“Don’t beam me up, Scotty!”
-at least not until “Eu-medicine” arrives

AAOM January 2012  Dr. David Lee Harshfield, Jr. MS, MD.

The uncanny resemblance between the uniquely configured ventricular cavities of the human brain (top right) compared with the exoskeleton of Star Trek’s USS Enterprise series 1701 may just be a vague coincidence conjured up by the vivid imagination of a Trekkie turned physician. It seems, those cherished but long ago, 1 hour daily escapes from my “24/7” approach to Medical School during my freshman year spent watching Star Trek reruns (from 5 to 6:00 o’clock on weekday afternoons) provided the subliminal but inexorable consequence of “mind melding” outer space adventure with an emerging medical career.

As a USS Enterprise Medical Officer wannabe, it was of great interest when the fledgling science of Space Physiology and Medicine began to reveal to the rest of us humans here on earth that there are measurable and predictable deleterious effects produced by even brief periods of space travel with regards to the function of the human central nervous system (CNS). Our current earthbound research group, the College of Integrative Medicine (coimed.org), has also been studying the deleterious effects of abnormal cerebrospinal fluid (CSF) flow on the CNS, but only as they pertain to the earth bound. In doing so, we have shown how CNS disturbances can be traced directly to disrupted homeostasis of the cerebrospinal fluid (CSF), a liquid that is produced, contained and travels in a predictable manner through those odd shaped ventricles when under the normal gravitation pull of earth.

The opportunity arose last year for us “meld” our “regular” with NASA’s “micro” gravity research when we presented our findings to a receptive group of scientists at NASA. It became apparent that collaboration between the two groups has the potential to rejuvenate the “Culture of Innovation” that propelled Americans through the latter part of the 20th century. And, in addition to CNS disturbances, micro gravity also markedly disrupts our immune system, thereby decreasing our ability to repair the CNS and other internal damage caused by space flight. And as fate would have it, our integrative medicine research also encompasses the study of Cellular and Regenerative Medicine. In so doing, we have been demonstrating worldwide how currently available, safe, simple and inexpensive cell based biological therapies can replace the existing risk laden and expensive surgical and pharmaceutical therapies.

The melding of the ongoing research efforts in “Space Physiology and Medicine” with the developing advancements in “Cellular Medicine” has a chance to facilitate evolution of those two schools of thought to form a new third entity; Eu-medicine (“eu” meaning “true”) that could provide the matrix upon which to precipitate and crystallize the ongoing correction of medicine.
For the last 50 years the **American Association of Orthopaedic Medicine (AAOM)** and its affiliate chapters have been the leaders in promoting and teaching an integrative approach to both the diagnosis and treatment of acute and chronic pain emanating from the musculoskeletal system. The AAOM is a uniquely “bottom up” organization that promotes **Orthopaedic Medicine (not Orthopedic Surgery)** by teaching multispecialty physician groups integrative diagnosis techniques and comprehensive/integrative nonsurgical treatment methods including proliferant injections (prolotherapy), fluoroscopic spinal interventions, osteopathic manual medicine, therapeutic exercise and interventions with various pharmaceutical/neutraceutical/herbal/homeopathic based treatments.

A collaborative commitment between NASA and the **American Association of Orthopedic Medicine (AAOM)** could provide the ground work for the creation of “Eu-medicine”. Such collaboration would have the potential to evolve into a wide reaching, patient centered health care approach dedicated to the development, teaching and training of Cellular and Regenerative Medicine therapy guided by advancements in Space Physiology and Medicine. Such a consortium would not only have the capability to change the cumbersome and time consuming way medical research is currently being conducted, but could markedly reduce the “bench research to clinical practice” time, thereby streamlining the safe introduction of new cell based therapies into our society.

The pace in which internet speed and access has increased combined with the rise of social media predisposes our society to rapid, sometimes irrational changes. Similar to the “Arab Spring” there may be a desire for a “Creative destruction of Medicine”, based more on Washington “group think” than on transparent, organized and forward thinking concepts. This potential danger for an “American Spring” type change in our scientific research ecosystem makes it even more imperative to bring NASA back into the debate. Americans, cognizant of the dire need to change the **US health care system**, can provide a unique opportunity for **NASA** to again become the leader of the “culture of innovation” by apprising **e-America** of the direct link between research in and support of space travel and the evolution of the health, well being and prosperity of the human race.

The **AAOM** has for years been reaching out to US agencies, as well as to other countries, particularly those that utilize socialized or single payer healthcare systems. Thus far, the disorganized and chaotic, “top down” US health care system along with the misguided FDA have had their “deflector shields” up to the idea of having the US implement the science of cellular biologic medical therapies. However, many other countries around the world are quickly realizing the enormous savings that occur by exchanging their outmoded dysfunctional health care systems for a system based on safe and low cost cellular based biologic therapies like proliferant therapy (Prolotherapy), platelet rich plasma (PRP) and SVF adult mesenchymal stem cell therapy. Mexico, our neighbor to the south, projects billions of dollars in savings over time that they will accrue by utilizing these cellular medicine therapies. And finally, representatives from the US Army are scheduled to attend the upcoming AAOM meeting in Cancun, Mexico to see firsthand how cellular medicine can impact Veteran’s Administration and Department of Defense spending.

The crushing rules, red tape, regulations and inherent lack of transparency dissuade anyone in their right mind from even thinking of working with any federal government agency. But the opportunity for the AAOM and other research groups to collaborate with NASA could be different. In doing so, the AAOM would have the unique opportunity to study how over short time intervals how micro gravity produces changes in the brains and immune systems of our astronauts that would otherwise take years to study in earth bound humans.

All that is required for this monumental task force to come to fruition would be to bring key government officials, NASA supporters and AAOM members together and begin discussions on how best to “meld” the two presently separate "silos" of knowledge: “Space Physiology” and “Cellular Medicine”. By merging the two perspectives on the growing understanding of the role of space flight induced CSF and immune system dysfunction, mankind could be on the road to uncovering the basic causes and treatments of many CNS diseases, thereby averting the looming health care system crisis that is occurring as the “baby boom” generation retires.
Gene Roddenberry didn’t just conceive of a “Gun Smoke goes to Outer Space” television show back in 1964. To millions around the world, with Star Trek, he gave voice to hope for the future, a philosophy of peace on Earth, acceptance of those not like us, and the importance of exploration of our universe as well as our home planet.

Mr. Spock from the original Star Trek series stated that: "The needs of the many outweigh the needs of the few or the one". This advice from a famous fictitious future science officer in the Federation of Planets can serve as guidance to us. The best future health care system will be the one that benefits all of us earthlings, not just the few currently in power. The ‘Greatest Generation” is retiring; no longer in position to make the necessary choices. And the generation left in charge hasn’t demonstrated the ability to solve the fiscal, much less the health care problems we face in this country.

But, let’s not mix science fiction with science fact. Today, peer to peer technology is giving users the ability to create content free from central planners. This “bottom up” capability allows us to blog, inform, empower and inspire each other. Similarly groups like the AAOM and NASA have an opportunity to similarly effect change at a grass roots level that could circumvent the ongoing bad decision making that if left unchecked will continue to unfavorably impact future generations.

By merging Cellular Medicine with Space Physiology, NASA will allow us to view our growingly urgent earthly challenges from the vantage point of the “final frontier”. That may just provide the perspective we need to better understand our health care priorities in the context of the advances in space physiology and space medicine, thereby morphing into “Eu-medicine” - revealing that ultimately, ‘it’s all in our head’.

Patient with Chiari I anatomy; cerebellar ectopia (better visualized with upright, weight bearing MRI imaging) that interferes with CSF flow, thereby predisposing to numerous diseases of the CNS

**Introduction**

As the “correction of medicine” trundles along, currently “led” by well meaning but under and uniformed government bureaucrats and academics, the inescapable challenge of “prioritization” is looming on the horizon. Every special interest group owns tightly held, well entrenched and defended ‘to do’ lists with regards to these inevitable and “necessary” changes. But it would behoove us to step back and try to imagine a future health care system based on the realities of the present but also from the perspective of the past. In doing so, we could initiate the discussion by developing a consensus on health care spending and research based on a prioritized line item “review of systems” of our species.
An old joke about the hypothetical argument between the various organ systems in the body essentially boiled down to a punch line in which the gastrointestinal tract reigned supreme over all other systems. In reality however, even the peskiest interference by the distal bowel can be addressed relatively easily by a “man made” colectomy. However, joking aside, the ultimate realization is that humans are most controlled by and least able to sustain damage to the central nervous system, a malady not so easily remedied by current “man made” capabilities.

Bring back NASA and revitalize the “Culture of Innovation”

Dr. Neil DeGrasse Tyson, an astrophysicist who was born the same week that the US Congress formed NASA, has a unique perspective on how humans can be “moved” to alter their priorities. The collective national future of Americans in the 1960’s was the product of the dream of space exploration, and the New York World’s fair early in that decade was the embodiment of those dreams. The STEM (science, technology, engineering and mathematics) fields were all stimulated by those aspirations of space flight and exploration, and ultimately led to numerous advancements not only in aeronautics, but in medicine.

The “fallout” from pursuing such “improbable aspirations” as space flight planted the seeds of economic growth benefiting our society in the 1960’s because we dared to “feed and water” them. To humans it seems, doing what has never been done before is intellectually seductive, even if it is deemed by “experts” of the day to be impractical. But by conducting those exercises in imagination, innovation follows; often in serendipitous ways that could not have been foreseen a priori. The future, it seems, always lies just beyond what is today considered the impossible.

The success of the correction of Medicine appears to be on a parallel, possibly coupled course with NASA. Mankind’s future may very well hinge on the growth or regression of the NASA space program. NASA has been shown to be an “engine of innovation” that can spread growth of knowledge and prosperity into a receptive and supportive culture. The innovations have come in the form of low tech and high tech solutions. This is a factor that can help to explain part of the problem in the current Cellular Medicine debate.

The preoccupation with high tech solutions may be the reason society (and government for that matter) has been slow to embrace the relatively low tech, low cost but remarkably effective solution of regenerative cellular medicine. But patients, and many physicians, are misinformed if they don’t realize that replacing an arthritic joint with a shiny, expensive prosthetic is anything other than merely trading one disability for another one. It is almost counter intuitive in this environment of “bigger is better” to accept that a relatively simple regenerative injection technique can treat the seemingly complex and enormous problem of musculoskeletal disorders. It is not a crime to be held hostage by our own limited knowledge, but curiosity is the cure for bias and narrow-mindedness.

Other similarities exist between the evolution of the health care and aeronautical industries. In the days of the Manhattan Project, the US did not have the scientists or expertise to develop atomic weapons, and undertook the importation of European trained scientists to acquire those skills. Soon after, the US became the world leader in those sciences. But as our culture lost interest in NASA, the scientists who had been coming to the US to train, began to return to their home countries whose cultures were eager for that knowledge. Now the US is no longer in such a position of strength in this arena.

Similarly, The American Association of Orthopedic Medicine (AAOM) over the last half century has evolved into the most important organization for training and research in the field of Integrative Cellular Medicine. Not surprisingly, the AAOM is a very “bottom up” organization. The AAOM not only nurtures US physicians and scientists, but cultivates members from the four corners of the world to attend our
conferences and populate our governing body. But because the FDA and other “top down” regulatory agencies of the US government continue to interfere and impede our progress, many of the breakthroughs have been moved “off shore” and are occurring in other countries. What the federal government should do, as Rick Perry the Governor of Texas is doing on a state level, is to declare that cellular medicine therapy is our new goal in this country for the correction of medicine, and then step out of the way and let innovators and scientists make it so.

Dr. Tyson’s philosophy supports that theory that individual human evolution is the product of cultural evolution. And thus will require a cultural “re-set” of existing priorities to effect appreciable correction of the health care system. When testifying earlier this year before the Commerce, Science and Transportation committee SR-253, the congressmen acknowledged Dr. Tyson’s strong case supporting the value that NASA provides by inspiring and motivating our children. But in these tight fiscal times, how do we make that value better understood by the average American, acknowledging the current cultural apathy and disinterest in science and technology? Dr. Tyson was specifically asked his opinion on how to go about effecting the necessary changes to return NASA to it pre eminent role in our culture. Dr. Tyson acknowledged that was the “multibillion dollar question”.

Dr. Tyson then went on to describe how our life experience has shown us that:

“We never have to train our kids to think scientifically because they are always experimenting… always. They are turning over rocks, and they are poking at objects that the adults don’t want them to poke at. And we spend a lot of our effort as adults squashing that creativity and that exploratory drive that every child has within them. So when I am asked what do we do to excite children to explore, first get out of their way and don’t disturb their natural curiosity as a child.

And the real problem with science illiteracy and loss of embracing science and technology is not, I don’t believe, found in that next generation of children. It’s in the current generation of adults who far outnumber children, and who vote, and who run the country.

I am not going to turn around and say we are having these problems because we are not training our children. The country has problems because not enough adults understand them.

But the concept that no matter how bad things are today, the dream that there will be a better tomorrow transcends partisan politics. And as goes the future of NASA, so too goes the future of this nation”

Dr. Tyson points out that the solutions to every problem encountered in space flight have resulted in improvements in life here on earth. For this reason, the New Year’s resolution for our research group is to continue to focus on collaborative efforts to support the NASA group currently utilizing the upright MRI in Clearlake (Houston), Texas to help maximize those discoveries. By definition, a New Year’s resolution is a decision to do or not do something in order to accomplish a personal goal or break a habit. It comes at a time when people look back at the past year and make an effort to improve themselves as the New Year begins. We all know what happened last year; that ship has sailed. The “multibillion dollar” questions are what we are going to do about it and who is going to do it?

There are 4 kinds of people in this world;

1. Those who make things happen
2. Those who let things happen
3. Those who when things happen say; “what happened?”
4. And those that when things happen say; “who cares?”

Hopefully, this editorial will inspire others to commit to “making things happen” in the coming year. The ensuing discoveries will no doubt be “unimaginable” from today’s perspective and likely come from unsuspected sources. And more likely than not, those revelations will come from those of us “down here” in the trenches, and not from those “up there” on the Beltway. But without the two groups working
together, none of it will matter. We have no way of knowing which of us earthlings will crack the next code that will advance our collective knowledge and therefore perpetuate the evolution of our species, thus emphasizing the fact that we don’t have a single soul to waste. After all, each of us is ultimately here with the capability to effect change on earth.

There is no greater impetus to pondering one’s future than the turning of the New Year. As we usher in 2013, at first glance, our future may seem rather bleak. Politicians continue to spend society deeper into debt. In 1826, John Adams observed: “There are two ways to conquer and enslave a nation… one is by sword… the other is by debt. As they continue to regulate endlessly in their attempt to legislate our way to prosperity, they are inadvertently exacerbating matters. New technology may give government more power, but apparently not wisdom. Wireless communications and drones make it easier for politicians to monitor and neutralize their enemies, and smaller better cameras allow governments to spy on its citizens in the name of making them safer. And computers will soon be a smart as humans, but without our self awareness.

It is said that music and math are the two highest forms of communication, but maybe a little humor mixed in with mathematics can put in perspective the “Fiscal Cliff”:

**Lesson # 1:**
- U.S. Tax revenue: $2,170,000,000,000
- Fed budget: $3,820,000,000,000
- New debt: $1,650,000,000,000
- National debt: $14,271,000,000,000
- Recent budget cuts: $38,500,000,000

**Let’s now remove 7 zeroes and pretend it’s a family budget.**
- Annual family income: $217,000
- Money the family spent: $382,000
- New debt on the credit card: $165,000
- Outstanding balance on the credit card: $1,427,100
- Total budget cuts so far: $385

**Lesson # 2:**
Here’s another way to look at the Debt Ceiling:
Let’s say, You come home from work and find there has been a sewer backup in your neighborhood and your home has sewage all the way up to your ceilings.

What do you think you should do ...... raise the ceilings, or remove the sewage?

Thus, there is a “Catch 22” to this idea of collaborating with NASA, a government agency, in hopes of effecting the correction of Medicine. But maybe an electorate electronically empowered with the dream of a better tomorrow through advances in space travel can redirect the government.

Dr. Tyson spoke of his reticence to “speak to Congress” when he was called to testify before a congressional committee Commerce, Science and Transportation. His is of the opinion that scientists and other leaders of men should not circumvent the electorate by going directly to Congress to effect change. Rather we should take our ideas to the people of this country, and if they are convinced and agree with our ideas, they can use their vote in our democratic system to elect the leaders in Washington who will bring about those changes.

The media warns us that ultimately technology will enslave us and computers will be our downfall. “Are Kids Too Wired?” Time magazine asked. Newsweek warns of panic and depression and psychosis in the iCRAZY world. But the scare mongers are almost always wrong.

More likely, technology will continue to make us healthier and wealthier if we can apply it to forward thinking, constructive purposes. As T. Boone Pickens likes to say; “the second best time to do anything is now”. And if we are going to commit to working with the government to solve our problems, who better than rocket scientists to show us how?
Acclimation during space flight: effects on human physiology


Patients on earth with illness can be described as people who live in a normal earth environment but who have abnormal physiology. In contrast, astronauts are people with normal physiology who live in an abnormal environment. It is this abnormal environment in space that, for the most part, causes unique alterations in astronauts' physiology that require the attention of clinicians and scientists. In this review, we build on the first article in this series and provide an overview of the many complex physiologic changes that take place in short- and long-duration space flight, most often in response to microgravity.

The goal of sending people farther into space and extending the duration of missions from months to years will challenge the current capabilities of space medicine. The knowledge and experience in bioastronautics, associated with almost 50 years of human space flight, will be critical in developing countermeasures and clinical interventions to enable people to participate in these missions and return safely to earth.

Acute changes in normal physiology in response to abnormal environments are labeled acclimation for short-term exposure (hours to days) or acclimatization for longer-term exposure (days to months). In this review, we use the term acclimation to describe the physiologic and psychological responses to the space-flight environment. Table 1 provides a timeline of these responses from launch to the period after landing.

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<thead>
<tr>
<th>Physiologic effects</th>
<th>Launch</th>
<th>Duration of flight</th>
<th>Landing</th>
<th>Postflight period</th>
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<tbody>
<tr>
<td>Fluid redistribution</td>
<td>• Redistribution of fluid to the torso and head, 10% decreased fluid volume in the legs</td>
<td>• 17% reduction in plasma volume</td>
<td>• Gradual decrease in erythropoietin secretion, leading to a 10% decrease in total blood volume</td>
<td>• Orthostatic hypotension from pooling of fluids in the legs</td>
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<td>Cardiovascular effects</td>
<td>• Space motion sickness</td>
<td></td>
<td>• Space motion sickness</td>
<td></td>
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<tr>
<td>Muscle changes</td>
<td>• Gradual decrease in muscle mass by 20%</td>
<td>• Gradual decrease in muscle mass by 30%</td>
<td>• Muscle soreness and tightness</td>
<td>• Full recovery of muscle mass and strength</td>
</tr>
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<td>Bone demineralization</td>
<td>• Gradual decrease in muscle strength (up to 50% loss observed)</td>
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<td></td>
<td>• Complete or almost complete restoration of bone density</td>
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<tr>
<td>Psychosocial effects</td>
<td>• Fatigue, sleep debt, isolation, emotional effects, stress to the astronaut’s family, multicultural crew environment</td>
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<tr>
<td>Immune dysregulation</td>
<td>• Possible reactivation of latent herpes viruses and impairment of cell-mediated immunity</td>
<td></td>
<td>• Numerous cellular and other changes leading to impaired immunity</td>
<td>• Gradual improvement in immunity (days to weeks)</td>
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Microgravity has the largest effect of the space-flight environment on human physiology; all organ systems are affected to some degree. Isolation and confinement can also have important effects on the psychological well-being of astronauts. Table 2 outlines the key effects of the space-flight environment on humans and the countermeasures that are taken to address them.

<table>
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<th>Table 2: Countermeasures to minimize risks to astronauts before, during and after spaceflight</th>
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<td><strong>Physiological effects</strong></td>
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<td><strong>Shift in body fluids (cardiovascular effects)</strong></td>
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<td>Long and short duration</td>
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<tr>
<td><strong>Space motion sickness (neurovestibular effects)</strong></td>
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<td>Long and short duration</td>
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<tr>
<td><strong>Muscle atrophy</strong></td>
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Shift in body fluids
Acclimation of the cardiovascular system to weightlessness is complex and not completely understood. Control mechanisms involving the autonomic nervous system, cardiac functions and peripheral vasculature all play a role. However, the primary cause of these acclimations can be attributed to a redistribution of body fluids toward the head. The supine prelaunch position with the lower limbs raised above the thoracoabdominal coronal plane initiates a fluid shift, which continues during orbit, with blood and other fluids moving from the lower limbs to the torso and head. During space flight, the volume in the lower limbs decreases by about 10% (1–2 L of fluid from the legs' vascular and tissue space) compared with preflight. The facial fullness and unique puffy appearance of the head coupled with reduced volume in the lower limbs associated with this fluid redistribution is referred to anecdotally as the “puffy face–bird leg” syndrome.

The difficulty acquiring data during the ascent and post-insertion (into orbit) phase of shuttle flight has resulted in the use of “6-degree head-down tilt” models to study cardiovascular changes in microgravity. The shift of fluid toward the head distends the baroreceptors of the central vasculature, which triggers suppression of the renin-angiotension-aldosterone system, release of atrial natriuretic peptide leading to increased renal excretion of salt and water, and a net reduction in plasma volume. The early cardiovascular changes associated with entry to microgravity differ from those observed in bed rest models, suggesting a more complex process of acclimation.

The first 24 hours of space flight are characterized by a 17% reduction in plasma volume that results in transiently increased levels of hematocrit. This appears to cause a decrease in erythropoietin secretion, leading to a reduction in the mass of red blood cells. The net effect is an overall reduction of about 10% in total blood volume.

Aerobic capacity can be maintained or improved in space, but it is decreased in the post flight phase largely because of reduced stroke volume and cardiac output in response to the orthostatic challenge of reacclimation to gravity. Redistribution of body fluids with pooling of blood volume back in the vasculature of the lower body in association with reduced intravascular blood volume contributes to landing-day orthostatic stress. Typically, 1 out of 4 astronauts is unable to stand quietly for 10 continuous minutes within hours of landing because of light-headedness, heart palpitations and syncope. Countermeasures during space flight focus on exercise to maintain aerobic capacity with a number of techniques and devices to redistribute body fluids before landing (Table 2).

Space motion sickness
Most astronauts experience symptoms of neurovestibular acclimation during the first 1–2 days after arriving in space. There is a similar period of reacclimation to gravity upon return to earth at the end of a mission. The predominant symptoms include facial pallor, cold sweating, stomach awareness, nausea and, in some cases, vomiting. The term space motion sickness has been used to describe this syndrome. The broader syndrome of space acclimation includes space motion sickness, facial fullness, headache and lethargy.

Terrestrial motion sickness typically occurs when there is a mismatch between the visual and neurovestibular perception of motion. Many astronauts report alterations in perception while working in the unique weightless, 3-dimensional environment of space where there is no up or down; these aspects of space may contribute to space motion sickness.

The redistribution of body fluids that occurs on entry into microgravity is thought to account for some of the early symptoms, and it may produce transient benign intracranial hypertension. The range of reported symptoms is most likely because of a complex interaction between the autonomic nervous system and the gastrointestinal system, as well as neurovestibular and cardiovascular changes. Typically, space motion sickness is a short-lived phenomenon, with rapid improvement over the first 2–3 days of a mission. Occasionally, some astronauts take longer to overcome the symptoms. In very rare cases, a crew member has been incapacitated by motion sickness for the duration of a shuttle mission.
Similar neurovestibular acclimations are noted after landing and persist for the first 1–2 days in a gravitational environment. Orthostatic intolerance may contribute to a multifactorial syndrome after landing, which includes light-headedness, vertigo, gait disturbance and motion sickness. This condition has, in some cases, required intravenous drug and fluid administration. This constellation of symptoms after landing is of particular concern for astronauts on long-duration missions, for whom the magnitude of the symptoms is greater than for those on shorter missions. Neurovestibular changes are important because they affect crew performance in the final minutes of the mission during the critical landing phase and impair the ability of the crew to leave the space vehicle in an emergency situation after landing. The measures to mitigate space motion sickness are described in Table 2.

In the coming decades, humans will return to the moon and will ultimately begin to explore Mars. To prepare for these missions, it is critical that we develop countermeasures to prevent or reduce motion sickness associated with adapting to space and gravitational environments. Future missions will expose astronauts to 3 days of microgravity while in transit to the moon. Once on the lunar surface, they will adapt to the lunar gravitational force, which is 16% of that of earth. Some of the Apollo crew members experienced space motion sickness during acclimation to microgravity, but no symptoms of space motion sickness were reported during acclimation to lunar gravity. Neurovestibular countermeasures will be developed to optimize astronaut performance while adapting to lunar gravity and the 38% gravitational field of Mars.

**Muscle atrophy**

Muscles lose both mass and strength during space flight. The muscles most affected are the postural muscles that maintain our bodies upright in a gravitational environment. After a 2-week space flight, muscle mass is diminished by up to 20%. On longer missions (3–6 months), a 30% loss is noted. The fundamental cause of this muscle atrophy is the absence of gravitational loading on bones and muscles during space flight. Muscle unloading results in biochemical and structural changes. Additional factors that contribute to muscle loss may be suboptimal nutrition and stress.

Gross muscle atrophy is paired with a reduction in the size, not the number, of muscle fibres. Protein synthesis in muscle fibres is decreased, and protein degradation is increased. In the new in-flight equilibrium state, protein synthesis is decreased by 15% compared with preflight, and fibre cross-sectional areas are reduced by 20%–50%. Type 2 fibres of the postural muscle groups seem to experience greater losses than type 1 fibres. Muscle biopsies after landing also indicate a phenotypic shift from type 1 to type 2 fibres, allowing the muscles to contract faster but resulting in more fatigue.

In concert with atrophy, muscles also lose strength. Following short flights, a 12% loss of peak knee extension torque was measured, and a 31% loss was noted after a long flight. The loss of volume and the loss of strength do not always correlate. After a 6-month mission, one astronaut lost 20% of calf muscle volume, while the explosive force of these muscles was decreased by 50%. The discrepancy between lost mass and decreased force may be due to alterations of motor unit recruitment, the contractile apparatus, electromechanical efficiency or muscle damage. After 4 months in space, muscle mass and strength seem to reach a new steady state, although the elevated level of nitrogen excretion in the urine persists.

Following return to earth, astronauts’ deconditioned muscles are once again loaded by gravitational forces. Astronauts then report muscle soreness, tight hamstrings and calves and, in some cases, symptoms of plantar fasciitis.

Preflight physical conditioning is used to optimize muscle strength and endurance, aerobic capacity and bone density before long-duration flights. The primary countermeasures against microgravity induced muscular changes are exercise during space flight and rehabilitation after landing (Table 1). Exercise during space flight is helpful, but it does not fully prevent muscle loss. Additional countermeasures must be developed for future flights because a required 2-hour daily exercise program consumes valuable resources on the International Space Station including oxygen, water, food and crew-time.
Each astronaut returning from the space station participates in an aggressive muscle conditioning and rehabilitation program. In most cases, muscle mass and strength are fully recovered after 1–2 months back on earth.  

**Bone demineralization**

Microgravity induces a loss of bone density. In the micro-gravity environment of space, astronauts are no longer statically loaded by gravity. Skeletal impact loads typically associated with running and walking on earth are greatly reduced or absent. Because skeletal remodeling is dependent on the level of strain within the bone, this absence of loading is significant. 10,11,17 Other factors that may contribute to bone loss in space include low levels of light, resulting in decreased vitamin D3, and higher ambient levels of carbon dioxide, leading to respiratory acidosis. 10

Bone demineralization begins immediately on arrival in space. During the first days of a mission, a 60%–70% increase in urinary and fecal calcium is noted, 10,14 which continues throughout the mission. Bone resorption markers are increased in urine 10 and the blood levels of parathyroid hormone and 1,25-dihydroxy vitamin D production are reduced. 11

The loss of bone density is about 1%–2% per month in weight-bearing bones such as the lumbar vertebrae, pelvis, femoral neck, trochanter, tibia and calcaneus. 10,12,14,15,33 In these regions, the loss of bone density after a 6-month stay on the space station is typically 8%–12%. 11 There are large differences in the loss of bone density between individuals, as well as between bone sites in a given individual. A voyage to Mars (a 2.5-year round-trip) would deteriorate bone to osteoporotic levels if no countermeasures were used. The loss of trabecular bone could be so great that osteoblasts would be unable to rebuild the bone architecture upon return to earth. 10,11,14,17

Preflight assessments of bone mineral density using dual energy x-ray absorptiometry and quantitative computed tomography have been used to evaluate changes in bone mineral density associated with long-duration missions aboard the International Space Station and to monitor the efficacy of rehabilitation after landing with resistance exercise and, in some cases, bisphosphonate therapy.

Following return to earth, the loss of bone density may continue. The recovery process is typically lengthy 33 and is frequently much longer than the time spent in space. Similar to patients on bed rest or with incomplete spinal cord injuries, bone recovery may not be complete for several years. Patients on long-duration bed rest experience similar patterns of bone loss and calcium balance (~180 mg/day) as astronauts, who experience elevated resorption markers, unchanged formation markers, decreased 1,25 vitamin D and calcium absorption, and increased serum ionized calcium. 12

After returning to earth, astronauts are temporarily restricted from participation in some activities, such as flying high-performance jets because of the axial skeletal loading associated with high G forces. 14,15 Most astronauts on long-duration missions to the International Space Station will fully recover their bone density within 3 years after flight. However, some astronauts will never regain preflight levels, 14 and the recovered bone may have different structure and mineralization. 34

There is concern that astronauts may become osteoporotic at an earlier age and that the risk of bone fracture may be increased. 14 Fractures could theoretically occur during strenuous spacewalks or upon return to earth. 11 Furthermore, elevated calcium excretion increases the risk of kidney stone formation. Kidney stones have been reported following shuttle flights. 10,11 Because it takes such a long time to regain lost bone mass after flight, the focus of countermeasures is on the prevention of bone loss during flight (Table 1).

**Psychosocial effects**

Astronauts possess a wide range of technical skills related to the objectives of the space mission and a repertoire of behavioral competencies that enable them to function in a multi-cultural crew setting. These competencies play a critical role in the psychosocial acclimation of an astronaut to space, where faults cannot be tolerated. 35 The operational setting in which time-critical decisions with major consequences are required may contribute unique stressors to crew interactions throughout the mission, particularly
during long-duration space flight. A number of these elements are presented in training for space-flight resource management. The same principles are directly applicable to medical practice, both to reduce errors and create peak-performing clinical teams.

Selection criteria for the recruitment of astronauts from the general population ("select-out") and assignment of astronauts to specific missions ("select-in") are used to prevent mission-critical behavioral issues. Extensive preflight training is used to develop "expeditionary behavior," a complement of space-related psychosocial skills that are typically associated with the success of missions. The ground-based medical support team also works to maintain the performance of the on-orbit crew by providing behavioral support via video teleconferences with family, private psychological conferences and provision of recreational material such as DVDs, books and musical instruments.

The unique space-flight environment (e.g., temperature extremes, circadian dyssynchrony, acoustic noise) and operational requirements of long-duration space flight can contribute to fatigue and sleep debt. Scheduled uninterrupted sleep periods, noise-attenuated sleep stations and the intermittent use of short-acting sleeping medications or modafanil can reduce the amount of fatigue experienced by the crew and the deleterious effects on performance.

Although the emotional effects of space flight are mostly positive, they are profound. These effects can be negative and may last long after a flight if a performance-related issue affects an astronaut during the mission. Fatigue, for example, increases an astronaut's probability of making an error and decreases the capacity of each crewmember to deal with adversity, frustration and interpersonal challenges.

Long-duration expeditions aboard the International Space Station are a major undertaking for the astronaut's family. The prolonged training phase and the international travel requirements add to the challenges experienced by the family. The prolonged stress of having a spouse or parent exposed to the time demands and risks associated with training and long-duration space flight can be deleterious to the well-being of the family. The astronaut's spouse must cope with all of the family and household responsibilities.

Support is provided after landing to astronauts and their families by behavior health and performance teams. A multinational behavior and performance working group has made a number of important recommendations to the International Space Station program to enhance crew performance. Many international partners have implemented family-support programs to help with the myriad issues faced by astronauts and their families.

The importance of developing the appropriate criteria for select-out and select-in decisions, as well as the training required to develop the necessary behavioral competencies for long-duration space exploration, will play a critical role in the future as we prepare to send people back to the moon and on to Mars.

Immune dysregulation

Immune dysregulation was first observed in astronauts following missions in the 1960s and 1970s. Half of the Apollo astronauts reported bacterial or viral infections that occurred during flight or soon after return to earth. Blood samples drawn from 9 astronauts after flight from the Skylab Space Station showed that lymphocyte activation by mitogens was significantly reduced compared with that of preflight samples and samples from control people.

Much is known about astronauts' immune status immediately following space flight, but less is known about immunity during space flight. The few in-flight studies that have been performed indicate that space flight may be specifically associated with reactivation of latent herpes viruses and impairment of cell-mediated immunity.

Observations of astronauts' immune status after landing have shown numerous changes, including altered distribution of circulating leukocytes, altered production of cytokines, decreased activity of natural killer cells, decreased function of granulocytes, decreased activation of T cells, altered levels of
immunoglobulins, latent viral reactivation, altered virus-specific immunity, expression of Epstein-Barr virus immediate-early/late genes, and altered neuroendocrine responses.  

Immediate immune impairment before and after space flight probably reflects the very high levels of physical and psychological stress endured by astronauts at these times. Causal effects for impairment during flight likely include physiologic stress, isolation, confinement, disrupted circadian rhythms or other flight-associated factors. Increased circulating levels of glucocorticoids and catecholamines, a common occurrence during space flight, 49 may mediate changes in the immune system. The role of ionizing radiation on immune dysfunction is not yet certain. Weightlessness may also contribute to flight-associated immune dysregulation. In-flight and ground-based studies have shown that the lack of gravity impedes signaling pathways essential for early T-cell activation 50 and leads to alterations in the organization of the cytoskeleton and microtubule organizing centres. 51,52

Potential adverse clinical events that may be related to prolonged dysregulation of the immune system include hypersensitivities, autoimmunity, allergies, infectious diseases, latent viral reactivation and even malignant diseases. Bacteria that were recently cultured in-flight were found to have significantly increased pathogenicity. 53 We need to determine the clinical risk related to immunity and space flight before initiating missions to the moon and Mars. 54

Most of our knowledge is limited to low earth orbital flights of short duration. Very few of the incidents of infectious disease during space flight 49 have jeopardized a mission. Nevertheless, countermeasures for before takeoff have been developed; including verification that astronauts’ hematological and immunological function are within normal ranges for healthy people, as well as a quarantine program to reduce exposure of the crew to communicable diseases (Table 1).

Future considerations include exposing astronauts to earth-like gravitational forces while onboard a spacecraft. Daily exposure to artificial gravity by use of short-radius centrifugation has been shown to be protective against immune dysfunction and other adverse physiologic changes (musculoskeletal, cardiovascular) associated with weightlessness. 18

Conclusion
Space physiology and medicine is a young discipline that has made great strides in the first half century of human space flight. We have a good understanding of the medical problems associated with short-duration space flight, and have successfully developed countermeasures. The new challenge is long-duration space flight. Clinicians are currently refining the delivery of medical care for astronauts who live for longer periods aboard the International Space Station. They also seek to better understand the medical issues that future astronauts will face when we venture back to the moon and eventually on to Mars.

Key points
- Physiologic acclimation to space flight is a complex process involving multiple systems.
- Countermeasures before, during and after space flight are essential to reduce health risks.
- Although most physiologic effects resolve shortly after return to earth, bone demineralization may be a permanent consequence of long-duration space flight.
- The recovery period after a long-duration mission may be longer than the mission.
- Countermeasures to mitigate medical risk of long-duration space flight are being evaluated on the International Space Station.
Contrary to existing "common knowledge" to the contrary, the health care community is slowly beginning to embrace regenerative cellular medicine therapies. Society is not only becoming intrigued with, but is acknowledging the enormous regenerative capabilities and safety of utilizing patients’ enhanced and redirected immune systems to correct musculoskeletal problems.

Mankind is literally on the brink of the Age of Longevity. In the book; 100 plus- How the coming age of longevity will change everything, from careers and relationships to family and faith, futurist and tech writer Sonia Arrison, states that- “we are about to enter the golden age of aging. During the Cro-Magnon era, average human life expectancy was eighteen years. By the European Renaissance it was closer to thirty. Today in the developed West it is approximately eighty. As a species we are rightfully proud of this testament to our will and ingenuity. But few among us are prepared for the revolution on our doorstep—the coming explosion of scientific knowledge that will increase the length and quality of life in ways that were unimaginable even twenty years ago. In 100 Plus, renowned technology analyst and Silicon Valley insider Sonia Arrison lays out a thorough roadmap of the exciting new world confronting us, where fresh organs for transplants will be grown in laboratories, cloned stem cells will bring previously unstoppable death-sentence diseases to their knees, and living past 100 will be the rule, not the exception. Arrison brings a decade of experience researching and writing about cutting-edge advances in life extension to 100 PLUS, painting a vivid picture of a future that only recently seemed like a science fiction fantasy but now is very real”.

Not to break the optimism, but it is becoming apparent that even if humans become physically functional well over the century mark in age, the incapacitation caused by neurodegenerative disease will trump even substantial gains made in improved ambulation and pain management. In other words, although we may become able to increase ‘life span’ overcoming the crippling consequences of arthritis and back pain well into our second century of life, dementia will almost certainly limit our ‘health span’ such that we won’t be able to remember where we parked the car when we were 70.

Thus, cellular medicine techniques are being utilized not only in the musculoskeletal system, but great advancements are being made in the cardiovascular, pulmonary, digestive, genitourinary and central nervous systems- just not in this country. The cardiovascular system should certainly be near the top of the list of priorities for our proposed health care system restructuring, as congestive heart failure alone consumes 1/3 of the health care dollar. However, the most inexorable challenge in the near future is going to be deleterious multisystem effects of neurodegenerative disease, as 10,000 baby boomers reach retirement age each day. The inevitable effects on the health care system from the coming tsunami of the ‘diabetes’ generation are not to be dismissed, but first things first- we must prioritize.

"Top Down” approach to health care reform

In the long run, central nervous system diseases such as Alzheimer disease and other forms of dementia may constitute the greatest challenge to our generation’s health care system, with enormous potential to alter human evolution. With regards to cardiovascular disease, most of us know the basic ‘causes’ and ‘cures’, even if as individuals we choose not to make the decisions that would allow us to take advantage of that knowledge.

But with neurodegenerative disease, the “general consensus” is that we don’t know what causes it, much less how to prevent or treat it. So, the current “top down” health care system is defaulting as it always does when confronted with such challenges to reactively putting all of the resources into “purchasing ambulances to place at the bottom of the cliff” off of which patients continue to plunge, without proactively utilizing resources to “put a fence at the top of the cliff”.

Matt Ridley, a British science journalist, wrote The Rational Optimist- how prosperity evolves from human ingenuity. His treatise is base on the premise that it is free exchange of ideas; not central “top
down” planning that is behind human progress. And further, cultural evolution is seminal to human evolution. So maybe the best approach would be to try to affect a ground roots, “e-Patient” centered “Cultural Revolution” in deference to the ongoing attempt to legislate our way to health care reform from Washington D.C. and the concomitant government regulations and bureaucracy of ObamaCare.

An article published recently in the New England Journal of Medicine describes the potential for government directed and other bureaucratic “top down” medical groups to facilitate the so-called "bystander effect". The NEMJ report provides the example of an acutely ill man with mysterious symptoms -- a nasty rash, kidney and lung failure -- who was admitted to Yale-New Haven Hospital where he was treated by 40 of its finest doctors. But because so many cared for him, two of the attending residents say, the 32-year-old patient was actually made sicker because of the "bystander effect".

Authors Dr. Robert R. Stavert and Dr. Jason P. Lott argue that because of changes in health care, more specialists get involved, leading to "decay in coordination of care." The psychological phenomenon, also known as "Genovese syndrome," was first coined in 1964 after Catherine "Kitty" Genovese, 28, was stabbed to death in New York City as others appeared to have been aware of the attack and did nothing, although the number of bystanders has become a matter of dispute.

One witness told police at the time, "I didn't want to be involved." A large body of research now shows that humans are less likely to offer help in an emergency when others are present. The key factor is "diffusion of responsibility": the larger the group, the less likely an individual will act. "We have talked a lot about the broader issues of healthcare -- and not just within our field -- and it really struck a chord," Stavert, a resident in dermatology at Yale, told ABCNews.com. "We came to realize that the people involved were really excellent doctors and all worked with really good intentions but it became apparent the pitfalls people could fall into."

"Bottom Up" approach to health care reform

Hope is emerging; however, as patient initiated Google searches are challenging the outmoded, often self serving advice from uninformed health providers. We are beginning to acknowledge the 3 important realities that:
1). We are not "man made", and in doing so the corollary follows that therefore;
2). No "man" can possibly "fix us", thus opening up the belief that;
3). With proper, often simple, non surgical or pharmacologic cellular medicine based therapies we can actually “fix ourselves”.

Usually, early adopters of new technology and ideas take the greatest risks and pay the highest costs in hopes of bettering their condition. But the reverse is true with regards to those early adopters of cellular medicine therapy, who are enjoying lower costs and negligible risk by adopting these safe and affordable cell based therapies and avoiding potentially dangerous surgery and toxic pharmaceuticals.

For the last 50 years the American Association of Orthopaedic Medicine (AAOM) and its affiliate chapters has been promoting and teaching an integrative approach to both the diagnosis and treatment of acute and chronic pain emanating from the musculoskeletal system. The AAOM is a uniquely “bottom up” organization which provides information and educational programs on the accurate diagnosis and comprehensive nonsurgical treatment of musculoskeletal problems.

The AAOM promotes Orthopaedic Medicine by teaching physicians from multiple specialties integrative diagnosis techniques and comprehensive/ integrative nonsurgical treatment methods including proliferant injections (prolotherapy), steroid injections, fluoroscopic spinal interventions, osteopathic manual medicine, therapeutic exercise and interventions with various pharmaceutical/ nutraceutical/ herbal/ homeopathic based treatments. The AAOM method of diagnosis/treatment is effective in providing relief to acute and chronic pain emanating from the Cervical Spine (neck), Thoracic Spine (midback), Lumbar Spine/ Sacroiliac Region (low back), Upper Limb (shoulder-elbow, wrist-hand), and the Lower Limb (hip-knee-ankle-foot).
Over view of stem cell therapy from the perspective of cardiovascular diseases

I learned early in my career as an interventional radiologist of the importance of prioritization and collaboration, although I was incapable of incorporating those concepts into the health care system of that era. In those days, unfortunately, the cardiovascular system was treated as two separate entities. The “cardio” (heart) part of the system was the “domain” of the cardiovascular surgeons and the cardiologists, while the “vascular” (peripheral vascular) system fell under the jurisdiction of the interventional radiologist. Although we conferred in weekly conferences as often as our schedules allowed, the three separate specialties inadvertently “succeeded” in dividing the cardiovascular system into separate silos of medicine; much to the detriment of our patients.

Streptokinase was being replaced by Urokinase, a much more expensive, frequently dangerous and since recalled thrombolytic drug. Urokinase was thus the new “standard of care” for dissolving blood clots and in those days the interventional radiologists were the clot busters of the cardiovascular community. I remember spending all hours of the day and night meticulously infusing Urokinase (liquid gold) into the lower extremity vasculature of our growingly ischemic population of Veterans. It was not uncommon to infuse thousands of dollars worth of Urokinase into a single patient, often depleting the special procedures’ budget for the entire month.

As it turned out, our post procedure “sense of success” was not only over blown, it was actually biphasic. The “short term” sense of satisfaction had its own short half life. That acute sense of success was often tempered by long searches throughout the hospital wards to document the miraculously restored pulses of our newly “cured” patients only to discover those men in the smoking area enjoying their favorite pastime. Holistic medicine was barely on the radar then, and we (patients and physicians alike) were just beginning to understand that low tech life style changes like smoking cessation, diet and exercise were actually just as important to outcomes as our high tech miracle cures.

Any residual “long term” euphoria from the successful clot lysis was ultimately extinguished by the realization that that patient’s leg claudication had been actually been cardio-protective. A more appropriate “sense of humility” soon set in. We had been busy patting ourselves on the back for restoring the patient’s lower extremity blood flow until we realized the unexpected/unintended consequences of our deed.

Prior to our “brilliant” peripheral vascular intervention, a patients’ claudication and leg pain usually limited them to mowing only their front yard in one session. The patients then needed a “half time” respite to allow the leg discomfort to dissipate before moving on to the back yard. But once we opened up their trifurcation vessels they could mow their entire yard, front and back, without taking a break to rest their legs. The only problem was that not uncommonly they would suffer a myocardial infarction because their leg function could then exceed their cardiac reserve and lung capacity. We finally realized, better late than never, that unless you “fix” the heart first, you are doing the patients a potentially deadly disservice if you only “fix” their legs.

There is a similar lesson to be learned with regard to cellular medicine therapy for peripheral arterial disease (PAD). We have a group in the Arkansas participating in a FDA approved limb ischemia trial utilizing bone marrow derived stem cells (so-called BMAC). Unfortunately, the FDA is opposed to utilizing that same cellular medicine therapy for cardiac disease in the US. Thus we will have to send our patients off shore or overseas to address their concomitant coronary disease, lest we are doomed to repeat the mistakes we made in the Urokinase era.

The following is a paper written by our distinguished group of cardiologists in Arkansas participating in the limb salvage trial, and provides an excellent overview of cellular medicine therapy from the perspective of the cardiovascular system.
Understanding the application of stem cell therapy in cardiovascular diseases

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Stem Cells and Cloning: Advances and Applications

Abstract: Throughout their lifetime, an individual may sustain many injuries and recover spontaneously over a period of time, without even realizing the injury in the first place. Wound healing occurs due to a proliferation of stem cells capable of restoring the injured tissue. The ability of adult stem cells to repair tissue is dependent upon the intrinsic ability of tissues to proliferate. The amazing capacity of embryonic stem cells to give rise to virtually any type of tissue has intensified the search for similar cell lineage in adults to treat various diseases including cardiovascular diseases. The ability to convert adult stem cells into pluripotent cells that resemble embryonic cells, and to transplant those in the desired organ for regenerative therapy is very attractive, and may offer the possibility of treating harmful disease-causing mutations. The race is on to find the best cells for treatment of cardiovascular disease. There is a need for the ideal stem cell, delivery strategies, myocardial retention, and time of administration in the ideal patient population. There are multiple modes of stem cell delivery to the heart with different cell retention rates that vary depending on method and site of injection, such as intra coronary, intramyocardial or via coronary sinus. While there are crucial issues such as retention of stem cells, microvascular plugging, biodistribution, homing to myocardium, and various proapoptotic factors in the ischemic myocardium, the regenerative potential of stem cells offers an enormous impact on clinical applications in the management of cardiovascular diseases.

Keywords: stem cell therapy, stem cell delivery, cardiovascular diseases, myocardial infarction, cardiomyopathy

Introduction

Each year, the American Heart Association updates its statistics on heart disease, stroke, and other vascular diseases. Mortality data related to cardiovascular diseases in 2008 accounted for 32.8% mortality, or one of every three deaths in the United States, suggesting a very high burden of cardiovascular morbidity and mortality.1

This emphasizes the need for new cardiovascular interventions that will have some impact on cardiovascular morbidity and mortality. Utilization of stem cell therapy, through the application of multiple new devices and methods, may offer rapid regeneration of effective myocardium, and thus impact cardiovascular morbidity and mortality. This provides a key to long-term survival in patients with permanent myocardial damage, either by stimulating local generation, or by providing a continuous supply of cardiac stem cells. The study of stem cells and their role in treating cardiovascular diseases is evolving at a rapid pace.

Regeneration and healing of damaged tissue by repair is critical to survival. Repair refers to the restoration of tissue architecture and its function after injury. This process occurs by means of two key steps: regeneration and healing. Some myocardial tissues can replace all the damaged tissue, with return of myocardium to more of a normal state; this is the repair process of regeneration. Other tissues may be incapable of restoring the tissue, and repair may partly or completely occur by the laying down of connective tissue or fibrous tissue, thereby leading to healing by scar formation or fibrosis (which involves extensive deposition of collagen as a result of chronic inflammation or necrosis). This repair process involves the proliferation of various cells and close interaction between cells, extra cellular matrix, and cellular paracrine function.

The aim of this review is to explore the concept of stem cell therapy for cardiovascular diseases, and to study the science supporting stem cell therapy and methods of delivery of this therapy to patients.

Stem cells and regeneration

Based on intrinsic abilities of the human body, tissues can be classified in one of three categories: continuously dividing tissues, stable tissues, or permanent tissues. Continuously dividing tissues, such as
hematopoietic cells in bone marrow, can readily regenerate. In the category of continuously dividing cells, the mature cells are short-lived and, as such, are continuously replenished by stem cells, creating a constant equilibrium between replication and dying mature cells. This phenomenon is evident in the multilayered epithelium of skin and in the gastrointestinal tract, which is a great example of a stem-cell niche of constantly replenishing dying cells. Stable tissue has cells that are in quiescence, with minimal replicative ability. Typical examples of such tissues include liver and kidney tissue, endothelial cells, fibroblasts, and smooth muscle cells; with the exception of the liver, all of these tissues have only limited capacity to regenerate after injury. Permanent tissue includes the tissues with terminally differentiated cells in postnatal life. Neurons and cardiac muscle cells were thought to belong to this category.

In the past, the accepted notion was that the human heart was a postmitotic organ without any regenerative ability. It was assumed that, in the period after birth to early adulthood, the heart had a relatively stable and slowly decreasing number of myocytes and that myocyte regeneration had little function.2 This view is now challenged, and evolving knowledge indicates that these tissues may be stable rather than terminally differentiated.

**Evolution of stem cell therapy in cardiovascular diseases**

Approximately 50 years ago, researchers discovered that bone marrow has at least two kinds of stem cells: hematopoietic stem cells, which give rise to blood cells such as red blood cells, neutrophils, basophils, eosinophils, monocytes, macrophages, B and T lymphocytes; and bone marrow stromal stem cells, which give rise to bone, cartilage, fat, and cells, called mesenchymal stem cells, that are needed to support the formation of blood and connective tissues. Early experience with intracoronary stem cell therapy for ischemic heart disease was reported by Strauer et al from Germany. In this study, researchers tested use of autologous intracoronary mononuclear bone marrow cells 5–9 days after percutaneous transluminal coronary angioplasty (PTCA; performed within 12 hours of myocardial infarction) in ten patients who received stem cell therapy after the PTCA. The patients showed improvement in segmental wall motion at three months.3 These results were confirmed in another study, by Assmus et al,4 of 20 patients who received intracoronary stem cell therapy 4 days after emergency PTCA for acute myocardial infarction. In this study, bone marrow mononuclear cells (BMC) were used in nine patients, and blood progenitor cells in eleven patients. Injection was performed in the culprit vessel, with reevaluation at 4 months. By as early as 2004, more than 150 patients had undergone stem cell therapy to attempt myocardial regeneration.5

In the United States, the FDA approved the first trial, by Perin et al.6 to evaluate BMC. This trial was designed to test BMC use in heart failure patients for hibernating myocardium by improving angiogenesis. This trial showed a 75% decrease in perfusion defects and an improved ejection fraction ranging from 20% to 29%. This pilot trial also demonstrated the efficacy of successful direct endocardial injection of autologous BMC. The feasibility and efficacy of intracoronary injection of peripheral blood stem cells, mobilized after granulocyte-colony stimulating factor therapy, was evaluated in the MAGIC stem cell randomized clinical trial.7 It showed improvement in cardiac function, and demonstrated promotion of angiogenesis in patients with myocardial infarction.

**Stem cell therapeutics**

By definition, the stem cells have to be self-renewing, clonogenic, and multipotent in vitro and in vivo. Stem cells must be able to divide asymmetrically into one daughter cell resembling the mother cell, and the other daughter cell that gives rise to multiple progenies. The result of this asymmetric replication of stem cells is that after each division of stem cells, some progeny enter into the differentiation phase while others remain undifferentiated stem cells, maintaining their self-renewal capacity.8

A number of experiments have shown that certain stem cells can differentiate into other than the predicted lineage (such as blood stem cell to cardiomyocytes), a process called transdifferentiation.9,10 Such stem cell differentiation into a specific stem cell type offers the possibility of a renewable source for the replacement of dead or nonfunctional tissues. It is now recognized that stem cells with the capability to generate multiple lineages are present in bone marrow and in other tissues. These are referred to as adult stem cells.
Whether these stem cells have the same differentiation plasticity, or differentiation capacity, as embryonic stem cells is the subject of ongoing research. One of the most exciting aspects of stem cell therapy is therapeutic cloning. This strategy involves using stem cell culture to produce large numbers of stem cells and then transplanting them into the target organ. In 2006, researchers had a breakthrough whereby they were able to reprogram adult cells to assume a stem cell-like state, called induced pluripotent stem (iPS) cells.

**Basic science and potential mechanisms**

Recent identification of different types of progenitor cells in the heart has suggested that the myocardium is not a terminally differentiated organ as previously believed. The remarkable potential of stem cells to develop into different cells within the human body during life, may serve as an internal repair system to replenish dead or dying cells. Such stem cells can be mobilized from bone marrow, fat, or blood, and then cultured to produce large numbers of cells for transplant into the area of injury.

Evidence challenging traditional wisdom that the heart is a postmitotic organ comes from the concept of cardiac chimerism. In this, female heart transplantation into a male host is followed by the display of significant y-positive myocytes in the female heart, suggesting that male stem cells in circulation went into the female heart and differentiated into three main local cardiac cells. This observation in the heart transplant patients, that putative stem cells and progenitor cells from recipients were found in the transplanted heart, supports the idea of ongoing regeneration, mediated by circulating stem cells.

Messina et al. have shown that myocardial cells from biopsies were found to have cells with the features of stem cells. These cells exhibited typical features of human circulating endothelial progenitor cells, such as CD34, CD31, KDR and c-kit positive. These markers suggested their origin was from bone marrow, and that subsequently accumulation was in the myocardium. The ability of these endothelial progenitor cells to generate functional myocardium is consistent with their role in cardiac repair.

Furthermore, bone marrow-derived endothelial progenitor cells could reverse the aging-associated decline in cardiac angiogenic activity shown in mice.

Subsequently, local injection of stem cells into myocardium, for myocardial regeneration, was shown in the experimental animal model in a study by Bearzi et al. The authors showed that injection of human cardiac stem cells directly into the myocardium of immune-suppressed mice led to the generation of a chimeric heart, which contained human myocardium with myocytes, coronary arterioles, and capillaries. This study resolved the question that human cardiac stem cells may be one of the therapies for cardiomyopathy. The mechanism of myocardial regeneration is unclear in the setting of little or no blood supply. Collateral vessels and oxygen diffusion from the endocardium may provide enough oxygen to preserve progenitor cells, thus allowing for repair; alternately, there may be cell migration from healthy adjacent myocardium, or directly from the circulation. These progenitor cells can differentiate into myocytes and coronary vessels. Several potential mechanisms are possible. Bone marrow mononuclear cells, mesenchymal stem cells, endothelial cells, and hematopoietic cells may have multifactorial mechanisms such as local neovascularization, neoangiogenesis, or involving their paracrine function. Furthermore, the paracrine function of stem cells may have the positive effect on endogenous cells of promoting angiogenesis and metabolism, or inhibiting apoptosis.

**Sources of stem cells**

As there is a rising interest in stem cell therapy, and reference is often made to the embryonic stem cell, one needs to be familiar with the terminology and the different types of stem cells, such as: embryonic stem cells, adult stem cells, cardiac stem cells, mesenchymal stem cells, and induced pluripotent stem cells. It is crucial to be knowledgeable about the multiple sources of stem cells and terminology used in the literature.

**Embryonic stem cells**

We are all formed from and made of stem cells. This begins with fertilization. The embryo has an inner layer called the endoderm. Endoderm cells have the potential to produce all kinds of cells. Mammalian development from embryonic stem cells is an irreversible process, in which cells become progressively specialized by a process of differentiation.
These embryonic stem cells have only a brief window of opportunity when all of the cells have a capacity to differentiate into any of 220 specialized cells. In the late state of the embryo, stem cells are already specialized to give rise to only a specific family of cells, such as muscle or bone, and these cells are called multipotent cells. In adults, there may be very few precursors of these embryonic stem cells that may help replenish cells in a particular organ, and these are called adult stem cells. These include bone marrow stem cells, blood stem cells, and fat stem cells.

**iPS cells**

iPS cells are cells that have been engineered to change their identity, with reversion to the embryo-like state, without the benefit of eggs or embryos. Like embryonic cells, iPS cells are pluripotent and have the ability to give rise to any type of tissue in an organism, body, or human body. These iPS cells are not extracted from the embryo but, rather, are created from regular adult cells by a “cocktail” of inducers or transcription factors, and are therefore called “induced” pluripotent stem cells. Takahashi and Yamanaka conceived the idea of introducing a combination of genes into an adult cell in order to reprogram the cell to behave like an embryonic stem cell, hence called a pluripotent stem cell. The challenge then, was to find the two dozen genes that are normally active in embryonic stem cells and introduce that cocktail into the adult cell, to create an iPS cell.

Subsequently, Yamanaka found that there was only a need of four genes, delivered by viruses such as Oct4, Sox2, c-Myc, Klf4, to accomplish this. The development of iPS cells is very exciting, as it avoids the controversial issues of human embryo research. The ability to harvest adult stem cells from an individual and transform them into iPS cells, and then transplant those stem cells into the desired organ, makes for a regenerative therapy of that tissue that is very attractive.

Thus, iPS cells will be genetically and immunologically matched with the recipient body. However, this raises many questions about whether it is really possible to turn back the biological clock of adult cells to an embryonic state. If this is true, this may provide a “fountain of youth,” and may help millions of patients escape, or markedly delay, the consequences of disease and aging. The use of cellular engineering to create iPS cells may be the only way to “trick” cells into behaving like embryonic cells, and to turn back the developmental clock of adult cells. The elaborate manipulation required for this process is called cellular programming.

When cellular reprogramming is done by means of nuclear transfer, the process is called cloning. Cloning involves injection of genetic material from a cell to an egg cell whose DNA has been previously removed. The injected DNA in the egg causes it to develop as an embryo, from which pluripotent stem cells can be extracted. The egg rejuvenates the genetic material of adult donor cells, with restoration of telomere length, which normally wears off with age (the caps protecting the ends of chromosomes). However, the process of cloning does involve embryos, once again raising ethical issues. iPS cells may offer the possibility of treating harmful mutations that cause diseases. In 2007, researchers showed that iPS cells brought about correction of sickle cell hemoglobin in the animal model, thereby opening the possibility of genetic treatment of known single mutations. Moreover, the idea of making iPS cells from patients, and then converting these into cell types involved in disease process, may unravel the mystery of treatment in heretofore untreatable conditions, and truly advance the field of new drug development for various diseases. Future research may focus on conversion of adult cells into iPS cells, and conversion of these iPSC to relevant cell types to treat individual diseases.

**Cardiac stem cells**

The human heart has cardiac stem cells that promote regeneration after myocardial infarction. Urbanek et al showed a 90-fold increase in cardiac stem cells in acute infarcts and a 26 fold increase in chronic infarcts, suggesting greater activation of cardiac stem cells in acute than in chronic infarct. The author further substantiated this with evidence of a large number of developing myocytes (10,000/gram), smooth muscle cells (1100/gram), and embryonic cells (3500/gram) in the border of the acute zone of infarction. Cell regeneration decreased by 70% in chronic infarcts, causing predisposition to chronic congestive heart failure.
In chronic infarcts, there was telomere attrition, leading to decreased telomerase levels. In this study, they also showed higher telomerase activity: an 8.6 fold rise in acute infarcts, as compared with a 2.6-fold rise in chronic infarcts. Telomerase activity is a marker of growth potential of cardiac stem cells, such as myocytes, endothelial cells, and smooth muscle cell lineages. This activity was very high in the border of acute myocardial infarction. Telomerase protects the DNA at the end of a chromosome during mitosis. As such, this finding has clinical implications for autologous transplantation in end stage cardiomyopathy, with the hope of increasing telomerase activity.

Mesenchymal stem cells
Mesenchymal stem cells are nonhematopoietic cells that exist in most of the adult tissues, notably in bone marrow and adipose tissues. These cells have the ability to differentiate, and can be modified in vitro to adopt phenotypic characters of cardiomyocytes and vascular cells. These cells have demonstrated the capacity of myocardial repair in models of cardiac injury. The mechanism of mesenchymal stem cell therapy appears to be predominantly mediated by paracrine function, rather than engraftment in the host myocardium. These cells have potential allogeneic therapeutic use.

Allogeneic stem cells
Use of an "off-the-shelf" product made from human mesenchymal cells from a single healthy donor has been proven safe in a Phase I trial. These mesenchymal stem cells are precultured from the bone marrow of a healthy donor, enriched with therapeutic properties, and are expected to target the myocardial site of injury due to stromal cell-derived factor-1 (SDF-1). These mesenchymal stem cells lack major histocompatibility antigen class 2 molecules and the phenotypes of these allogeneic cells in this study were CD145−, CD166−, and CD45−.

Use of such allogeneic cells have several potentials, including "off-the-shelf" intravenous use, and are supported by efficacy data in rodents and safety data in humans. These cells can differentiate into bone, tendon, fat, and muscle. These cells also secrete immunosuppressive cytokines. Moreover, these cells can be administered by minimal invasive approaches, such as the intravenous route. This stem cell type can target and differentiate into cardiac myocytes and blood vessels.

Ideal stem cell to treat cardiovascular diseases
The race is on to find the best cells for treatment of cardiovascular disease. There is a need to identify the ideal stem cell, ideal receptive environments, and optimal delivery strategies. There is also a need to define the ideal patient population, and ideal time of administration for stem cell therapy. The ideal receptive environment for cell therapy needs to include an environment which supports optimal cell proliferation. The ideal stem cell will be autologous, capable of differentiating into adult cardiac stem cells, and highly resistant to malignant transformation. These may include human mesenchymal cells, native cardiac stem cells, endothelial progenitor cells, or iPSCs. iPS cells closely resemble embryonic stem cells, which will be directed by a cocktail of proteins that support and regulate embryonic cardiovascular differentiation. Some of the important local factors may be those that inhibit inflammation and promote cell growth; for example, in rat experiments with hind limb paralysis, embryonic stem cell therapy worked only when adenosine derivatives were given in conjunction with cell therapy. Moreover, the use of heparin versus bivalirudin during intracoronary stem cell therapy is relevant, as heparin may block SDF-1/CXCR4 signaling, interfering with migration and homing of stem cells. Heparin may also decrease the circulating levels of vascular endothelial growth factor, which is needed for therapeutic angiogenesis.

Delivery of stem cell therapy
There are multiple modes of stem cell delivery to the heart, with different cell retention rates that vary depending upon method and site of injection, ie, intracoronary, intramyocardial, or via coronary sinus. Equally important is timing of delivery, as an early inflammatory response may create a hostile environment for local stem cell proliferation, thus inhibiting regeneration of new tissues. Also, a prolonged delay in stem cell delivery may allow fibrosis to set in, causing the therapy to be insufficient. The timing issue is like a dual-edged sword: early administration of cells may aid in retention of cells with better homing signals; however, a long delay may bring about scar formation. This logic has led to early delivery...
of stem cell therapy, in 5–7 days in the TIME37 study, and a delayed strategy in the Late-TIME trial,38 as it is harder to deliver stem cell therapy to most patients in the early strategy.

**Intracoronary stem cell therapy**

The conceptualization of intracoronary administration stems from the assumption of cell transplantation at the infarction site during the transcoronary passage of cells. This could provide a simple and effective treatment method for specific infarct-related territories, with maximal delivery of stem cells to the infarcted and peri-infarcted areas during the first injection, thus allowing intracoronary cells to “home-in” on these areas in a homogeneous fashion. Retention of cells in the target area will be a central issue. Studies have demonstrated extravasation of BMC to the infarcted area after intracoronary administration.39,40 This extravasation of stem cells may be affected by various factors, including chemokines and adhesion molecules induced by ischemic cell injury, and SDF-1. SDF-1 and beta-2-integrin appear to be the key factors.41–43

The intracoronary technique involves a standard percutaneous transluminal coronary angioplasty (PTCA) procedure, with use of an over-the-wire balloon with central lumen placed at a desired position. Coronary infusion of cells is performed four to six times, with 3-minute sequential balloon inflations followed by 3-minute rest periods, to create a “stop flow” situation for maximal retention. This delivery method allows maximum time for stem cells to come into contact with the microcirculation of the infarct-related artery, to maximize the opportunity for migration and retention of cells into the infarct and peri-infarct tissues for successful transplantation.

Baseline and post procedure LV angiograms should be performed. The patient must be monitored for 24 hours, with cardiac markers checked at 6 and 12 hours. It may also be intuitive to inject into a contralateral artery if there are well-formed collaterals, in the hope there may be better retention in the desired ischemic area. Imaging studies will be required to confirm whether giving contralateral stem cell injections encourages retention of cells in occluded artery territories. The crucial issues are: retention of cells, microvascular plugging, biodistribution, homing to myocardium and various proapoptotic factors in the ischemic myocardium.44 Hofmann et al45 showed that 14%–39% with CD34+ cells were retained in infarcted myocardium. This small study suggested that CD34+ may improve retention whereas Blocklet et al46 showed only 5.5% retention of CD34+.

Several randomized trials have shown that administration of intracoronary autologous BMC in patients with myocardial infarction results in improved ejection fraction.47,48 Other trials have shown evidence of improvement of regional wall LV function.49 The Repair-AMI trial50 showed a decrease in major adverse events. However after these initial positive publications, several studies have failed to demonstrate that bone marrow nuclear cells improve LV function in the setting of acute myocardial infarction.51–56 In the previous studies, most of the autologous bone marrow mononuclear cell implantations were performed 5–7 days following STElevation myocardial infarction.

Of interest is that, in a small cohort of patients in the Repair-AMI trial, it was observed that the most favorable effect on LV function was obtained by delivery of stem cells on the fifth day. It is a possibility that timing of cell delivery after myocardial infarction may have an influence on treatment. This has fostered much discussion over the timing of stem cell implantation after acute myocardial infarction. As we know, within hours of acute myocardial infarction there is a well documented increase in circulating progenitor cells released from bone marrow.57–59 This includes the release of increasing numbers of hematopoietic stem cells, endothelial progenitor stem cells, mesenchymal stem cells, and a very small number of embryonic-like cells with pluripotent properties.60

Some of the concerns in regard to negative findings have been related to inadequate cell count, improper processing, and timing of administration. The National Heart Lung and Blood Institute sponsored the Cardiovascular Cell Therapy Research Network and developed two prospective clinical trials, TIME37 and LateTIME.38 The TIME trial was designed to compare the effects of bone marrow mononuclear source cells delivered in patients with predominantly ST elevation myocardial infarction at 3 to 7 days. The Late TIME trial was developed to test the hypothesis as to whether delayed delivery of autologous bone marrow cells, at 2 to 3 weeks following acute myocardial infarction, would improve global LV systolic
function. Cell count and processing issues were clarified by the Late TIME trial,61 which did not show any detectable improvement in LV function over a period of 2 years.

**Intramyocardial stem cell therapy**

Intramyocardial injection of stem cells is the most invasive approach and is performed via an endocardial approach or during open heart surgery. During open-heart surgery, the injection process is simple. It is performed under direct visualization, allowing for evaluation of the potential target. With this method, one may not be able to access all the areas of the heart. Transendocardial injection guided by LV electromechanical mapping with NOGA™ software (Biologics Delivery Systems, Diamond Bar, CA) can help deliver therapy to the target infarct area.62 Using NOGA, cells are directly injected into nonviable myocardium, with an 8Fr MYOSTAR™ catheter (Biologics Delivery Systems). This catheter has nitinol tubing that contains a retractable needle for injections.

Depending upon the LV wall thickness, the needle length can be set up as 4.5–6 mm. Once endocardial contact is made and the appropriate angle under fluoroscopy is determined, 0.3 cc of stem cells are injected by manually advancing the needle. Additional injections are spaced by 1 cm, and will be guided by NOGA.63 However, it is important to refrain from using this transendocardial approach in areas of thinned myocardium (thickness less than 5 mm by MRI). After the procedure, LV angiography should be performed and the patient should be monitored for 18–24 hours. In the United States, the first FDA-approved trial was designed to test the hypothesis that intramyocardial injection of autologous BMC would benefit patients with heart failure by salvaging hibernating myocardium and by improving angiogenesis.6 This trial showed a 75% decrease in perfusion defects and improved ejection fraction ranging from 20% to 29%.

**Retrograde coronary sinus injection**

Several approaches have been used to deliver potentially therapeutic stem cells. Retrograde infusion using the coronary sinus is the least studied at this time. This modality typically involves placement of a double lumen catheter with a larger proximal balloon and a smaller distal balloon, with the delivery of therapeutic cells at, and beyond, the distal lumen. The distal balloon is used to prevent washout of cells. The cells are injected once catheter placement is confirmed angiographically in the mid- to distal interventricular vein, which runs parallel to the left anterior descending artery. In one of the swine models, 107 cells (in 10 cc) were injected at a pressure of 150 +/- 16 mm Hg for 8 +/- 3 seconds, and both balloons were deflated at 5 minutes post delivery, to maximize local delivery.36 In this study 43% +/- 3% delivered cell exit to lungs in retrograde coronary sinus injection and 41% +/- 1% exit to lungs with intracoronary injections. Furthermore, retention with the intramyocardial route was the highest, with 26% +/- 3% exit to lungs.

**Intravenous**

This is the simplest approach but, depending upon the IV access site, cells may become trapped in the lungs, liver, and spleen, so that only a small number may enter coronary circulation, and myocardial homing will be minimal.62 Myocardial homing depends on multiple micro environmental factors, such as expression of adhesion molecules, cytokines, and homing receptors.

**Discussion**

During life, an individual may sustain many injuries and recover spontaneously over a period of time, without even realizing the injury in the first place. Wound healing occurs due to a proliferation of stem cells capable of restoring the injured tissue. These stem cells contain the genetic blueprint or memory of how this particular tissue was constructed to begin with. Similarly, regenerative potential by stem cells offers an enormous impact on clinical applications. These potentials may arise from the multiple functions of stem cells, such as self-renewal, multipotency, and paracrine functions.

There may be benefits from the paracrine secretion of growth factors or cytokines by a number of retained cells, leading to further mobilization of endogenous progenitor cells. We do not understand the underlying mechanism of stem cell regeneration and healing, just as, at one time in history, we had no concept of the mechanism of action, and benefits, of aspirin, even though the benefits were there long before we understood the mechanism.
The amazing capacity of embryonic stem cells11 to give rise to virtually any type of tissue has intensified the search for a similar cell lineage in adults. However, these adult stem cells have the complex tasks of taking up residence in just the right place in order to gain the necessary shape, and of assuming paracrine functions, and then must perform their multiple functions in a complex variety of different cellular environments. Due to the remarkable plasticity of stem cells, one can imagine the exciting possibility of a universal stem cell that can circulate throughout the body and reside wherever needed to promote regeneration of local tissue.

However, the major challenge is retention of these cells after implantation via intracoronary, intramyocardial, and retrograde coronary sinus approach. Since a significant percent of stem cells leave the heart soon after administration,36 the clinical ramifications may be significant. These stem cells have multiple functions and can be proangiogenic and paracrine, thereby elaborating potentially detrimental substances in nontarget organs.

Perhaps the major hurdles to the clinical application of research in regard to adult stem cells are the small number of cells that can be isolated from any adult tissue with successful propagation of multipotent adult stem cells.64 and the development of perfect “cocktails” for optimizing the proliferation of adult stem cells.65 This implies that expansion of adult stem cells in culture may be the answer, although one must keep in mind that extensive cultures of human adult cells may suddenly change their intrinsic properties in vivo, rendering them unfit for restoring injured or diseased tissue in patients.

Obviously, stem cell therapy will have a wide spectrum of clinical applications in cardiovascular medicine. This treatment may even have a role in reversing the aging process, which is a natural phenomenon. With the aging process, there is a decline in stem cell number and viability. Moreover, aging and disease are interlinked. Therefore, stem cells may provide a treasure trove of renewable life, and a “fountain of youth.”

Disclosure
The authors report no conflicts of interest in this work.

References


The remaining 95% of the population is actually affected by genetic defects/predispositions. The remaining 95% have a normal genetic complement but still exhibit diseases because of how our genes are selected and expressed by our belief system.

Dr. Bruce Lipton
His revolutionary revision of cellular biology places in perspective the importance of regenerative medicine in the correction of medicine

In his publication The New Biology - Where Mind and Matter Meet, Dr. Lipton points out the problems with the current belief by traditional medicine based on the idea that our genes control our health.

“Recent advances in cellular science are heralding an important evolutionary turning point. For almost fifty years we have held the illusion that our health and fate were preprogrammed in our genes, a concept referred to as genetic determinacy. Though mass consciousness is currently imbued with the belief that the character of one’s life is genetically predetermined, a radically new understanding is unfolding at the leading edge of science. Cellular biologists now recognize that the environment, the external universe and our internal physiology, and more importantly, our perception of the environment, directly control the activity of our genes. Dr. Lipton is the proponent of the realization that the molecular mechanisms by which environmental awareness interfaces genetic regulation guides organismal evolution”.

Old Biology - Genetic Determinism
“We are controlled by genes.”

New Biology - Environmental Determinism
“We are controlled by our perception of our environment.”

“Only 5% of the population is actually affected by genetic defects/predispositions. The remaining 95% have a normal genetic complement but still exhibit diseases because of how our genes are selected and expressed by our belief system.”

While cloning cells, Dr. Lipton discovered that destroying the DNA did not appreciably affect the subsequent behavior of the cells. So the existing dogma that DNA was supposedly controlling the cell was challenged, but it was initially unclear what was actually controlling the cells once DNA was removed. The discovery that the “real brain” of the cell is not the nucleus or the DNA per se caused scientists to rethink the previously existing “belief” about the relationships amongst disease, genes and pharmaceuticals. So, despite the “conventional understanding”, it turns out that our beliefs and perceptions (and their chemical/electrical surface signals interpreted by our cell membranes) have a much greater influence over our lives than we ever knew before Dr. Lipton’s seminal work.

Newtonian Mechanics
Determinism is the Newtonian theory that occurrences in nature are causally determined by preceding events or natural laws thus- “We can predict the outcome”. According to the Newtonian vision, the Universe is a machine made out of physical parts. If we simply understand how the physical parts interact, we can understand everything there is to know about the machine. But in this Newtonian theory there is no “room” for energy in this philosophy, only the understanding of the physical parts of the machine. By the entertaining the belief in Newtonian Physics, medicine does not acknowledge that energy is involved in the healing process.

Determinism is flawed. If true, then we would be essentially “locked” into our fate. A self fulfilling prophecy that could result in our becoming irresponsible in our health care because of the fatalism of this misconception. But this assumption is not true; genes do not control who we are. The Newtonian concept of biology as it pertains to medicine is out of date by 75 years; because we entered into the era of quantum physics in 1925.

Evolution
And further, historically, it was not a purely Darwinian process that predetermined our biosphere, but more of a La Markian process. In other words, our evolution has not been so much the result of inter-personal competition based on a “survival of the fittest” (winner takes all), so much as survival having been based upon success of the individual that can best adapt to their changing environment- huge difference.

Darwinian:
1859 Darwinian evolution provides for biological diversity, and espouses the theory that the traits, characteristics, behavior and “success” of an individual are solely due to hereditary factors.

La Markian:
Organisms match their environment. When environments change, the organisms change to adapt. Whatever environment one occupies and whatever one’s belief system tells one about its environment will be adapted to by one’s genes. In essence, one’s genes will adapt to one’s beliefs.

Mission of Science (Before1600’s)
Before the 1600’s, the scientific belief was that God and Spirit infused the physical world, and thus man would benefit by trying to understand the spiritual nature of the world. The mission statement of the scientists of the era was: To gain an understanding of the “natural order” so that we can live in harmony with it.

Scientific Revolution (After 1600’s)
Descartes and Isaac Newton looked at the Universe and determined that man did not necessarily need a God to explain the almost “clock work” like mechanism of nature. The movements of the planets and sun could be mapped out, leading scientists to believe that the universe was a mere machine about which predictions could be made. Scientists began to look at the body not with respect to having an “outside” spiritual influence, but as a manifestation of the “inner” workings of a machine, “just like the Universe”. They theorized that if we could just understand the workings of the body, we could “fix” and “adjust” it just like a machine.
Mission of “Modern” Science (after the 1600’s)
To obtain knowledge that can be used to dominate and control nature. Rather than try and live in harmony with life, the new mission statement was to control and dominate nature.

Secrets of the Human Cell
50-70 trillion cells make up the community of cells we refer to as our body, only 10% of which are “us” (most cells are bacteria, fungi, and “non self”). Not uncommonly, in the process of cloning cells from a human body, the cells are placed in a Petri dish and may actually function better than when they were in the body because of the more favorable environment. Every function of the human body is also present in each and every cell (digestive, respiratory, excretory and nervous systems). Scientists study cells because cellular function and life cycle is almost identical to that of the body. But, until recently, scientists have only studied nature in the flawed terms of Newtonian Physics.

Newtonian Mechanics
1. Materialism
The belief in materialism (the world is just the sum of its “parts”), with no concern for anything outside the “physical” realm. Thus, when scientifically looking at the human body, one needs only look at the parts of the body.

2. Reductionism
The attempt to explain all biological processes by physical laws that chemists and physicists use to interpret inanimate matter “Take it apart and study the pieces”

3. Determinism
The theory that occurrences in nature are causally determined by preceding events or natural laws “We can predict the outcome”

The erroneous Watch Analogy
If one understands the parts that make up a watch, then when a watch is not working one needs only find the part that is faulty and fix or replace it. Along those lines, if the body is not functioning properly, take it apart and replace the faulty parts or administer drugs to improve function, thereby controlling the outcome; so called “determinism”. The theory is based on the belief that we can control the “machine” (human body) by replacing the faulty parts or altering them with the latest drug. Medical research is currently being driven by the current “drug model” of health care. It is the pharmaceutical industry that ultimately profits from medical research because as scientists discover how a body part works, a designer drug is introduced. But more and more we are seeing the errors associated with this faulty reasoning; i.e. drugs are not the answer to most health issues. For instance, according to a recent study performed in North Carolina, 50% of children taking Ritalin for attention deficit disorder do not have ADD.

“Life” defined according to Bruce Lipton’s philosophy of cellular biology
A signal (drug, chemical or hormone) when introduced into a protein matrix creates restructuring and change in shape (conformation) based on alterations in electric charge (energy). The movement that results from protein interaction and binding with a drug, chemical or hormone represents the source of Life. And a protein will not move (make work) without a signal. The body coordinates the function of the system by controlling the signals to the proteins, which then control their movement. That movement is converted into functional activities such as digestion, breathing, moving, etc. Proteins are the only “parts” (molecules) capable of movement (outside of random Brownian fluid motion), thus life can only come from the motion of proteins.

When we make the proteins as they move “do work”, then behavior comes from the movement of protein. Thus, life comes first from the static backbone that the proteins provide for the overall structure of the body, and secondly from the motion that results as proteins change their conformation (shape) in 3-dimensional space.

The test tube and the cell both contain the ‘essential’ proteins, but the in the test tube there is only random activity, while the cell has order, organization, orientation, i.e. “control” of the protein function to provide the source of life. Outmoded is the idea that loss of function due to a “depleted” protein could be
reversed by simply replacing the protein. And the thought that if we can find what replaces the protein then we can control the cell.

1859 Darwinian evolution provides for biological diversity, and the traits and characteristics and behavior of an individual are solely due to “hereditary factors” (which were unknown at the time).

1953 Watson-Crick the “hereditary factor” was discovered, as the DNA helix was shown to control the production of proteins through RNA. The patterns of the amino acids and protein “beaded strings” could be precisely traced back to the “code” on the DNA helix. Reinforcement for the relevance and apparent supremacy of the Watson-Crick model was the subsequent realization that DNA is extremely stable, and doesn’t easily break down or “wear out”, thus making it a highly efficient hereditary material. DNA from fossils thousands of years old could be utilized as a blueprint to make ancient proteins from animals that died 50K years ago. The Primacy of DNA seemed irrefutable.

The erroneous “Primacy” of DNA comes from the misunderstanding that since humans are made of protein, that is derived from RNA (the “Xerox” copy of the blueprint DNA), DNA must be the key ingredient to Life. And it also seemed logical to assume that if our “Character” comes from our protein make up, and our protein comes from DNA derived RNA, then DNA must be the determining factor of our “Character”. Therefore, who and what we are is predetermined in the blue print of our DNA.

Based on the “Primacy of DNA” theory, it should follow that our behavior, aggression, anxiety, happiness, alcoholism, obesity, must also be predetermined. Then the belief system arose that if only scientists could understand all of the genes, they would then be able to repair or replace any “broken” ones, and hence they could return to sick back to health. This was the noble concept that led to the human genome project completed in 1993.

The convention then was to believe that the nucleus was the “command center” of the cell because it contained the DNA, without acknowledging that 50% of the nucleus is protein. Every cell has all the same function as the entire human being, carried out inside the cell by miniature organs, organelles. It seemed to follow then that the cell has a nervous system, or “command center”, contained within the nucleus where all of the genes (DNA) are stored. And if the genes control who we are, then the nucleus being the repository of the DNA must be the source of control. This faulty reasoning resulted in the conclusion that the equivalent of the brain in a human being is the nucleus within each cell.

We know that if we take the brain out of any living organism, it will immediately die. But when you take the nucleus out of a cell it can live for two or more months. And the enucleated cell isn’t paralyzed, in fact it continues to grow, move around and interact with its environment. Thus the behavior of the cell is essentially unaffected by removing all the genes, thus the genes cannot be the “brain” of the cell. The logical conclusion is that the “Primacy of DNA” theory is incorrect; the genes do not control the cell.

But if the genes are not controlling the cell, what is? In 1985, Dr. Lipton’s research led him to refute the existing “science” of the “Primacy of DNA”. The lay news, mass media and scientific dogma of the day commonly misrepresented the role that genes played with the function of the cell by misusing the terms correlation and causation.

Correlation
A relationship existing between phenomena or things (an association, i.e. genes are correlated with our bodies- a gene has been found that correlates with obesity or cancer, etc.)

Causation
The act or agency which produces an effect (the error in using this term is that genes do not “cause” anything).

The “Truth” revealed
In 1953 (50 years ago), when DNA was initially decoded, the “hypothesis” was rendered that “genes control biology”. This “hypothesis” was so ubiquitous that it became a “truth”. The real “truth” is that
genes only have “potential”, whether they become activated or not depends on input from “signals” outside the cell. In other words, utilizing the analogy of a hand gun, the genetic predisposition for the disease are the bullets in the pistol, which can only be fired (enacted) by the environment.

1990
When a gene product is needed, a signal from its environment, not an emergent property of the gene itself, activates expression on that gene.

H. F. Nijhout

A gene is only a blue print, it’s just data, and blue prints have no ability to create or do anything. The blue print (DNA) doesn’t turn itself on or off, and has no ability to determine if it is going to be read or not. But what does turn on and off is who is whether there is a “signal” from the environment that initiates the reading of the blueprint.

Evolution to Eu-medicine: “eu” meaning true

History

Sir Robert Hutchison’s Petition and the Medical Humanities:

‘From inability to let well alone
From too much zeal for the new and contempt for what is old
From putting knowledge before wisdom, science before art, and
Cleverness before common sense;
From treating patients as cases;
And from making the cure of the disease more grievous than the
Endurance of the same, Good Lord, deliver us.’

“Sir Robert Hutchison was physician to the London Hospital and to the Hospital for Sick children at Great Ormond Street in the later part of the nineteenth and early part of the twentieth century. He is famous for his book ‘Clinical Method’, first published in 1897. The twenty-second edition of this path-breaking book on clinical examination has recently been published. Sir Robert Hutchison is famous for his clinical sayings and especially for his petition written in his later years”.

“The phenomenon of disease mongering has attracted attention recently. Disease mongering can turn ordinary ailments into medical problems, see mild symptoms as serious, treat personal problems as medical ones, see risk factors as diseases and frame prevalence estimates to increase the market for medicines. Knowing when to prescribe a medicine and when not to prescribe medicines is an important skill for a doctor. Using drugs for physiological conditions may not be a good option. Many conditions respond to non-drug measures and psychological counseling and support. Life style diseases are becoming more common and maintaining a healthy life style can reduce the prevalence of these diseases.”

Zeal for the new and contempt for the old

“In the second line Sir Robert Hutchison talks about too much zeal for what is new and contempt for what is old. I will first examine this statement in the context of modern drugs and then look at it in the context of other treatment modalities. Newer drugs are strongly promoted and marketed for a number of conditions. In many cases a new drug may not be the best treatment option available. Drugs are tested on animals and then undergo clinical trials on healthy volunteers and patients before they are marketed. The problem is that these studies are carried out on a limited number of patients only. Many conditions of normal use of the drug are not addressed in clinical trials. Considering the limitations of data obtained from clinical trials even after a drug is marketed it remains under post-marketing surveillance. Many adverse effects become evident only after marketing and widespread use of a drug.”

International Journal of Medical Education. 2010; 1:2-4 ISSN: 2042-6372 DOI: 10.5116/ijme.4b8a.fba9
Digital Medicine- Congressional mandate- but be wary of “Zeal for the new”

Online service upends traditional practice
ZocDoc represents the modern force of change

“Imagine trying to book a flight, but rather than going to Priceline, Expedia or Delta, calling each and every plane to find if it had available seats. That’s basically how we book doctors. So it’s no wonder the average wait time to see one is 20 days. Cyrus Massoumi, who comes from a family of physicians, wants to change that. After he ruptured his eardrum on a flight from Seattle to New York and couldn’t get a doctor’s appointment for four days, he decided there had to be a better way. So he quit his consulting gig with McKinsey & Company and founded ZocDoc”.

“ZocDoc is a free service that lets patients book doctor appointments online. Patients can read reviews and research physicians, be certain their insurance qualifies, and fill out medical forms online, before ever setting foot in a doctor’s office”.

Commentary on ZocDoc by Michael Wolff-USA Today

“Urged by the young people around me - my own doctor was on vacation - I used ZocDoc the other day. I entered my particulars: my ZIP code, my malady, my insurance. And bingo, I had my choice of doctors in the vicinity and available appointments that day. I chose an ear nose and throat man, a 10-minute walk from my house and picked an appointment slot that very hour. I told the doctor... and I detected that he would rather not be reminded that practicing medicine had come to this”.

“Years from now, you may recall this column and its advice that we all should drop everything and plunge into remaking medicine – that epochal money pit and gold mine”.

“… the following is now going to happen:"

- The total convenience and demystification of the market is going to make ZocDoc irresistible to everybody with an immediate casual medical issue.
- Its transparency will foster cutthroat competition and inevitable price shopping and price cutting.
- Not only will prices fall, but doctors will begin to compete with insurance itself – all non-surgical attention for less than you’d pay for anything but catastrophic illness. In other words, the individual mandate will be obsolete before we even finish arguing about it.
- Surgeons join ZocDoc, too. Everybody joins ZocDoc. This includes all variety of para-medical professionals – physical therapists, acupuncturists, podiatrists, ambitious nurses, dental hygienists, anybody with the vaguest licensing requirements – extending marketplace competition.
- Undoubtedly, there are reviews and ratings and all manner of Yelp-like chatter and advice, meaning ZocDoc itself becomes something very close to your primary care physician.
- In no time, ZocDoc, or whatever mightier competitor emerges in the space, will itself become the most important brand and the unifying principle of health care system – with unchecked powers and the ability to bend the system to its own advantage.

“Quite simply, the people who once controlled the book of business no longer do. Of course, they were all present when Amazon came along and all fully aware that their business was inept, inefficient and infuriating – and silly, too. But they did nothing.

“Anyone could have been Amazon. Everybody should have been Amazon”.

“In a better, more ambitious world, there would now be several more Amazons”.
There is, I fear, a developing idea, that the world is divided between most of us and the gifted or well-connected or technically adroit few who will mastermind the next big thing. Trust me; the latter are, by whatever circumstances, just the opportunists, who we all should be.

We know change is coming – we really do know it and can invariably see it – yet, we stand there slack-jawed and gob-smacked, letting adventure, opportunity, even immortality in our profession pass us by. This may not be an original New Year's message, but it is a sage and hopeful one: Seize the day. Otherwise, of course, it seizes you.

Dr. Eric Topol
How clinical research will be radically affected by digital medicine
Director of the Scripps Translational Science Institute and Editor-in-Chief of Medscape Genomic Medicine and theheart.org.

There are critical aspects of how we can reboot the future of healthcare by leveraging the big innovations that are occurring in the digital world, including digital medicine. One of the things that have been missed is that how we do clinical research will be radically affected as well. We have this big thing about evidence-based medicine and, of course, the sanctimonious randomized, placebo-controlled clinical trial. Well, that's great if one can do that, but often we're talking about needing thousands, if not tens of thousands, of patients for these types of clinical trials. And things are changing so fast with respect to medicine and, for example, genomically guided interventions that it's going to become increasingly difficult to justify these very large clinical trials.

For example, there was a drug trial for melanoma and the mutation of BRAF, which is the gene that is found in about 60% of people with malignant melanoma. When that trial was done, there was a placebo control, and there was a big ethical charge asking whether it is justifiable to have a body count. This was a matched drug for the biology underpinning metastatic melanoma, which is essentially a fatal condition within 1 year, and researchers were giving some individuals a placebo.

Would we even do that kind of trial in the future when we now have such elegant matching of the biological defect and the specific drug intervention? A remarkable example of a trial of the future was announced in May. For this trial, the National Institutes of Health is working with Banner Alzheimer's Institute in Arizona, the University of Antioquia in Colombia, and Genentech to have a specific mutation studied in a large extended family living in the country of Colombia in South America. There is a family of 8000 individuals who have the so-called Paisa mutation, a presenilin gene mutation, which results in every member of this family developing dementia in their 40s.

Researchers will be testing a drug that binds amyloid, a monoclonal antibody, in just 300 family members. They're not following these patients out to the point of where they get dementia. Instead, they are using surrogate markers to see whether or not the process of developing Alzheimer's can be blocked using this drug. This is an exciting way in which we can study treatments that can potentially prevent Alzheimer's in a very well-demarcated, very restricted population with a genetic defect, and then branch out to a much wider population of people who are at risk for Alzheimer's. These are the types of trials of the future and, in fact, it would be great if we could get rid of the randomization and the placebo-controlled era going forward.

One of things that I've been trying to push is that we need a different position at the FDA. Now, we can find great efficacy, but the problem is that establishing safety often also requires thousands, or tens of thousands, of patients. That is not going to happen in the contrived clinical trial world. We need to get to the real world and into this digital world where we would have electronic surveillance of every single patient who is admitted and enrolled in a trial. Why can't we do that? Why can't we have conditional approval for a new drug or device or even a diagnostic test, and then monitor that very carefully. Then we can grant, if the data are supported, final approval.
I hope that we can finally get an innovative spirit, a whole new way of a conditional and then final approval in phases in the real world, rather than continuing in this contrived clinical trial environment. These are some things that can change in the rebooting or in the creative destruction, or reconstruction, of medicine going forward.

Cultural evolution drives Individual evolution

Dr. Neil deGrasse Tyson speaks of our need as a culture to facilitate NASA’s power to capture the imagination of Americans, and help our society return to the productivity and cooperative environment enjoyed during the space race of the 1960’s. What he may be alluding to are the experiments that have shown that “it is shockingly easy to elicit a sense of solidarity among a group of strangers. Just tell them they’ll be working together as a team, and they immediately start working together as a team, all the while attributing to each other a host of positive qualities like trustworthiness and competence”.

Edward O. Wilson’s New Take on Human Nature

The eminent biologist argues in a controversial new book that our Stone Age emotions are still at war with our high-tech sophistication.

Edward O. Wilson of Harvard University discovered in his study of ants the power of a wildly successful sector of nature’s bestiary, accounting for maybe a quarter of all terrestrial animal matter—the same percentage of biomass that we humans can claim.

“In his newly published The Social Conquest of the Earth—the 27th book from this two-time winner of the Pulitzer Prize—Wilson argues the nest is central to understanding the ecological dominance not only of ants, but of human beings, too. Ants rule the microhabitats they occupy, consigning other insects and small animals to life at the margins; humans own the macroworld, Wilson says, which we have transformed so radically and rapidly that we now qualify as a kind of geological force. How did we and the ants gain our superpowers? By being super-cooperators, groupies of the group, willing to set aside our small, selfish desires and l-minded drive to join forces and seize opportunity as a self-sacrificing, hive-minded tribe.”

“There are plenty of social animals in the world, animals that benefit by living in groups of greater or lesser cohesiveness. Very few species, however, have made the leap from merely social to eusocial. “eu-” meaning true. To qualify as eusocial, in Wilson’s definition, animals must live in multigenerational communities, practice division of labor and behave altruistically, ready to sacrifice “at least some of their personal interests to that of the group.” It’s tough to be a eusocialist. Wouldn’t you rather just grab, gulp and go? Yet the payoffs of sustained cooperation can be huge”.

“Eusociality, Wilson writes, “was one of the major innovations in the history of life,” comparable to the conquest of land by aquatic animals, or the invention of wings or flowers. Eusociality, he argues, “created super organisms, the next level of biological complexity above that of organisms.” The spur to that exalted state, he says, was always a patch of prized real estate, a focal point luring group members back each day and pulling them closer together until finally they called it home”.

“Our hypersocial spirit is both a great blessing and a terrible curse. Experiments have shown that it is shockingly easy to elicit a sense of solidarity among a group of strangers. Just tell them they’ll be working together as a team, and they immediately start working together as a team, all the while attributing to each other a host of positive qualities like trustworthiness and competence—an instant five-star customer review”.

**Background on the role of CSF flow in neurodegenerative disease**

Two years ago, I submitted an editorial entitled; “The unifying concept of CSF/Cerebellar Ectopia” (published in the AAOM February 2011 newsletter) putting forth the hypothesis that disturbance of cerebrospinal fluid (CSF), the “forgotten” 4th circulatory system (with arterial blood, venous blood and lymph comprising the other 3) might be the final common pathway shared by most neurodegenerative diseases.

That editorial postulated that CSF obstruction produced by cerebellar tonsillar ectopia (CTE) over time causes the brain to lose compliance and precipitates a secondary venocongestion, the combination resulting in end organ “stiffness” and ultimately to disruption of the blood brain barrier (BBB). If so, and despite the central nervous system initiating a multitude of corrective measures (in an attempt at altering cephalic arterial and venous blood flow and CSF distribution), eventually the patient’s homeostatic corrective measures are unable to prevent the CNS degeneration that leads to the “classic” clinical pictures of each of a myriad of seemingly disparate CNS diseases.

A few months after that editorial, I came across a paper that had been written 27 years earlier by Dr. Michael Flanagan that even more eloquently described the consequences of disruption of CSF homeostasis that he also opined was a common denominator in many neurodegenerative diseases. I immediately contacted Dr. Flanagan, and along with Dr. Scott Rosa, a close friend and colleague, we began to collaborate on how best to go about proving this “final common pathway” theory.

As the radiologist of the group, my input was imaging based/biased, while Dr.’s Flanagan and Rosa provided the insight as to the clinical presentation/correlation and potential therapy for those patients with this malady. The following portion of the editorial will review what we have found, being based primarily on the capabilities of current imaging techniques in diagnosing and following these neurodegenerative diseases. Inarguably, the best way to “go where no one has gone before” with any new idea or concept is to first acknowledge and review where mankind has already been.

**Dr. Michael Flanagan - CSF Fountains, Pulsations and Flow**

Posted on December 18, 2011 by uprightdoctor

The famous neurosurgeon Dr. Harvey Cushing stated that cerebrospinal fluid (CSF) flow is the third circulation of the brain. More recently in chapter six of Clinical Neurology published by Lippincott in
2006, Dr. Joseph Madson and others elaborated on Dr. Cushings description of CSF flow. They stated that **CSF pulsations are the fourth circulation of the brain.**

The open sutures, as seen in the picture, on an infants skull are called **fontanelles**, which means *little fountains*. They are known as “soft spots” in layman’s terms. The soft spots were so named because you can feel the pulsations of the brain at the fontanelles.

The fontanelles separate the plates of bone that cover the brain called membranous bones. They are called membranous bones because they grow within the outside covering of the brain and develop along with the brain. The membrane of the brain is made of dura mater, which means hard mother in Latin, so the soft spots aren’t as soft as they appear. They are actually relatively tough and difficult to penetrate. If you look closely at the infant skull above you will notice that the edges of the sutures are relatively smooth compared to the adult skull below. The sutures develop their characteristic shape as an infant matures. In either case, like all bones, their shapes are caused by the stresses that strained them.

If a baby becomes dehydrated the soft spots will sink. On the other hand, if the volume of cerebrospinal fluid in the brain increases, such as in hydrocephalus, the soft spots will feel tense and bulge outward. Typically, the fontanelles eventually disappear and the membranous bones are joined by their opposing surface that forms into the shapes of surgical sutures. Hence, the joints of the skull are called sutures.

Hydrocephalus in children is caused by blockage of CSF flow. The blockage of CSF flow causes the volume of CSF in the brain to increase. The increase in CSF volume causes the sutures to stay open and the head to increase in size. On the other hand, in some cases, there is premature closing of the sutures called **craniosynostosis**. Most cases of craniosynostosis cause mild almost imperceptible malformations of the skull and have no impact on health. In certain cases, however, premature closure of the sutures can cause hydrocephalus due to resistance to growth and development of the brain and subsequently CSF volume.

In any case, the shape of the **soft spots and sutures of the skull are a reflection** of cranial hydrodynamics, which is **fluid mechanics in the brain and skull**. The fluid mechanics are the result of electrical, circulatory and respiratory waves. Those waves are further amplified and modified by upright posture.

Strong CSF pulsations are a sign of good circulation and health. Weak pulsations are a sign of ill health and old age. On the other hand, when they get out of hand, waves can move boulders in rivers and tear apart the most imposing shorelines and obstacles. They can also cause malformations of the skull, as well as cause the sutures to stay open, as mentioned above. The pulsations of the brain also cause the irregular wave-like shapes of the sutures. They even leave little impressions on the inside roof of the skull.
where special valves, called arachnoid granulations, squirt CSF into the venous drainage system of the skull called dural sinuses.

If the pulsations can shape, indent and move the bones of the skull they can easily compress, dent and deform the brain and, in fact, they do. When the heart contracts a considerable amount of blood is driven into the brain, which compresses the brain, veins and CSF pathways. This drives venous blood and CSF out of the cranial vault and brain. When the heart relaxes, the brain, veins and CSF pathways expand which draws blood into the tissues of the brain, and pulls waste out of tissue spaces and into the drainage system ready to be removed on the next cycle. The heart thus causes the brain to rhythmically expand and contract.

Problems occur when waves get out of control. I liken them to rogue waves and describe them in more detail on my prior post. When CSF volume gets out of control it can damage the brain. Likewise, when CSF waves get out of control they can damage the brain as well. The basal cisterns (wells) that surround the brainstem and cerebellum with CSF, are the first place to experience the brunt of rogue waves and the most likely to suffer the consequences. I suspect that chronic pounding from rogue waves can cause damage.

Rogue waves may play a role in arachnoid cysts, cystic ventricles as in Dandy-Walker syndrome and the variant of Parkinson’s called multisystem atrophy or Shy-Drager. It most likely plays a role in empty sella syndrome and hormonal problems, as well as other conditions. I further suspect that one of the likely sources for destructive rogue waves in the brain comes from the cervical spine.

The first and most likely source of rogue waves is from malformations and misalignments in the upper cervical spine. Another is back jets due to whiplash, a phrase coined by Dr. Frans Schelling. Still another cause of the destructive, reflected waves is spondylosis lower down in the cervical spine.

Spondylosis is the term for degeneration of the spine. Among other things, spondylosis compresses the spinal canal and vertebral veins, which affects blood and CSF flow, as well as causing standing waves in the basal cisterns of the brain. Blockage of the vertebral veins affects blood and CSF flow in the brain. Overtime, chronic pounding from standing waves (clapotis—see prior posts) in the basal cisterns can compress the parts they surround and damage the brain. I will discuss spondylosis, seawalls and standing waves in next post.

For further information on related topics go to my website at www.upright-health.com.
Multiple Sclerosis: direct relationship between encephalic venous outflow obstruction and CSF obstruction

- Although this hypothesis may seem new or even radical, the theory of a possible relationship between CSF and other similarly vital intracranial processes (such as encephalic venous outflow) have been on the minds of scientists for nearly two centuries.

- According to Putnam, who discussed vascular abnormalities in MS in the 1930s, the first observations related to abnormal vasculature or effects related to vasculature appeared in the work of Cruveilhier in 1839, more than 170 years ago.

- In 1863, Rindfleisch noted an engorged vessel in the center of a plaque, and in the same year, Charcot described vascular obstruction in MS. These observations would be noted many times over the next 135 years.

- Putnam himself appeared convinced that the etiology of MS lay in the venous system. To test his hypothesis, he proceeded to study the effects of obstructed venous flow in the cerebral veins of dogs. These animals developed a number of abnormalities (lesions), many of them similar to encephalitis or MS. He noted at the end of his article: "The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques.

- While we agree that there is disturbance of the encephalic venous outflow in patients with MS, our research utilizing upright MRI phase contrast cine CSF flow analysis shows that those venous changes are in fact secondary to the primary instigator - disruption of CSF flow homeostasis.

- The story continues with a reference to Borst, who suggests that vascular obstruction occurs to the point of complete obliteration and hyaline transformation.

- A similar loss of the venous vasculature has been reported using susceptibility-weighted imaging by Ge et al. in 2009. Some researchers describe the combination of congestion, perivascular hemorrhage and pigments (possibly hemosiderin or iron-related in encephalitis following measles.

- In the 1980s, Adams found the presence of hemosiderin in the form of old hemorrhage in 30% of cadaver brain MS lesions.

- In a recent review of the role of venous reflux, Simka stated: "It is hypothesized that pathological refluxing venous flow in the cerebral and spinal veins increases the expression of adhesion molecules, particularly ICAM-1, by the cerebrovascular endothelium."
Along these lines, Bergan demonstrated, by occluding a major vein in the rat, that the number of leukocytes migrating across the vessel wall increased progressively during occlusion.

Multiple microhemorrhages occurred upstream of the occlusion (usually 20–30 µm in diameter, but some as large as 200 µm). "The venular occlusion experiments showed that reduced flow can rapidly set in motion an inflammatory cascade, including hallmarks like leukocyte adhesion to the endothelium, migration into the interstitium, free radical production and parenchymal cell death that begins soon after occlusion..."

Bergan goes on to say: "Elevated pressures can also cause the formation of transcellular gaps through endothelial cells, which may be related to the development of microhemorrhages."

In the 1980s, Schelling believed that there was a significant mechanical nature related to the fact that the vascular damage follows a path opposed to the flow. He quotes Carswell as saying: "In inflammation, the local congestion commences in the capillaries, afterwards extends to the small veins, but never to large branches; in mechanical congestion (by venous flow inversion) the blood accumulates first in the venous trunks, which are always conspicuous, and afterwards in the branches and capillaries."

Further evidence of this mechanical effect comes from observations of Allen, who noticed the widened vascular beds around veins and the central widening of the venous tree indicative of intermittent increases in cerebral pressure.

It is also worth looking into Fog's work. He summarizes his results from a series of cadaver brain studies as "thirty plaques showed that they definitely followed the course of the veins, so that course and dimensions of the veins determine the shape, course and dimension of the plaques." He also closes his work with the comment: "Consequently, multiple sclerosis, pathologically-anatomically, must be considered a periphlebitis, as proved by the author in 1948 in the case of plaques of the spinal cord."

Recent revelations regarding the physiologic effects of microgravity during space flight have shown how disruption of the CNS function directly results in deleterious effects on all other bodily functions from musculoskeletal atrophy to disruption of the immune system to fluid imbalance. Studies with NASA utilizing the upright MRI system are allowing us to document both the “structural” and “functional” imaging changes that occur subsequent to a relatively short time period of space flight, that may provide the “forme fruste” for neurological diseases that take decades to develop in humans on earth. And the importance of understanding the causes and consequences of microgravity during space flight cannot be over emphasized in the context of the future of the human race.

Acclimation during space flight: effects on human physiology CMAJ June 23, 2009 vol. 180 no. 13 1317-1323 CMAJ June 23, 2009 vol. 180 no. 13 "Space physiology and medicine is a young discipline that has made great strides in the first half century of human space flight. We have a good understanding of the medical problems
associated with short-duration space flight, and have successfully developed countermeasures. The new challenge is long-duration space flight. Clinicians are currently refining the delivery of medical care for astronauts who live for longer periods aboard the International Space Station. They also seek to better understand the medical issues that future astronauts will face when we venture back to the moon and eventually on to Mars”.

Summary of Historical Background

- During the last two centuries there has been ample evidence that the venous system is strongly associated with, but not necessarily causative of MS. Integrating this information together with our findings of the central role of dysfunction CSF homeostasis yields a more complete picture of the secondary role the veins play, as a consequent of mechanical issues to immunological issues.

- The CSF theory continues to be complemented by growing information regarding perfusion deficits, evidence for venous effects in other diseases and the clinical evidence for major venous insufficiency in many other diseases alleviated by reversing CSF flow disturbances that can be seen with modern “dynamic” imaging technologies today.

Current Pertinent Literature pertaining to Diagnosis of CNS diseases

**Diagnosing Alzheimer’s - A Process of Elimination**

Dr. Peter V. Rabins, director of the Division of Geriatric and Neuropsychiatry at the Johns Hopkins School of Medicine and Medical Editor of the Johns Hopkins Memory Bulletin,

*For now, only an autopsy can conclusively prove the presence of Alzheimer’s disease, but the clinical diagnosis is usually accurate. The current approach to establishing the cause of memory loss involves ruling out some potential causes and finding evidence to confirm the presence of others.*

Once other conditions, such as depression, Huntington’s disease or hypothyroidism, have been ruled out, the diagnosis of Alzheimer’s is made by accumulating information on the individual’s history and mental status exams and by interviews with the patient, family members and friends over a period of several weeks. Diagnoses based on this type of clinical information are accurate about 90 percent of the time. Alzheimer’s diagnosis is typically a process of elimination characterized by symptom progression over time. Recently, the National Institute on Aging and the Alzheimer’s Association updated their diagnostic guidelines for Alzheimer’s disease.

Highlighting new clinical approaches and more advanced protocols for research, the guidelines address three stages of disease: early preclinical stage, mild cognitive impairment and dementia. They also discuss the potential use of Alzheimer’s biomarkers as well as new imaging techniques for diagnosis.

The guidelines were developed based on the idea that more biomarkers and other signal transduction mechanisms would be elucidated over time, allowing for changes to be made based on new technologies and advances in understanding the disease state. They reflect the fact that researchers are focusing on these two important approaches as a method for earlier treatment and perhaps prevention of Alzheimer’s disease.
While these guidelines might not change clinical care at present, they demonstrate that early detection will become important in the future when effective treatments and methods for halting disease progression are developed.

After perusing the extensive literature on MRI findings in Multiple Sclerosis patients, it has become apparent that many of the case study MRI images presented to demonstrate the “classic” MS lesions also reveal Chiari 0, cerebellar ectopia; but nowhere in these papers is there mention of the imaging finding. What is needed is to put together a series of MS and headache patients combined with a “meta analysis” of how many of the patients shown in previously published MS papers also have this potentially CSF disrupting anatomy. CSF maldistribution may be the “unifying concept” that provides us with a single mechanism that connects many seemingly unrelated CNS diseases, thereby heeding “Occam’s razor”; that one should not increase, beyond what is necessary, the number of entities required to explain anything.

“Functional” brain imaging here-to-for has been a standard tool in the basic and clinical neurosciences for many decades, and “structural” brain imaging has an even longer track record of successful use for diagnosis of neurodegenerative disease. The “Holy Grail” of imaging is being approached by investigators at the Virginia Tech Carilion Research Institute who have invented a way to directly image biological structures at nanometer-resolution in their natural habitats (a liquid environment). A high-resolution nanoscale window to the live biological world is a major advancement toward the ultimate goal of imaging biological processes in action at the atomic level.

However, most diagnostic uses of structural brain images to date have involved naked-eye diagnostics or focal univariate techniques for which specific areas in the brain are probed for the “static” imaging findings of cortical thickness, volume, or gray matter attenuation, to identify patients in the prodromal or early stages of neurodegenerative disease.

### “Static” Imaging Imaging Based Biomarkers

A recent paper demonstrated that the ‘static’ imaging finding of ‘frontal lobe atrophy’ has high specificity (i.e. low false positives) for the diagnosis of Alzheimer Disease in the right patient population, and correlates with clinical biomarkers of elevated B-tau levels and other CSF biomarkers (that require invasive spinal tap procedures to obtain).

Prior studies have already confirmed the association of several classic ‘static’ imaging findings that are associated with Idiopathic intracranial hypertension (IIH) including:

- empty sella,
- prominent perivascular spaces of Virchow-Robin,
- prominent Meckel Cave CSF spaces,
- posterior globe flattening,
- tortuosity of the optic nerve, and
- optic nerve sheath distention.

There is growing literature documenting the fact that most if not all of these ‘static’ imaging findings that serve as indirect evidence of increased intracranial pressure can easily be seen even when using recumbent MRI scanners. The current challenge is that the interpreting physician must know to look for them, be able to find them, and then dictate them as non urgent but important findings into the MRI report so that they become a permanent part of the patients’ electronic medical record (EMR).
“Dynamic” versus “Functional” Imaging Based Biomarkers

Previously, “functional” neuroimaging analytic tools have consisted largely of univariate techniques as well, mapping the neural substrates of cognitive operations, subjects’ states/traits, or other variables of clinical interest. These analytic tools have, however, recently been augmented by more complex multivariate techniques that look at brain-wide atrophy or activation patterns. Together with this increasing sophistication of analytic tools, neuroimaging has recently experienced a reversal of the research goals under the rubric of “brain reading”: rather than mapping the neural substrates of a known subject variable in brain-imaging data, such as, for instance, behavioral performance in a cognitive task or diagnostic status of a neurodegenerative disease, the goal has become to predict a priori unknown subject information from the brain-imaging data.

Our goal this coming year is to utilize the Upright MRI systems in current use across this country to obtain not only ‘static’ imaging findings specific for particular neurodegenerative diseases, but to establish “dynamic” (not necessarily “functional”) intracranial CSF, arterial and venous flow patterns along with compliance measurements enabling indirect determination of intracranial pressure. We now have the software to do this, but it will require commitment in time and education by the interpreting physicians, keying on the cooperation and collaboration of the clinicians.

Once we establish the norms for these “dynamic” intracranial findings (Dynamic Biomarkers such as CSF and encephalic blood flow velocity, flow volume, intracranial compliance and intracranial pressure), in conjunction with the ‘static’ imaging findings and clinical findings, we can utilize the resultant normative data banks. For the first time we will be able to identify, stratify and sub classify our patients with suspected neurodegenerative diseases. The goal, obviously, is to be able to make the diagnosis of neurodegenerative diseases much earlier, and once made, we will be able to document the effectiveness of our upper cervical therapies in a quantitative, measurable way.

CSF flow evaluation can provide the determination of the key biomarker of craniospinal compliance. We know that CSF flow in symptomatic patients with Chiari I malformation, unlike that in volunteer subjects, is characterized by flow jets, regions with a preponderance of flow in one direction, and synchronous bidirectional flow. Synchronous bidirectional CSF flow in the foramen magnum has been noted previously in patients with Chiari I malformation. A spatial variation in the time at which flow reverses would not explain the presence of bidirectional flow over as much as 25% of the cardiac cycle. Confounding effects of arterial or venous flow have been excluded. Since bidirectional flow appears in close proximity to regions with large jets, it seems to be related to countercurrents resulting from jets. Phase contrast MR flow imaging can non invasively demonstrate flow jets, synchronous bidirectional flow, and heterogeneity of CSF flow and aliasing.

In volunteers, higher CSF velocities are normally found in paramedian locations in the anterior subarachnoid space at the cervicomedullary junction. Findings in patients with Chiari I malformation include jets with even greater velocity in the anterior subarachnoid space, synchronous bidirectional flow, as well as regions with preferential aberrant flow direction and large shear velocities.

CSF movement in the caudal or cephalad direction through the foramen magnum cannot be characterized as “plug” flow (as is classified the blood flow in the abdominal aorta). CSF flow in the foramen magnum is highly complex both spatially and temporally, even in healthy subjects. Velocities of inhomogeneities in flow are greater during the phase of cephalad (diastolic) flow than during the phase of caudal (systolic) flow in both volunteers and patients. This higher cephalad velocity suggests relatively greater pressure differentials during the cephalad flow of CSF than during caudal flow as a manifestation of the greater fluctuations in CSF pressures in the spinal canal than in the cranial vault. This observation may help explain the greater incidence of spinal cord cysts compared with brainstem cysts in patients with Chiari I malformation.
Findings show markedly nonlaminar CSF flow in the foramen magnum in volunteers and, to a greater extent, in patients with symptomatic Chiari I malformation. The complexity of flow may affect the development of signs and symptoms in patients and skew the measurement of flow with standard phase-contrast MR imaging methods. This complexity may explain some discrepancies between the results of previously reported studies, all of which have been performed utilizing recumbent MRI scanners. More work is needed to characterize the flow of CSF in the foramen magnum, and especially to also perform the studies on upright MRI scanners. To characterize flow accurately, flow data must be acquired in multiple sections or as a volume, in multiple directions, and with the smallest possible voxels.

Multiple Sclerosis and CSF / Vascular correlation

Collateral Venous outflow from the brain

For more than a century, available data concerning principal and collateral venous outflow from the brain have received insufficient attention, as existing theories did not assign practical importance to them. Ideas concerning arterial blood supply and circulation of cerebrospinal fluid were considered more relevant. But available data afford a schematic model of cerebral venous outflow that does have important pathophysiological consequences.

In the upright patient, the principal outflow via the internal jugular veins is substituted almost completely by the large collateral vertebral plexuses, through communications at the cranial base. Emissary veins of the skull vault are small and few in number. Outflow from the deep venous system through the great vein of Galen can be substituted by choroidal, thalamic and striate anastomoses toward the basal vein. So-called intracerebral venous anastomoses through the centrum semiovale towards the convexity are nonexistent or negligible. Instead, a venous watershed exists separating periventricular white matter from a layer of subcortical white matter.

In most infants, the cavernous sinus is not yet connected to the cerebral veins. Once such communications have been formed, important collateral pathways exist through basal and Sylvian veins via the cavernous sinus to the pterygoid plexuses. Simultaneous hindrance of principal and collateral venous outflow will lead to elevated venous pressure and eventual insufficiency of cerebral blood flow (CBF). This will cause increased intracranial pressure, and ventricular enlargement due to periventricular atrophy. The slow phase of the two-compartment model of CBF coincides with the periventricular white matter area of the deep venous system.

In the neonate CBF was found to be still very low, and in the two compartments CBF increases at a different rate to a maximum in childhood. In hydrocephalus, measurement of CBF in the slow deep compartment, rather than the fast cortical one, will be most informative.

Data concerning venous anatomy, interstitial fluid pressure and cerebral blood flow indicate that obstruction of cerebral venous outflow (as a whole or involving the deep venous system alone) is the essential cause of hydrocephalus. Choroidal and ventricular veins both belong to the deep system. Choroidal venous pressure determines cerebrospinal fluid pressure (CSFP); pressure in the ventricular veins determines interstitial fluid pressure in the periventricular white matter. A decrease in deep cerebral blood flow causes periventricular atrophy. CSFP is higher than interstitial fluid pressure, normally and in venous obstruction.

CSF pressure can mediate/precipitate venocongestive edema (but not inflammatory edema) of the brain. Collateral venous pathways have been described. Venous obstruction causes hydrocephalus only when it leads to cerebral blood flow (CBF) insufficiency. Cerebrospinal fluid shunting causes increased CBF an essential therapeutic effect in hydrocephalus, but also causes venocongestive brain edema, which explains the decrease in ventricle size and the side effects of shunting.
Normal Pressure Hydrocephalus and CSF / Vascular correlation


Normal pressure hydrocephalus (NPH) is considered to be a combination of altered CSF resorption and a reversible form of cerebral ischemia. The hypothesis tested in this study was that a reduction in venous compliance in the territory drained by the superior sagittal sinus (SSS) is associated with NPH and cerebral ischemia. Vascular compliance is significantly different in the brains of healthy subjects as compared with that in patients with ischemia/atrophy or NPH.

NPH was first described in 1965 by Adams et al in a study of elderly patients with the clinical triad of gait disturbance, dementia, and urinary incontinence. Approximately two thirds of cases are associated with such conditions as arachnoiditis, meningitis, subarachnoid hemorrhage, trauma, and tumors, as well as ectasia and elongation of the basilar artery. Despite an awareness of these associated factors, a detailed understanding of the pathophysiology of NPH has remained elusive.

MR aqueduct flow quantification, infusion conductance tests, nuclear medicine cisternography, and CSF tap tests measure CSF flow and resorption abnormalities. Nuclear medicine and CT studies of relative cerebral blood flow (rCBF) measure ischemia in this disorder. The pathophysiological mechanisms of this disease appear to involve both reduced CBF and altered CSF resorption without producing an increase in CSF pressure. A single mechanism that explains both processes has remained elusive. Mase et al hypothesized that the most important factor in the underlying pathophysiology of NPH is a reduction in intracranial compliance.

The hypothesis is that, in NPH, a reduction in venous compliance in the superior sagittal sinus (SSS) territory leads to vascular compression and ischemia.

The intracranial system is semi closed, which leads to a degree of interdependence between the variables measured and to the formation of feedback loops. The working definition of vascular compliance as used in this study is the degree of volume change that occurs in all vessels that lie between the arteries at the base of the skull and the venous sinuses resulting from pressure changes that occur during the cardiac cycle. More formally, compliance in vessels is defined as the rate of change of the vascular volume with respect to the change in pressure (dV/dP); thus, the more elastic a vessel, the greater its wall will dilate to accommodate a pressure wave, such as the systolic pressure wave, and the greater its compliance.

In essence, this change in volume with the systolic pressure wave is the NSPV. It has been measured by obtaining the area under the systolic portion of the net blood flow graph. Vascular compliance is important in the brain because a rigid container (the skull) and an incompressible fluid (CSF) surround it. The blood supply is pulsatile, with the pressure in the arterial blood varying by the pulse pressure. The volume of blood entering the brain thus varies with the cardiac cycle. The arteriovenous difference (difference between blood entering and leaving the brain) shows a net intracranial inflow of blood during systole and a net outflow during diastole. This volume change must be accommodated by an exactly equal volume exiting the skull, because CSF is incompressible.

The amplitude, then, of the CSF pressure waveform depends on the arterial input, the compliance of the cranial contents, and the venous outflow. The vascular compliance is important in this process because the degree of vascular compliance determines the degree of the volume change, and it is this volume change that is translated through the CSF. If the vessels were totally rigid, none of the arterial pulsation would be transmitted to the CSF, and, as a corollary, if the skull were a totally closed system, the vessels within it would show no net pulsation.
Taking the whole of the cerebral vascular tree as a series of vessels, it can be seen that the delay between the center of the arterial flow peak and the venous flow peak is a measure of the pulse wave velocity through the vessels between these two points. The AVD thus can also be used as a measure of vascular compliance. It is known that NPH is associated with low intracranial compliance.

**CSF flow disturbance therapy based on low velocity Upper Cervical Adjustment**

There is a compelling and cogent argument for the clinical and scientific efficacy of orthogonally-based upper cervical chiropractic care. There is a logical chain of arguments that support specific upper cervical work. This chain is supported by evidence at each link, with the evidence for certain aspects being stronger than others. Given the anatomical, biomechanical and neurological complexity of the upper cervical spine, specific upper cervical work is the logical approach to adjust the upper cervical subluxation.
CSF flow disturbance can be restored if one understands the inexorable anatomic relationship between the spine, cranium and temporomandibular joint (TMJ). In the chiropractic field cranial manipulation or craniopathy and temporomandibular joint (TMJ) therapies are **not** "stand-alone" techniques. What this means is that to properly treat the cranium or TMJ the spine must be evaluated and treated for neuromusculoskeletal matrix dysfunction or subluxations.

Tensions upon the meningeal and myoligamentous aspects of the spine affect the central nervous system directly. For this reason, the adjustment and balancing of the spine and pelvis is always primary to any cranial or TMJ condition. Literature published in chiropractic journals has found relationships between the TMJ, cervical and lumbar spine, as well as a relationship between the sacroiliac joint and TMJ. In each case the spine has a primary role in treatment. Chiropractic literature has also discussed how cranial therapy or craniopathy is incumbent upon the balancing of spine and pelvis.

The dura mater is a tough fibrous membrane. It is the outermost covering of the brain and the spinal cord. The dura of the brain and that of the spinal cord are similar and continuous with one another at and through the foramen magnum. The dura mater is the outermost envelope of the central nervous system. However, within the cranium aside from surrounding the cerebrum and cerebellum, the dura mater also compartmentalizes each structure and separates one from another and the right from the left side. The external layer serves as the internal periosteum for the cranial bones and is continuous through the sutures with the periosteum of the external surface of the skull where it anchors and attaches itself. The internal meningeal layer has four folds; the falx cerebri, the tentorium cerebelli, the falx cerebelli, and the diaphragma sellae. The dura anchors strongly to the different areas of the inner cranial vault especially where the meningeal layer comes in contact with the periosteal layer.

The cranial dura is firmly adherent to the different points within the cranium, to the ring of the atlas and extends as the spinal dura having firm attachments to the foramen magnum, second and third cervical vertebrae. The posterior cervical epidural ligaments anchor the posterior dura mater to the ligamentum flavum. A connective tissue (myodural) bridge also has been noted between the rectus capitis posterior minor muscle and the dorsal spinal dura at the atlanto-occipital junction. Continuity is also "observed between the ligamentum nuchae and the posterior cervical spinal dura as the latter passes deeply from the midline toward the dura, but only at the first and second cervical vertebral levels. The ligamentum nuchae also passes bilaterally on to the occipital bone as far as the sutures between the occiput and the temporal bones, approaching the inferior nuchal line superiorly".
Meningovertebral ligaments (ligaments of Hofmann) are found along the spinal canal between the L5/S1 intervertebral level and cephalad up to T1. These ligaments appear to be more prevalent in the lumbar vertebral column but are also present throughout the thoracic vertebral column. It is theorized that the dural sac attachments to the posterior aspect of the vertebral bodies and the posterior longitudinal ligament could act as a fulcrum to traction of the dural sac in the event of nuclear bulge or hemiation. The spinal dura is a cylindrical sheath, which surrounds the spinal cord and spinal nerve roots, which passes through the intervertebral foramina. Along with the other dural spinal attachments an external aspect of the spinal dura has attachments by fibrous slips to the posterior longitudinal ligament and to a fatty connective tissue layer called epidural fat. This separates it from the peristome and provides additional cushioning for the spinal cord and nerves within the spinal cord. The various dural attachments allow stability, yet still enable flexibility. The lateral wall of the dura is stabilized internally to the pia mater and therefore also to the spinal cord by the denticulate ligament. The denticulate ligament attaches to the spinal dura at regular intervals from the foramen magnum to the conus medullaris by tooth-like extensions of the pia mater between each spinal nerve.

The study of chiropractic cranial and upper cervical therapy and TMJ notes the importance of the spine and vertebra for maintaining health of the nervous system. Effects of vertebral dysfunction can be far reaching, beyond the local related joint and mechanical dysfunction. There have been recent findings of dural connections to the muscles and ligamentous structures in the spine. The dura’s connection directly to the pia mater, by way of the dentate ligament, is profound because the pia mater is firmly adherent to the spinal cord, thus creating a direct connection between the vertebra and central nervous system. Upper cervical and TMJ therapies seek to enhance the balancing of meningeal tensions and are used in conjunction with chiropractic spinal adjustment(s).

Where have we been and where are we going?

If history can serve health care providers in making “bottom up” decisions on health care reform, then it can also help us predict the most likely (inescapable) consequences of the “top down” government input. The classic “never the twain shall meet” example typifying the inevitable outcome between the “oil and water” collision of the “top down” and “bottom up” points of view can be found by simply reviewing the history of the formation of the Food and Drug Administration (FDA) in the early 20th century.

Formation of the Food and Drug Administration – FDA

Upton Sinclair in 1905 wrote The Jungle: Muckraking the Meat-Packing Industry to expose the appalling working conditions in the meat-packing industry. His description of diseased, rotten, and contaminated meat shocked the public and led to new federal food safety laws. Before the turn of the 20th century, a major reform movement had emerged in the United States. Known as progressives, the reformers were reacting to problems caused by the rapid growth of factories and cities. Progressives at first concentrated on improving the lives of those living in slums and in getting rid of corruption in government (sound familiar?).

By the beginning of the new century, progressives had started to attack huge corporations like Standard Oil, U.S. Steel, and the Armour meat-packing company for their unjust practices. The progressives revealed how these companies eliminated competition, set high prices, and treated workers as "wage slaves." Theodore Roosevelt was the president when the progressive reformers were gathering strength. Assuming the presidency in 1901 after the assassination of William McKinley, he remained in the White House until 1909. Roosevelt favored large-scale enterprises. "The corporation is here to stay," he declared. But he favored government regulation of them "with due regard of the public as a whole."

The nauseating condition of the meat-packing industry that Upton Sinclair captured in The Jungle was the final precipitating force behind both a meat inspection law and a comprehensive food and drug law. Since 1879, nearly 100 bills had been introduced in Congress to regulate food and drugs; on 30 June
1906 President Roosevelt signed the Food and Drugs Act, known simply was the Wiley Act, a pillar of the Progressive era.

**The basis of the law rested on the regulation of product labeling rather than pre-market approval.**

Drugs, defined in accordance with the standards of strength, quality, and purity in the *United States Pharmacopoeia* and the *National Formulary*, could not be sold in any other condition unless the specific variations from the applicable standards were plainly stated on the label. Foods were not defined according to analogous standards, but the law prohibited the addition of any ingredients that would substitute for the food, conceal damage, pose a health hazard, or constitute a filthy or decomposed substance. Interpretations of the food provisions in the law led to many, sometimes protracted, court battles, many of which the newly formed agency lost. If the manufacturer opted to list the weight or measure of a food, this had to be done accurately. Also, the food or drug label could not be false or misleading in any particular, and the presence and amount of eleven dangerous ingredients, including alcohol, heroin, and cocaine, had to be listed.

Despite Congress’ mandate to focus on food standards, the newly formed agency decided to devote more effort to drug regulation, with some emphasis on the so-called patent medicines. While the law was much clearer about drug standards than standards for foods, misbranding was the source of considerable controversy in the regulation of drugs.

**Very early on, the FDA demonstrated a propensity to overstep the original congressional mandate, forcing the Supreme Court to rule that the law did not—contrary to the government’s interpretation—apply to false therapeutic claims.** An amendment to the constitution attempted to correct the language of the law and to put the growingly misguided bureau in the more difficult position of having to prove in court that manufacturers of drugs labeled with false therapeutic claims intended to defraud consumers. But instead of paying attention to the original impetus that precipitated the Congressional mandate to protect the public from contaminated food, the bureau continued down the path of attempting to regulate drugs, embarrassing the government by losing several cases against egregious products, including the famous debacle with the Coca Cola Company. But, undaunted, the “top down” organization was unstoppable and continued focusing on “misbranded and adulterated” drugs with seizures increasing into the 1920s and 1930s.

The editorial in last month’s AAOM journal focuses on the continued malfeasance of the now century old FDA entitled: *Are we witnessing a tipping point for “physician directed” Cellular Medicine versus the “FDA controlled” pharmaceutical industry?* The latest misadventure of the FDA’s reinterpretation of their mandate involved the deaths of several patients who were administered contaminated steroids. Several media sources reported that the same company had been found guilty of similar improprieties a decade ago. But, as we are so constantly reminded, those who do not learn from history are doomed to repeat it. And in this case, apparently the FDA was unable to keep tabs on a repeat offending, multimillion dollar compounding pharmacy because they were too preoccupied with other “more important” matters, not the least of which includes challenging cellular medicine physicians and literally rewriting the congressionally mandated definition of what constitutes the practice of medicine.

To put these misguided (and now proven dangerous) FDA “inactivities” into perspective, every 16 minutes someone in this country dies of a drug overdose. And this epidemic is not due to illicit drugs; these deaths are due to physician prescribed, FDA approved pharmaceuticals, recent debacle from contaminated steroids notwithstanding. Meanwhile, to date, there has never been a reported death or even a serious complication associated with the administration of autologous cellular medicine products. These facts are certainly food for thought. One must question the rationale behind the FDA’s current, unrelenting preoccupation with a safe, effective and non pharmaceutical cellular medicine therapy, leaving unattended the intermittently lethal malpractices of the corporate pharmaceutical industry they were mandated by Congress back in 1906 to oversee.
The following papers present “static” imaging finding that can serve as indirect evidence of increased intracranial pressure.

**Can MRI screen for CSF biomarkers in neurodegenerative disease?**

**Neurology** 10.1212/WNL.0b013e31827b9147 Article
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**Abstract**

**Objective:**
Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) may have overlapping clinical presentations despite distinct underlying neuropathologies, thus making in vivo diagnosis challenging. In this study, we evaluate the utility of MRI as a noninvasive screening procedure for the differential diagnosis of AD and FTLD.

**Methods:**
We recruited 185 patients with a clinically diagnosed neurodegenerative disease consistent with AD or FTLD who had a lumbar puncture and a volumetric MRI. A subset of 32 patients had genetic or autopsy-confirmed AD or FTLD. We used singular value decomposition to decompose MRI volumes and linear regression and cross-validation to predict CSF total tau (ttau) and β-amyloid (Aβ1-42) ratio (ttau/Aβ) in patients with AD and patients with FTLD. We then evaluated accuracy of MRI-based predicted ttau/Aβ using 4 converging sources including neuroanatomic visualization and categorization of a subset of patients with genetic or autopsy-confirmed AD or FTLD.

**Results:**
Regression analyses showed that MRI-predicted ttau/Aβ is highly related to actual CSF ttau/Aβ. In each group, both predicted and actual CSF ttau/Aβ have extensively overlapping neuroanatomic correlates: low ttau/Aβ consistent with FTLD is related to ventromedial prefrontal regions while high ttau/Aβ consistent with AD is related to posterior cortical regions. MRI-predicted ttau/Aβ is 75% accurate at identifying underlying diagnosis in patients with known pathology and in clinically diagnosed patients with known CSF ttau/Aβ levels.

**Conclusion:**
MRI may serve as a noninvasive procedure that can screen for AD and FTLD pathology as a surrogate for CSF biomarkers.

**Imaging features of idiopathic intracranial hypertension, including a new finding: widening of the foramen ovale**

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Abstract

Background:
Idiopathic intracranial hypertension (IIH) is a clinical disorder of unknown etiology manifesting with increased intracranial pressure in the absence of hydrocephalus, an underlying mass lesion, and demonstrating normal cerebrospinal fluid composition. IIH may exhibit several non-specific imaging findings including: an empty sella, posterior globe flattening, tortuosity of the optic nerve, and optic nerve sheath distention.

Purpose:
To introduce widening of the foramen ovale as a new imaging marker for IIH.

Material and Methods:
IIH is a syndrome which may exhibit several previously described non-specific imaging findings including: an empty sella, posterior globe flattening, tortuosity of the optic nerve, and optic nerve sheath distention. We hypothesize that chronically elevated cerebrospinal fluid pressure can lead to osseous erosions and we propose widening of the foramen ovale as a new imaging marker for IIH.

Results:
Average foramen ovale sizes were increased in patients with IIH compared to controls (30.03 ± 7.00 mm² vs. 24.21 ± 5.97 mm², P < 0.001). For a cut-off value of 30 mm², the sensitivity of FO area to detect IIH was 50%, with 81% specificity. Classic findings were significantly more common in patients with IIH compared to controls including: empty sella (65.9% vs. 0%), posterior globe flattening (65.9% vs. 4.5%), vertical tortuosity of the optic nerve (54.5% vs. 9.1%), and optic nerve sheath distention (52.3% vs. 11.4%, all P values < 0.001).

Conclusion:
Our study confirms the association of several classic imaging findings with IIH and supports widening of the foramen ovale as an additional imaging marker which may be incorporated into the evaluation of patients suspected to have this condition.

The entire dural sinus tree is compressed in patients with idiopathic intracranial hypertension: a longitudinal, volumetric magnetic resonance imaging study.

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Abstract

INTRODUCTION:
The objective of this study was to explore the volumetric alterations of dural sinuses in patients with idiopathic intracranial hypertension (IIH).

METHODS:
Standardized cranial magnetic resonance imaging (MRI) was used in 17 patients prior to and following treatment of IIH and in seven controls. Magnetic resonance venography (MRV) was employed for (a) judgment of circumspect dural sinus stenoses and (b) computation of sinus volumes. Cross-sectional areas (CSA) of the superior sagittal sinuses (SSS) were measured on T2-weighted images. Results of the initial MRIs were compared to those on follow-up MRIs and to results of controls.

RESULTS:
Stenoses of the transverse sinuses (TS) resulting in cranial venous outflow obstruction (CVOO) were present in 15/17 (88%) patients, normalizing in 7/15 cases (47%) after treatment of IIH. CVOO was not detected in the control group. Segmentation of MRV revealed decreased dural sinus volumes in patients with IIH as compared to controls (P = 0.018). Sinus volumes increased significantly with normalization of intracranial pressure independent from disappearing of TS stenoses (P = 0.007). The CSA of the SSS were normal on the initial MRIs of patients with IIH and increased on follow-up after treatment (P < 0.001). However, volumetries displayed overlap in patients and controls.

CONCLUSIONS:
Patients with IIH not only exhibit bilateral stenoses of the TS as has been reported, but volume changes of their entire dural sinus system also occur. The potential etiopathological and diagnostic roles of these changes are discussed.
Quantitative MRI Studies of Chronic Brain White Matter Hyperintensities in Migraine Patients
Headache: The Journal of Head and Face Pain, 12/28/2012
Aradi M et al.

Introduction:
The aim of this study was to examine chronic brain white matter hyperintensities in migraine and to gain data on the characteristics of the lesions. The magnetic resonance imaging (MRI) measurements denote tissue damage with axonal loss, low glial cell density, and an enlarged extracellular space with an increased extracellular water fraction. These radiological features might be the consequences of microvascular ischemic changes during migraine attacks.

Methods:
Supratentorial white matter hyperintensities of 17 migraine patients were investigated interictally with quantitative MRI, including quantitative single voxel spectroscopy, diffusion, and perfusion MRI at 3.0–Tesla. The findings were compared with data measured in the contralateral, normal–appearing white matter of migraineurs and in the white matter of 17 healthy subjects.

Results:
Significantly higher apparent diffusion coefficient values, prolonged T2 relaxation times, and decreased N-acetyl–aspartate and creatine/phosphocreatine concentrations were found in the white matter hyperintensities. The cerebral blood flow and blood volume values were mildly decreased inside the hyperintensities. Differences were not present between the migraine patients’ normal–appearing white matter and the white matter of healthy subjects.

Assessment of the Virchow-Robin Spaces in Alzheimer Disease, Mild Cognitive Impairment, and Normal Aging, Using High-Field MR Imaging
W. Chen, X. Song, Y. Zhang, for the Alzheimer's Disease Neuroimaging Initiative

Background and Purpose:
VRSSs are the perivascular spaces surrounding the deep perforating arteries in the brain. Although VRSS variations with age and disease pathologies have been reported previously, the radiologic characteristics of the VRSS in relation to AD are poorly understood. This study investigated the prevalence, spatial distribution, and severity of the VRSS in AD, MCI, and older adults who were CN. It also investigated the relationship of the VRSS to white matter changes.

Materials and Methods:
Structural MR imaging data were acquired from 158 participants (AD _37, MCI _71, CN _50, mean age _74.97 _7.20 years) who had undergone T1WI at 3T. The severity of VRSS in the white matter, basal ganglia, hippocampus, and brain stem structures was evaluated by using a semi quantitative scale, adapted from existing rating scales. A VRSS total score summarizing the subscales was calculated to assess the whole-brain VRSS.

Results:
VRSSs were observed in multiple brain regions of all participants, typically presented as _2-mm well-margined symmetric round-, oval- and linear-shaped hypointensities on T1WI. The VRSS total score increased with leukoaraiosis, atrophy, and advanced age (_P _0.01). Individuals with AD and MCI showed greater levels of VRSS than control subjects. The VRSS total score discriminated individuals with AD and those who were CN with an accuracy of 0.79 (95% CI, 0.69–0.89).

Conclusions:
VRSSs are common in older adults and are more severe in AD and MCI than in CN. Whether increased VRSSs can be reliably used to aid in AD diagnosis warrants further investigation.

Features of Virchow-Robin spaces in newly diagnosed multiple sclerosis patients
Received 9 March 2010; accepted 25 May 2010.

Abstract

Background:
Virchow-Robin spaces (VRSSs) are perivascular pia-lined extensions of the subarachnoid space around the arteries and veins as they enter the brain parenchyma. These spaces are responsible for inflammatory processes within the brain.
Objectives:
This study was designed to shed more light on the location, size and shape of VRSs on 3 mm slice thickness, 1.5 Tesla MRI scans of newly diagnosed MS patients in Isfahan, Iran and compare the results with healthy age- and sex-matched controls.

Methods:
We evaluated MRI scans of 73 MS patients obtained within 3 months of MS onset and compared them with MRI scans from 73 age- and sex-matched healthy volunteers. Three mm section proton density, T2W and FLAIR MR images were obtained for all subjects. The location, size and shape of VRSs were compared between the two groups.

Results:
The total number of VRSs was significantly more in the MS group ($p < 0.001$). The distribution of VRSs were significantly more located in the high convexity areas in the MS group ($p < 0.001$), while there was no significant differences in other regions. The round shaped VRSs were significantly more detected on MRI scans of MS patients, and curvilinear shapes were significantly more frequently observed in healthy volunteers, however there were no significant differences for oval shaped VRSs between the two groups. The number of VRSs with the size over than 2 mm were significantly more observed in the MS groups compared to controls. We also observed some differences in the characteristics of VRSs between the genders in the MS group.

Conclusion:
The results of this study shed more light on the usefulness of VRSs as an MRI marker for the disease. In addition, according to our results VRSs might also have implication to determine the prognosis of the disease. However, larger studies with more advanced MRI techniques are required to confirm our results.

Emissary Veins and Neuroanatomic Changes in Space
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Editor:
In the June 2012 issue of Radiology, Kramer and colleagues described moderate concavity of the pituitary dome with posterior stalk deviation in astronauts (1) along with ophthalmic findings previously reported following long-duration space flights (2), attributing these changes to a perceived "cephalad fluid shift" (1,2) with alteration of the blood-brain barrier or post capillary venous hypertension—presumably producing vasogenic edema.
We recently explained how the ophthalmic findings (2) are simply accounted for by anatomic features (3). The lack of pumping mechanisms and unidirectional venous valves in the head, neck, and upper torso necessitates gravitational assist to drain blood. In space, mildly increased venous and dural sinus pressures owing to such stasis will hamper cerebrospinal fluid resorption via the arachnoid villi, elevating cerebrospinal fluid pressure. In addition, decreased lymphatic drainage will give rise to epicranial edema. Uniform intracranial pressure elevation causes anatomic distortion only where the central nervous system is not fully encased in rigid cranium, such as in the vicinity of the foramen magnum or distal to the optic canal, where pressure gradients develop (3). In the orbital compartment, this will manifest as dural sheath expansion, posterior globe flattening, and papilledema or "papillary protrusion."
The pituitary gland, on the other hand, is partitioned from brain by sellar diaphragm and drained by emissary veins in communication with the extracranial compartment (4). It is thus susceptible to compression by raised intracranial pressure (5–7). Although fluids and fluid-filled tissues are essentially incompressible, the exodus of fluid via the emissary veins allows for a reduction of an otherwise incompressible compartment.
Investigators need not question the existence of raised intracranial pressure in space (1,2). The radiologic findings of pituitary compression with orbital signs including papillary protrusion may together be
considered pathognomonic (5–7). The emissary nature of the cephalic venous system must be accounted for to understand mechanisms of hydrocephalus and the radiologic and ophthalmologic findings, as well as to develop solutions for long-term human space travel.

Disclosures of Conflicts of Interest: D.H.K. No relevant conflicts of interest to disclose. C.F.P. No relevant conflicts of interest to disclose.

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We would like to express appreciation to Drs Kim and Parsa for their interest in and comments regarding our recent article (1). The physiologic and anatomic response to microgravity in humans is an area of continued active investigation. As microgravity is a unique environment without exact analog on earth, pathologic processes that develop during space travel may have novel causes and, thus, the term “pathognomonic” should be used with caution.

As we referenced without bias various hypothetical causal factors related to intracranial hypertension, we do concur that the loss of gravitational assist in supporting venous drainage and its potential contribution to intracranial hypertension in microgravity is another promising hypothesis. The challenge, however, will be to determine the extent of contribution for each of the hitherto considered factors under actual microgravity conditions and to demonstrate sustainability of each proposed hypothesis. The head-down tilt model, simulating fluid shifts in space and similarly impeding venous outflow from the head, when applied to rabbits, in fact demonstrates normalization of intracranial pressure in 7 days following initial intracranial hypertension (2). This is in contrast to visual and imaging abnormalities that increase in frequency in a subset of astronauts who have been exposed to more than 30 days of microgravity (1,3). It is therefore important to consider in any isolated causal model compensatory physiologic mechanisms,
alteration of anatomic compartments (4), and confounding conditions in the space environment (5) that may modulate or counteract any negative homeostatic disturbance dynamically.

Disclosures of Conflicts of Interest: L.A.K. No relevant conflicts of interest to disclose. A.S. No relevant conflicts of interest to disclose. K.M.H. No relevant conflicts of interest to disclose. J.D.P. No relevant conflicts of interest to disclose. D.R.H. No relevant conflicts of interest to disclose.

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Sayson JV, Hargens AR.

Rizzo AM, Corsetto PA, Montorfano G, et al.

Pathophysiology of low back pain during exposure to microgravity.

Sayson JV, Hargens AR.
Source- The Ola Grimsby Institute, San Diego, CA, USA. jojovsayson@comcast.net

Abstract
Astronauts exposed to microgravity frequently report low back pain. This pain is described as moderate to severe in intensity. This condition warrants investigation as low back pain may hinder an astronaut’s ability to perform challenging tasks by virtue of disruption of sleep and, subsequently, mental concentration. It is reported by astronauts that a “fetal tuck position” described as knees to chest position relieves back pain. It is possible that the pathogenesis of back pain in microgravity is discogenic (or mechanical) and somatic, referred from the sinuvertebral nerves due to excessive expansion of the lumbar intervertebral discs associated with reduction of gravitational compressive loads in space. The fetal tuck position may increase lumbar intervertebral disc hydrostatic pressure by flexion and transfer of spinal compressive forces toward the anterior region of the lumbar discs, subsequently reducing disc volume. Moreover, this position may reduce Type IV mechanoreceptor facilitation and nerve impulse propagation from the sinuvertebral nerves of the annulus fibrosus, and thus diminish low back pain perception. Elongated posterior soft tissues (apophyseal joint capsules and ligaments) with spinal flexion may potentially stimulate Type I and II mechanoreceptors. This neutralizes substance P in the spinal cord dorsal horn by increasing naturally occurring opioids such as enkephalins. Separately, other investigators have reported a higher incidence of herniated discs (HNP) in astronauts post flight. Further studies of countermeasures are recommended to prevent excessive spinal elongation and disc expansion, reduce low back pain in microgravity, and simulate 1-G disc homeostasis, which may also help prevent HNPs post flight.
The following papers present “dynamic” imaging finding that can serve as indirect evidence of increased intracranial pressure. All the literature cited in this list pertain to CSF flow are based on studies obtained from patients in recumbent (non upright) position.

CSF Flow Dynamics at the Craniovertebral Junction Studied with an Idealized Model of the Subarachnoid Space and Computational Flow Analysis
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BACKGROUND AND PURPOSE:
How CSF flow varies with the anatomy of the subarachnoid space has not been sufficiently well studied. The goal of this study was to develop an idealized 3D computational model of the subarachnoid space and then to use this model to study the detailed spatiotemporal effects of anatomic variations on CSF pressures and velocities.

MATERIALS AND METHODS:
We created a geometric model with a computer-assisted design program. The model contained a central structure for the brain and spinal cord axis and a second surrounding structure for the peripheral borders of the subarachnoid space. Model dimensions were adjusted to capture the main characteristics of the normal human posterior fossa and cervical spinal anatomy. CSF flow was modeled as water with a sinusoidal flow pattern in time. Velocities and pressures during craniocaudal and caudocranial flow were calculated with computational fluid dynamics (CFD) software. Simulated flow was compared with published phase-contrast MR imaging measurements of CSF flow in healthy human subjects.

RESULTS:
The model contained geometric characteristics of the posterior fossa and spinal canal. Flow velocities varied with the time in the cycle and location in space. Flow velocities had spatial variations that resembled those in healthy human subjects. Reynolds numbers were moderate, showing a laminar flow regime. Pressure varied uniformly along the long axis of the model during craniocaudal and caudocranial flow.

CONCLUSIONS:
In an idealized geometric approximation of the human subarachnoid space, CSF velocities and pressures can be studied in spatiotemporal detail with mathematic models. CSF flow patterns have a relationship to the anatomy of the subarachnoid space and hypothetically to the pathogenesis of syringomyelia and neurologic consequences of the Chiari I malformation, characterized by the descent of the cerebellar tonsils into the upper cervical spinal subarachnoid space. CSF flow measurements with phase-contrast MR imaging (PCMR) suggest that the obstruction of the subarachnoid space in the Chiari I malformation results in hyperdynamic CSF flow. Relationships between CSF flow and subarachnoid space dimensions have not been adequately characterized because of the great inter-individual variations in subarachnoid space anatomy and great spatial variation in CSF velocities through the subarachnoid space. Only a limited number of CSF velocity measurements are made in clinical studies because of the limited number of sections possible in a suitable examination time. Furthermore, pressure measurements are not obtained in the usual PCMR studies. The subarachnoid space dimensions that result in hyperdynamic flow and abnormal CSF pressures have not been determined.
Characterization of CSF Hydrodynamics in the Presence and Absence of Tonsillar Ectopia by Means of Computational Flow Analysis
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BACKGROUND AND PURPOSE:
Phase-contrast MR imaging (PCMR) has only partially characterized cyclic CSF flow and pressure, which, hypothetically, have a role in the pathogenesis of syrinx and symptoms in the Chiari I malformation. Our goal was to use computational flow analysis (CFA) to better understand CSF hydrodynamics.

MATERIALS AND METHODS:
High-resolution MR images were obtained in a healthy volunteer and a patient with Chiari I malformation. With standard segmentation and discretization techniques, 3D models of the subarachnoid space, cerebellum, and spinal canal were created. CSF flow during systole and diastole were simulated with the boundary element method in the models. CSF velocities and pressures computed in the patient with Chiari I malformation were compared with those in the healthy volunteer. Flow patterns were also compared with PCMR results for validation of the technique.

RESULTS:
The CFA and PCMR results agreed well. Inhomogeneous flow patterns characterized by fluid jets anterior and lateral to the spinal cord were demonstrated in both the Chiari I and volunteer models by CFA. Significant circumferential velocities were evident, suggesting swirling flow in the spinal canal. Higher magnitude jets were found in the patient with Chiari I than in the healthy volunteer. Relatively even pressure gradients were found along the spinal canal in both cases, with a 50% steeper gradient in the patient with Chiari I malformation.

CONCLUSIONS:
Circumferential velocities and pressure gradients in the spinal canal, which may be clinically relevant to Chiari I and other malformations, can be obtained by CFA in patient-specific geometries.