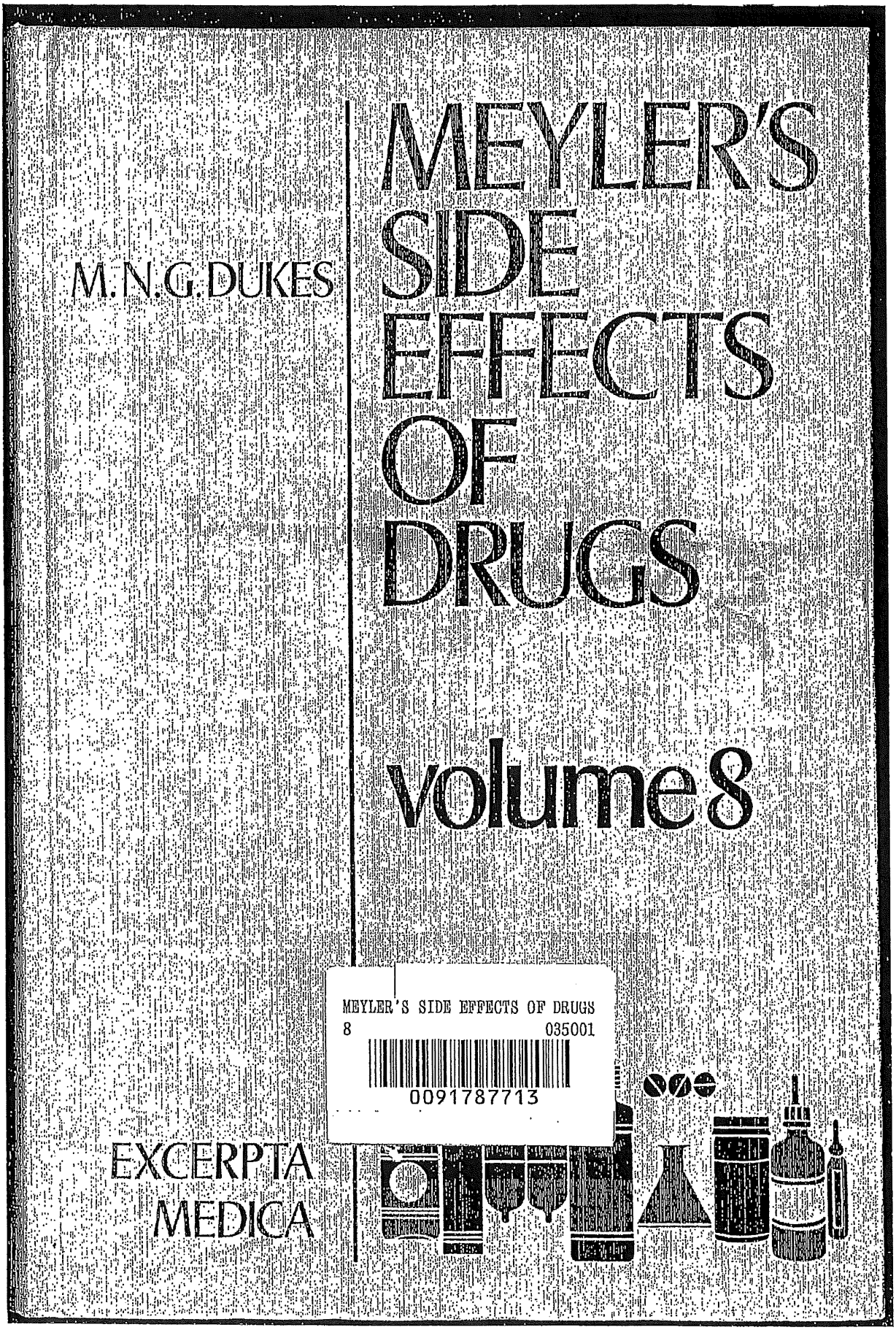
文献 5)　M.N.G.DUKES : Meyler's Side Effects of Drugs Vol.8, General Anaesthetics and Therapeutic Gases, P245 - 247, (1975).



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both in man and in several strains of pig. The mode of inheritance is autosomal dominant. The condition is more common in males than in females and the highest incidence is in children, adolescents and young adults ($21^R$).

In susceptible individuals, any potent inhalation agent or any skeletal muscle relaxant causes fever, often skeletal and cardiac muscle rigidity, arrhythmias, hyperventilation, cyanosis, hypoxia, respiratory and metabolic acidosis and hyperphosphataemia with a raised blood glucose. An initial hyperkalaemia and hypercalcaemia are followed by hypokalaemia and hypocalcaemia. Later there is elevation in the serum of various skeletal, cardiac and muscle enzymes. Patient mortality is in the order of 65–70%.

Strong evidence has been provided ($22^C$) that the clinical syndrome of malignant hyperpyrexia is produced by a raised concentration of calcium ions in the myoplasm. These calcium ions have been abnormally released because of an inherited defect in the calcium-storing membranes of the muscle cell, which makes them more sensitive to a wide variety of physicochemical stimuli. The serum level of creatinine phosphokinase (CPK) is useful as a screening test for malignant hyperpyrexia but does not provide certain identification of susceptible individuals. *In vitro* testing of muscle biopsy specimens from relatives of patients who have experienced malignant hyperpyrexia allows a much more accurate prediction of whether the patient has malignant hyperpyrexia or not ($23^r$).

Treatment consists of stopping anaesthesia, active cooling, sodium bicarbonate intravenously, measures to reduce hyperkalaemia and artificial ventilation. The use of procaine ($24^C$) or large doses of steroids has not yet been shown to be effective and certainly large doses of procaine may be detrimental in this situation. It is perhaps worth emphasizing that malignant hyperpyrexia is an extremely rare condition and the number of review papers and apparent case reports occurring in the world literature over the past few years may have given a misleading picture of the incidence of this condition. Most anaesthetists are unlikely to ever see a case.

## GASES

### NITROUS OXIDE

In normal volunteers 40% nitrous oxide in oxygen leads to a steady and apparently direct depression of myocardial function with peripheral vasoconstriction ($25^C$). Inhalation of Entonox (50:50 nitrous oxide in oxygen) leads to a depression of cardiac output of the order of 12% ($26^C$). The authors point out that Entonox is now commonly used for the treatment of myocardial infarction, particularly when patients are transported by ambulance. Although in their patients the fall in cardiac output was small it may be that the patient with a severe myocardial infarction may show more serious haemodynamic changes. As yet there are no reports of serious ill effects from the administration of Entonox in myocardial infarction but continued caution in its use is necessary.

In a review of the clinical pharmacology of nitrous oxide ($27^r$) it is suggested that since nitrous oxide appears capable of reducing renal blood flow it may predispose to the development of nephrotoxicity when employed in conjunction with methoxyflurane.

Broncho-activity was investigated in 5 adults breathing Entonox ($28^C$). All subjects showed a drop in specific conductance and the authors consider that an alternative analgesic should be considered in patients presenting with airways obstruction or with a history of asthma. Entonox is of course commonly used for relief of pain in labour and the alternative which should be considered is methoxyflurane which has a bronchodilator action in normal subjects.

A survey of the prevalence of the non-medical use of nitrous oxide made in mid-Michigan suggests an increase in usage ($29^r$). A study of 30 volunteers was made through self-administered pure nitrous oxide from balloons. Subjective findings generally indicated pleasurable effects which were in the main similar for those with previous drug experience (freaks) and those with none (straights). Cognitive defects were noted during the peak high but returned to normal within 5 minutes. The authors point out that nitrous oxide is not without dangers! Its effects will undoubtedly impair performance and there have been reports in the press and anecdotedly of individuals who suffocated by using nitrous oxide in a closed system.

### OXYGEN

Additional inspired oxygen may be needed whenever oxygenation is impaired,

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to allow essential metabolic reactions to occur. Thus oxygen may be required in a wide varity of conditions such as the respiratory distress syndrome, chronic bronchitis, asthma, pneumonia, cardiac infartion, shock, septicaemia and many other conditions. The purpose of oxygen therapy is to prevent the complications attributed to tissue anoxia. These include confusion and other signs of cerebral anoxia, cardiac arrhythmias, reactive pulmonary hypertension, lactic acidosis and tissue death. The most important danger associated with oxygen therapy is the development of carbon dioxide narcosis in patients with ventilatory failure. This may be avoided by careful assessment of the clinical condition of the patient and if necessary by administering oxygen under controlled conditions. Other complications are rare and largely preventable. They include the risk of fire and explosion, collapse of the lung and damage to the pulmonary epithelium. This latter is seen both in the newborn and in the adult and is associated usually with high inspired concentrations of oxygen. In addition the administration of oxygen to the newborn may lead to retrolental fibroplasia, which is particularly likely in premature infants.

Kafer ($30^{R}$) concluded that absorption atelectasis was the most important factor in the genesis of lung changes whilst breathing 100% oxygen for periods up to 70 hours. Weibel ($31^{r}$) has shown that breathing pure oxygen at one atmosphere leads to primary destruction of alveolar capillary endothelial cells; the epithelial cells were secondarily damaged. However, Clarke *et al.* ($32^{r}$), studying dogs under hyperbaric conditions, were unable to confirm that progressive lung damage was the main cause of death in their dogs dying from acute oxygen toxicity.

Infants born with hyaline membrane disease are often treated with high inspired concentrations of oxygen. It is now clear that such therapy will lead to further lung damage ($33^{C}$, $34^{C}$). The same situation seems to apply in the adult patient, particularly in those with pre-existing lung disease ($35^{C}$). Such patients obviously present a dilemma: on the one hand they require oxygen therapy for survival, and on the other excessive use of oxygen may damage the lung before it has time to recover from its previous problem. Stern ($36^{R}$) reviews the use and misuse of oxygen in the newborn infant and suggests that the major way of avoiding problems is by adequate measurement of both inspired and arterial levels of oxygen. Such methods of measurement for these values are now readily available in most hospitals. A further method, in the newborn infant, of reducing the inspired oxygen and yet improving arterial oxygen levels is by the use of positive end-expiratory pressure (PEEP) ($35^{C}$). The use of PEEP is also applicable in the adult patient and seems successful in reducing the requirement for a high inspired oxygen in many cases.

Retrolental fibroplasia associated with the use of high inspired oxygen concentrations in the premature newborn infant is regrettably still a problem. ($37^{C}$). It is important to recognize that it is the arterial oxygen concentration and not necessarily a high inspired oxygen concentration which is responsible for the eye damage seen in the premature infant. It is therefore important that all newborn babies to whom oxygen is administered should have both adequate monitoring of their inspired oxygen content as well as blood samples taken for arterial oxygen concentration.

In many parts of the world oxygen is supplied to the anaesthetists via a pipeline at a raised pressure. This pipeline is often paralleled by a similar pipeline conveying nitrous oxide also under pressure. Various forms of safety devices are incorporated at the end of these pipelines to avoid inadvertent cross-connection when the pipelines are connected to the anaesthetic machine. Regrettably such systems are not foolproof and currently in the United Kingdom there are 3 cases, all *sub judice*, where the connectors were accidentally interchanged leading to fatal results. The gas flows, of course, still register on the oxygen and nitrous oxide flowmeters. When both gases are in use even though the two supplies have been interchanged the resultant mixture inhaled by the patients is only mildly hypoxic. However, when an attempt is made to give pure oxygen (this will of course be pure nitrous oxide) then serious results have followed. In retrospect it may seem easy to detect that there was a problem, but at the time it did not seem obvious. Regrettably in 2 of the instances described above, when the first patient exposed to the hypoxic mixture had died, the problem was not recognized and a second patient also got into difficulties. It was only at this point that questions were raised about the validity of the gas supply.

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Constant vigilance would seem to be the only answer to avoid recurrence of pipeline problems.

## VOLATILE AGENTS

### HALOTHANE

The introduction of halothane in 1956 led to a major change in the practice of anaesthesia, in that inhalational anaesthesia could now be conducted easily and apparently safely by the majority. However, by the early 1960's it became apparent that halothane might have a major drawback in that it appeared to cause liver damage. Isolated clinical reports of post-operative jaundice ascribed to halothane began to appear in the literature. These led to numerous retrospective surveys, of increasing size, attempting to correlate post-operative jaundice with the use of halothane. Over the past 5 years these clinical reports and surveys have been gathered together and discussed extensively in many publications. By suitable arrangement of the data almost any theory relating post-operative jaundice to halothane can be supported or denied ($38^R$, $39^C$, $40^R$). No clear mandate has emerged and possible mechanisms, if halothane is culpable, remain undetermined ($41^R$). Halothane is the most commonly used volatile anaesthetic in the world. Usage varies from 50–70% of all anaesthesias, in countries where halothane is freely available. Indeed, it has been argued that once halothane has been used in an operating area, because it is absorbed by the rubber parts of the anaesthetic machine, in fact every patient will subsequently receive a small dose of halothane. Furthermore, halothane is then present in the atmosphere of the operating area and will be inhaled both by the patient and the staff. It is not always clear to non-anaesthetists why halothane is so widely used. The agent allows anaesthesia to be easily induced, safely maintained and recovery is rapid with relative absence of nausea and vomiting. There is, however, a conviction most commonly expressed by either hepatologists or pathologists that repeated exposure to halothane in some patients may lead to a reaction to the drug causing liver damage. These authorities have urged that halothane should not be used repeatedly, or be reserved for "only minor or major procedures", and should definitely not be given to any patient who has manifested liver dysfunction following a previous exposure to halothane. Such statements are easily made but it may be impossible to establish that the patient has had a previous anaesthetic or what agents were given. In addition liver damage is difficult to define and in most instances of post-operative liver damage the cause is usually clear and does not relate to the anaesthetic agents used ($40^R$).

*Liver damage following repeated exposure to halothane*

Mushin *et al.* ($42^C$) concluded that in patients who had had 2 halothane anaesthetics within a month, the risk of death without jaundice is $3\frac{1}{2}$ times that of the general surgical population. The chances of the same patient developing jaundice and dying are nearly 12 times greater. However, no data was provided on patients having repeated non-halothane anaesthetics. These authors estimated that the risk of jaundice among patients exposed to halothane more than once within a 4-week period seems to lie between 1 in 6,000 and 1 in 20,000. More recently ($43^C$) analysis of data derived from 130 reports of jaundice occurring after anaesthesia with halothane and reported to the Committee on Safety of Medicines showed a significant relation between the number of exposures to halothane and the rapidity with which jaundice developed after exposure. This was considered to provide strong evidence of a cause-effect relationship between the use of halothane and jaundice. Of the 114 patients analyzed 82% had been exposed more than once to halothane; of those so exposed 80% had been anaesthetized more than once in 28 days; 51% of the 130 patients died. This paper was accompanied by a letter, from the Committee on the Safety of Medicines, sent to all doctors, dentists and pharmacists in the United Kingdom. The letter drew attention to the article by Inman and Mushin ($43^C$). This was followed by a series of replies in the columns of the *British Medical Journal* criticizing the paper by Inman and Mushin primarily on the grounds that the data presented did not allow the conclusions given to be drawn ($44^R$). Nevertheless, the present position would seem to be that in a small number of patients there is a risk that repeated exposure to halothane, particularly at short intervals, may be followed by jaundice and other