Occupational Medicine

Toxic gases

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Summary: An overview of the widespread use of gases and some volatile solvents in modern society is given. The usual circumstances in which undue exposure may occur are described. The most prominent symptoms and general principles of diagnosis and treatment are given and are followed by more specific information on the commoner, more toxic materials. While acute poisonings constitute the greater part of the paper, some indication of chronic disorders arising from repeated or prolonged exposure is also given.

Introduction

Poisoning due to the inhalation of toxic gases, or asphyxiation as a result of inhalation of a non-toxic, but oxygen deficient, atmosphere is not uncommon. With the exception of poisoning by carbon monoxide these events fortunately result in relatively few deaths. In England and Wales in 1985, 145 accidental deaths were recorded in the group 'Gases and Vapours';¹ in the same year 1365 deaths from carbon monoxide poisoning were recorded.²

Uses of gases

Gases are used extensively in modern society. Many are simply chemical reagents. The electronics industry, for example, uses large volumes of highly toxic gases for etching and doping processes in the manufacture of silicon and gallium arsenide semiconductors; arsine, phosphine, borane and silane are examples of the gases used. The chemical industry processes large quantities of hydrocarbons, chlorine, ammonia, sulphur dioxide and many other gases in the manufacture of solvents, fertilisers, plastics and the myriad requirements of modern society.

Most welding is carried out using shielding gases to inhibit oxidation of the boiling and vaporizing metal at the weld point. Argon, helium and carbon dioxide are extensively used.

Liquid nitrogen is ubiquitous. Its boiling point is -199°C . Examples of its uses are for commercial freezers, in inert gas blanketing systems, in civil engineering for land solidification so that drilling and shuttering can take place in wet conditions, and in manufacturing to shrink fit metal parts.

As well as for breathing purposes in clinical and industrial locations, oxygen is used extensively for flame enrichment to provide much higher furnace temperatures than would otherwise be possible. This enables higher production at a more economic cost in smelting and especially in steel making.

Natural gas, which is largely methane, is an important industrial and domestic fuel. Volatile hydrocarbons are used widely in varying formulations as solvents in paints, enamels, and for the cleaning of soiled metal parts; exposures to them are probably those most commonly encountered in industry and in commercial life.

Characteristics of gases and vapours

A gas is a state of matter in which the molecules move freely, allowing infinite expansion. A vapour is a gas below its critical temperature which may be liquefied by an increase in pressure. Gas molecules mix easily with each other. Vapour pressure is the pressure exerted by a gas, a mixture of gases, or a vapour. Vapour pressure is directly related to volatility. Vapour pressure increases with temperature. Relative density is the density of a gas or vapour compared with that of air. The greater the density the more likely it is that the gas will creep to the lowest level it can find.

When considering exposures, the temperature of a gas matters rather more than its density: many gases in common use are stored or transported as liquids, often at extremely low temperatures. Cold gases, most commonly nitrogen arising from the liquid phase, will seek low places and can produce an unexpected irrespirable atmosphere. The degree of solubility of a gas may determine a local or systemic effect.

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Effects of inhalation of gases

Inert gases act as simple asphyxiants by diluting or displacing atmospheric oxygen. Some inert gases and many vapours, notably simple hydrocarbons and solvents, have anaesthetic properties. Some gases are highly reactive chemicals and are therefore irritant or corrosive. Some have acute or chronic systemic actions due to their specific chemical nature. A soluble corrosive gas or vapour, if inhaled in high concentration, will exert its effect mainly on the upper respiratory tract, laryngeal oedema or spasm causing death while the lungs may remain unsullied.

The upper respiratory passages, which bear the brunt of corrosive or severely irritant contact, are constricted at the larynx. This predisposes to laryngeal oedema. The total lung area available for gas exchange is about seventy square metres. The time taken for a gas molecule to traverse the lung and reach the brain is about 15 seconds. An increase in physical activity will clearly increase the uptake of a gas; ventilation rises from about 8 litres/minute at rest up to 120 litres/minute with violent exercise and so a poison which may take effect after some minutes in a resting subject, may be fatal in the same subject after only a few seconds of heavy exertion.

General principles of diagnosis

Non-irritant toxic inhalant exposures produce symptoms which may vary from lightheadedness to deep coma; mildly irritant inhalants may produce few symptoms at the onset but, depending on the gas concerned, may be followed by increasing severe breathlessness and pulmonary oedema.

Corrosive exposures are diagnostically straightforward but non-irritant ones may present difficulties. The age and sex of the patient and the situation where he or she was taken ill give most help. Young and old in domestic circumstances are more likely to be victims of carbon monoxide poisoning than anything else. Men working in heavy or light industry or as journeymen fitters are more likely to have been overcome by a toxic inhalant. There will probably be an indication of the cause, but every effort should be made to confirm the identity of any suspected toxic agent.

A patient with chronic ill-health will withstand acute respiratory, systemic or localized damage less well than a healthy person, so that at the least, a rapid cardiovascular and respiratory history should be taken, otherwise a relatively innocuous exposure may produce a confusingly severe response.

Classification of toxic gases and vapours

For clinical purposes it is convenient to clarify gases and vapours into those broad groups which produce acute or chronic effects. These may be further subdivided into those which are locally non-irritant, irritant to a mild or severe extent with acute or delayed responses, and those which have systemic actions. There is, of course, a vast number of these substances but in hospital practice only a relatively small number is important.

General principles of treatment

Standard monitoring and resuscitation procedures are necessary in all cases of collapse or unconsciousness. A chest film should be taken if there is any suspicion of pulmonary oedema. Urgent treatment for the adult respiratory distress syndrome may also be required. Whenever corrosive effects are apparent about the eyes, mouth, nose or skin, flooding with water for some minutes is important. Eyes subject to acid or alkali contact should be drip irrigated with normal saline from the inner canthus across the eye surface for at least 20 minutes, preferably longer.³ This is particularly important with alkali contact, the commonest gaseous contact being ammonia. Specific biochemical reactions may occur in some exposures, much the commonest being due to carbon monoxide, but which may rarely be due to cyanides, arsine or other gases.

Cold injury

It is appropriate to mention here the rare possibility of acute hypothermia in conditions of exposure to rapidly vaporizing liquid gas, or the less rare but still uncommon severe frostbite injury due to immersion in or splashing with a liquefied gas. The longer hypothermia takes to develop the more profound the biochemical disturbances. The essential first treatment is rest and rewarming. Monitoring of core temperature and blood chemistry is essential.

Frostbite injury may be severe and totally destructive. Gradual rewarming of the part by immersion in water kept at 40°C is the first objective. Freedom from infection must be ensured. Disruption of cell membranes by ice crystals is the essential lesion and upon the degree of damage will depend the chances of recovery. The pathogenesis and treatment of these injuries is well described by Worsley.⁴

Consequences of exposure and treatment

The results of inhalation exposure in the particular circumstances and to the most frequently encountered gas or vapour are now given along with the essentials of treatment.

A. Acute collapse with little evidence of local irritation

The most common causes are exposures to the following:

Solvent vapours 1,1,1-trichloroethane (methylchloroform) is a widely used general degreasing agent; trichloroethylene is a general degreasing agent; dichloromethane is a fire retardant; perchloroethylene is a dry cleaning solvent.

Liquefied petroleum gases used in welding and heating.

Fluorinated hydrocarbons used as refrigerants and specialized solvents. Many have anaesthetic properties.

Carbon dioxide met with in the brewing and pharmaceutical industries.

Methane natural gas.

Inert gases argon, nitrogen, helium and many others which are used in welding, as inerting agents or as chemical intermediates.

Oxygen deprivation confined spaces or tanks contaminated with any of the above.

Treatment for exposure to all these gases or vapours is the application of symptomatic resuscitation, the depth of unconsciousness being the indication for the energy of therapy. Oxygen is mandatory.

Carbon monoxide

Carbon monoxide (CO) is the commonest toxic gas. It is odourless, colourless and non-irritant. It is produced whenever combustion is incomplete; flame heaters in badly ventilated rooms are particularly hazardous.

The biochemical action of CO is to bind to haemoglobin and so to reduce the oxygen carrying capacity of the blood. There is distortion of the oxygen dissociation curve⁵ and tissue anoxia is greater than the simple reduction in oxygen-carrying capacity. Commonly found blood levels are: normal non-smoking city dweller – 2% carboxyhaemoglobin; average smoking city dweller – 7–10% carboxyhaemoglobin; and heavy smoking city dweller – 10–15% carboxyhaemoglobin.

Continual exposure to relatively low levels produces symptoms, the most prominent of which is headache. Table I (Guidance Note EH43:1984) gives the typical symptoms to increasing exposures.

Table I Clinical effects of carbon monoxide in air

<i>Parts per million</i>	<i>Effect</i>
50	Recommended Exposure Limit (8 hours time weighted average concentration)
200	Headache after about 7 hours if resting or after 2 hours' exertion
400	Headache with discomfort with possibility of collapse after 2 hours at rest or 45 minutes of exertion
1200	Palpitation after 30 minutes at rest or 10 minutes exertion
2000	Unconscious after 30 minutes at rest or 10 minutes exertion

Chronic symptoms are said to occur and are probably a result of direct action on cytochrome oxidase and perhaps other oxidative systems as well as an effective reduction in oxygen availability.⁶

In acute poisoning the classical cherry red appearance should not be relied upon. Levels of carboxyhaemoglobin between 20% and 50% produce, as well as headache, breathlessness, nausea, weakness and impaired judgement; collapse or fainting on exertion are common. Neuropsychiatric disorders may develop after severe carbon monoxide exposures; necrosis of the globus pallidus is a well recognized sequel.⁷

Victims of poisoning should be treated with 100% oxygen using a well fitting face mask. Intubation will be needed in unconscious patients. It is standard practice for physicians working in environments where exposures are not uncommon (some chemical processes, steel works, metal refining) not to allow victims home until the carboxyhaemoglobin level has fallen to 5%. Hyperbaric oxygen is advocated in patients with a history of unconsciousness and has been said to reduce the incidence of neuropsychiatric sequelae.⁸

In a comprehensive review of carbon monoxide poisoning, Meredith and Vale⁹ recommend the use of hyperbaric oxygen and give the contact numbers for naval compression units. The duty diving officer or duty staff officer to Flag Officer Portsmouth will advise on the availability of compression chambers: day – Portsmouth (0705) 822351, extension 41769; night – Portsmouth (0705) 822351, extension 22008.

Table II gives a list of NHS hyperbaric units willing to accept such cases after discussion with the unit.¹⁰ Patients resuscitated after having been unconscious should be assessed for neurological deficit after recovery.

Table II National Health Service Hyperbaric Units

Heatherwood Hospital, Ascot	0990 23333*
Whipps Cross Hospital, London E11	01 539 5522
Peterborough District Hospital, Peterborough	0733 67451
Royal Victoria Infirmary, Newcastle-upon-Tyne	091 232 5131
Monsall Hospital, Manchester	061 205 2393

* Telephone numbers

Cyanides

The gaseous cyanides are cyanogen (C_2N_2), cyanogen chloride (NCCI) and hydrogen cyanide (HCN). They are all used in chemical synthesis; HCN, and the solid sodium cyanide and potassium cyanide are used in solution in electroplating. Acrylonitrile (C_2H_3CN) is a volatile liquid, the liquid being easily absorbed through the skin and the vapour through the lungs. The CN radical inactivates cytochrome oxidase which is the last of a ladder of cytochromes being alternately reduced and oxidized. Reduced cytochrome oxidase is oxidized by molecular oxygen and the CN radical blocks this action.

Cyanogen chloride is much more toxic than the other cyanides and highly reactive, producing a bloody exudate from the respiratory tract and pulmonary oedema. Treatment is immediately for the adult respiratory distress syndrome. Insufficient CN radical is absorbed to inhibit cytochrome oxidase should the victim survive.

The rapidity of cyanide poisoning depends upon the rate of its absorption: the gaseous cyanides are immediately absorbed and if exposure is at all high, collapse occurs at once and death is imminent. Less intense exposures produce breathlessness and light-headedness: increasing drowsiness is the most important sign of a deepening degree of poisoning.

The victim should have been given amyl nitrite capsule inhalations at the place of work and probably oxygen as well. If these measures have not already been taken before arrival at hospital they should be taken at once. If there has been skin splashing, the victim should be stripped and showered. Blood should be taken for cyanide measurement. Levels of 300 mg/dl (111 mmol/l) have been recorded in victims successfully treated.¹¹ Decreasing consciousness is an indication for slow intravenous injection of chelating agent cobalt edetate ('kelocyanor'). This treatment may unfortunately produce a rapid fall in blood pressure, pulmonary oedema and acidosis (all of which may develop in cyanide poisoning anyway) and perhaps anaphylaxis.¹² Sodium nitrite 300 mg intravenously, followed by 25 g sodium thiosulphate in sterile water may be given if sodium edetate is ineffective.¹³

A treatment set containing all these drugs with

instructions for administration will usually accompany any victim of industrial exposure to hospital. Any severely affected victim should be treated in an intensive care unit, with 100% oxygen, with monitoring of pulmonary and cardiac function and of acidosis.

B. Acute collapse with varying degrees of irritation

Arsine

Arsine (AsH_3) is extremely toxic and moderately irritant. It is used extensively in the semiconductor industry. Exposure arises from accidental leakage of cylinders containing arsine, pipework failures or by the action of nascent hydrogen on a solution of an arsenic compound such as might occur in a scrap yard or crude smelter: the victim therefore is employed in handling or transporting cylinders, in sophisticated electronic manufacturing or in metal processing.

Arsine combines with oxidized haemoglobin. Haemolysis follows and depending upon the extent of exposure, may be almost total. The cellular debris and sludge affects the microcirculation, especially that of the kidneys. Muscle necrosis also takes place. Pulmonary oedema due to irritation and sludging in the pulmonary capillaries may occur. The bone marrow is itself poisoned. The victim is thus increasingly hypoxaemic and the essential systems on the brink of absolute failure.

The diagnosis is made by remembering the possibility of poisoning with arsine in patients with acutely increasing haemolysis and toxemia. Red urine, an enlarged liver and later, an orange pigmentation may develop.

The normal level of arsenic in blood and urine is less than 0.02 mg/l. Measurements should be made at once, and if the diagnosis is confirmed, every day. If the kidneys are still functioning moderately well, forced diuresis is useful. If renal function is failing, exchange transfusions are made. In very severely ill patients, exchange transfusion should take place immediately and may need to be repeated. The hypoxaemia is corrected and circulating arsenic removed. Convalescence is usually prolonged. A clear account of treatment of acute poisoning is given by Wilkinson *et al.*¹⁴

Hydrogen sulphide

Hydrogen sulphide (H_2S) is colourless and smells of rotten eggs. It occurs wherever sulphur is present, from decay of organic matter, in crude oils, in desulphurizing processes in oil refining, and as a by product in many processes. The gas is intensely poisonous; low concentrations are irritant. The gas is oxidized in the blood by uncertain mechanisms, but if

a level is reached which overwhelms these mechanisms, death occurs rapidly. One hundred per cent oxygen by tight fitting mask should be given if collapse is present: the eyes should be irrigated. Recovery has no long lasting sequelae.

Methyl mercaptan

Methyl mercaptan is an intermediate in chemical processes. Its toxicity is similar to that of hydrogen sulphide. It has an appalling stale smell. Pulmonary oedema can occur fairly quickly. Treatment is symptomatic.

Nickel carbonyl

Nickel carbonyl $[\text{Ni}(\text{CO})_4]$ is a liquid which readily vaporizes to a colourless gas. It is used in nickel refining and for nickel deposition processes. The gas is highly toxic, 30 ppm being fatal in half an hour. An intense pneumonitis occurs with dyspnoea, fever and leucocytosis.¹⁵ Frontal headache and tightness of chest are common early symptoms. Victims may need to be observed for up to 6 days because an early misleading recovery can occur after which deterioration takes place with increasing dyspnoea, dry cough, a mild fever, basal crepitations and prostration.

The effect of sodium diethyldithiocarbamate (dithiocarb) was studied by Sunderman.¹⁶ It was shown that protection was provided to otherwise lethal concentrations. Dithiocarb has been superseded in the UK by disulfuram ('antabuse'). The regime at a major nickel refinery (personal communication) when exposure is suspected is: (a) take history; (b) give oxygen at 4 litres/min; (c) obtain urine specimen.

If symptoms of poisoning are slight, the measurement of the initial urinary nickel is awaited. If this is less than $10 \mu\text{g}/\text{dl}$, exposure is mild. Delayed symptoms are unlikely. If the urine nickel concentration is between $10 \mu\text{g}$ – $50 \mu\text{g}/\text{dl}$, exposure is moderate. On the first day of exposure oral disulfuram is administered at $50 \text{ mg}/\text{kg}$ body weight as follows: $10 \times 0.2 \text{ g}$ disulfuram at once (0 hours); $5 \times 0.2 \text{ g}$ disulfuram at 4 hours; $3 \times 0.2 \text{ g}$ disulfuram at 8 hours; $2 \times 0.2 \text{ g}$ disulfuram at 16 hours. On subsequent days, $2 \times 0.2 \text{ g}$ is given 8 hourly until the urinary nickel is within the normal range.

If the urinary nickel concentration is over $50 \mu\text{g}/\text{dl}$ exposure has been severe. Most patients can be managed on the moderate exposure regime; severely ill patients should be given disulfuram parenterally, initially at a dosage of $25 \text{ mg}/\text{kg}$ body weight. Further management should be according to clinical indications. Alcohol should not be taken within a week of disulfuram treatment.

Phosgene. Nitrogen dioxide. Hydrofluoric acid, Methyl bromide. Ozone. Ethylene oxide. Sulphuryl fluoride

The importance of exposures to these gases lies in the fact that exposures are rarely intense so that irritant characteristics may not appear unduly significant; their action, however, continues at alveolar level and some hours after the initial exposure, when recovery may appear to have occurred, pulmonary oedema may rapidly supervene. Exposure must therefore be followed by attention to immediate symptoms and the maintenance of observation for some hours. Intensive care facilities are needed.

Phosgene Phosgene (COCl_2) is a colourless gas used extensively in the chemical industry. It may be formed in welding shops by the action of ultraviolet light from the arc on vapours of chlorinated hydrocarbon solvents. Acute high exposures cause immediate gross lacrimatory and respiratory symptoms. Lesser exposures cause delayed pulmonary oedema. Residual damage from high exposures may be severe and permanent. The cause of damage is considered to be the CO group of Cl-CO-Cl which destroys amino acids responsible for the maintenance of alveolar integrity. Treatment is symptomatic.

Nitrogen dioxide Nitrogen oxides arise from the reaction of ultraviolet light in welding, spillages of nitric acid on any organic material, acid manufacturing and metal dipping. Many exposures have arisen during welding and cutting operations in confined spaces.

Nitrogen dioxide (NO_2) is a reddish brown irritant gas used as a bleaching and oxidizing agent and in chemical processes. The dioxide exists as about 30% NO_2 in equilibrium with 70% N_2O_4 , and is traditionally called 'nitrous fumes'. Nitrogen trioxide (N_2O_3) dissociates and nitric oxide (NO) reacts in air to form the dioxide. Nitrogen dioxide reacts slowly with water to form nitric and nitrous acid, which itself further reacts to form more nitric acid. Treatment is symptomatic.

Hydrofluoric acid Hydrofluoric acid (HF) is an irritant colourless gas or liquid. It is used in glass etching and metal refining and pickling. Exposure to hydrofluoric acid fume is much more common than exposure to fluorine which is more aggressively corrosive. Severe pain and profound systemic effects can follow from skin splashing due to the penetration of tissue by the acid and the absorption of F ions which are mopped up by calcium and magnesium in the tissues. Skin burns of greater than 65 cm^2 can give rise to falling calcium levels and the risk of ventricular fibrillation.¹⁷ Affected parts must be flooded with cold running water and calcium gluconate gel massaged

into the burnt area for 10 minutes. Scabs should be removed. Serum calcium levels should be monitored frequently. After cold water irrigation for 10 minutes, calcium gluconate eye drops should be instilled into affected eyes. In all cases of inhalation, even slight, the action of the F ion continues in the alveoli and observation should be maintained for the onset of pulmonary oedema.

There are several other gases which hydrolyse rapidly to hydrofluoric acid, but they are uncommon: They demand the same therapeutic procedures as hydrofluoric acid.

Methyl bromide Methyl bromide (CH_3Br) or bromomethane, is odourless. It is widely used as a fumigant. A latent period of up to 24 hours can exist before symptoms develop. High exposures will produce sudden collapse but lesser concentrations produce delayed bronchial irritation and sometimes pulmonary oedema. Convulsions, peripheral paralyses, and kidney failure have been recorded. Liquid methyl bromide is intensely irritant to the eyes and copious irrigation is necessary. Treatment otherwise is symptomatic: the neurological disorders may take several months to clear.

Ozone Ozone (O_3) is used as an oxidizing agent. It is produced by the action of ultraviolet light on atmospheric oxygen in spark production and notably in arc welding, especially of aluminium. The gas is quite irritant and has a familiar prickling clean odour. Observation is necessary for some hours. Severe degrees of inhalation will produce pulmonary oedema. Recovery is very slow but usually complete.

Ethylene oxide Ethylene oxide ($\text{C}_2\text{H}_4\text{O}$) when mixed with carbon dioxide is widely used as a sterilant for medical disposables, and for some food products. In high concentration the gas is very irritant to the eyes and respiratory tract. Treatment is symptomatic as for ozone above. Chronic exposure has been associated with leukaemia; ethylene oxide is regarded as a putative carcinogen.¹⁸

Sulphuryl fluoride Sulphuryl fluoride (SO_2F_2) is a colourless gaseous fumigant. It is very irritant and produces pulmonary symptoms.

C. Rapid death

In high concentrations, most of the gases mentioned in the immediately preceding section can cause almost instant death. Notable in this regard are arsine, hydrogen sulphide, methyl mercaptan, nickel carbonyl, phosgene, nitrogen dioxide and methyl bromide. In addition, cyanides, carbon monoxide and

exposure to an atmosphere deficient in oxygen can do so.

The following less commonly encountered gases are also capable of overwhelming vital systems: germane (GeH_4), used in semiconductor manufacture, is a cousin of arsine and produces haemolysis. Hexafluoroacetone (F_3CCOCF_3) is a reactive chemical and especially damaging to the lungs. Hydrogen selenide (H_2Se), used in semiconductor manufacture is highly damaging to the lungs.

Phosphine (PH_3) is a toxic colourless gas with the odour of rotten fish – it is used in the semiconductor industry; and as a rodenticide and fumigant; it is released by the action of water on metallic phosphides and so the gas can be a contaminant of crude acetylene. High exposures have not so far been recorded but lower exposures produce cough, dyspnoea and diarrhoea. Pulmonary oedema can theoretically occur.

Silane (SiH_4) is a colourless gas with a nauseating smell, used in the semiconductor industry. The pure gas is spontaneously flammable but in mixtures containing under 3% silane, the gas is usually not flammable. Toxic effects are poorly documented. The gas is a cousin of germane and arsine, but has no documented blood effect.

D. Corrosive and highly irritant damage

All the strong organic acids are corrosive. These include hydrogen fluoride – described earlier, hydrogen chloride (HCl), and hydrogen bromide (HBr), fuming colourless gases, and hydrogen iodide (HI), also a fuming colourless gas, and, the most unstable of all, the hydrogen halides.

HBr and HI are more damaging than HCl . HI dissociates and the vapour of iodine is even more corrosive than the parent acid. Eye, skin and severe lung damage may follow exposures. Treatment was described earlier. Boron trichloride, dichlorosilane and nitrosyl chloride all hydrolyse to hydrochloric acid.

Sulphur dioxide

Sulphur dioxide (SO_2) is a common air pollutant formed whenever sulphur is burned, the main atmospheric source being oil and coal burning furnaces. Used extensively as a preservative and bleaching agent. Acts directly on the respiratory tract: liquid splashes may cause extensive damage to skin and eyes. Treatment is symptomatic.

Alkyl amines

Mono-, di-, and tri-methylamine and monoethylamine are all widely used in many industrial and

pharmaceutical processes. They are all strongly alkaline, have an ammoniacal odour and in high concentrations cause acute upper respiratory tract damage and laryngeal or pulmonary oedema.

E. Chronic disorders as a result of exposure to some gases and vapours

Most chemicals which cause chronic disease cause specific system disease. The results of damage however may affect many organs (Table III).

Table III Chronic disorders that follow exposure to gases and vapours

Liver fibrosis and cancer	– vinyl chloride – carbon tetrachloride – other halogenated hydrocarbons
Hepatitis	– trinitrotoluene – trinitrophenol – ethylene dichloride – acetylene tetrachloride – 1,1,2,2 – tetrabromoethane – pentachloroethane
Blood disorders	– benzene – nitro and amino compounds of benzene and its homologues – trinitrotoluene, trinitrobenzene, trinitrophenol (picric acid) – nitrous oxide
Cerebral symptoms	– possibly paint and solvent exposure – carbon monoxide (see earlier)
Neuropathies	– nitrous oxide – n-hexane – methyl ethyl ketone
Chronic conjunctivitis	– hydrogen sulphide (see earlier)
Chronic bronchitis	– sulphur dioxide (see earlier)

Vinyl chloride Vinyl chloride monomer ($\text{CH}_2=\text{CHCl}$) (VCM) is a moderate acute asphyxiant and, much more importantly, is a proven carcinogen. It probably exerts its effect by means of an immune complex disorder. Non-cirrhotic portal fibrosis is a precursor of angiosarcoma of the liver;¹⁹ by mid 1985 120 VCM-induced angiosarcomata had been recorded worldwide.¹⁹ It is also the cause of acro-osteolysis, mainly affecting the fingers and toes. When scleroderma and Raynaud's phenomenon are associated with acro-osteolysis, vinyl chloride is the cause beyond doubt.²⁰

Carbon tetrachloride Carbon tetrachloride (CCl_4) has been used historically as a solvent. Its main use now is as a chemical intermediate. Acute exposures to the vapour produce dizziness, collapse and acute liver

damage. Chronic exposures have resulted in liver changes. It is now regarded as a putative carcinogen.²¹

Trinitrotoluene and trinitrophenol Both these volatile compounds as well as producing methaemoglobinuria, can produce liver and kidney damage as well as haemolytic and aplastic anaemia.

Ethylene dichloride, acetylene tetrachloride, 1,1,2,2-tetrabromomethane and pentachloroethane These halogenated hydrocarbons are all narcotic in acute exposures and are all hepatotoxic.

F. Blood disorders

Benzene Benzene (C_6H_6) is a well established marrow toxin. The vapour is easily absorbed, oxidized to phenol which is then conjugated with sulphate and excreted. Inhalation of high volumes of the vapour causes chest tightness, breathlessness and collapse. Chronic poisoning may produce any of the following: clotting defects and purpura, mild haemolysis, granulocytopenia. Basophilic stippling of the red cells may be present. Recovery is the rule if the diagnosis is made and further exposure prevented. Continued exposure leads to pancytopenia progressing to aplastic anaemia. Lymphoid and myeloid leukaemia have also been reported.

Nitro and amino compounds of benzene and its homologues. Trinitrotoluene, trinitrobenzene, trinitrophenol These volatile materials all produce sulphamoglobinemia or methaemoglobinemia. People vary in their susceptibility. It is probable that a metabolite rather than the compound itself is responsible; methaemoglobin is darker than haemoglobin and when present at over 5 g/dl the face is blue-grey. Removal from exposure is therapeutic. At higher concentrations, 1% methylene blue in the dose of 1 mg/kg given very slowly will accelerate recovery. Methylene blue may itself produce toxic symptoms and should be stopped if chest pain or breathlessness occur. A more detailed appraisal of aromatic compounds has been given by Jackson.²²

Nitrous oxide It is now established beyond all doubt that chronic exposure to the well established anaesthetic nitrous oxide (N_2O), over about 1000 ppm, carries a risk of inactivation of vitamin B12 which leads to inactivation of methyl synthase; this results in a megaloblastic marrow and ultimately to megaloblastic anaemia. This risk is much greater in those severely sick people needing frequent short term anaesthesia. The risk is also greater in those who regularly use nitrous oxide in poorly ventilated circumstances. In rats, probably more sensitive than human beings, an

ED₅₀ of 5,400 ppm was established by Sharer *et al.*²³ An excellent review of the biochemical mechanisms and other issues involved is given by Nunn.²⁴ Nitrous oxide has been inhaled for its euphoric effect and some people have become addicted. It is therefore important to exclude exposure to nitrous oxide in patients presenting with what seems to be vitamin B12 deficiency as a cause of what may appear to be classical vitamin B12 deficiency. Peripheral neuritis, signs of sub-acute combined degeneration and of megaloblastic anaemia may have an occupational or addictive aetiology.

G. Cerebral symptoms

The cause of a variety of chronic mental disorders has been ascribed to regular occupational exposure to a variety of common solvents: affective syndromes, encephalopathies and generally reduced central nervous system (CNS) function as well as some peripheral neuropathies.

Among addicted solvent-sniffers, definite multi-focal CNS damage has been found: this does not imply of course that lesser degrees of exposure would produce changes but it makes the likelihood more credible. Very many epidemiological surveys have

been carried out among industrial and commercial painters of many sorts and of workers in textile and plastic industries where exposure to solvents may be common. A brief review paper by Baker & Fine²⁵ describes the present position. It is important to be aware of the possibilities of brain damage in this occupational group.

H. Neuropathies

The effect of nitrous oxide has been described earlier.

Ketones: methyl ethyl ketone and methyl n-butyl ketone.

Alkane: n-Hexane N-Hexane is a widely used and ubiquitous volatile solvent with acute narcotic effects. Chronic exposures can cause a polyneuropathy as well as cerebral effects such as dizziness and somnolence. Definite peripheral nerve conduction defects and electroencephalographic changes have been demonstrated.²⁶ Pathologically there is giant axonal neuropathy present mainly in the limbs.

Methyl ethyl ketone has been associated with neurotoxicity; there is clear experimental evidence that methyl n-butyl ketone is neurotoxic and its effect may be enhanced by simultaneous exposure to methyl ethyl ketone. A similar neuropathy to that associated with n-hexane has been identified.

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