TheGMS
The Gazette of Medical Sciences
https://www.thegms.co ISSN 2692-4374 DOI https://www.doi.org/10.46766/thegms

Endocrinology | Review

Energy Dynamics in the Metabolic Syndrome: Underpinnings of an Evolving Global Catastrophe

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Submitted: 19 May 2024
Approved: 06 June 2024
Published: 08 June 2024

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How to cite this article: Thorp KE, Thorp EM. Energy Dynamics in the Metabolic Syndrome: Underpinnings of an Evolving Global Catastrophe. G Med Sci. 2024; 5(1): 61-146. https://www.doi.org/10.46766/thegms.endocrinol.24051901

INTRODUCTION

In 1988 endocrinologist Gerald Reaven presented groundbreaking research that challenged existing ideas concerning the etiology of a handful of common clinical conditions – hypertension, obesity, hyperinsulinemia, elevated blood glucose and triglyceride levels – and pointed to their conjoined origins in a single overarching disturbance known as insulin resistance.

He noted that people with hypertension had elevated blood levels of insulin and, moreover, were relatively resistant to its actions. After a period of fasting such individuals had increased blood sugar levels which also occurs in diabetes. In addition, hypertensives often had elevated blood cholesterol and triglyceride levels. Observing that many obese and sedentary individuals were also resistant to insulin, Reaven reasoned that insulin resistance was the cause of all the other abnormalities.

Recognizing that hypertension, obesity, hyperglycemia and hyperlipidemia had earlier been shown individually to promote development of heart disease, Reaven deduced that this cluster of related conditions – what he designated as Syndrome X, later called Metabolic Syndrome – formed the primary basis of common chronic diseases like diabetes and heart disease.

'Although this concept may seem outlandish at first blush', he acknowledged, 'this notion is consistent with available clinical data' [1]. In advancing his unifying hypothesis and tying various known risk factors into a coherent framework, Reaven became one of the first 20th century researchers to step beyond the maze of cellular and molecular mechanisms.

Reaven's ideas set off a firestorm of controversy in the research community that continues to this day. Opinion as to the existence of the Metabolic

Syndrome (MetS) remains divided [2-5]. Some argue it is a statistical artifact rather than a bona fide clinical entity. In ascribing the origins of chronic disease to insulin resistance – which he left undefined – he opened the door, albeit unintentionally, to a more dynamic way of understanding these conditions.

A 2005 joint statement by the American Diabetes Association and the European Association for the Study of Diabetes concluded: . . . while there [is] no question that certain [cardiovascular] risk factors are prone to cluster . . . the Metabolic Syndrome [is] imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a [cardiovascular] risk marker. Our analysis indicates that too much critically important information is missing to warrant its designation as a syndrome' [6].

And as researchers continued their decades-long Nero-esque debate over the existence of MetS its numbers exploded across the globe on a scale that defies imagination [7-10]. Among adults in the US the prevalence of MetS rose by over 35% between 1998 and 2012 across every socioeconomic group and it now affects over 30% of the population [11]. Similar trends occurred globally. More worrisome, in testament to the long-term threat it poses, by 2020 about 3-5% of children and adolescents globally were affected by MetS [12]. Such rapid spread defies any genetic mode of propagation.

Not a disease per se, but an upstream cluster of pathophysiological alterations, MetS feeds directly into the escalating burden of chronic disease: it is associated with a 2 to 5-fold increase in cardiovascular disease, ~5-fold increase in diabetes, and ~1.5-fold increase in all-cause mortality [13-17]. It carries a heightened risk for clotting disorders [18-20], chronic kidney disease [21-23], dementias like Alzheimer's [24-26], stroke [27-29], atrial fibrillation [30-32], peripheral vascular disease [33-35], and various cancers [36-45]. Its cost in terms of human well-being, loss of productivity, and medical expenditures is inestimable. It is the human equivalent of global climate change.

MetS, as well as the escalating burden of chronic disease, is directly related to contemporary western lifestyles: energy-dense diets and sedentary, desk-bound activity patterns are its main drivers. All current medical treatments are palliative and temporizing; none prevent the progression of the underlying disorder. There are no magic bullets on the horizon. The mainstay of treatment involves lifestyle changes centered around dietary modifications, exercise, and weight loss.

The evolving crisis is inextricably linked to 20th-century experimental science. Insulin resistance was recognized within years following introduction of insulin into clinical practice and first reported in the medical literature in the 1930s [46]. As scientists focused on elucidating cellular and molecular mechanisms of diabetes it attracted little attention until researchers like Reaven studied it more closely. Despite tens of thousands of reports in the medical literature detailing its various aspects medical scientists are still unable to explain its basis with any degree of clarity. This points to a dramatic failure of 20th-century experimental science and the cellular/molecular paradigm.

In this article we describe the dynamic aspects of MetS and show the systemic nexus of derangements that occur in conjunction with insulin resistance (IR). But IR is not the primary problem and insulin, alas, is but an innocent bystander. In previous works we document the presence of an organized energy field taking origin in the blood through the contraction and dilation cycles of the heart. In the final analysis IR is secondary to a defect in the generation and availability of blood-borne energy. This is to say that all aspects of MetS and all ensuing states of organ dysfunction are manifestations of a progressing and cumulative energy deficit. On this basis it only stands

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to reason that all attempts at remediation must be aimed toward enhancing energy generation and flow in the blood.

INSULIN RESISTANCE & MICROVASCULAR DYSFUNCTION

Evidence emerging in the past 35 years substantiates Reaven's assertions. But, as 20th century science philosopher Karl Popper established in his influential work *The Logic of Scientific Discovery*, scientific hypotheses can never be proven, only substantiated [47]. The corollary to this is that scientific knowledge advances on the basis of negation of existing hypotheses. Given that no credible refutation has yet emerged, Reaven's thesis must be accepted as provisionally correct. We thus continue along the same path of inquiry using a similar mode of inductive reasoning.

If Reaven's work had a single flaw it lay in his inability to articulate the nature of IR which, at the time, was an unknown entity – literally 'Syndrome X'. This opened the door to a host of detractors who, expecting a cellular or molecular account, disputed (but never refuted) his claim. To reinforce and build on Reaven's work we demonstrate a wider nest of dynamic disturbances surrounding IR, all of which involve the vascular system and known energy pathways, and in so doing provide a more complete elucidation as to its nature.

The first and most relevant association is with the entity known as diastolic dysfunction. Around the time Reaven was formulating his hypothesis a radical upheaval was underway in cardiology regarding the nature of cardiac function. For much of the 20th century the heart had been conceived to function in the manner of a mechanical pump with blood propelled forward from the ventricles into the arteries during systolic contraction. In the 1980s negative pressures were discovered in the ventricular chambers during early diastole indicating the presence of a suctional force which actively drew blood forward [48-54]. It soon became apparent that diastole – not systole – was the determinant phase of the cardiac cycle.

Since this highly disruptive and unanticipated epiphany scientists have been at a loss to explain how the force responsible for the outward movement of the ventricles and antegrade movement of blood is generated. Their mechanical and chemical theories are laden with inconsistency [55-63]. In earlier works we show that diastolic expansion of both cardiac and arterial walls is secondary to generation of a magnetic field induced during the systolic phase [64]. This, in turn, explains the presence of abundant iron stores in the heart muscle and blood.

Within years of establishing the primacy of diastole it was recognized that impairment of the outward movement of the cardiac and arterial walls, known as 'diastolic dysfunction', was associated with a host of chronic diseases and, moreover, was often the first abnormality to appear [65, 66]. Diastolic dysfunction is now recognized as a leading predictor of all-cause mortality [67-70]. This is to say that the pandemic of chronic disease now spreading unchecked across modern societies, for which medical science has neither a satisfying explanation nor effective treatment, is primarily energetic in origin.

It is hardly surprising therefore to discover that every single component of MetS – hypertension, obesity, hyperinsulinemia, hyperglycemia, hyperlipidemia, as well as IR – has been linked to diastolic dysfunction [71-87]. But an association says nothing about causality nor does it in anyway explain the nature of IR. For this we must dig still deeper.

In the 1970s and 80s cardiologists observed increasing numbers of people who presented with typical angina-like chest pain and who, on exercise

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stress-testing, developed ECG abnormalities consistent with myocardial ischemia but had normal coronary arteries by angiography [88-90]. Called Cardiac Syndrome X, symptoms are secondary to diastolic dysfunction at the microvascular level. Overall, about 20-30% of individuals with angina have no obvious coronary plaques. Microvascular dysfunction is present in most if not all of these people [91-93]. And herein lies the connection between IR and MetS.

In the 1990s a spate of reports linked Cardiac Syndrome X not only to IR but to other aspects of MetS including hypertension, hyperinsulinemia, hyperglycemia and hyperlipidemia [94-111]. In such cases angina and IR often occurred in the absence of obesity but researchers nonetheless observed striking overlaps between Reaven's Syndrome X and Cardiac Syndrome X and increasingly began to view them as variations on a similar theme [112-117]. It was on this basis that the term Metabolic Syndrome gained currency so as to distinguish it from the cardiac entity.

Microvascular dysfunction is not limited to the heart but, rather, is a body-wide phenomenon. Multiple organs, including brain, kidneys, liver, muscle and more are involved [118-121]. Many with coronary microvascular dysfunction have abnormal brain perfusion and are at higher risk for neurologic problems like stroke and dementia. Consistent with its systemic nature, coronary flow abnormalities can be estimated by evaluating arterial pulsations in other vascular territories like the retinal arteries [122, 123]. Microvascular dysfunction forms the common etiological basis of diabetes, hypertension, and obesity [124-133].

The common denominator tying microvascular dysfunction into all components of MetS is inflammation. Impaired microvascular function results in diminished energy generation and mitochondrial dysfunction in endothelial cells triggering inflammation [134-136]. Scientists have spent the past half-century trying to explain inflammation on a cellular and molecular basis with little success. Inflammation is prima facie evidence of a blood-borne energy deficiency: oxidative stress in endothelial cells induces pro-inflammatory cytokine release triggering an immune response and the so-called cytokine storm. Such events are not restricted to the endothelium. Whether involving heart muscle cells, renal tubular cells, or brain neurons, microvascular dysfunction sets into motion a spiral of chronic low-grade inflammation.

It is thus not coincidental that intimate associations exist between inflammation, obesity, hypertension, IR, hyperinsulinemia, hyperglycemia, and hyperlipidemia [137-148]. Each is secondary to mitochondrial dysfunction and defective intracellular energy generation [149-167]. And herein lies the physiologic basis of IR.

Under normal conditions, when insulin is secreted into the blood by pancreatic β-cells it induces cellular uptake of glucose and, as a result, blood sugar levels decrease. In hypertensive and/or obese individuals with microvascular dysfunction, inflammation, and mitochondrial abnormalities, glucose metabolism is blunted and cellular uptake of glucose impaired [168-178]. As Reaven pointed out, even among subjects with normal glucose tolerance, sensitivity to the actions of insulin may vary by up to threefold and the reason why blood sugar levels remain normal in these people, and even in cases of severe insulin resistance, lies in the ability of β-cells to increase insulin secretion [179-186]. This forms the basis of hyperinsulinemia. But as the adaptive capacity of the pancreas diminishes blood glucose levels gradually rise and at some point an individual develops non-insulin dependent diabetes.

A similar though somewhat different mechanism mediates the relationship between IR and hyperlipidemia. When insulin is secreted into the

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blood it acts to inhibit the breakdown of fat and the release of fatty acids by adipose tissue into the blood, i.e., lipolysis. In individuals with IR, the ability of insulin to suppress lipolysis diminishes and thus fatty acid levels remain elevated or increase [187-191]. To compound the problem, as hyperlipidemia persists it antagonizes the actions of insulin and further worsens IR [192-195]. In any event IR is the culprit behind both hyperglycemia and hyperlipidemia and as it progresses so too do both of these conditions. Similar factors play into the development and perpetuation of hypertension.

Microvascular dysfunction and reduced energy flow into the kidneys induces oxidative stress and inflammation which leads to activation of the renin-angiotensin system by the adrenal glands and hypertension. The response is aimed at enhancing energy generation by the heart and its availability to the kidneys. When this response is insufficient then arterial blood pressure remains elevated and chronic hypertension ensues [196-207].

Hypertension initiates a self-amplifying, bidirectional spiral of deterioration: It worsens microvascular dysfunction which augments endothelial inflammation and reduces energy flow into the kidneys even further. Hypertension-induced microvascular dysfunction, in turn, leads to worsening of IR with resultant exacerbation of hyperglycemia and hyperlipidemia. All pathways lead back to deficient energy generation in the zero-sum dynamic of MetS.

SYSTEMIC ENERGY DEFICIT

Originally Reaven argued for an association between the cluster of metabolic abnormalities and coronary artery disease but later expanded the pathologic nexus to include clotting disturbances, kidney disease and various cancers. And the list just kept growing. In recent decades at least three widely prevalent entities, nonalcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome (PCOS) and depression have been connected to MetS each of which implicates an ever-widening spiral of systemic disturbances involving the immune system, gut, endocrine axis, and circadian system.

Over a course of decades, the prevalence of NAFLD exploded in parallel with MetS: by 2020 it affected ~30% of the global population with rates in certain regions like the Middle East over 40% [208-211]. NAFLD is now the most common chronic liver condition globally and a leading indication for liver transplantation. NAFLD composes a spectrum ranging from accumulation of fat in hepatocytes to progressive fibrosis, cirrhosis and liver failure [212-217]. Underlying dynamic causes are microvascular dysfunction [218-230], IR [231-239], mitochondrial dysfunction [240-247] and inflammation [248-256].

In NAFLD deterioration of liver function unfolds sequentially permitting one to observe the relative contributions of the different components. The earliest sign, intracellular fat accumulation, primarily reflects diastolic dysfunction, decreased energy generation and IR. It is generally accepted that hyperinsulinemia induces fat accumulation in liver cells [257-260]. A significant portion of people, up to 20-30%, develop NAFLD in the absence of obesity [261-264]. While lean individuals tend to have milder expression of the syndrome compared to obese they are still at heightened risk for progressive deterioration of liver function and cardiovascular events [265-268] **(Figure 1).**

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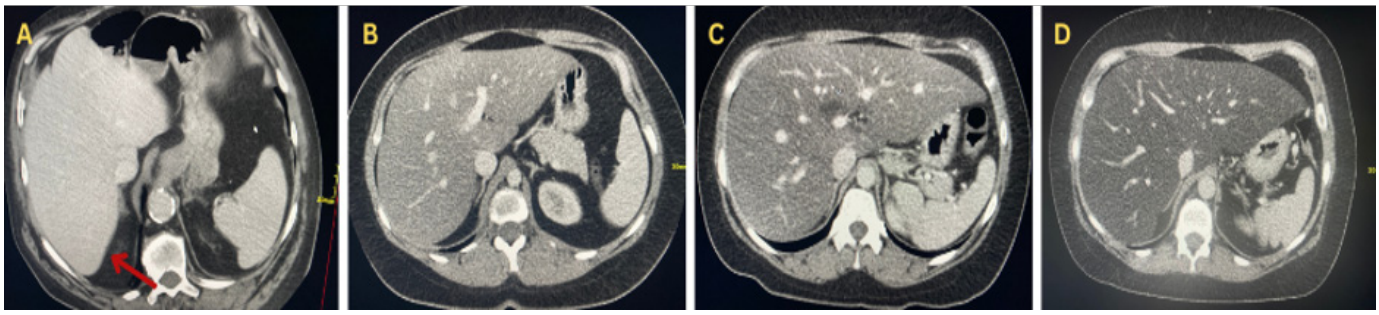

Figure 1. NAFLD: Far left image (A) shows normal density liver (red arrow). Observe that normal liver & spleen are relatively isodense and that as we move from left to right (B→C→D) and the fat content of the liver increases, it becomes progressively darker compared to the spleen.

As this state persists individuals, both lean and obese, progress into a second phase, nonalcoholic steatohepatitis (NASH), the result of a widening arc of inflammation, release of proinflammatory cytokines, immune cell activation and, ultimately, cell death; such events, in turn, trigger deposition of fibrous tissue in the liver and transformation into cirrhosis [269-271]. About 25% of people with NAFLD progress to NASH and 7-8% develop advanced fibrosis [272-275]. Like NAFLD, NASH is usually clinically silent; unlike NAFLD which can be detected by ultrasound or CT, NASH often requires biopsy for diagnosis.

Increased fat synthesis by hepatocytes compounds the energy deficit and further disrupts cell metabolism. With prolonged mitochondrial dysfunction and oxidative stress, cellular processes go awry: impaired lysosomal function produces deterioration of autophagy and protein homeostasis; accumulation of reactive oxygen species and acidification of the cytoplasm, in turn, induce structural damage and formation of toxic lipid by-products [276-279]. Ultimately cells enter the death spiral leading to mass programmed cell death, i.e. apoptosis. The priming event seems to involve NLRP3 inflammasome formation, i.e., coalescence of cytoplasmic structures into larger amorphous complexes, likely related to protein misfolding, which induce pro-inflammatory cytokines and immune cell activation triggering the cytokine storm [280-283].

Dysfunctional immune signaling induces apoptosis of necrotic hepatocytes with spillage of toxic lipid contents into the extracellular fluid space causing periportal inflammation, phlebitis and cholangitis [284-295]. Chronic inflammation and cell death induce collagen deposition leading to progressive fibrosis [296-306]. Obliteration of small and medium-sized venules increases portal venous pressure with restriction of flow into the liver [307-312]. Events leading from NASH to cirrhosis are now set in motion **(Figure 2)**. These very conditions, with or without cirrhosis, increase the risk for hepatocellular carcinoma [313-316].

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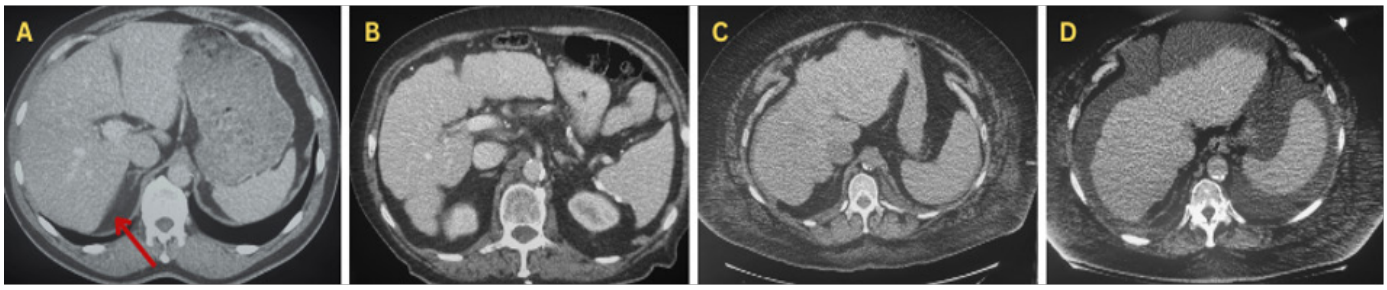

Figure 2. Image A depicts normal liver. As hepatocellular inflammation persists the liver becomes progressively more fibrotic, nodular and contracted ((B→C→D). With advanced cirrhosis portal venous hypertension leads to accumulation of intra-abdominal ascites (image D) surrounding the liver & spleen.

Deterioration of liver function is further amplified by processes in the bowel. Gut dysbiosis aggravates liver inflammation. Reduced bacterial diversity with proliferation of pathogenic species trigger immune dysfunction resulting in chronic low grade inflammation of the gut lining [317-326]. This, in turn, leads to increased permeability, aka 'leaky gut' syndrome, with upward passage of bacteria and endotoxins into the liver [327-330]. Elevated portal venous pressure and stasis enhance the pro-inflammatory milieu throughout the entire vascular compartment [331-333].

Recent reports document a similar spiral of deterioration involving the pancreas. In response to metabolic demands incurred by IR the pancreas undergoes an initial phase of hypertrophy and cellular hyperplasia but, due to the energy deficit, atrophies and becomes replaced with fat **(Figure 3).** Called nonalcoholic fatty pancreatic disease, it is associated with deterioration of pancreatic function, worsening of IR, increased tendency for pancreatitis, and heightened risk for pancreatic carcinoma [334-341].

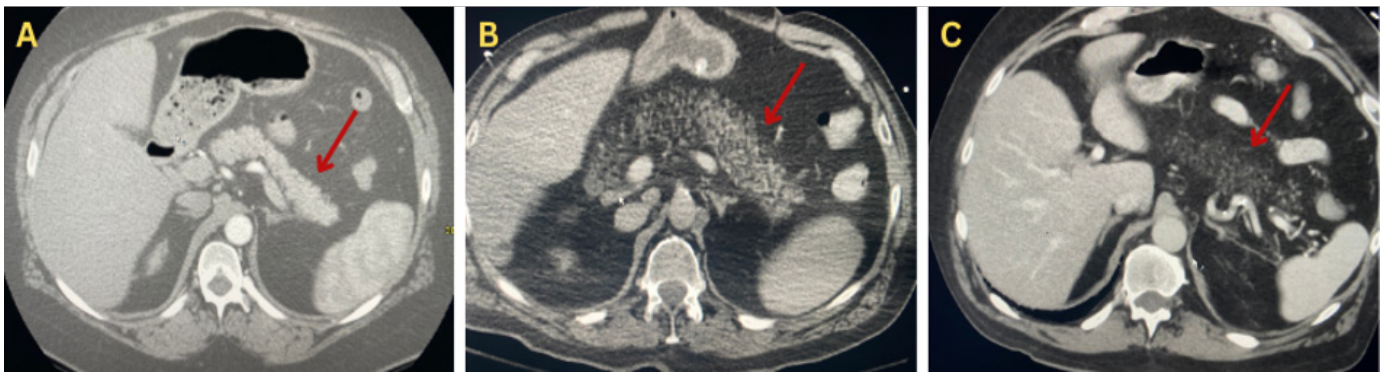

Figure 3. Far left image (A) depicts normal density pancreas (red arrow). With fat accumulation (images B & C) pancreas becomes progressively darker eventually blending in with the surrounding visceral fat.

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While researchers continued to debate the existence of MetS another ominous statistical association emerged that would take them down yet another rabbit hole. PCOS was described by Stein and Leventhal in the 1930s but there was little appreciation of its systemic nature until it had become too common to ignore [342]. Despite publication of diagnostic criteria in recent decades researchers continue to quibble over definitional issues [343-349]. If NAFLD is the hepatic manifestation MetS then PCOS is its ovarian equivalent.

PCOS, affecting 7-21% of women of reproductive age [350-353], is characterized by irregular often anovulatory menstrual cycles and infertility rates as high as 70-80% [354, 355]. 'Polycystic' refers to the defining pathophysiologic feature, accumulation of small cysts in the periphery of the ovaries, due to impaired maturation of ovarian follicles, resulting in the characteristic 'string of pearls' appearance on ultrasound scans **(Figures 4 & 5).** Widely regarded as an endocrine disorder, and presenting with elevated blood testosterone levels, affected women may also develop acne, hirsutism and male-pattern hair loss [356-358]. Despite exhaustive lab analysis and genome-wide association studies researchers remain uncertain as to its origins. It is generally believed to be secondary to genetic, environmental and/or behavioral influences which amounts to saying anything and everything [359-361].

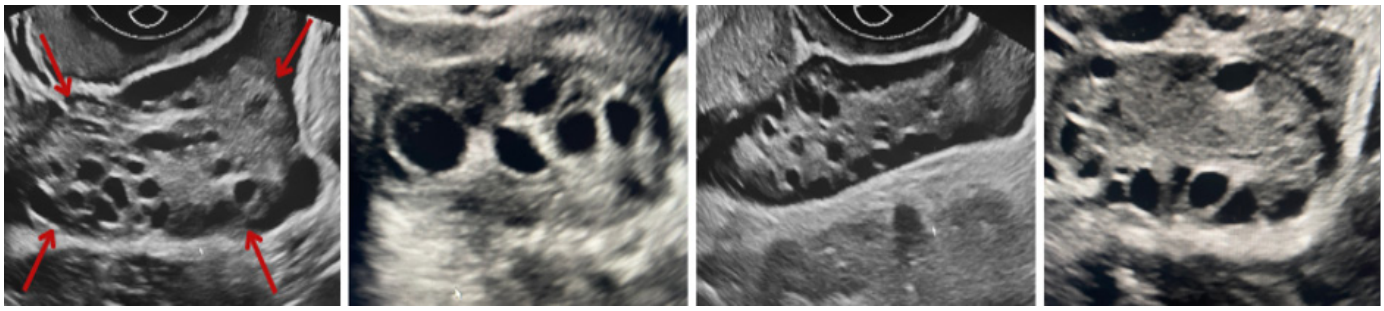

Figure 4. Ultrasound images of polycystic ovaries. Cysts appear as rounded black structures in the peripheral zone of the ovaries.

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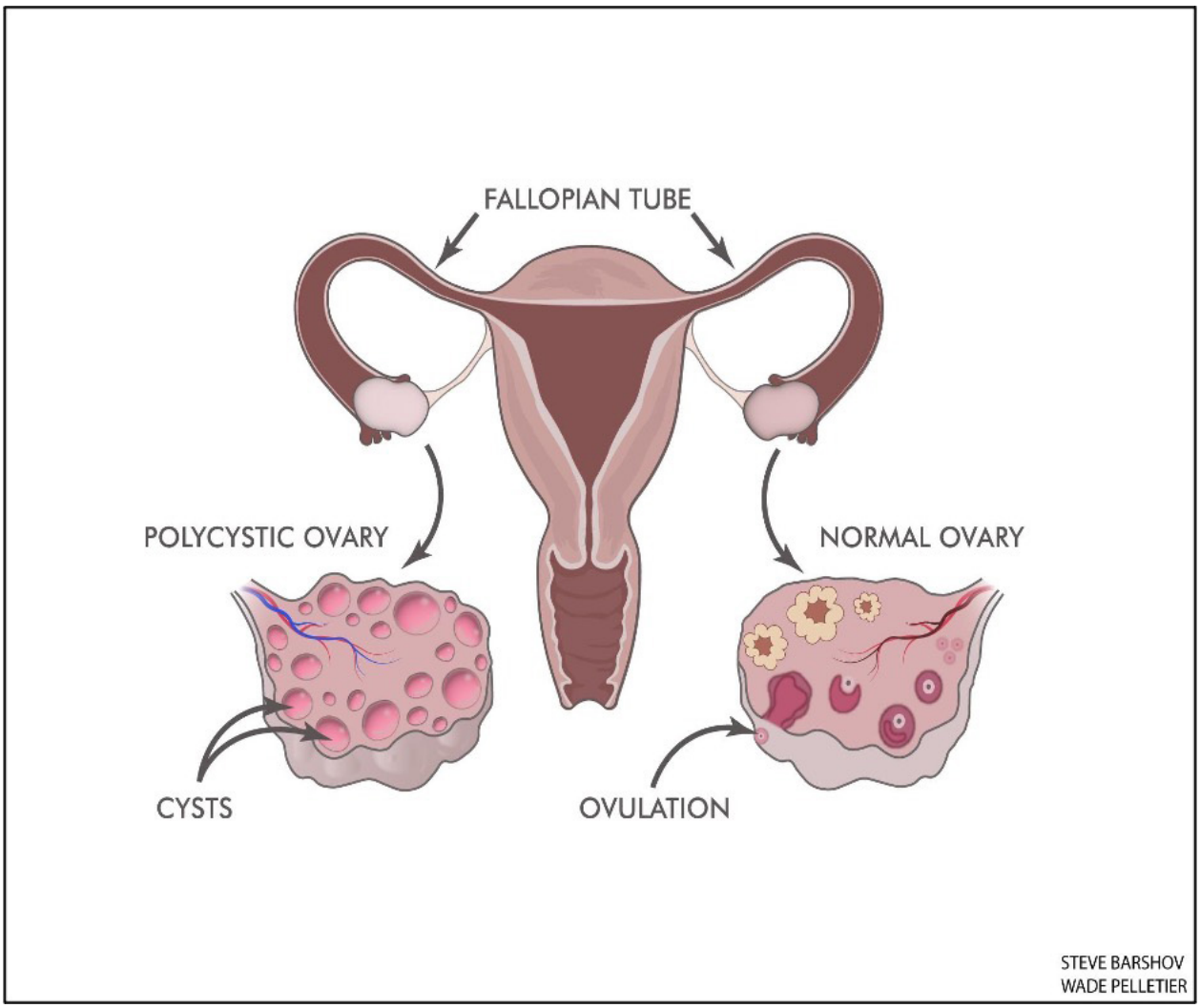

Figure 5. Image depicts interruption of normal follicular maturation in polycystic ovaries which leads to failure of ovulation and infertility.

Approximately 40-50% of women with PCOS have MetS [362-366]. About 40-70% have NAFLD [367-378]; 50-80% are overweight or obese [379-383]. Similarities don't end there. PCOS is associated with endothelial dysfunction [384-394], IR [395-400], mitochondrial dysfunction [401-406], inflammation [407-412], elevated proinflammatory cytokines [413-417] and pathogenic immune system activation [418-421]. Women are often hyperlipidemic [422-425] and at heightened risk for type II diabetes and heart disease [426-430]. As with NAFLD a significant number of affected women are lean [431-433]. Menstrual irregularities and infertility are energetic in origin.

Restricted blood energy generation along with cellular mitochondrial dysfunction adversely impact the ovaries. Theca and granulosa cells in ovarian follicles produce estrogen and progesterone which are necessary for proper follicular maturation [434-441]. During the synthesis process testosterone is converted to estrogen by the enzyme aromatase, part of the cytochrome p450 system, which is an energy-dependent step. The failure to convert testosterone to estrogen leads to its pathologic accumulation [442-444]. Elevated blood testosterone levels, as indicated, are a defining biochemical feature in women with PCOS [445-449].

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The most dire consequences of PCOS lie in the future. Many young women with PCOS appear to have been 'programmed' in utero by the hyperandrogenic milieu of their mothers [450-457]. Clinical evidence suggests that developmental exposure to high concentrations of testosterone 'androgenize' female offspring leading to subsequent expression of not just PCOS but other components of MetS [458-462]. If this proves true then the effects of industrialization and western lifestyle will be likely play out over multiple generations. In rapidly westernizing countries like China the prevalence of PCOS has increased nearly 65% in the last decade alone [463].

If there are lingering doubts as to the systemic nature of MetS or its energetic basis, its link with depression should quell skeptics. Traditionally regarded as a purely affective disorder, characterized by negative mood states like sadness, irritability, apathy, hopelessness or loss of self-esteem, individuals experience a range of functional disturbances such as low energy, fatigue, inability to concentrate, sleep disturbances, or changes in appetite. In recent decades depression has been tied into a wide range of pathologic bodily states as well [464].

According to WHO data, about 5% of the global population is affected by depression [465]. In the US over 36% of women and 20% of men have been diagnosed with depression at some point in their lives which, according to a recent Gallup Poll, is at an all-time high [466]. While depression affects all age groups, young and middle-aged adults have the highest rates; women are affected by about a 2:1 margin; depression is more common among minority groups [467]. About 30-40% of depressed people have moderate to severe symptoms. Its connection with MetS is grim.

MetS and depression have a bidirectional relationship: people with MetS are more likely to become depressed; individuals with depression are more prone to develop MetS regardless of age, gender, socioeconomic status, or lifestyle [468-474]. Studies consistently link depression with waist circumference, abdominal obesity, IR, dyslipidemia, hyperglycemia and hypertension [475-489]. As the number of MetS components increases so too does the severity of depressive symptoms. By the same token depression is more common among individuals with NAFLD and PCOS whether lean or obese [490-500]. Depression predisposes to diabetes [501-506]. People with major depression have a 4-fold higher risk for early death, mainly from cardiovascular causes [507-512].

As with the other dysmetabolic states, impaired energy generation and systemic inflammation are primary aspects of depression [513-516]. Depression and microvascular dysfunction go hand-in-hand [517-526]. Abnormal arterial waveforms are present in the retinal arteries of depressed individuals [527]. Many researchers regard mitochondrial dysfunction as a hallmark of depression [528-536]. Underscoring its systemic nature, mitochondrial dysfunction has been found in skin cells of depressed persons [537]. Depression is associated with elevated proinflammatory cytokines [538-541] and NLRP3 inflammasome formation [542-545]. Cytokine levels have been reported to normalize following recovery from depression [546]. One might thus regard the negative affective state of depression as a direct correlate of the systemic energy deficit. So how do scientists explain the origins of MetS?

Given that MetS has been associated with a rash of hormonal abnormalities some claim it is an endocrine disorder [547, 548]. Disturbances fall into three broad categories: Activation of catabolic pathways through the hypothalamic-pituitary-adrenal (HPA) axis with heightened sympathetic nervous activity and cortisol secretion [549-563]; resistance to and/or deficient production of anabolic hormones like insulin, growth hormone and estrogen [564-579]; and, as we will see shortly, resistance to the actions

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of thyroid hormone and its impaired ability to stimulate thermogenesis [580-584].

The hormonal causal thesis is supported by striking similarity between MetS and two classic endocrine disorders: Cushing's syndrome and MetS share multiple clinical features, i.e., abdominal obesity, hypertension, IR, predisposition to heart disease and diabetes; the overlap is so complete as to suggest they are one and the same disorder [585-596]. Similarly, hypothyroidism, characterized by weight gain, hypertension, impaired glucose metabolism, hyperlipidemia, NAFLD, and increased predisposition to heart disease and diabetes, seems to be little more than an alternate pathway into the same pathologic nexus [597-612].

Still others regard MetS as a result of disordered regulation of the 'biological clock' [613-616]. The circadian clock, said to be located in the hypothalamus, has long been recognized to play an important role in a host of physiologic processes like the sleep-wake cycle, body temperature regulation, energy expenditure, organ function, hormonal release, gene expression and more [617-626]. Circadian rhythmic disturbances are well recognized in chronic conditions like diabetes and heart disease [627-631] as well as MetS [632-637].

The biological clock hypothesis, proponents argue, also explains how various components of the modern lifestyle such as excessive artificial light exposure, controlled ambient temperature, shiftwork, frequent travel across multiple time zones – all of which have been shown to play into the genesis of chronic disease – assert their effects. Based on such considerations, some claim that disruption of the circadian system plays a major role in the genesis of MetS and, moreover, propose that it be renamed the 'Circadian Syndrome' [638, 639]. They argue that proper timing of the sleep-wake cycle and work schedules, adequate exercise, healthy food consumption, and alleviation of social stress must necessarily form the cornerstone of any and all attempts to halt the global epidemic of MetS. While this is undoubtedly true, it does not in any way imply that the circadian system plays a causal role in the development of MetS.

Neither the hormonal nor circadian hypotheses alone or in combination explain either hypertension, IR, hyperinsulinemia, hyperglycemia or hyperlipidemia, and certainly not mitochondrial dysfunction or inflammation. The only satisfying explanation for all the abnormalities associated with MetS, including NAFLD, PCOS and depression, is microvascular dysfunction and impaired energy generation by the cardiovascular system. The hormonal and circadian disturbances are simply further testimony for the all-encompassing systemic nexus of dysfunction.

The notion of a blood-borne energy field is neither new nor original. It was first articulated around 200 AD by Roman physician Galen, the most important medical synthesizer of the ancient world [640]. His humoral system of medicine – the central tenet being that the blood is the source of all bodily functions – was accepted by physicians for over 1500 years until it was arbitrarily discarded by early scientists without refutation. With recognition of the primary role of the blood-borne energy field in the genesis of MetS, medical thought now comes full circle. By the same token, it points to the abject failure of three centuries of speculative medical theorizing and the facilitative role played by 20th century science in the escalating global epidemic of chronic disease.

THE FAT PROBLEM

We have established the energetic basis of MetS as well as associated pathologic states like NAFLD, PCOS and depression, each of which has as its basis the core triad of microvascular dysfunction, impaired mitochondrial energy metabolism and inflammation. These three primary disturbances are present in any and all of the various permutations of

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MetS regardless of which clinical presentation may develop or dominate. In general, the more limited the number of components present in any given individual the more favorable the outcome; as that number increases the situation tends to deteriorate as one would expect.

The same pattern is seen in the overweight/obesity spectrum. For simplicity we use the term obesity bearing in mind that its relation to MetS is variable and poorly defined. Based on body mass index (BMI), with 'normal' being 18.5-22.9 kg/m^2, 'overweight' 23-24.9 kg/m^2, 'pre-obese' 25-29.9 kg/m^2, and 'obese' greater than 30 kg/m^2, one study found a progressive increase in the prevalence of MetS: 29.6%, 38.9%, 56.9% and 62.4% [641]. This is to say that up to 30% of so-called 'normal' weight individuals may have MetS while, conversely, 38% of obese individuals would appear to be unaffected. Obesity thus represents one aspect of MetS but not a defining feature. Once again this points to the primacy of the energy deficit.

Along this vein researchers identify a subset in the obesity spectrum they call 'metabolically healthy' obesity in which individuals remain sensitive to the actions of insulin and have relatively normal inflammatory markers [642-645]. Thus, we can speak only in general terms as to what happens when any particular individual happens to gain excessive weight and enter the spectrum. We thus focus upon those aspects of weight gain and obesity associated with MetS. While some of these are unique to fat tissue, the underlying metabolic disturbances are identical to those seen in all other organs.

There has been a seismic shift in how fat is conceived. Once regarded as a passive storage site for excess energy intake, it is now understood to be highly dynamic and adaptable, ranging from as little as 2% to over 70% of body weight, involved not just with energy storage but active heat production. Its functions are intimately entwined with those of the vascular, endocrine, and immune systems [646, 647].

Two primary forms of fat are recognized: white adipose tissue (WAT), serving the classic energy storage role; and brown adipose tissue (BAT), which functions to enhance energy dynamics through the release of heat, aka thermogenesis. Energy, stored in WAT as fatty acids, is released 'on demand' into the vascular compartment mainly under the influence of endocrine mediators. BAT, on the other hand, highly vascularized and laden with mitochondria, releases heat pulses promoting vasodilation and various cell functions primarily under the aegis of the sympathetic nervous system.

WAT, distributed throughout the body, localizes primarily in the tissues beneath the skin, i.e., subcutaneous fat, or in the abdomen surrounding internal organs, i.e., visceral fat [648, 649]. In lean, healthy people fat is confined mainly to these depots. In obesity, on the other hand, the fat mass expands and accumulates in regions such as mesentery, omentum, retroperitoneum, and pericardium **(Figure 6).** Along with fat mass expansion one observes progression of microvascular dysfunction and IR which [650-657], in turn, promote hyperlipidemia by release of fatty acids into the blood [658-662]. Increased visceral fat in particular predisposes to development of MetS [663-669]. NAFLD obviously represents part of the spectrum of pathologic fat accumulation [670].

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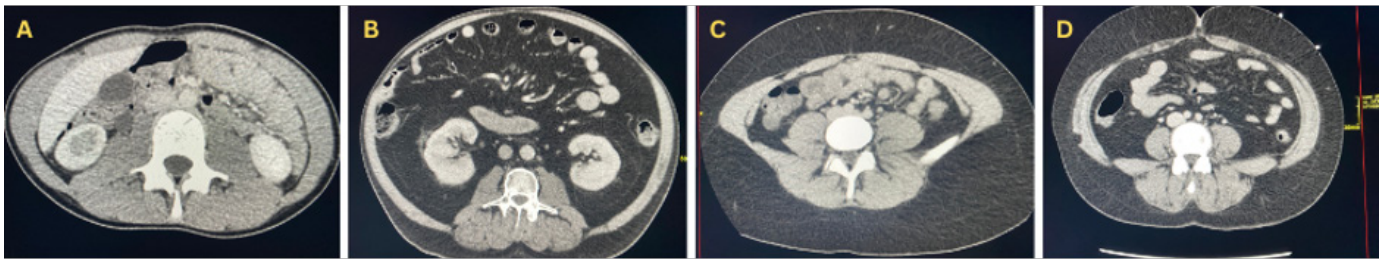

Figure 6. Axial CT images through mid-abdomen displaying variations in extraabdominal-subcutaneous and intraabdominal-visceral fat distribution. Image A = lean state; Image B = visceral fat dominance; Image C = subcutaneous accumulation; Image D = accumulation in both compartments.

Fat mass expands in two ways: In younger people it occurs mainly by formation of new fat cells, aka hyperplastic obesity, while in adults, rather than undergoing mitosis, adipose cells enlarge, aka hypertrophic obesity. This second mechanism is particularly disposed toward development of MetS [671-675]. Adipose cell size, independent of BMI, is directly related to IR [676-678]. The reason for this is related to dynamics between adipose tissue and the vascular system

Fat is highly vascularized to ensure not only sufficient delivery of oxygen/energy and nutrients but for release of fatty acids into the blood. Expansion of fat mass is tightly linked to the vascular system [679-682]. During this process adipocytes release vascular endothelial growth factor (VEGF) which triggers new blood vessel growth, aka angiogenesis [683, 684]. Impairment of angiogenesis plays a key role in the development of pathologic forms of obesity [685, 686]. Both vascular and adipose tissue, moreover, are mesodermal in origin and the vasculature serves as a source of multipotent progenitor cells that give rise to new adipocytes [687, 688]. Reduction of stem cell influx into fat deposits explains the differences between hyperplastic and hypertrophic fat mass expansion.

Studies found that adipose tissue in obese subjects, as compared to lean, has markedly decreased capillary density, 44% in one study, and VEGF levels (58%), resulting in 'capillary drop out' [689]. Consistent with this, numerous studies found decreased oxygen tension, i.e., hypoxia, in adipose tissue of obese people [690-697]. So, in pathologic obesity not only is there decreased energy generation in the blood but decreased blood flow into fat. This explains the origins of mitochondrial dysfunction, IR, and inflammation in pathologic obese states [698, 699]. It also explains why adipocyte size and not total fat mass is the crucial factor in the evolution of MetS [700]. Once this chronic energy-deficient state is set into motion a host of systemic endocrine, vascular, and immune interactions ensue.

In recent years increased attention has been focused on the endocrine aspects of adipose tissue [701, 702]. Fat releases hormonal substances that directly influence the vascular system, blood, and CNS. Leptin has a broad range of actions including regulation of appetite as well as energy expenditure. Leptin resistance is frequent in obesity [703-707]. Another hormone, adiponectin, through its effects on glucose and fatty acid metabolism, has anti-inflammatory properties in addition to improving insulin sensitivity [708-712]. While its plasma concentration is decreased in people with visceral obesity, its levels remain high in individuals with metabolically healthy obesity [713]. Clearly adiponectin influences energy disposition in the blood and cellular levels. Once the effects of these two fat-generated hormones become blunted,

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fat cells increasingly release pro-inflammatory mediators [714-722].

It has long been recognized that the vascular endothelium secretes substances that regulate fat metabolism but adipose tissue also directly influences blood vessels [723-730]. Most blood vessels are surrounded by 'perivascular adipose tissue' (PVAT), composed of both WAT and BAT, which secretes biologically active substances that regulate blood flow. In healthy states PVAT releases so-called 'relaxant' substances, including adiponectin, that enhance vascular dilation. In pathologic obesity, conversely, PVAT aggravates microvascular dysfunction with secretion of constrictor substances not dissimilar to the kidneys in hypertension through activation of the renin-angiotensin system. The end result in either case is to amplify the spiral of deterioration.

Hypoxia and reduced energy flow into fat cells induce mitochondrial dysfunction, oxidative stress, and inflammation with subsequent release of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6 and IL-18 [731-736]. Cellular distress signals, in turn, elicit migration of polarized macrophages into affected tissues which themselves exhibit mitochondrial dysfunction [737-744]. This results in worsening of the energy deficit with activation of the NLRP3 inflammation and cell death [745-748]. Necrotic fat cell death is up to 30-fold higher in obese versus non-obese individuals [749-751].

No pharmacologic agents meaningfully impact the development and evolution of MetS. Some like SGLT2 inhibitors reduce blood sugar levels, induce weight loss, and improve insulin sensitivity, but do not address the fundamental energy equation. Barring unforeseen and highly improbable therapeutic developments the only viable approach remains far-reaching lifestyle alterations.

Many studies document improvement in all parameters of MetS – microvascular dysfunction, mitochondrial impairment, insulin resistance, and inflammation – with dietary modification and weight loss [752-758] as well as exercise [759-768]. Short of such interventions the long-term prospect of curbing the global proliferation of MetS is bleak: multiple studies confirm direct transmission of the blood-borne energy defect from mother to offspring [769-777].

THERMOGENESIS & BAT

Understanding energy metabolism is one of the great challenges medical sciences has faced. One of the most perplexing issues concerns thermogenesis. Scientists have identified a handful of processes that contribute to the generation of body heat [778-780]. The first, basal metabolic rate (BMR), is said to account for about 60-70% of heat production. BMR, measured in caloric equivalents, is the amount of energy needed for organs and tissues to function. Another source, diet, accounts for about 5-15% of heat release; physical activity, primarily the work of muscles, amounts to 20-30%. Yet another, so-called adaptive thermogenesis, the generation and release of thermal energy, is said to produce about 10-15% of body heat. But such rote metrics obscure a towering edifice of confusion as to the exact role of heat in the energy economy of the body.

Scientists originally believed that heat was released by exothermic chemical reactions in the body. But when they compared predicted values to what was actually generated the numbers didn't quite add up: the heat produced virtually always exceeded predictions. Thermogenesis signals that the body is increasing energy production. It occurs throughout the day as pulses of heat related to physical activity. It also happens when individuals are exposed to the cold in order to offset heat lost to the outer environment [781]. Thermogenesis occurs during intense emotional states: the blushing of the cheeks

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and feelings of warmth during states of shame or anger are prime examples [782].

In the early 20th century scientists discovered increased heat release following meals [783-787]. Such 'diet-induced thermogenesis', during which the metabolic rate often increased by 10-20%, was originally thought to occur as a result of digestion and assimilation of nutrients; but once again when scientists calculated the caloric equivalents consumed the actual amount of heat produced was greater than expected, often by as much as 40-50%.

Thermogenesis varies widely even among healthy individuals. Some remain lean while consuming large amounts of food while others stay thin only by restricting caloric intake. Various studies found that when the two groups consume identical meals the high energy intake group has significantly increased thermogenesis, often twofold more, than the other [788-791]. Early 20th century scientists advanced the notion of 'luxuskonsumption', that the body adapts to overfeeding by activating energetically wasteful mechanisms to dispose of excess energy as heat [792, 793]. But this doesn't make sense. Rather than dissipating excess nutritional intake as heat the opposite seems to be the case: thermogenesis is necessary for processing of food materials.

The relation between obesity and thermogenesis is a case in point. During exercise, following a meal, or upon exposure to cold, obese individuals have diminished capacity to generate body heat, a so-called 'thermogenic defect', which is present at the onset of obesity and worsens as it progresses [794-814]. During cold exposure body temperature actually decreases in some obese people [815-817]. Impaired thermogenesis also explains why many who lose weight subsequently regain it. After diet and weight loss the thermogenic defect persists and, in some, actually worsens [818-823]. In many diabetics' thermogenesis disappears altogether [824-826]. Impaired thermogenesis would thus appear to be a cause rather than an effect of obesity. And as with MetS it appears to pass generationally from parent to offspring [827, 828].

Impaired thermogenesis is directly linked to IR and mitochondrial dysfunction [829-835]. In studies designed to measure the degree of glucose-induced thermogenesis, heat production deteriorated progressively in obese individuals as IR increased, with lowest levels in those with non-insulin-dependent diabetes [836-838]. In another study the thermic effect of food was blunted in obese versus lean individuals and, in each of these groups, lower in more insulin-resistant subjects [839]. Not surprisingly thermogenesis remains intact in metabolically healthy obesity [840]. Blunted thermogenesis has been reported in both NAFLD and PCOS [841-846]. We are thus drawn to conclude that defective thermogenesis is an integral aspect of MetS with the degree of impairment bearing inverse relation to microvascular dysfunction and systemic inflammation.

For decades it had been recognized that BAT played a key role in thermogenesis in hibernating animals and human infants but it was widely believed that BAT was absent in adult humans [847-852]. A 2007 study using PET imaging in adults found enhanced metabolic activity in fat depots confirming the presence of BAT [853]. Representing 1-2% of total body fat, it is found in the neck, axillary, mediastinal and paravertebral regions. BAT, a significant source of adaptive thermogenesis in humans, is also present in perivascular adipose tissue and invests large central arteries like the aorta.

The most potent stimulus for BAT thermogenesis is cold exposure. BAT likely evolved for this purpose. It was initially believed that shivering was the main source of body heat during cold exposure but studies found that thermogenesis occurred before shivering and so the term 'non-shivering thermogenesis' came into use [854]. While WAT

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metabolic activity is induced mainly by blood-borne mediators, BAT thermogenesis, as noted earlier, is activated by the sympathetic nervous system [855-860]. Heat pulses, released into the extracellular fluid space, quickly appear in the vascular compartment producing alterations in the blood that mediate systemic effects.

Studies document that BAT thermogenesis is associated with a host of desirable effects including lowering of blood glucose and triglyceride levels, improved insulin sensitivity, reduction of inflammatory markers, modest weight loss and improvement in hepatic steatosis [861-879]. Studies found that higher BAT mass in individuals is associated with cardiometabolic health [880-883]. Other studies suggest that as obesity increases BAT mass and function inversely decline [884-887]. Along this line reports suggest that maternal high-fat diets and intrauterine exposure to hyperglycemia impair BAT formation in the fetus [888,889].

Densely vascularized and laden with mitochondria (which impart its brown color) BAT cells contain numerous small lipid droplets (versus the large unilocular fat globule found in WAT) which predisposes to rapid mobilization of fat stores and energy generation [890-898] **(Figure 7).** Studies indicate that BAT activity influences triglyceride clearance from the blood [899]. Pharmacological blockade of lipolysis in BAT cells impairs thermogenesis [900]. Thermogenesis takes place along the inner lining of the mitochondrial membrane with heat pulses generated by so-called 'uncoupling proteins' (UCPs) which, researchers claim, diverts energy intended for ATP production into heat release, ergo the term 'uncoupling' [901-909].

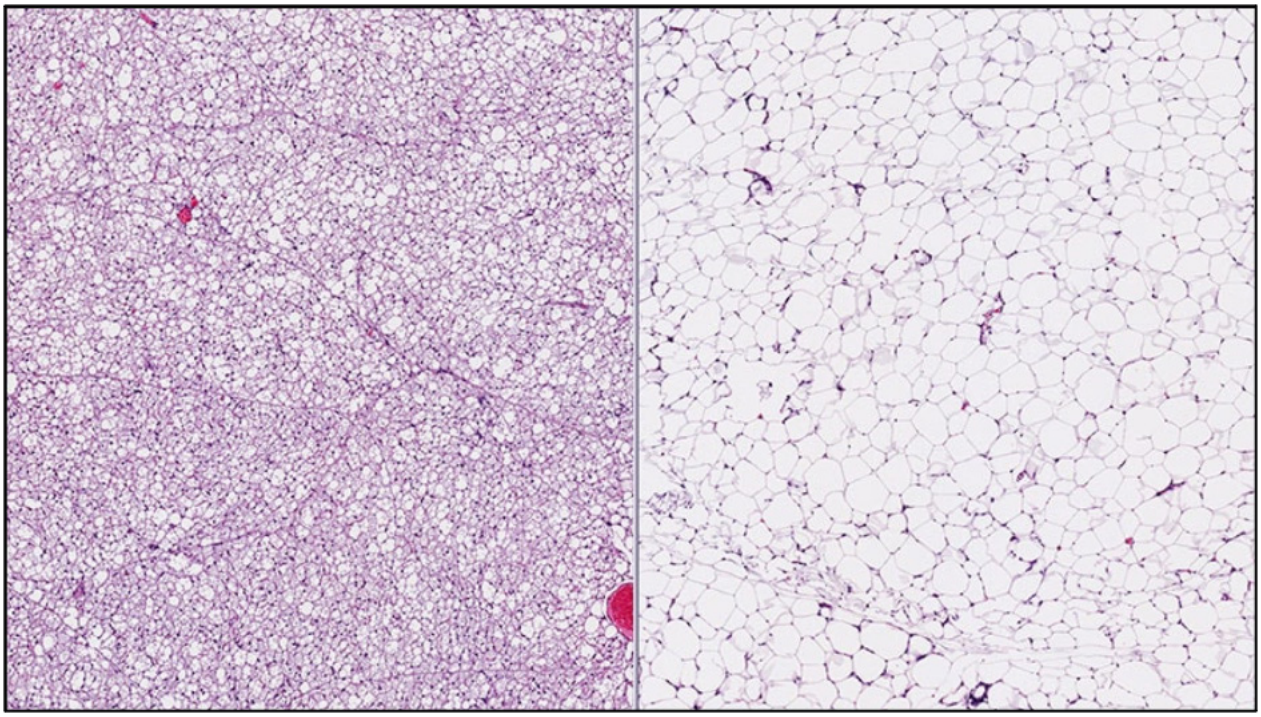

Figure 7. Histology sections of BAT (left) and WAT (right). Small multilocular fat droplets in BAT versus larger unilocular fat in WAT along with greater vascularization favor rapid mobilization of fat stores for thermogenesis. https://www.medscape.com/viewarticle/969659

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Studies find that even modest cold exposure (17°C/62°F) not only improves hyperglycemia and hyperlipidemia but induces changes in gene expression, BAT mass expansion and enhanced nonshivering thermogenesis [910-916]. One study reported that 4 weeks of daily cold exposure increased BAT volume by 45% and mitochondrial oxidative metabolism by over 180% [917]. PET studies indicate such improvements occur in conjunction with increased blood flow into BAT. This has led many researchers to suggest that BAT thermogenesis be employed to combat the obesity epidemic [918-925]. But closer inspection of evidence should temper such enthusiasm.

In an insightful December 2023 piece Carpentier and Blondin dispel the myth that BAT thermogenesis is sufficient to impact MetS outcomes. Based on its small volume the contribution of BAT to total body energy balance borders on negligible [926]. Likewise, BAT contributes less than 1% to clearance of glucose and fatty acids from the blood [927, 928]. In fact, BAT thermogenesis, on a *per unit basis*, is not impaired in obese versus lean subjects. Defective thermogenesis in obesity is related not to impaired lipid metabolism but to decreased total BAT mass [929, 930].

On this basis one must conclude that thermogenesis and IR are intertwined but distinct processes. Studies indicate that glucose uptake by BAT cells does not correlate with thermogenesis [931, 932]. Cold exposure and insulin assert their effects quite differently: Cold induces body-wide alterations in blood flow and sympathetic nerve activity; Insulin acts at the cell membrane [933, 934]. As IR progresses (and the passage of glucose into cells diminishes) the lipid content of BAT actually increases [935-937]. If BAT thermogenesis alone could improve MetS outcomes it would be equivalent to an over-unity energy generation device in which output is continually greater than input. Once again this points to the primacy of microvascular dysfunction and deficient blood energy generation in the origin and progression of obesity and MetS.

Even more problematic is that BAT is not the only tissue capable of inducing thermogenesis: PET studies indicate that the majority of fatty acids and glucose are taken up by muscle tissue which also contains uncoupling proteins and is the main source of body heat [938-951]. Such functional similarities are hardly coincidental given that fat and muscle share common mesodermal origins [952-955]. It would thus appear that BAT thermogenesis is but a subset in a wider nexus of thermogenic functions. To appreciate this we return to the heart and vascular system.

THYROID-HEART AXIS

In ancient biology the heart was conceived as a vital hearth and source of body heat. Aristotle claimed that 'innate heat' originated in the motions of the heart and gave rise to all bodily functions. Five hundred years later Galen agreed [956]. But thyroid function was shrouded in mystery.

Galen claimed the thyroid mediated interactions between the brain and heart but argued against any secretory function. The role of the thyroid and its relation to the heart began to emerge in the 1830s with Graves' descriptions of the hyperthyroid state and, later, isolation of thyroid hormone (TH) in the early 20th century [957]. The thyroid is now regarded as the master regulator of the metabolism with its effects mediated by the release of body heat. Yet after two centuries of focused investigation scientists remain uncertain as to how it all comes about.

Galen's claim that the thyroid serves as an intermediary between the heart and brain is not far off the mark: Innervated by sympathetic nerves, the synthesis and release of TH is induced by thyroid stimulating hormone (TSH) secreted by the pituitary

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gland. Based on relative quantities of TH in the blood and/or sensitivity of tissues to its effects, two nearly polar opposite metabolic states in the body ensue.

Once in the blood TH accelerates heart rate (HR). The motions of the heart, both contraction and dilation, quicken and become more powerful [958-963]. With more forceful dilation increased fluid is drawn into the veins from the extracellular fluid (ECF) space thereby expanding blood volume. Thermogenesis increases body temperature sometimes mimicking a low-grade fever. Hyperthyroidism was regarded by early physicians as a cardiac disorder. With chronically elevated TH levels individuals become hypermetabolic and may appear emaciated despite high caloric intake.

Hypothyroidism, as disparate from hyperthyroidism as winter from summer, is characterized by blunted thermogenesis, decreased body temperature and torpid metabolism [964, 965]. Symptoms include fatigue, drowsiness and cold sensitivity. Depression is not uncommon [966, 967]. Weight gain is frequent [968]. Loss of body heat and reduced metabolism have striking effects: coarse puffy features secondary to increased fluid in the ECF space; dry, scaly skin; hair loss; hoarse voice and sleep apnea due to thickening and swelling of the tongue; slowness of thought and memory functions.

The most striking changes involve the cardiovascular system [969-973]. Diminished HR, weakened systolic contraction, and restricted diastolic expansion. Ejection fraction may decrease by up to half. Loss of diastolic suction leads to retention of fluid in the ECF space with loss of intravascular volume which, in turn, leads to paradoxical hypertension due to constriction of peripheral arterioles. Individuals are more prone to heart failure.

But a puzzling discrepancy arises: Manifestations of hyperthyroidism like increased HR, tremor and anxiety mimic states of heightened sympathetic activity while those of hypothyroidism, lowered HR, somnolence and lethargy, suggest diminished sympathetic tone but, in fact, sympathetic activity is elevated in both states [974-979]. The contrasting clinical features must, in large part, be ascribed to alterations in body heat. But a more vexing question, which we address shortly, concerns the sympathetic nerves: What is their actual function in all of this?

The relation between thyroid dysfunction and the various expressions of MetS is seen vividly in subclinical hypothyroidism in which subjects have normal TH values but elevated TSH levels related to primary thyroid malfunction. Said to affect about 5% of people, it can be seen with iodine deficiency or in autoimmune disorders [980-982]. Subclinical hypothyroidism has been linked to all the various aspects of MetS: IR, higher BMI, waist circumference, elevated BP, hyperglycemia and hyperlipidemia, inflammation, NAFLD and PCOS [983-1002]. The incidence of MetS approaches 40-50% in people with elevated TSH levels [1003]. Thermogenesis normalizes when hypothyroidism is corrected [1004, 1005].

Subclinical hypothyroidism, a hypercoagulable state, is associated with a rash of adverse cardiovascular events such as heart attack, heart failure, atrial fibrillation as well as acute renal injury and stroke [1006-1027]. And once hospitalized for such maladies both 30-day and long-term outcomes are significantly worse than in those with normal thyroid profiles. On this basis impaired thyroid function must be regarded as yet another core component of MetS. So how does TH play into the body's energy economy?

The geneticist's retort would be that TH induces transcription of uncoupling proteins thereby enhancing thermogenesis but this ignores a vital priming step: TH stimulates heat release by the heart into the blood thus altering its energy state. Cardiac muscle is laden with mitochondria and uncoupling

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proteins [1028-1032]. Thermogenesis induces endothelial-dependent vasodilation [1033-1038] which enhances blood flow into tissues stimulating angiogenesis [1039-1043] as well as formation of new mitochondria [1044-1049]. An example is the 'browning' of WAT into so-called beige fat which, under the aegis of TH, becomes more vascularized and mitochondria-rich thereby altering its color and function [1050-1054]. Such cellular developments must be regarded as having dependent origination on the thyroid-heart axis and blood flow.

The centrality of this thermogenic nexus is apparent in neonatal hypothyroidism: Infants present with somnolence, diminished spontaneous movement, protracted jaundice, feeding difficulties, and delayed developmental milestones [1055-1057]. The face may appear edematous, tongue swollen and enlarged; impaired growth of skull bones leads to enlarged fontanels; reduced muscle development results in generalized hypotonia; there is an abundance of white fat [1058]. Studies indicate that fetal TH deficiency is associated with impaired thermogenesis along with decreased mitochondrial density in the CNS, muscle, liver, skeletal, and adipose tissues thus constituting a hypometabolic state [1059-1064].

Subclinical hypothyroidism in women during pregnancy is associated with adverse maternal and fetal outcomes [1065-1069]. Affected children are more prone to neurologic and endocrine abnormalities as well as obesity [1070-1073]. The inescapable conclusion is that TH and thermogenesis are essential for growth, development and maintenance of the metabolic field.

And while diet-induced weight loss in obesity neither reverses the thermogenic defect nor promotes browning of WAT [1074], regular exercise improves diastolic dysfunction [1075-1079]; enhances insulin sensitivity [1080-1085]; reduces inflammatory markers [1086-1091]; induces browning of WAT along with formation of mitochondria and synthesis of uncoupling proteins [1092-1102]; improves thermogenesis [1103-1111]; and, in conjunction with a balanced dietary regimen, induces weight loss [1112-1119]. The evidence is overwhelming and unambiguous: MetS and all its permutations are downstream manifestations of impaired energy generation and availability in the cardiovascular system and blood. The most consistent and reliable pathway to alter these pathologic dynamics is through the heart.

AFFAIRS OF THE HEART

The final issue with which we must grapple concerns experimental science and hinges on a single question: Given the sheer volume and compelling nature of the evidence, why didn't scientists recognize the obvious sooner? The question looms large once it is realized that the central role of the heart in the body's energy economy had been widely accepted among physicians for over 1500 years. Certainly, there was more than enough evidence in the medical literature to reach the same conclusion. So, what happened?

This lapse exposes a monumental flaw in scientific methodology that can only be ascribed to what science historian Thomas Kuhn called paradigm-induced blindness. A fundamental misinterpretation regarding the nature of cardiac function, introduced early in the 20th century, led to a series of conceptual errors that persist to this day and assured that subsequent discoveries pertaining to heart function would be misappropriated. It is worth briefly examining the trail of error:

Once the heart became conceived as a mechanical pump which propelled blood forward through the arteries on the basis of systolic contraction, and diastole became relegated to passive status, all subsequent events relating to heart function became subject to what could be called 'observer

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bias,' which is to say that while experimental facts were accurately recognized their significance was interpreted in light of this skewed notion of cardiac function **(Figure 8).**

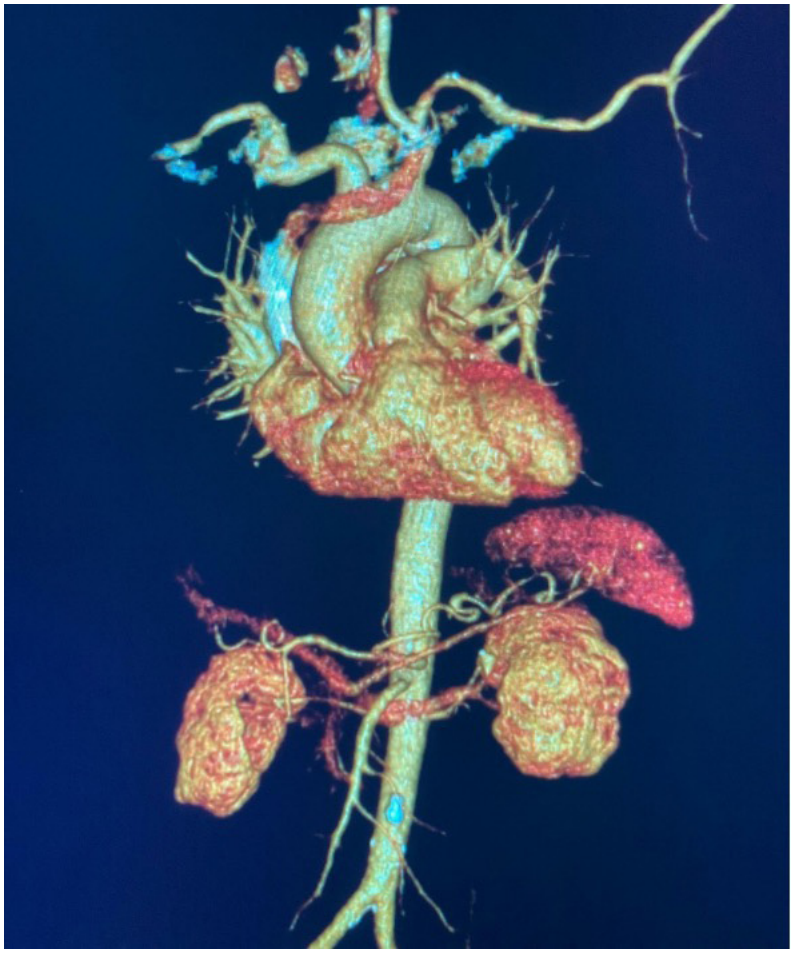

Figure 8. 3D reconstructed CT image of the heart a great vessels. Spleen (red) and kidneys (orange) take origin from the abdominal aorta.

The most glaring deficiency that ensued was the inability of scientists to explain how venous blood returned to the right side of the heart. The recognition by scientists in the early 1980s of a suctional force in the ventricles in early diastole settled the matter in short order [1120-1123]. Within years imaging studies reported spiral flow currents in arteries which can only arise on the basis of such a force [1124-1136]. Suction, in turn, is generated by an expansile force originating in the ventricular wall secondary to generation of a magnetic field.

An equally serious error involved the cardiac nerves: scientists claimed that they induced systolic contraction of the heart even though systole and diastole occur in the absence of nerves, what is known as cardiac automaticity. During cardiac transplantation, for example, surgeons sever the nerves from donor hearts and yet hearts continue to function in recipients. If nerves don't induce ventricular contraction what exactly is their function? This relates back to our earlier question regarding the sympathetic nerves.

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Concerning the origins of the magnetic field one need only examine the process of magnetic induction: An applied electrical current induces synchronous nuclear precession in iron atoms inducing a magnetic field which is repelled by intra-nuclear forces into the surrounding space. On the same basis flow of electrical currents through cardiac nerves during systole saturate the field thereby inducing nuclear precession in muscle iron stores and a 3D magnetic field that promotes active dilation of the ventricle. Diastole may be conceived as mutual repulsion of muscle fibers and, on the same basis, the cardiac cycle itself as alternating phases of attraction and repulsion.

Large heat pulses emitted by the heart were recognized early on by 20th century researchers but, once again, erroneously interpreted [1137]. Since it was assumed that the only purpose of heart muscle was contraction, heat release during diastole was regarded as energetically wasteful and due to inefficiencies in the conversion of glucose and fatty acids into useful work. On this basis scientists estimated the efficiency of the heart to be no more than 20-30% [1138-1141]. Yet even resting skeletal muscles release low quantities of heat, aka 'resting heat', which has been largely ignored by scientists [1142, 1143]. Mesodermal tissue, muscle and fat in particular, functions as part of an organized body-wide energy generating nexus we refer to as the metabolic field.

The discovery of uncoupling proteins led scientists down yet another rabbit hole. To explain the 'inefficiency' phenomenon, i.e., thermogenesis, scientists invoked the 'chemiosmotic hypothesis', advanced by Peter Mitchell in 1967, which held that phenomena like heat and voltage potentials are related to proton and ion fluxes across membranes based on gradient mechanisms [1144, 1145]. Mitchell was awarded the 1978 Nobel Prize for his grand theory. Unfortunately, within a few years it was shown to be wrong. Nonetheless scientists continue to pay homage to this golden calf purely due to the inertia of collective belief [1146-1151]. How does this relate to our concerns?

Mitchell's hypothesis assumed that protons and other ions exist inside cells in a free state but Gilbert Ling showed that all intracellular water and charged species exist in bound colloidal form [1152-1157]. There is no soupy broth inside cells; instead, they are gel-like in consistency. All intracellular proteins are surrounded by such colloidal water, known as the 'hydration layer', which is essential to their function [1158-1164]. It is axiomatic that all bodily functions – movement, secretion, nerve transmission, cellular replication – are effected by conformational changes in proteins (as in the contraction and dilation of the heart). As researcher Gerald Pollack asserts, proteins are 'the engines of life' [1165].

Ling's 'association-induction hypothesis' holds that cellular functions occur not via trans-membrane flux of charged species but on the basis of adsorption along the outer surface thereby inducing allosteric conformational changes in proteins. Other work supports Ling's hypothesis [1166-1172]. Bound cell water, in turn, freely communicates with energy-laden ECF water via ion and water channels at the cell membrane [1173-1177]. The inescapable conclusion is that current flow through sympathetic nerves into the ECF space stimulates thermogenesis via induced conformational changes in uncoupling proteins.

In recent years scientists have increasingly raised questions as to the source of BMR, now called ‘non-exercise activity thermogenesis (NEAT)’ [1178-1182]. If it doesn't originate from physical activity or cold-exposure, from where does it arise? Given that nerves themselves derive current flow from the ECF space it is not a giant conceptual leap back to recognition of the primacy of heart in the body's energy economy. One need only recall that once cardiac function ceases all bodily functions come to

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an immediate halt. This substantiates claims made by Aristotle and Galen concerning the centrality of the heart. What are the implications of this for MetS?

Had scientists recognized such relationships in a timely manner would they still be treating broad swaths of the population with lipid-lowering agents like statins knowing that hyperlipidemia is a direct consequence of impaired thermogenesis and reversible by diet and exercise? Would they continue to treat hypertension with β-blockers that blunt thermogenesis [1183, 1184], worsen IR [1185-1190], raise blood lipid levels [1191], and promote weight gain [1192-1194]? Would they continue to treat cardiac dysrhythmias with agents like amiodarone which impair thyroid function [1195-1197]? Or would they continue to freely dispense corticosteroids for a variety of chronic inflammatory conditions knowing that excessive blood cortisol levels are a defining feature of MetS [1198, 1199]? And while one cannot diminish the impact of insulin its supplementation does nothing to prevent MetS progression. Why weren't scientists looking elsewhere for answers?

The misinterpretation of heart function by 20th century medical science constitutes the most consequential and avoidable error in the history of medicine and one which forever seals its very dubious legacy. Nor did it help matters that scientists were unable to reach consensus on almost anything for over three decades. As the global footprint of MetS continues to expand one gets a distinct sense that scientists have exhausted their intellectual resources and have little more of import to say on the subject.

The wake-up alarm has sounded. A new day has dawned. As if global climate change weren't enough, a full-scale and progressive deterioration of human health is rapidly evolving, one which, like its environmental counterpart, will decisively impact humans for generations to come. There is no turning back. How will collective humanity confront this looming disaster?

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