

Episode 20: Nitrous Oxide: No Laughing Matter

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TRANSCRIPT

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be looking at nitrous oxide or, as it's more commonly known, laughing gas, and the history of nitrous oxide is really quite interesting.

So nitrous oxide was first discovered by Joseph Priestley, who many people might have heard of, more famously because he discovered, or was one of the people who discovered, oxygen as a gas. But he was heating ammonium nitrate over iron filings and he discovered that it produced a gas that was colourless and didn't support combustion and, interestingly, it had strange effects when it was inhaled. He didn't really fully investigate the physiological effects. It was actually somebody called Humphry Davy a few years later and, I love this, he was working at a place called the Pneumatic Institution in Bristol, so it was kind of an academic institution which investigated gases, essentially. And his job was to investigate possible medical applications of gases. And so Davy tested nitrous oxide, like all good scientists at the time, on himself and discovered that it produced really strange effects: euphoria, giddiness and, at high doses, hallucinations. And although it was suggested at the time that it could have medical uses, it became much more common to be used recreationally. So actually the recreational history of nitrous oxide has got a longer history than the medical uses.

And in 1844 an American dentist was at a laughing gas demonstration. So there were street shows where volunteers would be given nitrous oxide and they'd do silly things in front of a crowd and the crowd would love it. And a volunteer had taken a big hit of nitrous oxide and he hurt his leg, or rather he injured his leg, but he didn't show any pain. And this gave Horace Wells a great idea. As I say, he was a dentist, so the next day he inhaled nitrous oxide and got his colleague to remove one of his teeth and he didn't feel it, and anaesthesia was born. And he tried to actually showcase this in a public demonstration but it didn't work very well. He didn't give the gas properly, he didn't perhaps give it in a consistent enough way, and his patient was kind of moaning in pain in front of this crowd and actually it caused a bit of a setback. But finally, from the 1860s onwards, there was a rediscovery and it was used for tooth extractions. But it's not just used medically, is it, Rebecca?

So while nitrous has many uses in trauma settings to provide quick pain relief, in people who are in labour, and in dental procedures, it also has uses in the food industry to aerosolise cream and things like that. So whipped cream, whipped cream as we knew it growing up. But it's also used as an oxidiser in rocket motors and can also be used in street car racing to modify car engines and things like that. And as we said in the history, it's got a huge recreational scene associated with it as well.

So how does it work? So nitrous oxide's recreational use dates back to the late 18th century in the British upper class where they gathered and had laughing gas parties, which I found quite interesting when I was doing my reading for this episode. And these days recreational use is seen in quite a lot of wide settings, isn't it? We'll come on to the legal position of nitrous oxide in the UK a bit later on but I remember 20-odd years ago you used to see balloons of it for sale at festivals, you'd see use at parties and things like that.

Subjective effects, as you say, it's called laughing gas, right? So people describe feelings of giddiness, uncontrollable laughter, mild dissociation and, at extreme doses, you do see hallucinations and full dissociation. So what's the pharmacology behind this? How does nitrous oxide work?

Nitrous oxide works in a couple of different ways. So it can modulate a variety of ligand-gated ion channels and mainly acts to block NMDA receptors, therefore inhibiting the neurotransmitter glutamate and dampening down neuronal excitation, which can produce sedation and pain suppression as NMDA receptors kind of play a role in central pain. And it works in the same sort of way as ketamine, doesn't it, and quite a few drugs actually work on this pathway. Yeah. Common anaesthetic agents and dissociatives, things like that.

It's also thought to indirectly enhance GABAergic inhibition by stimulating GABA release, which can lead to sort of anti-anxiety and calming effects, in a similar way to benzodiazepines, and it's also thought to increase dopamine release and prevent reuptake of dopamine at the synapse, which leads to these feelings of euphoria and why some people get the giggles. It's got quite a complex mode of action, hasn't it really?

Yeah, and nitrous oxide is absorbed really, really quickly into the bloodstream and diffuses into tissues like the brain very easily so it has effects within seconds to minutes of inhaling it, but these effects are really short and only last about one to two minutes, therefore repeat dosing is apparently quite common.

Because it's not metabolised, so it goes into the lungs, gets absorbed into the blood, goes into the brain and then is essentially breathed out again quite quickly, so as quick as it goes in it comes out really. And it's really handy for things like trauma situations to provide that really fast-acting, immediate pain relief.

I remember a couple years ago when I was having a procedure done and was given nitrous it worked really, really well but the second they kind of tell you to stop inhaling it that pain comes back pretty quickly, which just emphasises how short-acting it really is. So while nitrous oxide can have some really useful effects like pain relief and can lead to euphoria, it can have some quite negative effects, so things like sound distortion and hallucinations. Some people report getting severe headaches, dizziness and short-lived feelings of quite severe paranoia.

There's also the sort of harms that come with inhaling a pure gas that hasn't got oxygen, right, so there's always this risk of asphyxiation. When you have medical nitrous oxide it's supplied as Entonox, which is a mixture of nitrous oxide with oxygen, which stops the asphyxiation risk, but actually if you're just inhaling pure nitrous oxide from a balloon there is a risk of asphyxiation, isn't there? And it has always been known to expand air pockets within the body so if you've got a bowel obstruction or a collapsed lung it can make that problem quite a bit worse.

I've not come across that. That sounds quite unpleasant. Yeah. Also you can see harms associated with people injuring themselves whilst high on nitrous oxide and falling over, that sort of thing. There's been a few high-profile car accidents as well, haven't there, involving either drivers that were impaired or I think there were a few cases in the Netherlands where it was drivers who were driving and trying to fill balloons at the same time.

Which is clearly not a good idea, but the other side of nitrous oxide is the toxicity that comes less from the acute use and more from chronic use. I don't think it's well defined as to what counts as chronic use but one of the more sinister sides of nitrous oxide is that actually it can be addictive and people can become dependent on it and, over a long period of time, nitrous oxide can actually inactivate vitamin B12 within the body.

And so one of the chronic harms that we see with long-term nitrous oxide use is B12 deficiency, a functional B12 deficiency whereby the cobalt atom in the B12 molecule is oxidised and it's no longer functional.

And I've certainly seen a few cases of this both amongst young people who were regularly taking nitrous oxide in a party situation but actually I'm aware of at least one case where there was a patient who had a connective tissue disease and they regularly came into A&E to have their shoulder put back in place and were regularly being given nitrous oxide medically and they actually ended up with a functional B12 deficiency and it can be quite severe, can't it?

It can cause severe neuronal demyelination and what we call subacute combined degeneration of the cord and that can be quite a significant medical event. It can lead to people losing the ability to walk and things like that. It's quite serious.

And because B12 is involved in the synthesis of DNA, when this happens in the bone marrow this can lead to what's called megaloblastic anaemia, so your red blood cells won't be formed properly and therefore can't carry oxygen as well. So some people experience symptoms such as fatigue, shortness of breath and paleness. B12 is also needed to recycle homocysteine to methionine so being B12 deficient will lead to an elevation of homocysteine levels which have been associated with arterial damage and risks of blood clots as well. We've looked at what it is, how it works and why it's used, so there was a recent change in legislation in the UK, wasn't there?

So on 8 November 2023 nitrous oxide was classified as a Class C drug under the Misuse of Drugs Act, making it illegal to possess if it is, or is likely to be, wrongfully inhaled. Wrongfully inhaled? Yeah, so they classify wrongful inhalation as inhalation other than for medical and dental purposes, and which is not accidental inhalation of nitrous oxide which has been released into the atmosphere.

So it's really, I find this really funny how poorly worded it is and how, for it to be classed as illegal, you have to be a mind reader. If you're supplying it for legitimate purposes you've got to almost predict that someone's going to be inhaling it wrongfully.

Yeah, okay, I mean there have been cases, haven't there, where cylinders of nitrous oxide have been marketed in a way that looks quite clear that it is for, what did you say, immoral inhalation? No, that wasn't what you said. Wrongful.

Wrongful inhalation. I've never actually looked into this but I've heard stories of there being cylinders containing flavoured nitrous oxide and things like that. And I know in some places you can get really fancy bags to carry your nitrous around on a night out, which again is obviously wrongful inhalation. But can you prove it's wrongful inhalation in a court of law, I suppose, is the argument. I'm not a legal scholar, I don't know how that's working out.

So when this was being thought about by the government, the ACMD, or the Advisory Council on the Misuse of Drugs, were consulted about the change and recommended that instead of it being made a Class C drug under the Misuse of Drugs Act it be inserted into Schedule 5 of the Misuse of Drugs Regulations 2001, and therefore they could amend it to include all of the legitimate uses for nitrous because it's not quite as clear-cut as just being in hospital or in a dental practice as legitimate uses for having nitrous.

I mean, are there non-medical cosmetic procedures and things like that where it might be legitimate? I'm not sure. Potentially, and I mean it's used in legitimate ways in the catering industry where it's not being abused but it has a role and a place in that sort of environment.

Because prior to this change it was technically covered by the Psychoactive Substances Act. Yep. And I vaguely recall one case, I can't remember whether I saw this in a paper or whether I was told this by a colleague or what, whereby, in fact it may not even have been a real thing, it may have been a hypothetical scenario, where somebody was stopped buying 12 cans of whipped cream on the grounds that they couldn't possibly want to eat 12 cans of whipped cream but perhaps were going to use it in an illegitimate way.

I like that the law also states you could be faced with an unlimited fine or visible community punishment. Visible community punishment. Visible wording. Which I'm assuming is just like community service but weirdly worded.

So does the shift to Class C from being controlled under the Psychoactive Substances Act, is this justified on the basis of the harms? What do you think?

It's a really tricky one. It's clear that in long-term use there is a risk of quite severe consequences so maybe a slightly more controlled approach is warranted, but I don't know whether having it as a Class C controlled

drug is just going a little bit too far in the wrong direction and, by clamping down on the really small cartridges that you kind of see littered in student cities, might be pushing people towards buying the really big cans and therefore you're not being able to control your dose as much.

You then risk people inhaling directly from the cylinders and getting cold burns and things like that, so it might have been done out of a positive interest in people's health and things but might have led things to go in the wrong direction.

Yeah, I've certainly heard the argument that it's moved people away from the smaller sort of catering whippet cylinders towards much larger cylinders which contain a lot more gas. Yeah, I think a lot of the decision to reclassify nitrous oxide as a Class C drug really was kind of a political decision. There was a lot of concern about cylinders being left in the park, which really isn't a drug issue, that's a littering issue, right?

Yeah. But as you say, the harms are real and I've certainly encountered numerous cases of B12 deficiency as a result of nitrous use. So here is a question: if nitrous, instead of being incredibly short-acting, lasted longer, would people still want to do it?

Oh, that is a good question. I'm going to suggest the answer is probably yes because one of the things we've noticed in the last couple of years is an increase in ketamine use and ketamine works in a very similar way to nitrous oxide, doesn't it? So has the shift, the ban on nitrous oxide, or the movement, it was already restricted under the Psychoactive Substances Act, but has the reclassification pushed more people towards ketamine use, do you think?

I mean, potentially. It'd be interesting whether the sort of people who partake in nitrous use at parties would necessarily want to move to something more long-acting like ketamine because maybe half the fun is that short burst of euphoria rather than being quite impaired for longer.

And how's the control of nitrous outside of the UK? Are we the only country that's tried to ban it like this? I know in South Australia in 2020 legislation was passed to restrict canister sales, I think to try and curb the problem a little bit.

And interestingly, in the US possession of nitrous oxide is legal but it is regulated by the FDA under the Food, Drug and Cosmetics Act. Because it counts as a food? I think so. It's got so much use in catering it does kind of make sense, doesn't it.

The Netherlands have banned possession for recreational purposes off the back of some of those high-profile car crashes I was talking about earlier. And it does appear that the EU are considering a harmonised classification of nitrous oxide as a Category 1B reproductive toxicant. Reproductive toxicant. I'm not entirely sure why but it would stop it being used for all purposes, including catering.

That feels heavy-handed. I guess the reproductive harms could be off the back of the DNA damage from chronic use that we were talking about earlier, the blocking of methionine synthase and DNA methylation pathways.

And interestingly, in 2024 at the UN climate change conference, nitrous oxide was brought up as it's approximately 270 times more potent than carbon dioxide in terms of warming the planet. And it's currently responsible for approximately 10% of net global warming since the industrial revolution. So it's actually quite a harmful thing in terms of its environmental impact.

So I think we're going to wrap this episode up here. I hope you've enjoyed listening this week.

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amazing week and we'll see you next time.

Bye!