Things Have Never Looked Brighter For M.E.

When it comes to finding the causes, treatment and cure for ME/CFS things have never looked brighter or more encouraging. There are several reasons for optimism.

In the last ten years more than 2,750 biomedical research papers have been published on ME (for references see "Beyond ME" 2015). This research provides irrefutable evidence that ME is a biomedical disease and further, provides strong evidence that ME is an autoimmune disease

To take just one example. In March 2015 the Centre for Infection and Immunity at Columbia University published a paper entitled "Unequivocal evidence of immunological dysfunction in ME/CFS has now been found". It was a sound and robust science based study.

That's great but, the immune system is a fiendishly complex and tracing the root causes of its dysfunctions including, finding out how, when and where it went wrong and how to fix it was until recently, a very difficult problem.

New Tools and Technology

There have also been important developments in technology that opens up new research possibilities. Autoimmune diseases are caused by dysfunctions in the immune system. This applies to ME but it also accounts for more than 80 other diseases such as: rheumatoid arthritis (http://1.usa.gov/28MWpi9), inflammatory bowel disease (http://1.usa.gov/28Npuu2) and type 1 diabetes (http://1.usa.gov/28OkpGN). Solving the ME problem could well lead to a solution for other autoimmune diseases.

At the Human Immune Monitoring Centre (HIMC) at Stanford. Director **Mark Davis** and his team have installed two CyTOF mass spectrometers. With these machines they can detect 1,000 immune cells per second, with 40 different components per cell. That's 2.4 million data points per minute.

That's a lot of data and analyses' but to make the job faster and easier they will be applying the techniques used in the Human Genome Project.

Initially it took 20 **years** to analyse the genetic make-up of a **single individual**, now the job can be done in twenty **hours** or less.

Dr José Montoya a familiar name in ME circles, runs an ME clinic at Stanford. He has asked the immune monitoring centre to look for meaningful patterns in 600 blood samples taken from both ME patients and healthy individuals. The aim is to quantify the normal range of immune components and to understand the relationships between the biochemical processes that drive the immune system in ME patients. It is estimated that this research will take about a year.

The Individual's Complete Viral History from a Single Drop of Blood.

It has long been thought that the trigger for ME was a viral infection but efforts to find that virus have so far failed. Going through an individual's viral history one virus a time is slow going and efforts to find that virus have so far failed.

However, **Steven Elledge** of Harvard Medical Hospital has now developed a breakthrough called "Viroscan". With Viroscan, from a single drop of blood the individual's complete viral history can be identified. **Steve Elledge** and his team are now applying this technology to the viral history of ME patients and hopefully, within a year or more they should have the results

This is all great stuff but and there's lots more. A review article claimed that since the 1930's there have been some 9,000 biomedical research papers published on ME. I can't vouch for that, but I can vouch that there have been over 2,750 published in the last ten years. I counted them!

But where are the follow-up studies? Where are the clinical trials putting all those research findings into treatments and cures?

In all 2,750 papers I could find only one **clinica**l research paper, the Rituximab study carried out in Norway by **Drs Fluge** and **Mella**. In a study involving 30 patients they achieved remission rates of 64% lasting for five years. Now they are carrying out a second study at five separate sites involving a total of 150 ME patients. This is due for completion in 2017. These studies came about by chance. In 2003. They were treating a patient with Rituximab for cancer. She also happened to have ME. To their surprise the Rituximab cured the ME and they were smart enough to follow it up. But, can we rely on chance events to find a cure for ME or do we need to plan?

The Norwegian government gave two million kroner, that's around £200,000 to fund the study with additional funding from the Norwegian ME patients' association. The next stage of the trials (Phase III) will involve around a thousand patients and cost millions. So where will all that money come from?

Time is of the Essence.

In July 2015 an article on the Norwegian Rituximab study by **Cort Johnson** appeared in Simmeron research.com. It examined the likely time-line for the use of Rituximab for treating America ME/CSF patients.

He pointed out that nothing was likely to happen in the U.S. until the Norwegian trials were completed in mid-2017. If the results are impressive and published in 2018, then America could get its own Rituximab trial started in 2019. Assume those results are in by mid-2020 and published in mid-2021. The data is then examined by the Federal Drugs Agency and early in 2022, it approves Rituximab for use with a subset of ME/CFS patients. Altogether, the process as presently planned is likely to take seven years.

An analysis of the time-line of the UK's ME/CFS Rituximab trial produces similar findings. A trial involving 30 ME patients is due to start at UCHL in the UK early in 2016. If the results are good and are published by 2019 a larger scale trial involving say 150 to 200 ME/CFS patients could be started in 2020 and completed and published by 2023 – eight years from now. But only if the money is available. The current 30 patient trial is costing almost £500,000, raised entirely from donations. At that rate a larger scale phase III trial would cost at least £2.5 million, an unrealistic amount to raise by donations from ME patients.

Seven years may not be long in the career of a biomedical researcher but, for a severely disabled ME patient, seven years is a life-time.

My son **Robert** got ME, at the age of 30, he is now 37. Over that time, he has been mainly house and bed bound 24/7. He is a typical case. When he was younger he was a good footballer, an all-round active sports man and a good musician. He's bright, speaks fluent French and did his University degree in France. His brother, an ex-senior engineer with the BBC has a degree in electronics and telecoms and now runs his own telecoms business. Who knows what **Rob** might have achieved?

It is argued that drug trials take a long time due to the need to test the safety and effectiveness of the drugs and its thought that not much can be done about that, but I disagree.

Reviewing the Norwegian and UK trials it can be seen that, around fifty per cent of the time is taken up by other things– collating, analysing and publishing the results, raising the funds for the larger scale trials needed and organising those trials.

Failing to plan ahead is the same thing as planning to fail. That applies as much too clinical drug trials and treatment in ME as too anything else.

Money and Resources for the Treatment and Cure of ME.

How many people have ME? In other words, what is the prevalence of ME and can you prove it? This may seem to be an academic question but it's not.

Being able to prove that ME is a **rare** disease, defined in the USA as a disease affecting 200,000 or fewer people or in the European Union and elsewhere as fewer than 5 in 10,000 (0.5%) of the population could open up substantial money and other resources for drug trials and clinical research and treatment in ME.

Can you help?

I am searching hard for any reliable information or evidence as to the prevalence of Myalgic Encephalomyelitis (**Not CFS or CFS/ME**). I will be grateful for any information that anyone can provide. Finding out how many people have M.E. could make all the difference to finding an effective treatment for the disease.

Table 1 attached shows estimates of the prevalence of ME obtained from national ME groups and associations and is generally around 0.3%. As far as possible we need to be able to verify this. There are an estimated 7,000 rare diseases and finding out how many people suffer from any given rare disease is never easy. They are just not studied. M.E. is better off than most rare diseases in this respect.

In the online literature, I found a **meta-analysis of 216 papers** on the prevalence of CFS/ME carried at Griffith University, Queensland, Australia. They found subjective assessments to be very unreliable but from clinical assessments they found an overall prevalence of 0.76 ranging from 0.42 to 1.41. It should be noted that these figures are likely to be inflated by the pairing of ME with Chronic Fatigue Syndrome. (CFS)

This was a rigorous statistical study and they eliminated all except 13 of the 216 papers, including those using only subjective assessment as being unreliable and also those that failed to use the 1994 Centre for Disease Control definition for ME.

The latter highlights a major problem for earlier prevalence studies. The diagnostic criteria defining ME have been considerably refined and developed in the more than 20 years since 1994, as shown for example in the 2012 International Consensus Criteria. See my article on the International Consensus Criteria.

It is difficult to obtain prevalence figures for CFS alone but it was estimated by the US Centre for Disease Control to be 2.56%.

Another study looked at the prevalence of ME/CFS in three different regions of England. It involved 143,000 individuals aged 18 to 64 and was a repeated cross-sectional study carried out in primary medical care. (BMC Journal Medicine July 2011) The prevalence for cases meeting the CDC-1994 case definition for ME was 0.19%, for cases meeting the 2004 Canadian ME definition it was 0.11%. It should be noted that this study omitted all UK paediatric cases of ME, and also the 25% of severely disabled UK ME patients that can't get to see a primary care doctor, nor in most cases does the doctor visit them.

Statistics are so boring.

For many people statistics are boring. But the figures on the prevalence of ME are crucially important. They will make it possible to register ME as a rare disease with the Orphan Drugs Act. This will then enable it to enlist professional help from pharmaceutical companies in carrying out clinical trials aimed at finding effective treatments and cures for the both the disease itself and its sub-diseases.

It offers the best prospect we have for cutting years of the suffering that ME patients endure. There are separate Orphan Drug Acts in different countries. For details of how they work see my paper on "The Orphan Drugs Act, Clinical Research on Myalgic Encephalomyelitis". This is written in non- technical language specifically for ME patients and their supporters.

Contrary to predictions the Orphan Drugs Acts have been such a phenomenal success that a number of other countries, e.g. the EU, Australia, Japan, South Korea, Taiwan, etc., have all enacted their own Orphan Drug Acts. By 2012 the US market for Orphan drugs was worth **$637 million dollars** and growing at the rate of 25.8 % compound per annum. In the USA by 2015 there had been 1,798 applications for Orphan Disease status 1,234 of these were successful.

The good thing is that patients and their supporters can apply to be registered in any one of the several Orphan Drug Acts in different countries **at the same time**. This has a number of positive consequences:

- If M.E. is accepted for registration as a rare disease in one country this should makes it more likely that it will be accepted for registration in another.

- M.E. is an umbrella term covering a number of phenotypes or sub-diseases. If more than one pharmaceutical company is working on M.E., then one can be working on one sub-disease whilst a second is working on another. I propose that ME patients be given the opportunity to suggest which sub-disease pharmaceutical companies should prioritise. See my paper on the 2012 "International Consensus Criteria for ME". for a listing of sub-diseases

This is best chance we will have for years to establish clinical trials and find a cure for ME. So come on friends and supporters of M.E... Let's work together, form an action group and get going. As I keep saying, "time is of the essence".

Table 1, Prevalence of ME Globally.

Country	Population (m)	ME Prevalence	% ME	Comments
EU	508	1.524,000	0.3	
Australia	23	75,000	0.328	
Belgium	11.3	33,000	0.3	
Denmark	5.6	10-20,000	0.2-0.4	
France	66	250,000	0.1-0.3	
Germany	81	300,000	0.37	
Italy	60	?	?	
Ireland	4.58	?	0.4	
Netherlands	16.9	30-40,000	0.2-0.4	
Spain	46,4	120-200,000	0,3- 05	
Sweden	9.7	40,000	0.024	
UK	64.7	250,000	0.026	
EU	508	?	0.3	5 in 10,000 rare disease criteria
USA	308	836,000 and 2.5m from ME/CFS	?	200,000 rare disease criteria
Japan	127.3	?	?	180.000 rare disease criteria