Guildford ME/CFS Support Group
(& West Surrey)

Newsletter

March 2018

Future dates

Open to all members and carers

For the upcoming meeting details please email our group at:
guildfordme@hotmail.co.uk

Note from Newsletter Editor

The two first articles in this newsletter serve to tie together some of the key insights and research that have been detailed in previous newsletters. And, as such, serve as useful overviews of some of the latest topics for ME/CFS sufferers and friends, family and professionals.

Unrest, the documentary of a 28-year-old Ph.D. student, Jennifer Brea that has been detailed in our recent newsletters is now available on Netflix

NETFLIX

Why patients with ME are demanding justice:

Source: www.independent.co.uk/news/long_reads/why-patients-me-demanding-justice-millions-missing-chronic-fatigue-illness-disease-a8133616.html

“I feel seen for the first time!” exalts one viewer. “I feel vindicated. I finally understand what’s wrong with me, I think I’ve had this all my life,” says another. A doctor admits, “I feel so ashamed.”

The film in question is Unrest, a documentary directed by and featuring Jennifer Brea, a former Harvard PHD student who, after developing the disease ME, started filming her experience. For those not directly affected by the illness, their go-to reference may be one of the many stereotypes that have proliferated in the British media: ME is “yuppie flu”; it’s an illness of lazy people or type-A personalities, malingerers, hysterical women, militant activists, scroungers, even people who are “a bit tired” and “don’t feel like going to work today” (according to a Ricky Gervais stand-up routine). For the first time, a major documentary is speaking back to decades of misinformation and showing what often doctors don’t even see: the daily life of sufferers, of whom there are about 260,000 in the UK.

Unrest follows Brea when she first becomes sick after a 40C fever. For the next year, she suffers repeated infections and her health declines dramatically. But doctors do not take her seriously – a state of play recognised by many young women who are dismissed by the medical system. When she finally sees a neurologist, he diagnoses “conversion disorder”. Hysteria. There must be a trauma that she can’t even remember. There is nothing physically wrong with her that could be causing her symptoms. And so, Brea decides to walk the two miles home – what could be the harm after all? When she arrives back, her brain and spinal cord feel like they are on fire. She is bed bound for the next two years and now, several years later, uses a wheelchair.

After eventually being diagnosed with ME, Brea was able to access some treatments in her native US, but there currently are no cures. Like most patients, an initial flu-like illness triggered the disease. Her symptoms include profound exhaustion (utterly unlike everyday “tiredness”), extreme pain and a worsening of symptoms after even minimal exertion – a symptom known as post-exertional malaise or PEM. ME, like autoimmune diseases, mainly affects women and is often developed in the prime of life, though children are also affected. Indeed, it is the biggest cause of long-term sickness absence from school. Since 1969, the World Health Organisation has recognised ME as a neurological illness although its precise mechanisms remain unknown.

The film features other stories too. Jessica, a young British woman spent four years from the age of 14 in hospital in a semi-coma because of ME. She improved slightly but was completely bedridden such that her feet didn’t touch the ground for years, during which time she grew four inches. “I’ve never stood up at my full height,” she explains matter-of-factly. In contrast, a very severe patient, Whitney, is completely unable to speak. He is so sensitive to stimulation that it is dangerous for others to even be in the same room as him. Fed by a tube in his small intestine, he passes his life in darkness and silence, unable to tolerate light or sound.

Such stories of extreme physical debility are not, however, the most shocking part of the documentary. What has prompted a global justice movement is the fact that many doctors still refuse to accept that ME exists at all.

During 1955 in London, there was a cluster outbreak of a mysterious disease among staff at the Royal Free Hospital in Hampstead. An estimated 292 people were affected, the majority were female nurses. Pathology investigations revealed inflammation of the brain and spinal cord, but the cause remains unknown. It is labelled “myalgic encephalomyelitis”, ME for short to reflect the severe muscular pains of patients and evidence of damage to the nervous system. In 1970 two psychiatrists, Colin McEvedy and AW Beard, published a paper that was to have a profound influence on the history of ME. The authors declared the illness to be “mass hysteria”, citing as evidence the fact that many who fell ill were young women. Neither of them had seen a patient.

Compounding this dismissal meant another blow to patients: the coining of a new name. In the US, the term chronic fatigue syndrome or CFS was introduced in 1988, which was later adopted in the UK. Not only did the new name trivialise the disease, it was also too vague to distinguish ME from other fatiguing illnesses, meaning different illnesses causing fatigue were unhelpfully lumped together.

For patients, communicating the seriousness of their illness is often impossible. “I had this experience of trying to describe my symptoms in words to my doctors for 18 months as I was getting worse,” explains Brea. “I would talk about a burning in my brain or my spine or the fact that I would lose the ability to speak or sometimes I would collapse on the floor and I couldn’t lift my head.” When she later requested her medical records almost all of these serious symptoms were translated into “headache pain”.

Psychosomatic explanations of the disease were being further developed by a small, but influential, group of psychiatrists in the UK. They developed a theory of ME based on the biopsychosocial model of illness, a framework for illness that has also been adopted by the Department for Work and Pensions (DWP), first fully embraced by New Labour. The biopsychosocial model states that illnesses are part biological, part mental, part social. This idea seems common sense, but in practice it is often the psychological elements that are emphasised. Thus, the “biopsychosocial” model of ME is that a patient may have originally had a virus but after that, symptoms are not primarily the result of an ongoing disease process at all. Instead, patients simply have “dysfunctional” or “false” illness beliefs and thus adopt the “sick role”. Spending too much time in bed is the reason they have physical abnormalities, as they become deconditioned due to “exercise avoidance”, and it is assumed that symptoms are reversible by the patient’s own efforts.

However, there is growing evidence that such an approach towards ME is not only inaccurate, but dangerous. Keith Geraghty, honorary research fellow at the University of Manchester and an expert in ME/CFS explains: “Many medical professionals do not view ME/CFS as a serious medical condition. Psychiatrists in the UK have done great harm to ME/CFS patients by promoting a largely psychological model of the illness that diverted research funding away from investigating the many biological abnormalities in the disease and this model has downplayed the severity of the illness.’

The two treatments that arose from this psychiatric model are cognitive behavioural therapy (CBT) and graded exercise. Currently, they are the only two treatments offered by the NHS for ME. Some psychiatrists take the extreme view that patients – including children – need to be admitted to a psychiatric ward, even if against their will and that of their parents. Unrest features a young, severely ill Danish woman, Karina Hansen, who was forcibly taken from her home by five policemen and admitted to a psychiatric ward. Her family were not told where she was being taken. She wasn’t allowed to be seen by any doctors other than psychiatrists. Three years after being taken, she was finally allowed home; she remains ill with ME. In the UK, child-protection powers are sometimes used to enforce psychiatric treatments for children with ME and hundreds of families have faced investigation for child abuse or neglect, though there are no official figures kept by UK health authorities. One charity, Tymes Trust, has advised around 200 families. None of these families were subsequently found to be at fault.

Robert was 12 when he first started graded exercise therapy. His mother, Lorraine, contacted The Independent to explain how the NHS physiotherapy he was asked to do drastically damaged his health. “Robert was moderately ill when the physio began but became severely ill and required a wheelchair after a few months. He was given exercises to do in a hydrotherapy pool, some involving swimming. After just a few months, he lost the ability to walk. His legs turned to jelly, he had severe pain, particularly behind his knees and he just couldn’t support his weight.

“The physiotherapist wouldn’t accept they were causing the harm and blamed my son for not trying hard enough, saying he didn’t want to get better; they would not accept that there was anything physically wrong with him.”

“He had a fit in the pool where they were doing the exercises, which the neurologist later said was caused by extreme pain. Eventually, we had to get a charity to intervene so that we could stop the graded exercise. My son is now 21 and is still severely ill and housebound.”

Robert’s story is one of many, although the NHS does not keep a record of harms caused by graded exercise for ME.

The biopsychosocial model, and the assumption that if people who become disabled from conditions like ME adopted the correct attitudes and behaviours they could recover, seems to appeal to politicians looking to cut the costs of disability payments. “Benefits can often make [ME] patients worse” claimed psychiatrist Simon Wessely, one of the originators of the biopsychosocial model of ME, in 1993 in a meeting with a minister for the disabled. If giving disability benefits to patients, such as those with ME, may foster a culture of dependency, then cutting these benefits can be presented as a positive intervention. According to a document promoting the biopsychosocial framework circulated by Lord Freud, the former minister for welfare reform, it is important for those with health problems like ME to “recognise that the sick role is temporary, in the expectation of recovery” and that giving disability benefits to such patients, may foster a culture of dependency.

However, serious problems with the research claiming to show that biopsychosocial approaches to ME can lead to patients recovering have now been identified. In 2011, controversies about these treatments came to a head when the results from a medical trial – known as the PACE trial – were published. The trial cost £5m and was part-funded by the Department of Work and Pensions; it tested graded exercise and cognitive therapy for ME. The researchers claimed it had been a success and that the treatments were “moderately effective”. However, the trial has faced severe criticism, especially outside the UK, with 100 experts signing an open letter asking for the retraction of one of the trial’s key papers. Among the criticisms was the fact that the trial’s definition of recovery was so weak that even if patients reported their health deteriorating on the trial’s two primary outcomes, they could still be deemed “recovered”. Objective measures of patients’ health failed to show a clinically useful improvement, but were often downplayed.

After a lengthy legal battle fought by patients, the trial scientists were required to release the raw data from the trial. Reanalysis showed no statistical difference between the different treatments offered: a null result. It also showed that previously reported recovery rates had been inflated fourfold. The trial authors maintain that the trial proves CBT and graded exercise are modestly effective.

As critics are increasingly pointing out, the problems with PACE went beyond bad science. A 2006 report by the parliamentary Group on Scientific Research into Myalgic Encephalomyelitis had already pointed out that there is a “vested interest private medical insurance companies have in ensuring CFS/ME remains classified as a psychosocial illness”. The report also mentioned cases where advisers to the DWP had also had consultancy roles in such companies. These links were investigated further by the Centre for Welfare Reform who stated in 2016 that: “Emphasising the importance of psychosocial factors and classing ME as a mental health problem could bring immediate financial benefits to insurance companies when policies limit payouts for mental health problems.”

Unum is the top disability insurer in both the US and UK, and a company which the Centre for Welfare Reform claims is lobbying the Government to promote private health insurance. An internal Unum report on “CFS” claimed the company could “lose millions if we do not move quickly to address this increasing problem.” It was argued that CFS claims should be managed “more aggressively and in a proactive rather than a reactive fashion” while attempting to present ME as “neurosis with a new banner”. Four of the PACE trial scientists disclosed conflicts of interest with the insurance industry.

Even as the international scientific community expressed concerns about the trial, the British media continued to promote it as a great success. When questionnaire results from PACE participants two years after they had received treatment were released, which showed that those who had received CBT and graded exercise reported being no better than those who did not, this was greeted with a front-page story on The Telegraph declaring that “Exercise and positivity can overcome ME”. The Countess of Mar has drawn attention to the Science Media Centre’s promotion of the trial, which led to such headlines, and the fact that Simon Wessely is a board member.

Throughout it all, patients were depicted as dangerous militants in the media for criticising the trial, even though they turned out to be vindicated. The tribunal which ordered the release of the trial’s data ruled that “assessment of activist behaviour was, in our view, grossly exaggerated”. The most severely ill (about a quarter of patients are bed or housebound) continued to receive no care at all, with 80 per cent of requests for home visits turned down by the NHS. Added to this, a dearth of social care and difficulty getting benefits meant many patients were left completely desperate and often without any support at all, with even family members often disbelieving their illness. The waste of human potential caused by ME was recently reckoned to cost the UK economy £3.3bn a year in a report by The Optimum Health Clinic Foundation.

Across the pond in the US, science is moving on. In 2013 the US government asked the Institute of Medicine to convene an expert committee to examine the evidence base for ME. Two years later, their report ‘Redefining an Illness’ was published. The report stated ME is “an acquired, chronic multi-systemic disease biological in nature” symptoms of which include “immune, neurological and cognitive impairment”. After reviewing thousands of medical papers, the report “stresses that this is a medical – not a psychiatric or psychological – illness”.

After the report found considerable evidence that “exertion of any sort can adversely affect several organ systems and many aspects of patients’ lives, often seriously and for long periods” and the controversy of the PACE trial, US health agencies removed their recommendations for CBT and graded exercise.

Over the past few years, studies have demonstrated that ME patients have metabolic, immune, neurological and other systemic dysfunction. Metabolites and proteins in the blood have been found to be abnormal, showing that the bodies of patients are in a hypometabolic state, causing the body to shut down and their cells become unable to produce energy. Neurological and systemic inflammation (along with a female bias) could point towards ME being an autoimmune disease. Evidence of immunodeficiency has been around since 1990 and more recently numerous studies have shown impaired natural killer cell function; a cell which helps control viral infections. ME science, however, is still in its infancy. More studies are needed to identify a cause and develop treatments.

Professor Ron Davis, one of the most eminent ME scientists in the US, used to work on the human genome. Now he has gathered a group of scientists, including three Nobel laureates, to work on “one of the most urgent areas in medicine today”. He is also the father of Whitney Dafoe, the severely ill young man featured in Unrest.

“This is a much more serious disease than many of the other things that people are worried about. It’s more common than MS, it’s more common than Parkinson’s disease, it’s more common than Aids. This is probably the last major disease that we know so little about. And it’s because of its nature that it’s been hidden. The severe patients are often just in their home being looked after by someone and no one knows they exist. But it can get very severe, people have tried to make some measures in terms of debilitating illness, it’s generally viewed as worse than many other diseases that have been ranked in terms of quality of life.’’

ME patients have always had to fight for their rights, but now with the advent of social media, bed-bound patients are able to connect globally and a social justice movement is flourishing under the twitter hashtag #MillionsMissing.

For Jennifer Brea, ME activists can learn a lot from history. “To fight stigma and to force the recognition from the health system, we need a movement for access to treatment, care and research. The HIV/Aids movement allowed extraordinary advancements in the space of a decade. That’s what we need here. It is about reclaiming our bodies and our experience; having a sense of pride in ourselves an in each other.”

And the movement is beginning to gather momentum. In the UK, the NHS has announced it will completely rewrite its guidelines for ME, after pressure from patients and concerned scientists. Medical research into biomedical causes is increasing, but remains seriously underfunded globally. “It’s 30 years wasted, which is a long time in research terms. We could have discovered the cause of ME in that time,” laments health researcher, Dr Keith Geraghty.

Historically, people with ME have been excluded from the disability rights movements in the UK and did not have the lobbying power to affect government policy but disability and ME activists alike are starting to come together, uniting under the slogan: “Nothing about us without us”.

“ME activists are so distressed and angry because we’ve had our reality denied by almost everyone around us,” explains Catherine Hale, an ME activist and leader of the Chronic Illness Inclusion Project. “The dismissal of our testimony is profoundly distressing, you can develop a PTSD response from it. It’s a kind of abuse. A treatment approach that harms people by saying it is our mindset that needs to be changed is a very oppressive experience. As patients, we’ve all been so isolated and are too ill to go out and protest and that’s why the ‘Millions Missing’ is really in its infancy, because we’ve come from so far down.”

Adam Lowe, an author and journalist with ME is also demanding accountability. “One of the most common misconceptions about ME patients is that we’re anti-psychiatry and resent all treatments that imply even a partially psychological cause for the illness. This is another myth that needs to be challenged. I’m a strong believer in adequate mental health provision for everyone as are most ME patients.

“We live with this illness in the dark, hidden in our bedrooms, desperate for answers. We can’t get proper treatment because they tie up limited national resources in endless, useless studies that conflate long-term fatigue with the very specific neuroimmune illness ME. They continue to harm and insult us, the way the LGBT and civil rights movements were harmed, denigrated and insulted in decades past. They are institutionally ableist in the way the Met was once labelled institutionally racist after the Stephen Lawrence inquiry. The only difference is that we die quietly, in the back rooms of our house, because of lack of proper care or effective treatment. No one sees, so the outrage is confined to those of us who know – those of us who already have this illness, and those who love and care for us.”

“Eventually, I think, the small cabal of people setting the negative medical and social narratives about ME will have to wake up and apologise for the harms they’ve caused to hundreds of thousands of people – just like psychiatrists recently apologised to LGBT people. History will not show them favourably, because I believe that justice will prevail in the end.”

Unrest has recently been shortlisted for an Oscar. The power of documentary film is that viewers are confronted by what is unseen – or ignored; it is a medium that conveys something words cannot. Maybe, finally, ME patients are beginning to be seen.

A reboot for ME/CFS research

Source: /www.nature.com/articles/d41586-017-08965-0
By Amy Maxmen 3rd January 2018

Research into this debilitating disease has a rocky past. Now scientists may finally be finding their footing.

Elizabeth Allen keeps careful records of the many treatments she has undergone to relieve the symptoms of chronic fatigue syndrome.

Name a remedy, and chances are that Elizabeth Allen has tried it: acupuncture, antibiotics, antivirals, Chinese herbs, cognitive behavioural therapy and at least two dozen more. She hates dabbling in so many treatments, but does so because she longs for the healthy days of her past. The 34-year-old lawyer was a competitive swimmer at an Ivy-league university when she first fell ill with chronic fatigue syndrome, 14 years ago. Her meticulous records demonstrate that this elusive malady is much worse than ordinary exhaustion. “Last year, I went to 117 doctor appointments and I paid $18,000 in out-of-pocket expenses,” she says.

Dumbfounded that physicians knew so little about chronic fatigue syndrome — also known as myalgic encephalomyelitis or ME/CFS — Allen resolved several years ago to take part in any study that would have her. In 2017, she got her chance: she entered a study assessing how women with ME/CFS respond to synthetic hormones.

After decades of pleading, people with the condition have finally caught the attention of mainstream science — and dozens of exploratory studies are now under way. Scientists entering the field are using the powerful tools of modern molecular biology to search for any genes, proteins, cells and possible infectious agents involved. They hope the work will yield a laboratory test to diagnose ME/CFS — which might have several different causes and manifestations — and they want to identify molecular pathways to target with drugs.

The US National Institutes of Health (NIH) in Bethesda, Maryland, bolstered the field last year by more than doubling spending for research into the condition, from around US$6 million in 2016 to $15 million in 2017. Included in that amount are funds for four ME/CFS research hubs in the United States that will between them receive $36 million over the next five years.

The stakes are high because the field’s scientific reputation has been marred by controversial research. A 2009 report that a retrovirus called XMRV could underlie the disease was greeted with fanfare only to be retracted two years later. And in 2011 and 2013, a British team reported that exercise and cognitive behavioural therapy relieved the symptoms of ME/CFS for many people in a large clinical study called the PACE trial. US and UK health authorities had made recommendations based on the findings, but, starting around 2015, scientists and patient advocates began publicly criticizing the trial for what they saw as flaws in its design. The organizers of the trial deny that there were serious problems with it, but health officials in both countries have nevertheless been revising their guidelines.

Patients, meanwhile, are adrift in a vacuum of knowledge about the condition, says Jose Montoya, an infectious-disease specialist at Stanford Medical School in California and one of Allen’s physicians. “ME/CFS has suffered from scientists applying the usual approaches,” he says. He hopes that sophisticated analyses of genomics, proteomics, metabolomics and more will help to change that. “It wasn’t until the microscope became available that an Italian microbiologist could link cholera to the bacteria that caused it,” he says. “In the same sense, we have not had the equivalent to the microscope until now.”

Early days

In 1984 and 1985, an epidemic of persistent fatigue broke out in Lake Tahoe, Nevada. The US Centers for Disease Control and Prevention (CDC) tested people for Epstein–Barr virus, one cause of the fatigue-inducing illness called mononucleosis or glandular fever, but the results were inconclusive and the investigation was dropped. Around 1987, researchers coined the name chronic fatigue syndrome. But the media snidely called it ‘yuppie flu’. Doctors often told people their symptoms were caused by neuroses and depression.

But a small fraction of clinicians listened closely to patients — who insisted that their debilitating exhaustion was not just in their minds. And whereas a little exercise might temporarily uplift someone with depression, individuals with ME/CFS would be bedridden for days after exertion. Some people also struggle with chronic impairment, some with intestinal disorders, and others completely lose the ability to walk. Anthony Komaroff, a physician-scientist at Harvard Medical School in Boston, Massachusetts, began conducting studies on the disease in the mid-1980s despite being discouraged by his colleagues. “I was emboldened by the fact that when I asked my colleagues why they were sceptical, they could not articulate a reason,” he says.

In the 1990s, Leonard Jason, a psychology researcher at DePaul University in Chicago, Illinois, started questioning basic epidemiological information on ME/CFS. For one thing, the CDC described the syndrome as rare and predominantly affecting white women. But Jason reasoned that clinicians could be missing many cases. Those who were diagnosed were the ones most likely to return for a second, third or fourth medical opinion. And people who felt stigmatized, were confined to bed, were poor or had little social support might not go to such lengths to get a diagnosis.

So, Jason’s team called almost 30,000 random Chicago phone numbers to ask whether someone in the household had symptoms of the disorder. If they did, the team brought them into clinics for evaluation. As a result of the findings from this and other studies, the CDC removed the word ‘rare’ from its description of the syndrome. In 2015, a report from the US Institute of Medicine (IOM) estimated that 836,000 to 2.5 million Americans have the disorder. Another study estimated that more than 125,000 people in the United Kingdom are living with ME/CFS. And a report from Nigeria suggests that the prevalence of the disease might be even higher there, perhaps exacerbated by other infectious diseases and poor nutrition. But these tallies are fraught, owing to the different ways in which doctors diagnose the condition.

In many ways, people with ME/CFS remain invisible. Most have been dismissed by at least one physician. And society often ignores them, too. In the United States, financial pressures are common because health insurers might consider experimental treatments unnecessary, and employers might not feel that disability payments are justified. Even in countries where health care is a right, the situation has been dire. Many patient advocates say that UK government agencies have essentially treated ME/CFS as if it were a strictly psychological condition, a conclusion that they argue was bolstered by the PACE trial’s findings that exercise and cognitive behavioural therapy relieve symptoms. The National Health Service (NHS) recommended these interventions, even after many patients complained that exercise dramatically worsens their condition.

Epidemiologists have suggested that the anguish of contending with the disorder and society’s general dismissal of it contribute to an up to sevenfold increase in the rate of suicide for people with ME/CFS.

Montoya will never forget one such tragedy. A decade ago, he opened an ME/CFS clinic for half a day each week at Stanford. One afternoon, he received a call from a crying woman whose 45-year-old daughter had returned home to California after falling ill with ME/CFS. The daughter had read about Montoya’s clinic online and wanted an appointment, but Montoya was booked for a couple of years. In her suicide note, he says, the daughter asked that her brain be donated to him for research. “I feel so guilty, since those were the years with hundreds of patients on the waiting list,” he says.

Immune system
Today, Montoya's clinic is open five days a week. And in his research, he's exploring several avenues. The hormone study in which Allen is participating is looking for changes in how the endocrine system is regulated among people with ME/CFS, a factor that might explain why the disorder is more common in women than in men. But Montoya's leading hypothesis is that ME/CFS begins with an infection that throws the immune system out of whack.

Infections generally lead to inflammation when protein receptors on T cells, a kind of immune cell, recognize corresponding proteins carried by bacteria, parasites or viruses. The T cells multiply and catalyse an inflammatory attack that includes the replication of antibody-producing immune cells, called B cells. In the past few years, researchers have revealed hints of an unusual immune response in ME/CFS. Most recently, last June, Montoya and his colleagues revealed abnormalities in the levels of 17 immune-system proteins called cytokines in people with severe cases of the syndrome. What disrupts the inflammatory response, however, remains unknown. One possibility is that, as in some autoimmune disorders, T cells mistakenly become alarmed by one of the body's own proteins, rather than by an invader, and B cells secrete self-reactive antibodies.

An accidental finding has lent support to this idea. In 2008, Øystein Fluge, an oncologist at Haukeland University Hospital in Bergen, Norway, treated a lymphoma patient with rituximab, an antibody therapy that kills B cells. The patient told him that the drug resolved their ME/CFS. Fluge and his colleagues then conducted a placebo-controlled trial with 30 people who had the condition (and not cancer), and found that rituximab improved their symptoms. As word spread, Fluge was flooded with hundreds of e-mails from people asking to take part in his trials, and doctors around the world fielded desperate requests for the experimental therapy.

Yet any hopes that Fluge dared to have were dashed last October, as he assessed data from an as-yet unpublished 151-person clinical trial and found that rituximab proved no better than the placebo. Fluge says the finer details of the trial might yet reveal whether a small subset of participants benefited. Like many others, he suspects that ME/CFS might turn out to be several diseases, with different causes and underlying mechanisms. Therefore, what helps some people might not help others. This effect might not be discernible until researchers can tease out how patients differ from one another. Still, the trial's overall failure suggests that autoimmunity is not the main cause of ME/CFS, says Derya Unutmaz, an immunologist at the Jackson Laboratory for Genomic Medicine in Farmington, Connecticut. Rather, he speculates that inflammation seen in ME/CFS might result from a problem on the regulatory side of a person's immune system, which normally reins in the T-cell response to innocuous viruses, mould particles or other non-threatening stimuli. "Rituximab's failure is very disappointing for patients, but the fact that such a trial was done is a very important thing in the field," Unutmaz adds. "By ruling this out, we can focus on other directions." This is the kind of scientific response that patient advocates have been fighting for since the 1990s.

Metabolic system and microbiome
Newsletters dating back decades document how activists have struggled to be recognized by scientists. In one column from 1998, the co-founder of an ME/CFS organization reports on a conference on the ailment in Boston. She notes that someone from ACT UP, a group known for driving research on HIV, was in attendance, "and may show us how to get more attention for the disease".

Through the 2000s, advocates accused the NIH of favouring grant proposals focused on psychiatric and behavioural studies, as opposed to those exploring physiological pathways. A sea change occurred in 2015, however, with the IOM's review5 of more than 9,000 scientific articles. "The primary message of this report," concluded the IOM, "is that ME/CFS is a serious, chronic, complex and systemic disease." Soon afterwards, NIH director Francis Collins said that the agency would support basic science to work out the mechanisms of the syndrome.

In September last year, the NIH announced the winners of new grants in support of research hubs looking into ME/CFS. Some of the projects sound as if they duplicate each other, but that's by design. Walter Koroshetz, head of the NIH's National Institute of Neurological Disorders and Stroke in Bethesda and chair of the Trans-NIH ME/CFS Working Group, explains that the NIH sees strength in replication. "There has not been a coordinated effort to follow up on publications and to figure out which findings are most important, which can be reproduced and which fall away when you look at a different patient population," he says. For this reason, one of the NIH grants goes towards a centre at Research Triangle Institute in North Carolina that will merge ME/CFS data.

A $10-million, 5-year grant is also going to Unutmaz, who is studying the interplay between the immunological, metabolic and nervous systems of people with ME/CFS. As part of this, he will collaborate with microbiologists to assess the bacteria living in patients' bodies, and to see how shifts in those populations alter metabolites, such as glucose, that may in turn affect inflammation. Unutmaz admits that his studies are at an early stage, and says the point is to generate data to form sharper hypotheses. "We don't know what we don't know in this disease," he says. Researchers at Columbia University in New York City and Cornell University in Ithaca, New York, have won NIH grants to explore some of the same themes, and to delve into inflammation in the brain.

Some CFS researchers argue that the NIH's contribution remains too lean. "A real problem is that funders want to see papers coming out in a short time period, but this is a complex disease that requires long-term studies that are expensive to conduct," says Eleanor Riley, an immunologist at the University of Edinburgh, UK. Beginning in 2013, Riley helped to launch and maintain an NIH-supported biobank of ME/CFS samples at the London School of Hygiene and Tropical Medicine. But the bank has been limited by funding constraints.

Ronald Davis, a biochemist who directs Stanford's Genome Technology Center, says that he too struggles to fund his lab's work on ME/CFS. He points out that although HIV affects roughly the same number of people in the United States — about 1.2 million — it received 200 times as much funding from the NIH as ME/CFS did in 2017.

In December, the Open Medicine Foundation in Agoura Hills, California, a research charity that Davis advises, announced its support for an ME/CFS collaborative centre led by him. In one project, the team intends to finish analysing the complete genomes of 20 people severely ill with ME/CFS, along with the genomes of their family members, to look for a genetic predisposition to the disease. Another project involves the development of what could be the first diagnostic test for ME/CFS.

That test uses a small device containing 2,500 electrodes that measure electrical resistance in immune cells and plasma from blood. When Davis exposed blood samples from people with ME/CFS to a stressor — a splash of salt — the chip revealed that the blood did not recover as well as samples from healthy adults. Davis is holding out on pronouncements, however, until he has conducted a study large enough to show clear and statistically significant effects — including a difference between people with ME/CFS and those with other conditions. "With XMRV, the problem was that people jumped to conclusions," Davis says. "I've learned that if it's exciting, it's probably wrong."

Davis knows the pain of disappointment personally. He started studying ME/CFS in 2008, when his son, Whitney Dafoe, became incapacitated by the disease. Dafoe volunteered to be studied at his father's centre. A member of the team, Laurel Crosby, recalls exchanging e-mails with Dafoe, discussing the research. But as Dafoe's condition got worse, he stopped replying in sentences, and began answering text messages with just a 'Y' or an 'N'. Then those, too, stopped coming. Dafoe, now 34 years old, can no longer speak. He communicates with his parents through small motions, such as ripping holes in the shape of hearts in paper towels.

A poster of Dafoe hangs in his father's office. In it, he is standing on a beach in northern California with his arms raised towards the sky. Davis took the photo on one of the last days his son could walk. "Now he cannot talk, he can't listen to music, he can't write, he lays in bed all day, and there are thousands of patients like this, patients who are embarrassed to be told that nothing is wrong with them," Davis says. So he is furiously testing the electrical device, as well as screening blood samples for proteins and genetic signatures that might reveal a biomarker for the disease. Not having clear criteria for a diagnosis has made clinical trials particularly challenging.

In 2015, David Tuller, a journalist turned ME/CFS advocate, published a critique of the PACE studies. Weeks later, six researchers signed an open letter to the editor of The Lancet, which published the initial PACE results, requesting a reanalysis of the data. Last March, scientists and advocates did the same in a letter to Psychological Medicine — the journal that published the 2013 PACE results — requesting a retraction. A leading criticism was that the investigators had changed how they measured recovery during the course of the trial, making that outcome simpler to achieve. The PACE investigators have denied this charge and others on their website, writing that changes were made before they analysed the data, and wouldn't have affected the results.

Patients and advocates disagree, and although the paper has not been retracted, the CDC subsequently abandoned the trial's recommendations. In September last year, the NHS announced that it would also revise its recommendations. In a corresponding report, a panel concluded that recent biological models based on measurable physiological abnormalities require greater consideration.

Despite the setbacks and the long delays, many argue that science is operating as it should — being self-critical and open to revision. In five years' time, researchers should be able to pinpoint specific aberrations in the immune, metabolic, endocrine or nervous systems of people with ME/CFS, and perhaps find genetic predispositions to the condition. These indicators might yield diagnostic tests — and, further down the road, treatments.

Elizabeth Allen did not enrol in Montoya's study with the expectation of a cure around the corner. She says she'll be happy if — at the very least — a younger generation can avoid the complete bewilderment she felt when her body suddenly failed her. "I know how long science takes," says Allen. "I am going to try and do whatever I can do to make it move forward as fast as possible."

A new hypothesis and drug for ME/CFS

Source 1: www.healthrising.org/blog/2018/02/08/cortene-way-new-drug-trialed-chronic-fatigue-syndrome-mecfs-soon-pt/

Source 2: www.healthrising.org/blog/2018/02/17/cortene-chronic-fatigue-syndrome-hypothesis/

Cort Johnson of health rising has created a 3 part article about a new theory and drug for ME/CFS. The following is most of parts 1 and 2. Please refer to the source links above for the full articles. The 3rd part has not been released yet and will likely be included in our June 2018 newsletter.

Research funding for chronic fatigue syndrome (ME/CFS) has been poor at best but clinical trials have elicited a wholly different degree of disappointment altogether. Few clinical trials are ever done and those often involve alternative approaches. The six active clinical trials listed in clinicaltrials.gov, for instance, include treatments like acupuncture, moxibustion, oral rehydration and CoQ10.

It's been assumed that repurposed drugs – drugs already in use in other disease – would be tested in ME/CFS to improve symptoms – and only later, as we understood the disease better, would we get to a drug that gets at the core problems in ME/CFS. A group believes they have a drug that gets at the core of ME/CFS now, and in the first quarter of this year they expect to test that drug. While this drug is new, it probably enjoys a more robust theoretical foundation than any other drug that's been tested in ME/CFS.

Gerard Pereira didn't know much about ME/CFS but what he was hearing was setting off all sorts of bells and whistles in his head. Sometime before, he'd come across an intriguing drug (CT38) being developed by the pharmaceutical division of Proctor & Gamble. CT38 prevented muscle wasting in animals, and it had been through a Phase 1 clinical trial and tested safe in healthy humans. Despite the promising test results, after Proctor & Gamble decided to exit the drug industry entirely, CT38 was left available for licensing.

Pereira, though, was intrigued. CT38 targeted the stress response – a system getting a lot of attention, and it appeared to impact inflammation – a bigger and bigger concern all the time. Plus, the animal data was really good. Eventually Pereira decided to license the drug and start his own company, Cortene Inc. He and his partners (Sanjay Chanda, Hunter Gillies, Michael Corbett) would try to develop the drug themselves.

Pereira took a deep dive into the ME/CFS literature. The more he saw, the more he liked the fit. He was particularly taken by four facets that seemed to separate ME/CFS from other diseases: the diversity of the apparent triggers, the unusual suddenness with which the disease often appeared, the gender imbalance, and the wide range and variability of symptoms – both across patients and over time. Explaining those four facets, he thought, might lead to the cause of the disease. Most of the current hypotheses couldn't. Could he?

Take the idea that a pathogen or an immune system issue was the key culprit. Could either explain how a healthy person – often a female – could be turned into an invalid, sometimes overnight? He didn't think so. Too many different pathogens had been connected to ME/CFS for one pathogen to do it, and pathogens usually affected both genders equally. Plus, no one had been able to definitively show a pathogen was still present and/or still responsible for the symptoms seen in the chronic phase of ME/CFS.

The immune system was certainly involved, but the patient stories he'd heard suggested that the disease happened too fast for the big guns of the immune system – which took time to get worked up – to take down a patient so suddenly. Too many people with ME/CFS caught a cold, and then were suddenly floored by the illness, for that to make sense. He didn't think the metabolic ideas sweeping the field fit the bill either.

Metabolic changes were certainly present, but a rapid metabolic breakdown that happened predominately in females was hard to explain. Instead, he thought the initial insult (infection, stress, etc) must have caused changes in some integral system; a system able to touch the immune and autonomic nervous systems and ultimately even glucose metabolism.

An adaptation (or perhaps maladaptation) of the limbic system that determines our responses to stressors like infection, trauma, emotional distress, etc., could fit the bill. The limbic system had been considered in ME/CFS for decades, but no one had ever proposed a drug for it.

A change to the stress receptors governing those responses could happen very quickly. When it did, Pereira thought it would push the immune system in exactly the way it's showing up in ME/CFS – and impair patients' ability to fight off infection. That made sense given the Dubbo study reports that more severe, difficult to fight off infections, tend to trigger ME/CFS. It could also affect the autonomic nervous system, and eventually impact the glucose metabolism. The more he looked, the more he liked the idea that alterations to the stress receptors in the limbic system could explain ME/CFS. These were the same stress receptors that CT38 was designed to work on.

The HPA axis received a good deal of study in ME/CFS early on, but the results weren't always consistent, and interest had waned somewhat over time. Still, the axis had a way of popping up. Gordon Broderick's models suggested issues with the HPA axis could explain the gender imbalance in ME.CFS, and Dr. Bateman had proposed that ME/CFS might be an inflammatory disorder centered on the hypothalamus. Just a month ago, a study suggested an immune-neuro-endocrine interaction might be causing the fatigue in ME/CFS.

The main endocrine finding in ME/CFS was low cortisol (hypocortisolism). Hypocortisolism also occurs in chronic stress, where the initial excess of cortisol becomes low cortisol over time – and the development of something like cortisol sensitivity.

Pereira thought the HPA axis might be able to explain the gender imbalance issues as well. Women have more stress receptors than men, and another part of the hypothesis (covered in the next blog) fits women particularly well. Because the stress response is intended to take control and divert resources to/from critical/non-critical functions, it impacts most of the systems in the body. All in all, Peireira thought HPA axis issues could explain the wide range of symptoms in ME/CFS.

Now comes the most intriguing and exciting part of Pereira's hypothesis. Pereira doesn't need long-term animal safety data because he doesn't plan on doing long-term treatments. If his hypothesis is correct, he believes CT38 will be able to reset the limbic system almost as quickly as it fell off the tracks in the first place; i.e., a couple of treatments might be enough to return the system to normal and begin the healing process.

If the idea of a more or less instantaneous reversal after decades of illness seems like some sort of fairy tale, consider that Suzanne Vernon and Gordon Broderick proposed something similar about ten years ago. Their model suggested that an HPA axis reset – by dramatically lowering cortisol levels for a short period of time – could cause the system to spontaneously reset.

This is not to say that over time other medical issues haven't shown up in some ME/CFS patients that could complicate their situation. That's to be expected in any decades long disease. If Pereira and Cortene are right, though, the core of this disease might be amenable to a dramatic change.

Stress

"Stress" is an unfortunate term. Usually we think of stress as emotional; in biology, though, stress means any threat that disrupts the balance (or homeostasis) of the body. The stress response or HPA axis, prepares the body to respond to the threat. Any threat then, whether infectious, emotional, physical, chemical, etc…, will initiate the stress response.

Once triggered, the stress response suppresses non-critical functions such as growth and metabolism (i.e., hypothyroidism, long linked to ME/CFS) and reproduction (i.e., hypogonadism, also connected with ME/CFS). It also releases cortisol to make sure the brain, heart and muscles have sufficient glucose (at the expense of less critical functions like digestion). Cortisol also primes the immune system for action (and has a delayed proinflammatory effect).

Studies indicate that chronic stress causes a progression from high to low cortisol and can result in the development of cortisol sensitivity – a situation in which the body becomes more responsive to cortisol. (When cortisol sensitivity occurs low cortisol can have the same or greater effects than high cortisol does in healthy individuals.) This increased cortisol sensitivity cannot be measured by cortisol/synacthen tests (which measure level not effect) but it does results from epigenetic changes that can be shown.

Studies indicate that ME/CFS patients show the same alterations in cortisol levels and cortisol sensitivity seen in chronic stress. These findings help to explain the overlap of immune and metabolic symptoms found in ME/CFS and chronic stress but they do not explain the neurological issues found in ME/CFS.

The stress response also involves brain neurotransmitters such as serotonin, norepinephrine, dopamine and GABA (gamma-aminobutyric acid), which focus on and deal with the stress in a stressor-specific way. These neurotransmitters – which may have been under-appreciated in ME/CFS research – are at the core of Pereira's hypothesis.

Animal studies indicate that short, medium and long term responses to stress are governed by two factors, CRF (corticotropin-releasing factor) and UCN1, that affect the release of serotonin (and norepinephrine) in the brain and cortisol (and epinephrine) from the adrenal glands.

If these two factors do indeed govern the response to stress in humans, Pereira/Cortene believe that if they can get at the switch controlling them they can reset the stress response system. That can be achieved they believe by altering the receptors found on the neurons that govern the stress response.

A dysfunctional system appears

Step I: serotonin release
Serotonin producing neurons and serotonin play key roles in Peireira's hypothesis. Serotonin is the bogeyman in this hypothesis. In the brain, serotonin is produced by the raphe nuclei in the brain stem, and serotonin neurons extend throughout the limbic system (including the hypothalamus) and the prefrontal cortex, affecting all the other neurotransmitters and coordinating the response to stress.

Step II: desensitisation
The raphe nuclei and limbic system shape the stress response (by incorporating assessments of risk, reward, history, etc), but under intense stress they can desensitise the 5HT1A autoreceptors that normally halt the stress response – allowing it to run amok. Pereira/Cortene believe this is what is happening in ME/CFS.

No stimulatory part of the body is ever designed to be "on" all the time. Because stimulating any system for too long will cause it to break down, any stimulating response comes equipped with brakes. The brakes on an out-of-control serotonin response in the brain are the 5HT1A serotonin autoreceptors. ("Auto" meaning that when these receptors sense serotonin around a particular neuron, they reduce that neuron's release of serotonin).

Studies in both animals and ME/CFS patients suggest that riding the serotonin stress-response system for too long causes the 5HT1A "brake" to fail and the 5HT1A autoreceptors become desensitised.

With that the foundation of this hypothesis is complete.

Step III: Chronic Fatigue Syndrome (ME/CFS) begins
In situations of intense stress (e.g., infection, trauma, emotional distress), high levels of CRF in the raphe nuclei (and limbic system) propel serotonin promoting CRF2 receptors to the surface of serotonin producing neurons. The high levels of serotonin produced cause the 5HT1A "brake" to fail. Once that happens, high serotonin levels prevent the release of UCN1 and the re-establishment of homeostasis.

UCN1, remember, causes the serotonin promoting CRF2 receptors to disappear back into the neuron. With UCN1 unable to return the system to normality, the CRF2 receptors remain on the neuron's surface – telling it to keep pumping out serotonin.

With the neurons (in the raphe nuclei and limbic system) now packed with serotonin-producing receptors (CRF2), and the brakes on serotonin release gone (desensitised 5HT1A autoreceptors), the HPA axis has become sensitized. Now even minor stressors, like exercise or emotional stress, or even stimulation (light, sound, conversation) can initiate a major stress response. This is what Pereira/Cortene believe is happening in ME/CFS (and probably in related diseases such as fibromyalgia).

Animal studies demonstrate how this progression occurs. Intense or prolonged stress (particularly early in life) causes CRF2 receptors to remain on the surface of the neurons long after the triggering stress has gone causing 5HT1A desensitisation and behavioural issues (impaired memory and learning ability, anxiety, PTSD-like behaviour).

There is hope for these animals, however. Removing the serotonin promoting CRF2 receptors (via sophisticated experimental techniques) eliminates the 5HT1A desensitisation and the behavioural issues.

Consequences of excess serotonin

If ME/CFS patients' brains have been turned into serotonin pumping machines, what causes the immense fatigue and post-exertional malaise found in this disease? It turns out that serotonin plays a vital role in the motor cortex and spinal cord as well. At low levels, it increases motor neuron excitability, making the muscles more responsive. As activity increases, serotonin levels increase, and the motor neurons/muscles become even more responsive. However, when serotonin levels become too high, they inhibit motor neuron signals, preventing muscle contraction (to avoid muscle damage). Several studies suggest that reduced motor cortex excitability, motor preparation, motor performance and central activation during exercise may be present in ME/CFS.

Pereira/Cortene believe that the hypersensitive serotonin response in ME/CFS patients causes them to reach this threshold very quickly. Intriguingly, their hypothesis also may illuminate an unusual experience that many people with ME/CFS may feel: that their muscles feel more like they're stuck or paralyzed than that they've have run out of energy – and that any stimulation can make the situation worse.

Increases in serotonin have been directly implicated in increased pain sensations, cognitive dysfunction, migraine, sensitivities (light, sound, etc.), sleep dysfunction and depersonalization. Indirectly, by stimulating other neurotransmitters such as dopamine and norepinephrine, serotonin regulates everything from behaviour (e.g., mood, perception, reward, anger, aggression, attention, appetite, memory, sexuality) to physiology (e.g., gastrointestinal functioning, blood coagulation, blood pressure, heart rate).

But why have these postulated CRF2/CRF1 maladaptations not shown up in the ME/CFS research to date? Tests of blood and other bodily fluids will not pick up a problem existing only on specific neurons in the brain. Nor can the serotonin output of these specific neurons be measured. While cerebrospinal fluid can get close, it lacks the precision to identify a problem involving a tiny subset of neurons in the brain. Biopsies of specific neurons in the raphe nuclei and limbic system in the brain are needed.

Please refer to the source link at the beginning of this article for further information…