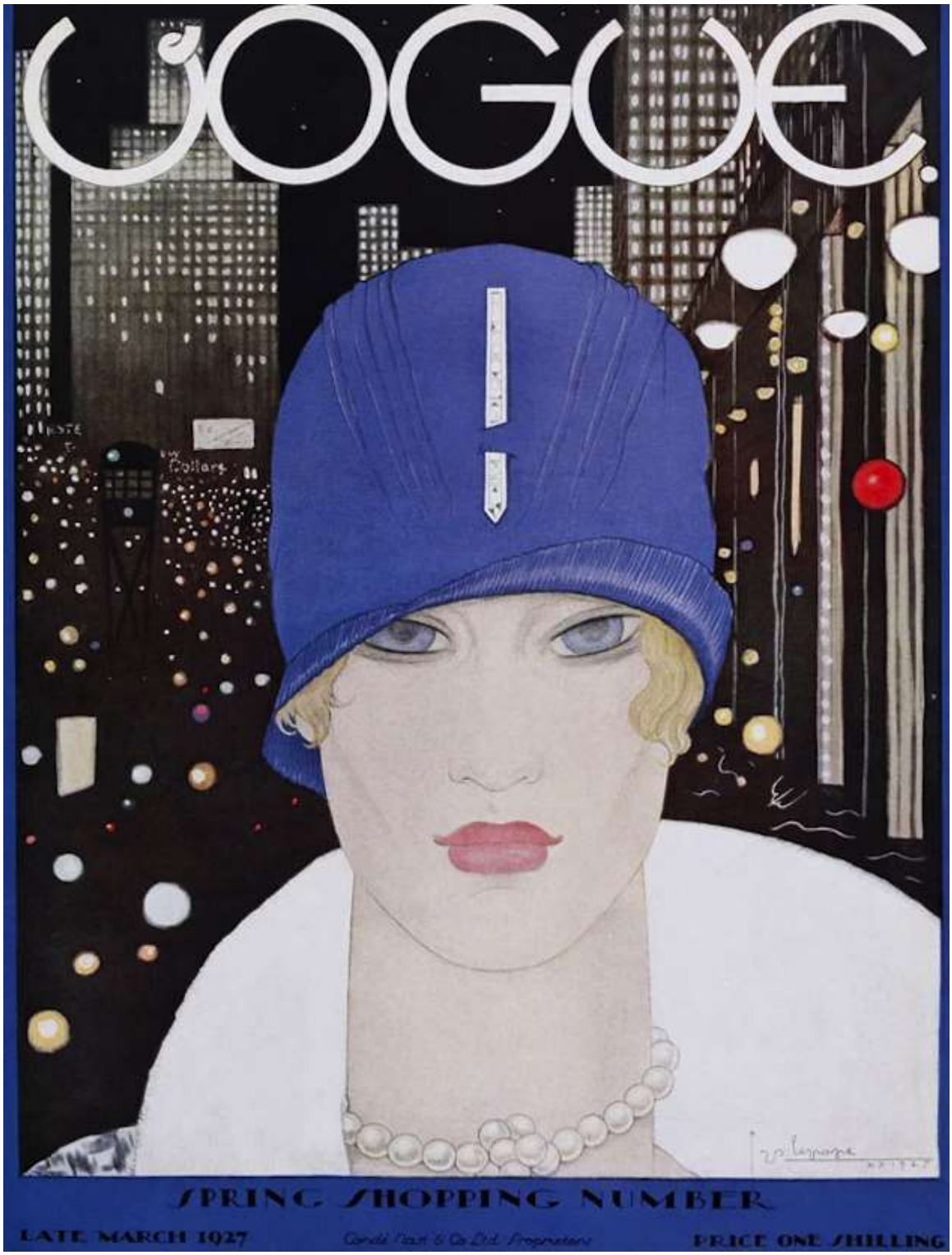
THE NORTHERN HOSPITAL

DISULFIRAM TOXICITY



Lee Miller, Vogue Cover, March 1927, Georges Lepape

"What was chic at Vogue in the winter of 1927 included short hair, Art Deco, Cloche hats, and Cubism, but above all, New York itself - "the crowding of Fifth Avenue with motors flashing in the sun, the tumult of the smart restaurants, the anguished haste of dressmakers and modistes, and the sandwiching of picture exhibitions and special matinees for the illuminati between luncheons at Marguery's and first nights of the luscious and glittering...reviews. Lee Miller looked as if she were one of the smart set, someone for whom modistes stitched and matinees were arranged. Her features would suit the March issue, on the new Paris fashions. She would make her first appearance in Vogue on its cover.

In the 20s it was not yet the practice for magazines to use photographs as cover art. Conde Naste publications featured the work of well-known illustrators like Georges Lepape, who earned as much as $1000 per drawing. Before the war, Lepape had become famous in Paris for his work on Paul Poirit's fashion albums. His sylphs, garbled in sinuous silk and swirling larme, had decorated Vogue for the last ten years, but their poses now looked too languid to illustrate Naste's belief that times had changed. About this time Vanity Fair announced emphatically: "Women don't faint at the slightest provocation. Most girls, before they are twenty, become interested in the world in general and in some work in particular!"

Lepape's cover presents Lee as one of these "girls" - but also as the spirit of the city that had become her theatre of operations. Against the background of Manhattan's night sky she looks straight ahead, a determined figure in a helmet like cloche. His depiction of her short bob and purposeful gaze brought out an androgynous quality, one that was often present in his illustrations but until then had not found its subject. Unlike the willowy figures of earlier Vogue covers, this twenty year old is not only interested in the world but prepared to meet it head-on. The image of Lee Miller as unflappable flapper evoked all that was "moderne", the term in use for streamlined furiture and free-spirited behaviour alike.

The March Vogue actually appeared a month before Lee's twentieth birthday, like an announcement of her emancipation. The issue featured a "confidential guide" to the new French fashions, in which the American reader learned that the Parisienne's approach was not so different from her own. Vogue also promised to simplify the job of shopping in Paris by explaining the rituals of its Spring season. "It is far better to be too informal than too formal", it told the perplexed. Lepape's image of Lee Miller implied that Paris chic could be naturalized in New York provided if one had the right spirit - a blend of determination and insouciance.

Suddenly Lee Miller was in demand with the best-known photographers in New York..."

Carolyn Bourke, "Lee Miller; A Life", Knopf, 2005.

All great Artists, have their inspirations; their ideals, their country, their religion, their philosophy, their madness, their anger, their joy, their pain, the age they lived in, their fiery passions, but above all these, there are also those inspirations a Monarch of past ages would have described as their "courtesans" or the wealthy of the Parisian, "Belle Epoch", their "demimonde". But to Artists, inspiration had to be more than these, they

had their "muses". Lovers, yes, but also, soul mates, kindred spirits and in their own rights, often talented Artists, themselves.

The list of the muses (female on the whole yes, but occasionally male as well) is long and endlessly fascinating; personalities often brilliant, sometimes full of the "joie de vivre", but sometimes disturbed and tortured as well, and sometimes all these at the same time. In the Twentieth century one muse stood apart. He name was Lee Miller, but the term "muse", seems hardly appropriate for her. In truth she was no man's "muse", she was a child of the roaring Twenties, quintessentially chic and very "moderne"; the very prototype of the liberated "flapper". In her "muse" relationships with two of the Twentieth century's most famous and influential Artists, Pablo Picasso and Man Ray, indeed it was difficult to tell who was "muse" to who. Lee called the shots, men would fall at her feet - if they didn't like that arrangement, she swiftly moved then on! She lived an extraordinary life; her guiding principle being security but not at the expense of her independence or freedom. She was able to live the extraordinary life that she did and that she wanted for varied reasons, not the least of which were her privileged background, her boundless sense of adventure and her liberated sexuality; but there was one particular gift above all these that fortune bestowed upon Lee - she was one of the most beautiful women of the Twentieth century. All these assets would combine to make her one of the most famous of women in the twenties, the thirties and the forties. Beauty of course is only skin deep, its allure gives power according to the eye of the beholder. Lee could not have lived the life that she did if all she had was her looks. Self-educated in the "school of life", she was hopelessly untamed for any formal schooling, she was constantly able to adapt to the rapidly changing world of the Twentieth century - dancer, flapper girl, vogue super-model, muse to Edward Steichen, Man Ray and Pablo Picasso, professional photographer to the rich and famous, wartime photojournalist and correspondent, (an extraordinary achievement for a woman in the 40s, and one in which she also saw active combat, the only female journalist to do so in the Allied Armies in Europe), in her later years she became one of the earliest "celebrity gourmets".

Natures endowments, and innate talents, are not always enough to ensure success in life. The great leveler of course is also the factor of pure contingency or opportunity! Lee Miller, like Marilyn Monroe, Claudia Schiffer, and the Pre-Raphaelite "stunners" of the previous century, was "discovered" by pure accident! Whist crossing a busy New York street one day she was almost run over by a speeding car, only to be rescued at the critical moment by none other than Conde Nast - owner of Vogue Magazine. Nast was looking for a girl who would define for his readers, the essence of the "moderne", the confident and independent flapper girl of New York City - he could not possibly have done better!

Nature assuredly smiled on Lee Miller, but she was far from the perfect goddess of legend. She was constantly torn between her desire for security and her ungoverned passion for independence - perhaps we see in this an explanation for her two husbands and innumerable lovers - frequently juggled at one and the same time! Raped at the age of 7 years, sexually promiscuous, she suffered what would today be termed PTSD due her experiences in the Second World War, in particular in relation to the horrors of Dachau, to which she was an eye witness. Lee in her later years suffered from depression and heavy alcohol use. Today we understand much more clearly the syndrome of PTSD as

well as the desperate ravages of uncontrolled alcohol abuse. We apply a range of strategies to combat this abuse amoung them, the deterrent agent disulfiram. This agent is not suitable for everyone. An iron discipline is required, as well as the strictest of supervision and control. One suspects that disulfiram would not have been an ideal strategy for the brilliant but troubled Lee Miller. Like Lee herself, it is interesting to note that disulfiram was discovered quite by accident!

Left: Lee Miller, silver gelatin black and white photograph, 1930, Man Ray

Right: Lee Miller, Vogue super-model, 1928, Edward Steichen.

DISULFIRAM TOXICITY

Introduction

Disulfiram (trade name in Australia, **"Antabuse"**) is a drug designed to act as a deterrent to alcohol consumption in patients as an aid to their overall management of chronic alcoholism.

It acts by blocking the action **o**f **aldehyde dehydrogenase** thereby allowing the build up of this toxic metabolite of alcohol, which normally is rapidly eliminated from the body by the action of **aldehyde dehydrogenase.**

The unpleasant symptoms that occur as a result of acetaldehyde act as a deterrent to further alcohol consumption.

If alcohol consumption is nonetheless continued and/or disulfiram overdose occurs in conjunction with alcohol consumption, then serious toxic effects can occur as a result of excessive acetaldehyde accumulation.

Serious adverse effects can also occur with disulfiram overdose in patients not consuming alcohol, due to intrinsic toxicity of disulfiram itself.

See also separate document on Disulfiram (in Drugs folder).

History

The drug's action was discovered by accident in 1948 by researchers Erik Jacobsen, Jens Hald, and Kenneth Ferguson

The substance was intended to provide a remedy for parasitic infestations; however, workers testing it on themselves reported severe symptoms after alcohol consumption.

Preparation

Tablets:

- 200 mg.

Pharmacokinetics

Absorption:

- Absorption of disulfiram from the gastrointestinal tract is rapid but incomplete and approximately 20 % is excreted in the faeces.

Distribution:

- Disulfiram has high lipid solubility

It is therefore widely distributed and accumulates in various fat depots.

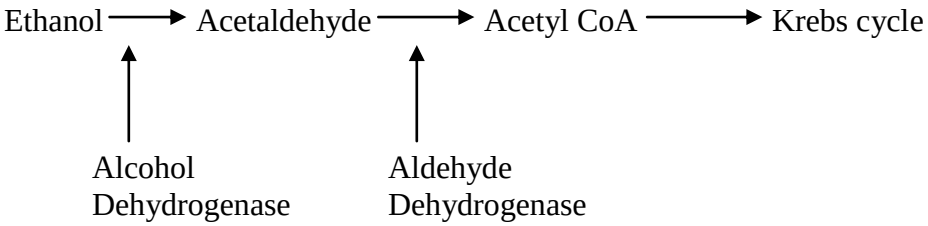
Up to 20 % of a dose may remain in the body for one week or longer.

Metabolism and excretion:

- Disulfiram is rapidly metabolised to di-ethyl-di-thiocarbamate (DDC), which is partly excreted as carbon disulfide in the expired air and is partly metabolised in the liver to Me-DDC.

Pathophysiology

The predominant pathway for alcohol metabolism is as follows:



Disulfiram prevents the usual metabolism of alcohol by irreversibly inhibits aldehyde dehydrogenase, thus blocking acetaldehyde breakdown, which causes unpleasant, and potentially serious effects if alcohol is consumed.

Disulfiram *itself* is toxic if taken as an overdose, regardless of whether concurrent alcohol has been consumed.

Serious **neurotoxicity** has been observed.

Basal ganglia lesions that develop after disulfiram toxicity may be due to carbon disulfide, one of the disulfiram metabolites. Symptoms induced by carbon disulfide, including Parkinsonism and peripheral neuropathies, resemble those of disulfiram intoxication. [5]

Risk assessment

Alcohol associated:

The milder adverse effects of disulfiram are to be expected as a “normal” response if alcohol is consumed.

If larger amounts or ongoing alcohol is consumed and/ or the patient overdoses on disulfiram whilst consuming alcohol, adverse effects become much more serious and can be life-threatening.

Non-alcohol associated overdose:

Disulfiram can have its own intrinsic and potentially serious adverse effects if taken in overdose, even in the absence of concurrent alcohol consumption.

Although **most patients** will develop symptoms within the first **12 hours**, there are case reports of clinical deterioration days after an overdose, with slow recovery and long-term sequelae. [5]

Children may be more prone to toxic effects

Clinical features

Disulfiram taken with alcohol:

Disulfiram is relatively pharmacologically inert when taken in small doses.

Ingestion of alcohol results in a raised blood acetaldehyde concentration, which gives rise to the aldehyde reaction which includes:

1. Tachycardia / palpitations
2. Headache.
3. Intense flushing
    - The cutaneous flushing is caused by vasodilatation
4. Sweating
5. Restlessness/ anxiety and a sense of impending doom may develop.
6. Chest pains
7. Dyspnoea/ hyperventilation

Note that unpleasant effects may occur after taking even small amounts of alcohol used in cooking.

Disulfiram-ethanol reactions often develop within **15 minutes** after exposure to ethanol; symptoms usually peak within **30 minutes to 1 hour**, and then gradually subside over the next few hours

After stopping treatment **new** alcohol dehydrogenase must be synthesized before metabolism of alcohol returns to normal. This usually takes 7–10 days, but may take as long as 3 weeks.

Patients may still experience adverse effects if they drink alcohol within **7 days** after ceasing treatment.

Note that there is marked *individual variation* in response to alcohol; some react to very small amounts while others may have relatively little reaction despite consuming large doses of alcohol.

The milder adverse effects of disulfiram are to be expected as a "normal" response if alcohol is consumed.

If ongoing alcohol is consumed and/ or the patient overdoses on disulfiram whilst consuming alcohol, adverse effects become much more serious and can be life-threatening.

The more severe / life-threatening reactions can include:

1. CNS:
    - Seizures
    - Coma
2. Vomiting
3. CVS:
    - Initial hypertension
    - Hypotension
    - Cardiac electrical disturbances:
        - ♥ QRS prolongation is a complication of sodium channel blockade and may be associated with life threatening ventricular arrhythmias
        - ♥ QT prolongation occurs due to potassium channel blockade and may provoke torsade de pointes ventricular tachycardia.
4. Respiratory:
    - Dyspnea Bronchospasm/ hypoxia
    - Respiratory depression

Rarely:

5. Methaemoglobinaemia may be induced.

Disulfiram overdose in the absence of alcohol: [5]

Features may be delayed for up to **12 hours.**

They may include:

1. GIT upset:
    - Nausea, vomiting, abdominal pain, diarrhoea
2. CVS:
    - Tachycardia
    - Hypotension
3. Tachypnoea
4. Hyperthermia
5. CNS:
    - Drowsiness
    - Delirium
    - Reduced tendon reflexes
    - Seizures/ coma (in severe cases).

    Rarely:

    - Sensorimotor neuropathy
    - EEG abnormalities, encephalopathy
    - Psychosis and catatonia, which may appear several days after overdose.
    - Dysarthria
    - Movement disorders:
        - ♥ Myoclonus
        - ♥ Ataxia
        - ♥ Dystonia

- ♥ Akinesia

These movement disorders may be related to direct toxic effects on the basal ganglia.

Persistent neurologic abnormalities lasting for weeks to months can occur in both adults and children.

6. Metabolic:

- Hyperglycaemia
- Ketosis (often disproportionate to the degree of dehydration)
- Methaemoglobinaemia has been reported.

If alcohol has also been coingested patients may *also* have serious toxic disulfiram-ethanol reaction.

Investigations

Blood tests:

1. FBE
2. U&Es/ glucose
3. LFTs
4. Blood alcohol level
5. Methaemoglobin concentration

Others as clinically indicated:

5. ABGs/ VBGs/ lactate
7. Lipase

ECG:

Look for:

- Arrhythmias
- Prolonged QRS

- Prolonged QT

Management

Alcohol related reactions:

1. Immediate attention to any ABC issues

2. Seizures are treated along standard lines.

3 Hypotension

- IV fluids as required

- Inotropes as required:

  ♥ Noradrenaline is possibly the best inotrope to use.

  Disulfiram and its chief metabolite, diethyl-di-thiocarbamide (DDC) also inhibit the enzyme dopamine-beta-hydroxylase. This results in reduced synthesis of **noradrenaline,** which may contribute to hypotension. [3]

4. QRS and QT prolongation:

- Sodium bicarbonate may reduce the QRS duration and risk of arrhythmia

- Magnesium sulphate should be administered urgently to patients with torsade de pointes.

  Magnesium sulphate can also be given to patients with prolonged QT to reduce the risk of torsade de pointes; however, administration of magnesium does not shorten the QT interval.

5. Consider treatment with **methylene blue** if methaemoglobin concentration is 30 % or more.

- Note that methaemoglobinaemia may recur after treatment. If cyanosis recurs, check methaemoglobin concentration again. [4]

6. Antihistamines may be given for distressing flushing

7. **Fomepizole** (where available) may be considered for severe reactions.

- **Fomepizole** or **4-methylpyrazole** is used as an antidote in confirmed or suspected methanol or ethylene glycol poisoning.

It is a competitive inhibitor of the enzyme **alcohol dehydrogenase.**

It may provide benefit by *blocking the conversion of ethanol to its toxic acetaldehyde metabolite.* [4]

8. Hemodialysis: [6]

- Hemodialysis has not been systematically evaluated in the context of the disulfiram-ethanol interaction.

  However it has been used in life-threatening cases, with apparent success at removing ethanol, acetaldehyde, and disulfiram, resulting in relatively prompt reversal of symptoms.

Overdose not associated with alcohol use:

1. Immediate attention to any ABC issues

2. Charcoal:

- The benefit of gastric decontamination is **uncertain.**

- *Consider* activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if an adult has ingested more than **30 mg/kg within 1 hour**, or for any amount in a child. [5]

- Patients should be alert, cooperative and stable.

2. Seizures are treated along standard lines.

3 Hypotension

- IV fluids as required

- Noradrenaline infusion, as required.

4. Consider treatment with **methylene blue** if methaemoglobin concentration is 30 % or more.

Disposition

Patients who have taken alcohol whilst on disulfiram:

- Asymptomatic patients should be observed for 6 hours after ingestion.

- Observe symptomatic patients for a **minimum** of 8 hours post ingestion. [4]

Patients who have overdosed on disulfiram:

- Onset of symptoms may be delayed for up to 12 hours. [5]
- Patients should therefore be observed for a *minimum* of 12 hours.
- Longer term follow-up may be required for persistent neurological symptoms.

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Dr J. Hayes

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