Proposed Stroke and Heart Attack Mechanisms

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Abstract *This is an account of possible causes of stroke and heart attack, which include dehydration, sticky cells, high blood sugar, magnesium deficiency, and inflammation. This report does not discount the usual list of risk factors largely provided by the Framingham Studies, which includes atrial fibrillation, high blood pressure, and cholesterol. I propose that the Framingham 50+ year effort has been severely compromised, having used cohorts mostly from wealthy countries. This effort thus appears to be more of a study of food choices than stroke and heart attack causes. A new concept for prevention of cardioembolic events is discussed where the strategy needed for prevention of cardioembolic events depends upon where you live. Subjects, who live in countries where food is rich in sugar and fat, develop cardiovascular disease of the type C, where arterial plaque leads to clot formation. Subjects, who live in the tropics, however, develop type D, characterized by dehydration and magnesium deficiency conditions. In the latter type, sickled cells and parasite-infected cells tend to clump with other deoxygenated hemoglobin, deforming red blood cells and causing blood to clot.*

Introduction

Sustaining an embolic stroke following a 37-year career with NIH and Pfizer on medically related topics, apparently conditions an inquisitive mind to view stroke and heart attack differently from conventional ideas of the diseases. You will find that I have thoroughly endorsed the following Einstein quote: "Foolish faith in authority is the worst enemy of truth."[1]

While documenting my stroke experience coupled with intensive literature searches over the past seven years, a major departure from usual stroke thinking was developed: a schematic was constructed showing proposed mechanisms explaining how and why blood clots can form in the heart–not relying upon arrhythmia.

- Why African Americans will have a higher stroke and heart attack risk than Caucasians.
- Why transient ischemic attack (TIA) effects are of short duration, and without residual tissue damage.

I am going to try to make a rational case for how a state of dehydration coupled with any of a variety of cofactors could together supply the mechanism for clot formation leading to embolic stroke and/or heart attack. Each of the potential cofactors will be separately discussed to build a plausible hypothesis of stroke mechanisms. There are of course the conventionally recognized stroke risk factors to be considered in any comprehensive account–age, blood pressure, lipid profile, etc.

During the course of my experience with embolic stroke, I formulated these proposed stroke/heart attack mechanisms which seem to lie outside of the traditional accounts. Those who are trained in stroke matters may be able to endorse or refute these ideas as subjects of common knowledge, ignorance, or naïveté, maybe all of the above. The reader may decide.

There are two hypothesized stroke mechanisms at work beneath all others. The

first is a mechanism to account for warning strokes and warning heart attacks. This mechanism involves the formation of spastic blood vessels, which temporarily shuts off blood supply to a small portion of the brain or heart. This version of the mechanics accounts for the temporary effect of a TIA, since the vessel will relax rather quickly allowing blood supply to resume.

The second mechanism, involving permanent tissue damage is where a blood clot migrates to a site in the brain or heart, blocking blood flow. This leads to more permanent damage because the clot cannot dissolve fast enough to allow reperfusion of the tissue. Magnesium deficiency can cause blood vessels to spasm and sticky cells leading to clot formation.

This hypothesis does of course offer an explanation as to why we can quickly recover from a mini-stroke or mini heart attack without after effects, while with a full blown stroke or heart attack, we are left with permanent damage. Interestingly, the TIA, spasm, as well as a full stroke or heart attack, can also be the product of a magnesium deficiency, but probably is coupled with elevated stress hormone, as both can cause blood vessels to spasm.

Schematic Introduction

The proposed mechanisms of stroke and heart attack are condensed into the schematic/flowchart (**Figure 1,** p. 73).

There are four pillars supporting the structure: dehydration, inflammatory agents, red cell clumping agents, and insulin resistance. The general pattern of stroke and heart attack development is shown as the convergence of several possible cofactors that produce a sticky cell stage, which is followed by clot formation. Those events are then followed by the ultimate catastrophes of heart attack or stroke.

Schematic Interpretation

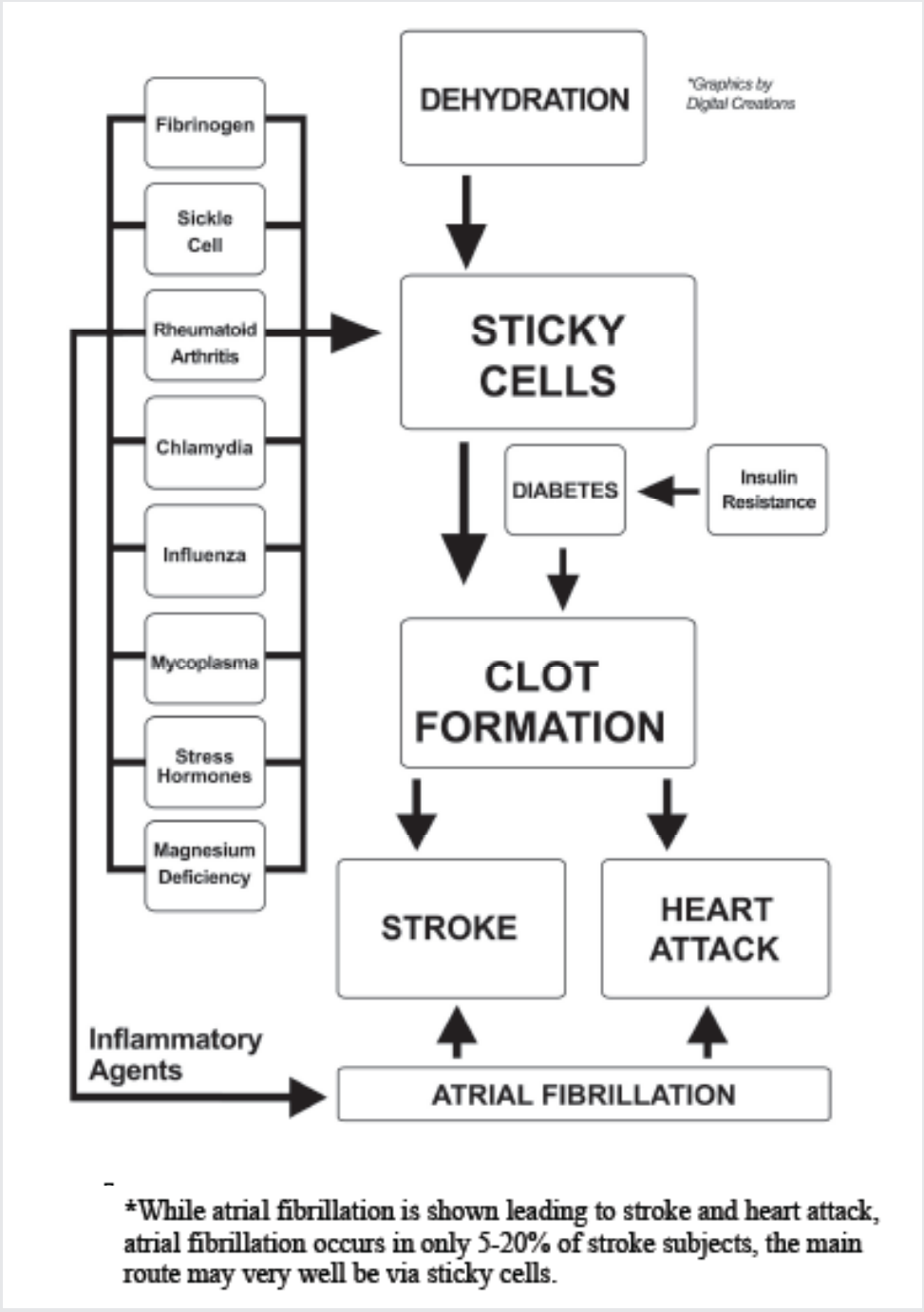
Following dehydration, the next major step in the proposed mechanism for stroke and heart attack is the sticky cell stage, or phase.

Sticky cells are pictured as the necessary preconditioning step for red cells and platelets that enable them to readily clot. This is a more formalized idea of why clots form during the course of stroke and heart attack development, which does not rely on pooling of blood during atrial fibrillation (AF) to provide a likely mechanism. Naturally, formation of clot serves as the final villain for stroke and heart attack etiology. Shown on the left side of the schematic are eight potential cofactors that can couple with dehydration to produce sticky cells.

Here is what welds this schematic into a coherent pattern: each of the eight cofactors shown on the left side of the schematic, from fibrinogen through magnesium deficiency is, by itself, capable of inducing or promoting AF. The vehicle that ties them together is inflammation. Thus, while AF seems to get a lot of credit for stroke and heart attack, it should be clear according to this proposed flow chart, that actually AF, per se, is only guilty by association. Beneath AF is an entire complex of inflammatory agents which, alone or in concert, are at the true roots of stroke and heart attack.

You will notice too, the prominent role of insulin resistance and subsequent diabetes that are shown as a means by which the sticky cell stage can be bypassed, since diabetes and its associated metabolic syndrome components are capable of inducing clot formation directly. I think it is fair to speculate that the one thing AF does bring to the table is to provide a theoretical mechanical means to reduce clot size to a range that can block small vessels, allowing them to migrate either to the heart for heart attack, or to the brain for stroke. It should be noted that AF is associated with stroke risk at a rate of 5% and is responsible for 70,000-100,000 strokes/year.[2] According to the CDC's Morbidity and Mortality Weekly Report,[48] some 66,875 deaths have been attributed to AF, "resulting in an age-adjusted death rate of 24.7 per 100,000 population." According to Borczuk,[3] the total number of strokes each year is 115,000, which means that AF cannot be attributed to the increased risk of stroke

Figure 1. Schematic for Proposed Stroke/Heart Attack Mechanisms.



*While atrial fibrillation is shown leading to stroke and heart attack, atrial fibrillation occurs in only 5-20% of stroke subjects, the main route may very well be via sticky cells.

among all people. As I interpret the data, 80-95% of subjects with AF, have no increased stroke risk so that AF should not be the sole target when trying to prevent cardioembolic events.

When we speak of our bodies as being dehydrated, we simply mean that our bodies are producing more fluid as waste than we are consuming–not a safe arrangement. Fibrinogen does not itself cause or prevent a stroke but can help cause the conditions where a stroke or heart attack can occur. Fibrinogen is a pro-enzyme in our blood that helps stop bleeding after injury, but too much can be harmful, causing clots to form when we do not need them. In fact you could think of magnesium deficiency, chlamydia, influenza, and mycoplasma infections, as well as sickle cell, and rheumatoid arthritis (RA) as not causing stroke or heart attack, but rather increasing risk by providing the conditions for clots to form that lead to stroke and heart attack. Diabetes seems to be the exception by directly causing clot formation, and thus and even higher risk of stroke.

Characteristics of Atrial Fibrillation

AF is recognized with four different patterns per Borczuk[3]:

• Paroxysmal AF – can last up to 7 days, but ends spontaneously
• Persistent AF – lasts more than 7 days and requires chemical or electrical intervention to terminate
• Permanent AF – continuous AF that has failed attempts to control
• Lone AF – term used to describe AF subjects without structural, cardiac, or pulmonary disease. This group has low risk for clot formation.

AF as seen clinically:

• AF with structurally normal heart
• AF associated with cardiovascular disease
• AF with predisposing illnesses such as hypothermia, hyperthyroidism, or as post-operative subjects.

The proportion of strokes associated with chronic AF is 14.7% as reported by Wolf et al.[4] Stated another way, approximately 85-95% of embolic strokes, have no relationship with AF.

Arrhythmia and Atrial Fibrillation as Related To Stroke

Arrhythmia and its more virulent form, AF, have some common features. Both are forms of an irregular heartbeat mediated by magnesium deficiency, as well as by stress hormones, and by histamine. I am hypothesizing, in contrast to the usual thinking in which AF is considered a stroke risk factor where blood is said to pool in the heart, allowing it to form clots, that the real mechanism for clot formation is a product of any of several agents that have the capacity to precondition red cells shown in Figure 1. This feature preconditions red cells giving them the property of sticky cells. The sticky cells then are the true precursors for a rational clot mechanism that does not rely upon the ill-defined pooling of blood to account for clot formation leading to stroke and heart attack.

Dehydration

Dehydration is the first element of the stroke story; here is how the idea evolved. I had a hard time accepting the common explanation that embolic stroke was a product of a blood clot arising from an unstable heart beat (i.e., AF). Until a reasonable mechanism for clot formation was uncovered, I found no incentive to continue either my investigation of stroke or the recording of my personal experience.

Interestingly, in the middle of this dilemma, I came across a book by Batmanghelidj,[5] an Iranian physician who was able to make surprising observations, while a political prisoner in Iran tending fellow inmates without the help of medicine. Publication of his book, *You're Not Sick, You're Thirsty*, changed everything for purposes of my studies. Stroke and 17 other maladies were catalogued as having dehydration as a common cause. Following this clue, I immediately wanted to find out if dehydration could play a role in the missing mechanism for clot formation in the vascular system as related to stroke and heart attack. I

have summarized my thoughts and findings which represent an amalgamation of medical studies extracted from numerous sources that suggest there may be a notable relationship between possible changes in blood chemistry associated with dehydration, as well as other medical factors which could promote clot formation and stroke/heart attack risk– all fashioned into the schematic.

This path of reasoning led me to conclude and predict that dehydration eventually will be identified as a major stroke risk factor once appropriate studies are sponsored by the National Institute of Neurological Disorders and Stroke. It is obvious that we need not look to the pharmaceutical industry to produce a study for such a non-prescription remedy. Dehydration, while not currently recognized as a stroke risk factor, merits serious consideration when one becomes aware of the story presented herein. However, there is no gold standard to reliably measure dehydration, so we are left mostly with the perceptive work of Batmanghelidj.

As general support for the role of dehydration in stroke, the report of Berginer et al[6] is informative. They point out that in an arid climate the average daily incidence of stroke in the Negev desert area was about twice as great on relatively warm days as on relatively cold ones, implying loss of body fluid.

Picking up on Batmanghelidj's clinical experience, it appears that as we age, along with increased stroke risk, the thirst signal diminishes, noted by Kenney and Chiu.[7] Also, it is commonly observed that dehydration is manifested by frequent constipation in elderly and the sedentary.

Looking at stroke through a different lens, I see suggestive evidence that dehydration, as shown in the Figure 1, may be a rather obvious cofactor for clot formation that only very few authors quote. Evidence for dehydration may fall into the anecdotal category because there seems to be no record of controlled investigations (that I could find) and thus is not mainstream thinking. This face of stroke is seldom mentioned and thus is essentially undocumented. The need to recognize dehydration is strengthened by the fact that stroke prevalence increases with age, and as we age the thirst signal, according to Phillips et al,[8] is not as strong as in youth.

Published reports surrounding dehydration as related to stroke are fairly common but not widely quoted. For example, The Hydration Influence on the Risk of Stroke (THIRST) Study,[9] concluded that:

"…elderly patients presenting with acute ischemic stroke or transient ischemic attack have high plasma osmolality levels, suggestive of volume depletion. This seems to be an early phenomenon and possibly a contributing factor to cerebral ischemia."

Friedrich Manz et al[10] stated in his report that: "Hemoconcentration, Polycythemia, and Travel Thrombosis are risk factors for thromboembolism that are possibly intensified by dehydration." They also noted "after acute ischemic stroke, venous thromboembolism was increased in patients with serum osmolality values more than 297 mosm/kg," and that in vitro tests show that changes in hydration can significantly impact adhesion, causing normal erythrocytes (red cells) to display adhesive properties similar to those of sickle cells."

According to the Texas Heart Institute Information Center Information Sheet,[11] "even a moderate elevation in red blood cell count can be a risk factor for stroke. A high number of red blood cells thicken the blood, leading to blood clots."

Testing for Dehydration

One would think that all that is needed to clinch the stroke-dehydration question is to measure the hydration level in stroke victims as compared with hydration level of control patients. But here is the problem, captured by Armstrong in *Assessing Hydration Status: The Elusive Gold Standard.* [12]

Although a significant number of test procedures have been used to reflect hydration status that range from simply noting the color of urine, to one called direct-segmental bioelectrical impedance analysis (BIA) for measuring both intra and extra cellular water with 96-97% accuracy when compared

against hydrostatic weighing, according to Powers et al,[13] using bedside BIA for measuring total body water. What complicates the problem is that children, for example, have a higher percentage of water than adults, with women less water than men, and fat more than thin–and morbidly obese may have only 36% water, and the older the body, the less water retained in the cells–causing wrinkles and dry skin. Making an unambiguous assessment of hydration state for disease comparison probably accounts for the lack of solid data and any significant progress in assessing the impact of dehydration on stroke, in particular. Any number of biochemical assessments has been made, with none yielding unchallenged data that I could find. The case for dehydration as a factor in stroke can be supported most convincingly by the observation that "strokes occur most frequently before noon." Kelley-Hayes[14] and Gusev et al,[15] point out that people with ischemic stroke had three variants of circadian patterns of viscosity and hematocrit, with peaks at 9 am, 3 pm, and 9 pm. They mentioned that for some patients a strong correlation between the time of stroke onset and circadian pattern was observed.

It is not a theoretical leap to suggest that dehydration is in lock step with urine output and fluid intake. Would it be so difficult to observe a cohort of well hydrated subject's verses normally hydrated subjects, to settle the question? One immediate problem I see would be the loss of opportunity for scientists to offer new complicated metabolic pathways. Also, would be the loss of pharmaceutical remedies to treat dehydration. A comprehensive study of hydration is needed for every disease facing mankind.

For those who awaken at night to urinate on multiple occasions, it can be said, with confidence, that without water consumption the source of water for urine production is satisfied only by dehydration. Part of this equation is also related to sleep quality since our metabolism is more active if we are only at a shallow level of sleep; the more metabolically active at rest, the more urine output. It is thus clear that dehydration associated with nocturnal bathroom habits also could help explain why strokes occur more often before noon. As previously discussed, it is entirely feasible that the relative concentration of the clotting pro-enzyme fibrinogen/red cell relationship is distorted by dehydration, thus inviting increased opportunity for red cell and platelet aggregation-associated clot formation and subsequent migration to brain, leading to stroke, or migration to the heart leading to heart attack.

Seen as a total package, the published data surrounding dehydration seems to be sufficiently compelling that a serious effort to produce a controlled study must be considered—if that is what it takes to get the attention of the stroke and heart attack management industry. Perhaps it is time to let some common sense prevail in the selection of our national research targets. If one is looking for additional convincing evidence for dehydration contributing to stroke, there is a rather compelling geographic pattern of stroke in America. I am referring to the stroke belt[16] that extends through the southeastern states. When you think about this pattern of stroke as possibly related to dehydration, it is easy to justify this clustering of stroke. The fact that those states are characterized as both hot and humid creates an environment for excessive perspiration and thus increased dehydration potential. Of course there are other factors that enter the picture, such as the increased population of African Americans. A case is also made herein for higher stroke risk in African Americans due to their propensity for sickle cell which adds another layer of risk to that population according to the hypothesis developed around the schematic.

Insulin Resistance

When glucose is absorbed into the bloodstream, some of it is picked up by the hemoglobin in red blood cells. This glycated (glucose-carrying) hemoglobin holds onto the glucose until the red blood cells die in about 120 days. The more glucose there is in the blood, the more glucose that is carried by the hemoglobin—so a direct correlation ex-

ists between blood glucose level and glycated hemoglobin, which is measured to determine the hemoglobin A1C level.

Insulin resistance, aside from depleting magnesium as a partner of diabetes, is an important stroke risk factor since about 40% of the "normal" population is in fact, insulin resistant per Kernen.[17] One of the things I found that happens after a stroke is to continually test yourself by asking such things as, "Why do my stroke symptoms seem to ebb and flow with no apparent provocation?" As a case in point, at 23 months post stroke, in spite of everything I had tried to accelerate recovery, nothing seemed to have any effect. I began to question why my symptoms of peripheral neuropathy, numbness in left foot, hand, and calf and gradual loss of functionality seemed so much more pronounced on some days than others. I continually searched for clues, starting most notably from my observation that if I consumed any high glycemic food such as sugar, that often within minutes my left foot, calf, and hand would feel significantly more numb, cold, and swollen although visually unchanged. This observation, repeatedly noted, usually subsided within a few hours or by morning awakening. These events led me to question whether I could possibly be experiencing a coincident diabetic neuropathy exacerbated in stroke affected limbs. Since my neurologic symptoms seemed to perfectly parallel those described for diabetes, I began a study of a possible stroke-associated insulin resistance. A quick check of the literature revealed the astounding fact that insulin resistance affects nearly one half of all patients with stroke or TIA.[17]

One of the major avenues leading to stroke is how blood sugar is managed as related to insulin resistance and diabetes. However, in my opinion, there is a serious flaw in the interpretation of insulin resistance data that is having a significant impact on how we deal with it and its subsequent partner seen as diabetes. It all begins with the tool that is used to assess the status of our path to diabetes. I am referring to the A1C test.

The A1C Test

One of the most common tests for how well our bodies deal with sugar is the A1C test. The A1C test is a general measure of diabetes status, while conventional home glucose monitoring measures a person's blood sugar at a given moment. The higher the A1C value, the more sugar on average that was floating around. The A1C value often is used to decide whether a body is insulin resistant, meaning on its way to diabetes.

Experts seem unable to decide what level of A1C constitutes a normal value. So it appears that anyone interested may decide what to consider a normal value. The American Diabetes Association states A1C should be 7% or below, the American Association of Clinical Endocrinologists stays with 6.5% or below, most others state 7% or below. However, in the EPIC-Norfolk study, Khaw[18] showed that an A1C of 6% compared to an A1C of 5% had an increased risk of cardiovascular death of 28% higher. If I understand this right, you can see that selection of the normal A1C value could have a high impact on associated risk. Within each of the recommendations, they say that the A1C should be as low as possible without hypoglycemia, and that coexisting health conditions must be factored in. The major testing laboratories usually say the normal range is 4.0-6.0%.

Bernstein[19] as written in *Bernstein's Diabetes Solution* indicated that as far as he has been able to determine, a truly normal A1C ranges from 4.2- 4.6%, a huge difference it seems to me. So take your pick. In my case, I had an A1C of 5.7% when tested about 30 months post stroke. By most standards that would not implicate insulin resistance, but by Bernstein standards, it sure would.

What does all of this have to do with heart attack and stroke? Those who are insulin resistant are known to feature depleted magnesium levels. Magnesium is critical for prevention of red cell auto-clumping. Without adequate magnesium, the clumped cells are more capable of clot formation and migration to the heart or brain. Magnesium depletion also is associated with arrhythmia, which in its ultimate pathologic form, mani-

fests as AF. Thus it is easy to see why that although it is AF that is considered to be the risk factor, it appears that before that probably came magnesium depletion, and before that, probably insulin resistance.

Insulin Purpose

The primary purpose of insulin is to control how the body converts and stores the sugar we eat. Insulin can be thought of as an escort to help sugar gain entry into the types of cells that need it to convert sugar into energy. Not all cells need this help however, so that whereas muscle, liver, and fat cells must rely on insulin, other cells such as brain, kidney, and red blood cells do not. The amount of insulin needed by the body is related to the amount of sugar in the blood stream. The higher the sugar load, the greater will be the insulin level. So what happens if sugar gets out of control? Well that is where insulin resistance enters the picture.

Resistance to Insulin

Too much of anything can be toxic for our bodies. A perfect example is the effect of too much sugar in our diet resulting in too much of it floating around in our bodies, and then followed by too much insulin. One result is that receptive proteins are able to combine with the glucose to form chemical complexes called advanced glycation end products (AGEs) by a process known as the Maillard reaction (Verzijl et al).[20] This reaction is recognized in several ways. For example, as foods are cooked they often assume a brown color as do fried potatoes. In our bodies the accumulation of these complexes can contribute to age-related increase in lens crystals implicated in cataracts, and to the brown spots noticed on the back of the aging hand.

So too, with prolonged presence of AGEs comes a decrease in elasticity of skin and connective tissue collagens. The browning reaction also is implicated in age-related diseases such as diabetes, atherosclerosis, and Alzheimer's disease. AGEs also leads to oxidative inflammatory changes associated with plaque accumulation in vascular diseases.

As discussed above, the more sugar that enters our diet, the more insulin that is produced to control it, and ultimately the insulin itself rises to a toxic level. This is when we develop resistance to insulin. When this happens the body no longer can produce insulin fast enough to compensate for the accumulating sugar that cannot get into the cells that need it to produce energy. The body responds by signaling a need for even more sugar which shows up as a craving, and thus begins the endless cycle that earns the name of Type-2 diabetes.

To complicate matters even more is the fact that as we age, just like some of our senses such as thirst decline, so too the process of aging by itself also is at work to reduce insulin sensitivity. Thus, just by our nature we must face the prospect that insulin resistance is just waiting to be discovered in our aging bodies. One would think this reality would be enough for our primary care physicians to include a test for insulin resistance in routine annual physical exams. From my experience, doctors who are alert to this need are in a small minority (although this could be a Medicare issue). Given the strong association between diabetes and stroke, accumulating this knowledge should become high priority in health care strategy. Controlling insulin is one of the most powerful anti-aging strategies you can possibly implement. It all starts with sugar consumption control. This requires that you eliminate high glycemic foods from your diet and that you understand the role and need for adequate magnesium in your diet, as described shortly.

To amplify some of these thoughts, we recognize that our bodies have met and solved all sorts of biochemical challenges for millennia, so they long ago provided a defense for controlling excess sugar with the hormone insulin. Each time we eat, insulin is released into our tissues to help convert sugar into energy as quickly as possible, or at least convert it into a less harmful storage form called glycogen. When the storage capacity for glycogen is exceeded, the glucose is stored as saturated fat (usually abdominal). As our pancreas produces an increased level of insulin to meet the otherwise toxic sugar

load, the level of insulin itself rises to a toxic level. In an effort to protect itself, the body developed a strategy to make the cells resistant to the signal given by insulin to convert more glucose into energy. The liver cells are the first to become resistant followed by muscle tissue, then fat cells.

As resistance to insulin increases at the same time as demand for insulin is high, the body becomes diabetic. This path is now termed insulin resistance, Syndrome X, or Metabolic Syndrome. Those terms are invoked when a combination of risk factors for type-2 diabetes occurs. These factors usually involve chronically elevated insulin, low HDL, abdominal obesity, and high blood pressure. Syndrome X often is found in families with a history of early heart disease. Some of the symptoms of insulin resistance are said to be fatigue, poor memory, agitation, or depression, along with the increased blood pressure and fasted insulin level.

Here is another confounding fact: Insulin plays a role in the storage of magnesium and if you are insulin resistant, your critically important magnesium supply is readily depleted.[21] It is known that claims for magnesium include the fact that magnesium deficit causes constriction of blood vessels leading to elevated blood pressure, sticky red cells, and platelets, and also to arrhythmia which is associated with TIA and stroke. This is especially crucial when coupled with dehydration in my opinion.

There are drugs said to be helpful in restoring insulin sensitivity, and I refer you to the most authoritative book on the subject I know of, called *Syndrome X* by Gerald Reaven.[22] Reaven is credited with discovery of the metabolic syndrome also known as Syndrome X. Here he offers dietary advice on how to manage insulin resistance. Additionally, according to Thompson and Barnes[23] in their book, *The Calcium Lie*, they assert that early type-2 diabetes is treatable and reversible simply by increasing sodium intake in the form of rock or sea salt, along with what they describe as ionic mineral supplement (which, likely contains magnesium). I suggest you consult their book for details.

To conclude this story, I reemphasize that the problem with insulin resistance is that as the body senses elevated blood sugar, it in turn signals the need for more insulin which then depletes the sugar (as well as magnesium), and the body then starts craving sugar with the cycle repeating endlessly driving our bodies toward full blown diabetes, thus increasing the risk of a cardioembolic event.

Red Cell Clotting Mechanisms

The following eight agents represent proposed mechanisms by which red cells could, in theory, lead to clot formation and then migrate to the heart or brain to cause heart attack or embolic stroke. The list is not meant to exclude other possible microbial, physical, or chemical agents. Quite apart from any speculation, one can look at diseases known to affect properties of red cells and see whether the incidence of stroke is changed in those populations. Batmanghelidj's[5] book is a must read for a full review of the scope of the dehydration problem.

There are three keys to understanding the crucial role of adequate hydration:

1. As we age, we gradually experience sensory loss which manifests as hearing and sight loss, as well as thirst, taste and sexual loss;

2. Drinking fluids is not the same as drinking water, as many fluids actually contribute to dehydration such as coffee, alcohol, and sodas; and

3. The body seems to allocate water, so the brain, for example, gets first dibs. However, over the years, the effects of chronic water shortage are so insidious it may be hard to spot them until a disease shows up.

I scanned numerous general health texts to make note of the frequency that dehydration was identified as an associated cause of disease. If mentioned at all, it was usually as related to constipation, cataracts, or macular degeneration. Dehydration was not even in the index of most of the health related texts that I viewed. Batmanghelidj seems to have it right, as inferred from him: dehydration in health management is seldom a consideration.

Inflammation-Induced Arrhythmia

A key feature of this thesis is the proposition that arrhythmia and AF are products of inflammation, and that each of the agents shown in the schematic are capable of causing inflammation.

(1) Fibrinogen

Within the general thesis of a stroke-dehydration relationship, one of the most powerful players is the role of fibrinogen. Wilhelmsen et al[24] published a paper on fibrinogen as a risk factor for stroke and heart attack. They concluded that "although causality cannot be inferred from these data, it is possible that the fibrinogen level plays an important part in the development of stroke and myocardial infarction."

This speculation has been amplified and confirmed numerous times. For example: Bots et al[25] analyzing EUROSTROKE data concluded that "Fibrinogen is a powerful predictor of stroke." Gaspar de la Serna[26] stated that "during the last decade, several epidemiological studies have reliably demonstrated that plasma fibrinogen is a strong and independent risk factor for cardiovascular disease." They go on to observe that "the risk of developing a cardiovascular event such as ischemic heart disease or stroke, is 1.8 to 4.1 times higher in subjects with fibrinogen levels in the top third than those with levels the lower third." Kofoed et al[27] quoted data from 8,755 subjects that "suggest a doubling in risk of ischemic stroke for high verses low fibrinogen."

If the body is sufficiently dehydrated, one could easily imagine how an unusual blood chemistry shift could change the normal pattern of red cell and platelet association with fibrinogen balance with nothing more needed. In fact, it was reported by Gaspar de la Serna[26] that "During the last decade, several epidemiological studies have reliably demonstrated that plasma fibrinogen (a blood clotting enzyme) is a strong and independent risk factor for cardiovascular disease that is at least as important as more traditional risk factors for the disease."

(2) Stress Hormones

Stress hormones, as commonly recognized, usually reference the fight or flight response. Ben-Shahar[28] describing the fight or flight response, points to adrenaline, as "…secreted as a direct reaction to stressful situations…" Notation was also made that "adrenaline is also an excitatory neurotransmitter in the CNS (indirectly controlling its own production)."

Also mentioned was that during preparation for fight or flight, there is:

- Increased heart rate, blood pressure, and respiration
- Increased sugar in the blood
- Thickening of the blood by platelets, to stop bleeding quickly
- Secretion of body wastes to make the body lighter

In a report by Black and Garbutt,[29] they state: "…inflammatory events, caused by stress, may account for the approximately 40% of atherosclerotic patients with no other known risk factors. Stress, by activating the sympathetic nervous system, the hypothalamic-pituitary axis, and the renin-angiotensin system, causes the release of various stress hormones such as catecholamines, corticosteroids, glucagon, growth hormone, and renin, and elevated levels of homocysteine, which induce a heightened state of cardiovascular activity, injured endothelium, and induction of adhesion molecules on endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall. An acute phase response (APR), similar to that associated with inflammation, is also engendered, which is characterized by macrophage activation, the production of cytokines, other inflammatory mediators, acute phase proteins (APPs), and mast cell activation, all of which promote the inflammatory process. Stress also induces an atherosclerotic lipid profile with oxidation of lipids and, if chronic, a hypercoagulable state that may result in arterial thrombosis. Shedding of adhesion molecules and the appearance of cytokines, and APPs in the blood are early indicators of a stress."

(3) Influenza Virus

Influenza infection is one of several mechanisms by which clots could form leading to stroke. Influenza virus is capable of agglutinating red cells. Powerful support for this thesis is found in numerous reports showing a reduced stroke risk in influenza vaccinated subjects.[38,47]

These observations were of particular interest to me in the context of my study of the literature, since the influenza-stroke correlation occurred within an interval where a viremia would be expected, and lasted until a viremia likely would have abated. Here is where the influenza connection gets more interesting; quoting from the paper by Lipsitch and Viboud,[30] titled *Influenza Seasonality: Lifting the Fog*, they state: "Influenza is perhaps the seasonal disease of most profound interest, because it is responsible for much of the seasonal variation in other infectious and noninfectious causes of morbidity and mortality. Influenza virus activity display strong seasonal cycle's in temperate areas of the world, and less defined seasonality in tropical regions."

Similarly, in an article by Viboud et al,[31] they noted that "In temperate regions, there are clear seasonal variations in the occurrence of influenza, with a marked peak in cold winter months." To provide a broad view of the possible relationship between influenza infection and stroke, consider too, the study provided by the American Heart/Stroke Association written in 1995, referring to the Framingham Study[14] titled, *Temporal Patterns of Stroke Onset*, in which they state: "Winter was the peak season for cerebral embolic stroke. Significantly more stroke events occurred on Mondays than any other day, particularly for working men. For intracerebral hemorrhages, a third happened on Mondays in both genders. The time of day when strokes most frequently occurred was between 8 AM and noon. This pattern was true for all stroke subtypes."

I am not suggesting that influenza virus infection per se is a significant cause for stroke; the discussion is more to point out the possibility of a heme agglutinating type of agent that could provide a mechanism for clot formation ultimately associated with embolic stroke, especially when coupled with dehydration.

(4) Chlamydia

There is a history of an association between chlamydia and cardiovascular and other diseases. Since it is not my intent to produce a review of the subject, representative studies include: Campbell et al,[32] *Chlamydia pneumonia and Cardiovascular Disease*, and another by K. F. and K. M. Poehlmann,[33] *Chlamydia Linked to Heart Disease, Stroke, and Alzheimer's*.

Here are some of the features of chlamydia:

• Considered nanobacteria thus among the smallest of all bacteria

• Two genetically different strains of concern: C. pneumoniae–a mild form of pneumonia followed by a long term infection; C. Trachomatis–the sexually transmitted form of Chlamydia

According to K. F. and K. M. Poehlmann, "C. pneumoniae is a major factor in stroke, dementia, heart disease, and arterial sclerosis."[33] On the other hand, Campbell et al[32] were more cautious concluding:

"A causative role of C. pneumoniae infection in cardiovascular disease has not yet been firmly established. However, the high frequency of infection found in human atherosclerotic tissue in comparison to normal tissue, the induction and progression of atherosclerotic-like inflammatory changes in infected animal models of atherosclerosis, and the early results from antichlamydia intervention studies in humans are consistent with a causative role of C. pneumoniae in the disease process."

Apfalter[34] in an editorial wrote of *Chlamydia pneumoniae, stroke, and serological associations*. Also from the Northern Manhattan Stroke Study is the work of Elkind et al.[35] This documentation is supplied in support of the schematic.

(5) Mycoplasma

As another example of red cell agglutination in terms of stoke, there is a relationship between Mycoplasma infection and

stroke. Mycoplasma are red cell agglutinating agents, and although not numerous, there are scattered reports linking Mycoplasma with stroke such as: Fu et al,[36] Ngeh and Goodbourn,[37] and Grau et al.[38] I am not suggesting this is a major stoke partner, only that the findings are consistent with a stroke-agglutination mechanism.

In terms of Mycoplasma infection and stroke, Nghe and Goodbourn,[37] wrote "that the risk of stroke/TIA appears to be associated with the aggregate number of chronic infectious burden of atypical respiratory pathogens such as C. pneumoniae, M. pneumoniae, and *L. Pneumophilia*." Grau et al[39] in their paper *Recent Infection as a Risk Factor for Cerebrovascular Ischemia*, stated the following: "Bacterial infections dominated among patients but not among control subjects. Infection increased the risk for cerebrovascular ischemia in all age groups; this reached significance for patients aged 51 to 60, and 61 to 70 years. Infection remained a significant risk factor when previous stroke, hypertension, diabetes mellitus, coronary heart disease, and current smoking, were included as covariate in a logistic model (OR, 4.6; 95% CI, 1.9 to 11.3)."

(6) Sickle Cell

Sickle cell anemia is a condition that influences red cell integrity, and cell-to-cell association. Checking stroke incidence, one finds definite evidence of increased stroke risk associated with sickle cell anemia. Verduzco and Nathan,[40] report that 24% of sickle cell disease (SCD) patients have a stroke by age 45 years. As reported by the American Heart Association,[41] children with SCD are 221 times more likely to suffer stroke.

African American Stroke Risk

The hypothesis presented herein easily leads to some interesting speculation, for example: African Americans have a known increased risk for sickle cell anemia. This is a disease characterized by "sticky red cells" as previously described. It is immediately tempting to put the notion of "preconditioned red cell" hypothesis to a test by predicting that a more accurate stroke and heart attack risk assessment for African Americans could be calculated if we identified members of that cohort with and without known sickle cell. Those who are skilled in assessing public health risk can surely refine this idea and deliver a reliable statistical statement to account for the true difference in heart and stroke risk between African Americans and Caucasians. That exercise would go a long way in deciding the validity of the hypothesis. Those subjects with sickle cell anemia will have a measurably higher incidence of stroke and heart attack, if the hypothesis is valid.

(7) Rheumatoid Arthritis

Reasoning that agglutination of red cells has been used to test for evidence of RA, one also can find ample evidence of increased stroke risk among those affected by this rheumatological disease.

Examples of studies connecting rheumatoid arthritis with cardiovascular diseases may be found in the work of Gonzalez-Gay et al[42] in their paper *Rheumatoid Arthritis: A Disease Associated with Accelerated Atherogenesis*, and in the work of Van Doornum et al,[43] *Reducing the Cardiovascular Disease Burden in Rheumatoid Arthritis*. Also in *Therapy Insight: Managing Cardiovascular Risk in Patients with Rheumatoid Arthritis* by Giles et al.[44] Additional studies include *Cardiovascular Risk in Rheumatoid Arthritis* by Nurmohamed[45] and a review by Kaplan.[46] Reference to dehydration in the rheumatoid arthritis group also was noted by Batmanghelidj.

(8) Magnesium

In terms of its relationship to stroke, magnesium has been found to possess the following properties: helps to ward off formation of unwanted blood clots (i.e., minimize stickiness as a result of the mineral's capacity to reduce platelet-dependent thrombosis); lowers blood pressure; prevents some of the complications related to diabetes; and limits the effects of free radicals. Magnesium is needed for nerve transmission, and is especially helpful in maintaining normal heart rhythm or even restoring normal heart

rhythms during episodes of arrhythmia (as I can personally testify to).

Effects of Magnesium Deficiency

According to the Linus Pauling Institute's Micronutrient Information Center[21] the following conditions are related to magnesium deficiency: prolonged diarrhea, Crohn's disease, malabsorption syndromes, celiac disease, diabetes mellitus/insulin resistance, and chronic alcoholism. Also noted were several studies demonstrating that elderly people have relatively low dietary intakes of magnesium; worsened by intestinal absorption that tends to decrease with age while urinary magnesium excretion tends to increase with age. All of this fits well with the known increased stroke risk with age, since aging is associated with increased disease prevalence as well as magnesium deficiency (>50 years of age).[21]

Discussion

In a paper titled, *Strokes caused by infection in the tropics*, the author stated that "Almost three out of every four people in the world who suffer a fatal stroke live in developing countries."[49] The author goes on to say, "There are estimated to be 500 million cases of malaria every year." In addition, "Chagas disease is an independent risk factor for stroke in South America," and that "… at least 20 million people have the chronic form of Chagas disease." The author also noted "other less common causes of stroke are haemorrhagic fevers due to arenavirus and of flavavirus." The author concluded by stating that, "Several diseases that are endemic in the tropics can be responsible for up to 10 percent of the cases of strokes in adults."

If there are 500 million cases of malaria every year worldwide, and if 10 percent of them are associated with stroke, this would mean that 50 million cases of stroke are associated with that parasitic disease. Add to that, 20 million cases of Chagas Disease would translate to 2 million stroke events associated with that parasitic disease in South America. The total world burden of this type of embolic stroke (i.e., denoted by me as 'Type D') would be in the vicinity of 52 million, none of which are even recognized as a target for prevention by adequate hydration and magnesium supplementation.

This, of course, does not account for the number of embolic strokes, denoted by me as the 'Type C' category. The Type C-based strokes are largely found in developed countries, and there would be a scarcity of this type of stroke found in undeveloped tropical areas, and thus stroke prevention strategy does indeed depend upon where you live.

According to my observations of strokes, in developed countries with dietary excesses of fat and sugar, the preponderance of embolic strokes would be of the Type C variety (i.e., clot/plaque induced); based upon Framingham studies. In undeveloped countries, on the other hand, the preponderance would be from the Type D variety (i.e., dehydration combined with red cell agglomerating conditions). This latter category of stroke was a product of deductive reasoning based upon the observation that Warfarin is associated with stroke prevention only about 66.7% percent of the time;[50] as I understand the data. This implies that about 33% of the time strokes can also occur due to agglomeration of red cells/platelets capable of forming blockage to the brain and the heart. Thus, this substantial portion of embolic strokes cannot receive protection from Warfarin, since there is no true fibrinous clot involved. I have offered the notion that Type D prevention can best be accomplished by improved hydration and by magnesium supplementation.

In terms of the mechanism of action in Type D embolic stroke, we should not overlook the fact that the class of viruses involved, are often but not always, latent viruses. This is important because latent viruses usually operate in the presence of their specific antibody, and that condition is important since antigen-antibody complexes could in theory act as blood blocking agents and lead to heart attack and stroke. This notion predicts that anything that activates the release of latent virus particles could be expected to foster increased heart attack and stroke risk. This idea no doubt needs epidemiological supporting

data to assess its validity.

The central message is to emphasize that stroke prevention requires an awareness of the possible simultaneous occurrence of both types C and D, which is highly likely. Embolic stroke prevention must accommodate both forms: C, with the Framingham recommendations; and D, with hydration and magnesium supplementation.

Conclusions

If you have experienced a type D embolic event, heart attack or stroke and you fail to maintain adequate hydration, forever following the heart attack or stroke event, you will have met the criteria needed to ensure another embolic event in the near future where every stroke, for example, predicts the next. If dehydration contributed to your first embolic event, and you fail to correct that part of your lifestyle, then how could you expect to prevent repeat events? Admittedly, authorities do not even acknowledge that dehydration is a risk factor–so you must rely on your common sense, no matter how many pills are prescribed.

Competing Interests

The author declares that he has no competing interests.

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