Watching the detectives: tracking the source of Europe's latest *E coli* outbreak

David Payne examines the response to the recent deadly outbreak of *E coli* in Germany

"It was like a crime thriller where you have to find the bad guy," said Helmut Tschiersky-Schoeneburg, head of Germany's consumer protection agency after hearing the likely source of the country's *Escherichia coli* outbreak.

Last week the death toll rose to 39 as the outbreak, linked to contaminated bean sprouts from an organic farm in the northern state of Lower Saxony, claimed its first child—a 2 year old boy.

By then 3235 people had been infected with the 0104 strain, most of them in Germany. More than 780 people have developed haemolytic uraemic syndrome (HUS), which can lead to kidney failure. Unusually, most of the cases are in adults aged between 16 and 60. Those most at risk of developing HUS are normally the under 5s and over 60s.

On the trail

The number of cases has been much lower since 10 June, when bean sprouts were identified as the likely cause after three case-control studies by Berlin's Robert Koch Institute, the federal body responsible for disease control and prevention in Germany. The breakthrough was the institute's "restaurant recipe cohort study" of five groups of diners (112 in total), including 19 with enterohaemorrhagic *E coli* (EHEC) infection who had dined at the same place.

Each was asked what they had eaten. Kitchen staff were questioned. One group, a travel club, had taken pictures. Some showed the dishes they had ordered.

Customers who had eaten bean sprouts (perhaps unknowingly) had an 8.6-fold increased risk (95% confidence interval 1.5 to 8) of EHEC/HUS illness compared with those who did not. All of the ill people had eaten bean sprouts.

David Risling, Associated Press's Berlin correspondent, hailed the breakthrough as "simple detective work trumping science after a month of searching and testing thousands of vegetables."

It was this last study[1] that finally gave the all clear to Spanish cucumbers, salad, and tomatoes, which had been originally identified by the Lower Saxony state agriculture department as the source of the outbreak.

The alarm was first sounded on 19 May, when Hamburg's chief medical officer asked the Koch Institute to investigate three cases in children.

As other cases emerged in north Germany over the next 24 hours the investigation team conducted a preliminary epidemiological assessment, followed by more detailed case-control studies, to explain the growing number of cases.

Epidemiological analysis showed that those affected consumed raw tomatoes, cucumbers, and lettuce significantly more often than healthy study participants.

Gérard Krause, one of the institute's investigators, said: "There were a number of things that were unusual. It wasn't a paediatric outbreak at all. There turned out to be a lot of adult female cases, and they were rather well educated, very food conscious people.

"It gave us a very good idea of what people had eaten. There were the usual suspects—milk, meat, bean sprouts, but we concluded it was most likely to be raw vegetable products, although we couldn't at that stage narrow it down."

In the UK, the epidemiological investigation was overseen by the Health Protection Agency. Dilys Morgan, the agency's head of gastrointestinal, zoonotic, and emerging infections, said: "The first thing that hit us was the European early warning response system alert sent out on Sunday 22 May, saying there had been 30 cases of HUS in Germany.

"We didn't believe it, to start with. Had they got it right? To get 30 with many adult females is exceptional. We tried to contact the Koch Institute to tell them we were also having an [unrelated] VTEC (verotoxin producing) outbreak in the UK, but we didn't hear from them, presumably because they were so busy. They were in an unenviable position."

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Gérard Krause talks about the outbreak in a *BMJ* podcast

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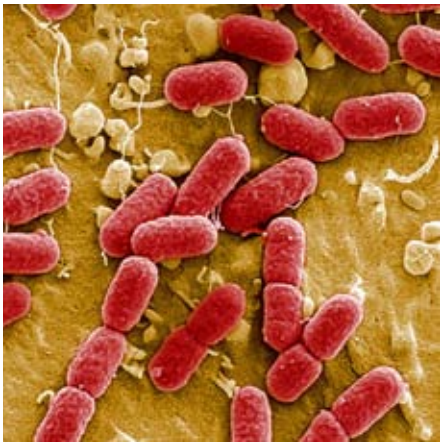
News: Bean sprouts are identified as cause of *E coli* outbreak (*BMJ* 2011;342:d3737)

News: European *E coli* outbreak claims further victims (*BMJ* 2011;342:d3610)

News: Cause of outbreak of *E coli* in Germany is still uncertain (*BMJ* 2011;342:d3454)

News: Outbreak of *E coli* in Germany is linked to cucumbers from Spain (*BMJ* 2011;342:d3394)

***Escherichia coli* 0104; Gérard Krause of the Robert Koch Institute, Berlin; unwanted cucumbers in western France; Karolin Seinsche, an *E coli* patient in hospital in Hamburg, 6 June 2011, the organic farm in Lower Saxony, growers of the contaminated bean sprouts; Hugh Pennington, University of Aberdeen**



JACQUES BRINON/AP/PA

Communication problems

On Tuesday 24 May the BBC reported 80 cases of EHEC ingestion in Germany in advance of a European alert confirming this figure and stating that the likely foodborne source was unknown.

Did the country's federal structure slow down the risk communication process? Germany's mass market *Bild* newspaper described "chaos on killer germs." Its competitor, *Der Spiegel*, asked why Germany lacks the early warning systems of other developed countries such as Japan and the US.[2]

Hugh Pennington, emeritus professor of bacteriology at the University of Aberdeen, who led inquiries into the 1996 *E coli* 0157 outbreak in Lanarkshire, Scotland, and the 2005 outbreak in south Wales, thinks the federal structure may have contributed.

He said: "How quick were they to identify this outbreak? Did their local and federal system work?

"In Germany, they have had a lot of STEC [shigatoxinogenic *E coli*] cases over the years, but I wonder if they were taken by surprise? Their systems are working well now, but were they well oiled enough at the beginning?"

Professor Pennington also questions Germany's focus on HUS. Had the communication also asked people if they had experienced bloody diarrhoea, there might have been more notifications earlier, he said.

Echoing the conclusions drawn in a recent *Lancet* editorial that described communication as "haphazard at best, dismal at worst,"[3] he added: "I think the Germans do have something to learn about communication. There were lots of government messages going out.

"In Hamburg there was the agricultural minister for Lower Saxony. Another agricultural minister in the east talked about cucumbers in a rubbish dump.

"In the UK we usually have a single well briefed authoritative person, someone the public can trust, not lots of different voices," he said.

However even this can go awry, he said, as happened with swine flu. "England ran into some problems when the chief medical officer described a worst case scenario of 50 000 cases by tea time."

The US Centers for Disease Control, he believes, did a better job as the lead agency by choosing its assistant surgeon general Anne Schuchat.

"When she wanted to make an important point, she'd wear a vice admiral's uniform. She did a lot of press conferences, and if she didn't know the answer she'd say so."

Dr Krause defends Germany's approach, which was to release regular joint statements from the Koch Institute, the Federal Office of Consumer Protection and Food Safety (BVL), and the Federal Institute for Risk Assessment (BFE).

He said: "In any large government structure there is a subdivision of duties and mandates, even in centralised countries. There are hierarchies and structures. We have two dimensions of separation and duties.

"I'm not sure that having one authoritative person would simply make things better. Different specialties have different things to communicate. A chief medical officer may be too authoritative.

"If official agencies communicate in a conservative way it creates a media vacuum which is quickly filled by a doctor with too much time or too little information on his hands."

Dr Krause points to the inevitable delays in identifying cases to the local health department. "Cases of HUS are notifiable, and this should happen within 24 hours. But patients don't see their physician straightaway, and the physician doesn't get a microbiological test done straightaway. So yes there are delays."

In an ideal world, there would be a central database and a more automated notification process: "For example, the local health department could see names and have access to the dataset. But the public health people would have limited access, without names and addresses.

"I worked in the US for a number of years. They invested millions of dollars in a system. They still do not have it working. Perhaps some smaller countries that do not have such a sensitive history of data confidentiality could have such a system."

Nevertheless, Dr Morgan commends the Koch Institute for releasing the first case-control study, which identified lettuce, tomato, and cucumbers as possible causes, within days of the first cases coming to light. It involved a team of 15 interviewers working in the areas where people then in intensive care lived. "To get a case-control study done so quickly is pretty impressive," she said.

Professor Pennington defends the scientific process of building up the crucial evidence.

"With the Lanarkshire and South Wales public inquiries we looked in great detail at how the public health people had done their detective work. We were lucky in Scotland because there was a jug of leftover gravy.

"You have a nasty bug, you need to find the source and cut it off. Speed is of the essence, and the German authorities did manage to rule out meat very early on because they had appropriate controls. The cucumbers did have a virulent *E coli* on them, so it was quite a reasonable assumption to make.

"People were eating the bean sprouts without being aware of it. They needed to do the more detailed study, looking at menus, what people had bought, photos of the food. And of course when they did that, lo and behold, everything became clearer."

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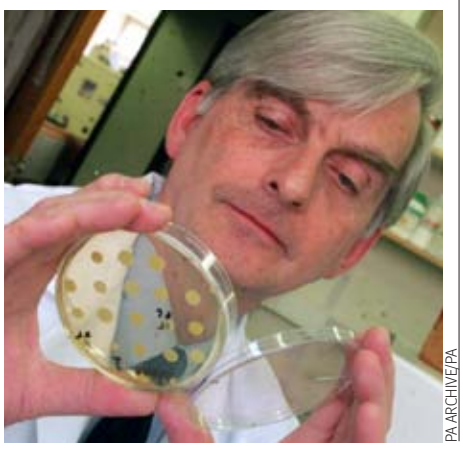
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- News: Science asks researchers to withdraw paper on chronic fatigue syndrome and infectious retrovirus (*BMJ* 2011;342:d3505)
- News: Chronic fatigue syndrome is not caused by XMRV virus, study shows (*BMJ* 2010;341:c7358)
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The dangers of research into CFS/ME

Nigel Hawkes reports how threats to researchers from activists in the CFS/ME community are stifling research into the condition, Ollie Cornes shares his frustrations from a patient perspective, and Trish Groves considers the unanswered research questions

There are jobs that carry a risk, such as volunteering as a human cannon ball at a funfair. There are jobs that attract opprobrium and abuse, such as becoming an estate agent, driving a white van, or selling double glazing over the telephone. And then there is the job of trying to conduct research into chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).

CFS/ME is a common condition, and very debilitating. The evidence suggests a population prevalence of at least 0.2-0.4% in the UK.[1] Patients are incapacitated for years, unable to move, sometimes bed ridden and fed through a tube. Yet it doesn't prevent some people, who claim to be its victims, from conducting a relentless personalised attack on doctors and academics who are trying to discover its cause and improve its treatment.

Simon Wessely, professor of epidemiological and liaison psychiatry at King's College School of Medicine in London, has been the target of such attacks for years. He's been compared on the internet to Josef Mengele, the Nazi doctor who performed experiments on inmates of concentration camps. He's had threats against his life, been accused of throwing a boy into a swimming pool to check if his paralysis was genuine, been bombarded with offensive emails, and had complaints against him made to his employers and to the General Medical Council.

The campaign has gained new life since the publication in March in the *Lancet* of the PACE trial, a comparison of four treatments for CFS that concluded, to the fury of the campaigners, that cognitive behavioural therapy and graded exercise therapy can be effective. Pacing, a treatment favoured by leading ME charities, was found to be ineffective.[2]

"The paradox is that the campaigners want more research into CFS but if they don't like the science they campaign to stop it"

The publication prompted a 442 page response to the Medical Research Council (MRC), which part funded the trial, and a shorter 43 page rebuttal to the *Lancet*. Both were written by Malcolm Hooper, emeritus professor of medicinal chemistry at the University of Sunderland, who branded the trial "unethical and unscientific." He wrote: "Entry criteria were used that have no credibility; definitions and outcome measures were changed repeatedly; data appears to have been manipulated, obfuscated, or not presented at all (so it cannot be checked) and the authors' interpretation of their published data as 'moderate' success is unsustainable."

Both the MRC and the *Lancet* have considered the submission and rejected it, the *Lancet* commenting that the volume of critical letters it received about the PACE trial smacked of an active campaign to discredit the research.[3] Frances Rawle, head of corporate governance and policy at the MRC, who spent several days reading the 442 page rebuttal, says it "made many accusations of bias." She adds: "I responded and two weeks later got another list of questions."

Personal attacks

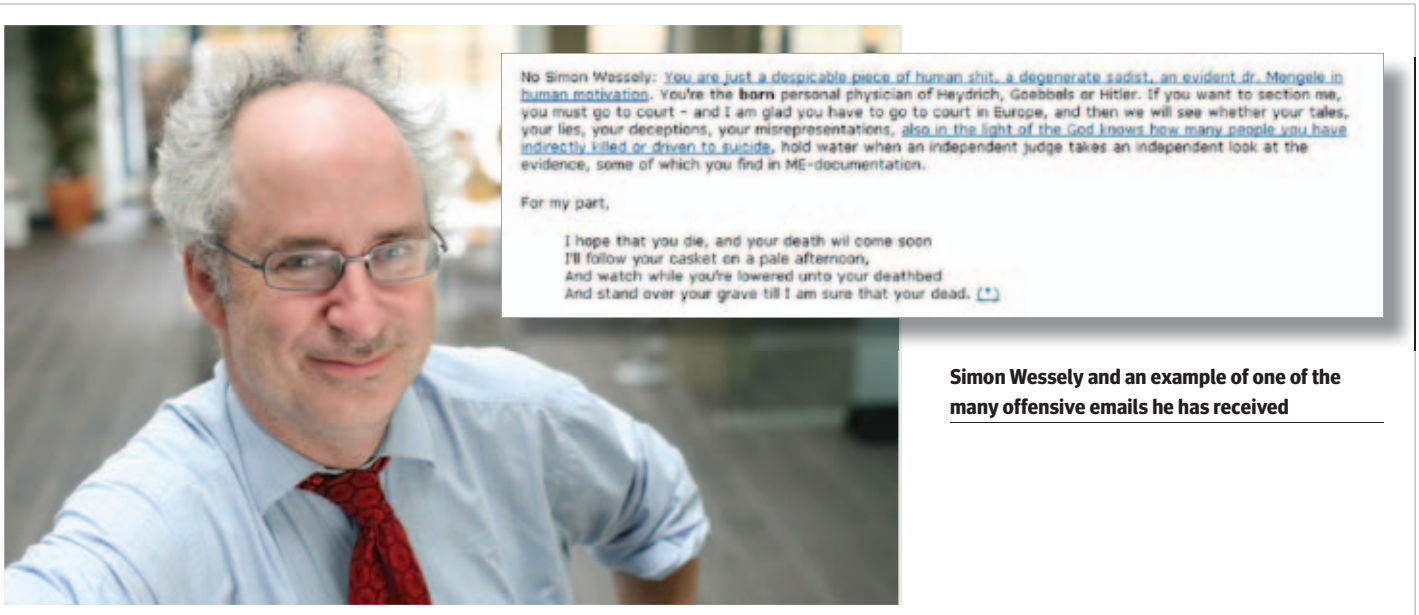
Asking detailed questions about an important trial is a legitimate and proper activity, though questioning academics' integrity and honesty is not normally part of the process. But far more unpleasant are the activities of a group of activists who have resorted to threats and personal abuse.

"It is a relentless, vicious, vile campaign designed to hurt and intimidate," Professor Wessely says. "For some years now all my mail has been x rayed. I have speed dial phones and panic buttons at police request and receive a regular briefing on my safety and specific threats.

"Since PACE was published this has become more intense, and at present the police are looking into two cases in which specific threats have been made to my physical safety. These people are sulphurous, vicious, horrible."

Professor Wessely is not alone. All of those who approach CFS/ME from a psychiatric perspective are the targets of critics who believe the disease has a physical cause that would have been discovered by now if the debate, and the research money, had not been cornered by what they see as a conspiracy of psychiatrists, characterised by them as "the Wessely school."

This point of view, if not the actions it inspires, is defended by Charles Shepherd,



Simon Wessely and an example of one of the many offensive emails he has received

medical adviser to and trustee of the ME Association. "The anger and frustration patients have that funding has been almost totally focused on the psychiatric side is very justifiable," he says. "But the way a very tiny element goes about protesting about it is not acceptable.

"It's not representative of the patients as a whole. It's a very very tiny minority—50 to 100 people, maybe. What they do is not pleasant and totally unacceptable."

Dr Shepherd has good reason to know, as he has been the target of attacks. One website claimed he had a psychotic illness, was physically violent, and "a medical failure." He consulted the police. More recently his scepticism about the claim that CFS/ME is caused by the retrovirus XMRV has exposed him to further attacks.

The personalised nature of the campaign has much in common with that of animal rights activists, who subjected many scientists to abuse and intimidation in the 1990s. The attitude at the time was that the less said about the threats the better. Giving them publicity would only encourage more. Scientists for the most part kept silent and journalists desisted from writing about the subject, partly because they feared anything they wrote would make the situation worse. Some journalists have also been discouraged from writing about CFS/ME, such is the unpleasant atmosphere it engenders.

While the campaigners have stopped short of the violent activities of the animal rights groups, they have another weapon in their armoury—reporting doctors to the GMC. Willie Hamilton, an academic general practitioner and professor of primary care diagnostics at Peninsula Medical School in Exeter, served on the panel assembled by the National Institute for Health and Clinical Excellence (NICE) to formulate treatment advice for CFS/ME.

"Our report, based on a solid review of the evidence, was that graded exercise and cognitive behavioural therapy were the best, indeed only, treatments. This position was resisted vociferously by the patient representatives on the committee, using a very strange mixture of quasi-scientific arguments—"the trials were biased"—and utterly unscientific claptrap.

"Actually, it was a visceral fight not to allow graded exercise and cognitive behavioural therapy to be approved by NICE. Why? To this day I don't know."

The NICE guidance was taken to judicial review, its opponents claiming that the experts were biased or had conflicts of interest. The case was dismissed, the judge, Mr Justice Simon, warning that: "Unfounded as they were, the allegations were damaging to those against whom they were made and were such as may cause health professionals to hesitate before they involve themselves in this area of medicine."

After this, the argument got even more personal. "I was reported to the GMC," says Dr Hamilton. "The complaint was risible. I was accused of breaking almost every rule in the GMC rulebook. And of course the GMC fell totally into the trap.

"Instead of accepting that its complaints process can be hijacked by pressure groups, it treats all complaints the same. So I had all the rigmarole of a formal complaint, which naturally dragged on for months. Eventually it was chucked out and I got an utterly ungracious letter from the GMC saying the complaint won't lead to a case but I'm to make sure to obey the GMC rules anyway. It sounded as if it thought I'd got off on a technicality and needed a good telling off."

Peter White, professor of psychological medicine at Barts and the London School of Medicine, was the principal investigator of PACE. He says the campaign against the trial has gone on ever since it was first funded. "There was a campaign by the ME Association, lots of letters to organisations involved, not least the MRC, and a petition to No 10 Downing Street.

"It did upset our ability to recruit patients, and it took up a lot of time. Complaints and Freedom of Information requests have to be dealt with properly. The paradox is that the campaigners want more research into CFS, but if they don't like the science they campaign to stop it. They want more research but only research they agree with."

Professor White has been accused of coercing patients, paying general practitioners to enlist patients, having conflicts of interest, and accepting improper financial contributions. These accusations, which he insists are all untrue, have also been sent to his employers. In Dr Hamilton's case, the dismissal of the complaint to the GMC was followed by Freedom of Information requests for the evidence the GMC had gathered from his five employers and in its case handling. "The GMC hadn't the grace to tell me this—it still hasn't—but my employers did," he says. "As far as I know this stage still grumbles on."

While psychiatrists and those who work with them have been the main targets, others also come into the activists' sights. Esther Crawley, a paediatrician and consultant senior lecturer at Bristol University, is principal investigator for the SMILE trial, which aims to investigate a treatment called the Lightning Process. Developed by Phil Parker, an osteopath, the process claims to combine the principles of neurolinguistic programming, osteopathy, and clinical hypnotherapy to

treat a variety of conditions, including phobias and CFS/ME. There has been no proper medical study of whether it works.

Critics of the method opposed the trial, first, Dr Crawley says, by claiming it was a terrible treatment and then by calling for two ethical reviews. Dr Shepherd backed the ethical challenge, which included the claim that it was unethical to carry out the trial in children, made by the ME Association and the Young ME Sufferers Trust. After re-opening its ethical review and reconsidering the evidence in the light of the challenge, the regional ethics committee of the NHS reiterated its support for the trial.

Dr Crawley says it doesn't make sense to argue that the trial should not be carried out in children. "The aetiology of CFS in children is different, and so is the prognosis. Ninety four per cent of children get better, while only a third of adults do. So you couldn't just do the trial in adults. Anyway, we're recruiting teenagers, not children."

The attacks soon turned personal. "They said I was having an affair with a lightning practitioner, they doctored a video I appeared in, they reported me to the GMC. It was very harassing. The GMC said I didn't have a case to answer."

Research threatened

Dr Crawley runs the biggest CFS/ME service for children in the UK, seeing about 200 a year. "If the Lightning Process is dangerous, as they say, we need to find out. They should want to find it out, not prevent research.

"It's not representative of the patients as a whole. It's a very very tiny minority —50 to 100 people, maybe"

"I expected families and patients to have a twisted view of research, given the amount of stuff [criticisms, personal abuse, etc] there is on the internet about CFS, but they don't. We have to warn them there is this stuff out there, and they get very angry about it—they say we need answers and you mustn't be stopped."

Professor Wessely, whose research interests have moved away from CFS/ME, still sees patients and agrees that their attitudes are completely different from those of the campaigners. "I still do the clinic, and it's perfectly fine. We've seen 2000 patients, with very few complaints. The service is the least complained about in the Maudsley [hospital]."

The underlying belief of the campaigners is that CFS/ME has a "real" cause, which would have been discovered by now if serious efforts had been made. So there was great excitement in 2009 when a US team from Whittemore Peterson Institute in Reno, Nevada, published a paper in *Science* claiming a link between CFS/ME and the XMRV retrovirus. The paper said that they had found the virus in 68 out of 101 CFS/ME patients tested. Annette Whittemore, whose husband made money in property and who has a daughter with CFS, had funded the institute. She was joyful at the discovery. "It ends the debate," she said. "CFS is not and never was a psychological disorder. Those who are ill have always known this."

Alas, at least 10 follow-up studies, including one in the *BMJ*,[4] have now failed to reproduce the original results, prompting *Science* to issue an "expression of concern." But some of those who failed to reproduce the finding have found themselves the object of the same intimidatory behaviour as the psychiatrists. John Coffin from Tufts University in Boston, whose team showed that XMRV is a laboratory hybrid, has said that nobody went in with the intention of disproving the link between CFS/ME and the virus. Criticisms of his motivations from patient advocates had been "painful" to read.

Professor Wessely says that scientists have been appalled at their treatment and that some have sworn never to work in the field again. "Many scientists end up being threatened if they publish any research that gives the 'wrong' results. So most just stop."

Pretty typical is a response posted on the ME Association website to the republication of a *Nature* story reporting the failure to reproduce the XMRV results. It quoted Jonathan Stoye, a retrovirologist at the National Institute for Medical Research, as saying; "It's a bust. People who are

COMMENTARY Ollie Cornes

Living with CFS/ME

During my career I have co-written several books on computer software, worked as a software engineer, and set up and sold two small technology businesses. But in April 1999 I developed tonsillitis with its usual malaise and fatigue. I naturally assumed I would be back to health fairly quickly, but, although the tonsillitis cleared, the malaise and low energy levels persisted. I felt like I was running on fumes. I had no idea why. Then my health deteriorated further.

Months passed, then a year, and now 12 years. I have occasional periods when I'm bed bound, and I am often house bound. I'm always exhausted. I often move around at home like a frail, unstable, elderly man—at the age of 38. It's certainly made worse by my not knowing what is causing it.

My general practitioner, and many books, suggested the illness was in some way psychosomatic ("yuppie flu," not a proper illness). I knew in myself this wasn't true, but there was a nagging doubt. Maybe they're right? Am I making this up? Am I really sick?

To ensure the illness was not psychological, I worked extensively with a psychotherapist. Rather than finding evidence of emotional issues that could cause my symptoms, the therapy suggested the opposite—that, given how sick I am, I have surprisingly good mental health. It delivered no improvement in my health. In fact the only things I have found that help are to get lots of sleep; to eat a simple diet of fish, vegetables, and pulses; and to almost entirely avoid meat and junk food.

Imagine having the flu, being severely jetlagged, and having not slept for two days but without the sinus and lung congestion—that's the closest I've found to a description of what this illness is like,

interested in this condition will have to move on." The comment, posted by somebody calling himself Soloman, reads: "Will HE move on to some decent research instead of just knocking down others' work? And what do we move on to—more nonsense from the psycho-terrorists?"

Dr Crawley admits she did get "very low" as a result of the pressure and was planning to leave the field. "But there isn't anybody else in my generation who's come in and stayed in. If I stop, they'll have won."

Dr Shepherd is more sanguine. "The problems don't relate to all researchers. There are some who would say they haven't had any trouble. It may discourage some people, those on the psychiatric side, because they know about White and Wessely and they know they're going to get the same flak. But what discourages people on the biomedical side is this atmosphere in laboratories that you shouldn't be involved with this at all if you want to advance your career, that it's all a psychiatric condition and there's no point in searching for a physical cause when we've had so many negative results."

Dr Shepherd is pleased by a new initiative by the MRC, which has set aside £1.5m for CFS/ME research. He credits Stephen Holgate, an immunopharmacologist at Southampton University, who set up an expert group to advise the MRC, with moving the process forward. Professor Holgate believes that a lack of good scientists working in the field has held up progress, and the new MRC funding is designed to rectify that. Proposals, which had to include at least one scientist who does not already work on CFS/ME, had to be submitted to the MRC by 7 June. Whoever wins the grants "will have tremendous support" from patient groups, Dr Shepherd promises.

Time will tell if his optimism is justified, but it does little to help those who have been categorised as enemies by the activists. The law appears relatively powerless, just as it did for many years during the campaigns against scientists working with animals.

"I regularly go to see a lawyer on the Medical Defence Union," says Professor Wessely. "They say, 'Yes, it is a gross libel. But if you took them to court, they'd love it. They'd get what they want.' I did get an injunction against the person who was comparing me with Mengele. That was a particularly nasty example, because my grandparents may actually have been murdered by Mengele—they were transported to the camp where he worked and never seen again."

The motivation of the most persistent campaigners puzzles those who are their target. "My gut feeling is that some don't even have this illness at all," says Dr Shepherd. "They have personality problems." Professor Wessely says: "They're damaged and disturbed, with an obsession about psychiatry. With these people, it isn't that they don't want to get better but if the price is recognising the psychiatric basis of the condition, they'd rather not get better."

Dr Hamilton has also been advised by lawyers not to answer complaints—"the complainant will simply twist anything you say." He says he is at a loss to know how to deal with them. "There's no morality here. The judicial review's wrist slap would have made anyone with any conscience stop playing this game. It hasn't. I get hate emails—that's what the delete button is for. The GMC need to realise they are losing the trust of the medical profession by its procedures. Very few doctors feel they will receive 'natural justice' from it." As for Professor Wessely, he gave up active research on CFS/ME 10 years ago. He now specialises in the problems of war veterans. "I now go to Iraq and Afghanistan, where I feel a lot safer," he says.

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but it understates it. Sickness has become the new normal for me—my "I'm fine, thanks" is probably the same as your "I feel like death, I need to go back to bed."

On a scale of 1-10, my energy levels typically range from three to five. Since becoming ill I lack mental clarity; I mix up words, and I have memory problems and trouble focusing. I have an enormous need for sleep, which never refreshes. There is an overwhelming, permanent, and intense malaise. Pushing my limits—for example, with aerobic exercise—provokes a severe worsening.

But I'm actually one of the lucky ones; many are far sicker than me and largely invisible. Doctors will usually see patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) only on a "good" day. Nancy Klimas treats both HIV/AIDS and CFS/ME patients at the University of Miami. In 2009 she told the *New York Times*, "I split my clinical time between the two illnesses, and I can tell you if I had to choose between the two illnesses . . . I would rather have HIV."[1]

The Canadian consensus case definition criteria for CFS/ME clearly distinguish it from the UK's broad, wastebasket CFS diagnosis. The Canadian definition requires the classic symptom of CFS/ME: delayed, post-exertional malaise and fatigue. Even Peter White, who led the largest UK CFS study to date, said recently: "The PACE trial paper refers to chronic fatigue syndrome (CFS) which is operationally defined; it does not purport to be studying CFS/ME." I believe CFS/ME is a specific, identifiable disease subset of the UK CFS definition.

Harvey Alter, of the National Institutes of Health, recently said, "I'm absolutely convinced that when you define this disease by proper criteria, this is a very serious and significant medical disease, and not a psychological disease. It has the characteristics of a viral disease."[2]

"I have enormous sympathy with general practitioners faced with patients who say 'I'm tired all the time. I just can't get out of bed.'"

I'm not aware of any treatments offered by the NHS to patients like me, only illness management (pacing, cognitive behavioural therapy, and so forth). My view is that because the UK has used such a loose illness definition we have ended up in this appalling situation where the term CFS is used to group together people with severe depression (or other emotional difficulty) with a group of patients who to the untrained eye look pretty much the same but who have what seems to be a distinct physical illness, particularly characterised by post-exertional malaise. I have enormous sympathy with general practitioners faced with patients who say, "I'm tired all the time. I just can't get out of bed." How do they tell the difference? I'd like to see the UK adopt the Canadian definition to encourage research and new clinical approaches with what we may find is a treatable viral or immune dysfunction condition.

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COMMENTARY Trish Groves

Heading for a therapeutic stalemate

In late May I went with an open mind to the sixth Invest in ME conference in London to listen to research presentations and take part, on behalf of the *BMJ*, in a concluding panel discussion. Although I was aware of Invest in ME's stance against the recent PACE trial[1] and other research on non-biological approaches, I was heartened by the conference theme: "The Way Forward for ME—A Case for Clinical Trials." I knew that laboratory science had not yet yielded biological evidence that would lead to large scale clinical trials, so I hoped to hear about trials of health services and supportive interventions to improve patients' experiences and lives.

I heard about just one clinical trial at the conference, however. Oncologists Oystein Fluge and Olav Mella, from the University of Bergen, talked about their recent placebo controlled trial of the monoclonal antibody rituximab in 30 patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). They had found positive results for some secondary outcomes, but not for the primary outcome (self reported symptoms and quality of life at three months[2]), so it was impossible to draw any firm conclusions about the efficacy of this costly and often toxic drug. (The trial has not been published yet, and we were asked not to report any detailed results.) Most of the other speakers reported, in highly technical language and with densely packed slides, exploratory studies on associations between CFS/ME and numerous biomarkers. Nobody discussed how this disparate collection of small scale laboratory studies might fit together with each other or the wider evidence base. By the end of the day the case for clinical trials had not been made.

I was particularly puzzled that Judy Mikovits of the Whittemore Peterson Institute reported her laboratory's continuing work on xenotropic murine leukaemia virus related virus (XMRV) as a possible infectious cause, without mentioning the increasing number of studies refuting that hypothesis. And although other speakers, such as microbiologist Andreas Kogelnik, reported disconfirming work, this was done almost in passing with no discussion. Why was there no scientific discourse about the conflict between these two sets of high profile results? One possible answer for this reticence came a couple of weeks after the conference, when Dr Kogelnik and colleagues published a study in *Science* firmly refuting the XMRV theory and suggesting contamination by virus samples from mice.[3]

"There could soon be a therapeutic stalemate, with most patients and campaigners believing that only drug treatments based on biological causation will help"

This paper was accompanied by another disconfirming study[4] and an expression of concern from the editor in chief[5] about Mikovits and colleagues' 2009 *Science* paper that first proposed the theory.[6]

As the concluding panel discussion over-ran and it was almost time to run for my train, "the lady from the *BMJ*" was asked to comment on the day's research. I said I'd hoped to hear about more patient centred research and admitted that I hadn't understood many of the presentations. When I defended the PACE trial's design and findings—albeit for a clearly defined, large subgroup of patients—and disclosed that I had a background in psychiatry, several people in the audience started shouting aggressively. It ended more constructively, with my offer accepted (I think) to speak at next year's conference about the kind of research questions and study designs that might attract national research grants and be publishable in mainstream medical journals.

Personal abuse and threats from a vociferous minority to doctors and scientists researching CFS/ME are indefensible.[7] But how much of this awful behaviour is at least partly fuelled by angry responses from a wider group of campaigners to any suggestion that the condition might be helped, at least in some patients, by interventions such as cognitive behavioural therapy? How much by campaigners' insistence that the definition of CFS/ME must include a criterion that exercise causes a dangerous deterioration in symptoms and hence cannot be treated with even gradually increasing activity and exercise? And how much by doctors' dislike of patients who won't at least try something that research has shown to be effective and safe in well conducted trials?

There could soon be a therapeutic stalemate, with most patients and campaigners believing that only drug treatments based on biological causation will help, and most doctors believing that patients who won't try graded exercise or cognitive therapy are untreatable. Campaigners may have a point when they complain that focusing only on the trials and systematic reviews (mostly of exercise and cognitive behavioural therapy) might skew research agendas, peer reviewers' and editors' priorities, clinical guidelines, healthcare purchasing decisions, assessments for incapacity benefit, and media interest so much that people with chronic and severe fatigue and debilitation (whatever the cause) who are unable to try such interventions (for whatever reason) may be unfairly underserved.

Why can't CFS/ME be like other common chronic conditions where patients, carers, doctors, and researchers work together to pose research questions, gain understanding, and—in the absence of clear explanations and cures—at least find ways to respond to patients' needs, help them live with and manage symptoms, and get more out of life?

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