INERT GAS NARCOSIS — AN INTRODUCTION

I. P. UNSWORTH, B.M., B.Ch., L.R.C.P.,

Walton Hospital, Liverpool

INERT gas narcosis is the physical and mental disturbance, both subjective and objective, that occurs when breathing gas mixtures containing certain members of the inert gases under pressure. These include krypton, argon, xenon, nitrogen and possibly neon. The phenomenon of narcosis associated with nitrogen has been alternatively termed "nitrogen intoxication" though "narcosis" is the generally accepted name. (Unsworth, 1960; Miles, 1962.)

It is more than a hundred years since the first report in print of the problem that has been facing divers ever since their descents went deeper than 100 feet or the ambient pressure increased above 4 atmosphere—nitrogen narcosis. For many years, it was only helmeted divers and caisson workers who were subject to this condition, but with the introduction during the last three decades of self-contained underwater breathing apparatus, free divers are even more liable to the serious and fatal side effects of nitrogen narcosis.

The significance of inert gas narcosis has a bearing not only on naval diving in warfare but also undersea salvage and exploration. With the introduction of high pressure chambers into the field of anaesthesia and surgery, the inherent properties of nitrogen narcosis may have wider implications, as, for example, the possible use of nitrogen or other inert gas, under pressure as an anaesthetic agent, or as a side-effect when high pressures of compressed air are used.

Historical

In 1826 Colladon, a French physician, describing a prolonged descent in a diving bell, remarked upon his "state of excitement as if I had drunk some alcoholic liquor". It is doubtful if, in fact, Colladon did suffer from narcosis as the bell only descended to 20 metres although his comparison with alcohol would suggest it. Another Frenchman, Junod, in 1835, noted that under pressure "the functions of the brain are activated, imagination is lively, thoughts have a

peculiar charm and in some persons, symptoms of intoxication are present". It was not until 1861 that a professional diver described his own signs and symptoms, and suggested a precautionary measure. J. B. Green, an American, reported that on his deep dives of 150 feet or more, he noticed a feeling of excitement followed by drowsiness, and he considered it important that at this stage, the diver should be brought up. From Green's full description it is clear that he noted hallucinatory changes and impairment of a diver's judgement. Paul Bert (1878) remarked upon the objective signs when nitrogen is breathed under pressure but at that time did not pursue their cause though he established that dissolved nitrogen was the aetiological factor in decompression sickness or the "bends".

The next report of nitrogen narcosis came from Damant (1930) during the British Admiralty Deep Sea diving trials to 320 feet. Damant described the findings of Hill and Selby, that although the divers were all picked men who had been put through a specially searching medical examination, some of them became abnormal mentally or emotionally. The effect was attributed at first to the high ambient air pressure and oxygen poisoning, or to impurities such as carbon dioxide or monoxide. But careful work ruled these out, and though oxygen and carbon dioxide were no longer held responsible, no incrimination of nitrogen was made.

The first definitive theory that nitrogen was the aetiological factor in mental changes while under air pressure was put forward in 1935 by Behnke, Thompson and Motley. They stated that air at, and higher than, 3 atmospheres, pressure exerted a narcotic effect on man, with euphoria, mental retardation and loss of neuromuscular control, with coma intervening at higher pressures.

Since the end of the war, research on substitution diluents continued and in 1948 the oxygen-hydrogen mixture was introduced (Zetterström: Burjstedt and Severin). Ten years earlier, how-

ever, Behnke and Yarbrough, and End (1938) had used helium as diluent in gas mixtures. This eliminated nitrogen narcosis from deep dives though both hydrogen and helium had difficult features, the former being explosive with a higher oxygen concentration than 4 per cent, and the latter posing problems of decompression, voice distortion and thermal conductivity.

Considerable experimental work has been carried out on the qualitative and quantitative measurement of mental disability of nitrogen under pressure, with that of Bennett and his co-workers outstanding. They used both electroencephalographic changes and flicker-fusion frequencies in estimating time of onset of narcosis. (Bennett and Glass, 1957; Bennett, 1958, Bennett and Cross, 1960.)

Other workers attempted to relate changes in performance efficiency to pressure of inert gases. (Shilling and Willgrube, 1937; Kiessling and Maag, 1960; Frankenhaeuser, Graff-Lonnevig and Hesser, 1963; Poulton, Catton and Carpenter, 1964.) These latter workers, in their initial experiments, found evidence of performance impairment in subjects at only 2 atmospheres absolute but more recent work has not revealed any abnormality below 4 atmospheres absolute.

Clinical Features

The signs and symptoms of inert gas narcosis are variable in time of onset, and in regard to the pressure at which it appears, individuals show some effect soon after reaching 4 atmospheres absolute. Sensitivity differs among divers and some may have demonstrable signs at less pressure while others may not be affected till the pressure reaches 5 or 6 atmospheres. Many factors influence the pressure at which the onset of symptoms may occur and the severity of the attack. Exertion, previous fatigue, alcoholic excess prior to a dive, even apprehension, may both advance onset and increase severity. It also appears that carbon dioxide retention, through either ineffective apparatus or an increased proportion of carbon dioxide in the respired gas, also speeds the onset of narcosis.

The symptoms which generally, though not inevitably, appear first are lightheadedness, dizziness, euphoria, and apparent mental stimulation associated with great self-confidence. The completion of a difficult underwater task will seem easy and straightforward, and safety precautions, usually meticulously observed, appear to become superfluous. The subject shows a great tendency to become jovial and talkative, and easily amused. Later, mental concentration

becomes difficult and the recollection of ideas requires great effort. Other symptoms noticed include peripheral numbness, lip trembling not unlike that of oxygen poisoning, and hallucinations. Occasionally this initial phase of nitrogen stimulation may be passed very rapidly and almost unnoticed, the diver then being affected very profoundly by the phase of extreme lethargy and drowsiness.

The signs of nitrogen narcosis are most conveniently observed in a pressure chamber. These include delayed responses to sensory stimuli particularly visual, auditory and tactile. Mistakes are made in mental arithmetic that would not normally be made on the surface. A loss of fine neuro-muscular control and co-ordination renders a delicate manipulation impossible. Although all individuals are narcotised to some extent under pressure, an emotionally stable person reacts to the stress by increased effort and may carry out his task quite well until consciousness is lost. The unstable individual is incapable of any further purposeful effort.

As the pressure is increased, the signs and symptoms become more severe, there is loss of memory that may last for many hours, and between 10 and 13 atmospheres loss of consciousness occurs. With a helmet diver, this is not so dangerous as with a free diver in whom the loss of the mouthpiece would result in death by drowning.

The similarity between the presenting features of nitrogen narcosis and acute alcoholic poisoning is very close and hence the first description of Junod is so apt and observant. The French name for the condition, "l'ivresse", is that used for the vice of drunkenness. Another interesting parallel between nitrogen narcosis and alcoholic poisoning is the variability and individual susceptibility that exist. Resistance to nitrogen narcosis (and alcohol) can be built up by practice and experience, and adaptation does occur.

Theories

Many theories have been proposed to explain inert gas narcosis. The first, put forward in 1835 by Junod and later in 1881 by Moxon, suggested increased pressure alone as the factor involved. Junod considered that "the increased density of the air lessened the calibre of the venous vessels, resulting in greater blood flow in the arterial system and towards principal nerve centres especially the brain, protected by its bony case from direct pressure". He thought that this increased blood flow stimulated the nerve centres and resulted in narcosis. Moxon,

on the other hand, regarded the increased pressure as driving the blood from the surface of the body into parts not accessible to respiratory exchange and that this devitalised blood caused emotional changes. These theories are patently incorrect. If pressure did affect superficial blood flow, cutaneous blanching would be obvious but this does not occur. The physical properties of the body are such that it may be regarded as incompressible, with pressure being equalised throughout the body bulk. A further argument against pressure alone being responsible for inert gas narcosis is the later demonstration that breathing gas mixtures of different constituents at the same pressures induced different levels of mental and physical change.

The psychological aspect of deep diving was once blamed as the cause of narcosis (Hill and Greenwood, 1906). When psychological tests were carried out on divers who had failed to complete tasks under pressure, Phillips (1931) showed that many of these subjects were of the suppressed nervous type who habitually exercised control and that they suffered from latent suppressed claustrophobia. Phillips had little hesitation in ascribing the objective mental changes of his deep divers to mental instability. However, if divers, or subjects in a pressure chamber, are supplied with different gas mixtures at the same pressure, the severity of signs and symptoms may be altered. It is unlikely that claustrophobia or other psychological deviation contribute directly to inert gas narcosis although they may provide a background of instability against which early changes of narcosis become more apparent.

Breathing oxygen at atmospheric pressure causes subjective and objective reactions in some individuals and Birch (1859), reporting these, maintained that they were not of psychological origin. Thus the stimulating effect of increased oxygen tension in compressed air was postulated as a cause of the "compressed air" syndrome. In 1878 Bert made this assumption that high oxygen tensions produced such effects, and he utilised high air pressures in his experiments into oxygen toxicity. Other workers since then have been of the same opinion (Binger, Faulkner and Moore, 1927; Smith, Heim, Thomson and Drinker, 1932).

Not until Donald (1947) did anyone clearly define the salient features of oxygen poisoning and when compared with those of nitrogen under pressure, there should be no doubt that there exist two separate conditions. Damant (1930) was convinced that the subjective and objective changes associated with air under

pressure were not due to oxygen. Recently the interest in high partial pressures of oxygen as a cause of narcosis has been re-aroused by Fenn (1965). His hypothesis stems from some interesting work done on the fruit fly, *Drosophila*, in atmospheres of oxygen and nitrogen under pressure. From his experiments he demonstrated that a correlation exists between the proportions of oxygen and nitrogen, and the survival rates of the flies while under pressure. Though he states that his results are not directly applicable to human diving, he does suggest that it may be possible by keeping the oxygen tension low or normal to avoid the narcotic effects of nitrogen at depth. This would certainly substantiate the claims of Albert Bühlman and Hans Keller (1962) that nitrogen narcosis does not exist, even with 90 per cent nitrogen, at 600 feet. But, although Fenn suggests a lowering of the oxygen partial pressure, this has been strongly criticised by many workers as dangerously incorrect. The effect of decreasing the P_{O_2} without substituting a third gas, would be to increase the inert gas tension, and thereby markedly potentiate narcosis.

Narcosis experienced under compressed air was attributed to nitrogen by Behnke, Thompson and Motley (1935). The manner in which nitrogen acted was considered to be due to its oil/water solubility ratio, acting in the same manner as the diphasic anaesthetic agents. The correlation between solubility of anaesthetic agents in water and lipid and its depressant action had been described much earlier by Meyer (1899). Behnke and his co-workers found that if nitrogen is replaced in a gas mixture by helium, the narcotic effect is lessened or abolished. Conversely if argon is substituted, the narcosis is more profound and with earlier onset. Such gases as krypton and xenon have also been used in mixtures at atmospheric pressure and have produced definite central nervous system depression and anaesthesia in both animals and man. (Lawrence, Loomis, Tobias and Turpin, 1946; Cullen and Gross, 1951; Carpenter, 1953). The ease with which a gas promotes narcosis under pressure is directly proportional to its fat solubility and oil/water distribution coefficient (Table 1), and this led early workers to use hydrogen or helium as diluent in gas mixtures to be used under pressure, as narcosis only occurs with these two under extremely high pressures.

A further agent once thought to be the cause of the narcosis associated with inert gases is carbon dioxide. The narcotic and anaesthetic

TABLE 1
GAS SOLUBILITIES

	Solubilities in mg./ml. solvent at 37°C.		
<u>Gas</u>	<u>Water</u>	<u>Fat</u>	<u>Distribution coefficient</u>
Argon	0.027	0.140	5.2
Nitrogen	0.013	0.067	5.1
Hydrogen	0.017	0.036	2.1
Helium	0.009	0.015	1.66

TABLE 2
GAS DENSITIES

	Hydrogen-oxygen	Helium-oxygen	Nitrogen-oxygen (air)	Argon-oxygen
Viscosity relative to air	0.35	0.66	1	1.13
Wt. in lbs. of 1 cu. ft. at 1 atmo.	0.022	0.026	0.081	0.193

effects of this gas were noted by many early workers (Bert, 1878; Hill and Flack, 1908). Case and Haldane (1941) found that carbon dioxide added to compressed air enhanced the narcotic effect, and noted the increase in respiration associated with a rise in partial pressure of CO_2 in compressed air. Bean (1945; 1950) has put forward the most detailed theory and he considers CO_2 an important contributor to, if not chief cause of, those reactions attributed to nitrogen. Bean postulates that compression increases the partial pressure of carbon dioxide by interfering with the dynamics of air flow within the respiratory tree, and leads to hypercapnia. As pressure increases, air density rises and ventilatory efficiency is reduced. As Miles (1957) has shown, if air is breathed at 200 feet, the maximum breathing capacity is reduced by 50 per cent, and at 600 feet, the reduction is 75 per cent.

A study by Bean (1950) on the rapid compression of anaesthetised dogs showed a pronounced increase in alveolar Pco_2 . The experimental data put forward, though limited, were considered to provide evidence that changes in alveolar CO_2 , and alterations of blood and tissue CO_2 caused, or contributed to, nitrogen narcosis. However, one point made by Bean to explain the lack of hyperventilation in response to high blood Pco_2 was that the response to a given CO_2 increase in compressed air may not be the same as the response at normal pres-

sure. It is true that a large excess of CO_2 may diminish rather than augment ventilation, and that an increased partial pressure of oxygen may modify the response to carbon dioxide (Dripps and Dumke, 1943) but the Pco_2 increase may not be large (Rashbass, 1955) or alternatively the Po_2 may not be greatly raised. It is possible that compression using nitrogen causes a desensitisation to carbon dioxide, and therefore CO_2 retention with no hyperventilation. The increased density and viscosity of air, and other gas mixtures (Table 2), contribute to the diminution of effective pulmonary ventilation. When carbon dioxide is added to the inspired mixture, this has an additive effect on nitrogen or inert gas narcosis. It has been suggested that the vasodilatation of increased partial pressures of carbon dioxide, particularly on the cerebral circulation, allows the effects of high oxygen partial pressure to become apparent and that the picture under these circumstances is a combination of nitrogen narcosis and oxygen toxicity. Work of Hesser and his colleagues (1963) has shown that oxygen excess has a potentiating effect on nitrogen narcosis, and that performance efficiency decreased with increasing oxygen pressure. It was suggested that this increase in narcotic effect was possibly due to interference with carbon dioxide elimination from the tissues, one of the factors involved in simple oxygen toxicity. Thus raised partial pressures of oxygen increases that of carbon

dioxide and nitrogen and carbon dioxide have a synergistic narcotic action.

Bühlman (1963) believed he could explain the sensations and difficulties attributed to nitrogen narcosis by altered respiratory physiology, mainly CO₂ retention due to hypoventilation. His protégé Hans Keller has dived to 600 feet using 90 per cent nitrogen without apparent signs of narcosis. However, several of Bühlman's divers other than Keller, complained of abnormal sensations under high pressures of nitrogen and argon. Bühlman suggested that, under pressure, some specific and reversible gas configuration formed in the brain, dependent, not on the nature, but on the density of the gas, a view not incompatible with the nitrogen hypothesis.

Of the several agents proposed to explain pressure narcosis, nitrogen, or other inert gas, has been most widely accepted. Carbon dioxide retention will contribute to the severity of signs and symptoms initiated by an inert gas but it is doubted if it alone produces the clinical picture.

Electrical Studies

In an attempt to discover upon which part of the nervous system nitrogen and the inert gases acted, Bennett and his co-workers (1957; 1960) investigated the EEG patterns of human subjects under pressure. Earlier experiments (Marshall, 1951; Jullien, Roger and Chatrian, 1953) had shown that EEG waves were altered by increased air pressure. The main and most important finding by Bennett and Glass was the abolition of alpha-wave blocking. This occurrence of alpha-blocking is found in 50 per cent of normal subjects at atmospheric pressure when the subject concentrates on mental arithmetic or similar problem. It was found that if the subject was exposed to a high enough pressure for a long enough time, the alpha-blocking was abolished. The time from beginning of exposure to pressure till abolition was found to be inversely proportional to the square of the pressure. The relationship between time to the abolition of desynchronisation of alpha rhythm and pressure has suggested a nitrogen or inert gas diffusion gradient into some part of the central nervous system (Hempleman, 1952) producing impairment of mental efficiency. If after abolishing alpha-blocking, an oxy-helium mixture is substituted for the nitrogen-oxygen mixture, alpha-blocking will reappear. This would suggest nitrogen as the agent responsible, as any concurrent signs and

symptoms of narcosis would be alleviated at the same time.

An alternative method of determining the onset of changes in cortical activity in subjects under pressure has been used by Bennett and Cross (1960). They showed that using fusion frequency of a flickering neon light and electroencephalography, the time to abolition of alpha-blocking and maintained fusion of flicker are the same. This method of flicker fusion may be used in those individuals who do not show alpha-blocking even at atmospheric pressure.

Site of Action

The site of action where inert gases under pressure induce narcotic change is still not entirely clear. It seems probable that the cortex is not affected directly but via some part of the brain stem. One site that has been suggested is the reticular formation of the mid-brain and hypothalamus, a neuronal system connected with consciousness (Magoun, 1952; French, Verzeano, Magoun, 1953). Magoun showed that stimulation of this activating system roused an animal from sleep, converting the EEG pattern from slow sleep waves to more rapid lower voltage waves of activity. He also demonstrated that the electrocorticogram was blocked upon stimulation of the reticular formation. It is thought that the action of high pressure nitrogen and other inert gases is upon the reticular formation, and the time to abolish alpha-blocking may be due to gaseous diffusion throughout the brain stem and thalamus.

On a cellular level, it is less easy to define the site of action of inert gases as narcotic agents. The reticular formation is an extremely complex system of neurones, short nerve fibres and synapses, and inert gas molecules under pressure may affect any one or all of these constituents.

Marshall (1951), using nitrogen and argon up to 96 atmospheres, could not show any effect on isolated frog sciatic nerve, and no effect on frog nerve-muscle preparations with nitrogen at 82 atmospheres. But she did find that spinal synapses and therefore reflexes were sensitive to inert gas pressures. More recently, Gottlieb and Weatherley (1965) confirmed that high pressures of helium, neon, nitrogen and argon up to 15 atmospheres had no effect on transmission across neuromuscular junctions or along nerve fibres, in frog sciatic nerve-gastrocnemius muscle preparations. Work of French and others (1953), points to the synapses of the reticular formation as possible sites of interference with normal conduction, and has

shown that synaptic transmission in the central nervous system is more susceptible to the effects of narcotics than the conduction process in nerve fibres, and some members of the inert gases may be included among the narcotics. Bennett (1964) using auditory provoked stimuli recorded from the cortex of cats, has suggested that the most likely sites for blockage are the central synapses, and that the level of narcosis is related to a critical concentration of inert gas molecules at these sites.

A further theoretical site of action of nitrogen is within the neurone itself or within the neurone/glia unit which has been demonstrated so well by Hyden (1962). He describes how the glial supporting cell entirely covers the neurone and acts as the barrier between the neurone and the capillary, and the two constitute a biochemical and functional unit. Even the protagonists of the theory that the neurone is affected by nitrogen, are divided as to the exact mechanism. There are those who support the lipid theory originated by H. H. Meyer in 1899 and modified by Clements and Wilson (1962) to state that nitrogen under pressure acts at lipid interfacial films within living cells. The antagonists of the lipid theory (Pauling, 1961; Miller, 1961) claim there is a protein-binding action with formation of microcrystals within the cytoplasm.

Clements and Wilson believe that inert gases can interact significantly with the interfacial lipoprotein of living cells altering both permeability and enzyme relationships, and thus interfering with oxidative phosphorylation and electron transport which probably are associated with the lipoproteins of the mitochondria. They suggest an histotoxic anoxia, a view supported by Russek (1962), Miles (1962), Bennett (1963), and earlier work of Ebert, Hornsey and Howard (1958) on the effect of irradiation on growth of bean shoots in inert gases. It was suggested by Ebert and his colleagues that oxygen was responsible for radiosensitivity, and displacement of oxygen from sites within the cell by nitrogen reduced this sensitivity. Using an anti-psychotic agent Frenquel, Bennett (1963) showed a protective action in rats not only against inert gas narcosis but also oxygen poisoning. Bennett suggests that nitrogen narcosis is an histotoxic hypoxia, increasing the metabolic work of the central nervous system in the production of central inhibition.

Hyden describes the biochemical and functional interrelationship between the neurone and its supporting element, the glial cell. He

showed that the glia provides a maintenance system for the neurone and acts as the blood/brain barrier, the two forming a close unit, anatomically, histologically and metabolically. When he subjected preparations to atmospheres of low oxygen tension, the glial cell converted from aerobic to anaerobic production of energy resulting in a drop of efficiency from 55 per cent to only 3 per cent. This permitted the neurone to utilise all available oxygen. Hyden pointed out that the glial cell was composed of 70 per cent lipid material while the neurone was only 5 per cent. Thus the glial cell might be expected to absorb more nitrogen than the neurone and be more affected by any deranging influence. Should this occur, oxygen consumption of the glia will drop as will its efficiency. This depletion of energy may cause delay in ionic potassium and sodium exchange with the neurone, to delay in substrate transfer and ultimately to cessation of adequate function of neurone and glia. This would support the histotoxic hypoxia and lipid theories as proposed by Clements and Wilson, and other workers. A similar theory of decreased membrane permeability was proposed by Mullins (1954) although he argued that it was inert gas molecules accumulating in the membrane pores that hindered permeability of ionic material. It may be that the point at which aerobic respiration within the glia gives way to anaerobic glycolysis coincides with the abolition of alpha-blocking on the EEG.

The argument that the brain consists largely of water and is, therefore, unlikely to be influenced by highly fat-soluble compounds is put forward by antagonists of the lipid theory of narcosis and anaesthesia, mainly Pauling (1961). He offers, as alternative, a theory of microcrystal formation within cell cytoplasm quite independent of lipid cell membranes or other structures. Pauling suggests that nitrogen and other inert gases such as xenon, take part in the formation of clathrates, in which the gas atoms occupy chambers in a framework of molecules. These molecules interact with one another through hydrogen bonding to give nitrogen or xenon hydrate. The clathrates to be present at body temperature must be stabilised by cytoplasmic proteins, hence this theory is sometimes referred to as "protein binding". Pauling postulates that these microcrystals act in two ways—by trapping electrically charged ions associated with impulse conduction and damping down electrical circuits, and by preventing close enough contact of enzyme/substrate configurations and thus decreasing the rate of chemical

reactions and, therefore, metabolic rate of cells. A somewhat similar theory has been proposed by Miller (1961) but which does not involve the formation of clathrates. Featherstone and Schoenborn (1964) have reviewed the biophysical aspects of both lipid- and protein-binding theories proposed and they conclude that there is no clear evidence that either preponderates but that probably a mutual relationship exists.

Conclusions

Although the narcosis from inert gases under pressure may be avoided by the use of substitution mixtures, the academic investigation as to the exact cause of this phenomenon continues. The use of hydrogen, helium and possibly neon, as diluents, and of anti-narcotic drugs, as yet theoretical, have been investigated and help to reduce the incidence of narcosis. The elucidation of inert gas narcosis being histotoxic anoxia remains as the latest of much work to be done on problems associated with nitrogen and other inert gases under pressure.

Summary

Inert gas narcosis is a condition affecting the physical and mental state of subjects breathing air or mixtures containing certain of the inert gases at pressures greater than 4 atmospheres. The signs and symptoms are described and possible theories advanced, from which the most tenable are nitrogen, or other inert gas, and carbon dioxide retention. The protein and lipid binding properties of inert gases under pressure are mentioned. Finally, several sites of action are suggested, among which are the centre synapses and the neuroglial cell.

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