2021: WE THANKS FOR PARTICIPATION

ME-KONFERANSE STRYN

A BIOMEDICINAL ME/CFS CONFERENCE

Report

ME conference Stryn, arranged digitally, Tuesdag April 13th to wednesday April 14th:

Visit our website:
www.mekonferansestryn.no

The report contains an introductory part first with a few words from the organizer. Then comes the report about the lecturers who participated. The professional conference: David Tuller, Mady Hornig, Björn Bragée, Jonas Bergquist, Karl Johan Tronstad, Ingrid Guvrin Rekeland, Øystein Fluge, Kristian Sommerfelt, Ola Didrik Saugstad, Linn Christin Skjevling, Line Melby, Anne Kielland. Evening lecture Ola Didrik Saugstad and Jørgen Jelstad.

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Report

Tuesday April 13th: Evening lecture, from 6 p.m. to 8.30 p.m.

Tuesdag April 13th to wednesday April 14th: Professional conference from tuesday 11.30 p.m. to wednesday 1 p.m.

These are the Norwegian counties that were present at the conference: Vestland, Møre og Romsdal, Rogaland, Agder, Oslo, Viken, Vestfold og Telemark, Innlandet, Trøndelag and Troms og Finnmark.
Sweden and Finland were also present at the conference.

Participation in the professional conference, tuesday April 13th – Wednesday 14th : about 85 participants, including 11 physicians.

Participation in the evening lecture, tuesdag April 13th: about 160 participants.
Several different professions were present, including physician, nurse, physiotherapist, ergotherapist, environmental therapist, socionom, teacher, school nurse, with more....

As the organizers of this conference we were approached by a Norwegian parliamentarian who wanted to participate after the registration deadline. We then agreed to offer all the parliamentarians that sits on the Health- and care services committee in the Norwegian parliament, to participate as guests to listen and learn from the presentations. We regarded such a participation from Norwegian parliamentarians as somehting that would be of great benefit to ME patients and their next-of-kin. Unfortunately, only two parliamentarians took advantage of this offer, and participated in the conference (on from Ap (the Norwegian Labor Party) and SV (Socialist Left Party))
(All the parliamentarians that constitutes the Health and care committee, as well as the parliamentarians in the Labor and social welfare committee got their invitations to participate in january.)

Unfortunately, very few politicans from the municipal and county level participated in the conference. In all, 300 invitations to this conference was sent out by mail throughout all of Norway, as well as between 500 and 100 emails, containing

reminders, marketing with ads and more. We had hoped that a lot more would participate in the conference, but we are thankful for those that did participate to listen and learn more about the ME disease. Even now, in 2021, knowledge and understanding when it comes to ME is, generally, bad. There are about 10 000 to 15 000 patients in Norway and about 20 million ME patients worldwide that are in a dire need of being able to receive an adequate and proper medical treatment, just like other patient groups.

We were lucky enough to get Pål S. Schaathun to make a recording for us. In this he filmed and interviewed the lecturers from Bergen; Kristian Sommerfelt, Ingrid Gurvind Rekeland and Øystein Fluge. This clip is 20 minutes long, so we are hoping that everyone will take the time to watch it. The corona pandemic created restrictions in our ability to get interviews on tape before the conference. The clip that was produced is available on our Website: www.mekonferansestryn.no , as well as on YouTube. Some of the Power Point presentations from the lecturers will also be put on our Website, as well as more information. We are hoping that everyone that is interested in this topic visits our Website to go through these new posts.

If you missed the digital ME Conference in Stryn, that occured from April 13th to April 14th, we have come up with a solution that allows people, for a limited time period, to buy access to recordings of the videos from the conference.

Lecturers in the professional conference, tuesday April 13th – Wednesday 14th

- *Journalist and academic at the School of Public Health at the University of California, Berkeley:* **David Tuller**
- *ME researcher, immunologist and professor of Epidemiology at Columbia University, New York:* **Mady Hornig**
- *Specialist in Anesthesiology / Intensive care and pain relief, Bragée clinics, Stockholm:* **Björn Bragée**
- *Professor of Analytical chemistry and Neurochemistry at the Institute of chemistry - Biomedical Center at Uppsala University in Sweden:* **Jonas Bergquist**
- *Professor at the Institute for Biomedicine, the University of Bergen:* **Karl Johan Tronstad**
- *Doctor at the Department for cancer treatment and medicinal physics at Haukeland University Hospital, Phd- at the University of Bergen:* **Ingrid Gurvin Rekeland**
- *Doctor at the Department for cancer treatment and medicinal physics at Haukeland University Hospital, Professor at the University of Bergen:* **Øystein Fluge**

- *Professor of Child neurology, at the Children's clinic at Haukeland University Hospital: Kristian Sommerfelt:* **Kristian Sommerfelt**
- *Professor Emeritus in Pediatrics, researched at the University of Oslo:* **Ola Didrik Saugstad**
- *Doctor in specialized education and scholarship holder at the University Hospital in Northern Norway (UNN) Harstad:* **Linn Christin Skjevling**
- *Senior researcher at Sintef, the Department of Health, Project Manager for «The Services and ME»:* **Line Melby**
- *Researcher at Fafo*: **Anne Kielland**

Lectuers Tuesday April 13th: Evening lecture, from 6 p.m. to 8.30 p.m.

- *Professor Emeritus in Pediatrics, researched at the University of Oslo:* **Ola Didrik Saugstad**
- *Research journalist and author:* **Jørgen Jelstad**

Lecturers in the ME Conference Stryn 2021:

- Jørgen Jelstad. The first subject day. Tuesday April 13th
- Håvard Selseng. The evening lecture on tuesday April 13th and the second subject day, wednesday April 14th.

We start with the report from the subject conference comes first, and end with the report with the evening lecture.

Introduction and welcome speech:

Before the subject conference and the evening lecture started in the third ME Conference in Stryn, that in 2021 was all Web-based, Gunn Skrede opened the conference with a text focused on her sister Agnete. Agnete is an ME patient herself, and she spent a long time writing the text that she was to ill to read out herself. The opening of the conference is some of Agnete's thoughts from the point of view of an ME patient.

Summary of the opening, that lasted about 10 minutes.

«I have had a lot of thoughts and experiences that I have pondered on these years. - But to sort them out, and choose the right words to describe them, that is not easy. As a matter of fact, to have ME is intself very difficult, sometimes unbearable. When I

write about our needs and what kind of support we need, my initial thought is that this is something that can easily be made a reality. But still, nothing happens!

– There's a lot of us that clearly and plainly have been expressing the need for ME patients to be treated with respect and understanding, as well as receive the support we need from the health services, for years now. There's a need for more funds for biomedicinal resarch. And most importantly, where are our rights by law when we actually need them?

Maybe it is the case that to understand how much trust matters, how much it matters to feel safe in the care of the health services, one has to experience the opposite, namely not feeling safe. Experience that the bridges of trust get burnt to the ground. Feel the frustration and experience betrayal from the legal order that surronds you, in spite of hiring the best lawyers there are to fight your case. If I hadn't experienced all of this first-hand, I wouldn't be aware of it either.

You will dwell on the feeling of injustice when, no matter what you do or have done, they use it against you. For years, I was asked in every physician consultation how much I had exercised, and how physically active I had been. Because my level of activity was high, and in spite of the fact that I did say where I had to reduce my activites and be less physically active, had to withdraw from competitions and the like, the conclusions were, for years, that my function level was good, and that I therefore couldn't be ill. I was never examined for ME, before the disease had become severe.

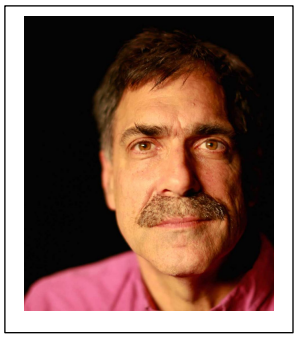
The difference from one subject field in the health service to another, and observing how different patient groups are being treated so differently, makes it hard for me to find the right words for it. I've been through several different subject fields and different cases in my life, and I will now comment some examples of both the worst and best when it comes to practice. - The goal for the health service should be to strive to do what's best for the patient and those close to them, who are in the middle of a crisis.

Those that have done the best work are those that stay updated on new knowledge, who can see the person behind the diagnosis, who understands what kind of support the patient needs and, to their best ability, aim to help the person that is in a sore need of help.

Someone has to fight, and that fight comes with a price. – They call us activists. I am probably one of the people who gets labeled that way. It is really a neutral word, an

activist is someone that fights for a cause. At the same time, on starts thinking about those that try to brand us in a negative light. We who haven't been able to get rid of this disease, after having tried one type of therapy afther the other. Are we a buch of activists on a warpath? All we want is the help we need and to receive a good treatment from the health service. There's no pre-prepared paths, no tracks to follow. There are no protest marches with torches putting forward demands for ME patients to receive a good medical treatment from empathetic health care workers.

This means that we have to fight this fight ourselves. That is why this conference exsists. I am hoping that this can be the first step on the road to achieve better knowledge, a deeper experience and ultimatley improve the health care that is provided to our group."



DAVID TULLER

Journalist and academic coordinator of Health policy and Journalism at the University of California, Berkeley.

Quote from Jørgen Jelstad's blog debortegjemte.com from 2015:. *«After the American journalist David Tuller wrote a comprehensive article with a critical eye on the largest treatment study in the ME field ever, there has been a lot of debate about the PACE study ».* The PACE study has also had influence on guidelines for treatment of ME in the health services around the world." - www.debortgjemte.com
Jelstad writes several posts about the topic, and has translated the original articles David Tuller wrote on the science blog virology.ws. about the PACE study in 2015.

David launched the "Trial By Error" series in October, 2015, with a 15,000-word investigation of the disastrous PACE trial, published on Virology Blog. Since then, David has written hundreds of blog posts about that piece of crap and related issues not only in the UK but in the US, the Netherlands, Norway, and many other countries, written many articles for major news organizations, authored or co-authored peer-reviewed papers, and given talks in multiple countries

In 2020, the focus was on Norway, and the study that include cognitive behavioral therapy (CBT) plus music therapy as a treatment for chronic fatigue in adolescents after acute Epstein Barr virus infection EBV (aka mononucleosis and glandular). When it comes to the Norwegian study it was a smart patient initially pointed out some of the issues to the journal, and David followed up with multiple posts and letters to BMJ. (Unfortunately, the journal posted a very bad revised version, but still.)

In the lecture David gave at the ME-conference Stryn, he addresses the above-mentioned Norwegian study and the PACE-study. **The PACE- study** was published in The Lancet i 2011, and was funded by over 60 million in public funds.

The Biopsychosocial Approach to "CFS": PACE, Music Therapy + CBT, and Other Crap

Big Question for All of This Research:

- Open Label/Unblinded Trials
- Subjective Outcomes

Question: Can trials combining these two elements provide good data?
Answer: No

Big Questions About PACE

- Does a study in which participants had already met outcome thresholds for primary measures at baseline have a legitimate place in the domain called "science"?
- Is there a place in "science" for a study in which participants were simultaneously "disabled" and "recovered"?
- Why has a study containing this paradox been defended for so long by the U.K. (and Norwegian) academic and medical establishment?

PACE Trial: "Definitive" study of CBT/GET:

- Open label with subjective outcomes (all objective measures failed to show success, so they dismissed them as irrelevant)
- Use of bogus Oxford criteria conflating chronic fatigue and ME
- 641 participants
- Four trial arms: CBT, GET, APT, SMC
- Principal investigators: Dr. Peter White (QMUL), Dr. Michael Sharpe (Oxford), Dr. Trudie Chalder (KCL)
- Based on unproven theory that all symptoms due to deconditioning because of patients' "dysfunctional cognitions" about their illness

PACE Trial:

- 2011: First results in Lancet, 59-61 % "improved" with CBT/GET; "twice as many...back-to-normal"
- Lancet commentary by Dutch: 30 percent met "strict criterion for recovery"
- 2013: Psychological Medicine: 22 % "recovered" with CBT/GET
- October, 2015: Virology Blog publishes "Trial by Error" series
- August, 2016: Tribunal orders QMUL to turn over raw trial data in scathing decision

- March, 2018: BMC Psychology publishes full reanalysis of "improvement," "recovery" and long-term results

Conclusion: PACE outcome-switching changes null or placebo-induced results into decent ones. No long-term benefits from CBT/GET

Expert Responses to PACE:

- Professor Bruce Levin, Columbia: "The height of clinical trial amateurism"
- Professor Jonathan Edwards, University College London: "It's a mass of incomprehensibility to me."
- David Tuller, UC Berkeley: "A piece of crap."
- MP Monaghan: "One of the biggest medical scandals of the 21st century"
- Sir Simon Wessely: "A thing of beauty"
- Professor Esther Crawley, Bristol University: A "great, great" trial

Is PACE an example of research misconduct?

- Misrepresentation of data, for example suppression of relevant findings and/or data, or knowingly, recklessly or by gross negligence, presenting a flawed interpretation of data (MRC)
- Misrepresentation of interests, including failure to declare material interests either of the researcher or of the funders of the research (MRC)
- Falsification: Manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record (NIH)

Conclusions About PACE:

- Reported PACE results cannot be taken at face value and proved that treatments in "definitive" trial didn't work
- The data manipulations, lack of informed consent, and other issues could lead to the conclusion that this is research misconduct, according to standard definitions.
- PACE authors are the "anti-science" crowd, like climate-change deniers--not PACE patients.
- Best use of PACE—pedagogical tool

Norwegian Study: CBT and Music Therapy for Post-GF Fatigue (GF = glandular fever):

- Published in high-profile BMJ Paediatrics Open
- Research Question: Can CBT prevent chronic fatigue post-GF?
- Population: Adolescents with glandular fever
- Intervention: Half got CBT plus music therapy, half did not

Broken Peer Review System:
Open peer review:
Reviewer #2: I haven't read "beyond the abstract". In other words: Abstract was reviewed, but not the rest of the paper THIS DID NOT BAR PUBLICATION IN BMJ PAEDIATRICS OPEN!!!! HARD TO DESCRIBE HOW SHOCKING THIS IS

Main Concern: Not a Feasibility Trial:
Designed in protocol as a full-scale trial. Disappointing results.
Re-purposed to be a "feasibility trial"—to ask for future funding This could be considered research misconduct!!

Other Concerns:

- **Post-hoc outcome**: PEM not in protocol, but added later and cited positively in conclusions
- **Primary objective outcome**—average #steps/day
  BOTH GROUPS WALKED—BUT INTERVENTION GROUP DID WORSE
- Not mentioned in conclusion
- **Recovery measure does not include primary outcome**

Resolution: Retract and Replace:

- New Version as bad as the old one—just not referred to as a "feasibility" trial
- BMJ blames itself rather than authors for false information about trial
- PEM still included, main outcome still not mentioned in conclusions
- No mention of failure of peer review
- It is still CRAP, and findings still presented in misleading manner.

At the end David Tuller thanked the follow:
Brilliant patients/advocates who first deconstructed and dissected the science—too many to name. Vincent Racaniello for trusting in Davids reporting. UC Berkeley for valuing academic freedom. The Center for Global Public Health for supporting him. Faculty colleagues at SPH and Berkeley who recognize nonsense

MADY HORNIG

Professor and researcher at Columbia University Mailman School of Public Health

The theme of Mady Hornig's lecture at the ME conference Stryn was «Robust evidence for ME/CFS as a biological disease – distinct immune signatures in the cerebrospinal fluid in ME suggest immune dysregulation in the central nervous system as a function of sub-group and disease course».

In 2015, she said: «We now have firm evidence to support the idea that ME is not psychological. Our results indicate a distinct immune signature in the cerebrospinal fluid in ME. This suggests an immune activation of the central nervous system». Her research team's findings concluded that ME/CFS patients had, in the part of the peripheral blood known as plasma, significantly higher levels of many immune and inflammatory markers known as cytokines, but only in the early stages of the disease. In the later stages, patients mostly had lower levels of these immune system markers than healthy control subjects.

Dr. Hornig is participating in the The Center for Solutions for ME/CFS at Columbia University, one of the new research centers financed by the National Institutes of Health (NIH) in the United States. Research in these centers is focusing on the microbiome and its interaction with the intestinal system, and how this can influence the immune system and thereafter affect the brain. Mady Hornig and her team are also actively pursuing research into how COVID-19 may lead to ME/CFS in some individuals, with several ongoing studies on the subject and more being planned.

More about the 2015 plasma cytokine publication (*Science Advances*):
The 2015 report from the Institute of Medicine, which helped confirm ME/CFS as a disease, was released around the same time as another important medical report. Dr. Mady Hornig and her team had looked at the cytokine pattern of ME patients. They had distinguished between those who had had ME for a short time – 3 years or less, and those who had had ME over a longer period. First they saw this in blood, then in the cerebrospinal fluid where they also found altered cytokine levels depending in part on the presence of “classical” clinical features as compared with a less typical clinical presentation.

The different cytokine patterns in the cerebrospinal fluid thus tell us something about the central nervous system - an immune dysregulation in the central nervous system, with ME patients showing altered inflammatory molecules in the central nervous system. The altered cytokine profiles in the cerebrospinal fluid pointed toward the possibility of autoimmune diseases, infections with viruses and bacteria, central nervous system dysfunction, brain hypoperfusion and/or chronic inflammation of the white matter (myelin) part of the brain.

Together the immune profiling studies in the plasma and cerebrospinal fluid suggest potentially important new biomarkers for ME, and fit very well with many patients’ own impressions as to changes in their symptoms over time.

Dr. Mady Hornig: *"It appears that ME/CFS patients may have inappropriate and persistent elevations of cytokines until around the three-year mark, at which point the immune system begins to show evidence of exhaustion and levels of many cytokines start to drop," says Dr. Hornig. "Early diagnosis, aided by immune and other biomarkers, may provide unique opportunities for treatment that likely differ from those that would be appropriate in later phases of the illness."*

Here is a link to the press releases: https://www.mekonferansestryn.no/post/usa-2015-me-cfs-er-en-biologisk-sykdom

Typical and atypical subgroups:

Defining subgroups can help clinicians identify and treat the complex disease ME / CFS: Scientists at the Center for Infection and Immunity (CII) at Columbia University's Mailman School of Public Health are the first to report immune signatures differentiating two subgroups of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): "classical" and "atypical.

Typically, symptoms of ME/CFS begin suddenly following a flu-like infection, but a subset of cases classified by the investigators as "atypical" follows a different disease course, either from triggers preceding symptoms by months or years, or accompanied by the later development of additional serious illnesses.

To uncover evidence of these disease types, first author Mady Hornig and colleagues used:

- immunoassays to measure levels of 51 immune biomarkers in cerebrospinal fluid samples taken from 32 cases of classical and 27 cases of atypical ME/CFS.
- All study participants were diagnosed using the same standard criteria
- but atypical cases either had prior histories of viral encephalitis, illness after foreign travel or blood transfusion, or later developed a concurrent malady—seizure disorders, multiple sclerosis-like demyelinating disorders, Gulf War Illness, or a range of cancers—at rates much higher than seen in the general population.

"We now have biological evidence that the triggers for ME/CFS may involve distinct pathways to disease, or, in some cases, predispose individuals to the later development of serious comorbidities," says Hornig. "Importantly, our results suggest that these early biomarker profiles may be detectable soon after diagnosis of ME/CFS, laying a foundation for better understanding of and treatments for this complex and poorly understood illness."

- In the new study, both subsets of ME/CFS patients showed signs of an unbalanced or dysregulated immune system within the central nervous system, with immune markers different than those seen in healthy individuals.
- However, the dampened immune profiles previously observed after the three-year mark were only observed in individuals with the classical form of the disease, not in those with atypical ME/CFS.
- Among subjects in the atypical group, levels of cytokines and chemokines were more likely to remain steady or increase.

According to Hornig, instead of the immune exhaustion seen in later phases of classical ME/CFS, atypical patients may be experiencing a "smoldering inflammatory process" in which the immune system is still working to recover, although she acknowledges that much work remains to be done to confirm this hypothesis.

Ongoing studies at CII are exploring other subgroups,

- including patients with allergic disorders
- high levels of cognitive dysfunction
- gastrointestinal disturbances.

Multiple biological pathways are likely involved in the pathogenesis of ME/CFS, with a range of clinical subtypes relating to variability in the types of environmental triggers, genetic and epigenetic vulnerability, as well as comorbidity patterns

Here you can read more:
https://www.mekonferansestryn.no/post/undergrupper-av-me-og-varigheit-av-sjukdomen

Daniel Peterson's patient collection of data and samples - including precious spinal fluid samples:

In 2010 the Simmaron Research Foundation for ME/CFS opened its doors. Dr. Daniel Peterson, one of its founders, was restless. Ever since people with a strange, debilitating illness began knocking on his door in the Incline Village outbreak in the mid-1980's, he'd been focused on ME/CFS. Since then he'd been patiently collecting data and samples - including precious spinal fluid samples - and biding his time until the researchers were ready - and now he thought they were. With the formation of the Simmaron Research Foundation, Peterson was given the opportunity to put his experience and samples to the test. It turned out that the ME/CFS research community was very interested in what he had to offer.

Since its founding, the Simmaron Research Foundation has enjoyed a special relationship with Dr. Mady Hornig and internationally renowned virologist Dr. Ian

Lipkin at the Columbia Center for Infection and Immunity. Dr. Lipkin's interest in chronic fatigue syndrome (ME/CFS) – which began with Dr. Peterson – dates back to 1984.

Mady's Hornig studies:
The studies started with a collection of samples from many of Dr. Peterson's sickest patients, which Dr. Hornig called "unparalleled" in their breadth and rigor. Simmaron sent off two sets of spinal fluid samples - one to Mady Hornig and Ian Lipkin at the Center for Infection and Immunity (CII) for a pathogen and cytokine study and another smaller set to Griffith University researchers in Australia to assess for immune abnormalities.

Gut-immune-brain axis
Dr. Hornig is internationally known for her work in the growing research arena exploring the mechanisms of gut-immune-brain axis functioning. She has a keen interest in how diet, exercise and environmental factors affect each individuals intestinal bacteria the so-called gut microbiome which then influences brain function through alterations in blood-borne molecules.

She uses immune profiling, metabolomic, proteomic, epigenetic and microbiome approaches to uncover markers of disturbed immunity and metabolism correlating with the severe clinical disease mechanisms that underlie ME/CFS.

Back to Dr. Daniel Peterson:

Since its inception, Simmaron has collaborated with the Columbia Center for Infection and Immunity on several gut microbiome studies, including, in 2017, the first study to characterize ME/CFS patients gut flora all the way down to the species level. Prior to this study, ME/CFS gut studies had identified genera, each of which contain many different species, some with very different characteristics. This time, the researchers used a new approach called metagenomic sequencing to get at the actual players in the gut - the bacterial species. For the first time, the gut flora of ME/CFS patients with and without irritable bowel syndrome (IBS) was assessed, as well. Such dramatic differences in bacterial species showed up between the two groups that the researchers were able to distinguish the two simply by comparing their gut flora.

Here you can read more about Simmaron and Dr. Daniel Peterson:
https://www.simmaronresearch.com/blog/2020/03/simmaron-celebrates-ten-years-of-innovative-research

Dr. Hornig talks a bit about phenotypes in her lecture (phenotypes include the different clinical characteristics that may underlie the heterogeneity of ME, including comorbid gastrointestinal or allergic disorders, or higher degrees of cognitive problems; the different inciting events and exposures – including infections – that herald its onset; and may also be influenced by genetic factors that contribute to the expression of the observable traits and disease risk of an individual as well as the "epigenetic factors" that alter what genes get turned off or on across one's lifetime.

Why phenotype? Better phenotyping allows for discovery of clinical subsets in ME that may both improve precision medicine strategies and help determine which patients are most likely to benefit from specific treatments.

BJÖRN BRAGÉE

Specialist in anesthesiology / intensive care and pain relief, Bragée clinics – Stockholm:

The theme of Björn Bragée's lecture at the ME conference Stryn was «Research and a published study that indicates there's a coexistence of hypermobility and constriction of the neck column. Examination of the brain and the cervical spine by magnetic resonance imaging (MR). Constriction of the cervical spine. Changes in the optic nerve that can indicate an increased pressure in the fluid surrounding the brain»

A research team at Karolinska Institutet and the Bragée clinics in greater Stockholm published a study in a prestigeous neurologic journal in the fall of 2020, that's showcasing formerly unknown underlying causes. The physicians at the specialist clinic were taken aback from seeing so many cases of simultaneous hypermobility and constriction of the neck column as an indication of neck damages. They initiated a study with all the willing participants out of the first 229 admitted pasients diagnosed with ME. This study showed that half of the pasients had general joint mobility, which is way above average. In a magnetic-field camera probe (MRI) of the brain and the upper part of the spine the resarchers found a higher occurrence of constricton of the upper part of the spine than they had expected.

There's a link to the published professional article from Karolinska Institutet and the Bragée clinics in the Stockholm region on the Website to the ME Conference Stryn, under the tab titled «Diverse informasjon om ME» (Miscellaneous information about ME»):

https://www.mekonferansestryn.no/post/eit-forskarteam-ved-karolinska-institutet-og-bragée-klinikkene-i-stockholm-regionen-publiserte

In his lecture at the ME Conferense in Stryn, Björn Bragée, said the following about the insufficient funding for research. – I do not know what the situation is like in Norway, but in Sweden, there's very little funding of this kind of research. This is research that are primarily being funded by the one's conducting the research (the center/the clinic.). They are hoping that Covid19 might have the consequence of increasing the funding for this kind of research.

In their research, they found displacement in the neck in 4 out of 5 patients. A little less than half of the patients also had a lowering of the cerebellum, causing a narrow foramen magnum.
Foramen magnum is the anatomical term for the opening in the skull where the spinal nerve exits the brain.

They also found that a large number of the patients had fibromyalgia, and only a few of the patients had a normal pain threshold.

Changes in the optic nerve:
In addition to this, a lot of the patients had changes in the optic nerve that indicates an increased pressure in the fluid surrounding the brain. The width of the optic nerve was measured with an ultrasound apparatus against the eye. Increased brain pressure can cause inflammation, cloudy vision, «brainfog» and head ache.

Summary:
- Displacement in the neck/brain might be a normal result of ME
- Increased brain fluid pressure migth be a normal result of ME
- Increased pressure might cause inflammation in the central nervous system
- It is necessary to verify these findings in further studies.

In the round of questions after the lecture the issue of surgery came up. Bjørn Bragée's answers were, in summary:
Surgery is usually not recommended as a first measure, but surgery has been performed on patients with displacements in the neck, and this has lead to improvement among several of these patients. A much better option is to use medicine to reduce the fluid pressure.
Physiotherapy can play a key role. Not in the form of graded exercise or normal exercise, but it can function as symptom reduction, where the patients can be taught about posture, and how to identify and control their autonomous reactions.

JONAS BERGQUIST

Professor of Analytrical chemistry and Neurochemistry at the Institue of chemistry - Biomedical Center at Uppsala University in Sweden

Open Medicine Foundation (OMF) are financially backing the creation of a third ME/CFS related resarch center, at Uppsala university in Sweden. This new research center in Uppsala is lead by Jonas Bergquist (MD, Phd), member of the scientific board at OMF. This newly added research center will focus and targeted molecular diagnosing of ME/CFS. The goal is to produce falsifiable strategies for treatment. There has been a considerable effort in Uppsala to produce an analysis of cerebrospinal fluid as a unique source of neurochemical biomarkers of ME/CFS.

The theme of Jonas Berguist's lecture at the ME conference Stryn is «Molecular diagnosis and treatment of ME/CFS – analysis of cerebrospinal fluid as a unique source for Neurochemical biomarkers for ME/CFS». Research on COVID-19 might produce important information on the research on ME»

In the research group led by Jonas Berquist from Uppsala, who will be part of the ME Conference Stryn 2021, they have had a longtime interest to study pasients that might have neuroinflammatory diseases, especially Myalgic encephalomyelitis (ME).
Over 20 million people have ME/CFS worldwide. Jonas talked a little bit about the ME symptoms:

Main Diagnostic Symptoms

- Post-exertional malaise (PEM) - symptoms worsen after exertion
- Reduction or impairment in ability to carry out normal daily activities, accompanied by Profound Fatigue
- Unrefreshing sleep
- Cognitive Impairment
- Orthostatic intolerance (symptoms worsen when sitting or standing upright)
- Severe body pain and worsening headaches

Neurological or Cognitive Symptoms

- Brain Fog
- Confusion & Disorientation
- Difficulty concentrating
- Short-term memory issues
- Ataxia and muscle weakness
- Hypersensitivity to noise and light

Autonomic, Immune & Digestive Symptoms

- Orthostatic intolerance
- Postural Orthostatic Tachycardia Syndrome (POTS)
- Irregular heartbeat
- Recurrent flu-like symptoms
- Sweating, fever, chills and night sweats
- Nausea & Irritable Bowel Syndrome
- New sensitivities to food, medication, chemicals
- Recurring sore throat
- Joint pain without swelling or redness
- Tender lymph nodes
- Light-headedness
- Shortness of breath
- Change in body weight
- Temperature instability

Like Björn, Jonas' research group also looks at some of the pain picture, cognitive problems, headaches, brain fog, etc.

Then he comes to what we knows about ME:

- Demonstrated changes in the autonomic nervous system and the central nervous system.
- Metabolism and especially energy metabolism affected.
- Altered immune phenotypes and functions
- Neuroinflammatory processes activated.

He also mentions with some uncertainty:

- changes gut microbiome (?)
- changes in gene expression along with epigenetic changes (?)

What we do not knows about ME:

- what mechanisms cause the disease symptoms?
- what leads to the changes we see in different systems?
- what links the changes and what is the trigger(s)?
- Is there a common explanatory model for all the symptoms?

Jonas talked about this with autoimmune diseases, (which many others mention during their lecture at this conference):

- A group of 60 to 80 chronic inflammatory diseases with genetic predisposition and environmental modulation
- A prevalence of 5 to 8% in USA
  Higher incidence in females than in males (2/3)

- 4th largest disease class in women

Molecular diagnosis and treatment of ME/CFS:
Jonas talked about the collaboration they have both nationally, in Europe, and with OMF at Standford.
Various research studies and projects in Uppsala that he talks a bit about:

- one where they look at the neurotransmitter pathway - the metabolism pathway, as they call the kynurenine pathway or metabolic trap, where they look at metabolites that have to do with seratonin, tryptophan, melatonin, kynurenic acid.
- one where they look at neuroinflammation - inflammation in the brain. What happens when you get inflammation in the brain? Parallel Covid study.
- One where they look at Autoimmune way

Applying proteomics and metabolomics - (Mady Hornig also talked about that) have instruments using electromagnetic fields where they can separate and interpret molecular structure, and map changes in body fluid in an effective way. So Jonas says that their «favorite fluid» in the central nervous system is cerebrospinal fluid. The fluid that surrounds the brain

Molecular diagnosis and treatment of ME/CFS:
Clinical trial with kynurenine:

→ STUDY AIM: The purpose of the study is to evaluate whether kynurenine is directly connected to ME/CFS patient symptom severity.
→ POTENTIAL: To understand potential disturbances in the tryptophan metabolism and to test the benefits of treating people with ME/CFS with Kynurenine.

The clinical trial might improve symptoms caused by too little kynurenine or too little kynurenic acid, a known neuro-protectant. Dr. Bergquist's expertly designed clinical trial of kynurenine in ME / CFS to improve brain fog, memory, and headache is important.

Study autoantibody in blood and cerebrospinal fluid:
This study was designed to validate the increase of autoantibodies observed in the blood of people with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME / CFS) that was observed in a previous study. In addition, the study investigated potential differences in autoantibody levels in the blood and cerebrospinal fluid (CSF) of those with ME / CFS and healthy controls.

→ The increased autoantibodies observed previously in the blood of people with ME / CFS appear to be targeting 'signaling molecules' (named adrenergic and muscarinic receptors) on cell surfaces that are responsible for regulating energy metabolism, immune system activation, muscle activity, heart muscle activity and neurocognitive function.

Results from this study validated those previously found of an increase of autoantibodies against adrenergic and muscarinic receptors in the blood of people with ME / CFS.

This is a published study that you can read more about here:
https://www.mekonferansestryn.no/post/ny-studie-frå-uppsala-university

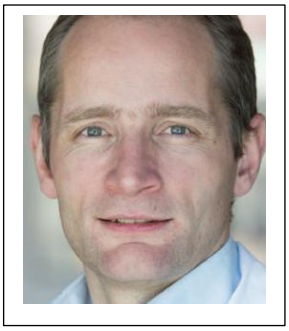
Research on COVID-19 might produce important information on the research on ME:
Finally, Jonas talks about ME and covid. Mentions a bit of history that other researchers also do with other corona viruses such as SARS and pandemics that have been. What they want to study is whether pasients that have gotten a severe COVID-19 infection, have a similar post-viral exhaustion, and if so, to what extent this occurs. We do know about such a connection from other great pandemics, inkluding the Spanish flu, the Asian flu and SARS.

The research group is already looking for neuroinflammatory markers and nerve celle markers with ME pasients, so they are also trying to find these markers in the spinal fluid of COVID-19 pasients. This might show a connection and provide data on what kind of pasients risk suffering longterm , or even chronical, health problems.
If this is the case:

- what is the composition of these biomarkers and what other organs are simultaneously affected?
- Can one see a pattern where different infections that affect the nervous system behave in the same way?
- Now they intend to follow up and study the state of pasients that are under intensive care that have neurological symptoms.

Here you can read more: https://www.mekonferansestryn.no/post/covid-19-kan-gje-viktig-informasjon-til-me-forskninga-uppsala-universitet-i-sverige

For those who want to follow what is happening at Uppsala and what they have published so far and future studies, you can sign up for the newsletter on Open Medicine Founatiton's website and read more here:
https://www.omf.ngo/collaborative-center-uppsala/



KARL JOHAN TRONSTAD

Professor at the Institute for Biomedicine. the University of Bergen

In collaboration with Øysten Fluge and Olav Mella at the Cancer department at Haukeland University Hospital, Tronstad is leading the project «Defective energy metabolism in ME/CFS». The project, that has received grants from the Norwegian Research Council, aims at developing new knowledge about the disease mechanisms, with a particular emphasis on the energy metabolism amongst pasients with ME/CFS.

His research group are focusing on how metabolic deviations can contribute to diseases, by, among other thins, studying the functions of the mitocondria (the power plant within the cells). By looking for metabolical changes in pasient samples, and then compare the findings in laboratory studies on grown cells, the group aim to find out more about mechanisms resulting in ME/CFS. The strategy is to measure the biochemical composition in the blood samples from ME/CFS pasients, to then look for a connexion that can explain symptoms, the severity degree and the of the duration of the disease.

They have found changes to the components in amino acids, and the results indicates a malmanagement of central parts of the energy conversion. Now they are moving on to other substances in the body, like lipids (fats) and substances with particula functions, like vitamins. In addition they are looking for genetical changes, and possible connections with deviances in the energy metabolism, in families affected with ME/CFS. This way, through detailed biochemical and genetic studies, they are seeking to identify key factors that kan build the foundation for the development of biomarkers and a new treatment.

During the ME Conference in Stryn, Karl Johan Tronstad, talked about the following topic: «Is ME/CFS caused by an energy failure in the cells of the body?» - resarch within energy metabolism.
Several studies have shown that ME patients have an impaired metabolism. The resarch that has been done by the team in Bergen has produced clear signs of problems with energy production.

Tronstad started off with laying out the goal of the research and its work methods.
The goald of their resarch: To map out biological mechanisms causing ME/CFS.
Clinical studies, biobank and lab work.

An illustration showing where the clinic is located, with clinical studies and intervention. By doing the clinical studies that have been conducted; in all 6 published studies have been made in collaboration with the research group at Haukeland - that

Ingrid and Øystein will talk abour more in their lectures – , an extensive biobank with tissue samples have been built up. The researchers have formed hypotheses and are looking for biochemical changes. In the lab, they are performing tests by using advanced, technological apparatuses, looking for different mechanisms that can cause the illness, as well as looking for markers.

ME/CFS is a disease that can worsen if the patient is active

Some key traits that can indicate this biological mechanism:

- The beginning of the disease: Newly established, often after an infection
- Systemic symptom: Fatigue, pain, feeling ill, cognitive problems, sleep disorders and autonomous disurbances
- Activity induced worsening (PEM): Aftereffects, different duration
  Severity degree – Ranging from mild to extremely severe

Main focus:

- To find possible metabolical anomalies (weaknesses)
- To understand the underlying biological mechanisms causing the disease

Here are the 4 main work methods in their study:

1) To preserve a ME/CFS biobank
2) An extensive analysis of blood samples (metabolite measuring using metabolomics)
3) To identify risk genes (sequencesation of families, some particularly hardly affected families)
4) Examine hypotheses / mechanisms (lab work).

If zooming in on energy metabolism, and what goes on in the cells, some of the theories on causes to the disease is cellular energy failure. Tronstad shows an illustration of a cell getting supplied by the blood (blood veins or blood arteries):

1. Impaired supply to the cells, from the blood, a factor that can be part of determining energy metabolism.
   - Oxygen – The cell needs oxygen, their might be an insufficient intake.
   - Energy sources – Normally, the body vil adapt and make use of the energy sources that are available, most of the time.
   - An impaired ability to adapt to activity/rest – There is an adjustment in the body when one moves from activity to rest, if something is not functioning optimally in this regard, that can be a contributing factor.

2. An outright injury/error in the cells – inside the cells
   - Metabolical functional loss – damaged mitochondria
   - Disregulation, damages, toxicity, like mercury (they don't think that ME kan be

caused by toxicity), deficiency (e.g. vitamines, nutritional deficiency, exposure to micropollutants et. al.) How can these different factors influence the function in the cells of the body.
- Energy-saving and back-up solutions (The cells kan change into different modes. Having back-up solutions is very important.)

3. Genetic factor
   - Mutations in enzyme (maybe not the primary defiencyi, but has ripple effects, which means you have to scale back all the way to the primary cause).
   - Indirect mechanisms – when one tries to interpret a complex data set, one has to focus on multiple thoughts at the same time.

Metabolical differences with ME: analyzing metabolites in the blood serum. (Blood serum is the liquid phase of blood after it has been coagulated. Serum has the same chemical composition as plasma, except from fibrinogens, who in the process of coagulation turns into unresolvable fibrin. That means that serum also cotains the antibodies that the body has created in relation to infections is has been exposed to.)

Concrete further findings in the lab: utilizing knowledge from other fields of research. The ME field: We know what is happening on the patient level, but there's not models that are good enough when it comes to lab work. There's hope to eventually achieve this as we learn more about this disease.

The first study: Measering aminoacids in the serum. Got an idea about what level the changes occurred in the decomposition process. That's when Karl Johan Tronstad brought up the enzyme PDH.

The main energy pathway in energy metabolism (the illustration can be found in the Tronstad's Power Point presentation posted on our Website):
Starting off with glucose that is transformed to pyrovate. This is then absorded by the mitochondria. This is were the actual process of catabolusm occurs. In addition to this there is also aminoacids from protein that can enter at different stages of this main energy pathway. Fatty acids also enters straight into the mitochondria. For everything to be functioning the way that it is supposed to, enzyme has to be here. It is the enzymes that does the actual work. We need vitamines and minerals, that – in addition to other co-factors – are important. If one of these factors are missing, the main energy pathway won't function properly.

Early on, the research group found and focused on a finding that the enzyme was disregulated. The findings have been interpreted as something that has happened in the mitochondriac part of the main energy pathway. The researchers chose to focus on a key enzyme called PDH – Pyruvate Dehydrogenase.

PDH – Pyruvate Dehydrogrenase: an important energy enzyme : In 2016 a new study was published, partly financed by the Kavli fund, implying that when it comes to ME patients the PDH enzyme (Pyruvate Dehydrogenase) have been inhibited, something that would explain both the energy deficiency and the increased lactic acid production.

- «In earlier studies of foreign groups there have been findings of a reduced level of a few amino acids in the blood of ME patient. In our particular study all the 20 common amino acids were mapped out, in the blood from 200 patients included in the clinical studies, as well as samples from 100 healthy control persons.

- «Here we found a specific decline in the amino acids that gets broken down independently of the PDH enzyme with ME patients, compared to the healthy persons. These findings imply that when it comes to the ME patients the PDH enzyme is not functioning the way it is supposed to, which causes an increased consumption of certain amino acids as an energy source, as opposed to sugar».

- Findings of certain amino acids that the body burns to produce energy, were most prominent among women suffering from ME. When it comes to men with ME, there were less dissimilarities compared to healthy men. On the other hand, we found an increased level of a particular amino acid that reflects the breaking down of proteins in muscles among men with ME. Since men have more muscle mass than women, this can serve as an extra supply that increases the accessibility of amino acids as fuel".

Energy deficit in the muscles:

- The PDH enzyme is essential in one of the most important pathways to forming energy from carbohydrates, which takes place in the mitochondria.
- Inhibition of the PDH enzyme therefore will result in consumption of alternative fuel, something that might explain the changes we found in the amino acid profile in the blood samples from the ME patients.
- The ability of the cells to adjust the metabolism depending on the energy need will, however, be severely impaired.
- For example; physical activity might, in a short amount of time, create an energy deficit in the muscles, at the same time as the lactic acid is building up.
- These are normal processes occuring amongt the healthy during a slightly hard workout, but when it comes to ME patients with a severe state of illness, this symptoms can occur after minimal strain, for example from getting up from bed or walking a few steps.
- The feedback from patients has been that they can relate to this model of

explanation, it suits with the energy deficit and feeling of sicknes with lactic acid pain in the muscles after physical acitivity.

Gene expression:

They then moved on to measuring the gene expression (mRNA) in the white blood cells for a number of regulators of the PDH enzyme. The findings showed that there were ME patients that had an increased level of several important factors that inhibit the PDH function. It was interesting to see that these changes in the gene expression were present among both women and men with ME. These findings implies that the PDH inhibition itself is the same for men and women, but that the ripple effects on the metabolism can be partially determined by gender.

Source: *Forskingsgruppa sin vitenskaplege studie i 2016 vart presentert på Kavlifondet sine sider. [The scientific study from 2016 conducted by the research group, presented on the Kavli fund Website]* https://kavlifondet.no/2016/12/ny-studie-om-sykdomsmekanismer-ved-me-fra-forskningsgruppen-i-bergen/

PDK_4 –pyruvate dehydrogenase kinase 4

They are also using a marker for radio activity to try to see what happens with the cellular fuels (not in glucose but the mitochondria). They mark different substrates with radioactive markers and measure the CO_2 coming out from the cells. If radioative sugar enters a cell, it is possible to measure how much of the sugar is actually being burnt in the cell by collecting the carbon dioxide, since it will be radioactive. It is also possible to use amino acids, fatty acids and pyruvate for this. It is then possible to se what parts of the human body that might by affected.

- PDK_4 turns off a switch on the enzyme that make it so that the PDH can not work as hard as earlier.
- The researchers took the genes from this protein and added an extra gene that they had cultivated into the cells. The cells then got an increased level of PDK_4.
- It makes on think that the PDH have been impaired. This caused a doubling of the fatty acid oxidation as a compensation. This might be relevant to ME patients, and the researchers are working on exploring these processes.

PDK_4 alone is enough to change the metabolism and increase the oxidation of fatty acids. PDK_4 can be used as a marker on fatty acid oxidation.
Tronstad said that this might imply that ME is a systemic illness and that there is something in the ME blood that causes stress to the energy metabolism. There have been tests on the maximal oxygen uptake in the cells to examine the mitochondria energy production. The findings showed increased oxygen consumption and increased lactate production triggered by strain, that might be a sign of a systemic disease.

A new study: They have measured about 1500 metabolites in serum, using metabolomics. Metabolomics – a lot of findings relating to amino acids and lipid.

Key findings:
- Amino acids metabolism
- Lipid metabolism
- Recognizable signatures for increased energy strain.
- Both common and varying effects within the patient groups.

A «map» of metabolical changes:
Common effects: *Metabolites related to energy failure, changes that can concur with a deficient oxygen supply to the cells.*

Varying effects: *Adaptastion and compensation, affected by nourishment, acitivity, disease, and more*

Both the primary and secondary metabolical changes kan influence the bigger picture of symptoms and the degree of ME/CFS.

Conclusion and the way forward:
- *Metabolical signatures of cellular energy deficiency*
- *Probably an underlying driving disease mechanism*
- *Both primary and secondary metabolical changes*
- *Might be compatible with hypoxia in the body tissue*
- *Possible consequences on the cell and tissue level: - A constant struggle for energy (ATP)*
- *Absence of metabolical rest*
- *A lowered threshold for excessive strain*
- *Activity triggered injury mechanisms*

The way forward: The connections between immuno deficiency and energy failure. Energy failure: Protein studies (proteomics), factors that kan be linked to improvement/worsening, possible risk genes.

INGRID GURVIN REKELAND

Acting chief physician at the Department for cancer treatment and medicinal physics, Haukeland University Hospital, PhD scholarship holder at the University of Bergen.

ØYSTEIN FLUGE

Chief physician at the Department for cancer treatment and medicinal physics, Haukeland University Hospital, and professor at the University of Bergen.

Since 2008, Øysten Fluge and Olav Mella has shown interest for ME pasient and ME research. They eventually established a research group at the Department of cancer treatment at Haukeland. The research group has expanded the last years, and is composed of physicians and researchers, nurses, research technicians, molecular biologists and exercise therapists, collaborating with the group lead by Tronstad.

Øystein Fluge has lead multiple clinical studies and an extensive laboratory work. The last couple of years his research group has conducted two studies trying out different types of medication; RituxME and CycloME. Rituximab is an antibody that depletes B cells from the circulation, whereas cyclophosphamide is a cell cancer that influence both the B cells and the T cells. The hypothesis is that ME is a type of auto immune disease, and that the immune system is key as far as the mechanisms cauing the disease is concerned. After finishing of the clinical studies, the research group has focused on the biobank samples taken during the studies, and the situation regarding potential medications, moving forward.

In 2020 this group contucted a study with continuous registration of acitivity with the help of the activity wristwatch Fitbit. The participators did not receive any treatment, but the goal was to find out whether this was a good method for assessing pasients participating in future studies. They have mapped out the natural cause of symptoms and activity through a 6 month period.

Ingrid Gurvin Rekeland is working 50 percent as acting chief physician at the Department for cancer treatment, Haukeland University Hospital, with a 50 percent PhD scholarship from Helse Vest (the Health Trust West). She har been working in the ME research group and with laboratory work and anlyses tied to the clinical studies. In 2018, she started her doctorate project “Myalgisk encefalopti (ME): Medikamentell behandling, sykdomsmekanismer og biologiske markører” (“Myalgic encephalomyelitis (ME): Medicinal treatment, disease mechanisms and biological markers”). Her main

focus now is analyzing biobank samples, with the goal of understanding the mechanisms behind the disease and identify possible biomarkers.

Rekeland's doctorate is based on the published clinical studies;

- «B-lymphocyte Depletion in Patients with Myalgic Encephalopathy/Chronic Fatigue Syndrome», RituxME
- «Cyclophosphamide intravenous infusions in Myalgic Encephalopathy/ Chronic fatigue Syndrome», CycloME

There's an extra focus on analyses and lab work connected to the CycloME study, but also the RituxME study. The goald is to map out disease mechanisms and to find the patients that might benefit from the immune-modulating therapies. The goal is, without a doubt, to figure out what constitues a good treatment. There are still a lot of prejudices. There is a lack of knowledge and the research on the disease is scarce. As long as no-one has found a known biomarker, studies will typically contain different types of patients, and therefore be difficult to interpret. That is why it is important to map out and find different sub-groups.

Still, the level of research on this disease is increasing. The ME Association from England have produced a summary of all the studies that have been done so far. https://meassociation.org.uk/wp-content/uploads/ME-Association-Index-Published-MECFS-Research.pdf

Summary of the history: In 2004 an ME patient contracted lymphoma, and could report that the cancer treatment had had a positive effect on the symptoms stemming from ME. The chemotherapy regime contained ifosfamide (resembling cyclophosphamide, which has an extensive effect on several type of immuno cells.) In 2008 a patient with a perennial severe ME disease contracted an aggressive non-Hodgkin lymphoma. She could reported a significant improvement to the state of her ME disease after a treatment that consisted of rituximab in addition to a chemo therapy that also contained cyclophosphamide.

Rituximab has a selective effect on the B lymphocytes. Later on there were 7 observations of ME patients who had and improvement in regards to their ME symptoms after their cancer treatment. There were studies of Rituximab and Cyclophosphamide, in separate clinical studies.

It is important to note that Rituximab and Cyclophosphamide are to different substances with entirely different effect mechanisms.

Rituximab: Only goes for the surface of the B cells. It is used to treat lymphoma (B cell lymphoma) and some autoimmune diseases. It creates a reversible reduction in both

malignant and normal B cells.

Cyclophosphamide: Has a broad effect on white blood cells and other cells that undergo mitosis. It affects both the hereditary, innate immune system and the adaptive immune system.

Clinical studies at Haukeland: First, a pilot study on Rituximab was conducted in 2009, sthen the KTS-1-2008 study was conducted in 2011 (Rituximab/placebo). The KTS-2-2010 study came in 2015 (rituximab maintenance treatment). All this, before the big RituxME study, that was published in 2019 (a double-blind, placebo controlled phase III study, with rituximab or placebo). At the same time an open phase II study with cyclophosphamide was conducted, and it was published in the spring of 2020.

The CycloME study: The response data were good, but there weren't a placebo group. How shall these results be interpreted? One should take a step back and consider different mechanisms, when RituxME turned out negative. There was an extended follow-up of the Cyclo study, 2-3 years and 3-4 years. It turned out that some of the patients suffered a setback. After 4 years 68 percent still had a stable response. The criteria that was set up for the study was: fatigue-score SF-36 (a questionnaire about health), total function level, step measuring.

You can read more on the published Cyclo study here:
https://www.mekonferansestryn.no/post/cyclofosfamid-studien-ved-haukeland-er-publisert-29-04-2020-med-tittelen

RituxME study: negative. There were no significant difference between those that received rituximab and placebo, and the conclusion was that rituximab is not a useful treatment for a larger group of ME patients, chosen based on the Canada criteria. In the analysys of this study, one found that those with a mild form of the disease and the shortest disease spand had the most fluctuating course. However, one negative study does not rule out that ME is a disease in which the immune system is of significance. The immune system consists of so much more then this particular cell. The immune system is a very complex.

For more information about the RituxME study, click this link:
https://www.mekonferansestryn.no/post/studie-viser-ikkje-effekt-av-behandling-med-rituximab-hjå-pasientar-med-me-cfs

A brief summary on the immune system:

- The innate immune system, which is present from birth.

- The adaptive immune system, lymphoid cells, the body «remembers» and produce antibodies.

→ B cells are the plasma cells, they produce antibodies against foreign materials so that the immune response comes quicker the next time the body is exposed to these foreign materials.

→ T cells attack foreign materials and infections inside the cells. During «immune therapy» they attack cancer cells.

- Auto immune diseases makes the immune reponse go after the body's own proteins.

Several factors point to the immune system playing a part in ME:

– there is often an outbreak of ME in the aftermath of infections
– a majority of women, which is typical for diseases in the immune system
– slightly increased risk for lymphoma in older pasients with ME. A chronically activated immune system?
– A high occurrence of auto immune diseases among first-degree relatives
– Studies of gene expresscions in immune cells and cytokine
– Genetic predisposition for ME/CFS
– Association to specific immune genes (the HLA gene)

<u>Conditions that can, partly, overlap with ME where the immune system plays a part:</u>
- fibromyalgia, IBS (irritable bowel syndrome), POTS (Postural Orthostatic Takyardia Syndrome), CRPS (Complex Regional Pain Syndrome), orthostatic intolerance, and possibly Long Covid.

HLA-risk-allels: There's two genes that might be associated with ME. A study has been conducted in Oslo (OUS), containing a larger group of ME patients and control persons, where the researchers identified two potential HLA-risk allels. HLA C*07:04: and HLA DQB1*03:03. In RituxME 16.7% either had one of these two HLA-risk-allels or both, in CycloME the number was as hight as 30 %.

A lot of lab analyses have been done in conjunction with the Cyclo study. These analyses examines auto-antibodies, white blood cells/lymphocytes, differences when it comes to response vs. non-response, severity degree, disease duration and whether ME/CFS was triggered by infection or not. They find differences, but still no “biomarker”.

They think that the improvement that was found in the Cyclo study can be explained by a medication effect, but this cannot be said with certainty until either a placebo

controlled study has been conducted or other biomarkers that can predict a response is found.

Øystein Fluge: «Disease mechanisms and intervention – the way forward»

Which biological system is out of order, causing the many-faceted ME/CFS disease picture?

The RituxME study is negative, which means that for a group of ME/CFS patients, selected on the basis of the Canada criteria, Rituximab is not a suitable treatment. But the study has produced information about the natural course of symptoms through 2 years of treatment. Some of the patients expericend a considerable gradual improvement, over a period of time.

There is no certain knowledge about mechanisms related to this disease, and no standardized ways of measuring objective endpoints.

Factors that will have an influence on the outcome of the study:

- Patient heterogenity (different disease mechanisms among the participants)
- Patient selection (Infection before outbreak of ME/CFS?, severity degree, duration)
- Placebo mechanisms
- Natural symptom variation over time

The RituxME study shows the necessity of randomized and placebo controlled studies. The questionnaire about health related quality of life, SF-36, was filled out a total of 9 times during the study.

In this baseline study, there were low SF-36 values, meaning that the patients had a lot of symptoms. 14 out of 29 patients were experiencing a considerable response" in the rituximab maintenance study. SF36 and PF (physical function) have often been examined in different studies, and can be used to compare the different patients that are included in the study. There is a significant difference between the patients that reported a SF-36-PF on a scale from 15 to 30 vs those that reported this on a scale from 50 to 60. These are two completely different patient groups. In the RituxME study there were on average an increase on around 12. One can also see a similar increase in the placebo group.

What does it take for something to be labeled a response in a study? In some studies and increase above 10 on the SF36-PF is considered as a significant improvement.

How can future studies:

- reduce the problem related to patient heterogenity?
- measure the response?
- improve "the end points"?
- find out what kind of patients experience a "stable course over time"?

- find out what kind of patients experience a significant fluctuation of symptoms? When it comes to this question, it will be hard to determine which of the fluctuations that are medication effect and which ones that are fluctuations in the course of the disease.

The Fitbit study:
This is a study that follows 27 patients closely, using documentation of their activity level for 6 months, where the goal is to find out more about the natural variation over time.

The goal was to find out whether an objective documentation of a step count, and possibly the resting heart rate as well, can be used as a measure of the effect in a new study. This measuring of physical data was then compared with self-reported data that was filled out every 4th week. Most patients found it OK to juse the fitbit watch, and to fill out the questionnaires.

In the study the they included patients diagnosed with the Canada criteria, in an age group ranging from 18 to 65 years old, with a disease duration lasting for at least 2 years. They knowingly also incluced some patients with relatively moderate symptoms, to be able to look for any variation over time in the different groups (mild to moderate symptoms, moderate symptoms, moderate to severe symptoms).

The numbers show fluctuations in the disease course among the patients with the mildest symptoms, compared to the most ill patients, who had a more stable disease course. This shows that the degree to which the disease is severe or not can tell us something about what kind of fluctuations we can excpect over time.

In an intervention study it is important to have a pasient group that is as “stable” as possible, withouth too much natural fluctuations in the disease course.

The hypothesis still is: **ME/CFS is a type of auto immune disease, where B cells/ plasma cells and auto antibodies matter**.

The fact that Rituximab does not work on ME, does not mean that it is not an immunologic mechanism. There are several known auto immune disease, for example lupus and Sjogren's syndrome, where we know that some patients experience an effect from Rituximab, even though a majority of the patients does not have this experience. This is because the auto antibodies production comes from the plasma cells and because other parts of the immune system are also important for the disease mechanism when it comes to lupus.

The statistical curves are very similar to the curve in the RituxME study. One wonders whether there is an auto antibody present in a subgroup of ME/CFS patients, and if this is the case, whether this auto antibody plays a pathogenic role or not. And how, in that case, can B cells/ plasma cells or the auto antibody provide a clinical picture like ME/CFS?

Working hypothesis for the time being:
The belief now is that there is an auto antibody response that cause a disturbance to the regulation of the blood flow to the body tissue, and that this creates a nourishment and oxygen deficiency when it comes to the needs of the tissue, especially while experiencing a strain (cognitive/physical).

The belief is that there is a immune disturbance stemming from an infection, and that this cause production of antibodies from the plasma cells, which influence the autoregulation in the blood flow that then causes a low oxygen level in the tissue, hypoxia. The theory now is that this hypoxia then cause an energy deficiency, PEM symptoms, and that a lot of what is being measured is secondary adaptations to this situation. These are metabolic adaptations, or secondary adaptations, that constitute the body's response to the problem. This can resemble the normal phsyiological mechanisms that is activated by hypoxia, hunger or endurance activity.
They believe that this is a reversible process, and are now continuing to work to find out how these disease mechanisms can be affected to cause an improvement in the health of the patient.

Study published on March 2021: Endothelial function
(Link to the professional article and the article on the Website of the Kavli fund can be found on the Webside ME Conference Stryn, below the table “Diverse informasjon om ME” (Miscellaneous information about ME»)
The research group on ME/CFS at Haukeland University Hospital have published a new article about possible circulation disturbance among patients suffering from ME/CFS. Examination of the blood veins of the patients using ultra sound have been an important part of the study, that have been conducted with support from the Kavli fund.

Conclusions from the science article:
«Patients with ME/CFS had a reduced endothelial function affecting both large and small vessels compared to healthy control people. Changes in endothelial function did not follow clinical responses during follow-up after cyclophosphamide IV intervention».
https://www.mekonferansestryn.no/post/ny-vitskapstudie-frå-forskingsgruppa-ved-haukeland-universitetsjukehus

KRISTIAN SOMMERFELT

Professor of Child Neurology at the Children's Clinic at Haukeland University Hospital

Kristian Sommerfelt has a background in working with ME in pasients that are children and young persons up until the age of 18, that were diagnosed before they turned 15. He has over 20 years of experience with ME and have solid advice to give pasients, next-of-kin and health care workers.

Sommerfelt has been working with a lot of different extreme diseases and severe disabilites. He's pointing to an odd peculiarity when comparing ME to other pasient groups. In cases of severe disability, an extensive support system and service apparatus is set in motion. But when it comes to ME, there's no apparatus that's automatically being set in motion. Pasients with severe or extremely severe ME are not able to use the specialist health services in an ordinary way, because it is hard to transport these pasients when their sickness is that severe. It is of the essence that health care personell turns a new leaf and starts visiting this pasients in their homes. It is also important to take care of the next-of-kin of these pasients. Sommerfelt thinks that the ME pasients might overreport how much they are able to do. It is important to have clear, objective measuring parameters, or at least ask the pasient's next-of-kin about the function level of the pasient.

The theme of Kristian Sommerfelt 's lecture at the ME conference Stryn was «Pitfalls and useful strategies during diagnosis and follow-up treatment». ME research and prognosis among children and the young.

About 1 out of 200 are suffering from ME, a sizeable increase since 2005, also in the age group from 30 years to 40 years. Most girls/women are affected, particularly among adults. The prognosis of the disease duration is for the most time several years, some never recover. Anyone can get it. There are no psychosocial risk factors. It is not associated with psychiatric disorders / conditions, or a particular type of personality. ME *is* however, associated with:

- 80 % of the days / weeks after infection symptoms
- First and second degree relatives with ME (20 %?)
- Auto immune diseases in the family (two times the occurence)

So far, no one has discovered an effective treatment. The most important thing right now is recognition for this disease, both for the patient internally and generally speaking, in greater society as a whole. The patients should not expect to do more than they are capable of. There is symptom relief treatment available, for example when it comes to migraine, other types of pain, nausea and sleep disorder. The other

kind of migraine, that does not come in intervals, is harder to treat. Sommerfelt says that for some ME patients, the "ME head ache" is not the worst part of the disease. Melatonin might help when it comes to having trouble with falling to sleep.

Treatment, why are there so much controversy surrounding ME?

- The patients that have the worst type of ME is not seen by the rest of society, other patients might seem healthy when they are out and about and meet other people. If they have pushed it too far when it comes to being active, they will typically get PEM for days or weeks afterwards. The patients will rarely complain, they do not focus a lot on disease. They are used to constantly having to master things that healthy people can't even begin to imagine – like chemotherapy treatment.
- Blood samples are normal and there are no bio markers.
- It seems that the attitude to this phenonenon from the health service seems to be: "Can't they fix it"! It seems more comfortable to say that ME does not exist and that "everybody gets tired".

How is it like to have ME? «The maleficent e-mail inbox»:

ME patients are used to constantly mastering something that those of us that are healthy can not even begin to imagine – like chemotherapy treatment. EVERYTHING an ME patient does / thinks / experiences HAVE A COST. Some actions will also have positive side-effects, but it is NEVER the case for an ME patient that an activity have only upsides to it. EVERYTHING causes an energy drain. Movement, thoughts, word, sounds, light, changes, excetera, constitutes and extreme strain and can lead to a worsening of one's state of health.

→ While talking about the ME brain, Sommerfelt has come up with this simile: The ME brain is like an e-mail inbox where ALL the emails have to be opened and read.

Little research on ME:

There's still not a lot of research on ME: maybe one percentage of the amount of research being done on multiple schlerosis (MS). But ME is about as common a disease as MS. Getting an increase in the research field on ME has been a slow and difficult process, but now things are happening! There is an increased consiousness on biological research.

How to get an increase in the research?

- Recognition of the disease. Among adult patients the disease is not very visible, but among children and teenagers it is very visible, when the patients cannot attend school.
- For these young patients, the best thing is if they are being monitored for a

longer period of time. The best thing that can happen is if a teacher can keep an eye on their development. The second best observer is their personal general practitioner. Hopefully, the general practitioner will have known the patient before he or she developed the disease. The specialist health service is the least suited for monitoring the development, because it does not follow the patient over time.

The school project «the tool box».

- An early diagnosis and facilitation is very important, but often, this does not happen.
- In Rogaland, some people sprung into action because they recognized how important it is to make the school realize that they have pupils with ME. These pupils need to be understood and they need for the school to adjust to their needs. This obviously relates to the pupils who are ablo to attend school. Those with a severe type of ME cannot attend school. In Rogaland they have created a project titled «ME and school: «the tool box». This is based on the Internet, and it is free of charge. It has been recommended that teachers, principials, parents and others participate. Those that have created it are experienced professionals; including a psychologist, a special educator and a teacher with experience on ME.

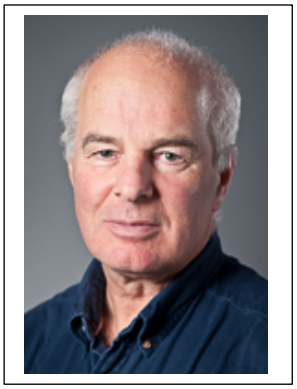
Useful advice:

- Recommended activities that can be put on hold (gaming, painting, poetry and more....)
- Talking to others is an activity that **cannot** be put on hold. School/break time cannot be put on hold, but sometimes a reassessment of priorities focusing on social affiliation is important.
- For school: It is recommended that one single person is given the task of accruing knowledge about and closely follow the patiet. It is important to have a productive dialogue with the school. It is possible to use a robot stand-in for the pupil in the class room, recording what's going on (but experiences with utilizing this have, for the most part, been bad). Different kinds of adjustments where the school tries to meed the special needs of the patient.
- Listen to people that are next-of-kin.
- Avoid activities that requires an overuse of energy, causing PEM. Sometimes, the patient will do this anyway, but then, it better be worth the consequences.

Conclusion:

Do not make a tough situation more difficult – recognize ME for what it is. An important factor in the work of getting increased recognition of ME, is to increase the focus on ME among children/the young. The compulsory nature of primary education

forces society to see the severity of this disease. People with a severe or very severe kind of ME disease and their families need to get a whole lot more attention than what is the case currently.



OLA DIDRIK SAUGSTAD

Professor Emeritus in Pediatrics, Oslo University Hospital, ME researcher at the University of Oslo.

Ola Didrik Saugstad gave two lectures at the ME conference Stryn, one in the evening and one at the professional conference. Dr. Saugstad worked at the pediatric research institute until 2017. He then retired from that position, but continued working as a researcher at the University of Oslo, where a large research group is going to study ME from a immunological and genetical perspective, thorugh the «ImmunoME study». Blood samples from pasients will be a focal part of the study.

The theme of Saugstad's lectures the professional conference was the «ImmunoME study» - published research findings and the findings of possible subgroups

ImmunoME:
They want to use their professional competence within immunogenetics in auto immune diseases to examine whether there are any auto immune characteristics and environmental factors that, when put together, determines whether someone develops these diseases, or not. If the situation is similar when it comes to CFS/ME, this calls for studying as many individuals as possible to identify potential risk factors. With their projects dei want to contribute to increase the knowledge about possible biological processes, pathological types of cells and clinical subphenotypes of CFS/ME, and potentially find som useful biomarkers.

Examine whether the immune system plays a role in the development of ME, and will conduct a thourough mapping out of genes that is essential for the immune system to look for differences between ME patients and control persons. They will also examine the occurrence of antibodies among ME pasients. – One of our ongoing studies revolves around a thourough documentation of primary genetic associations in the HLA region on chromosome 6, that contains hundreds of immunologically important genes in addition to the HLA genes. One HLA association is one out av several essential traits of an auto immune disease, and possible findings in this regard will serve as motivation for further immunogenetic studies on CFS/ME.

The research group published a science article in the spring of 2020 in the journal Scientific Report (Sci Rep) with the title: “Human Leukocyte Antigen alleles associated with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)”.

A link is available on the Website to ME Conference Stryn under the table titled «Diverse informasjon om ME» (Miscellaneous information about ME). You can read more by clicking this link: https://www.mekonferansestryn.no/post/immunologi-og-genetikk-ved-myalgisk-encefalopati-me

The biomedicinal research is progressing with giant leaps. In his lecture, Saugstad starts off with saying that the team participating in this study, were professionals coming from different fields are represented. When it comes to funding, they applied for and got financial support from the Kavli fund to conduct the study. It is important to highlight this, because the Kavli fund have done so much work for the ME research in Norway. When the research team received financial support, the focus then became to find a doctoral fellow. Asgeir Landa is a doctoral fellow – with a disputation in May, with the final test to get his doctorate. Eventually, the research team received financial support from the Research council.

They are collaborating with Haukeland, and CFS/ME center at Oslo (Elin B. Strand and Daisy D. Sosa). Patient samples have been provided from both the CFS/ME center and from Haukeland, the research group led by Olav Mella and Øystein Fluge (RituxME). Saugstad stresses that it is possible to also create a large research group in Norway dedicated to this topic.

This is det largest study on this field on ME patients that have been diagnosed based on the Canada criteria. The study also includes very sick ME patients. Ola Didrik Saugstad and Asgeir Lande travelled near and far to retrieve blood samples from many of the most ill patients. – Just to make this clear, for the ME patients that have it the worst, having one's blood sampled, can in itself constitute enough of a strain for the patient to cause PEM (Post Exertional Malaise), Saugstad stresses.

When this study also included severely ill patients, that was a first.

ImmunoME: ME is a clinical diagnosis. That means that there's a discussion and that it can be difficult to arrive at this diagnosis. Better tools to diagnose the patients is needed. The causes behind the disease are still unknown, even though one is starting to find pieces of information so that the bigger picture is starting to become a bit more clear. We do know that a immunologic dysregulation have been described and that autoimmunity is a possible explanation. The purpose is to study immuno genetics in regards to ME.

Hypothesis: Auto immunity is important in the pathophysiology of ME.
Purpose: To test this hypothesis we have studied immunogenetics.

They have taken a look at the HLA (Human Leukocyte Antigen) gene that is essential in regulating the immune system. When it comes to auto immune diseases one typically finds a higher or lower frequencies av certain variants of these genes. They compared the frequency of different gene variants (that are labelled alleles) in 426 ME patients with 4511 healthy control persons. That is a very large control group.

At the start of this study they started looking at earlier studies made in other countries. These were to narrow to be ablo to draw any conclusions and they had used old diagnose criteria, therefore it was important to conduct a larger study in this field.

Why study HLA?
- The HLA molecule is regulation the immune response by presenting peptide (a piece of a protein) that can get activated and then activate T cells (which is a immune cell).
- HLA associations: An increased tendency and protection against auto immune diseases is associated with certain HLA alleles.

Autoimmunity:
- Associated with the HLA gene (Saugstad shows a list over several known diseases associated with HLA, for example arthritis, hypothyreosis (slow metabolism), Bekhterev's disease , MS etc.)
- Narrow, earlier studies have have shown an overoccurence of certain HLA genes and ME/CFS, but the studies are to limited for any conclusions to be drawn.
- Therefore there was a need for a more extensive study to study the connection between the HLA gene and ME.

The method: They had created a questionnaire and got feedback from patients that they also included. They wanted to see whether they could find any sub groups based on the severity degree and how the disease have lasted, ME triggered by an infection and ME not triggered by an infection. The cases that were triggered by an infection had a differend HLA pattern enn the cases that were not a infection triggered disease. Saugstad continued to present and talk a little about demographical and clinical characteristics.

HLA alleles that showed association with ME/CFS in 425 patients and 4511 health control persons:
- Found that 4 HLA alleles are associated with ME/CFS.
- ME patients with one or two of these HLA genes had a 2,3 times greater risk for other auto immune diseases: Thyreodite/hypothyreosis, psoriasis, reumatoid,

arthritis, alopecia areata, Chron's disease

Autoimmunity and ME:
- Autoantibodies have been detected for example against neurotransmitter receptors
- Comorbidity with other auto immune diseases
- Auto immune diseases are often triggered by an infection
- Single-nucleotide polymorphism (SNP) in certain genes are associated with the risk of developing an auto immune disease
- Some of these are significantly higher among those with an infection triggered ME vs. control persons.

The HLA-genes are essential when it comes to regulating the immune system:

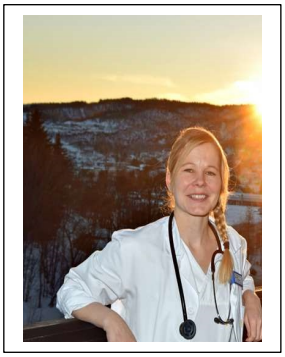
- found that two particular gene variants occured more often among ME/CFS patients than among healthy control persons. In cyclophosphamide study 30 percent of the participants one av these «risk» variants.
- Furthermore, the results showed that 83 percent (10 out of 12) participants that tested positive for this kind of gene variant could report about a positive development in the CycloME study, compared to 43 percent (12 out of 28) that did not have any of these HLA variants.
- This can point towards a possible connection between these gene variants and the degree to which a treatment with cyclophosphamide had an effect. This type of correlation betweene the HLA gene and the effect of the treatment have been found in regards to other auto immune diseases.

Question: - Does HLA testing say anything abouth whether there is an effect from cyclohposphamide? The answer is that we do not really know that yet, but that there can be an indication that is possibe to make the treatment better adjusted to the individual patient than what have been the case so far.

You can read more about CycloME and HLA from the presentation from the Kavli fund Webpage following this link: https://www.mekonferansestryn.no/post/lovende-resultater-fra-forsøk-med-kreftmedisin-ved-me-cfs

Conclusion:
- This is the largest study in this field on ME patients diagnosed using the Canada criteria.
- The study strengthens the hypothesis that considers ME to be an auto immune disease.

In the future maybe these analysis kan be used to single out patients that responds to a certian kind of treatment.



LINN CHRISTIN SKJEVLING

Physician in specialization at UNN Harstad

In a collaborational project between the medical department and the physiatry department at UNN Harstad, a study on people with the CFS/ME illness will be conducted. This study has been titled «The Comeback Study». This project that have received fundings from the Research Council in the spring of 2017 (5 millions NOK). The study has a Facebook page, where you can follow updates: https://www.facebook.com/thecomebackstudy

Dr. Skjevling is a scholarship holder for the study on irritable bowel syndrome at the medical department UNN Harstad. They have recently contucted a study treating irrital bowel syndrom with fecal transplants. Through this work, they got on the trail of the theory of applying the same treatment principle on CSF/ME pasients.

- When looking at studies concerning other diseases, we now know that an unbalanced intestinal flora can be normalized through transplanting bacteria from a healthy donor to the intestines of the pasient.
- Findings have shown increased markers in the immune system that can be a sign of bacteria leaking from the intestines.
- It will be a doubleblind placebo study. Meaning that neither the donor nor the pasient will know who will receive the specific kind of treatment.

Dr. Skevling presented the up-to-date information from «The Comeback Study». They are still in the clinical phase, so she will not present any conclusive results, just the background for this study and the development in the study, so far.

The theme of Dr. Skevling's lecture was: the research project Fecal microbiota transplantation - a doubleblind placebo study, which is an update from The Comeback Study».

Hypothesis:

- A: CFS/ME is caused by dysbiosis in the intestinal flora, something that causes a leakage of bacterial products, a low grade immune activation and disturbance in the energy metabolism of the host.

- B: Re-establishing a normal intestinal flora, using fecal microbiota transplantation (FMT) – also known as fecal transplant therapy – will diminish the symptoms and can possibly even induce a remssion of CFS/ME.

Microbiota:

- The occurence of prokaryotes (cateria) living on a surface, a lot of them in the colon. We call this intestinal microbiota.
- The microbiome is of great importance to our health as humans. It takes part in the process of breaking down and digesting food, et. al.

FMT in the case of irritable bowel syndrome:
The doctorate study by Johnsen. The study: 83 participants. Found that 65 % of the recipients of donor FMT experienced an effect as opposed to only 43 % in the placebo group. Improvement when it comes to abdominal pain. They also found an improvement when it comes to fatigue, even during abdominal pain.

Intestinal flora related to CFS/ME:
A project conducted in the USA where 49 patients and 39 healthy control persons. A reduced variety of intestinal bacteria and anti-inflammatory bacteria species and an increased occurence of pro-inflammatory bacteria.

The role of the intestinal microbiota and the virome:
We are all carrying a large quantity of viruses without getting sick, but a virus-induced inflammation kan increase the permeability in the epithelium of the bowel system.

Metabolites and energy metabolism:
35 patients and 25 control people. The conclusion; increased production of Short-chain fatty acids (SCFA) in the bowels of people suffering from ME, that can have a damaging effect on the energy metabolism of the host body.

Ailments having to do with the intestinal flora:
CFS/ME, Irritabel bowel syndrome, mental disorders, antibiotic resistance

The setup for the study in the comeback study – Randomizing and study population:
80 participants. 40 in each group. One group gets active treatment while the other one gets placebo. 40 control persons. Participants are divided into groups of four, where two gets placebo, one get a transplant from donor A and one get a transplant from donor B. The point of the randomizing is to achieve a random distribution of patients to different groups to achieve a random distribution of possible contributing factors. Preferably a heterogenous group, but mainly people with a mild to moderate illness.

→ **Recruiting participants to the study:**

The Facebook page - «The comeback study». The project has come in contact with quite a lot of people there. The plan is also to use local contacts in the health services, and the TV program «Helsekontrollen» (Health control) on the Norwegian TV-channel TV2. So far, 528 people have shown an interest, and it still possible to voice a personal interest to participate in the study.

Data collection: They gather samples of blood, urine and fecal matter before the administration of treatment and repeat the process with 3 and 12 months control. They will utilize neuro psychological work as a controller and map out any fatige symptoms; 1, 3, 6, 9 and 13 months after the treatment.

REDCap: electronic questionnaire: FSS, HADS, SF-36, Modified DePaul Questionnaire, AE, Intake of antibiotics, other medication and supplements, ME condition

Fatigue Severity Scale (FSS): A scale to group fatigue symtpoms on a scale from 1 to 7.

Neuro psychological test RBAN

→ Tests: attention span, verbal skills, immediate and postponed memory, concentration, visuospatial ability

End point

Primary: Reduction in individual FSS score compared with a baseline score.
Secondary: Improvement in FSS, life quality, RBANS, HADS, and the number of participants that experience side-effects.

An overview of the program:

- phone screening with info about disease history
- inclusion --> a vast program with possibility for breaks, between 2 to 3 hours
- intervention – set up for treatment
- 3 months control
- 12 months control

If the treatment have had an effect, the individual patient kan get an offer to receive an active treatment afterwards.

Donor selection

Young and healthy people between 16 and 30 years old. Tested before and after donating. Blood sample, fecal matter sample and urine sample. Mapping out a dysbiosis test, screening for MRSA and Covid 19. Five potential participants after having tested over 70 people.

Transplant and research biobank, preparation for treatment:

Production of the transplant – Cool it till it reaches 80 ° Celsius.
Establish a fecal lab in Harstad. Take sample and document the treatment. The collection makes it possible to study the composition both before and after the treatment? Is it resembling that of the donor?

→ **Preparation for treatment – FMT:** The bowel system has to be drained. Emptying the intestines and not eating. Will however be able to eat and drink freely after

the treatment. FMT - enema treatment.

Implementation FMT: Can be administered using different methods; through colonoscopy or enema, possible using freeze-dried capsules. Common side-effects from FMT are transient and self-limiting.

State of the study:

- 52 have been included, 11 more have been added to the list.
- Depending on what will happen when it comes to resources and the corona pandemic.
- The goal is to complete the clinical part by the end of 2022.

→ **Experiences so far:** The study is taking its toll on the participants, but it is doable. It is too early to say anything about the results, but there is agreement on finishing the study.

Timeline FMT Harstad: Begun with Johnsen's doctorate work. The fecal bank is delivering results for clinical use. This is part of several projects.

Research dissemination – Participated in a conference in London et. al. Received the research prize for 2019 from Helse Nord (The Public Health Enterprise for Northern Norway). It is important to continue with this work. There is a plan to increase the focus on clinical studies in the future.

Questions:

- A sudden change among ME patients, or are they hosts to an intestinal flora with an increased risk?
- Particular dietary advice? No definite answers, but it is probably best to make no changes. Keep on eating normally and have as varied a diet as possible.
- Why choose FSS to measure fatigue? Different question. It is hard to come up with a score board system that can document the symptoms the most accurate way possible. FSS was chosen because it is frequently used in international research.
- Examined in relation to C-section births? Haven't seen anything in regard to this subject matter.
- If this succeeds, how long will it take before this can become a way of treating ME? Possibly a larger multi center study to document the effect if this study is successful. This will take time.
- Shall they be tested for hormons as well? Initially, there are no plans to be testing for hormons, but different age groups will participate in the study.
- Will those that receive placebo also get an offer of treatment if the treatment is positive? Yes, they will get that offer.

- Is digital technology being used to test the flora? Yes.
- What about early treatment with antibiotics. Is it possible that this might have an effect on the intestinal flora? Yes, it might seem like use of antibiotics in an early age does play a role.
- What might be the reason that some ME patients gets better from using antibiotics for a longer period? Haven't achieved any knowledge in this regard.
- It might seem as giving individual patients FMT is not a lasting treatment, but that the process has to be repeated to establish a new intestinal flora. There's little knowledge in this regard.

Was it an abscence of good bacteria or an abundance of bad ones that was the problem? That is difficult to determine, but one can se a connection to the disturbances.

LINE MELBY
Senior researcher at Sintef, the Health department

ANNE KIELLAND
Resarcher at Fafo: «The Services and ME»

The researchers from Sintef and Fafo have started up a new social studies research project titled «Tjenesten og Meg» («The services and ME»). This project got grants from the Research Council through BEHOV-ME in 2017 . In the research project «Tjenesten og MEg» the researchers are studying the needs of ME pasients and their families, including the use of and experience with health- and welfare services. The research project has a Facebook page where updates can be followed: https://www.facebook.com/TjenestenogMEg

The main goal of the study is to find new knowledge in order to create good public services that corresponds to the actual needs of ME pasients and their next-of-kin.

The researchers are going to study the demographic and socioeconomic background of the ME pasients and their families, their encounters with public services such as education, the health services, the social services, including the occurrence of ME in Norway.

The project consists of 3 work packages, each one with their own sub-goals and methods. Work package 1 is a registration study, work package 2 consists of in-depth interviews, work package 3 consists of a survey (Respondent Driven Sampling - RDS)

In the ME-konferanse Stryn 2021, Line and Anne will present this project together. The researchers have gathered a lot of data from patients. They are working on several articles based on interviews with patients and their next-of-kin.

Line Melby's lecture is titled «Tenestetilbod og tenestebehov: Ein analyse av misforholdet mellom tenestene ME-pasientar får, og kva de treng» («The service apparatus and the serivce needs: An analysis of the mismatch between the services that ME patients receive, and what they acually need»:
Line lectured about the mismatch between needs and services:

- the services that are available to not match up with the needs of the patient
- «services» that primarily are meant to serve the needs of the system
- services that becomes available too late
- services that are needed, but do not exist

Implications of dissatisfaction and little contentment:
A low trust level and little hope can cause an increase in the dissatiscation with the services. Dissatisfied patients will typically be looking for alternative treatment and/or withdraw from the services that they are offered. The groups might feel marginalized in regards to the ordinary services, and in worst case, in regards to society as a whole.

Why does these mismatches between what the pasients and their next-of-kin need and what the services has on offer occur?
According to the informants this is because of:

- A major lack of knowledge in the services
- It is possible for someone to look well, even though the person is severely ill
- The health services (are experiencing that they) do not have anything to offer

Line gave some concrete examples of patients that were included in work package # 2, the in-depth interviews, and the mismatch between the services the patients receive and what they need. Here's 3 examples, regarding:

- **Getting help to be able to sleep:** « - And then I wondered whether I could get some help with my sleep disorder. It has been a major problem for all these years; not sleeping at night, to then sleep through the morning and noon. And their answers were:.. "Have you tried to get up earlier and go to bed earlier?", You see? These basic sleep hygienic advice. But I have already tried all that over and over again, and it does not work. (household # 4)

- **The school making adjustments: «-** They said that they had had some good result using a psycologist, a municipal psychologist [the municipality], that took

care of these things. So, they decided to bring him in. They used him for all minors, at school, no matter the case. Then he entered the frame and turned everything into an absolute chaos. He forces [the kid] to run and work-out, run around in the school yard and walk up and down the steps in the school and everything. [The kid] was supposed to be exposed to school and schoolday situations. That was the thought behind it (household # 18)»

- **A lack of understanding of needs:** «The Pain department at [Hospital], was asolutely awful. First of all, they were late, and for me it was like.... Just going outside and moving forward was a terrible experience. Every time I had to use a cab, I was lying in the back seat with an ice bag between my legs, because my legs where shaking from lactic acid and pain. So I never sat upright in a cab, and I was pushed in sitting in a wheel chair. And sitting and waiting; at that point I had sat there for fifty minutes... When they finally came to get me, I was in a very bad state. The first thing I asked for when I entered was to ask if I please could lie down, and then they only looked at each other and one of them said "I think you're probably able to sit upright" (household # 2)»

Conclusion

- Often patient satisfaction surveys are being used in work for improvement. Can this be supplied with «patient dissatisfaction surveys»? (according to Coyle and Williams, 1999)
- We have found out that ME patients and their families are worn out from having contact with the service apparatus, and that they want, most of all, to just be left alone.
- More people turn to alternative, undocumented treatment
- Is really no help at all going to be the best kind of help?
- A health service that can come closer to fullfilling the needs of the pasient group.

Anne Kielland presented some selected findings from the survey in the project. The subjects were; experiences with services such as rehabilitation, work try out programs and the Child Protective Services; to be seen and understood while receiving a service; and hope and optimism in a challenging day to day life. She briefly touched on prevalence across diagnose boundaries, based on the project's cooperation with Leonard Jason and DePaul University.

Anne presented the results from the quantitative work. The selection method have been working out very well in the pasient group. Group representativity (equilibrium selection) was achieved after onle 300 to 400 participants, while the recruitting continued until they had enough of a data foundation to be able to make som new

occurence estimates. The numbers backs up the findings in the qualitative interviews. Many pasients with the disease enjoy the social aspect related to rehabilitation and work try out programs, but the vast majority gets more ill from these measures.

Effect on the disease course:

The consequences from work try out programs were particularly severe. The participants in the survey were diagnosed on the basis of DePaul Symptom Questionnaire and the SF-36 algorithms for, among others, the Canada criteria. Here they found support for the theory that a lot of people with ME pasients have been ill for a long time without getting diagnosed, and that personal resources (measured by the individual's level of education) increases the possitiblity to get a G93.3 diagnosis.

It appears that how the patients themselves identify their own disease, is a stronger indication to whether or not they meet the Canada criteria, then the label that they have received from the health services. They conclude that a detected diagnose that was either late or flat out wrong probably have had a negative effect on a disease course, that registered data is an imprecise foundation to form occurrence estimates, and that the knowledge about their own disease that can be found among the patients seems to be of such a quality, that it would behoove the rest of society to start listening more closely to what they have to say.

Recruitment overview

Anne presented the survey (part 3 in the project) and showed an image of the recruitment overview in her presentation during the ME Conference Stryn. Here we add the text that they published on the Facebook page «Tjenesten og MEg» («The services and ME») together with an image av one of the four recrutiment overviews published on November 23rd 2020 – survey Part 3 in the study:

«Now that we have rounded off our RDS, that being the survey about the ecperiences with public services among people suffering from ME and similar fatigue diseases. It has been exiting to follow the recruitment process; at first things went slow, then it sped up considerably, untill it slowed down again.
All in all, we recieved 660 complete answers in this survey, using our chain recruitment method (Respondent-Driven Sampling). The goal with RDS is not that as many participants as possible are supposed to participate, but that us as researchers can be able to say anything, on statistical gorunds, about how representative our selection was considering our target group (people suffering from ME and other fatigue diseases).

This ME survey is, so far, the largest RDS that we her at Fafo have conducted, and we think that the data will give us a really good calculation foundation to come up with solid measurement methods in our further work on analysis.

Of the respondents that answered, the vast majority were either G93,3 (the specialist health services giving the ME diagnosis) or A04 (the general practitioners giving the ME diagnosis) or both. A minority had diagnoses like fibromyalgia, neurasthenia, and worn out and burnt out. It was important that we were able to include these as groups for comparison. We would like to say thank you to everyone that have responded!

ABOUT THE ILLUSTRATION:
Inclusion: As you have seen in earlier posts on this page, it is hard to show so-called «recruitment trees» for the RDS examinations. These kind of «trees» can show how the participants with different traits have recruited one and another. For example they can show whether women have recruited men, or whether people by and large recruit people belonging to the same gender.

A concern we ran into while using the chain recruitment among ME patients, was that we would quickly end up with used members of the ME patient organization recruiting each other. If this had been the case, we would not have gotten perspectives of the non-members.

In the tree in the illustration we have color-coded how members (red dots) and non-members (blue dots) of the ME patient organization have recruited one another. This tree (and the other trees as well) shows us that what actually happened was an active recruitement process across the two groups of members and non-members. We were happy about this discovery. While the «seed» (the first one rectruied) in this tree was a pretty active member in the ME patient organization, and this person recruited 4 other patient organization members, it was the case that non-members were recruited by members as early as the secound round of recruiting

I will also add a «tree» that shows the recruitment process per county in the comment thread below. We are very pleased with the distribution of recruited participants when it comes to this factor as well.

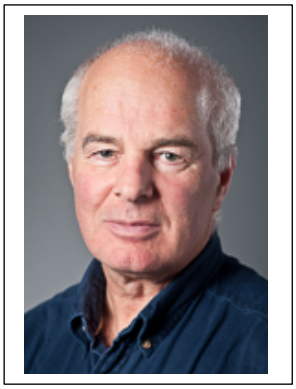
THE WORK FROM NOW ON:
The next step in our work with this data is to calculate different measures. In collaboration with Maddison and Leonard at the DePaul University we will analyze and code the data the participants have reported in the DSQ module of the survey, before vi continue the analysis work.» - [End quote] from Facebook November 23rd, 2020

→ The way forward for this work: The status by May, 2021: The process described about in the last section about the «recruitment tree» in regards «THE WORK FROM NOW ON», have now been done. They are currently writing on 4 different

articles. One about methods, diagnosing and prevalence, one about particular rehabilitation and work try out programs, one about health and one about the Norwegian Social Security system. Something will also be written in regards to minors, possible with a particular focus on the Norwegian Child Protective Services.

Follow the way forward for this project, through the Facebook page:
https://www.facebook.com/TjenestenogMEg

The evening lecturer:



OLA DIDRIK SAUGSTAD

Professor Emeritus in Pediatrics, Oslo University Hospital, ME researcher at the University of Oslo.

Saugstad has made several voluntary trips to visit those that have been hit by ME the hardest. He might be the one person in Norway who has seen the largest number of severly ill ME pasients. Saugstad has described this experience as shocking. The ME pasients er amongst the sickest among the sick. Many of them are bedridden in severe pain, and the sickest in this group is living in a state of semicomatose. Pain might not be the first thing that comes to mind when thinking about ME. What struck Saugstad while visiting the ME patients was the resemblance to pasients with encephalitis (inflammation of the brain). – The biggest betrayal done by the Norwegian health care services is the lack of curiousity in finding out the ins and outs regarding this disease, especially considering the severeness of the disease for a lot of the pasients in this group. A lot of Norwegian ME pasients have been treated poorly, says Saugstad.

Ola Didrik Saugstad have been working on the case of ME or over 20 years, and on the ME Conference Stryn 2021 he held the one lecture in the evening, titled: «Nytt lys på ME» - oppsummering av nokon av dei siste forskningsfunna («New light on ME – a summary of some of the latest research findings). In the beginning of the lecture, Saugstad said that after having listened to all the medical lectures, he felt more and more humble for being given the chance to sum up the research findings.

Saugstad elaborated parts of the background for why ME is such a controversial disease, and some of the bacground for the debate on whether ME is a psychosomatic or physical disease, and about how wrong the conclusion of that debate can get. The medical research improves with giant steps. There have been a large increase the last couple of years. It is not the case that researchers are being scared off from engaging in this field, as some people in the media are saying, quite the contrary.

<u>The Royal Free epidemic.</u>

«In the summer of 1955, 300 members of the staff at the five London hospitals of the Royal Free Group were struck by a new and unknown disease. It behaved like an outbreak of a severly infectious disease where the patients had symptoms stemming from the nervous system. It was not possible however, to find any infectious agent, like a virus or a bacteria, even though thorough examinations were employed. They even startet examing the water, milk and the food that had been consumed without

finding neither something that could trigger an infection nor toxins that could explain the state.

Several of the people that were affected ended up with long-lasting impairment for several years, and some never recovered. The hospital were closed for 3 months and the outbreak lasted from July to November, but the cause behind the disease were never found. The disease never found its way into textbooks. Because so many of the patients were experiencing strong pains in their muscles and there were symptoms stemming from the nervous system, the condition was labeled benign myalgic encephalomyelitis – ME.

15 years later, the two psychiatrists McEvedy and Beard reanalyzed these cases of illness. Without examining or contacting the patients in question, they came to the conclusion that: There was a small probability that the patients had had an organic disease that also were an infection. Their conclusion was that a likely explanation of this outbreak was what they called an epidemic hysteria, because *there were a higher occurence among women than men of a mismatch between the reported feeling of illness and the low fever the patient would typically have, all the examinations came out normal, the cause was unknown, the patients did not look ill, they did not receive treatment and there were no diagnostic tests.»*

This set off the debate on whether the condition was physiological or psychosomatic. The patients objected to McEvedy's and Beard's conclusion. But the psyciatristis McEvedy and Beard won the battle for the public opinion for the next 40 to 45 years.

In 1988 a similar epidemic broke out at Lake Tahoe in Nevada, and this was actually also labeled a pandemic. This condition was given the name Chronic Fatigue Syndrome. This time around, there were also a lot of researchers who labelled the whole phenomenon as hysteria.

Saugstad said that he could remember hearing about something called the Bamle illness while he was still a student, that resembled the one in Iceland. Later on, Saugstad has developed the theory that this was actually ME.

The psyciatristis were looking at the 15 outbreaks, particularly the one in London, and thought that the whole ting was «mass hysteria», that they then gave the name myalgic nevrosa.

<u>58 years later, on Boxing Day, December 2020, what acually had happended during «Roaly Free Disease» was published:</u>
Some female physicians, Rosemary Underhill and Rosemaria Baillod examined what happened during the «Royal Free Disease». They were medical students at the time

and did not have access to the hospital because of the epidemic and the fact that the hospital was on lock down, so they did not contract the disease themselves. They got in touch with the remaining survivors (who by that time had turned 75 to 80 years old). They found that some had made a complete recovery, but that a lot still were living with the disease. They showed that the conclusion of the two psychiatrists was completely wrong, and that they had even manipulated some of the data that had been available to them. Underhill and Baillod are saying that ME is an «organic disease».

Røysumtunet in Hadeland **– a future center for ME treatment?**
Røysumtunet have a goal to become a research- and competence center for ME patients. There are 12 bedspaces and it is possible to supply for treatment through one's personal general practitioner. This is an offer for severely ill ME patients. At the same time, it provides for ample opportunities to do some research.

The research includes:
1) to register basic physiological variables on all the committed patients (Steps, calorie consumption, sleep and sleeping pattern, pulse, heart rate variability)
2) to do randomized studies on new interventions, for example saline infusion, B-12, abilify
3) to collaborate with research groups from other countries, primarily in Sweden and Denmark

ME and Covid 19
Contact with Paul Cheney have been established. There have not been written that many research reports. Some of the reason might be that ME patients are isolated, but also because they have an activated immune system and thay they may be better equipped to endure Covid19, but we do not know this for sure yet. But because of the activated cell one can have complications from vaccines, it is still an additional strain for ME patients to get the vaccine. We do not know yet that more people will develop ME because of covid, but we do know that an increasing number of people developing ME wind up with a long-term illness.

The Swedish physician Svensson: both long term Covid-19 and ME is characterized by a significant drain of energy. It is an inflammatory condition. The thyroid gland might be playing a role.

Vaccines
FHI (The Norwegian Institute of Public Health) do not have any specific council for patients suffering from ME. The same is true for auto immune diseases. More producers have plans to conduct studies in different vulnerable patients groups. Paul

Cheney does not have a lot of experience with this either. Is it recommended for ME patients to get the Covid-19 vaccine? For now, there is not enough certain knowledge to have a definite answer to that question. Finally, it comes down to each individual person's choice, preferably after consulting with that person's general practitioner. There is just not enough data on this issue.

Interesting research results about covid and ME

- ME patients have a slightly weaker response to the endothelium function. (A study published in March: https://www.mekonferansestryn.no/post/ny-studie-viser-nedsatt-evne-til-regulering-av-blodomløpet-hos-pasienter-med-me-cfs)
- Ingrid Rekeland: A studiy presented earlier on the subject day, where Ingrid Rekeland and Øystein Fluge were talking about the study where they gave CucloME to 40 patients and had a 55 % response.. (You can read more about what was presented on this further into the report).
- 612 metabolites among 45 ME patients. 80 % of the metabolites had been weakened among ME patients. This implies that ME patients are reacting to exterior pressure.
- Does inflammation occur in the central nervous system among ME patients? Neuro inflammation is spread throughout the brain among patients with ME. Research have also shown that the lactate level among ME patients are too high. There is a lot of agreement that there's a wide-scale neuro innflammation in the brain of ME patients.
- A new study: 'ME: The human herpesvirus are back'. There have been some interesting findings, amongst others, a reduced memory response.
- After covid 19: There are some that thinks that the right treatment is cognitive behavioral therapy. Could not find any cognitive difference between those that went through cognitive behavioral therapy and those that were administered placebo.
- A fatigue study. A study were people that had had infectious mononucleosis and had experienced fatige were recruited. They are saying that there is no harm in cognitive behavioral therapy. Saugstad does not agree with this. The study has too many weaknesses. Those that received the treatment got worse. The authors still conclude that is is possible to run these kind of studies.

But, when are we going to get a functioning treatment ready? What about a biomarker? Saugstad thinks it will come, but that is highly uncertain when that will happen.

JØRGEN JELSTAD

Research journalist and author of the book «De Bortgjemte» («The Hidden Ones»)

The book «De bortgjemte» («The Hidden Ones») is a result of over two years work. After the book came out in 2011, Jelstad has written updates from the research field on his blogg www.debortgjemte.com. Throughout several years he has held lectures about this subject and participated in the public debate about ME. Jelstad has been following this field closely the last decade, and he is really up to date on the lates from the research field, domestically and internationally.

He's now working on a new book that will be published in the spring of 2021: "Våre liv, våre stemmer" ("Our lives, our voices"). This is an interview and photo book about ME and is a collaboration with Morten Borgersen, Fin Serck-Hanssen. Two of the initiators tied to the ME polyclinic at Sørlandet Hospital, Kim Fangen and Ole Rysstad, is involved in the project as well. Thousands of Norwegians are living with ME. In this book you get to meet them up close and personal; the pasients, their next-of-kin and the researchers that are working to come up with answers.

The theme that Jørgen Jelstad wants to talk about on the ME Conference Stryn 2021 is «ME – Utviklinga når det gjeld forsking, synet på ME, og økonomisk midlar til biomedisinsk forsking gjennom tiår» («ME – The development in regards to research, the general perception on ME, and economic funds for biomedical research throughout decades»)

Shows a graph with a curve showing how ill the ME patients are – the health condition curve

There is no doubt that ME is a disabling disease. It is a disease that have large consequences for each individual patient, their next of kin and society as a whole. SF-36 is a validated quality of life form, that several of the lecturers have touched upon. SF-36 have been an essential tool in the research on ME/CFS. SF-36 is a form that maps out the health related quality of life, and it is a standardized and validated instrument for measuring that is often used in health related research.

The patients are filling out the form themselves and set up a score for their experience about their own health through several questions divided up in eight sub categories. These eight categories are physical function ability, physical role, bodily pain, general health, vitality, social function ability, emotional role and mental health.

Compared with healthy, as well as other pasient groups, such as people with cancer, arthritis, depression ME patients have a lower health score (study from 2011). They have a low score on life functions and physical health. The starting point is to acknowledge that people suffering from ME are severely ill, and have not received the treatment that they deserve, neither in research nor in society in general.

Video clip of Jennifer Brea:
Brea is a former doctoral student at Harvard. She got ME and became severely ill. She almost got an Oscar nomination for a documentary and a lot of prizes. The point of the clip is Brea explaning how she got ill and how working with her documentary made her come in contact with ME patients across the entire world that have told her that they are struggling with the same problems as her: rejection of the disease and more. **«How can a disease that is that common and this destructive be forgotten by the medical world»**

➔ This question is essential! Jelstad wants to try to say something about this.

It is common that articles about ME patients are not taken seriously , or not even believed. Children and young persons that wants to participate in activities, but that can not are being asked to explain whether they are ill or not.

How have we gotten here?

- The intitial mistake with the name: It was a mistake that this disease was given the name chronic fatigue syndrome. It started in 1988. This is not a name that commands the right amount of attention and gravity. Would you like to say that you are suffering from it?
- We do not know for sure what it is and it affects more women than men. There is still some old and outdated conceptions about «the frail female psyche». That leads to making conclusions that go like this: «We couldn't find anything + It is a woman = psychosomatic.
- ME has therefore gone straight to the bottom of the disease hierarchy. A condition like ME will wind up in this place because of these two aforementioned reasons. There is a lack of research sources and knowledge. There is also stigma, trivializing and shame. This turns into a vicious cycle.

This is a simplification, but these are important reasons, and it takes time to turn around these kinds of phenomena. This pattern can be seen elsewhere as well, like

other diseases such as asthma and autism, where the view is that it is the patient and the next of kin that is the problem. This leads to a heated debate in society at large. Some have been talking about this illnes as if it is a fashionable disease, hysteria, imagined suffering and the like. It is important to stress that none of these statements are backed up by any research whatsoever! On the contrary, we know that it is a severe disease rooted in a biological mechanism. But this also affects the research community and how the health service treats the ME patients.

Follow the money! - meaning the research money. The numbers on what research funds that the American research institute have granted on this particular disease have been retrieved. MS gets close to a billion Norwegian kroner every year, while ME gets very little. One single year of research on MS is the monetary equivalent of over 20 years of research on ME. There are consequences from this in the research literature. Since 1990 there have been an explosive development in the research field regarding a lot of diseases, while there have barely been any research on ME. There are a couple of hundred studies every year on ME while there are 5000 research articles on MS every year. **A lot of luck is needed to crack the puzzle of the ME disease with this little research going on**. A lot can improve, but luckily, there are some improvements happening.

Media coverage with illustrations that does not give a correct portrayal of ME, is one phenomenon that says a lot about the perceptions on ME. These will typically be illustrations of people that are tired or burnt out at work.

Parts of the disagreement in the research environment is about who the ME patients actually are.

The diagnostic criteria from the National Academy of Medicine.

- A considerably weakend ability to function. Severe and newly emerged fatigue that does not improve after having rested.
- The disease getting worse after activity.
- Sleep disorder
- Either an impaired cognitive function or an orthostatic intolerance.

The diagnosis also depends and how often the symptoms occure and how severe they are.

One issue is that quite a few have disregarded all of these factors and simply say that what constitutes ME is simply a newly emerged fatigue.

Diagnostical criteria – the battle lines:
Someone thinks that ME is to be diagnosed on a broad basis while others will use very narrow criteria. The more narrow/stricter criteria are being used by those that think of ME as a biological disease: According to these criteria, 0,2 % of the population have ME (2 to 4 per 1000 citizens). A broader set of criteria is being used by those that think ME is a biopsychosocial disorder, and based on this set of criteria 2,5 % have ME (25 per 1000 citizens).

How many actually have ME? Jørgen Jelstad showed how significant the difference between the two schools of thought becomes in a small municipality like Stryn with around 7000 citizens. If you define ME as a biological disease, then 0,2 percent of the citizens in this municipality is about 14 patients. A biopsychosocial model of understanding that includes 2,5 percent of the citizens translates into 175 patients. Obviously, what school of thought one abides by will affect what kind of group one selects for research. This will make the different research results differ. These are some of the battle lines between the research groups.

What have happened the last years and why are we acually approaching better times?

The report from the Institute of Medicine:
The major breakthrough came with the report that the Institute of Medicine released in February 2015. The backgroud for this report is 15 researchers looking at 9 000 articles / research reports on the subject, and then coming to the conclusion that ME/CFS is a severe, physical, chronic disease, and a a complex multiple disease that is severly impairing the body's functions. ME/CFS is a physical disease that attacks several of the body's systems. The report clearly stated that misconceptions about this disease constituted a major strain for the ME patients.

What does the research tell us?
* ME/CFS is often triggered by an infection.
* Deviations in the immune system, central nervous system and the circulatory system.
* Impaired cognitive function – memory and focus.
* More women than men (about 70 %).

Link to the report from the Institute of Medicine can be found here:
https://pubmed.ncbi.nlm.nih.gov/25695122/

The report came to the conclusion that a stronger set of criteria is needed.
The report lead to a couple of changes. Francis Collins went public and said that the research community need to get a whole lot better when it comes to this issue. 300

million Norwegian kroner were made available. These funds were granted to three different research centers in the USA:

- one in Columbia, : https://www.mekonferansestryn.no/post/me-senter-nr-1-virusjeger-immunekspert-og-sjarmen-med-tarmen
- one in the Jackson laboratory, : https://www.mekonferansestryn.no/post/me-senter-nr-2-betennelse-i-hjernen-og-samtaler-mellom-celler
- one in Cornell University. : https://www.mekonferansestryn.no/post/me-senter-nr-3-betennelser-t-celler-og-pasienten-har-alltid-rett

A lot of their research work will focus on the immune system and inflammation functions. Ronald Davis; one of the world's most prominent researchers on genetics. He has a son that is severely impaired by ME. Davis have been getting in touch with several contacts, with the goal to initiate more research on ME.

ME is now being mentioned, in a whole different scope, in essential research journals. Earlier, articles on this issue, like the ones we have seen the last five to six years, simply were neither written nor published. However, there are still prominent voices in the public debate about this issue in Norway that claim that the dominant global view on this disease is pointing to psychological causes. This is not true!

Covid 19

It appears as though quite a few of patients with Covid-19 are sufferening from the after-effects, a long time after contracting the disease. There has been quite a few cases on Long COVID. Why does this matter in regards to ME? We do not really know this quite yet, but this is also an example of a longterm disease after infections. From the ME field, this is already well known. There is not a lof of certain knowledge on this issue, but we do know that a lot of patients with Covid-19 became severely ill after an infection without recovering. After a couple of infections some studies show that from 10 to 15 percent of the cases fit the criteria for ME, six months later. After two years, this percentage drops to below five percent. A lot of patients are suffering for a long time, but the majority do recover or have their condition improve within a couple of years. Even so, a significant number of these patients do not recover. A study on SARS shows that 27 % of SARS patients checks out when it comes to the criteria for ME, 4 years after getting this acute illness.

A lack of knowledge! There is little knowledge on the impact from Covid-19 on ME. But the pandemic have shone a light on ME! There is now a significant group of people that are struggling with after-effects. This will make this issue impossible to ignore. If we envision that 5 to 10 percent will suffer with the after-effects from Covid, than this, clearly, will constitute a gigantic problem.

All of this is starting to change to debate in regards to ME. The history of ME is now being used as a horrible warning on how one is not supposed to treat patients. It is essential that the voices of these people are being heard, and that these new groups of patients do not have to go through what the former batches of ME patients had to go through. All of this have lead to concrete results, for example 10 times the funding going to research on Long Covid than what has ever been granted on research on ME. But this research will also be of benefit to the research on ME. A lot of things have happened over the past five years, and we are now at a turning point. We are almost certainly entering a time periode that will be decisive in the development of research on ME.

All patient groups, regardless of their disease, deserves to be properly treated by the health service system. Jelstad firmly believes that when it comes to this issue, things will actually improve and get to where they need to be, eventually.

Contribution to this report:
In addition to the Skrede family, we have, among others, been getting aid from Kristin Hatledal.
Translation from Norwegian to English by Anders Hamre Sveen.