Just Nanging Around

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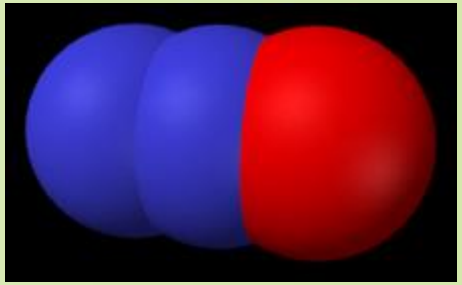
Nitrous Oxide: Background

- Colourless gas
- First synthesised in 1772
- 1844 – first administered as an anesthetic for a tooth extraction



Nanging, nagging, whippets laughing gas

standard N_2O bulb or cartridge has 8 grams of 100% N2O

N_2O

- Oxidation of cobalt ions in vitamin B12 causing inactivation.
- This leads to reduced recycling of homocysteine to methionine.
- Prevents methylation of myelin proteins, thus causing demyelination within the CNS & PNS

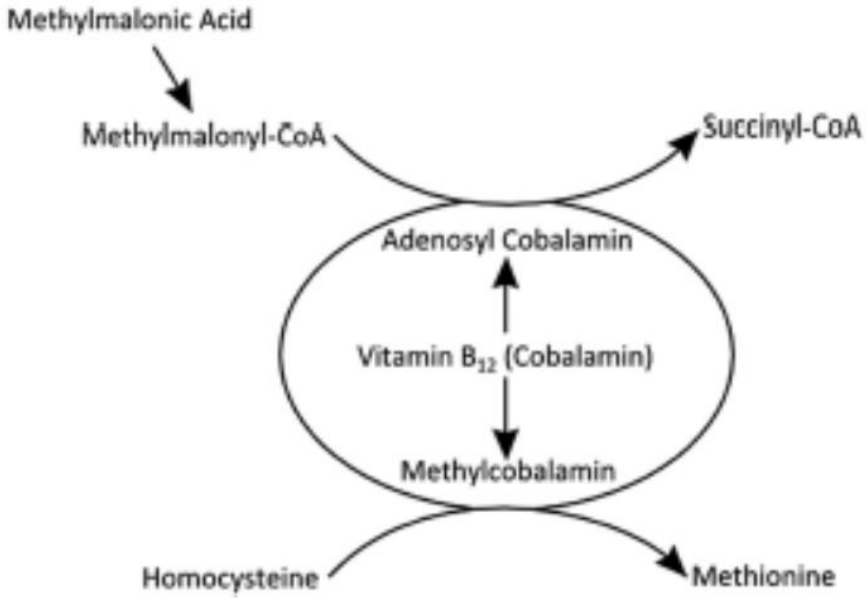
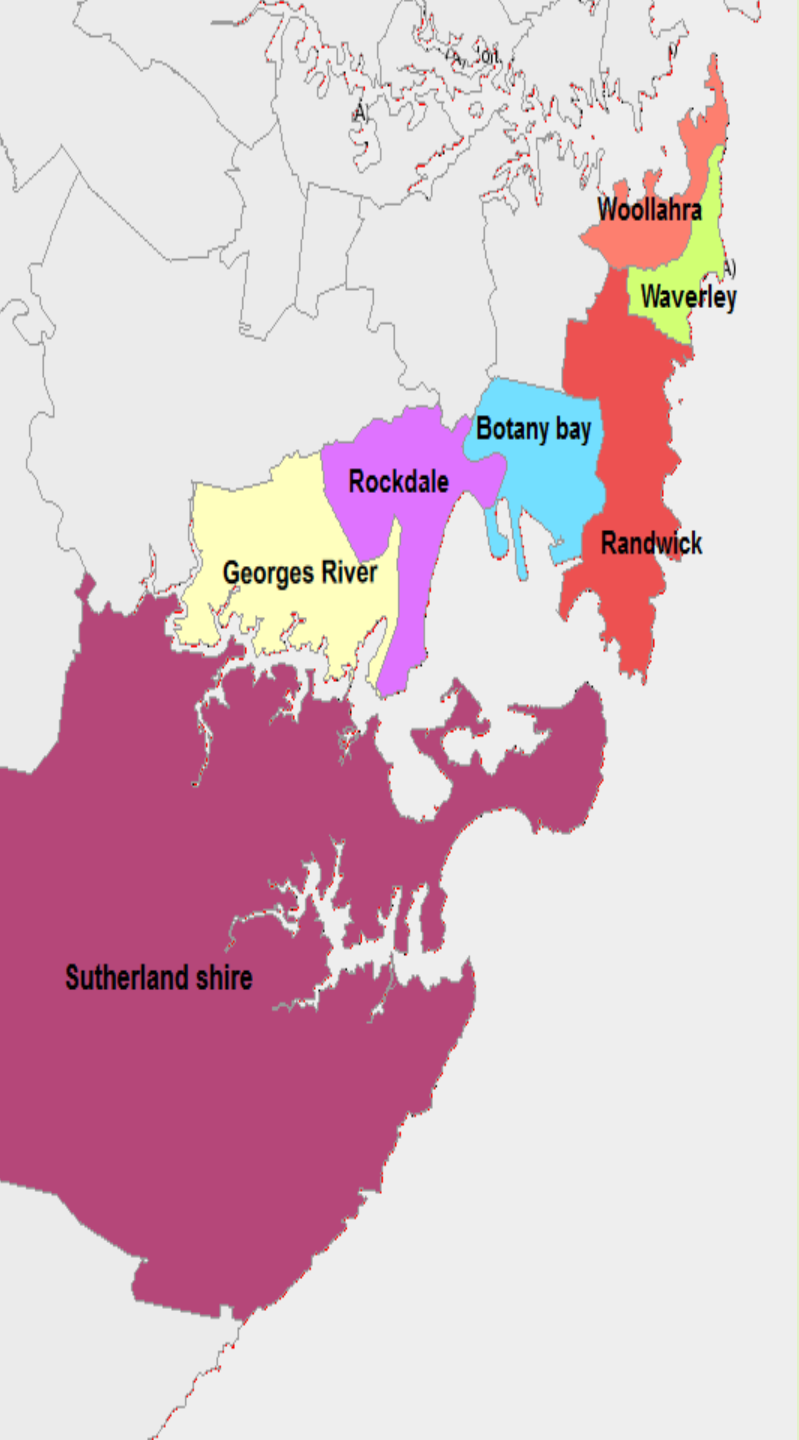


Figure 2 Vitamin B_{12} (cobalamin) is a cofactor in conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA and of homocysteine to methionine. Elevated levels of the substrates methylmalonic acid and homocysteine can be used to detect 'functional' B_{12} deficiency despite normal serum B_{12} concentrations.

Clinical Effects of NO Abuse

- Neurological:
  - Numbness, weakness, change in gait, falls
  - myeloneuropathy
  - subacute combined degeneration
  - peripheral neuropathy or polyneuropathy
- Psychiatric:
  - depression, hallucinations
  - delusions
- Haematological:
  - Anaemia
  - Bone marrow suppression
- Resp:
  - acute respiratory distress syndrome
  - pneumothorax
- Frostbite of the mouth



Case Series: Just Nanging Around

- A retrospective review
- SEATS database
- N_2O presentations – chronic users
- Jan 2017 – June 2019
- Medical records reviewed

- Aim: review the clinical characteristics and outcomes of chronic N_2O use

Demographics

- 7 patients were identified
- 5 patients – chronic use
- 2 acute – 1 frostbite to mouth x 1 ingested cannisters
- 4 females
- Age range: 20 – 26y

Cases

- 20 F:
  - Unable to walk
  - 200 bulbs/day for months
- 23 F:
  - presented unable to walk - 1 week
  - 720 bulbs/day for 1 month
- 20 F:
  - bilateral leg weakness + numbness – 3 weeks
  - 4 months use b/w 360 bulbs/day to 360/week
- 19F:
  - LL numbness (2 m) + LL weakness (2 w)
  - 160 - 360 bulbs/day for 1 year
- 26 M:
  - Hearing voices and depressed
  - 100 bulbs / day for many months increased to 300 bulbs / day for 1 week

Case A

- 20 F

- Bought into hospital by friends with:
  - Confusion
  - Hypotension
  - Fever
  - Difficulty mobilising and multiple falls

History

- Friends report she abuses nitrous oxide ?? amount
- Found lying on the couch with a canister next to her and didn't appear to recognise them
- Patient denies this history when asked and states she has felt unwell for the past few days but cannot elaborate any further
- States only uses NO at parties with friends

Examination

- Observations:
  - Temp: 38.3˚C
  - Systolic BP = 80, HR = 120 bpm.
  - GCS =14 as she is confused.
  - Multiple bruises over her upper and lower limbs and on her face
  - At this time no neurological examination is done

- The initial diagnosis by the junior emergency doctor is she is intoxicated with nitrous oxide causing confusion and possibly has an infection.

Neurological Examination

Investigations

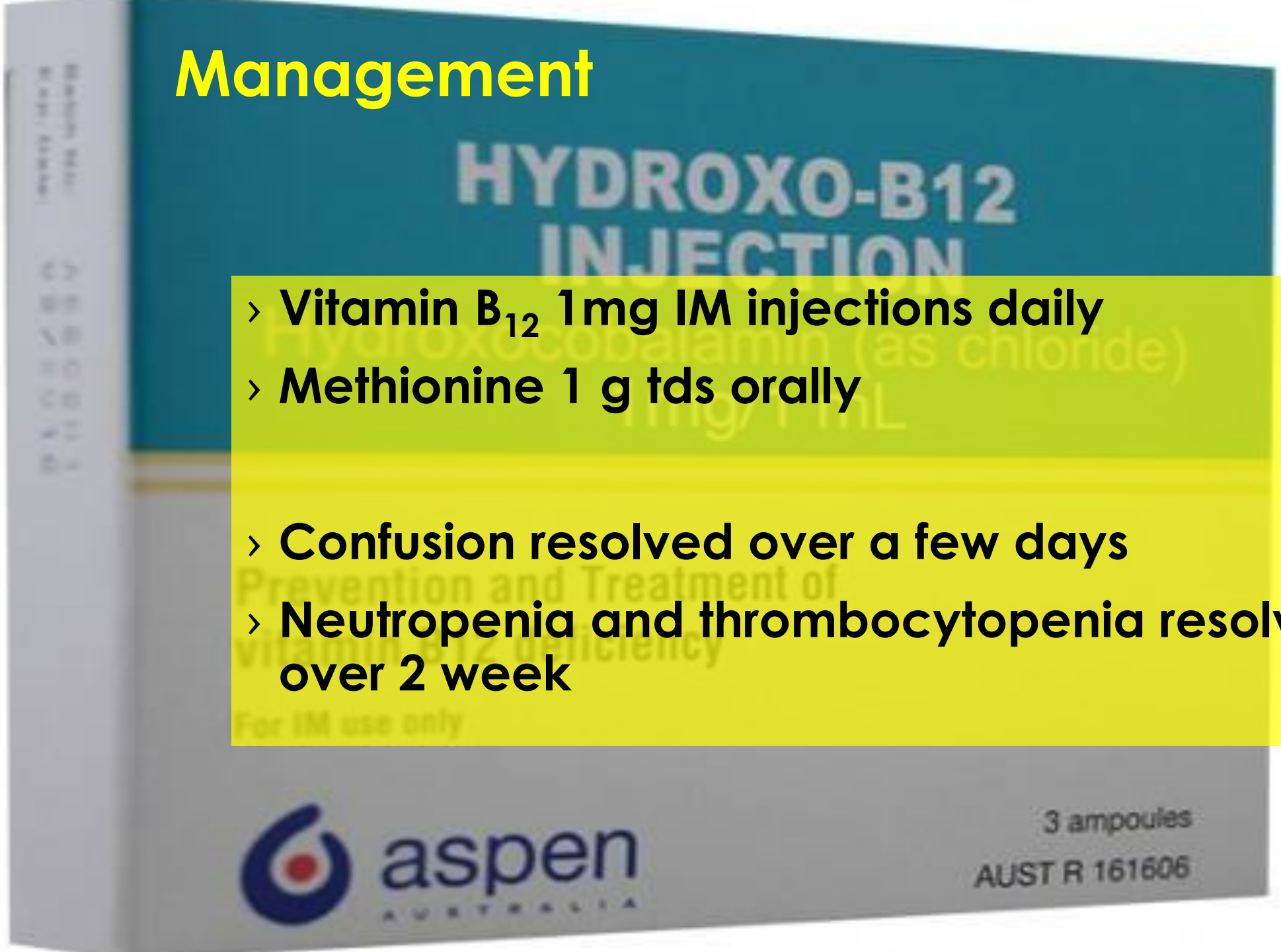
- FBC:
  - WCC 2.81 x 10^9/L with neutrophils 0.34 x 10^9/L (low)
  - Platelets 99 x 10^9/L (low)
  - Hb 74 g/L (low): MCV, MCH and MHCH (all in normal range)
- Iron studies – within normal range
- Vitamin B_{12} : 44 pmol/L (normal range > 221 pmol/L)
- Folate 29.5 nmol/L
- CK 2400 U/L

Neuro Ix

- **MRI:**
  - Bilateral T2 hyperintensity in the dorsal column of the cord giving an "inverted V sign" appearance.
  - Extends from cervicomedullary junction to T5/T6
  - c/w subacute combined degeneration of the spinal cord

- **Nerve conduction studies:**
  - Not well tolerated by the patient so ceased midway
  - Despite the limited study, results appear consistent with a length dependent sensorimotor neuropathy

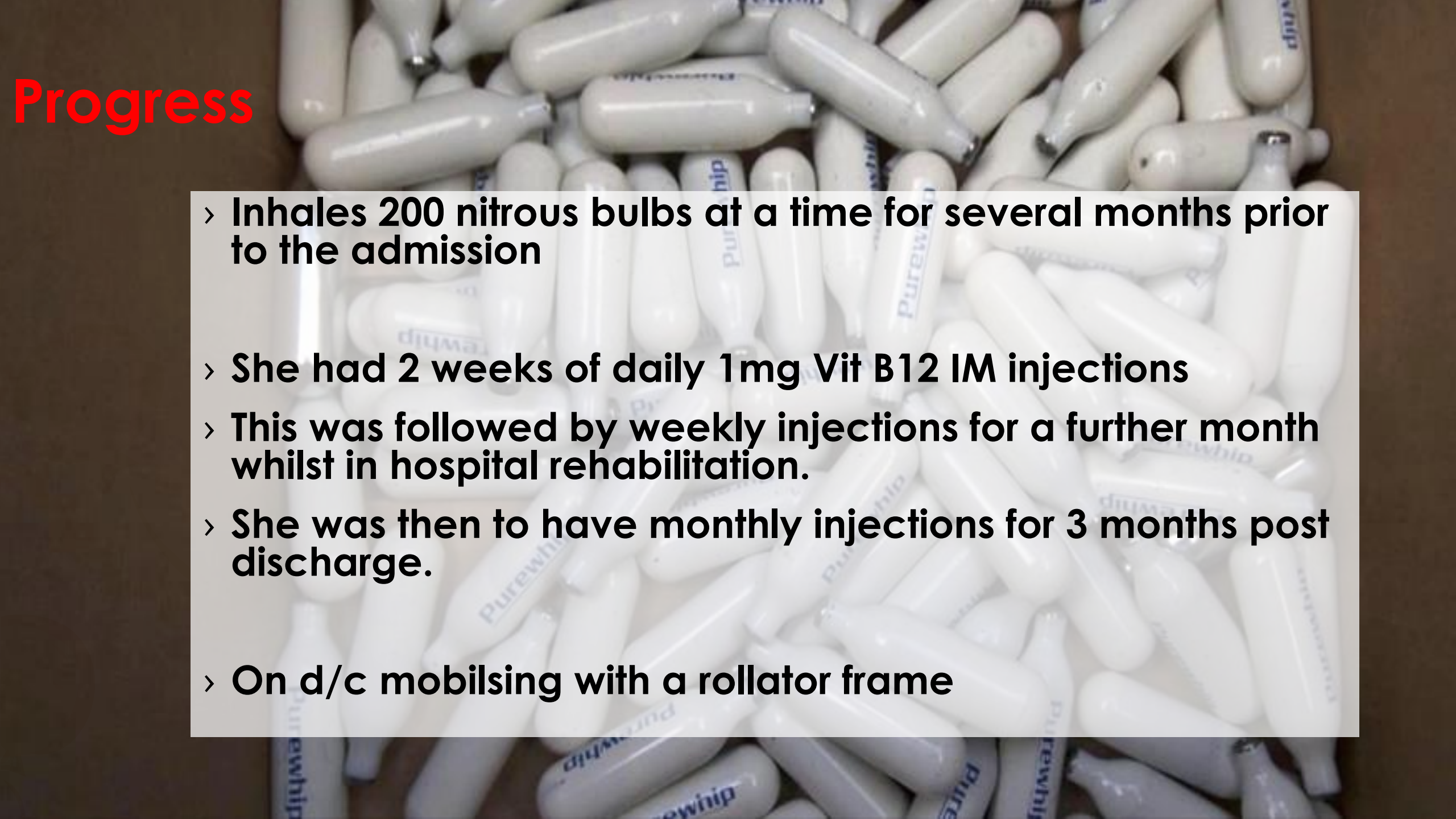
Management



- Vitamin B_{12} 1mg IM injections daily
- Methionine 1 g tds orally

- Confusion resolved over a few days
- Neutropenia and thrombocytopenia resolved over 2 week

Progress



- Inhales 200 nitrous bulbs at a time for several months prior to the admission
- She had 2 weeks of daily 1mg Vit B12 IM injections
- This was followed by weekly injections for a further month whilst in hospital rehabilitation.
- She was then to have monthly injections for 3 months post discharge.
- On d/c mobilsing with a rollator frame

Case Series (5 patients): Investigations

- All 5 patients had a low vitamin B_{12} or holotranscobalamin (active B_{12}) levels.
- 2 patients had evidence of bone marrow suppression.
- 4 neuro Sx:
  - MRI: 3 showed SACD, 1 normal MRI
  - Nerve conduction study in 4 showed sensorimotor axonal neuropathy

Management

- All 5 were treated with high dose vitamin B_{12} and methionine.
- 4 of the 5 had only minor improvement and they were all left with longstanding impaired mobility and sensory deficits.
- 2 represented due to ongoing N_2O use and falls

Prognosis

- No clear evidence to guide prognosis in those with neurological toxicity
- Improvement is slow & most have persistent symptoms neurological symptoms despite vitamin B12 replacement
- Myelin sheath loss will resolve but axonal loss is permanent.
- Case reports suggest prognosis determined by:
  - degree of impairment on presentation
  - length of the abnormality on spinal MRI
  - Romberg & Barbinski signs

Conclusions

- N_2O abuse can result in permanent neurological deficit

- Management involves:
  - Abstaining from further N_2O use
  - Vit B12 IM
  - ?Methionine

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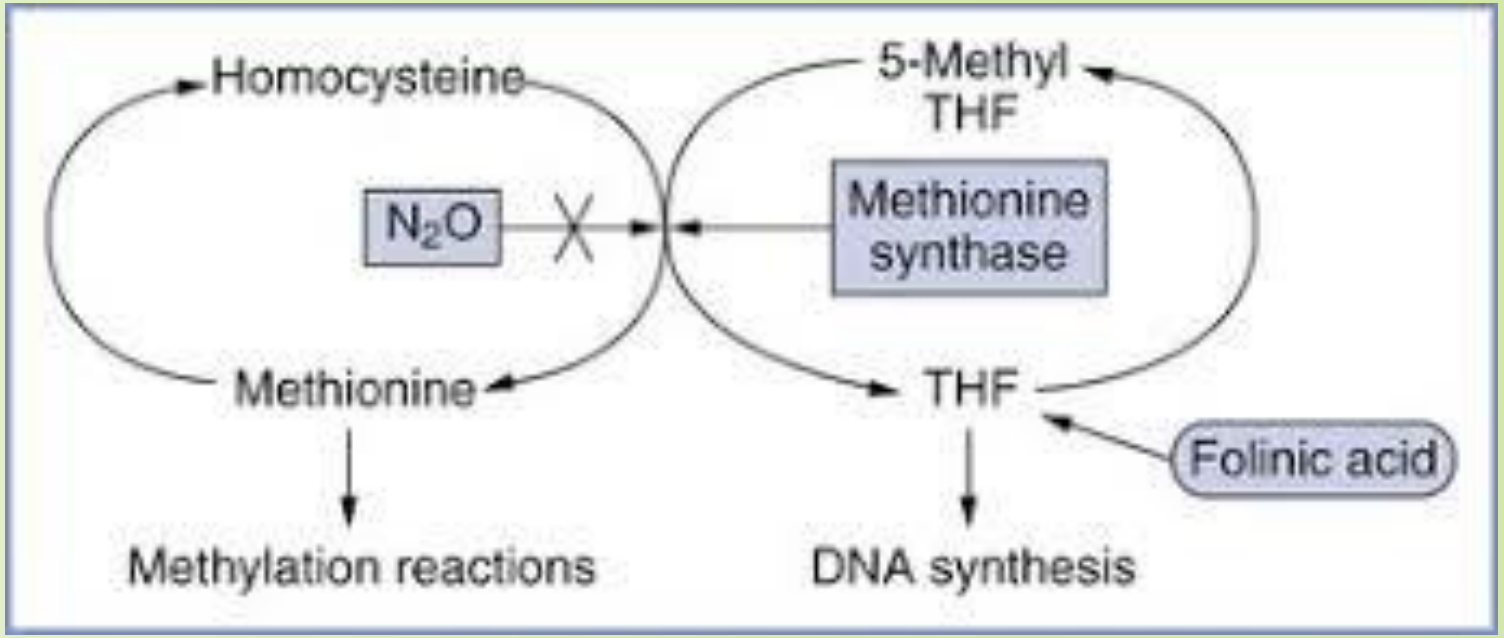
Discussion:
How many bulbs cause neurotoxicity ?

- No known neurological toxicity threshold
- Toxicity related to:
  - Amount of use – exposure
  - Patient's level of Vit B12 (nutritional status)
- Range of use from "few" bulbs to 750 cartridges a day – with large use causing symptoms within weeks
- Reports of SACD resulting from a single short exposure to nitrous oxide anaesthesia in a patient with Vit B12 deficiency

Treatment: Vit B12

- Cease nitrous oxide use.
- IM vitamin B12 injections can aid recovery, even if serum vitamin B12 levels are normal.
- Suggested Vit B12 IM regimen:
  - 1 mg daily for 5 d
  - followed by weekly 1 mg for 2 months

Methionine



- Exogenous methionine provides a direct substrate for methionine synthase, while the body slowly replaces the inactive vitamin B_{12} and commences repletion of endogenous methionine
- Limited evidence – case reports
- Dose: 1g tds oral (SAS) ? Duration