Immunology | Review

Energy Dynamics in the Autoimmune Disorders: The Unity of Immunity

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INTRODUCTION

The autoimmune disorders, the last major class of disease to be recognized by medical science, present us with a paradox concerning the immune system: originally conceived as a barrier against pathogenic microorganisms that would breach the body's external boundaries, one is led to question why, inexplicably, it should suddenly turn against the body and attack its own tissues? The notion was so counterintuitive that early 20th century immune researcher Paul Ehrlich advanced the doctrine of horror autotoxicus, arguing that such a possibility would be utterly 'dysteliologic' [1-3].

And yet evidence in support of autoimmunity was present from the beginning. By the early years of the 20th century, it was known that immune reactions could be damaging rather than protective: in 1902 Richet reported on anaphylaxis; in 1906 von Pirquet described allergy and immune-complex disease. Perhaps such reactions seemed more palatable to turn-of-the-century scientists as they were directed against environmental substances. Autoimmunity, however, remained a conceptual bête noire until mid-century.

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The paradox dissolves once one recognizes that it originated largely in how scientists expected the immune system should behave. Early in the formation of their science they seized upon certain notions, like the nature of inflammation or the primacy of the antibody response, that rather soon became accepted as fact. In the century that followed a stream of reports challenged these orthodox conceptions and begged for a fundamental reappraisal of ideas but this never happened. The recent SARS-CoV-2 pandemic exposed grave flaws in 20th century immune theory that must now be rectified.

Equally, it raises concerns about experimental science itself and the inability of researchers to reexamine their assumptions and make in-course corrections. Reflexivity has never been a defining attribute of the science community. Instead, scientists have been subject to speculative (and reactive) thought formation as well as to the sway of opinion leaders who, by and large, have steered its development. From the onset science possessed all the characteristics of other mass movements that came to define the 20th century.

As in other mass phenomena scientists were collectively swayed by a sense of awe over its potential to amass power and effect change. Peter Medawar, one of the architects of 20th century immune theory and co-recipient of the 1960 Nobel Prize wrote: 'In terms of the fulfillment of declared intentions, science is incomparably the most successful enterprise humans have ever engaged upon. Visit and land on the moon? A fait accompli. Abolish smallpox? A pleasure . . .' [4] (Figure 1). Scientists' confidence in their venture has never waned even an iota.

Figure 1: Immunologist Peter Medawar, discoverer of immune tolerance, co-recipient of the 1960 Nobel Prize, claimed that the basis of the immune response centered around the ability of the immune system to distinguish between self and non-self.

(From: https://quotesgram.com/peter-medawar-quotes/)

Early 17th century scientists coined the maxim *Plus Ultra*, meaning 'further beyond', implying no limit to the advance of scientific knowledge or the power science would accrue. Three-and-a-half centuries later Medawar echoed the same sentiment: 'Never once in the history of science have we reached a *Non Ultra*', i.e., a point beyond which no further progress is possible, 'nothing can impede or halt the advancement of scientific learning . . .'. Science became destiny.

But it would seem that scientists have met their match in the surging epidemic of chronic disease: autoimmune disorders, chronic heart failure, chronic kidney disease, neurodegenerative disease, epilepsy, diabetes, the metabolic syndrome, and a host of cancers now spread unchecked across the globe and are largely refractory to their treatments. Heroic science-based physicians can perform life-saving organ transplants but can't cure a simple case of asthma. Something is amiss.

In the 1980s evidence surfaced in the medical literature overturning the accepted model of cardiac function that had dominated 20th century medical thought. This was but the first of other dominoes that would fall. Emerging evidence now points to the presence of an organized energy field originating in the blood through the contraction and dilation cycles of the heart that organizes all bodily functions [5, 6].

This blood-borne energy field was described in detail by 2nd century Roman physician Galen and was accepted as fact by physicians for over 1500 years until it was arbitrarily discarded by chemically-oriented physicians in the 17th and 18th centuries [7]. Central to Galen's humoral system of medicine was the doctrine of *omnia incipit in sanguine,* everything begins in the blood. Based on this notion all bodily inflammation was regarded as an indication of deficient energy generation in the blood.

In this paper we examine the autoimmune disorders (AIDs) not from a cellular/ molecular standpoint as scientists have attempted for decades but from a dynamic energy-based perspective. Not only does this framework account for the origins of these disorders but it explains phenomena that cell-based mechanisms cannot. In addition, we examine the historical basis of 20th century immune theory and point to serious errors in the research literature that have lain unrecognized for over a century and which led to broad misconception of immune functions.

THE MANY FACES OF INFLAMMATION

The AIDs represent a clinically diverse group of conditions said to arise from 'dysregulation' of the immune system leading to inappropriate activation of lymphocyte and macrophage cells, production of auto-antibodies (auto-Abs), and increased levels of pro-inflammatory cytokines like tumor necrosis factor-α, interferon-γ, interleukin (IL)-1, IL-2, IL-6, IL-17 and others in affected tissues and the blood. Scientists claim such dysregulated immune activity results from a loss of 'self-tolerance', i.e., inability of immune cells to distinguish between self and non-self, which they ascribed to genetic mutations [8, 9].

Over 80 self-directed inflammatory syndromes have been described ranging from relatively common conditions like type I diabetes, thyroiditis and rheumatoid arthritis to rare disorders like Guillain-Barre syndrome, myasthenia gravis or scleroderma [10]. They may affect single organs as in the case of multiple sclerosis, thyroiditis or diabetes, or manifest systemically and involve multiple organs as with systemic lupus erythematosus (SLE) or vasculitis. A single entity like diabetes can cluster in multiple family members while multiple AIDs can affect the same individual. In recent years so-called overlap syndromes have been described in which distinct entities like rheumatoid arthritis and

SLE, called 'rhupus,' coexist in the same individual [11-16]. The AIDs defy simple classification [17].

In the liver inflammation may affect hepatocytes to manifest as hepatitis or involve bile ducts and present as primary biliary cirrhosis. In the skeletal system it may present as rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis. Psoriasis, on the other hand, characterized by chronic, recurrent skin lesions, may coexist with arthritis, inflammation of ligaments and tendons, or uveitis [18]. Crohn's disease, with origins in the bowel, frequently coexists with extra-intestinal disease involving the skin, joints or eyes [19, 20]. Given the striking overlap of symptoms, distinguishing among the different AIDs is challenging and diagnosis often prolonged and costly. And despite recent advances in treatment only a minority of affected individuals experience sustained remission.

The AIDs occur at any age although each subtype has a typical age of onset. Most AIDs disproportionately affect women with some, like SLE, having prevalence ratios as high as 10-15:1 [21, 22]. Current opinion suggests that AID represents a complex interplay between genetic and environmental factors. Genome-wide association studies have implicated hundreds of genes in the various AIDs but none have significant predictive value. The concurrence of AID in identical twins is only 12-67% indicating that factors other than heredity are in play.

A plethora of environmental influences have been identified including diet, gut microbiota, infection, smoking, hormones, as well as geographical influences such as latitude and sunlight exposure [23, 24]. Included in this list are some of the very medicines used to treat the AIDs as well as vaccines [25-27]. While some of these factors play a permissive role, others such as sunlight exposure and infection are more directly involved.

The complex relation between infection and autoimmunity highlights the pivotal role inflammation plays in both disorders [28]. Bacterial infections can trigger self-directed inflammatory reactions that can be short-lived or become chronic and resemble the autoimmune state. Reactive arthritis, formerly known as Reiter's syndrome, may occur following infections in the genitourinary or digestive systems and present as inflammatory arthritis, uveitis, and skin lesions resembling those of psoriasis [29-32]. Behçet's disease is a systemic vasculitis characterized by recurrent ulcers in the mouth and genital regions, skin lesions and uveitis. The cause of Behçet's disease remains unknown but evidence points to an infectious etiology [33-35].

More striking is the relation between the AIDs and viral illness. For decades it has been recognized that viral infections can trigger AIDs like SLE, rheumatoid arthritis, multiple sclerosis, vasculitis, and more [36-39]. Offending viruses include herpes, Coxsackie B, hepatitis B & C, cytomegalovirus, parvovirus and the whole gamut. Mechanisms are poorly understood but ascribed to 'molecular mimicry', i.e., cross-reactivity based on similarities in protein structure between viral antigens and that of the body which, in turn, is said to activate lymphocytic T-cells and the inflammatory cascade. But this says nothing about why such events should occur in some cases and not in others.

The SARS-CoV-2 pandemic revealed striking similarities between COVID-19 infection and the AIDs on multiple levels: overlap of clinical symptomatology; nearly identical inflammatory response patterns, particularly cytokine profile and appearance of auto-Abs; and worsening of pre-existing AIDs or appearance of new AID syndromes after COVID-19 infection.

While fever, respiratory symptoms and sore throat are primary manifestations of COVID-19, frequent

ancillary phenomena include muscle [40-42] and joint [43-45] pain as well as skin rashes [46-48] which also affect various AIDs. Widespread endothelial inflammation is the primary pathogenic mechanism underlying COVID-19 infection and vasculitis of small, medium and large arteries is ubiquitous [49-56]. Endothelitis, as we show in earlier writings, is a direct consequence of decreased energy generation in the blood [57, 58]. In most cases acute-phase phenomena are transitory and disappear with resolution of the illness.

Excessive release of pro-inflammatory cytokines, aka the cytokine storm, was originally believed to be a characteristic feature of the AIDS but in recent decades has been linked to a variety of infectious and non-infectious conditions. It is now regarded to be a generic accompaniment of inflammation *per se* [59-63]. The cytokine storm is common in COVID-19 syndrome and correlates with disease severity. In severe cases the hyperinflammatory state induced by the cytokine storm drives subsequent respiratory distress syndrome, multi-organ failure and coagulopathy, all of which reflect progressive deterioration of blood energy generation.

Early on the presence of auto-Abs in the blood was regarded as pathognomonic for the AIDs but this too has been refuted by a flood of contradictory evidence [64-68]. Numerous studies document the presence of auto-Abs in COVID-19 infection and the number increases in proportion to the severity of infection. Up to a dozen different auto-Ab varieties have been detected some individuals. Anti-nuclear antibodies were found in up to 35% of affected persons; anti-Ro/SSA in 25%; anti-rheumatoid factor in 19% [69]. Such auto-Abs are present in the blood of individuals with SLE and rheumatoid arthritis.

The most compelling evidence for the conjoined nature of the AIDs and COVID-19 is found in a spate of reports documenting worsening of pre-existing AID or triggering of new AID after COVID-19 infection or vaccination including: SLE [70-74], rheumatoid and other inflammatory arthritidites [75-86], inflammatory myositis [87-95], myocarditis [96-99], vasculitic syndromes like Kawasaki's disease [100-104], type I diabetes [105-110], multiple sclerosis [111-117], autoimmune encephalitis [118-120], Guillain-Barré syndrome [121-125], autoimmune thyroid disease [126-129], autoimmune hepatitis [130-134], autoimmune hemolytic anemia [135-139], autoimmune dermal conditions [140-144], scleroderma [145-148], and sarcoidosis [149-154]. Either we regard these events as random and coincidental or we must accept the primacy of inflammation in both forms of disease. Similar adverse effects are observed with therapies scientists employ to treat the AIDs.

In recent decades so-called 'biologic' agents have become popular treatments for various AIDs [155-156]. There are up to a dozen monoclonal Ab preparations that target one or another aspect of the 'dysregulated' immune response – either interleukins, interferons, tumor necrosis factor, or B- & T- lymphocytes – and thereby mitigate (but not eliminate) the inflammatory response. Aside from their inconvenience (they must be given intravenously) and prohibitive cost ($10,000-$30,000 per year) they induce a range of inflammatory effects similar to what we just saw in viral illnesses [157].

In addition to injection site reactions [158], acute hypersensitivity and immune-complex phenomena [159-161], as well as predisposition to infectious complications like tuberculosis [162], auto-Ab formation and AIDS are not infrequent. Clinical symptoms include skin rashes, arthritis, muscle pain, oral ulcers, and photosensitivity [163-166]. Various studies report anti-nuclear Abs in 40-

100% of cases, anti-DNA auto-Abs in 11-62%, and antiphospholipid auto-Abs in 2-12% [166-169]. Autoimmune syndromes include multiple sclerosis, optic neuropathy, uveitis, psoriasis, vasculitis, inflammatory bowel disease, and inflammatory myositis [170-193]. Another not uncommon occurrence, 'paradoxical inflammation', presents as exacerbation of the very condition for which the treatment is intended and, often, appearance of psoriasis-like areas of inflammation involving the skin [194-198].

To assert that AIDs have any kind of distinct and independent existence is an absurdity. They are instead variable, amorphous entities that come and go based on ambient conditions in the blood. The only plausible explanation for autoimmune inflammatory phenomena seen in relation to viral illnesses or treatment with biological agents is that inflammation *per se* is the primary driver of such events and must itself be secondary to some prior and more fundamental cause, which we have ascribed to a deficiency in the blood-borne energy field. We examine the energetic aspect in greater detail.

CARDIOVASCULAR DYNAMICS

In recent years another unexpected link between the AIDs has emerged: a shared predisposition for cardiovascular disease. Cardiac manifestations are the leading cause of morbidity and mortality in SLE; affected women are said to have a 7-8-fold increased risk of developing coronary artery disease compared with other women [199, 200]. Cardiovascular disease in rheumatoid arthritis occurs up to a decade earlier than in the general population and individuals are twice as likely to develop heart disease [201, 202]. One study found evidence of myocardial ischemia in rheumatoid arthritis patients at a rate comparable to that seen in diabetics [203]. But the trail of evidence doesn't end there.

Similar adverse scenarios have been documented in most of the common AIDs including multiple sclerosis, scleroderma, type 1 diabetes, psoriatic arthritis, ankylosing spondylitis, Sjögren's syndrome, dermatomyositis, polymyositis and others [204]. Despite all emerging treatment options individuals with AIDs have reduced life expectancy in large part due to cardiovascular causes which include myocardial ischemia, inflammation and fibrosis, conduction and rhythmic disturbances, heart failure, and valvular disease. In most cases cardiac abnormalities are present years before individuals develop symptoms. What is happening here?

Scientists are at a loss to explain this excess cardiovascular risk. Some ascribe it to systemic inflammation induced by the cytokine storm and spillage of reactive oxygen species into the vascular system related to impaired cell metabolism. Others point to widespread endothelial dysfunction associated with various AIDs. The answer is both of the above: defective energy generation in the blood directly impairs endothelial function and cell metabolism. This compels us to reexamine conventional ideas about cardiac function.

For most of the 20th century medical scientists regarded systole as the primary phase of the cardiac cycle. Such notions were originally advanced by William Harvey in *Anatomical Studies on the Motion of the Heart and Blood* (1628): 'the heart does not act in diastole but in systole for only when it contracts is it active,' and later, 'likewise, it is not true, as commonly believed that the heart by its own action or distention draws blood into the ventricles' [205]. Harvey rejected a line of medical thought that went back nearly 1500 years to Galen who argued for the primacy of diastole and its energetic origins [206].

In the 1980s reports described negative intraventricular pressures in the early diastolic

phase of the heart cycle which, researchers soon realized, must account for the forward movement of blood and diastolic filling [207, 208]. A 1986 article in *Scientific American* entitled 'The Heart as a Suction Pump' proposed a new diastolic-centered model of cardiac function [209]. In the mid-1990s another paper refuted Harvey's propulsion theory of heart function [210]. Numerous studies describe spiral arterial flow currents which can only be explained on the basis of a suctional force which itself can only be explained on an energetic basis [211-224].

For over a century, cardiologists have claimed systolic contraction is induced by nerves that course over the outer surface of the heart but is this correct? In animal experiments Galen observed that when the heart was cut out and placed in a fluid bath it continued to dilate and contract, a phenomenon known as cardiac automaticity. By the same token, transplanted hearts continue to function in recipients even though nerve conduction has been interrupted. Could cardiac nerves serve another purpose?

What happens during systolic contraction of the ventricle is similar to that which happens during induction of an external magnetic field by electrification of ferrous objects. As the ventricle contracts, iron in the myocardium and blood is brought into closer apposition while nuclei align and precess synchronously on the basis of field interactions. Electrical potentials in the nerves saturate the field and induce transient formation of a 3D magnetic field in the heart wall and ventricular chamber which forms the energetic basis of diastole. Expansion is brought about by conformational change in blood and heart proteins [225-227].

By the late 1980s numerous studies had affirmed the primacy of diastole in the cardiac cycle and, moreover, found that impaired outward movement of the ventricular and arterial walls, aka 'diastolic dysfunction', was the defining feature of a wide range of chronic conditions including the AIDs, hypertension, diabetes, obesity, depression, cancers, as well as organ failure syndromes like chronic heart failure and chronic kidney disease [228, 229]. This is to say these conditions all share common energetic origins. The spiral of deterioration begins with a single ubiquitous phenomenon known as microvascular dysfunction.

In the 1970s cardiologists noticed increasing numbers of people who complained of typical angina-like chest pain and who, on exercise stress-testing, developed ECG abnormalities consistent with myocardial ischemia but, surprisingly, were found to have normal appearing coronary arteries by angiography. Named Cardiac Syndrome X, symptoms result from diastolic dysfunction at the microvascular level. Blood inflammatory markers like C-reactive protein are often elevated. A preponderance of those affected are post-menopausal women [230-233]. Originally thought to be benign it is now regarded as a progressive condition linked to poor quality of life and increased mortality.

Microvascular dysfunction is not limited to the heart but, instead, is a body-wide process. Multiple organs, including brain and kidneys, are affected [234-238]. Many with coronary microvascular dysfunction have abnormal brain perfusion and are at higher risk for neurologic problems like stroke. Consistent with its systemic nature, coronary flow reserve can be estimated by measuring waveforms in other vascular territories like the retinal arteries [239].

During periods of increased physical activity or emotionally stressful situations microvascular dysfunction impairs energy flow to the myocardium, aka 'decreased coronary flow reserve', producing scattered areas of muscle ischemia which evoke

anginal symptoms. Impaired microvascular function results in mitochondrial dysfunction in endothelial cells causing inflammation [240-242]. Such 'oxidative stress' in endothelial cells induces the so-called cytokine storm triggering an immune response. Whether involving the heart, kidneys, or brain, microvascular dysfunction sets into motion a spiral of chronic low-grade inflammation which is subsequently made worse by a host of risk factors [243-250]. Coronary microvascular dysfunction is increasingly recognized as a contributor to poor outcomes in the AIDs [251].

Rheumatoid arthritis (RA), the most common AID, with a 3:1 female-to-male pattern of involvement, characterizes the intertwined relation between the AIDs and heart disease. Most individuals with RA die of cardiovascular causes [252-255]. Hypertension is present in 50-70% of subjects [256-260]. Blood inflammatory markers are commonly elevated [261, 262]. Diminished coronary flow reserve, microvascular and diastolic dysfunction are found in significant numbers of people with RA even in the absence of cardiovascular symptoms [263-272]. One study found echocardiographic evidence of ischemia in 67% of RA subjects, over twice that seen in the control group (31%), and nearly that in diabetics (79%) [273]. Such ischemic phenomena lead to fibrosis and remodeling of the myocardial wall. Ventricular dysfunction, both diastolic and systolic, are present in 30-50% of subjects [274-279].

Studies in women with SLE found decreased coronary flow reserve compared with healthy controls. The degree of reduction is proportional to disease activity and duration [280-288]. One study, conducted over 5 years, examined SLE patients with chest pain using MRI and CT angiography and found up to half had microvascular ischemia in the absence of obstructing lesions in large coronary vessels. After 5 years most had persistent chest pain, and nearly half had similar or worsened

myocardial perfusion [289]. Other studies find that a high percentage of Individuals with SLE have subclinical myocardial injury [290].

Systemic sclerosis (scleroderma), which primarily involves connective tissues and has a female-to-male preponderance of up to 8:1, is characterized by skin sores, more common in the fingers and toes, and fibrosis affecting the skin and other organs like the lungs [291-293]. Primary myocardial involvement and blunted coronary flow reserve are common early features [294-299]. One study employing cardiac MRI found at least one cardiac abnormality in 75% of subjects with scleroderma. Other findings included diastolic dysfunction (35%), reduced ejection fraction (23%), and wall motion abnormalities (31%) [300].

Another MRI study in scleroderma patients with no history of heart symptoms found that, on average, 45% *already* had myocardial fibrosis. This increased to 59% in subjects with more diffuse disease. Almost 80% had subendocardial perfusion defects with associated elevated blood inflammatory markers [301]. One can only conclude that fibrosis as well as systolic and diastolic ventricular dysfunction are the result of chronic inflammation induced by microvascular ischemia. Such a connection is seen vividly in the commonly encountered entity known as Raynaud's phenomenon.

Raynaud's phenomenon, seen in multiple AIDs, is a microvascular disorder characterized by episodic vasospasm and ischemia most commonly associated with cold exposure [302, 303]. Raynaud's, a frequent accompaniment of scleroderma, causes digital ischemia that may result in chronic skin ulcers. Cardiac imaging with thallium-201 found simultaneous cold-induced perfusion defects in the heart, even in subjects without cardiac symptoms, highlighting the systemic nature of microvascular dysfunction [304-307]. Along this same line, retinal microvascular abnormalities have been described

in rheumatoid arthritis [308, 309], SLE [310-313], scleroderma [314, 315], multiple sclerosis [316, 317], type 1 diabetes [318-320], inflammatory bowel disease [321, 322], Kawasaki's disease [323], Sjögren's syndrome [324] and autoimmune thyroid disease [325]. As Galen claimed, the heart and arteries function as one.

Since the 1980s heart rate variability (HRV), which assesses the beat-to-beat fluctuations in cardiac rhythm, has been regarded not only as a strong indicator of cardiac health but a leading predictor of all-cause morbidity and mortality [326]. Easily obtainable with standard ECG equipment or wearable devices, the most common methods are known as time- and frequency-domain analyses [327-330]. Decreased HRV has been reported in *every single* chronic disease, including the AIDs. In addition, decreased HRV is seen in many acute conditions including COVID-19 infection and the long-COVID syndrome [331-337].

HRV is said to reflect moment-to-moment changes in autonomic balance, i.e., between sympathetic and parasympathetic pathways, which, furthermore, is said to drive all adaptive cardiac functions. Early in the 20th century Nobel Prize-winning neurophysiologist Charles Sherrington, in his highly influential work *The Integrative Action of the Nervous System* (1906), advanced the concept of the 'dominant brain' claiming that all bodily functions were under the control of the brain [338]. This assumption formed the basis of J. N. Langley's 1903 work on the autonomic nervous system which, in his formulation, consisted of a network of one-way outflow pathways originating in the brain that either increased (sympathetic) and decreased (parasympathetic) heart rate [339]. Such notions are now generally regarded as highly problematic if not outright wrong [340].

Decreased HRV has been reported in rheumatoid arthritis [341-343], SLE [344-346], scleroderma

[347-349], multiple sclerosis [350-352], Guillain-Barré syndrome [353, 354], psoriatic arthritis [355, 356], inflammatory bowel disease [357-359], Sjögren's syndrome [360-362], type 1 diabetes [363-365], Behçet's disease [366, 367], autoimmune thyroid disease [368] and more. But what does decreased HRV actually imply? Studies indicate it is associated with higher average heart rate [369-373] along with stiffening of arteries [374-381] both of which reflect heightened sympathetic activity. In addition, numerous studies document a tight inverse relation between HRV and inflammation: as inflammatory markers increase HRV decreases [382-387]. Decreased HRV is a hallmark of hypertension, obesity, diabetes and the metabolic syndrome all of which are characterized by microvascular dysfunction, increased sympathetic activity and systemic inflammation [388-392].

Researchers claim that imbalance between sympathetic and parasympathetic systems, aka 'cardiac autonomic neuropathy', forms the basis of the AIDs [393-399]. And because HRV studies consistently point to diminished parasympathetic activity they conclude that the vagus nerve in some manner possesses anti-inflammatory properties [400-407]. On this basis they seek strategies to augment parasympathetic activity such as enhancement of cholinergic nerve transmission and implantation of vagal nerve stimulator devices [408-419]. But all of this is premised on the dominant brain model and whether or not the autonomic nervous system actually controls the heart.

In a recent article examining the energetic basis of the neurodegenerative disorders we show that both the brain and peripheral nerves derive current flow through the cerebrospinal fluid and extracellular fluid pathways [420]. Diminished energy generation in the blood impacts current flow through the nervous system. In sudden cardiac arrest there is immediate cessation of all nerve

transmission and brain function indicating the primacy of the heart and cardiovascular system.

Decreased HRV has less to do with autonomic imbalance than decreased energy generation in the blood. The kidneys are the first organ to sense this state of affairs and, through the renin-angiotensin system, induce activation of the sympathetic axis via the adrenals so as to increase energy generation by the heart. This, in turn, diverts current flow from parasympathetic pathways. It is excess sympathetic not decreased parasympathetic activity that best correlates with inflammation and reduced HRV which, in the end, is just another way of assessing microvascular dysfunction. The AIDs are primarily energetic in nature. But this leaves us with a plethora of questions regarding the nature of the immune system that must now be addressed.

RETHINKING IMMUNITY & AUTOIMMUNITY

What we now know as the science of immunology has its origins in the closing decades of the 19th century. It is difficult to separate concepts of immunity that emerged during this era from early biological ideas regarding the nature of species and speciation. By the time immunologists came onto the scene Darwin's theory of evolution thoroughly dominated biological thought and strongly influenced not only the focus of experimental research but how facts would be interpreted.

Darwin had broken rank with ancient ideas concerning the nature of species and regarded them as evolutionarily emergent entities that spontaneously arose among inbreeding groups of organisms, a notion which would seem to engender a chicken and egg conundrum. Without resolution of such incongruities evolution became conceived as the sole driver of progressive speciation; species, in turn, were regarded as distinct and differentiated biological entities which, in the end,

were genetically determined. This is 20th century biology in a nutshell.

As medical historian Pauline Mazumdar recounts in her insightful work *Species and Specificity: An Interpretation of the History of Immunology* [420], there arose two opposing factions in 19th century biology, what others have referred to as 'splitters' and 'lumpers,' those who would explain immune phenomena on the basis of their differences and who saw experimentation as a means of making increasingly fine distinctions, and those who sought to integrate experimental phenomena into an overarching unity. One group saw variation and divergence, the other unity within diversity. These two organic modes of perceiving immune phenomena locked into fierce conflict during the closing decades of the 19th and early decades of the 20th centuries.

German bacteriologist Robert Koch argued forcibly for the distinct identity and autonomy of the various bacterial species. His opinions dominated late-19th century bacteriological thought. Different bacterial species, in turn, produced their characteristic clinical syndromes on the basis of specific attributes. On this logic it only stood to reason that such sicknesses should be treated with specific medicines.

Physician-chemist Paul Ehrlich, arguing that all cellular functions were chemical in nature, advanced the notion of Abs and antigens (Ags). All immune reactions, he claimed, were based on specific molecular interactions in which the two opposing entities joined together in lock-and-key fashion (Figure 2). By the same token Ehrlich, an early proponent of cell receptor theory, argued that specific drugs, what he called 'magic bullets', could combat a host of specific diseases. This forms the basis of virtually all 20th century pharmacological strategies including vaccines.
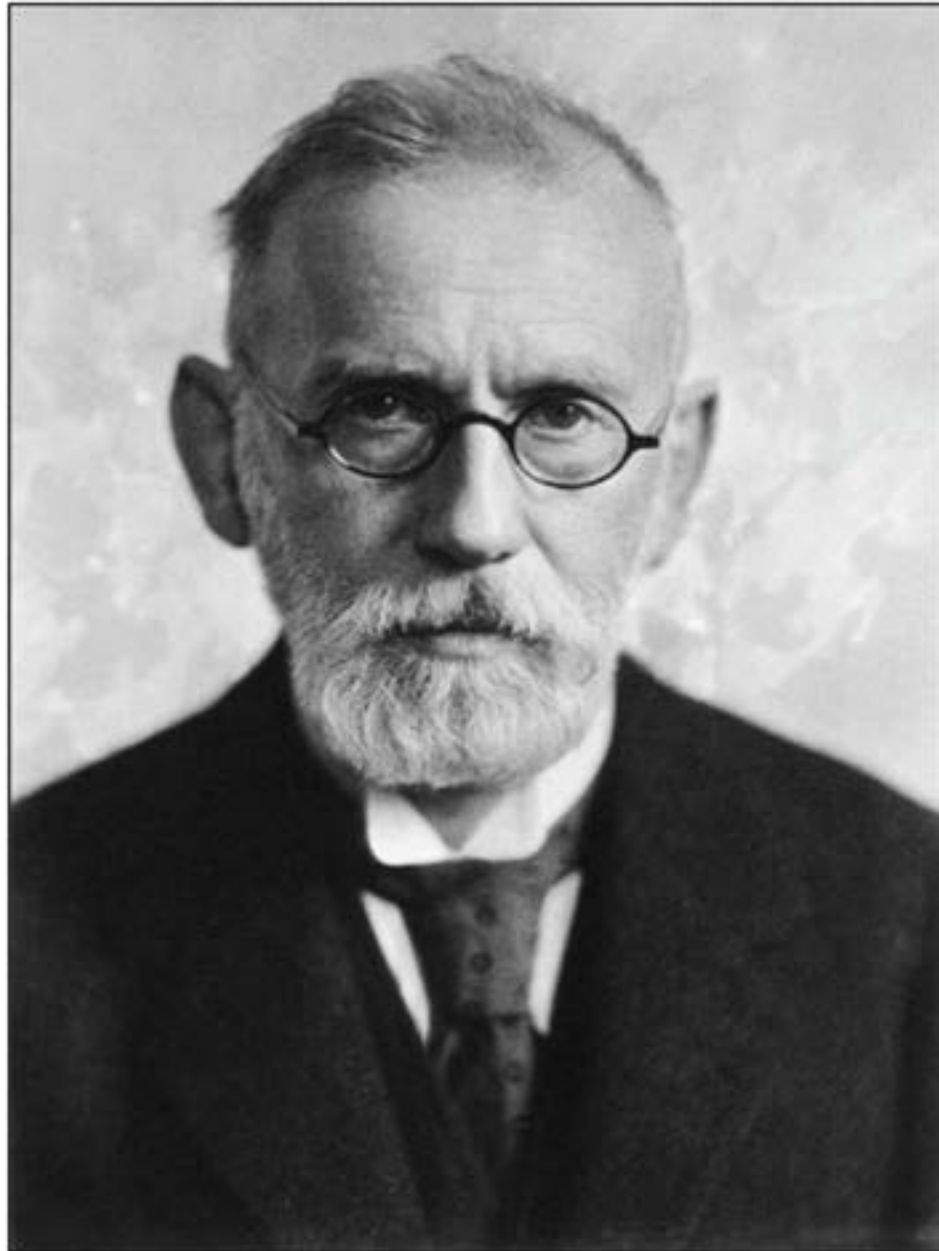
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Figure 2: Physician-chemist Paul Ehrlich, co-recipient of the 1908 Nobel Prize, claimed that antigen-antibody interactions formed the basis of the immune response.

(From: https://fineartamerica.com/art/paul+ehrlich)

In the 1880s biologist Elie Metchnikoff observed under the microscope cells of developing starfish larvae wandering about in the tissues. Suspecting they played a role in the breakdown of cellular substances, he introduced a rose thorn into an organism and watched as cells surrounded the foreign object [422-424] (Figure 3). Calling them phagocytes or 'eating cells', Metchnikoff argued that such cells, now called macrophages, formed the basis of the immune response and were part of a more general set of primitive functions, an internal digestive system so to speak, the purpose of which was to mediate the breakdown of molecular and cellular substances (Figure 4).
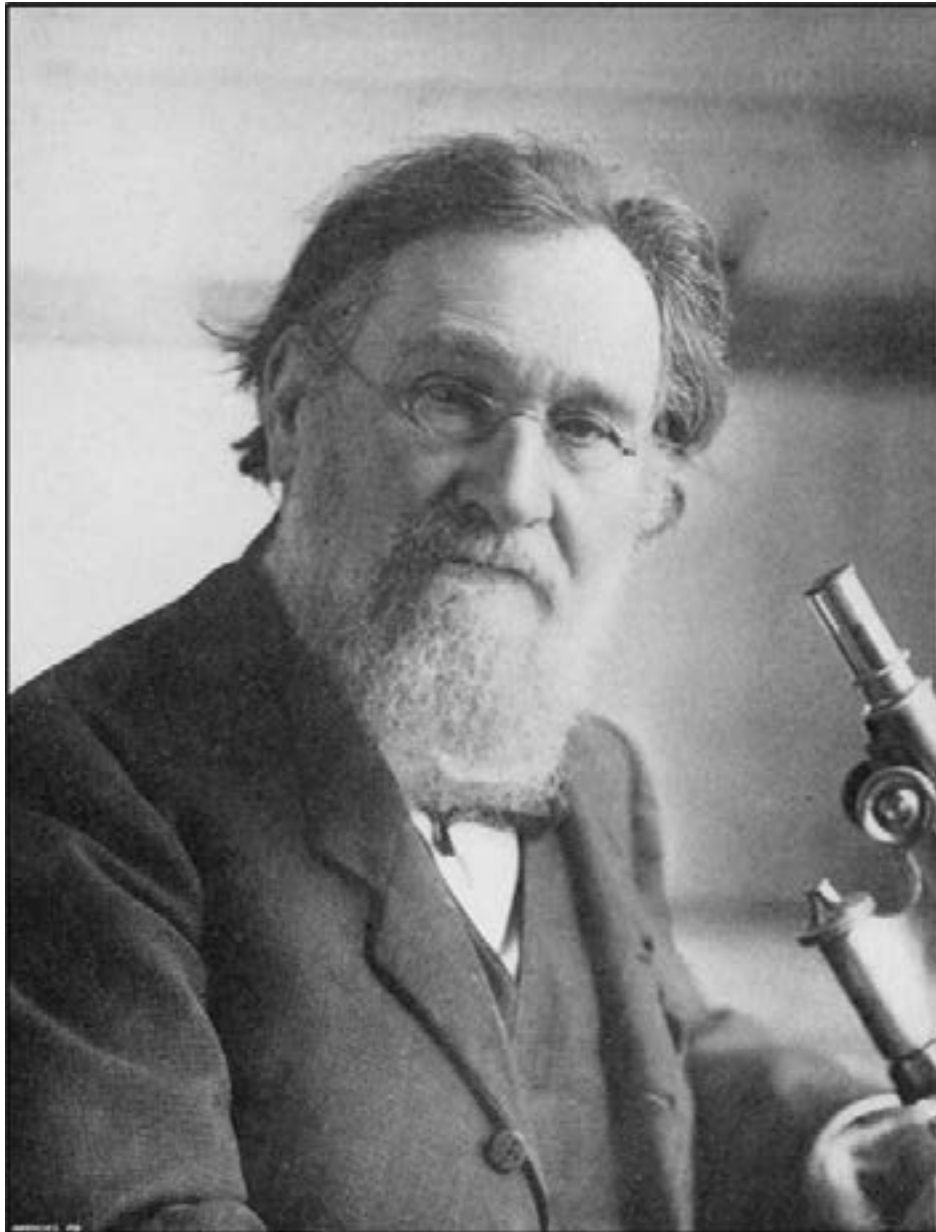
Figure 3: Zoologist Elie Metchnikoff, discoverer of phagocytosis and phagocytic cells, co-recipient of the 1908 Nobel Prize, argued that such cellular activities formed the cornerstone of the immune response.

(From: https://fineartamerica.com/featured/1-elie-metchnikoff-ilya-ilich-mechnikov-mary-evans-picture-library.html)
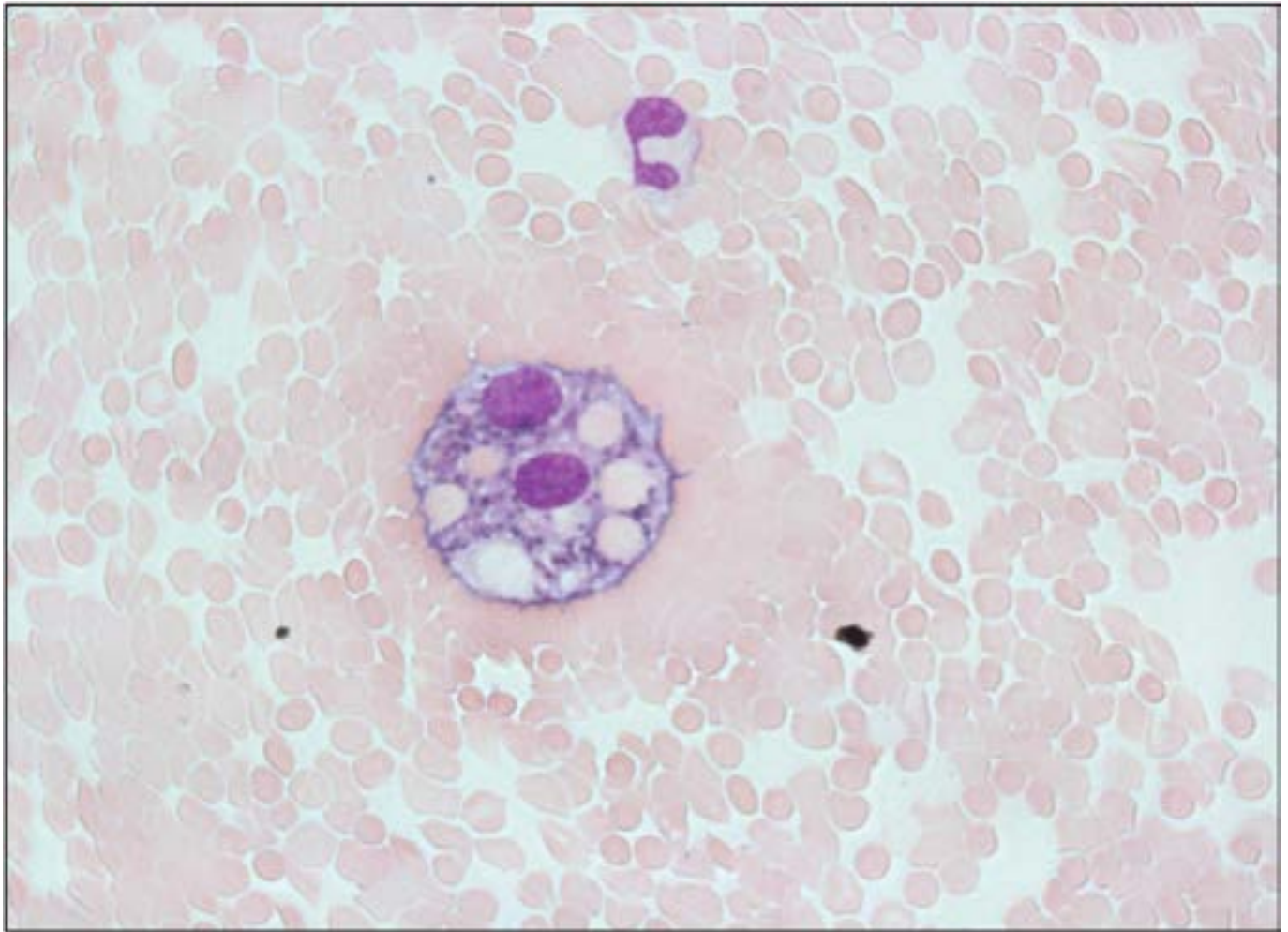
Figure 4: Stained histologic preparation of macrophage.

(From: https://openeducationalberta.ca/mlsci/chapter/macrophage/)

It is fact that the main advocates of the two opposing factions, Ehrlich and Metchnikoff, jointly shared the 1908 Nobel Prize – seemingly a nod in each direction – but their fates sharply diverged: the cellular perspective fell into steep decline for almost a half-century as chemists grabbed the reins and sought to define the immune response on a molecular basis, a period immunologist Arthur Silverstein, in his acclaimed work *A History of Immunology*, calls the Dark Age of experimental immunology [425].

This clash of ideas can be seen in terms of a broader historical dialectic. It is said that controversy is the most productive form of scientific discourse. When assumptions are roundly agreed upon, they are more likely to remain unquestioned and unexamined. Disputation forces concepts to be made explicit. Over the course of the 20th century, each opposing perspective would have ample opportunity to state its case and it would be left to later generations to draw necessary conclusions and complete the synthesis.

In 1948 Rose observed agglutination of red blood cells (RBCs) in a woman with rheumatoid arthritis, the first formal recognition of auto-Abs. The auto-Ab, called rheumatoid factor, was later found to

be an IgM Ab directed against IgG Abs [426]. In 1951 Harrington injected sera from subjects with idiopathic thrombocytopenic purpura into healthy volunteers and observed an abrupt decrease in their blood platelet counts [427]. Auto-Abs had reacted with volunteers' platelets and caused their destruction. In the mid-1950s various studies found that serum from subjects with autoimmune thyroiditis had auto-Abs directed against thyroglobulin. Since that time hundreds of auto-Abs capable of reacting against self-tissues have been described in the AIDs. Auto-Abs are now regarded as the hallmark of the AIDs and the gold standard for diagnosis [428, 429].

In the 1960s researchers distinguished between two classes of lymphocytes, so-called thymic-derived T-cells, responsible for cell-mediated defense functions, and B-cells, originating in the bone marrow, involved with Ab production. T- and B-cell responses are antigenically driven and directed toward specific pathogenic sources, whether infectious, toxic, neoplastic, or the AIDs.

Increasingly scientists came to distinguish between 'adaptive' immune responses, involving Ag/Ab and receptor-mediated responses, and 'innate' immune functions subsumed by the phagocytic system [430].

In the late 1950s Australian biologist MacFarlane Burnett, a staunch critic of chemically oriented theories, advanced the first major synthesis of 20th century immunology with his Clonal Selection Theory: all immune activities, including synthesis of molecular mediators, are effected by cellular functions (Figure 5). Burnett jointly shared the 1960 Nobel Prize with Peter Medawar. Thereafter auto-Abs, and thus the AIDs, became conceived as a consequence of mutations in particular cell lines, aka 'forbidden clones', that proliferated and synthesized self-directed Abs. Studies surfacing during the SARS-CoV-2 pandemic call into question the primacy of the Ab response and adaptive immune system as well as the nature of auto-Abs.

Figure 5: Biologist MacFarlane Burnett, co-recipient of the 1960 Nobel Prize, argued for the primacy of the cellular response in the immune reactions. Advanced the Clonal Selection Theory which explains the genetic basis of the adaptive immune response.

(From: https://www.bilgiustam.com/frank-macfarlane-burnet-kimdir/)

During COVID-19 infection, Abs rarely appeared in the blood before 12 days and sometimes not for 21 days. In many cases symptoms resolved before Abs even appeared. Once present in the serum, anti-spike protein IgG Ab levels waned and by 3-5 months were usually negligible [431-440]. By contrast, Ag-specific memory B cell levels often remained unchanged for 6 months or more [441]. Evidence clearly points away from Abs and toward cellular dynamics in the immune response.

Another provocative line of evidence: a significant

portion of COVID-19 infected individuals, as confirmed by PCR testing, never developed an Ab response. Such 'nonseroconverters' ranged from a low of 5% in one study to a high of 36% in another; other studies found rates in the 15-25% range. Nonseroconverters tended to have milder disease, more rapid viral clearance and lower blood inflammatory marker levels [442-447]. Such findings point to the pivotal role of the innate immune response in early infection.

Other studies found that individuals with more severe disease had higher Ab levels than asymptomatic or mildly affected cases [448-464]. Hospitalized patients had Ab levels up to 3000-fold higher than milder cases or during the recovery period [465-468]. Researchers have no satisfying explanation. Another study found obese individuals with the metabolic syndrome, a group which had worse clinical outcomes, also had higher Ab levels [469]. This is to say that mildly affected and asymptomatic individuals, those with the best clinical outcomes, paradoxically had the lowest Ab responses.

Such findings make no sense unless one accepts that Abs have only a supporting role in the immune response. It seems likely that Ab production is a fallback mechanism implemented when innate immunity is deficient. This inconvenient fact overturns Ehrlich's 120 year-old entrenched dogma. By the same token it explains why COVID-19 vaccines, which stimulate Ab production and provide short-term protection, don't confer long-term immunity. Equally damaging to modern immune theory is the auto-Ab phenomenon.

COVID-19-infected subjects had marked increases in auto-Ab levels compared with non-infected individuals. As in the AIDs, an array of auto-Abs directed against cytokines, chemokines, cell surface proteins as well as RNA and DNA appeared during the course of infection. Auto-Abs,

depending on type, were present in 10%-50% of cases. Studies found that auto-Ab levels tracked directly with rising levels of anti-SARS-CoV-2 Abs and with disease severity suggesting they formed spontaneously during the course of the illness [470-480]. What does this mean?

Genetic mechanisms explain neither the appearance of auto-Abs during the acute phase of the illness nor formation of auto-Abs themselves. Genes code for the primary structure of proteins, i.e., the amino acid sequence, but the secondary and tertiary structure, i.e., the 3D conformation of Abs, is determined solely by energy dynamics. Once formed, primary polypeptide chains are surrounded by cell water, called the hydration layer, and interactions between separate chains as well as folding itself are effected on the basis of energy-driven colloidal interactions [481-485].

Numerous early 20th century scientists questioned Ehrlich's notion of lock-and-key specificity. By that time tens of thousands of antigenic substances had been identified and it was argued that there could not possibly be enough genes to code for such a vast number of Abs. Austrian Researcher Karl Landsteiner, discoverer of the ABO blood groups, argued in favor of a much smaller number of Abs with overlapping specificities. Landsteiner has been proven correct on this point. He also argued that electrochemical forces mediate specific affinity. In his electrolysis experiments, charged acidic and alkaline colloids not only moved toward opposite poles but actively precipitated each other [486].

When undergoing conformational change, aka allosterism, proteins reorganize three-dimensionally to form dynamic linkages between often widely separated domains, either on the same chain or between different chains. Such activities are effected by hydrogen bonding and dipole-dipole interactions that originate in the surrounding fluid milieu. Ag/Ab interactions occur

in the same way. Evidence indicates that auto-Abs are simply misfolded proteins whose altered specificity overlaps with the body's own tissues. On this basis one is once again drawn back to blood energy dynamics.

The question thus arises as to the actual role auto-Abs play in the genesis of the AIDs. There has been increasing recognition of the presence of a wide array of auto-Abs in normal, healthy individuals. Called 'natural' auto-Abs they are said to occur in 5-10% of healthy blood donors and up to 50% in selected groups of asymptomatic individuals [486-490]. Some argue they result from forbidden clones due to failure of clonal selection; others regard them as evolutionarily conserved mechanisms that clear 'physiologic debris' from the body. But why would this be necessary when there are phagocytic cells?

In recent decades evidence necessitated formulation of a new class of disorders, the 'autoinflammatory diseases', to accommodate a growing number of chronic conditions like Familial Mediterranean Fever, Still's disease and Behçet's syndrome characterized by episodic inflammation associated with fever, skin rashes, ocular manifestations and arthritis *in the absence of auto-Abs* [491-496]. Such disorders, which are said to have a genetic basis, are now recognized to originate from innate immune dysfunction.

Evidence thus points to one inescapable conclusion: auto-Abs are neither necessary nor sufficient to explain the AIDs. This being the case, where do we look for answers?

SPLEEN & INTERNAL DIGESTION

The spleen was overlooked for much of the 20th century and its functions incompletely understood. As the only major organ that can be removed without immediate dire consequence it was regarded by many as mainly a storage compartment for red and white blood cells. The so-called ductless gland has been a source of speculation throughout history.

Structurally possessing connections only to the vascular system, and beginning its early development as an ingrowth of blood vessels and primitive immune cells, its entire raison d'être seems tied to the blood and vascular system [497, 498]. Plato claimed it kept the blood 'bright and shining'. Aristotle and Galen regarded its functions as primarily digestive in nature. In addition to its role in immunity the spleen functions as a filter for clearance of aging cells, foreign pathogens and other substances from the blood as well as a serving as a reservoir for blood elements.

The spleen is formed by alternating strata known as the white pulp, composed of lymphocytes and macrophages, and the red pulp, consisting of sinusoidal channels laden with RBCs, lymphoid elements and macrophages (Figure 6). Between the white and red pulp lies the marginal zone consisting of other lymphoid and macrophage lines. While macrophages in the white pulp are phagocytic and serve classic immune functions, red pulp macrophages perform scavenger and metabolic duties like RBC breakdown, bile pigment production, and iron recycling. Another subset, M2 macrophages, engage in regenerative and repair functions.
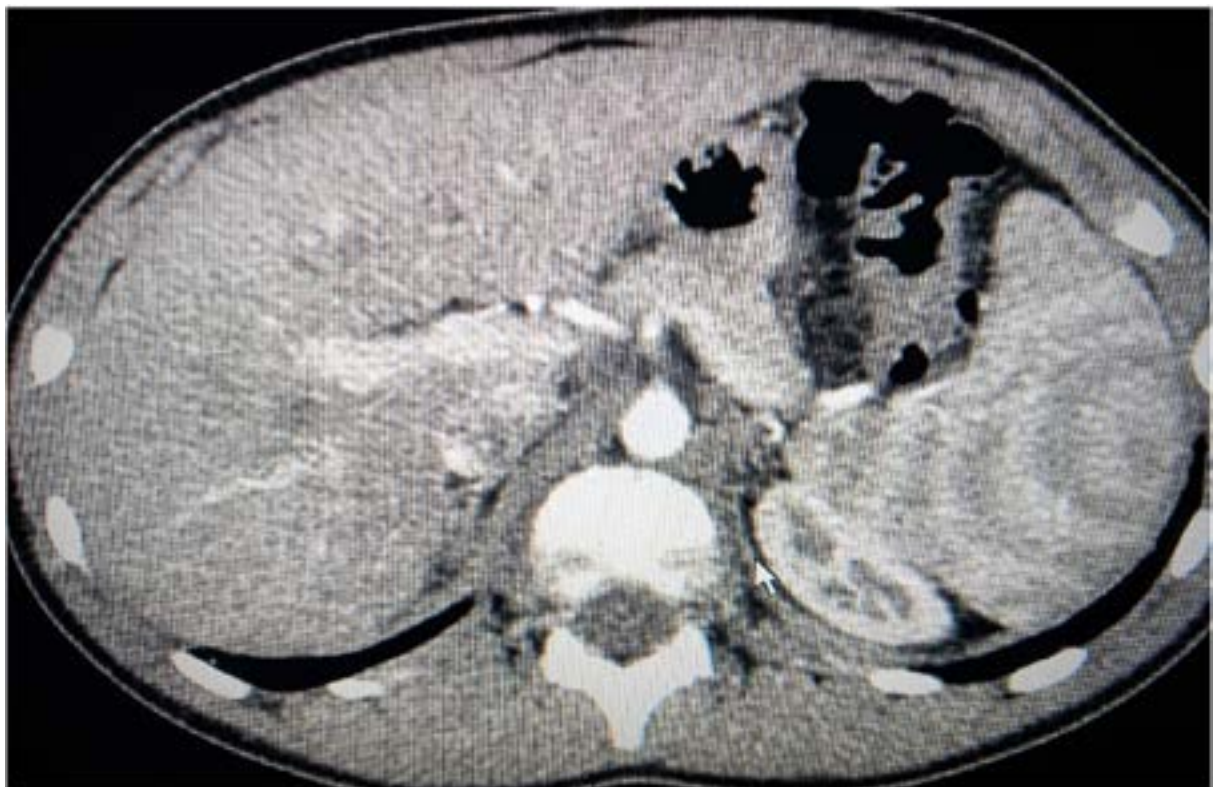
Figure 6: Contrast-enhanced CT image of the upper abdomen with zebra-striping of the spleen in early arterial phase. Lighter areas represent the highly vascular red pulp which opacifies first. Darker areas represent delayed opacification in the less vascular white pulp. Upon equilibration moments later the spleen becomes uniformly dense.

In the early 20th century surgeons increasingly performed splenectomy for enlargement of the spleen, aka hypersplenism. In the late 1920s reports began to trickle in describing cases of sudden, severe sepsis and death in otherwise healthy individuals who had undergone splenectomy years, sometimes decades, earlier. It wasn't until the 1950s that the causal connection became clear [499]. Now called OPSI, an acronym for 'overwhelming post-splenectomy infection', patients develop bacteremia caused by encapsulated microorganisms, usually without any obvious source of infection, along with septic shock and disseminated intravascular coagulation. Mortality rates are in the 50-70% range with death ensuing over 24-48 hours [500-502].

Over the next several decades clinical syndromes very much similar to that seen with OPSI were recognized in people with intact spleens and gradually the concept of 'functional hyposplenism' evolved [503-507]. Originally described in children with sickle cell anemia, it occurs more frequently than previously thought and can be seen in celiac disease, alcoholic liver disease, hepatic cirrhosis, lymphomas and a spectrum of AIDs including SLE, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, ulcerative colitis and autoimmune thyroiditis [508-516].

When stained blood smears from subjects with functional hyposplenism are examined microscopically so-called Howell-Jolly bodies, remnants of RBC nuclei normally removed by the spleen, along with 'pitted' RBCs containing defects in their membranes, are observed [517] (Figure 7). Radionuclide scans show decreased colloid uptake by the spleen suggesting impaired phagocytosis. The spleen is usually smaller than normal. Thus, in addition to an immune defect and increased susceptibility to infection, evidence points to impaired filtering by the spleen. Where does all this lead us?
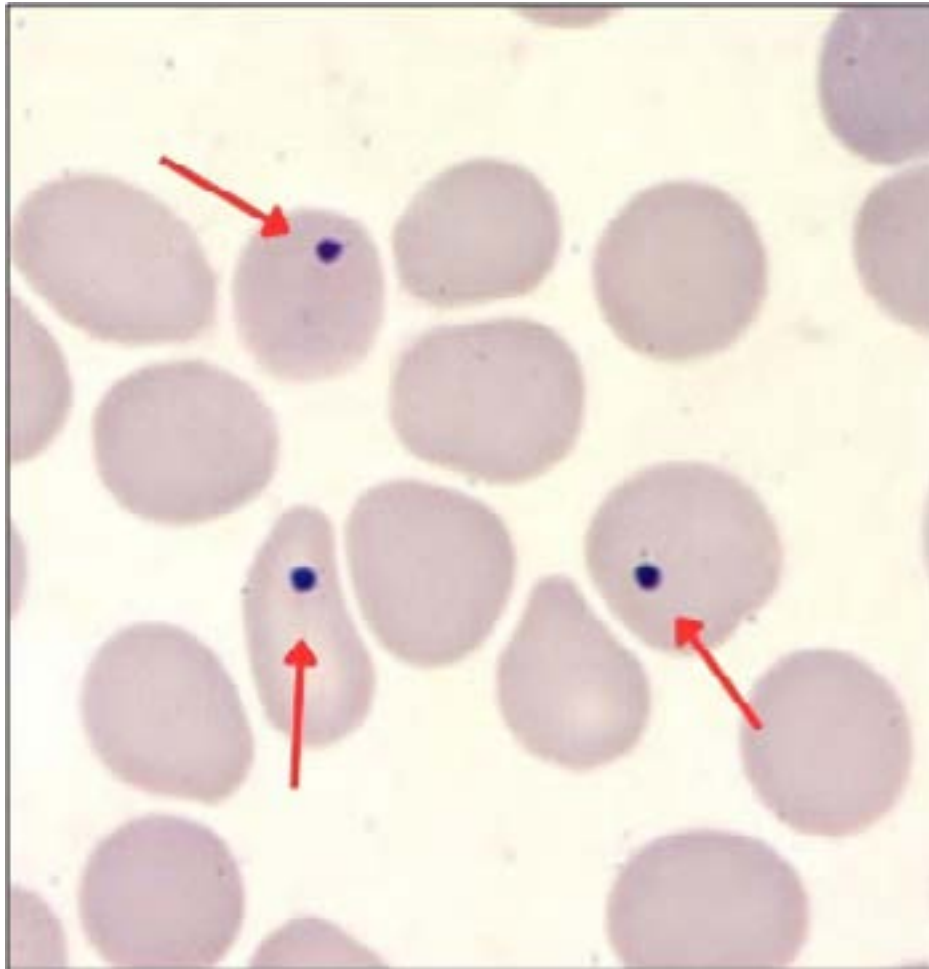
Figure 7: Stained blood smear of Howell-Jolly bodies seen in hyposplenism. Howell-Jolly bodies represent basophilic remnants of RBC nuclear material that are normally removed by phagocytosis in the spleen.

(From: https://4.bp.blogspot.com/_EUkaWdQ4i64/TQjAJIV1XBI/AAAAAAAABds/D5U1oPMUP3E/s400/hn.jpg)

In the ancient framework blood was said to be composed of four humors. Health was defined as a state of balance (*krasis*) between the humors. Sickness, on the other hand, arose from imbalances with one or another humor present in excess. The humor known as black bile (*melan chole* or *atra bilis*) was a central concept in the ancient system that endured well into the early scientific era [518]. Based on natural correspondences derived from the Earth-Water-Air-Fire cosmology, it was partly empirical and partly speculative in origin. No other aspect of ancient thought has been the subject of more scorn and ridicule than black bile.

The ancients regarded black bile as a toxic substance that caused a wide range of disease. There were references to it in the Hippocratic text *On the Nature of Man* but we never get a clear idea of what black bile actually was or what it did. From the earliest time the spleen was regarded as a key player in its disposition. Galen, the 2nd century synthesizer of ancient medical thought, was the first to elucidate the nature of black bile.

Galen placed great emphasis on the role of the spleen in health and disease. He claimed it was

involved in the transformation and excretion of black bile. Black bile, he said, possessed a sharp, biting quality. It accumulated naturally during the fermentation of grapes into vinegar. It had a corrosive action that induced effervescence on contact with calcareous (chalky) earth. And he linked it to the incompletely digested food and juices in the condition we know as acid reflux and heartburn. But the ancients had no concept of acid and thus Galen simply referred to it as *oxys*. He claimed that the spleen attracted oxys to aid in digestion and, moreover, somehow used it for its own nourishment [519].

Soon after his discovery of lysosomes in the 1950s, Belgian biologist Christian de Duve under electron microscopy observed delivery of membrane-bound cellular material to lysosomes and coined the term autophagy to designate the orderly process by which cells self-digest [520-522]. During autophagy acid is actively concentrated in lysosomes and catabolic enzymes activated not unlike in the stomach. Autophagy not only culls aging and damaged cell structures but generates energy during periods of nutrient deficiency. Evidence suggests it represents a frontline defense against infection and, when deficient, is associated with various inflammatory disorders including the AIDs (Figure 8).

Figure 8: Electron microscopy of a macrophage containing phagosomes, light-colored inclusion bodies with ingested materials (arrows), lysosomes, dark-colored intracellular bodies (arrows), and phago-lysosomes in varying stages of digestion.

Many infectious agents, including the SARS-CoV-2, gain access to the body by colonizing epithelial cells where they attempt to reproduce and spread. Autophagy is the primary cellular response to such intrusions. Bacteria are enveloped in a membrane-bound structure, the phagosome, which fuses with acid-laden lysosomes to initiate digestion. If autophagy in epithelial cells is effective then further spread is averted; in cases where it is not the organism reproduces, initiates cell lysis, and spills into the extracellular fluid (ECF) space. During cell lysis, damage- and pathogen-associated molecules as well as cytokines are released which attract local macrophages [523-525].

Activated macrophages converge at the infection site and initiate phagocytosis to contain spread. Macrophages possess a multitude of acid-driven mechanisms by which to dispose of the infectious vector: the agent is walled-off in a sealed membrane limiting access to nutrients; release of polypeptides like defensin and cathelicidin destroy the outer bacterial membrane; acid and metals within the phagosome trigger the organism's own self-digestive enzyme systems; the catabolic degradation process amplifies to produce highly reactive substances like nitric oxide and free radicals which further degrade the ingested particle.

If such autophagy-driven mechanisms are successful then infection is contained and the immune response terminates; if insufficient then macrophages release pro-inflammatory cytokines to elicit support from circulating neutrophils and the adaptive immune system. Spread of infection thus involves successive breaches of barrier functions, first in epithelial cells, then macrophages in the ECF space, related to inadequate autophagy. Metchnikoff was correct. In chronic energy deficient states like the AIDs this process goes haywire.

Studies assessing splenic hypofunction in various AIDs like SLE, rheumatoid arthritis and inflammatory bowel disease for example, found impaired clearance of immune complexes and RBCs from the blood with inverse relation between the quantities of such substances and splenic hypofunction [526-548]. It is believed that renal damage accompanying SLE is related to deposition of Ag/Ab complexes in the kidneys due to impaired splenic filtration and saturation of the phagocytic system. The most dramatic example of deficient internal digestion is seen in a phenomenon known as neutrophil extracellular traps (NETs).

Neutrophil extracellular traps (NETs) are mesh-like structures that protrude from suicidal neutrophils intended to trap particulate materials [549-556] (Figure 9). Recruitment of neutrophils, highly phagocytic white blood cells, imputes a primary failure of macrophage functions in the spleen and ECF compartment. Increased numbers of NETs, called NETosis, are found in a wide variety of pathologic conditions including COVID-19 infection and the AIDs. NETs contain antigenic intracellular materials like DNA, RNA and oxidized proteins that trigger auto-Ab formation, worsening of endothelial dysfunction, and intravascular thrombosis.
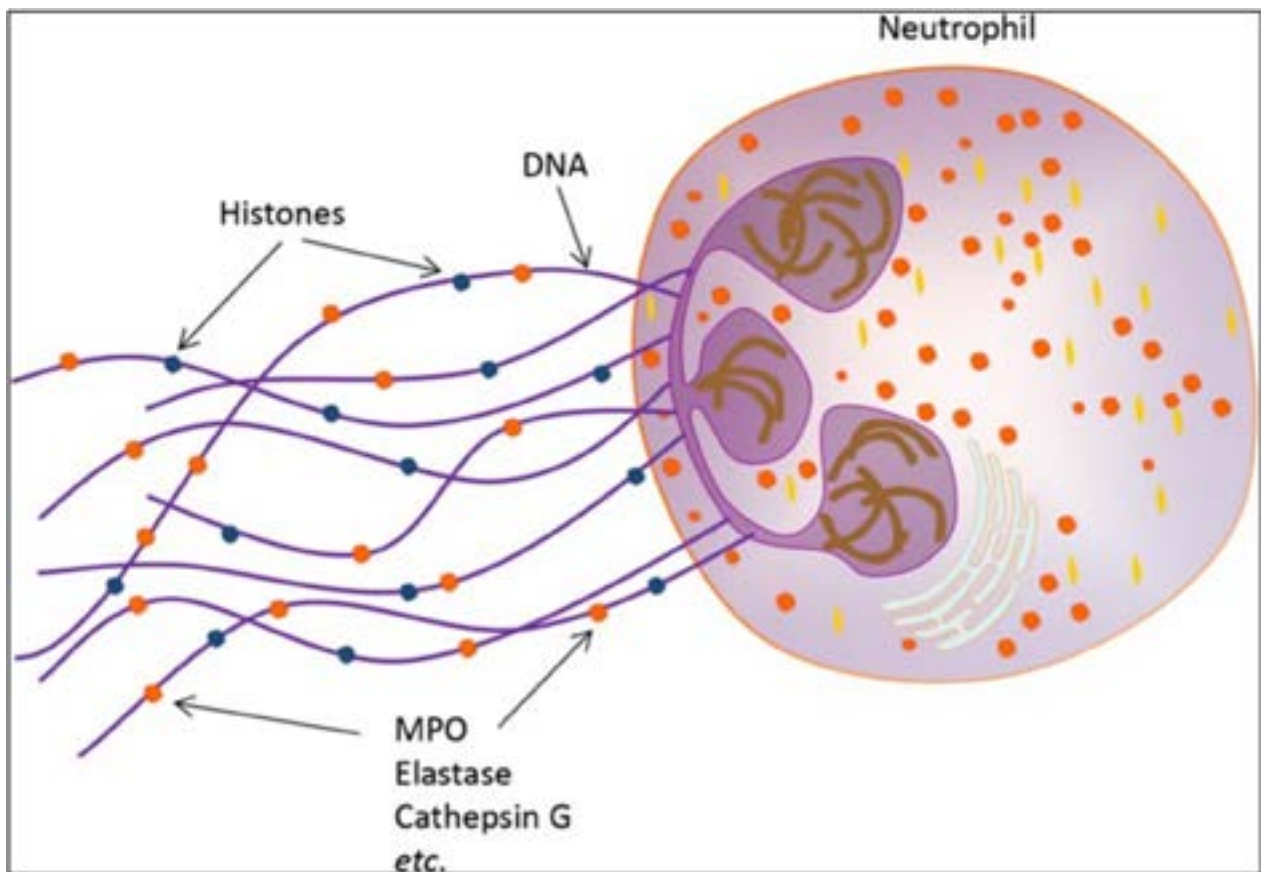
Figure 9: Neutrophil extracellular traps (NETs). Web-like chromatin fibers expelled from suicidal neutrophils intended to trap and bind pathogenic materials. Excess accumulation of NETs, called NETosis, plays a pathogenic role in a wide range of inflammatory disorders, both infectious and non-infectious, as well as cancers, heart disease and stroke.

(From: https://www.researchgate.net/publication/349705669_Neutrophil-Induced_Liver_Injury_and_Interactions_Between_Neutrophils_and_Liver_Sinusoidal_Endothelial_Cells/figures?lo=1)

Autophagy impacts virtually every aspect of innate immune function. Impaired autophagy, in turn, is a hallmark of the AIDs [557-567]. At the intersection between the two pathologic states, we once again stumble upon microvascular dysfunction and inflammation [568-571]. Autophagy is an energy-driven process: acid is actively pumped into lysosomes *against* its concentration gradient by selective ion channels. In energy deficient states this mechanism is among the first to fail. Impaired autophagy is associated with mitochondrial and ion channel dysfunction [572-582]. Autophagic dysfunction is associated with elevated pro-inflammatory cytokines and other inflammatory markers [583-585].

Once this dynamic is set into motion a series of lethal events ensue: impaired mitochondrial function, compounded by lysosomal dysfunction, results in buildup of intracellular acid and reactive oxygen species. Progressive acidification of the cytoplasm impacts functions like protein synthesis and folding. Such events, in turn, trigger cytokine release, NLRP3 inflammasome formation, and cell death (apoptosis). Spillage of cell contents into the ECF space further aggravates already impaired phagocytic functions initiating a self-amplifying spiral of deterioration. This is likely what the ancient concept of black bile hinted at.

The digestive system thus represents an ensemble of functions that orchestrate the orderly breakdown, assimilation and elimination of organic substance. The two primary digestive organs, stomach and spleen, have conjoined origins in the upper left abdomen and use similar means centered around acid metabolism and acid-activated enzymes, i.e., black bile, to mediate their activities.

The two organs constitute an integrated functional nexus: the stomach takes in material from the outside which, upon decomposition, is drawn upward through intestinal veins to the liver where it is altered and subsequently transported through arteries to the ECF space for assimilation by cells; the splenic phase of the cycle, the internal digestive system proper, begins with the breakdown of intracellular materials via autophagy, extrusion of waste into the ECF space, uptake by phagocytic cells, and return of materials to the spleen for elimination or recycling. The two aspects of digestion are united through the cardiovascular system and blood. This leads us to consider one final aspect of splenic function.

A connection between the spleen and heart was first recognized around 1950 when researchers observed that electrical stimulation of splenic nerves improved ventricular function in laboratory dogs [586, 587]. They suggested that the spleen played a supporting role in cardiac function but the report generated little interest and sat on the shelf for over a half-century.

More recent studies found that during acute events like heart attack, stroke, infection and sepsis splenic volume decreases and, after a variable period of days, returns to its previous size. Splenic contraction appears to play an important role in such events and correlates with increased numbers of RBCs, monocytes, neutrophils, and lymphocytes in the blood. Studies suggest that splenic volume decreases in relation to disease severity. In recent years we thus find increasing references to the 'cardiosplenic axis' [588-592].

The spleen varies in size but on average is about 10×6×3cm and, due to its sinusoidal structure, is capable of greatly expanding and storing up to 20-30% of total blood volume [593-595]. In disease states like heart failure splenic size correlates positively with cardiac output and inversely with blood pressure. Decreased splenic size, influenced by hemodynamic factors such as blood volume and sympathetic nerve activity, is an independent predictor of poor outcomes in heart failure and other conditions [596-598] (Figure 10).
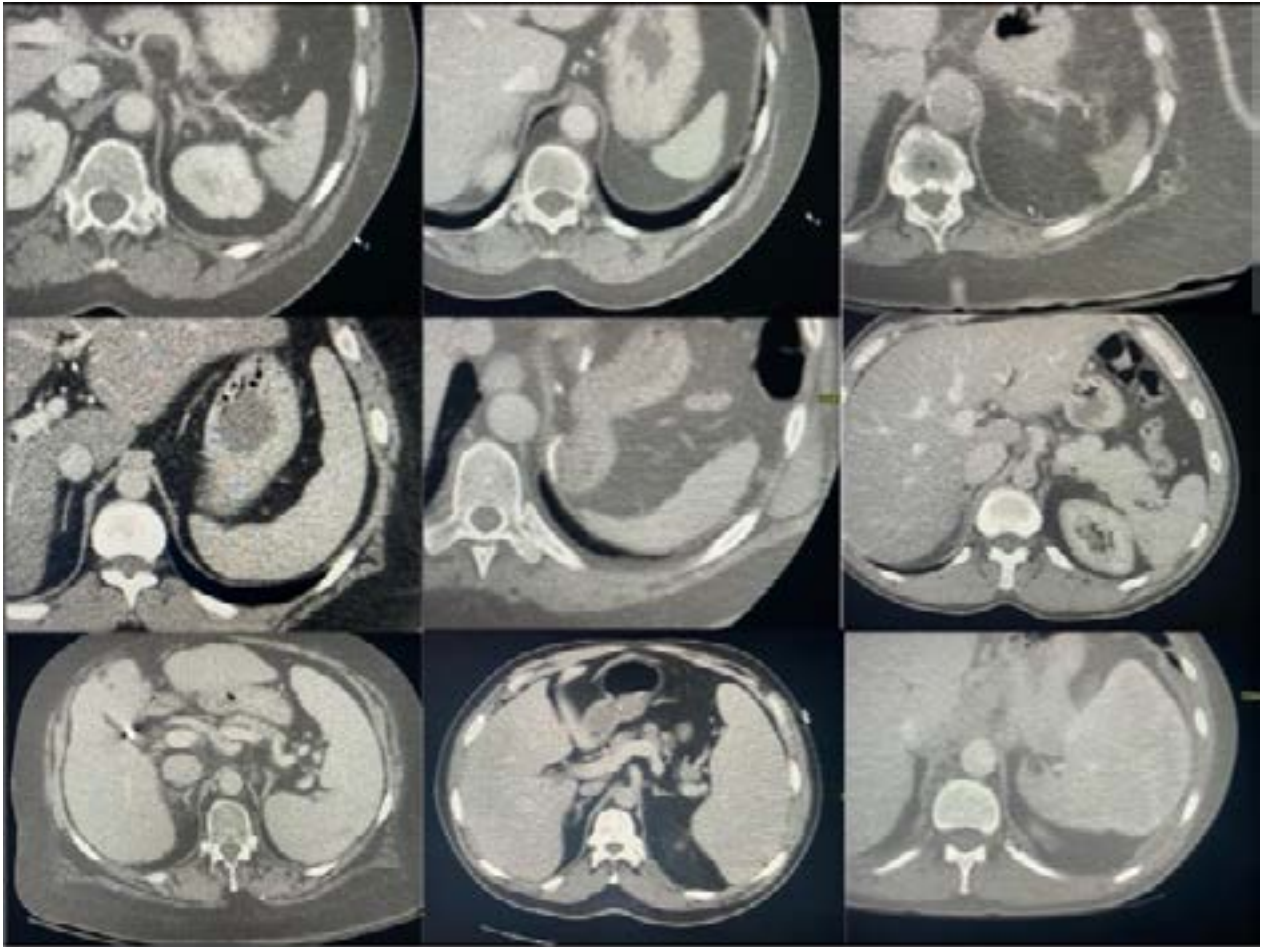
Figure 10: The many shapes and sizes of the spleen in health and disease. (Courtesy of Cynthia Wheeler, MD & Robert Hills, DO)

Larger than normal spleen size has been reported in elite endurance athletes and indigenous populations that engage in prolonged breath-holding activities beneath the sea surface [599]. Elite athletes not only have larger splenic volume but enhanced contractile capacity which, in response to exercise, dramatically increases blood RBC and hemoglobin levels. The spleen contracts during high-altitude mountain climbing as well, serving as a sort of 'auto-transfusion' to buffer the low-oxygen tension in the upper atmosphere [600-602].

Scientists claim such adaptive responses are intended to increase blood oxygen levels and while this is no doubt correct there is a more compelling reason. In earlier papers we show that the preconditioning (PC) phenomenon, a period of heightened systemic protection following periods of stress like ischemia or exercise, is mediated by enhanced energy generation in RBCs [603, 604]. The PC response is now recognized to be the most powerful protective mechanism yet discovered.

It appears likely that splenic contraction amplifies the effects of the PC phenomenon. It is also likely that its contraction occurs early in other systemic assaults like COVID-19 infection and provides an energy boost for immune cells that are also released. This would explain the generally milder course of illness in young and healthy people as well as higher morbidity and mortality in aging

and infirm populations in whom the PC response is blunted or absent. And it is likely that splenic contraction plays into the immune dysfunction seen following acute events like heart attack and stroke. To wit:

In response to systemic injury and infection large numbers of monocytes are released from the red pulp of the spleen, hone in on affected organs, and differentiate into macrophages. So-called M1 and M2 macrophages effect not only the phagocytic/ digestive phase of the response but are central to healing and regeneration [605-608].

Many chronic heart failure cases develop after heart attack and most of these result from failure to terminate the inflammatory response and transition to the healing phase. Much of the damage is mediated by cells originating in the spleen. Metabolic activity in the spleen increases after such events and is associated with activation of pro-inflammatory cells, increased C-reactive protein, and endothelial inflammation. Mitochondrial dysfunction in splenic derived macrophages promotes inflammation and suppresses tissue repair [609-616].

Lab studies in animals document the deleterious influence of splenic monocytes on promoting inflammation in a wide number of systemic conditions including stroke and heart attack, what is called the 'systemic inflammatory response syndrome' [617-619]. Splenectomy in mice with established heart failure reverses pathological cardiac changes and inflammation. Splenic cells transferred from mice with heart failure to healthy mice target the heart and induce immune-mediated inflammation and fibrosis. Recipient mice, in turn, undergo splenic remodeling and generate their own activated pro-inflammatory monocytes [620, 621].

None of these phenomena make a bit of sense unless there is already diminished energy availability in the blood, which brings us back full circle to microvascular dysfunction and inflammation. Inflammation begets more inflammation because it is a primary sign of diminished energy generation by the cardiovascular system. The spleen and internal digestive system, intimately related to the heart and blood, cannot complete its assigned functions without sufficient energy, highlighting a central tenet of ancient medicine: *omnia incipit in sanguine,* everything begins in the blood. Therein lies the unity of immunity.

THE GREAT DELUSION

Experimental medicine is exactly what its name implies. Since the turn of the 20th century scientists have engaged in a grand experiment upon populations across the globe to test their hypotheses regarding the causal primacy of cellular and molecular mechanisms in the body. Over the past century science dominated intellectual discourse in modern societies and, as observed in the arrogant commentary of Sir Peter Medawar, sought to establish scientific knowledge as invincible and the experimental method as a gold standard for attainment of such knowledge. This was pure delusion.

Early on in the experimental science experiment a rash of interpretive errors regarding cardiovascular function, organization of the nervous system, immune theory, and the primacy of genetics became deeply enmeshed in its theory structure making any kind of unifying synthesis all but impossible. Medical science became trapped in a conceptual labyrinth of its own design and its quest for unity and insight as elusive as the mythical Holy Grail. In the process science became a never-ending 20th century fable.

Such developments correspond to science historian Thomas Kuhn's notion of a paradigm collapse. Once a science reaches the point where

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its knowledge no longer accurately explains phenomena, and its theory structure littered with errors and internal contradiction, it becomes useless and obsolete. Such is the current state of scientific medical knowledge. And once a theory is shown to be wrong, a logical corollary follows that it was wrong from the beginning, which is to say scientists should have been more critical and circumspect of the theories they propounded.

By 1970, ten years after receiving the Nobel Prize for his Clonal Selection Theory, Macfarlane Burnet had soured on experimental medicine. In *Genes, Dreams and Realities* he argued that the contribution of laboratory science in unlocking the problem of disease had come to an end and that further research would amount to little more than filling in of details. Most of the breakthroughs in 20th century medicine, he noted, were observational in nature and not based on experiment.

Burnet claimed that 'too much sensational material was being written about the future significance of discoveries in molecular biology'. He pointed to the increasing burden of chronic diseases and lack of meaningful change in their outcomes in the previous 3-4 decades. Modern science, he wrote, 'is by no means the triumphal march toward perpetual health and well-being' as popular accounts would suggest. By this time science had become a collectively shared cultural delusion. And far from stunning breakthroughs he warned that molecular science 'might release some new and nasty problems on a world that already has more than it can cope with'.

Fifty years on Burnet looks like a minor prophet. An explosive epidemic of chronic diseases has spread across the planet on a scale unrivaled in history. Over the last half of the 20th century, one observes striking parallel rises in the burden of chronic disease and healthcare costs in all industrialized nations. Today, 120 years since the advent of the modern therapeutic era, medical science has yet to cure a single class of disease, and its physicians do little more than manage the progressive and unrelenting course of these intractable conditions.

No matter how scientists may wish and hope to pull the rabbit out of the hat one more time with their magic bullets there is no *Plus Ultra*. Scientific knowledge has reached its limit and the experimental era is dead. The length of time spent beating a dead horse has no bearing on the degree of death. Meanwhile societies must come to terms with this monumental failure and begin to devise and implement solutions to confront a looming disaster.

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