those who were consistently free of metabolic syndrome (1.92 per 1000).

After multivariable adjustment, patients who recovered from metabolic syndrome had a lower MACE rate than those who consistently had metabolic syndrome (incidence rate ratio, 0.85). In addition, those who developed metabolic syndrome had higher MACE risk than those who never developed it (IRR, 1.36).

The authors write: "Our study encourages health care providers to pay attention to a history of [metabolic syndrome] even in persons who are currently free from" it." [(14)]

Response to Injury causing arteriosclerosis

The "Response to Injury Theory" now has widespread acceptance among scientific and medical scholars. This theory holds that the earliest event in atherogenesis is injury to the endothelium, which can be triggered by any number of insults, either alone or in combination. These include:

- Physical injury or stress as a result of direct trauma or hypertension
- Turbulent blood flow, for example, where arteries branch
- Circulation of reactive oxygen species (free radicals), e.g., from smoking or air pollutants
- Hyperlipidemia (high blood concentrations of LDL or VLDL)
- Chronically elevated blood glucose levels
- Homocysteinemia, which results from an inherited metabolic defect that leads to very high levels of the homocysteine, a metabolite of methionine; high concentrations are toxic to the endothelium.

Cholesterol

High cholesterol levels are seen as a cause of dangerous deposits in the bloodstream, which lead to arteriosclerosis. Low-density lipoprotein (LDL) is commonly referred to as the "bad cholesterol", because it promotes atherosclerosis. In contrast, the "good cholesterol", high-density lipoprotein (HDL), helps transport excess cholesterol out of the bloodstream and can counteract an inflammatory reaction in damaged vessel walls.

“It has long been known that HDL has a protective function in cardiovascular diseases that are based on atherosclerosis", reports Prof. Eicke Latz, Director of the Institute of Innate Immunity at the University of Bonn and who is further affiliated with the German Center for Neurodegenerative Diseases (DZNE) and the University of Massachusetts Medical School in the USA. "The molecular causes to which this protective effect of HDL can be attributed were unclear until now". For instance, studies had shown that therapies that simply increase HDL levels in the blood of patients are not sufficient to reduce the incidence of atherosclerosis. HDL has anti-inflammatory effects on immune cells – however the mechanisms have remained unclear until now. The research group has now investigated how HDL acts upon inflammatory processes.

Australian researchers Dominic de Nardo and Larisa Labzin were able to filter out a candidate gene from the wealth of regulated genes. This gene is found in phagocytes, which act in the body like police on the beat and, as part of the innate immune defence system, arrest intruders. These patrolmen are supported by a kind of "criminal file", the so-called Toll-like receptors (TLR). With their help, the phagocytes can distinguish between "good" and "bad". If it is a dangerous intruder, the TLR can also trigger the release of inflammatory substances via biochemical signalling pathways. The transcriptional regulator, ATF3, plays a key role in this process. "It reduces the transcription of the inflammatory genes and prevents further stimulation of inflammatory processes via the Toll-like receptors",

The immune system uses inflammatory processes to keep pathogens in check, to detect damaged tissue, and then repair it. In sustained inflammatory reactions, however, there are dangerous consequences –including organ failure. "The transcriptional regulator ATF3 acts to reduce these inflammatory reactions by suppressing the activation of inflammatory genes following excessive stimulation of immunoreceptors", reports Dr. De Nardo. In the end, high-density lipoprotein (HDL) is

responsible for down regulating the inflammatory reactions, via the activation of ATF3. "To put it simply, high HDL levels in blood are an important protective factor against sustained inflammation."

"Our studies also indicate that the amount of HDL in blood alone is not decisive for the protective function of HDL, but that the anti-inflammatory function is probably more important. These results also suggest a molecular approach for treating inflammation in other widespread diseases, such as diabetes", sums up Prof. Latz . (4)

Lipoprotein A

Lipoprotein(a) (also called Lp(a) or LPA) is a lipoprotein subclass. Genetic studies and numerous epidemiologic studies have identified Lp(a) as a risk factor for atherosclerotic diseases such as coronary heart disease and stroke. The association between Lp(a) levels and stroke is not so strong as that between Lp(a) and cardiovascular disease. Lp-a concentrations may be affected by disease states (for example kidney failure), but are only slightly affected by diet, exercise, and other environmental factors. Some studies have shown some reduction with alcohol, but these are not consistent.

Most commonly prescribed lipid-reducing drugs have little or no effect on Lp(a) concentration. A new product Repatha, reduces levels dramatically, but as yet the improvement in vascular outcomes has only been shown when combined with a statin. We await further studies.

Niacin has been shown to reduce the levels of Lp(a) in individuals with high levels of low-molecular weight lipoprotein(a). Niacin's amide Nicotinamide has a reparative effect in vascular disease in animal studies, and has also been shown to improve collagen synthesis. B3's primary use at present is reducing skin cancer risk, but there are early studies suggesting its benefits will be in reducing other cancer risk. In clinical practice there is no real place for niacin, but Nicotinamide should be considered at an early stage. Of course, this is only in animal studies at this point.

Nicotinamide

Nicotinamide is currently being studied in prevention and management of Alzheimers's disease as well as its known benefit in skin cancer. It has been shown to be protective of the CNS in rodent models of Parkinson's disease and Motor Neurone Disease. (12) The broad clinical effects of nicotinamide may be explained by its role as:

- a cellular energy precursor
- a modulator of inflammatory cytokines
- an inhibitor of the nuclear enzyme poly(adenosine diphosphate-ribose [ADP]) polymerase [PARP], which plays a significant role in DNA repair, maintenance of genomic stability, and cellular response to injury including inflammation and apoptosis (cell death).

Not everyone can tolerate it, and as it works at the very grass roots of our metabolic pathways, it may be possible it could have deleterious effects in some people. I do think these people recognize the side effects soon after taking it, and stop it. Once started, as we have found treating skin cancers, if ceased, the cancers quickly return (something we are also seeing in products such as denosumide when used in osteoporosis and prevention of metastases in breast and prostate cancer.)

Apolipoprotein E (APOE) and link to Dementia

In peripheral tissues, APOE is primarily produced by the liver and macrophages, and mediates cholesterol metabolism. In the central nervous system, APOE is mainly produced by astrocytes, and transports cholesterol to neurons via APOE receptors, which are members of the low density lipoprotein receptor gene family. APOE is the principal cholesterol carrier in the brain. This protein is involved in Alzheimer's disease and cardiovascular disease.

APOE is polymorphic, with three major alleles: *ApoE2*, *ApoE3* and *ApoE4*. Although these allelic forms differ from each other by only one or two amino acids at positions 112 and 158, these differences alter APOE structure and function. These have physiological consequences.

APO E4 E4 has an allele frequency of approximately 14 percent. E4 has been implicated in atherosclerosis, Alzheimer's disease, impaired cognitive function, reduced hippocampal volume, HIV, faster disease progression in multiple sclerosis, unfavourable outcome after traumatic brain injury, ischaemic cerebrovascular disease]sleep apnoea, accelerated telomere shortening and reduced neurite outgrowth. A notable advantage of the E4 allele (relative to E2 and E3) is a positive association with higher levels of vitamin D, which may help explain its prevalence despite its seeming complicity in various diseases or disorders.

Although 40-65% of AD patients have at least one copy of the ε4 allele, *ApoE4* is not a determinant of the disease - at least a third of patients with AD are *ApoE4* negative and some*ApoE4* homozygotes never develop the disease. Yet those with two ε4 alleles have up to 20 times the risk of developing AD. There is also evidence that the ApoE2 allele may serve a protective role in AD. Thus, the genotype most at risk for Alzheimer's disease and at an earlier age is ApoE 4,4.

Treatment has generally been with statins, but studies using retinal photography and carotid intimal thickness scanning suggest that once again the ARB medications provide more concrete results. Our research is using retinal arterial photography and carotid intimal thickness scanning - so far only Atacand has been employed, but pre-publication studies confirm both small vessel and larger vessel damage can be stopped, and the intimal thickness that reflects inflammatory damage can be reversed. Pathology companies have avoided mentioning the increased dementia risk with the APO E4 allelle for fear for terrifying people, as well as making them uninsurable, but that I believe is not acceptable with the knowledge that the progression can be blocked.

Statins

Statins are currently the most powerful cholesterol-lowering drugs available. They act by inhibiting the action of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme in the sequence of steps by which cholesterol is synthesized in the liver. The liver has two sources of cholesterol: it can take up LDL particles from the blood, or it can synthesis cholesterol using HMG-CoA reductase. The diagram below illustrates cholesterol homeostasis in a liver cell. LDL (shown in red) can bind to LDL receptors on the surface of the liver.

Statins act by inhibiting HMG-CoA reductase and shutting off internal cholesterol production. In this way, statins reduce cholesterol concentrations in liver cells, which causes increased production of LDL receptors and increased uptake of LDL by the liver. This ultimately results in a lowering of blood concentrations of LDL cholesterol, and this generally results in a slower progression of atherosclerotic plaques and a reduced risk of plaque rupture. However, observers also report regression of atherosclerotic plaques in patient on statins. These benefits have been shown to be more in the more recent statins Lipitor (atorvastatin) and Crestor (rosuvastatin.)

Because of their effectiveness in reducing CAD in patients at high risk, some advocate the use of statins to people who did not necessarily have elevated cholesterol levels. A number of large, well-done clinical trials have demonstrated that statins can reduce the risk of CAD in low-risk individuals, but most experts caution against this because of the cost and the risk of side effects.

Other causes of arteriosclerosis

These traditional pathways explain only 50 to 60% of the patients. The rest are generally ignored, dismissed as genetic or environmental factors. Genetic predisposition does play a major role, but with increasing knowledge of these, these can often be overcome. The increasing use of DNA has made this perfectly obvious, with knowledge of genetic variations especially in IL-6, APO E4, and oxidative stress eg eNOS and SOD-2. Methylation mutations especially MTHFR and COMT can play a large role in increased vascular risk (MTHFR) and ability to deal with catecholamines (COMT). These reduce the body’s ability to deal with the pro-inflammatory effects of the Interleukin response and the oxidative stress that occurs in the tissues themselves.

Stress and Inflammation

Large studies conducted on veterans in the USA with PTSD suffer from an increased burden of cardiovascular autoimmune diseases and dementia. Studies have found that PTSD is associated with elevations in pro-inflammatory cytokines especially IL-6, IL-1β, TNF-α and interferon γ.

Stress-related disorders are associated with excess risk for cardiovascular diseases, with a 64% higher risk for any CVD during the first year following diagnosis of stressful life events compared with unaffected siblings. Stress patients had excess relative risks for ischemic heart disease, cerebrovascular disease, hypertension, and heart failure. After 1 year, relative risks generally were lower (i.e., 29% excess risk for any CVD). Similar results were obtained for comparisons with matched controls and by specific stress-related disorder. Psychiatric comorbidity did not modify risks. [(7)]

Interleukin-6 (IL-6) is the end-product of a cytokine signaling cascade and is secreted by specialized immune cells during inflammation. It has a great influence on many functions, including differentiation, stimulation, and activation of immune cells, or other cells of neuroendocrine origin. Thus, IL-6 serves as a key messenger in its communication with the neuroendocrine system, and serves as a potent activator of the hypothalamic-pituitary-adrenal axis at all levels. Changes in the levels of expression of this cytokine and its receptor have been observed during chronic inflammatory disease, and have been associated with tumorigenesis. [(8)]

Takotsubo phenomenon

Takotsubo cardiomyopathy is a temporary heart condition that is brought on by stress. It has the same symptoms as a heart attack but is not caused by any underlying cardiovascular disease. It is also known as stress cardiomyopathy, apical ballooning, or broken heart syndrome.

Takotsubo cardiomyopathy most often affects women between the ages of 61 and 76 years. The condition commonly occurs immediately after experiencing extreme emotional or physical stress. This accounts for many presentations to emergency departments with chest pain. I believe it is grossly under-diagnosed, and many people experience this without the traditional changes on echocardiogram. Traditional thought suggests that the sudden release of stress hormones, such as norepinephrine, epinephrine, and dopamine, "stuns" the heart.

Whether the patients recover or not is influenced by the levels of the inflammatory response which are associated with IL-6. There is a lot of similar findings through the POTS study we are undertaking, but while as yet we cannot differentiate whether the process is from the sudden cascade of catecholamines or the inflammatory response as seen in the high IL-6 levels, the relative stability of heart rate variability studies in many of the POTS patients during provocation would suggest the damage is more inflammatory than autonomic.

MINOCA

MINOCA (Myocardial Infarction without Coronary Arterial Obstruction) is currently being studied in a large global study, including on the Gold Coast. MINOCA refers to the 5-10% of acute myocardial infarction patients with minimal to no discernable high grade, critical, coronary arterial stenoses. despite the lack of severe coronary arterial stenoses, MINOCA patients frequently do have manifestations of atherosclerotic disease in other territories, for example, peripheral vascular disease. In addition, mortality rates are substantial for MONICA patients in the years following their MINOCA event. In the nationwide, Swedish SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy), 14% of these patients died during a 4.5 year follow up.

A number of possible pathophysiologic mechanisms suggested, including Takotsubo, transient coronary arterial spasm, coronary arterial embolization, endothelial dysfunction, coronary arterial dissection, and even occlusion of a small coronary arterial branch that was missed on angiography.

Approximately 6% of MINOCA patients subsequently suffered a second MI. Coronary angiography at the time of the second MI revealed that half of the MINOCA patients with a recurrent MI had developed clinically important coronary arterial stenoses since their last coronary angiogram. In other words, there had been progression of the atherosclerotic disease process in half of the patients. The second MI occurred on average approximately 2 years after the initial MINOCA event. As noted above, the prognosis for MINOCA patients was not benign and worsened further with the second MI. Twenty-two percent of the MINOCA patients in the Swedish registry who developed a re-infarction died during a 3.5 year follow-up. Half of the deaths were from cardiovascular causes. Investigators did observe that patients who received evidence-based therapy (EBMT) for MI, that is, beta blockers, renin-angiotensin system blockade (ARBs), and statins, had better long-term outcomes compared with MINOCA patients who did not receive this therapy. (9)

Discussions with the Gold Coast cardiologist reveals the path is leading to microembolic damage and once again the level of damage dependent on the inflammatory response, where once again IL-6 plays an important role.

The complexity of vascular disease is not simply obesity, smoking , hypertension and cholesterol. Even the cause of hypertension must be considered inflammatory. Environmental factors especially sustained stress with the release of catecholamines and inflammatory response, and factors such as sustained sedentary behaviour must be considered.

Prevention (and treatment) of vascular disease and ageing must consider all these factors. The current research we are doing in POTS, fibromyalgia and migraine shows a dovetailing of inflammatory processes. The increasing knowledge that vascular compression in areas especially the axillae, causing Thoracic Outlet Syndrome produces the same type of inflammatory responses, as well as microemboli from simple venous obstruction, with the likelihood of microtrauma causing microemboli and an inflammatory response, opens the door to many other diseases where these inflammatory responses are present. These include possible implications for Multiple Sclerosis, Parkinsons Disease, and even other IL-6-driven diseases such as diabetes, Hashimotos disease, diverticular disease, colonic polyps, breast and prostate cancer.

The reversal of dilatation of ascending aorta dilatation with the antirheumatoid agent Tocilizumab (an IL-6 Receptor Inhibitor) provides an exciting possibility for the future with all of these diseases. Interesting journal searches reveal the improvement in myelodysplasia when co-existing RA was treated with this medication. (13) I look forward to exploring these pathways further and the evolution of newer management strategies that are not based on traditional modelling of cholesterol and blood pressure.

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