

My prog-MS ezine

For people with progressive MS and other interested people

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Hello and welcome to the latest edition of my ezine about progressive Multiple Sclerosis and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer who lives in Birmingham, UK. I'm 62 years old.

In this issue are six pages of prog-MS news stories. There are also two features. One on page 5 is about my ten years of using a catheter - initially once a day and now at least four times daily. There's also a feature on the much publicised mRNA breakthrough into Covid 19, and why in could, in turn, lead to an MS vaccine and treatment breakthrough . See page 10 for details.

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Restless legs syndrome linked to more disability in progressive MS, researchers say

People with progressive MS who experience restless leg syndrome are more likely to have greater disability than those who do not, a new study by Austrian researchers has found.

In the study participants filled out questionnaires such as the International Restless Legs Syndrome Study Group Rating Scale, which assesses severity, the Epworth Sleepiness Scale, which looks at the likelihood of sleepiness during the day, and the Pittsburgh Sleep Quality Index, which assesses sleep habits and quality over the past month.

The study found a quarter of people with MS experienced restless leg syndrome, which was seven times higher than in the control group of people without MS.

People in the MS group were not more likely to have daytime sleepiness and poor life quality than the control group, but the scores for these factors were significantly higher in people with MS who had restless leg syndrome than those who didn't, with 78% of the restless leg syndrome MSers experiencing impaired sleep compared with 21% of those with MS but not restless legs.

People with restless leg syndrome were also found to have higher scores in the Expanded Disability Status Scale, and more spinal lesions found from MRI scans.

Researchers also concluded that DMT (Disease Modifying Therapy) drug choice didn't have an impact on the severity of restless leg syndrome, sleep quality, or daytime sleepiness.

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Nasal Drug Sees Promising Immune Effects in Phase 1 Trial

Nasally-administered foralumab, a potential treatment for progressive MS, appears safe and well-tolerated, and shows immune-modulating and anti-inflammatory effects in healthy volunteers, an updated analysis from a Phase 1 trial has found.

"Nasal administration of Foralumab is a unique approach to treat patients with neurodegenerative diseases such as progressive MS, amyotrophic lateral sclerosis (ALS) and Alzheimer's disease," Howard Weiner, MD, the Harvard Medical School neurology professor who reformulated foralumab for nasal delivery, said in a press release.

Foralumab, developed by Tiziana Life Sciences, is an experimental antibody targeting the CD3 receptor on immune T-cells. This lessens T-cells' potentially damaging immune responses, while increasing the activity of separate regulatory T-cells that work to prevent inappropriate immune reactions.

Both the oral and nasal routes of administration are designed to stimulate the immune system associated with mucous membranes to provide a disease-modifying effect, said Weiner, who is also chair of the scientific advisory board at Tiziana.

The treatment's safety and preliminary signs of effectiveness are being investigated in a group of healthy volunteers participating in a Phase 1 trial at the Brigham and Women's Hospital, Harvard Medical School, in Boston.

Participants received ascending doses of 10, 50, and 250 micrograms of foralumab, or a placebo, once daily for five consecutive days. Results showed that all doses were well-tolerated, with no signs of severe toxicity or of a potentially life-threatening condition called cytokine release syndrome. The 50-microgram dose had the greatest effect on immune T-cells, which can turn on the body's own tissue in autoimmune disorders such as MS.

This dose of foralumab had three statistically significant effects: it reduced T-cell subsets over 14 and 21-day periods, increased CD8-naïve T-cells, and boosted production of the anti-inflammatory molecule IL-10 while suppressing the inflammatory molecule interferon gamma. "This study demonstrates for the first-time that nasally administered Foralumab, at the identified optimal dose of 50 mcg [micrograms]/day, induces immunomodulatory effects capable of providing clinical benefit to treated subjects," a research spokesperson said. "Our immediate focus," he added, "is on developing foralumab for treatment of progressive MS." **For details of all stories go to page 13**

Male Immune Cells Drive More Severe MS, Study Suggests

Certain immune cells cause more severe disease in males than females, according to a new study in a mouse model of MS. The findings could help to explain why men with MS tend to have more severe disease.

The study, "Male sex chromosomal complement exacerbates the pathogenicity of Th17 cells in a chronic model of central nervous system autoimmunity," was published in Cell Reports. Biological sex has well-established effects on MS: data show that while females are substantially more likely to develop the disorder, males usually have more severe disease. The reason for this difference, however, is not completely understood.

Now, a team led by researchers at Université Laval, in Canada, have sought to better understand how biological sex affects the activity of immune cells. The researchers performed a series of experiments in mice with experimental autoimmune encephalitis (EAE) — a mouse disease commonly used to model MS — to examine cells believed to be involved in driving the condition. Specifically, the team looked at a type of immune cell called T helper 17 (Th17) cells.

First, immune Th17 cells were taken from either male or female mice, and stimulated so they would be inflammatory. These cells then were put into other mice. Experiments indicated that male Th17 cells produced higher levels of interferon gamma, a signalling molecule that drives disease-causing inflammation in MS. The male cells also had greater plasticity, which is the ability to rapidly change cellular activity.

The researchers then sought to understand what was causing this sex-based difference. Biologically, males have one X chromosome and one Y chromosome, and their bodies have higher levels of "male" hormones, called androgens. By contrast, biological females have two X chromosomes, and higher levels of "female" hormones such as oestrogen.

First, the team tested whether the sex-based difference in pathogenicity — or disease-causing capacity — could be a result of hormonal differences. To do this, they repeated similar cell-transferring experiments using Th17 cells from mice that had had their gonads (ovaries or testis) surgically removed so that they would not produce sex hormones.

The results were similar to the original experiments: Th17 cells from male mice were more pathogenic, and those from females were less pathogenic, irrespective of the hormonal differences. "These findings represent an important advance in our understanding of how biological sex acts as a determinant of disease severity in [MS]," the researchers concluded

For details of all stories go to page 1



Becoming a happy self-cather

Next month will mark ten tears since I started to self-catheterise. Back in August 2011 my "self cathing" was once a day. Ten years later, as my condition has progressed, I use a catheter three or four times daily. I now find it increasingly hard to empty my bladder or "void" in the usual way.

I estimate that in my decade of self catheterising I have used about 10,000 catheters and that these catheters would probably stretch 3 kilometres if placed end to end. That's a lot of self-catheterising and it's quite a journey in every sense of the word. It's also quite a lot for me to reflect on after 10 years.

As well as using a catheter more often than back in 2011, there have been other changes too. When I started self-cathing I used a slim size 12. I now use a sturdy size 14. That's to say that my catheter is now wider than the one I used a decade ago. I will explain why later on, but first a bit of background info.

A size 14 catheter is basically a wider tube than a 12 and has the advantage that it drains urine more quickly, meaning you spend less time on the loo with the catheter inside you. But a size 14 has its disadvantages. Being thicker, it is more difficult to insert. In the early days there were one or two awkward moments when I couldn't get it in and round the bend that sits in the middle of the nine inch long "S" shaped male urethra. Ouch!

I quickly learned that patience really pays and to use the words of Kellee Patterson's 1970s disco song: "if it don't fit, don't force it". Yes, I have learned not to force the size 14 around the S bend. I "just relax" as Kellee's song advises, and relaxing works It goes round the bend, so to speak.

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Continued from page 5. My personal journey to self catheterisation actually started a little earlier than a decade ago. It was 11 years ago when a visit to the local MS nurse ended up in my first visit to a continence clinic where a bladder scan revealed I was walking round with 200 ml of urine in my bladder even after toileting. I was told to use a catheter urgently and handed a box of size 12s but being a bit traumatised I just ignored the box and the advice too.

What changed my attitude to self-cathing was that shortly afterwards I started to see white "blobs" in my urine. These white blobs are basically segments of the bladder epithelium (lining) which can detach when the bladder is overfilled and stretched. They can also appear when you get repeated bladder infections as bacteria burrow down into the bladder wall leading bits of the wall to detach. The appearance of the white blobs was my call to action.

I promptly plucked up courage and started self-cathing. But, quickly I noticed that these white blobs clogged up the thin size 12 catheters I had been given. A quick return trip to the continence clinic and I walked away with size 14 catheters. Now any blobs glide down the wider tube more easily and I am glad to say that the wider catheter, along with its more frequent use, has led to an improvement in my bladder health.

Using a wider catheter hasn't been the only thing I have done to tackle my "white blob" problem. Some years ago I had a bladder "flushout". This is where the bladder is "hosed down" and the white blobs or "debris", as my urologist likes to call it, are all washed away. This flushout takes place under general anaesthetic so fortunately you don't really know much about it. Since the bladder flushout and since taking a bladder disinfectant drug called Hiprex my bladder infections have largely disappeared. I wouldn't be so bold as to say the bladder is a problem solved, but things look better on the bladder front than they have done for several years.

I would be lying if I said self-catheterisation was something I look forward to doing or something I always find easy. If I could regain control of my bladder muscles I would never use another one again, but as this is unlikely to happen I am reconciled to self-cathing for life. I am not exactly a happy cather but I recognise that I have done what I had to do. Catheters have probably helped me better manage my MS over the past decade and will hopefully help me to continue to manage it for the next ten years and beyond.

More information on page 13. **Page 5 Picture: Coloplast**

Simple Amino Sugar May Be Treatment for Progressive MS

Markedly low levels of a simple amino sugar called N-acetylglucosamine (GlcNAc) were found in the blood of people with progressive forms of MS and were linked with greater disease severity and disability, a study has reported.

These findings support GlcNAc as a potential biomarker for more severe forms of MS. A recently completed Phase 1 trial tested the safety of GlcNAc at specific doses. Researchers hope to conduct further clinical studies to evaluate GlcNAc as a potential MS therapy, and one that might promote myelin repair. The study, "Association of a Marker of N-Acetylglucosamine With Progressive Multiple Sclerosis and Neurodegeneration," was published in the journal JAMA Neurology.

"In progressive MS, neurodegenerative processes steadily multiply and cause more and more neurons in the brain and spinal cord to die," Alexander Brandt, MD, the study's lead author and an associate professor of neurology at the University of California, (UC) Irvine, said in a press release. "However, we still do not know what exactly causes this disease variant."

After proteins are synthesized, some are modified by adding complex sugars (N-glycans) in a process known as glycosylation, creating so-called glycoproteins. An essential precursor in this process is GlcNAc, a common sugar and part of a regular diet. Brandt and colleagues at the Experimental and Clinical Research Center (ECRC) in Berlin, with collaborators at UC Irvine and the University of Toronto, wondered if the levels of GlcNAc in the bloodstream of people with MS were altered.

After adjusting for age, those with progressive MS had markedly lower concentrations of N-acetylglucosamine in the blood serum than in healthy people or patients with relapsing-remitting MS," Brandt said. In this study from Berlin, "we found that low serum levels of GlcNAc are associated with the development of the progressive form of the disease, clinical disability and neurodegeneration," said Michael Demetriou, MD, PhD, the study's senior author and a professor of neurology with an MS specialty at UC Irvine. "This opens up potential new avenues for identifying, at an early stage, which patients are at higher risk of progressive MS and adjusting their treatment accordingly," Demetriou said.

"Our hope is that we can use GlcNAc and the associated glycosylation mechanism to promote myelin repair and thus reduce neurodegeneration," Brandt said.N-acetylglucosamine can be bought online as a food supplement and its easy availability and safety may make it easier to surmount the various regulatory hurdles needed for approval as a prog-MS therapy. **For details of all news stories go to page 13**

Robotic Exoskeleton Intervention Improves Mobility and Cognitive Function in prog MS

Four weeks of Robotic Exoskeleton-Assisted Exercise Rehabilitation, (REAER), worked better than conventional approaches to improving mobility and cognition in MS patients with substantial walking difficulties, according to a small trial.

A robotic exoskeleton consists of an externally worn device that encases a user's hips, back, and legs during rehab, providing greater physical performance.

The study, "A pilot randomized controlled trial of robotic exoskeleton-assisted exercise rehabilitation in multiple sclerosis," was published in the journal Multiple Sclerosis and Related Disorders.

This pilot trial, which was partly funded by the National MS Society, involved 10 highly educated adults (mean age 49.9) with MS and significant disability. The participants were randomly assigned to undergo either a 30-45 minute session of REAER (six patients) or conventional gait training (four patients), twice a week for four weeks (about one month).

The results showed that patients undergoing REAER had large improvements in functional mobility, cognitive processing speed, and brain connectivity after the four-week intervention. Indeed, as an example, these patients took about 59% more steps during the last session compared with the first.

In the conventional training group, meanwhile, the patients' outcomes remained stable or worsened after the intervention.

These findings suggest that REAER-related improvements in brain connectivity "might explain downstream adaptations" in motor and cognitive function, the researchers wrote.

The team behind the research plans to design a larger trial to further study the effects of robotic exoskeleton-assisted exercise rehabilitation.

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Immersive Virtual Reality May Improve Treadmill Walking Training

"Immersive virtual reality" may make treadmill exercise more engaging and effective for people with progressive MS or other conditions that can make walking difficult, according to new research.

The findings were published in the Journal of NeuroEngineering and Rehabilitation in a study titled "Immersive virtual reality during gait rehabilitation increased walking speed and motivation in patients with multiple sclerosis and stroke".

MS and other neurological impairments, such as stroke, can cause gait disorders or walking difficulty. Physical therapy and exercise therapy are part of standard care for gait disorders, and this often involves time spent on a treadmill. Exercising on a treadmill, especially doing so regularly over a long period of time, can be repetitious and boring. As such, researchers are looking for ways to increase people's motivation for this type of exercise.

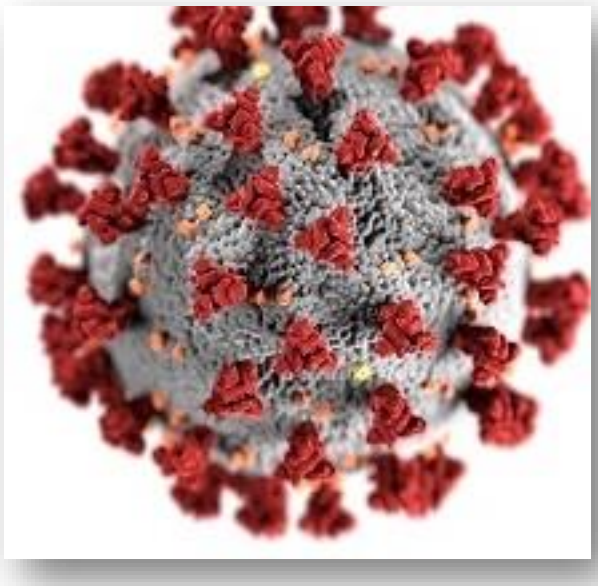
One potential strategy is using virtual reality, or VR. In general, VR research has used one of two types of devices: a head-mounted display (HMD), which goes over the face like a pair of goggles, providing a fully immersive experience or a less immersive approach where participants walk in front of a projector or television screen a few feet away. In the new study, researchers in Germany set out to compare these two VR approaches, in terms of their usefulness for gait disorder therapy.

"For the first time, the current study provides a direct comparison of immersive, semi-immersive VR-based gait rehabilitation and conventional gait rehabilitation with patients, which is essential to reveal the advantages and disadvantages of the respective methods," the team wrote. Building on previous research, the scientists designed two VR systems — one immersive using a HMD, the other less immersive using a television screen. Then, they had 36 students at their institution perform walking tests three times: once with each VR system, and once with no VR system.

With both forms of virtual reality, participants walked more quickly than they did without any VR. Walking speeds also were significantly faster with the HMD setup than with the less immersive form of virtual reality. Overall, 89% of the students and 71% of the patients reported liking treadmill training with the head-mounted device better than the other two setups.

While the results are promising, the researchers stressed that this was a small study done at a single institution, so the results should be interpreted with appropriate caution.

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Why Covid vaccine could lead to new progressive MS treatments

An MS specialist from the USA says an MS vaccine and treatment for MS progression could be an outcome of the current COVID-19 vaccine development.

Dr. Yashma Patel an MS specialist at Valley Neurology in Spokane Valley. Washington DC says the breakthrough technology deployed to vaccinate against COVID-19 also has led to a promising new approach to preventing the progression of multiple sclerosis. “It is exciting, definitely exciting,” she said.

So far, the new MS vaccine has been the subject of only a handful of studies in mice, the results of which were published earlier this year in the highly regarded journal Science. But though they were limited, the results may also open up a new path toward successfully treating MS according to Patel and Dr. Annette Wundes, director of the Multiple Sclerosis Center at the University of Washington. While acknowledging that it’s “obviously still very early on,” Wundes said the approach analysed in the Science study “allows a completely new way of dealing with MS.”

Existing approaches to combating the disease fall into two main camps, according to Wundes. One approach is “chemo-like,” she said, in that you’re attempting to suppress the immune system so it relents in its attacks on the nervous system.

The other approach, Wundes said, involves modulating the immune system or, put simply, “strengthening the good guys and weakening the bad guys” to reduce the severity and effectiveness of the immune system’s attacks on the nervous system. “We have made huge strides in treating in MS,” Wundes said, “but to a varying degree, (those treatments) come at the price of higher risk as well.”

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Continued from page 10 Current therapies also "don't stop (the disease) and don't fix anything," Patel said. But the new approach of modulating the immune system could do exactly that: prevent the disease's progression and improve existing symptoms without affecting normal functioning of the immune system. It may also stop the disease from ever taking hold in the first place.

A key to achieving these ground-breaking results is messenger RNA, or mRNA, vaccine technology, which has been in development for three decades but was first successfully deployed late last year with the Pfizer vaccine for COVID-19. "When you get a vaccine, any traditional vaccine, you're given a small amount of a virus, either a live virus or dead virus," Patel explained. That injection triggers the immune system to make antibodies so "your body fights it off" and prevents you from getting a full-blown infection, she said. But mRNA vaccines take a fundamentally different approach. Instead of giving you a virus, Patel said, they inject mRNA, which is "essentially a code" that "tells your body how to make" an antigen that triggers the production of antibodies that ward of infection.

One of the successful mRNA COVID-19 vaccines is Comirnaty, which the biotech company BioNTech created with the American firm Pfizer. BioNTech's CEO, Dr. Ugur Sahin, is behind the effort to employ the same mRNA vaccine technology to combat MS.

The study Sahin published with a team of fellow researchers in the journal Science found that mice administered the MS shot produced an antibody that prevents the immune system from attacking myelin. "Basically, what they found is the mice who got the vaccine didn't display any further symptoms of MS and didn't see any further damage to the myelin," Patel said. "It would basically stop any progression of MS." But while the research published earlier this year is promising, far more work remains to determine whether that promise can be fulfilled.

Wundes also said, though, the article published in Science indicates that researchers did "a really good job" of looking thoroughly at the vaccine's effect on the mice who were given it. She also said the success of mRNA vaccines for COVID-19 boosts the odds that the MS vaccine will work. Now that the new vaccine-delivery technology is in use, Wundes said, it can be "adapted very quickly to new targets. And if you can apply it to autoimmune disease," she said, "that would obviously be very fantastic." Ultimately, though, no specific cause of MS has been identified. And that means preventing the disease is essentially impossible. Unless, that is, the vaccine works.

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New MRI techniques could pave way to predict disability in MS

Advanced MRI techniques can detect very early changes in the brains of people with MS which may lead to more accurate predictions about MS progression, according to a study led by UCL (University College, London) researchers.

The authors of the paper, published in the journal Brain, say these previously unseen changes could have the potential to predict how disabled a person might become in the future.

Funded by the MS Society and Rosetrees Trust, the study combined advanced MRI techniques to show microscopic changes happening in the MS brain. The team at the Queen Square MS Centre observed 42 people who had experienced their first MS symptoms in the previous three months and, compared to healthy volunteers, found their MRIs showed alterations in sodium concentration, a fundamental element for our brain function, and the brain microstructure.

Crucially, the scale of these changes corresponded to subtle signs of disability, like slower walking speed and higher Expanded Disability Status Scale (EDSS) score, suggesting these previously undetectable changes could be contributing to such disability. If they also prove to be related to disability build-up, they could even be used to more accurately predict how someone's MS will affect them in the future.

Lead author Dr. Sara Collorone (UCL Queen Square Institute of Neurology) said: "This development is exciting because these new techniques go way beyond what we can do with conventional MRI, allowing us to see damage and alterations in brain tissue that we haven't seen before in early MS. This approach can provide valuable information about early MS damage that previously has only been obtainable through post-mortem studies on brain tissue from people with advanced MS.."

The conventional MRI findings used in practice today are unable to show the clinical variability of MS. Currently, white matter lesions in the brain and spinal cord are visible as white spots on an MRI scan, but these white spots provide comparatively little information on the degree or scale of damage, and the study found no association between white matter lesions and disability. Disability in MS is driven both by inflammation and nerve loss, with the latter causing the gradually worsening, irreversible disability seen in progressive forms of MS. The alterations visible using these new techniques are indicative of damage to nerves, and may prove to be a very early indication of the likelihood of progressive disease. Such understanding could be particularly important if neuroprotective drugs start to emerge. **For further details of all features go to page 13**

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For further details on the Coloplast Speedicath flex check out

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To Contact me email iancookjournalist@yahoo.co.uk or via twitter@iancookMSer

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