Regular Review

Occupational hazards of anaesthesia

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"The people of the city said to Elisha, 'You can see how pleasantly our city is situated, but the water is polluted and the country is troubled with miscarriages.'"
2 Kings 2, 19 (*New English Bible*).

The concept of pollution causing miscarriage is evidently not novel, and the atmosphere in operating theatres is invariably contaminated by anaesthetic gases; in the absence of special precautions background levels for the two most important inhalational anaesthetics, halothane and nitrous oxide, ranged from 0.1 to 60 and 30 to 3000 parts per million (ppm) respectively in a study of theatres in 20 hospitals in Britain.¹ Furthermore, bromide, produced by biotransformation, accumulates in appreciable quantities in the blood of anaesthetists exposed to halothane.²

Anxieties about the possible hazards of working in this polluted environment were triggered by the results of a survey reported by Vaisman in 1967.³ A questionnaire was sent to 354 Russian anaesthetists (of whom 28% used halothane, 59% nitrous oxide, and 98% ether) and 303 replies were analysed. Of these, 110 related to women who reported a total of 31 pregnancies, of which no fewer than 18 had ended in spontaneous abortion. Vaisman did not, however, specifically single out pollution of the operating theatre atmosphere as the likely cause of this and other health problems (such as headache, insomnia, and liver disorders) reported by her colleagues; she drew attention to other unfavourable aspects of the anaesthetists' lot—long and irregular hours of work, constant mental stress, and exposure to extremes of temperature—as important factors.

Vaisman's paper inspired a great deal of animal experimentation and epidemiological research undertaken to try to shed further light on any occupational risks for anaesthetists and other operating-theatre personnel. Most workers have been concerned with possible fetotoxic or carcinogenic hazards, but some have looked at other problems such as the occurrence of hepatic or renal disease. This work has, in general, focused on long-term exposure to low concentrations of anaesthetic gases as the suspected cause rather than on the other factors mentioned by Vaisman. This choice seems to be due partly to the development of improved methods of measuring trace levels of anaesthetic gases, partly to recognition that the metabolism of anaesthetic gases may lead to the release of toxic substances in the body, and partly to the generally high level of concern about possible teratogenic and carcinogenic effects of drugs.⁴

Not surprisingly, most animal studies have been concerned with mice, rats, rabbits, or guinea-pigs. The uncertainties of extrapolating the findings in such species to man are well known. Experiments in which very large doses of anaesthetic agents in liquid form were given by unusual routes (by mouth,

for example) should clearly be ignored, but the results of studies seemingly more relevant may still have been distorted by insufficient attention to detail. Resorption of the fetus in rats, for example, can be induced by relatively minor stress such as handling or changes in patterns of feeding or lighting; any disparity between experimental groups with respect to variables such as these could easily lead to incorrect conclusions.

Several workers have investigated the effects of anaesthetic gases on chromosomal breakage or have sought other experimental evidence of mutagenicity, since 90% of carcinogens are also mutagenic.⁵⁻⁶ The results with the Ames test and mammalian cell cultures have been negative except in regard to certain anaesthetics containing a vinyl group, and, of these, only trichloroethylene is now used as an anaesthetic in Britain.⁷⁻¹¹

Early animal studies of the possible carcinogenic and teratogenic effects of inhalational anaesthetics produced some suspicious findings,¹²⁻¹⁴ but more recent experiments based on exposure to subanaesthetic concentrations have been more reassuring.¹⁵⁻²¹ Lansdown *et al*¹⁵ and Pope *et al*,¹⁶ for example, have conducted studies in which animals were exposed throughout gestation to concentrations of anaesthetics at least 500 times higher than those likely to occur in the operating theatre. No evidence of teratogenicity and no significant increase in fetal loss were found. Coate *et al*¹⁷ exposed rats to halothane 1 ppm combined with nitrous oxide 50 ppm or to halothane 10 ppm combined with nitrous oxide 500 ppm. Though extended exposure at both levels resulted in chromosomal damage to bone marrow and spermatogonial cells, exposure before and after mating (seven hours a day and five days a week) did not produce any teratological or abortifacient effects. Exposure to anaesthetising concentrations of certain agents, on the other hand, including nitrous oxide, does appear to cause an increased incidence of abortion and fetal malformations in rodents.²²

Baden *et al*¹⁸ concluded that, in the conditions of their experiment on Swiss/ICR mice, lifetime exposure to halothane at its maximum tolerated dose was not associated with an increased incidence of neoplasia. A similarly negative result was obtained with 300 Fischer rats exposed to halothane 10 ppm and nitrous oxide 500 ppm for seven hours a day, five days a week for 104 weeks.¹⁹ An important study by Eger, Corbett, and others²⁰ has refuted the earlier finding by Corbett¹² that the anaesthetic isoflurane (Forane, never released in Britain) was a transplacental carcinogen.

With the consensus of data from animal experiments at subanaesthetic concentrations yielding no convincing evidence of either fetotoxicity or carcinogenicity, epidemiological studies in man assume particular importance. Investigations of this type published before the end of 1977 have recently been reviewed by MPV.²³ This review was limited to studies in which control data were collected; after sifting the literature

12 investigations were considered to be eligible for inclusion.²⁴⁻³⁵

Three of the studies considered only the pattern of mortality in anaesthetists. The first two^{24 32} were concerned with deaths among members of the American Society of Anesthesiologists during the intervals 1947-66 and 1967-71. Both studies had serious methodological shortcomings, but the results suggested that anaesthetists are at an increased risk of death from suicide. In addition a modest excess of deaths from tumours of the lymphatic and reticuloendothelial systems had been noted in the earlier period, but no such difference was apparent in the later period. The third study³⁵ concerned over 20 000 male British doctors followed up for 20 years. Of these, some 1250 were full-time or part-time anaesthetists. No excess was found either in overall mortality or in deaths from tumours of the lymphatic and reticuloendothelial systems, though five deaths from pancreatic cancer were observed among the full-time anaesthetists, while only 1.7 would have been expected on the basis of data from other doctors.

The remaining nine studies (four North American, three British, two Scandinavian) were concerned with a wide range of possible hazards, though most attention had been paid to spontaneous abortion (seven studies) and to the birth of malformed offspring (seven studies). In three studies these outcomes of pregnancy had been examined in the wives of men exposed to anaesthetic gases as well as in exposed women themselves. The standard approach in each study was to identify a group of persons who had been exposed (usually anaesthetists or anaesthetic nurses) from a register and to send out a questionnaire inquiring about the past occurrence of the disorders under investigation. For control purposes, similar information was sought from a group of unexposed persons (usually doctors other than anaesthetists, and nurses other than anaesthetic nurses). This methodological approach is not, of course, satisfactory for the study of diseases leading to retirement or death, especially those running a short course. The response rates in the various study groups were rather low, varying from about 40% to about 85%. A particularly serious problem was noted in the largest of the investigations³¹; response rates in the unexposed groups were much lower than those in the exposed groups. The questionnaires used in some of the studies were found to be heavily "loaded," being entitled, for example, "Effects of waste anaesthetics on health," while many of the events recorded (such as spontaneous abortion and minor congenital malformation) were ill defined and open to the influence of reporting bias.

Viewed against this methodological background, the various studies were nevertheless found to provide reasonably convincing evidence of an increase of about 40% in the risk of spontaneous abortion in exposed women (but not in the wives of exposed men). Even this result might, however, possibly have been attributable to reporting bias. The evidence relating to other suspected hazards considered in the review (cancer, malformation, stillbirth, altered sex ratio, low birth weight, and infertility) was judged to be unconvincing, nor is it likely that trace concentrations of anaesthetics have any appreciable effect on mental performance.³⁶⁻³⁸

Two further epidemiological studies have been published since the appearance of the review. The first, by Tomlin,³⁹ concerned 340 anaesthetists in the West Midlands region of England, of whom 314 completed a survey questionnaire. About half the anaesthetists were trainees; an unknown proportion of the remainder must have been included in earlier British surveys conducted by Knill-Jones *et al.*^{27 33} In the absence of a proper control group, Tomlin used for

comparative purposes those pregnancies experienced by anaesthetists (or their wives) either before they took up anaesthetics or after a year or more away from the operating theatre. Tomlin concluded that spontaneous abortion, various congenital malformations and "non-acquired anomalies," low birth weight, infertility, cancer in adults and children, and (possibly) impaired intellectual development in children were all health problems of anaesthetists and their families. Careful examination of his data, however, shows that only the rates for spontaneous abortion in exposed women were significantly in excess of the control values.^{40 41} Many other major criticisms have been directed at Tomlin's study,^{42 43} which, while provocative, seems to add little that is concrete to the existing literature.

In the second study, by Cohen and his colleagues in North America,⁴⁴ male dentists and female chairside assistants who used anaesthetic gases (mainly nitrous oxide) were compared with those who did not. At first sight, this design would appear to have overcome the problem of finding an appropriate control group. In the event, however, users of anaesthetics were found to be younger than non-users: though allowance was made for this age difference in the analysis, doubts must remain about the comparability of the groups in other respects. As with other, similar studies, there may also have been biased reporting since the purpose of the inquiry was well known. Furthermore, the response rate was disappointing: only 78% of the 138 000 dentists originally mailed a postcard by the American Dental Association responded and, of the responders, only 74% of those selected for detailed investigation returned a questionnaire. Nevertheless, the study showed a highly significant association between exposure to anaesthetic gases and spontaneous abortion in the chairside assistants (the rate rising from 8.1 per 100 pregnancies in those without exposure to 19.1 per 100 pregnancies in those heavily exposed). An association was also observed in the dentists' wives, but the differences (6.7 per 100 for non-exposed against 10.2 per 100 for heavily exposed husbands) were much less impressive. There was no increase in congenital malformations among the children born to exposed dentists. The corresponding data for chairside assistants showed a weak association, but no dose-response relation was apparent and the findings were of borderline statistical significance.

Liver diseases and kidney diseases (renal lithiasis in dentists, genitourinary infection in chairside assistants) were reported significantly more often by those exposed to anaesthetics, but differences in reported cancer rates were minimal and not significant at the 5% level. There was, however, a substantial increase in the reporting of non-specific neurological symptoms in those exposed to anaesthetic gases. A condition resembling subacute combined degeneration of the cord has been reported in 15 persons who had been abusing nitrous oxide (14 of whom were dentists)⁴⁵ and this condition might be related to the inactivation of vitamin B₁₂ by nitrous oxide.⁴⁶ Levels of nitrous oxide polluting the air in American dental operatories are generally much higher than in operating theatres.⁴⁷

Where, then, does all this evidence point? Firstly, it is reasonably conclusive that there is an increased risk of abortion in theatre staff, and two of the studies we have cited^{22 44} firmly suggest that high concentrations of nitrous oxide may be the causative factor. Secondly, intermittent exposure to high concentrations of nitrous oxide can apparently induce lesions indicative of interference with vitamin B₁₂ metabolism. The other suggested hazards may be real but the consensus of evidence is not, in our opinion, conclusive at present. Nevertheless, steps should be taken to reduce contamination of the

atmosphere in operating theatres as much as is reasonably possible—which, of course, is DHSS policy⁴⁸—and scavenging systems are now being installed in many operating theatres. While these systems may not succeed in reducing pollution levels to those recommended by the American National Institute of Occupational Safety and Health (not more than 2.0 ppm for halothane and 25 ppm for nitrous oxide) they may considerably improve on the concentrations found in the absence of pollution control.¹ Nevertheless, to a large extent the recommended levels are arbitrary and no “safe” level of exposure has yet been defined.

On the present evidence, a theatre nurse or female anaesthetist becoming pregnant or wishing to become pregnant should be advised to avoid working in an environment contaminated with anaesthetic gases, such as an operating theatre without an effective scavenging system (but there is no certainty that some other occupations in the hospital service, or elsewhere for that matter, are any more favourable). On the information at present available, there are no grounds for recommending

therapeutic abortion for the working theatre nurse or anaesthetist who becomes pregnant, and Cohen (personal communication) concurs with this view.

Prospective studies are in progress which it is hoped will assess the hazards of work in operating theatres after the introduction of scavenging systems. There are formidable difficulties in quantifying the long-term exposure of an individual anaesthetist or nurse to waste anaesthetic gases, but only the relation of exposure to hazard will indicate whether any part of the apparent risk of working in an operating theatre may be attributed to the inhalation of trace concentrations of anaesthetic gases.

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- ¹ Davenport HT, Halsey MJ, Wardley-Smith B, Bateman PE. Occupational exposure to anaesthetics in 20 hospitals. *Anaesthesia* 1980;**35**:354-9.
- ² Duvaldestin P, Mazze RI, Hazebruck J, Nivoche Y, Cohen SE, Desmonts JM. Halothane biotransformation in anaesthetists. *Anesthesiology* 1979;**51**:41-6.
- ³ Vaisman AI. Work in operating theatres and its effect on the health of anaesthetists. *Experimentalnaya Khirurgiya* 1967;**12**:44-9.
- ⁴ Anonymous. Vapour alarms. *Lancet* 1976;ii:842-3.
- ⁵ McCann J, Choi E, Yamasaki E, Ames BN. Detection of carcinogens as mutagens in the salmonella/microsome test: assay of 300 chemicals. *Proc Natl Acad Sci USA* 1975;**72**:5135-9.
- ⁶ McCann J, Ames BN. Detection of carcinogens as mutagens in the salmonella/microsome test: assay of 300 chemicals, part II. *Proc Natl Acad Sci USA* 1976;**73**:950-4.
- ⁷ Baden JM, Simmon VF. Mutagenic effects of inhalational anaesthetics. *Mutat Res* 1980;**75**:169-89.
- ⁸ Sturrock J. Lack of mutagenic effect of halothane or chloroform on cultured cells using the azaguanine test system. *Br J Anaesth* 1977;**49**:207-10.
- ⁹ Sturrock J. No mutagenic effect of enflurane on cultured cells. *Br J Anaesth* 1977;**49**:777-9.
- ¹⁰ Waskell L. A study of the mutagenicity of anaesthetics and their metabolites. *Mutat Res* 1978;**57**:141-53.
- ¹¹ White AE, Takehisa S, Eger EI, Wolff S, Stevens WC. Sister chromatid exchanges induced by inhaled anaesthetics. *Anesthesiology* 1979;**50**:426-30.
- ¹² Corbett TH. Cancer and congenital anomalies associated with anaesthetics. *Ann NY Acad Sci* 1976;**271**:58-66.
- ¹³ Fink BR, Shepard TH, Blandau RJ. Teratogenic activity of nitrous oxide. *Nature* 1967;**214**:146-8.
- ¹⁴ Basford AB, Fink BR. The teratogenicity of halothane in the rat. *Anesthesiology* 1968;**29**:1167-73.
- ¹⁵ Lansdown ABG, Pope WDB, Halsey MJ, Bateman PE. Analysis of fetal development in rats following maternal exposure to subanaesthetic concentrations of halothane. *Teratology* 1976;**13**:299-304.
- ¹⁶ Pope WDB, Halsey MJ, Lansdown ABG, Simmonds A, Bateman PE. Fetotoxicity in rats following chronic exposure to halothane, nitrous oxide, or methoxyflurane. *Anesthesiology* 1978;**48**:11-6.
- ¹⁷ Coate WB, Kapp RW, Lewis TR. Chronic exposure to low concentrations of halothane-nitrous oxide: reproductive and cytogenetic effects in the rat. *Anesthesiology* 1979;**50**:310-8.
- ¹⁸ Baden JM, Mazze RI, Wharton RS, Rice SA, Kosek JC. Carcinogenicity of halothane in Swiss/ICR mice. *Anesthesiology* 1979;**51**:20-6.
- ¹⁹ Coate WB, Ulland BM, Lewis TR. Chronic exposure to low concentrations of halothane-nitrous oxide: lack of carcinogenic effect in the rat. *Anesthesiology* 1979;**50**:306-9.
- ²⁰ Eger EI, White AE, Brown CL, Biava CG, Corbett TH, Stevens WC. A test of the carcinogenicity of enflurane, isoflurane, halothane, methoxyflurane and nitrous oxide in mice. *Anesth and Analg (Cleve)* 1978;**57**:678-94.
- ²¹ Wharton RS, Mazze RI, Baden JM, Hitt BA, Dooley JR. Fertility, reproduction and postnatal survival in mice chronically exposed to halothane. *Anesthesiology* 1978;**48**:167-74.
- ²² Lane GA, Nahrwold ML, Tait AR, Taylor BS, Beaudoin AR, Cohen PJ. Nitrous oxide is teratogenic: xenon is not! *Anesthesiology* 1979;**51**:S260.
- ²³ Vessey MP. Epidemiological studies of the occupational hazards of anaesthesia—a review. *Anaesthesia* 1978;**33**:430-8.
- ²⁴ Bruce DL, Eide KA, Linde HW, Eckenhoff JE. Causes of death among anesthesiologists: a 20-year survey. *Anesthesiology* 1968;**29**:565-9.
- ²⁵ Askrog V, Harvald B. Teratogen effekt af inhalationsanaestetika. *Nord Med* 1970;**83**:498-500.
- ²⁶ Cohen EN, Bellville JW, Brown BW. Anaesthesia, pregnancy, and miscarriage: a study of operating room nurses and anaesthetists. *Anesthesiology* 1971;**35**:343-7.
- ²⁷ Knill-Jones RP, Rodriques LV, Moir DD, Spence AA. Anaesthetic practice and pregnancy. Controlled survey of women anaesthetists in the United Kingdom. *Lancet* 1972;ii:1326-8.
- ²⁸ Corbett TH, Cornell RG, Leiding K, Endres JL. Incidence of cancer among Michigan nurse-anaesthetists. *Anesthesiology* 1973;**38**:260-3.
- ²⁹ Rosenberg P, Kirves A. Miscarriages among operating theatre staff. *Acta Anaesthesiol Scand* 1973;**53**, suppl: 37-42.
- ³⁰ Corbett TH, Cornell RG, Endres JL, Lieding K. Birth defects among children of nurse-anaesthetists. *Anesthesiology* 1974;**41**:341-4.
- ³¹ American Society of Anesthesiologists, Ad Hoc Committee on the Effect of Trace Anaesthetics on the Health of Operating Room Personnel. Occupational disease among operating room personnel: a national study. *Anesthesiology* 1974;**41**:321-40.
- ³² Bruce DL, Eide KA, Smith NJ, Seltzer F, Dykes MHM. A prospective survey of anesthesiologist mortality, 1967-71. *Anesthesiology* 1974;**41**:71-4.
- ³³ Knill-Jones RP, Newman BJ, Spence AA. Anaesthetic practice and pregnancy. Controlled survey of male anaesthetists in the United Kingdom. *Lancet* 1975;ii:807-9.
- ³⁴ Pharoah POD, Alberman E, Doyle P, Chamberlain G. Outcome of pregnancy among women in anaesthetic practice. *Lancet* 1977;ii:34-6.
- ³⁵ Doll R, Peto R. Mortality among doctors in different occupations. *Br Med J* 1977;ii:1433-6.
- ³⁶ Smith G, Shirley AW. Failure to demonstrate effect of trace concentrations of nitrous oxide and halothane on psychomotor performance. *Br J Anaesth* 1977;**49**:65-70.
- ³⁷ Cook TL, Smith M, Starkweather JA, Winter PM, Eger EI. Behavioral effects of trace and subanaesthetic halothane and nitrous oxide in man. *Anesthesiology* 1978;**49**:419-24.
- ³⁸ Frankhuizen JL, Vlek CAJ, Burm AGL, Reijer V. Failure to replicate negative effects of trace anaesthetics on mental performance. *Br J Anaesth* 1978;**50**:229-34.
- ³⁹ Tomlin PJ. Health problems of anaesthetists and their families in the West Midlands. *Br Med J* 1979;ii:779-84.
- ⁴⁰ Doll R. Health problems of anaesthetists and their families. *Br Med J* 1979;ii:1078.
- ⁴¹ Vessey MP. Health problems of anaesthetists and their families. *Br Med J* 1979;ii:1078-9.
- ⁴² Vowles M, Pethybridge RJ, Brimblecombe F. Health problems of anaesthetists and their families. *Br Med J* 1979;ii:1079.
- ⁴³ Spence AA, Knill-Jones RP. Health problems of anaesthetists and their families. *Br Med J* 1979;ii:1144.
- ⁴⁴ Cohen EN, Brown BW, Wu ML, et al. Occupational disease in dentistry and chronic exposure to trace anaesthetic gases. *J Am Dent Assoc* 1980;**101**:21-31.
- ⁴⁵ Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 1978;ii:1227-30.
- ⁴⁶ Amess JAL, Burman JF, Rees GM, Nancekivell DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. *Lancet* 1978;ii:339-42.
- ⁴⁷ Whitcher CE. Levels of exposure to trace anaesthetic gases. In: Cohen EN, ed. *Anesthetic exposure in the workplace*. Littleton: PSG Publishing Company, 1980:9-31.
- ⁴⁸ Department of Health and Social Security. Health services development. Pollution of operating departments etc by anaesthetic gases. London: HMSO, 1976. (Circular No HC(76) 38.)