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How widespread is variant Creutzfeldt-Jakob disease?

The disease seems rare but "infection" may be relatively common

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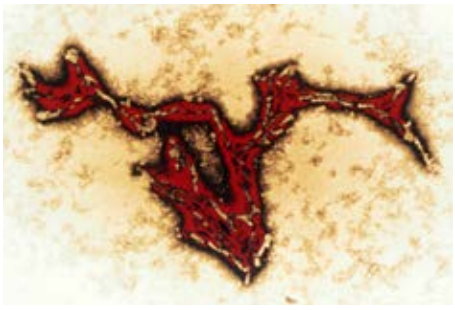
Variant Creutzfeldt-Jakob Disease (CJD) is the human form of bovine spongiform encephalopathy or "mad cow disease." It is one of the family of mainly neurodegenerative diseases known as spongiform encephalopathies because of their histological appearance. These diseases afflict animals and humans and are widely accepted as resulting from the toxic build-up of an aberrant form of a normal cellular protein, the prion protein. Bovine spongiform encephalopathy was common, with more than 36 000 cases in the peak year of the cattle epidemic in the United Kingdom (1992).[1] However, variant CJD has remained mercifully rare, with 177 cases in the UK to date (51 in the rest of the world, 27 of which were in France), and only one in the past two years.[2]

So, is variant CJD yesterday's news? The linked paper by Gill and colleagues helps make clear why this is not the case.[3] Sporadic CJD, the "usual" form of CJD, was first described early last century and is found worldwide, with an annual incidence of around 1/1 000 000 population. Prion infectivity is notoriously difficult to inactivate and sporadic CJD had been shown to be transmissible by neurosurgery in case studies published as long ago as 1974. Transmission can also occur by injection or implantation of infected material derived from the central nervous system, as in the epidemic of CJD in recipients of human growth hormone derived from cadaveric pituitaries.[4]

In variant CJD, there are also concerns about spread from peripheral tissue and blood because disease related prion proteins have been demonstrated in lymphoreticular tissue.[5] Variant CJD has been transmitted by blood components and products from donors who later developed the disease, although a convincing case of transmission of variant CJD by surgery has not been documented.[6]

UK health agencies have taken several costly steps to secure the blood supply (leucodepletion of blood, exclusion of certain donors, and sourcing of blood products from outside the UK) and to reduce any risk of horizontal transmission by surgical instruments.[7] How necessary, or cost effective, these measures are depends mainly on how many people in the UK are "infected" with



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Gill and colleagues in their painstaking examination of more than 30 000 appendix samples arrive at a prevalence of 1/2000

the variant CJD prion. Blood tests in specialist settings have been described,[8] but a test (ideally two tests) that could be used widely for diagnosis and screening remains elusive and would transform the approach to the problem.

In the absence of a blood test, anonymised population prevalence surveys using archived tissue from appendicectomies and tonsillectomies were carried out. Although abnormal prion protein was almost entirely absent from tonsils,[9] a previous survey of appendixes suggested a prevalence of 1/4000.[10] Gill and colleagues in their painstaking examination of more than 30 000 appendix samples arrive at a prevalence of 1/2000, the same order of magnitude. Unlike in clinical cases of variant CJD, no particular age group or geographical region was affected, and no susceptible genotype was identified. In the UK, patients with variant CJD have a modal age at death of 28 years and are diagnosed more often in the north of England and in Scotland. Confirmed cases have all been methionine homozygous (MM) at codon 129 of the gene encoding the prion protein (*PRNP*).[11] It is possible that abnormal deposition of prion protein in the appendix is simply a non-specific finding, so appendicectomy tissue from the 1970s and earlier, before bovine spongiform encephalopathy appeared, is being examined.

If "infection" with variant CJD prion proteins is common then precautionary measures are likely to be in place for a long time, and clinicians need to understand the logic behind them. Clinicians may encounter people deemed, in the words of UK public health agencies, to be "at increased risk" of CJD.[7] These are people who have received blood from someone with CJD or been operated on with surgical instruments that have been used on someone with CJD. The chance of these people having acquired the disease is thought to be great enough that they could, in turn, transmit the disease themselves. They are thus banned from donating blood and special arrangements need to be made for surgery that involves tissues in which prion proteins might be found. Advice from local public health or infection control teams should be sought. Local teams will also probably wish to seek more expert help, usually through the CJD Section of the National Centre for Infectious Disease Surveillance and Control of Public Health England that acts as a clearing house for queries and can link them with the UK's various specialist clinical and research teams.

Although we know much about these fascinating, if terrible, diseases, particularly at the protein chemistry and cellular level, many important questions remain. What is the disease phenotype and natural course of variant CJD in genotypes other than MM? What other animal prion diseases may be zoonotic? The replication mechanisms first seen in prion proteins have now been identified in other proteins involved in other common neurodegenerative diseases, including Aβ, amyloid-β in Alzheimer's disease, α-synuclein in Parkinson's disease, and tau in several different conditions.[12] How often, if ever, are any of these transmissible? The UK's prion research capacity with expertise in human and veterinary disease surveillance and pathology, as well as animal facilities for transmission experiments, is well placed to answer such questions. Further disinvestment would be premature.

Competing interests: From 2007 until its dissolution in 2011, I was a member of the UK's Spongiform Encephalopathy Advisory Committee (SEAC) and I have been a member since 2011 of the Advisory Committee on Dangerous Pathogens. Both these independent scientific advisory groups took an active interest in this work and encouraged the UK government to fund work on the prevalence of spongiform encephalopathies.

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RESEARCH, p 11

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Read Ruth Malone's editorial on changing *Tobacco Control's* policy on tobacco industry funded research at http://bit.ly/17oXogn

Journal policy on research funded by the tobacco industry

The *BMJ*, *Thorax*, *Heart*, and *BMJ Open* join *Tobacco Control* in no longer considering such research

Fiona Godlee editor in chief, *BMJ*
Ruth Malone editor, *Tobacco Control*, BMJ Journals
Adam Timmis current/outgoing editor, *Heart*
Catherine Otto incoming editor, *Heart*
Andy Bush coeditor, *Thorax*
Ian Pavord coeditor, *Thorax*
Trish Groves editor in chief, *BMJ Open*, BMJ Journals, London WC1H 9JR, UK tgroves@bmj.com

As editors of the *BMJ*, *Heart*, *Thorax*, and *BMJ Open* we have decided that the journals will no longer consider for publication any study that is partly or wholly funded by the tobacco industry. Our new policy is consistent with those of other journals including *PLoS Medicine*, *PLoS One*, *PLoS Biology*[1]; *Journal of Health Psychology*[2]; journals published by the American Thoracic Society[3]; and the *BMJ*'s own *Tobacco Control*.[4]

Critics may argue—as many did when journals stopped publishing cigarette adverts—that publishing such research does not constitute endorsing its findings and that, as long as funding sources are fully disclosed, readers can consider that information and make up their own minds about the quality of the work. Peer review should prevail, goes this line of thinking: it's not the editor's job to make these kinds of judgments. However, this view ignores the growing body of evidence that biases and research misconduct are often impossible to detect,[5] and that the source of funding can influence the outcomes of studies in invisible ways.[6 7]

Underlying all the activity of peer review, editing, and publishing is the assumption that medical journals exist for the purpose of advancing knowledge that can be used to promote health and reduce disease. But the deputy editor of *JAMA*, Drummond Rennie, who has perhaps studied the process of scientific publishing longer than anyone, has written about what he calls "little murders." These are deceptive publication practices that are "destructive of the delicate web of trust between colleagues that keeps the whole enterprise functioning and afloat."[8] The editor's job, observes Rennie, is to "try to separate the insufferable behaviors of mere jerks from the illegal actions of bona fide crooks."

The tobacco industry, far from advancing knowledge, has used research to deliberately produce ignorance and to advance its ultimate goal of selling its deadly products while shoring up its damaged legitimacy.[9] We now know, from extensive research drawing on the tobacco industry's own internal documents, that for decades the industry sought to create both scientific and popular ignorance or "doubt." At first this doubt related to the fact that smoking caused lung cancer; later, it related to the harmful effects of secondhand smoke on non-smokers and the true effects of using so called light or reduced tar cigarettes on smokers' health.[9-12] Journals unwittingly played a role in producing and sustaining this ignorance.[9]

Some who work within public health and who buy the notion of "harm reduction" argue that the companies that now produce modified cigarette products and non-cigarette tobacco products, including electronic nicotine delivery devices (e-cigarettes), are different from the tobacco industry of old, or that the tobacco industry has changed. For "hardened" cigarette smokers who can't or won't quit cigarettes,[13] the argument goes, new tobacco products could represent potential public health gains, and company sponsored research may be the first to identify those gains.

The tobacco industry has used research to deliberately produce ignorance and to advance its ultimate goal of selling deadly products

NICHOLAS RIGG/GETTY IMAGES

But one fact remains unassailably true: the same few multinational tobacco companies continue to dominate the market globally and, as smaller companies develop promising products, they are quickly acquired by the larger ones. However promising any other products might be, tobacco companies are still in the business of marketing cigarettes. As US federal court judge Gladys Kessler pointed out in her judgment in the case of US Department of Justice versus Philip Morris et al, the egregious behaviour of these companies is continuing and is likely to continue into the future.[14] And just this summer documents leaked from one company showed a concerted campaign to "ensure that PP [plain packaging of tobacco products, bearing health warnings but only minimal branding] is not adopted in the UK."[15] The tobacco industry has not changed in any fundamental way, and the cigarette—the single most deadly consumer product ever made—remains widely available and aggressively marketed.

Editors of *BMJ* journals are committed to integrity in scientific publishing and to ensuring that—as far as possible—their journals publish honest work that advances knowledge about health and disease. Back in 2003, the editor of the *BMJ* defended publication of a study with tobacco industry funding saying "The *BMJ* is passionately antitobacco, but we are also passionately prodebate and proscience. A ban would be antiscience."[16] But it is time to cease supporting the now discredited notion that tobacco industry funded research is just like any other research. Refusing to publish research funded by the tobacco industry affirms our fundamental commitment not to allow our journals to be used in the service of an industry that continues to perpetuate the most deadly disease epidemic of our times.

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- Head to Head: Should electronic cigarettes be as freely available as tobacco? (*BMJ* 2013;346:f3845)
- Observations: E-cigarettes and the marketing push that surprised everyone (*BMJ* 2013;347:f5780)

bmj.com/poll See the results of our poll on e-cigarettes as medicine at bmj.com/about-bmj/poll-archive

European Union's tobacco products directive

Many questions remain about the influence of industry

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On 8 October 2013, the European Union moved a step closer to strengthening tobacco control when members of the European Parliament (MEPs) voted for a European Commission proposal for a revised directive on tobacco products, albeit with extensive amendments. The appointed rapporteur, Linda McAvan MEP, will now seek agreement with representatives of the commission and the Council of the European Union (comprising national governments).

It is remarkable that the proposal has made it this far. The tobacco industry did everything possible to derail it, with Philip Morris spending up to €1.25m (£1.06m; $1.7m) in 2012 in intensive lobbying,[1] mostly directed at MEPs.[2] However, the legislation still faces many risks. The parliament, commission, and council must agree on the text, and the council presidency will rotate from Lithuania, whose health minister is a staunch advocate of tobacco control, to Greece, where Philip Morris is investing heavily in a new distribution facility.[3]

So what does the legislation currently propose? It builds on the 2001 Tobacco Products Directive that increased the size of compulsory labels on cigarette packs and allowed member states to introduce graphic warnings.[4] However, many of the commission's proposals have been watered down, whereas some of the most effective, such as standardised packaging and bans on point of sale displays, were removed earlier.

The proposal that pictorial warnings cover 75% of both sides of packs was reduced to 65%, better than the industry's goal of 50%. Moreover, the warning must be at the top of the pack and not, as industry wanted, at the bottom, where it could easily be hidden by display cases. Cigarettes will no longer be sold in packs of 10, which are more affordable for children. Provisions to increase traceability of cigarettes will be strengthened to tackle smuggling, in which the industry has been complicit.[5] However, the effectiveness of these provisions is questionable—Interpol is supporting a system with known weaknesses, developed after a $15m grant from Philip Morris.[6]

B. BOISSONNET BSIP/SPL

Bubble gum or cotton candy?

The earlier directive required additives simply to be listed. Now, those that impart a flavour will be banned, except for menthol, which will be permitted for another five years. This is a great victory for the industry, which adds menthol to about 90% of its products, even when not described.[7] Menthol interacts with nicotine to increase the impact of the first inhalation and reduces the throat irritation experienced by novice smokers.[8] Consequently, many products have been designed to maximise these effects. The industry also benefits from the widespread view that menthol cigarettes are healthier.[9]

The most contentious area is e-cigarettes. The commission proposed treating them like any other nicotine delivery device and regulating them as drugs, a view supported by many governments, including that of the United Kingdom, after careful review of the evidence. The parliament was, however, influenced by intensive lobbying against this, although the meaning of the alternative text is unclear. Now, "all nicotine containing products" will be subject to the same restrictions on cross border advertising and sponsorship as cigarettes. Although cigarette brand names will be banned, the many flavourings, such as bubble gum and cotton candy, which increase their appeal to children, will not. However, the draft text goes on to urge governments to "ensure that they can be made available as widely as tobacco products," reflecting unsubstantiated claims that they are a "game changer" for smoking cessation.[10] The draft legislation fails to address the rapid growth in sales of products designed to resemble real cigarettes as closely as possible. This subterfuge is widely viewed as a way to renormalise smoking, a key goal of those seeking to recruit child smokers, and to counter some of the effects of smoking bans.[11]

Fortunately, nothing prevents governments from adopting more effective legislation, such as standardised packaging, but much needs to be done before a workable text is ready, and it is unfortunate that so many opportunities have been missed. However, this experience may bring other benefits. The co-chair of the parliament's public health committee has condemned most MEPs for doing "the bidding of the tobacco industry,"[11] focusing much needed attention on the role of industry lobbyists in Brussels.

Competing interests: None declared.

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- News: Children don't think that stimulant drugs for ADHD rob them of their "authenticity" and moral responsibility (*BMJ* 2012;345:e6947)
- Views & Reviews: Has Ritalin replaced the rod? (*BMJ* 2012;345:e8532)

Prescribing methylphenidate for moderate ADHD

Has NICE guidance unwittingly exposed a new challenge for assessing this condition?

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Why has the National Institute for Health and Care Excellence (NICE) issued a reminder that first line treatment for moderate attention-deficit/hyperactivity disorder (ADHD), which affects about 8% of school aged children and young people in the United Kingdom,[1] should not include methylphenidate?[2] This recent bulletin follows the annual report by the Care Quality Commission, which showed that methylphenidate prescriptions for ADHD in primary care in England rose by 56% between 2007 and 2013.[3]

The 2006 NICE technology appraisal guidance for the use of methylphenidate in ADHD in children stated that "it is not anticipated that this guidance will result in a major increase over current trends in the rate of prescribing for ADHD."[4] Although the Care Quality Commission report didn't clarify what proportion of methylphenidate prescriptions are for moderate ADHD, NICE's bulletin suggests that the institute is worried that it has underestimated prescription trends and that clinicians may not be heeding its guidance. What could be causing this increase in methylphenidate use?

The commission's report explains that between 2011 and 2012 the prescription of methylphenidate in primary care continued to rise steadily, by 11%. In the commission's opinion "this reflects increased diagnosis of, and prescribing for" the treatment of ADHD.[3] However, the NICE guideline on ADHD for children and adults,[5] and its recently published quality standard,[1] do not recommend drugs as first line treatment for school aged children and young people with moderate ADHD, or for any preschool children. It does recommend drugs as first line treatment for "severe" ADHD, which NICE estimates has a prevalence of 1%.[4 5] NICE advises offering children and young people with moderate ADHD referral to a psychological group treatment programme.[1] It defines "moderate ADHD" as when "symptoms of hyperactivity/impulsivity and/or attention, or all three, occur together and are associated with at least moderate impairment in multiple settings and multiple domains."[5]

The adjective "moderate" isn't clarified, but the *Oxford English Dictionary* defines it as "average in amount, intensity, quality or degree." So, moderate means average, but what does average mean in the context of behaviour in school aged children? NICE guidance on ADHD infers confident clinical discrimination between moderate and severe, but is there a valid and reliable severity rating process in the assessment of ADHD?

BSIP, MENDIL/SPL

Watch out! It stunts your growth

Neurodevelopmental conditions are conceptualised as disorders of behaviour that can be assessed by direct observation.[6] Two decades of successful research innovation have enabled the assessment of autism spectrum disorder to become the paradigm for this observational approach. In autism, instruments are increasingly used for taking the history of parents and carers and direct clinical assessment of the patient. When assessing patients, experienced clinicians using the *Autism Diagnostic Observation Schedule* can grade the severity of clinical presentation according to coding outcomes.[7] ADHD researchers have developed instruments to help gather information from parents, carers, and teachers that contain a severity measure, in terms of the degree rated by the clinician, or the level of score provided by the informing adult (for example, the ADHD rating scale[8]). However, ADHD assessment research has not provided an equivalent of the schedule for assessing autism. In the clinic (or classroom/playground) it is not easy to judge accurately whether the child has moderate or severe ADHD, because the assessing clinician relies mostly on information provided by non-clinicians.[6]

An additional factor that may contribute to the Care Quality Commission's findings is that the diagnosis of ADHD is inextricably linked with consequent drug treatment for its core symptoms, whereas this is not the case in autism.[9] Doctors may also not have access to psychological therapy for the large numbers of patients with moderate ADHD, even if they request it. For all of these reasons, the current increasing tendency for doctors to prescribe methylphenidate for any diagnosis of ADHD is unsurprising. Because of this growing trend, precious capacity within child and adolescent psychiatry (and, to a lesser extent, community paediatrics) has become monopolised by demands for ADHD drugs.[3] We need to consider other issues as well.

Why hasn't research into the assessment of ADHD been able to deliver an equivalent of the schedule for assessing autism? Can we really go on diagnosing up to 9% of our children with a psychiatric condition that cannot be directly assessed in a valid and reliable way? The prescription of methylphenidate for ADHD often spans most of a patient's childhood and adolescence, if not beyond. How effective are busy clinicians at identifying those patients who were initially judged to have severe ADHD but who now have moderate disease and no longer need drug treatment?

The NICE bulletin quotes Professor Tim Kendall, consultant psychiatrist and member of the ADHD guideline's development group, speaking to BBC Radio 4's *Today* programme about the commission's report.[2] When asked about the side effects of methylphenidate, he said that, if taken for a year it is likely to reduce children's growth by about three quarters of an inch. He also said that there was increasing evidence that the use of methylphenidate "precipitates self harming behaviour in children," and that there was no evidence that the drug reduces the long term problems associated with ADHD. Given the burgeoning cost of rising numbers of methylphenidate prescriptions, alongside often irreversible iatrogenic consequences (such as growth retardation), is there really no other way to help these children and their families?

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