Medical Intelligence

Anesthetic Pollution:
What Is Happening to Us?

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Within the last decade a succession of epidemiologic studies4-6 has established that people who work in operating rooms run certain important health hazards inherent in their environment. Probably of greatest concern are the high abortion and miscarriage rates among exposed persons or their spouses and the incidence of developmental defects in their offspring.

The anesthesiologists who made these studies have usually suspected latent poisoning by the trace quantities of volatile anesthetics present in the local atmosphere. Some feel strengthened in their suspicion by the evidence that day-long exposure to an anesthetizing concentration evokes damage or death in animal fetuses,7 confirmed recently in hamsters exposed to nitrous oxide and halothane.8 Such evidence clearly contraindicates the administration of general anesthetics, singly or in combination, during at least the first three months of human pregnancy. Also, tending to reinforce such caution is the recent interesting observation by Sturrock and Nunn9 suggesting that the side effects of two simultaneously administered anesthetics may summate more potently than the anesthetic effects. These investigators find that nitrous oxide and halothane act synergistically and not additively in producing nuclear abnormalities in dividing fibroblasts. Nitrous oxide alone, however, in analgesic concentrations for 12 hours, does not impair the multiplication of leukocytes in the body.10 Low concentrations of at least some inhalation anesthetics fail to affect division of cells in culture,11 rapid axonal transport,12 cell motility,13 mitochondrial metabolism,14 and numerous immune processes such as phagocytosis,15 lymphocyte transformation,16 and cell-mediated cytotoxicity.17 All the cited laboratory studies indicate that the toxic threshold concentration is a hundredfold or even a thousandfold higher than the level found in operating room atmospheres. The dramatic reaction of seminiferous tubules to persistent exposure to nitrous oxide, recently described by Kripke and colleagues,18 was elicited by a concentration of 200,000 ppm.

The recognized hazard of relatively brief exposure to an anesthesiologic concentration of anesthetic does not logically imply an equivalent risk in prolonged exposure to a much lower concentration, even if equivalent in so-called "MAC" hours. This could be as fallacious as expecting indefinite exposure to a subanesthetic concentration of anesthetic eventually to produce narcosis if only endured long enough. Also, it should be stressed that a causal connection between the epidemiologic findings and the presence of anesthetic vapor in the atmosphere of the operating room has not been established. Although there is evidence that molecules of anesthetic or of anesthetic metabolite may linger in the body for many days after a relatively brief period of full general anesthesia,19 there is no proof yet that such retained substances are in fact harmful, nor information on how much retention occurs with exposure to trace concentrations. Direct evidence on these questions is badly needed.

A few attempts have been made to test the effects of prolonged exposure to traces of anesthetics on animal reproduction in the laboratory. Bruce20 showed that halothane inhaled 7 hours daily, 5 days a week, for 6 weeks, at a concentration known to exist in the operat-
Table 1. Accidental Premature Termination of Pregnancy in Anesthesiologist and Non-Anesthesiologist Physicians

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pregancies</th>
<th>Control</th>
<th>Anes-th.</th>
<th>F</th>
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<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>0</td>
<td>31</td>
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<td>3</td>
<td>115</td>
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<td>.01</td>
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<td>4</td>
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<td>15</td>
<td>18</td>
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</tr>
<tr>
<td>6</td>
<td>776</td>
<td>9</td>
<td>17</td>
<td>.01</td>
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* Not significant.

ing room air (15 ppm), did not have any deleterious effect on rodent (mouse) reproduction. On the other hand, Corbett obtained an increased fetal death rate in pregnant rats exposed to 1,000 ppm nitrous oxide 8 hours per day for 5 days (P < 0.05), but not with exposures to 100 ppm. Thus, the published evidence is equivocal. Furthermore, unpublished results obtained by Corbett with methoxyflurane (cited by Cohen et al.4) were negative, and unpublished data obtained in the laboratory of one of the present authors (Fink) showed no difference between the numbers of young born to a group of eight pregnant rats that breathed 500 ppm halothane and 5,000 ppm nitrous oxide 8 hours a day throughout pregnancy and a concurrent group that breathed air. Of course, species differences in teratogenicity of agents cannot be excluded, nor for that matter, differences in the susceptibilities of individuals, or the presence of unidentified teratogens. In mice, 24-hour isolation and food deprivation on day 14–15 of pregnancy is sufficient to induce development of cleft palate.22 Many other pitfalls attend teratogenicity studies.22

Anesthetics may have been seized on as the culprits in the human epidemiologic studies partly because drugs are tangible entities and easy to assay. The alarm first rung in Russia by Vaisman (table 1) was subsequently sounded again by Askrog and Harvold,2 who reported that women employed as anesthetists suffered a doubled incidence of abortion or premature termination of pregnancy, while men incurred a doubled incidence among their wives. Here the subjects

served as their own controls. In other studies (tables 1 and 2) the controls were different, but the trend of the findings was about the same. However, the “National” Study by Cohen et al.2 contradicted Askrog and Harvold in the matter of male transmission of disability: in the United States, the abortion rates among wives of male nurses were the same whether the husbands practiced anesthesia or not. Furthermore, doubt about the roles of anesthetics as occupational teratogens or abortifacients emerged from data presented by Rosenberg and Kirves,7 obtained from four groups of nurses, working respectively as anesthesia, casualty department, intensive-care unit, and scrub nurses. The results, according to the authors, pointed to stress as the cause of the observed increased rate of spontaneous miscarriages during hospital employment. A correlation between emotional stress and abnormal pregnancies has indeed been demonstrated in man.23–27 Gorsuch and Key,27 for example, showed that women who had abnormal pregnancies had significantly greater anxiety levels and life stresses during the first trimester, compared with a control group of women who had normal pregnancies. A mechanism for these complications of pregnancies is unknown, but may involve hypothalamic stimulation and altered neuroendocrine and autonomic activity. Stress and elevated serum steroid levels have been associated with abnormal fetal osteogenesis in the mouse.27 An abnormality in serotonin metabolism has also been suggested as an etiologic factor.27

On the whole, then, scavenging of anesthetic gases from the operating room atmosphere is of uncertain relevance as an antifertility measure, although it is surely an important precaution, because anesthetic contamination of the atmosphere is not absorbed from other deleterious consequences. Drug (antipyrine) metabolizing ability, measured by Wood and colleagues,29 was 21 per cent higher in anesthetists and anesthetic technicians than in matched controls, confirming similar evidence with 14C-halothane obtained by Cascorbi.29 Whiter and colleagues29 had found halothane levels of 5–10 ppm within a 3-foot radius of the semiclosed
## Table 2. Accidental Premature Termination of Pregnancy in Anesthetist and Non-anesthetist Nurses, before and during Period of Hazard

<table>
<thead>
<tr>
<th>Reference</th>
<th>Incidence of Abortions (Per Cent)</th>
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<tr>
<td></td>
<td>Pregancies Before</td>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>Anesthetist nurses</td>
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</tr>
<tr>
<td></td>
<td>General-duty nurses</td>
<td>34</td>
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<tr>
<td>5</td>
<td>Anesthetist nurses</td>
<td>94</td>
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<tr>
<td></td>
<td>Casualty unit nurses</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Intensive-care unit nurses</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>Instrument nurses</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>Anesthetist nurses</td>
<td>1,826</td>
</tr>
<tr>
<td></td>
<td>General-duty nurses</td>
<td>1,948</td>
</tr>
<tr>
<td></td>
<td>Operating-room nurses</td>
<td>2,781</td>
</tr>
</tbody>
</table>

* Not significant.
† One-sided t test.

C circles anesthesia circuit; Quimby et al.,31 after exposing rats to 10 ppm of halothane 8 hours a day from conception to the age of 2 months, reported that the young later manifested deficits in learning ability. Note should also be taken of tests by Bruce et al.,22 on 20 medical students, tending to show that 500 ppm nitrous oxide with 15 ppm halothane produces sleepiness and significant decrements in perceptual and motor skills. Analogous effects have been reported to occur with 110 ppm trichloroethylene in an industrial setting.23

Several instances of illness ascribed to the inhalation of halothane vapor discharged from the gas machine are on record. These include at least three cases of impaired hepatic function among anesthetists.31,32 Less well known, perhaps, is one case affecting the heart, causing atrial fibrillation,37 or another affecting the larynx, causing laryngitis with headaches and lassitude.24 In the last-mentioned instance, ether, trichloroethylene, and nitrous oxide were without effect. A case of ophthalmic hypersensitivity to halothane has also been described.29 As regards other anesthetics, Elder et al.,30 have reported that a nurse anesthetist suffered exacerbation of subclinical myasthenia gravis by occupational exposure to methoxyflurane, but not to halothane, cyclopropane or nitrous oxide. Industrial workers exposed to trichloroethylene may develop a blotchy erythema after they drink alcohol, and the same reaction has also been elicited in experimental subjects.41 A delayed asthmatic response following exposure to enflurane has recently been reported.42

That the catalog of suspected occupational mischiefs includes cancer should occasion neither surprise nor premature alarm. Bruce et al.,43 in a retrospective study, had originally raised concern over deaths from malignancies among anesthesiologists. A subsequent prospective study,44 however, diminished that concern. It found that death rates of anesthesiologists in the United States, both overall and in various categories including malignancies, were lower than those for the control groups in the general population. (The one exception was suicide.) The "National Study"45 suggested that the incidence of cancer in anesthesiologist physicians was probably higher than that in pediatricians, although only in females. The uncertainty has lately been ventilated in the lay press, and may soon be resolved as regards halothane, because it is now 20 years since halothane was introduced into clinical practice, a period about as long as the expected induction time of cancer in man.

Occupational cancer in operating room per-
sonnel, if the entity exists, could also implicate stress as a causative factor. Such people often work long and inconvenient hours, and handle many critically ill patients. Numerous studies have suggested an association between emotional stress and the pathogenesis of cancer in man45–47 and an association between emotional stress and the growth rate of established cancer.18 There is also some evidence for an association between stress and immunity and cancer in animals.48–51 Current thought holds that cancer may result from immunologic deficiency and a failure of surveillance mechanisms that recognize and destroy foreign cells. Stress and anxiety may influence immunologic function via the central nervous system and neuroendocrine function.52 Serum corticosteroid levels increase during stress, and steroids are known to inhibit many immunologic phenomena important in defense against cancer. These include phagocytosis,53 lymphotoxic kinetics,53 lymphotoxic transformation,54 chemotaxis,55 and cell-mediated cytotoxicity.56

In short, chronic inhalation of trace amounts of anesthetics is undesirable for a variety of reasons; the scavenging of volatile anesthetics is therefore an important prophylactic measure. Nevertheless, it is premature to conclude that long-continued trace exposure probably causes abortion, congenital malformation, and cancer. Although such a relationship may eventually be proven, in our opinion the present evidence is wholly inconclusive.

Note added in proof: Results of psychomotor tests by Smith and Shirley (Br J Anaesth 48: 274, 1976) appear to conflict with the observations of Bruce et al.52

References

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