

My prog-MS ezine

For people with progressive MS and other interested people

Issue number 25, May/June 2019

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

In this issue are eight pages of important prog-MS news stories plus two features about issues that matter to prog-MSers. In the first feature (page 5) I look at some surprising research into smoking and MS .

The second feature looks at a stage play that I went to see recently which explores what it's like to live your life with progressive MS. See page 10.

IN THIS ISSUE



Making a drama out of a crisis in progressive MS – pages 10-11

Walking drug trial to end later this year – page 2
Sugary drinks link to more MS disability, study finds – page 13

Phase 3 Trial of MS Walking Drug Amantadine set to end later this year by September 2019

A Phase 3 trial testing ADS-5102 (amantadine) extended release capsules for all types of MS is looking at whether the capsules can improve walking speed.

A total of 570 adults with MS, ages 18 to 70 years, who have difficulty walking have been recruited for the randomized trial (NCT03436199) at multiple sites across the U.S. The trial, which recruited its first patient in April 2018, is set to conclude by September this year.

ADS-5102, marketed by Adamas Pharmaceuticals under the brand name Gocovri, was approved by the U.S. Food and Drug Administration in August 2017 to treat levodopa-induced dyskinesia, which refers to involuntary and jerky movements experienced by people with Parkinson's disease receiving the drug levodopa.

The Adamas-sponsored study in MS patients is assessing the effectiveness and safety of two ADS-5102 doses — 137 and 274 mg — given once daily at bedtime for 21 weeks, compared with placebo or dummy pill.

The primary goal was to measure changes at 12 weeks in the Timed 25-Foot Walk test (T25FW), in which patients are instructed to walk 25 feet as quickly and safely as possible. Secondary measures, also at 12 weeks, included the Timed Up and Go (TUG) test of mobility and balance, and the Two-minute Walk Test.

Treatment with ADS-5102 was associated with improved walking speed in a four-week, double-blind Phase 2 trial (NCT02471222) in 60 MS patients with walking issues. ADS-5102, given at 137 mg in the first week and 274 mg in subsequent weeks, significantly improved T25FW scores by 16.6%, compared with placebo, and resulted in a 20% or greater improvement in walking speed in a greater proportion of patients than the control group.

For details of sources for all news stories go to page 14

Phase 2 Trial to Assess Mesenchymal Stem Cells to Treat Prog- MS

The US National Multiple Sclerosis Society is funding a new Phase 2 clinical trial to test the effectiveness of stem cell therapy in progressive MS using mesenchymal stem cells taken from participants' own bone marrow.

The bone marrow stem cells are expanded in laboratories, and triggered to become mesenchymal stem cell-derived "neural progenitors" which means the stem cells readily differentiate into neurons.

Cells are then put back into the patients, infused into the spinal fluid in multiple doses. Once mesenchymal stem cells are infused, they are believed to produce growth factors that stimulate the repair of damaged tissues, and possibly act as inhibitors of immune responses associated with MS.

Mesemchymal stem cell therapy does not aim to replace the person's own immune system, and so does not require pre-treatment with cancer chemotherapy drugs, as is the case in the more widely publicised autologous haematopoietic stem cell transplantation (often shortened to AHSCT, or HSCT).

The US trial will have 50 participants with progressive MS. Participants will receive six injections of stem cells at two month intervals in one year. Patient recruitment is ongoing. Researchers will assess changes in patients' disability by using the Expanded Disability Status Scale (EDSS), based on examination by neurologists. The study also will assess changes in bladder function and possible adverse side effects associated with the treatment.

The study is a follow-up of a Phase 1 trial led by researchers at Tisch MS Research Center of New York. The National MS Society has offered $1 million over three years to help support Phase 2 clinical trials testing stem cell therapy in progressive MS.

For details of sources for all news stories go to page 14

New Progressive MS Phase 2 Stem Cell Trial Enrols First Patient

The first patient has been enrolled in another Phase 2 multi-centre clinical trial testing a stem cell treatment for progressive MS in the US.

The open-label trial (NCT03799718), titled Safety and Efficacy of Repeated Administration of neuron (MSC-NTF Cells) in Participants With Progressive MS, will enrol and treat up to 20 adults with progressive MS at several sites. Both primary progressive MS (PPMS) and secondary progressive MS (SPMS) patients are eligible.

The idea behind BrainStorm's NurOwn cellular technology is to take mesenchymal bone marrow stromal cells (MSCs) from patients with a neurodegenerative disease, and modify them to become able to produce neurotrophic factors (NTFs) — biomolecules that support the growth, survival, and maturation of brain cells.

These bone marrow-derived MSCs are expanded and modified outside the patient, referred to as MSC-NTFs or NurOwn cells. The company aims to use this therapy approach to target disease pathways important in a range of neurodegenerative disorders, including MS, amyotrophic lateral sclerosis (ALS), and Huntington's disease. The goal is to ultimately slow or stabilize disease progression.

The 20 progressive MS participants in the trial will undergo a bone marrow biopsy to collect patient MSCs. Participants will receive three intrathecal transplants — injections into the cerebrospinal fluid of NurOwn within 16 weeks, and will be followed for 12 weeks to determine the treatment's safety and effectiveness.

Researchers will evaluate the safety of the procedure by the incidence of treatment-emergent adverse events up to 28 weeks after treatment. To confirm that MSC-NTFs are delivering neurotrophic factors and immunomodulatory signalling molecules as expected, the team will look for an increase in the amount and type of these biomolecules in the cerebrospinal fluid following NurOwn transplant.

For details of all news stories go to page 14



My mum, my MS and the smoking gun

As an MSer one of the first things you learn is there is a genetic component to your illness. You also learn MS is associated with other auto-immune diseases.

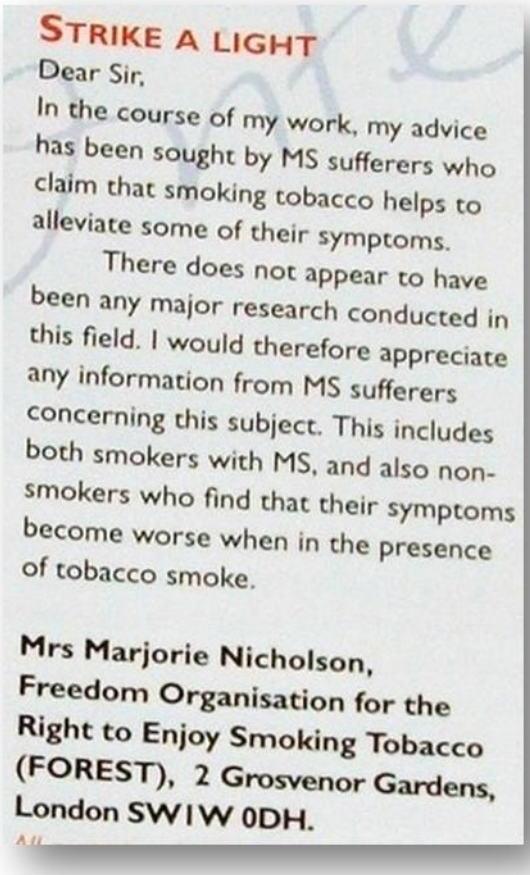
So, when diagnosed with MS, it was no surprise to discover that my mother (pictured) who had long standing ulcerative colitis (UC) was in fact suffering too from an auto-immune disease . My mum had been diagnosed with UC at more or less the same age as I'd been diagnosed with MS, in her 30s. And because of other similarities between the two conditions I started to take a keen interest in similarities between UC and MS as well as their respective treatments.

The first UC treatment I looked at was nicotine.(Strange but true) Back in the 1990s nicotine was being touted as a wonder treatment for UC, something I thought was odd because smoking, and I assume nicotine, was said to be the worst thing of all if you had MS. To make things more puzzling I discovered smokers, who are more likely to get MS, are actually less likely to get UC. At the time it was assumed nicotine conferred some sort of protection in UC – strange but true.

Then in the late 1990s the nicotine theory was put to one side and a new theory about smoking and ulcerative colitis started to do the rounds. This new theory was that cigarette smoke irritates the lungs and this stress is immunosuppressive, dampening down an overactive immune system. Interestingly this theory has recently been explored in MS research. A paper published in the International Journal of Molecular Sciences earlier this year looked at the effect of cigarette smoke on two types of mice with "mouse MS" - Experimental Autoimmune Encephalomyelitis (EAE).

continued on page 6

Continued from page 5



STRIKE A LIGHT

Dear Sir,

In the course of my work, my advice has been sought by MS sufferers who claim that smoking tobacco helps to alleviate some of their symptoms.

There does not appear to have been any major research conducted in this field. I would therefore appreciate any information from MS sufferers concerning this subject. This includes both smokers with MS, and also non-smokers who find that their symptoms become worse when in the presence of tobacco smoke.

Mrs Marjorie Nicholson, Freedom Organisation for the Right to Enjoy Smoking Tobacco (FOREST), 2 Grosvenor Gardens, London SW1W 0DH.

The paper found that cigarette smoke "ameliorated the EAE clinical score" in a group of mice. Commenting on the research the Barts neurologist David Baker who appropriately names himself "mouse doctor" made a suggestion about why this was. Writing in the Barts MS blog he said: "Cigarette smoke is irritating to the lungs and I guess this would be stressful to the animals and stress is immunosuppressive."

So, if this is the case why isn't smoking immunosuppressive in MS? I don't know the answer but while speculating I recalled a curious observation made in 1995 in the MS Society's "MS Matters" magazine. It was carried in a letter from Marjorie Nicholson, executive director of FOREST, the Freedom Organisation for the Right to Enjoy Smoking Tobacco. Mrs Nicholson's letter, titled "Strike a Light" (See above) said the following: "In the course of my work my advice has been sought by MS sufferers who claim that smoking tobacco helps to alleviate some of their symptoms. There does not appear to have been any major research conducted in this field."

Whatever your views on the seemingly absurd suggestion about smoking alleviating MS symptoms I think Mrs Nicholson was right about one thing, there has been a lack of "major research" in this area. It is always assumed that tobacco is bad for MS but given the research done in ulcerative colitis and the well-known fact that Parkinson's Disease, another neurological condition, occurs less often in cigarette smokers than in non-smokers, it makes you wonder whether the assumption about tobacco and MS is just that – an assumption. And as Oscar Wilde put it: " When you assume, you make an ass out of you and me".

COI: None. I am an ex-smoker, whose dad died of lung cancer. I disapprove strongly of smoking tobacco and have never been paid a penny by a tobacco company

For further details go to page 14

Licensed estrogen receptor drug can remyelinate

An estrogen receptor modulator drug used to treat menopause related bone thinning may have a role to play in remyelination according to research carried out by US academics.

Based on experiments in which mice were given the drug Bazedoxifine it was found possible to get oligodendrocyte precursor cells (OPCs) to differentiate into functioning, myelinating cells (oligodendrocytes). Bazedoxifine seemed to work on human oligodendrocyte precursor cells in lab tests.

For several years the search for therapeutic targets to support remyelination in MS has proved challenging as existing oligodendrocytes in the brain do not remyelinate demyelinated axons.

Bazedoxifene is a selective estrogen receptor modulator and several of this class of drugs have been suggested as having the potential to make oligodendrocyte precursor cells (OPCs) differentiate into functional myelinating cells.

In the latest research scientists found Bazedoxifene increased the differentiation of OPCs into functional oligodendrocytes (both in mouse and human cells) and did so when axons were demyelinated after an induced lesion.

Bazedoxifene is already approved in the US by the Food and Drug Administration (as it is regularly prescribed for vasomotor menopausal symptoms in women) and is known for having relatively few side effects, which makes it a promising therapeutic drug for remyelination in MS.

It may have fewer regulatory hurdles to surmount in the UK than other drugs because it's already licensed and the drug was approved in the European Union by the European Medicines Agency in 2009.

The question is: will anyone lobby to get this drug taken up for us prog MSers? Over to you.

For details of all news stories go to page 14

Plant protein compound may prevent MS progression

A unique compound derived from a plant protein called T20K seems able to prevent or slow MS disease progression, according to data from preclinical studies.

Researchers from the Medical University of Vienna (Austria) and the University Medical Center in Freiburg (Germany) have shown that T20K is able to block the activity of pro-inflammatory cytokines (molecules that mediate immune and inflammatory responses), such as interleukin-2 (IL-2), and reduce symptoms of MS in animal models without toxic side effects.

Preclinical studies carried out last year have shown how T20K is absorbed and distributed in the body. Based on these findings, researchers expect that the medication can be administered at low doses, every two weeks or monthly. They believe that T20K may have a significant effect on the long-term quality of life for MS patients.

Results have also shown that T20K is slowly eliminated from the body, meaning that at any given time very small amounts of the compound are in circulation, which reduces the risk of drug toxicity.

“If T20K continues to demonstrate its effect in human studies, which we have no indications otherwise, we believe that this could transform the way we look at severe autoimmune diseases such as MS. Both how we treat the disease but also how patients perceive a diagnosis since their outlook would have changed,” Kjell G. Stenberg, CEO of Cyxone, said in a press release.

“We are excited to know more about [T20K] abilities in the upcoming clinical studies,” Stenberg added.

Cyxone is finishing the preparations to launch the first Phase 1 clinical trial to evaluate the effects of T20K in healthy volunteers. According to the company, the trial’s application will be submitted during the second quarter of this year.

For now, current studies will focus on determining the optimal dose for T20K to halt disease progression and, at the same time, guarantee it is not dangerous to other vital body functions

For details of all news stories go to page 14

The high energy cost of being a progressive MSer

People with progressive MS use up to three times more energy on average for simple mobility tasks, compared to those without the condition. That's according to a new study published in the Archives of Physical Medical Rehabilitation.

In areas of life apart from simple mobility tasks things are even worse for us progressive MSers. The study found people with progressive MS had significantly higher oxygen use in climbing steps (3.60 times more), rolling in bed (3.53), walking (3.10), lying to sitting (2.50), and sitting to standing (1.82).

The reasons why progressive MSers use more energy is complex but may be due to deconditioning, i.e. simply being unfit. There may be other reasons such as perceptions of fatigue.

It is not well known how the brain perceives fatigue but a higher oxygen cost during physical activity is measured by the body and results in a greater perception of fatigue. The reason why marathon runners can run mile after mile is that they are conditioned to do so and have trained their brains not to feel fatigue.

Lessons from elite marathon runners and the findings from the new study suggest that rehabilitation that increases endurance during physical tasks will help reduce fatigue in people with progressive MS.

The question of course is how to get NHS resources allocated to setting-up a national exercise and training programme for MS-related fatigue and how to get us progressive MSers to buy into the benefits of regular exercise no matter how disabled we are.

I know from personal experience this is easier said than done, but that is no excuse not to get it done; it needs to be done. Please note, it is also not only about exercise, but how we live our lives.

For further information on news stories go to page 14



Making a drama out of progressive MS

When a play about progressive MS came to my local Repertory Theatre I managed to persuade the theatre to give free tickets to a small group of local MSers, myself included. I was pleasantly surprised when the theatre said "yes".

The play "Duet For One", pictured above, is about a top classical musician forced to abandon her musical career because of her progressive MS. Some say the play is loosely based on the life of cellist Jacqueline Du Pre who became unable to play cello because of her rapidly progressing MS and died in 1987 just 14 years after diagnosis, at the age of 42. The musician in the play has been asked by her composer husband to see a psychiatrist to help her deal with the psychological turmoil that has come with her rapidly progressing MS. She both talks of suicide and also reassures the psychiatrist that she is not "losing it".

As someone who has is now living through the progressive phase of the illness I found myself engrossed in the play, asking myself whether I too am going through the same inner torment as Stephanie. Am I angst ridden, out of control and unable to cope with what she describes as "the creeping paralysis"? And am I in danger of "losing it", in need someone to guide me? Or do I have everything under control in my life? **Continued on page 11**



Ctd from p10 The play ends with Stephanie accepting the psychiatrist's offer to help, with him dismissing her talk of suicide, telling her that the purpose of life is life itself.

As a stumbled out of the theatre on my elbow crutch I reflected the play was moving, insightful yet also disturbing. It asked the question that people like me (who can barely walk and for whom living becomes ever more difficult) often dodge. What should I do with my life now that MS has taken away so much? Should I wallow in self-pity? Should I resort to anger and hostility like Stephanie, and talk of ending it all? Or should I try to find some new purpose? Should I try to move on and make something out of this new life? And if so, is it possible to make anything positive out of something as negative as progressive MS?

In a beautifully written monologue the psychiatrist Dr Feldman challenges Stephanie's negativity about what MS has done to her life in robbing her of her musical career. He says: "You say you had your only purpose, and now it is gone forever, and indeed it is a deep loss for you and for us also. But there are a thousand, a million endless other purposes you can enjoy: the sun on your body, reading, writing – even with a pencil held in your mouth to operate a keyboard if necessary. It is so difficult, I know, Stephanie, but it is so easy too. The tree of life has more than merely one wretched apple on it. Reach! Pick. "

As my MS has advanced I have occasionally indulged in self-pity and sometimes asked myself questions like "why me?" failing to find answers. But leaving the theatre I felt myself asking the question "should I reach for new apples on the tree of life?" The answer is "yes". I must do that.
Photos Credit Robert Day. Thanks to Birmingham Repertory Theatre for the fee tickets!

Ibudilast Slows Brain Shrink in PPMS, Not SPMS, Trial Shows

Treatment with ibudilast slows brain shrinkage in patients with primary progressive MS (PPMS), but not secondary progressive MS (SPMS), according to a Phase 2b clinical trial. It is believed this may be partially due to faster disease progression in PPMS.

Ibudilast is used in Japan and Korea to treat asthma and some complications of stroke. It reduces inflammation and acts on a number of biochemical processes in cells associated with nerve damage and myelin repair. Previous studies have suggested it may have a neuroprotective effect in MS.

The present study, "Response to Treatment According to Progressive Disease Type: Analysis from a Phase II Progressive MS Trial of Ibudilast," is being presented at the 2019 American Academy of Neurology (AAN) Annual Meeting, taking place later in May in Philadelphia, USA.

Although PPMS and SPMS have been increasingly regarded as having more similarities than differences, whether they differ in response to treatment is still unclear. To address this, scientists evaluated the impact of ibudilast on PPMS and SPMS The 96-week, randomized, and double-blind study compared treatment with Ibudilast with a placebo in 255 adults (ages 21–65) — 134 with PPMS and 121 with SPMS. Participants took up to 100 mg of ibudilast in capsules per day.

The latest analysis has revealed that ibudilast significantly slows brain atrophy in patients with PPMS but not in those with SPMS. According to the investigators this may have been driven at least partially by the results in people on placebo, as controls with PPMS showed faster atrophy progression than controls with SPMS.

For further details of all news stories go to page 14

News

Sugary drinks linked to more disability in MS, study finds

MSers who drink about 290 calories of sugar-sweetened beverages — the equivalent of about two cans of non-diet soda — per day may have a higher level of disability compared to those who seldom consume these drinks, according to a new study.

The research, "Dietary Intake and the Effect on Disease Progression in People with Multiple Sclerosis," will be presented at the American Academy of Neurology's Annual Meeting, in Philadelphia, U.S. from May 4–10.

A team at St. Josef Hospital and Neurologische Universitätsklinik, in Germany, and Johns Hopkins School of Medicine, in the U.S., analysed 135 MS patients: Each participant completed a 102-item diet questionnaire.

It was found that MSers who drank the largest amount of soda, flavoured juices, and sweetened teas and coffees had a five-times greater risk of having severe disability, than those who seldom drank these beverages. Twelve of the 34 patients in the top intake group had severe disability, in contrast to only four of the 34 participants in the bottom group.

"While overall diet quality was not associated with disability status in this preliminary study, we observed potential association between [sweetened beverages] and higher disability status in MS patients," the team wrote**.**

Protein found in demyelinated lesions may help remyelination

A protein that promotes nervous system repair through remyelination — the creation of myelin, the protective sheath around nerve cells — in mice also is found in remyelinating plaques in brains of multiple sclerosis (MS) patients, new research shows.

This protein potentially represents a new therapeutic target in demyelinating disorders like MS.

The research article reporting the findings is titled "TMEM10 Promotes Oligodendrocyte Differentiation and is Expressed by Oligodendrocytes in Human Remyelinating Multiple Sclerosis Plaques," and was published in the journal Nature Scientific Reports.

For further details of all news stories go to page 14

References contact details etc

Page 2

Amantadine story

https://multiplesclerosisnewstoday.com/2019/03/22/ms-patients-recruited-phase-3-trial-ads-5102/?utm_medium=desktop-push-notification&utm_source=Notifications&utm_campaign=OneSignal

Page 3 Stem cells story

https://multiplesclerosisnewstoday.com/2019/03/13/trial-assess-mesenchymal-stem-cell-therapy-progressive-ms/?utm_medium=desktop-push-notification&utm_source=Notifications&utm_campaign=OneSignal

Page 4 Smoking and MS

The Marjorie Nicholson letter was published in the first issue of MS Matters, the UK MS Society's bi-monthly publication

page 7 bazedoxifene story

source: https://www.reddit.com/r/MultipleSclerosis/comments/bc6sng/bazedoxifene_a_selective_estrogen_receptor/

page 8 Plant protein story

source: https://multiplesclerosisnewstoday.com/2019/03/26/t20k-preventive-treatment-ms-early-data/?utm_source=Multiple+Sclerosis&utm_campaign=c047e2aa93-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-c047e2aa93-71290133

https://multiplesclerosisnewstoday.com/2019/01/25/positive-safety-data-high-dose-temelimab-ms-treatment-candidate/

Page 9 exercise story

Devasahayam et al. Oxygen cost during mobility tasks and its relationship to fatigue in progressive Multiple Sclerosis. Arch Phys Med Rehabil. 2019 Apr 23. pii: S0003-9993(19)30257-6.

Plus https://multiple-sclerosis-research.org/2019/04/exercise-exercise-exercise/

Page 12 Ibudilast story

https://multiplesclerosisnewstoday.com/2019/04/04/aan2019-ibudilast-slows-brain-atrophy-ppms-phase-2b-trial/??utm_medium=desktop-push-notification&utm_source=Notifications&utm_campaign=OneSignal

Page 13 sugary drinks story

https://multiplesclerosisnewstoday.com/2019/03/08/aan2019-sugar-sweetened-beverages-linked-disability-level-ms/?utm_medium=desktop-push-notification&utm_source=Notifications&utm_campaign=OneSignal

TMEM Story

https://multiplesclerosisnewstoday.com/tmem10-demyelinated-ms-lesions-contribute-remyelination/?utm_source=Multiple+Sclerosis&utm_campaign=bc5c0477f3-RSS_NON-US_EMAIL_CAMPAIGN&utm_medium=email&utm_term=0_b5fb7a3dae-bc5c0477f3-71290133

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

DISCLAIMER:

This ezine is strictly a news and information ezine/website about MS . It does not provide medical advice, diagnosis or treatment. This content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your doctor or other qualified health provider with any questions you may have regarding MS or any a medical condition. Don't disregard professional medical advice or delay in seeking it because of something you have read in this ezine.

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