CHRONIC EXPOSURE TO ANAESTHETICS: A TOXICITY PROBLEM?

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IT IS NOW ESTABLISHED that acute clinical concentrations of anaesthetics can be toxic.[1] The details of mechanisms, extent and frequency, of this toxicity continues to be debated. The fact remains, however, that morbidity and mortality, although rare, can result from anaesthetic toxicity. It is therefore of more than normal curiosity and concern to explore the possible implications of inadvertent chronic exposure to subclinical anaesthetic concentrations that might not only be experienced by patients but also by operating and recovery room personnel.

(I) EVIDENCE INDICATING POSSIBLE SOURCES OF ANAESTHETICS FOR CHRONIC EXPOSURE

There are four possible sources of chronic exposure to anaesthetics in the operating room. These are:

(1) *Operating Room Pollution*

Only recently have reports appeared which document concentrations of anaesthetic agents in the vicinity of the anaesthetist[2–5] in the operating room. These trace amounts, in parts per million (ppm) are summarized in Table I. They are in the following broad ranges: nitrous oxide, 50 to 250 ppm; halothane, 5 to 15 ppm; methoxyflurane, 2 to 10 ppm. These measurements were made in modern, well ventilated operating rooms.[2–5] It is interesting to note, in contrast, a study reported in 1929[6] that showed an ether concentration of 20 to 500 ppm in poorly ventilated rooms where open drop techniques were employed. An exposure to 500 ppm of ether is above the recommended threshold limit value (TLV) established for ether.[5]

Furthermore,[2–4] small but measurable amounts of halothane and methoxyflurane have been detected in end-expired air of anaesthetists and nurses 16 to 30 hours after exposure (Table I). Concentrations of methoxyflurane were detected in the end-expired air of patients for as long as 10 to 18 days after anaesthesia.[4]

In one recent study, halothane present in the ambient atmosphere was continuously measured during the conduct of surgical anaesthesia.[5] Concentrations were determined on-line with a mass spectrometer and found to vary with sampling site, breathing system used and the scavenging system employed to remove overflow anaesthetic gases. The two operating rooms studied measured

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TABLE I

CONCENTRATIONS OF ANAESTHETICS IN OPERATING ROOMS AND PERSONNEL*

Sampling site	Anaesthetic	Concentration (ppm)**	Study
Ambient Air	Nitrous oxide	50–250 (130)	Linde and Bruce (1969)
Operating	Halothane	5–15 (10)	Linde and Bruce (1969)
Room	Halothane	– (4.9)	Whitcher (1971)
	Methoxyflurane	2–10	Corbett (1971)
	Diethyl Ether	20–500‡	Hirsch (1929)†
End-Expired Air			
Nurses	Halothane	0.21	Whitcher (1971)
Anaesthetists	Halothane	0.46	Whitcher (1971)
	Halothane	0–12 (1.8)	Linde and Bruce (1969)
	Methoxyflurane	1	Corbett (1971)
Urine	Total Fluorine	8.1 μg/ml§	Linde and Bruce (1969)
	Fluoride	1.3 μg/ml‡¶	Linde and Bruce (1969)
Factory	Benzene‖	100	Erf (1939)

*Semi-closed circle nitrous oxide 4–5 L/min.
†Open-drop no ventilation.
‡Threshold Limit Value (TLV) for ether = 400 ppm.
§Normal value is 5.0 μg.
¶Normal value is 1.0 μg.
‖Anaesthetic at 1–2 per cent.
**Parts per million.

about 4,500 cubic feet and were air-conditioned, without recirculation, at flow rates of 650 to 700 cubic feet/minute. This provided a total air exchange once every six to seven minutes. Waste air was vented to the outside. Ventilation inflow was located near ceiling level and the outflow was six inches from floor level on an adjacent wall. These specifications are comparable to those of the Vancouver General Hospital for a similar size theatre except that our flow rates are almost twice as great (1200 cubic feet/minute on entry; 1100 cubic feet/minute on exit). The total air exchange is also better, at four to six minutes. (10 to 14 times per hour).

Although concentrations of halothane in the operating room atmosphere were usually below detectable levels at the beginning of the day, measurable concentrations were obtained within minutes after the beginning of anaesthesia regardless of the breathing circuit used.

(2) *Residues in Anaesthetic Equipment*

Only recently has it become apparent that patients may receive an unintended exposure to an anaesthetic agent by virtue of the ability of the anaesthetic to be absorbed in anaesthetic apparatus.[7,8]

Cyclopropane, diethyl ether, halothane and methoxyflurane have all been found to be absorbed by rubber, plastic and soda lime or baralyme.[7] Small concentrations of these agents may be delivered to the patient from anaesthetic circuits even if the vaporizer is shut off. The comparative cumulative uptakes of cyclopropane, diethyl ether, halothane and methoxyflurane by rubber in a complete anaesthetic circuit[7] have been compared. As a consequence, as much as

TABLE II

NON-ANAESTHETIC "VOLATILE" SOLUTIONS COMMONLY USED IN OPERATING ROOMS

Basic Vehicles	Product	Use in Operating Room
Propylene Glycol	Aerosol spray:	
Ethyl Alcohol	Vi-hesive	Draping when vi-drape used
Benzyl Alcohol	Aeroplast	Covers wounds
Sodium Benzoate-Benzoic Acid	Alcohol (tinctures)	Pre-operative prepping fixations for cytology
	Acetone	Removal of nail polish
	Mastisol	Drapes stabilized
	Whitehead's varnish	Post-operative wound cover
	Brazilian oil	Marking
	Chlorothene	Tape removal
	Collodion	Seal wounds
	Dematome glue with ether	Skin graft surgery
	Medi-air	Kidde tourniquet
	Simplex liquid	Charnley Mueller total hip replacement

300 ml of anaesthetic vapor may be routinely transferred from one case to a subsequent patient when agents are switched between cases.

At equipotent anaesthetic concentrations, the absolute amounts of anaesthetic vapour absorbed by the breathing circuit are nearly the same for all agents. Absorption and elimination (washout)[7,8] of these agents are proportional to:

(1) linear function of the square root of time
(2) the vapor concentration in rubber, if a near-zero circuit concentration is maintained by a high flushing rate for the system
(3) rubber-gas, and soda lime-gas partition coefficients, which for any particular agent are constant
(4) the surface area of the systems and
(5) the square root of the diffusion coefficient of the agent in rubber, which is also constant for a particular agent.

Samulska and co-workers[8] clearly demonstrated that whether a different anaesthetic agent is used or an anaesthetic machine is idle for days, makes no difference to the fact that halothane may be delivered for hours from a previously exposed anaesthetic machine. It was evident from their studies that most patients in operating rooms must receive halothane. With a circle system and the vapourizer shut off, halothane was delivered for more than nine hours. Samples taken from operating room anaesthetic machines in ordinary clinical use showed the concentrations varying from a low of 0.0003 to a high of 0.139 per cent.[8] These concentrations, admittedly low, cannot be dismissed, for reasons discussed under possible hazards resulting from long-term exposure to anaesthetics.

(3) *Solvent Contaminants and Intravenous Agents*

Not all long-term exposure to potentially toxic vapours prevalent in modern operating room theatres are necessarily from anaesthesia. Table II lists spray solvent propellants currently used in the Vancouver General Hospital operating rooms and in most other surgical suites of the world. It is interesting to note the

frequency with which propylene glycol, acetone, ethyl alcohol, benzene and benzoic acid derivatives recur in the basic ingredients of these preparations. Benzene is anaesthetic at 1 to 2 per cent[9] (Table I).

Parenterally administered anaesthetic agents may be carried in solvents (e.g. the solvent for Diazepam (Valium®) contains benzyl alcohol, ethyl alcohol, propylene glycol, sodium benzoate, and benzoic acid. This can be irritating to venous intima and lead to thrombophlebitis) and associated with preservatives that may prove toxic in themselves.[10,11]

It is conceivable that some of the toxic and/or allergic (hypersensitivity) reactions reported in the anaesthetic literature may be due, not to the anaesthetic agent, but to other substances with which it is combined in the clinical administration.

Some intravenous anaesthetic agents may have potential toxicity effects on chronic (repetitive) exposure e.g. ketamine,[12] thiopentone, narcotic-analgesics.

(4) *Radiation Plus Chronic Exposure to Anaesthetics*

Exposure to radiation in the operating room is well documented. Only one recent report relates radiation exposure of anaesthetists to the associated long-term anaesthetic exposure problem.[3] Exposure to radiation was measured by an electrostatically-charged chamber dosimeter worn by each of the ten anaesthetists while in the operating room. Dosimeters were read at weekly intervals with an electrometer. Although the average exposure to radiation over the period of study was well below the currently acceptable limit of 100 milli-roentgens per week (5 roentgens per year), two values in the first week approached this limit. After the first week, the individual and average values tended to decrease sharply and to level out. This phenomenon is well known to health physicists. A dosimeter makes the wearer conscious of radiation and more cautious, thus his exposure soon drops.[13]

It does appear possible, however, that anaesthetists could easily be exposed to excessive amounts of radiation. The effects of radiation and anaesthesia could be additive. The effects of long term exposure to low doses of both radiation and anaesthesia have not been reported as yet. Such studies are reportedly forthcoming.[3]

(II) Documented Data Speculating Potential Hazards Associated with Chronic Exposure to Anaesthetics

The question now is whether this long-term exposure to low concentrations of anaesthetics is harmful. Table III summarizes theoretical potential effects discussed in recent publications.

(1) *A Direct Toxic Effect*

For a drug to be classified as having a direct toxic effect, the agent should fulfill criteria[14] as listed in Table IV which include:

(*a*) Organ damage, of a distinct histological pattern, appearing after a predictable and usually brief latent period following exposure to the offending agent.

TABLE III

POSSIBLE TOXIC EFFECTS OF CHRONIC EXPOSURE TO ANAESTHETICS

1. Direct Toxicity
2. Increased Metabolites
3. Hypersensitivity
4. Post-operative Hepatitis
5. Suppression of Cell Division
   - Abortion (embryotoxic)
   - Teratogenic
6. Immunosuppression
   - Lymphoid malignancy
7. Haemostatic Suppression
   - Inhibition of Platelet Aggregation
8. Renal Toxicity
9. CNS
   - Emotional Instability (Depression)
   - Functional (headaches, fatigue, anoxia, nausea, loss of memory)

TABLE IV

CRITERIA FOR A DIRECT TOXIC EFFECT OF A DRUG

(*a*) Specific organ, histology and follows exposure
(*b*) Toxic to ALL exposed and reproducible
(*c*) Dose-related

(*b*) The damage is elicited in all exposed individuals and can be reproduced in experimental animals.
(*c*) Damage is dose related and other tissues are often affected.

These conditions are met with chloroform and methoxyflurane. None of these conditions is met by halothane. Of interest, large quantities of halothane have been ingested by man without ill effect.[14]

(2) *Increase in Metabolites*

As halogenated anaesthetics are metabolized by man, and many other species, a metabolite could act as a hepatotoxin. If the causal agent were a normal metabolite it should fulfill the criteria already referred to for a direct toxic effect. If it were an abnormal metabolite, it might be expected to relate to a genetic or familial association. None have been demonstrated.

Of interest from a chronic low-dose exposure point of view is the work of Sawyer[15] and colleagues, who have recently described concentration dependence of hepatic halothane metabolism. Exposure of patients to lower concentrations resulted in more metabolism and removal of halothane by the liver. The exposure to higher halothane concentrations resulted in less metabolism of the agent.[16] If the metabolites of halothane are responsible for liver damage, low concentrations of delivered halothane would then be more dangerous than high ones. In view of these facts and speculations, the low concentrations delivered for hours from anaesthetic machine residues are significant. On this basis the P.A.R. period and area may not be without hazard to both the patient, where in vivo concentrations fall, and personnel who are exposed to exhaled concentrations of patients. In

contrast, methoxyflurane appears to differ from halothane in that metabolic degradation is dose-related, i.e. the higher the exposure concentration of methoxyflurane is the higher the percentage of metabolites produced.[17]

(3) *Hypersensitivity*[18–22]

For a drug to act as an antigen in an hypersensitivity response, certain criteria[14] as listed in Table V should be satisfied.

(*a*) The drug should be a large or a reactive small molecule, or be capable of combining with proteins or other molecules in a body, or be metabolized to a substance which can do the same.
(*b*) Skin rashes, eosinophilia, arthralgia, fever or other signs or hypersensitivity are commonly seen.
(*c*) There is usually a history of previous exposure to the antigen.
(*d*) Hypersensitivity once established is usually long-standing. (Delayed hypersensitivity tends to diminish with time.)

Paradoxically, the very fact that halothane and other anaesthetics are present in low concentrations in the atmosphere of well-ventilated North American Operating Rooms, can be detected in the expired air of operating personnel, and that metabolites can be found in their urine is evidence against a hypersensitivity mechanism from chronic exposure in operating room personnel. Indeed, if hypersensitivity was the basic problem, in view of the large number of operating room personnel exposed to halothane throughout the world it would be expected that a much higher incidence of toxicity would be reported, when, indeed, the incidence is very low.

Another aspect of this problem, however, is that if one accepts a relationship between halothane and hepatitis, then the possibility of a so-called "cross-sensitivity" theory between halothane and methoxyflurane[23] should now be reviewed with some reservations, in view of the established fact that patients might well be receiving halothane unknowingly, from a *residual* source in anaesthetic machines, despite the fact that the vaporizer is turned off and that the methoxyflurane is contributing in no way. Of course, enzyme induction phenomenon and drug interaction are always unknown quantities.

(4) *Post-operative Hepatitis*

Nevertheless, post-operative hepatitis has been linked with hypersensitivity. A small number of anaesthetists, other operating room personnel, and one worker manufacturing halothane, have also been alleged to have developed hypersensitivity.[20,24] One case reported by Klatskin[20] has been reported in detail. An initial illness diagnosed as viral hepatitis was followed by recurrent attacks of hepatitis after direct challenge with halothane. A review of the case history, however, reveals that although this physician frequently relapsed soon after re-exposure, on at least one occasion he was exposed to halothane for a lengthy period of time without adverse effect. It is also of note that this subject was not challenged with anaesthetic agents other than halothane. Furthermore, tests for smooth muscle antibody and hepatitis associated antigen (HAA) (Australia Antigen)[25] were not

reported subsequently. It is entirely possible that chronic active hepatitis (subclinical) was an alternative diagnosis in this well-publicized case.

(5) *Suppression of Cell Division*

In Denmark in 1956, by chance, prolonged nitrous oxide was found to give rise to leukopenia in tetanus patients.[26] Reports followed on four children treated with prolonged nitrous oxide administration for myeloid leukaemia.[27] The striking example of cellular inhibition by a chronic exposure to a central nervous system (CNS) depressant was reported from England in 1961 by McBride[28] who concluded from a retrospective study that a supposedly harmless sedative, Thalidomide, taken early during pregnancy, could cause congenital abnormalities in the human foetus. Extensive now well-known reviews have covered this subject.[29]

The urgent question is raised whether or not all CNS depressants, especially from low concentration chronic exposure, share deleterious effects on the dividing cell and are therefore potentially *teratogenic.*

Because the generation cycle of a cell is a continuum,[30,31] a delay in one phase may, for instance, be the result of a specific pharmacologic effect in one or in a completely different phase.[30]

Many studies have shown that most anaesthetics, in addition to some narcotics and tranquillizers, interfere with normal cell division.[30,31] A recent publication concluded that halothane in low clinical concentrations specifically prolongs a mammalian (rat) cell generation cycle in vivo by *prolonging the period of DNA synthesis* without affecting the mitotic act itself.[32] Other phases of the cell cycle apparently were unaffected. Other investigators claim that anaesthetics arrest mitosis in metaphase.[31] The two possibilities need not be incompatible. The truth of the present situation is that the site of action is not yet really known. We do not even know if mitotic changes and teratogenicity are related.[30] Anaesthetics affect membrane permeability and transport, and could deprive the embryo of sufficient nutrients at a time when development is particularly rapid. Mitotic inhibition, on the other hand, may lead merely to cell death and not appear as a subsequent malformation. Until a relationship has been established, it is advisable to keep an open mind and be willing to consider mitotic changes and teratogenic effects as unrelated phenomena.

Animal studies of toxicity at the low concentrations reported in operating rooms are virtually non-existent. Rats exposed to 100 ppm halothane for months showed only histologically normal but larger spleens than paired controls.[33] There is no laboratory evidence that exposure to concentrations of anaesthetics encountered in operating rooms today is harmful.

Very few chemicals are known to predispose to termination of pregnancy. It is of particular interest to be alerted to anaesthetics as possible predisposing agents. In a recent report, Cohen, Belville and Brown[34] have shown a relationship between employment in the operating room and a significant increase in the incidence of spontaneous abortion.

The demonstration that concentrations of inhalation anaesthetics higher than those used clinically may produce teratogenic responses in both avian and mammalian species[34,35] has raised concern as to their effects, although in very much

TABLE V

CRITERIA FOR A HYPERSENSITIVITY RESPONSE

(*a*)	Large or a reactive small molecule (or metabolic products) combines with proteins
(*b*)	Skin rashes, eosinophilia, arthralgia, fever, commonly seen
(*c*)	History of previous exposure
(*d*)	Long-standing, once developed

TABLE VI

MISCARRIAGES IN OPERATING ROOM PERSONNEL AND CONTROLS*

	159 Operating Room (O.R.) and General Duty (G.D.) Nurses (1966–1970)†		131 Anaesthetists and other Physicians Practising (1965–1970)†	
	O.R. Nurses	G.D. Nurses	Anaesthetists	General Physicians
Number of Miscarriages	10	3	14	6
Miscarriages/ Pregnancies	29.7%	8.6%	37.8%	10.3%

*Summarized from: E. N. Cohen, J. W. Bellville, & B. W. Brown. Anaesthesia, pregnancy and miscarriage: a study of operating room nurses and anesthetists. Anesthesiology **35**: 343 (1971).

smaller amounts, on nurses and anaesthetists who work daily in operating rooms contaminated with trace concentrations of anaesthetics.

Several preliminary reports in the European and Scandinavian literature suggested that such continued low-grade exposure may be related to an increased spontaneous miscarriage rate and to an increase in the incidence of foetal anomalies.[36–38]

The recent American report[34] is of interest. The results of this study (Table VI) indicated that during the years 1966–1970, 29.7 per cent of pregnancies in operating room nurses (67 interviewed) ended in spontaneous miscarriage, compared with only 8.6 per cent in the control group (92 general duty nurses interviewed). A similar pattern was observed in a second study of 50 anaesthetists and 81 physicians practicing in specialties other than anaesthesia. During the six year period 1965–1970, the anaesthetists evidenced a 37.8 per cent spontaneous miscarriage rate, compared with 10.3 per cent in the control group. Furthermore, miscarriages occurred earlier in both operating room nurses and anaesthetists compared with their control groups (eighth versus tenth week).

There can be little doubt that the spontaneous miscarriage rate is significantly higher in both operating room nurses and anaesthetists compared with their control groups. However, the precise aetiological factors involved are difficult to define. It is possible that the slightly greater ages in the experimental groups compared with their controls (34.4 versus 30.9 years for the nurses and 39.6 versus 36.8 years for the physician) might have influenced the rates of spontaneous miscarriage observed. No other differences between the control and study groups were apparent except the extended periods of time spent by the latter in the oper-

ating rooms. The data suggested to the authors that there is a significant difference between the spontaneous miscarriage rates in the two groups. Furthermore, they suggested that this may be related to something in the operating room environment, possibly trace concentrations of anaesthetic gases present. A somewhat higher miscarriage rate in the physician anaesthetist group versus the operating room nurse group may reflect the former's exposure to the higher gas concentrations adjacent to the anaesthesia machine.[34,39]

Unmeasured factors in this type of study may also have contributed to the results observed. It is entirely possible, for example, that periods of unusual high stress in the operating room, special sprays and solvents used in the operating room (antiseptic solutions, propellants, adhesive solutions etc.), as well as other unknown factors may be incriminated.

Additional studies are indicated to confirm whether the trend revealed by these surveys is real or not. The least of which would be to include an annual survey to evaluate the effects of adequate precautions to reduce the trace concentrations of anaesthetics in operating rooms. If, over a period of years, following the institution of clean air in the operating room the miscarriage rate were reduced to that of the control group, there would be a more confident relationship to the trace anaesthetic concentrations formerly present in the operating room.

One thing is clear, although halothane and methoxyflurane have been the most commonly measured agents, concentrations of nitrous oxide, cyclopropane and diethyl ether, are also present in the operating room atmosphere. It is, therefore, not possible to associate the observed increase in spontaneous miscarriage rate with any particular anaesthetic agent. In fact, in one European preliminary report,[35] the only anaesthetics used were nitrous oxide and diethyl ether. Thus, if anaesthetics are queried, until proven or disproven all of them present in the operating room must remain suspect.

(6) *Immunosuppression*

The Immune Response[40,41]

The clinical manifestations of the immune response will depend upon the antigen and the particular cellular reaction elicited. Antibodies may be immunoglobulins, which circulate or are fixed to specifically sensitized cells. These, in turn, will promote a variety of reactions, such as enhancement of phagocytosis of antigen, haemolysis, activation of serum complement causing inflammation, and cellular release of substances such as histamine, serotonin and lysozyme. The clinical consequences of these events run the gamut from resistance to infection, anaphylaxis, and natural resistance to development of cancer, to tissue transplant rejection.

Effects of Anaesthesia on the Immune Response

Present evidence indicates that anaesthesia interferes with both the afferent and efferent components of the immune response, but mostly the afferent system.[40] Mobilization of phagocytes is inhibited during anaesthesia. It is currently believed that this is a direct depressant effect of the anaesthetic upon these cells.

The apparent decrease in concentration of opsonins probably results from an

effect of anaesthesia on the lymphocyte. Prolonged exposure to any of the commonly used anaesthetic agents, in clinical or greater concentrations, causes a circulating leukopenia and lymphopenia.[42,43] Since the immune response involves rapid proliferation of appropriate lymphocytes, and virtually all anaesthetics inhibit cell division, the reaction wherein lymphocytes divide and initiate the efferent arm of the response may be blocked. There is evidence that the effect of anaesthesia on the immune process is nonspecific.

There is no specific evidence that anaesthesia predisposes man to bacterial infections.[44] As a matter of fact, diethyl ether consistently protects against anaphylaxis in animals.[45,46] Anaesthetics appear not to interfere with the reaction of preformed antigen and antibody, so if protection is provided it must be by interference with the mediators of the response to anaphylaxis (e.g. histamine, 5-hydroxytryptamine) and their actions on the end organs involved in the response.

On the basis of effective immunosuppressive therapy in man[47] and experiments indicating that immunosuppression in animals aids the experimental induction of malignancy by carcinogenis chemicals are also immunosuppressives if given in appropriate dosages, interference with immune mechanisms by anaesthetics would be expected to influence the cause of tumour development.[40]

It is interesting to relate this concept to a recent publication of causes of death amongst 441 American Society of Anesthesiologists members during the years 1947 to 1966 inclusive[48] (Table VII). There were 17 cases of malignant neoplastic lymphoid – reticuloendothelial system deaths. These accounted for almost one-fourth of all malignancies recorded; whereas the deaths from the usually more common malignancies of the gastrointestinal and respiratory systems were lower than expected.

The death rate from lymphoid and reticuloendothelial system malignancy is twice as great as for the white male population of U.S.A. and the white male policyholders of standard ordinary life insurance with the Metropolitan Life Insurance Company but may not be causally related to the practice of anaesthesiology. On the other hand, it could relate to the toxicity of inhaled anaesthetics or to an environmental hazard as yet unidentified. Radiation exposure as a cause seems highly unlikely due to the normal death rate for leukaemia, a disease well established as causally related to radiation.[49]

Another speculated implication of anaesthetic-induced immunosuppression would be to relate it to the development of *post-operative hepatitis*. Perhaps, in some of these cases, latent viral hepatitis which had been kept under control by natural defense mechanisms becomes active as the scale is tipped in favour of the virus.[40]

(7) *Haemostatic Suppression*

Although it has been found that a number of tranquilizers and common volatile anaesthetics, added to platelet-rich plasma, at pressures which correlate with those achieved clinically, inhibit adenosine diphosphate (ADP)-induced platelet aggregation,[50,51] no studies from chronic exposure to trace concentrations have been reported.

TABLE VII

CAUSES OF DEATH OF 441 AMERICAN SOCIETY OF ANESTHESIOLOGISTS MEMBERS FROM 1947–66*

Cause	Number	Per cent
Coronary, A.S.H.D.	203	46.0
Malignant Neoplasms		
Digestive	23	5.2
Respiratory	9	2.0
Leukemia	6	1.4
Lymphoid – R.E.S.	17	3.8
Suicides	35	7.9

*Modified from D. L. Bruce, K. A. Eide, H. W. Linde, and J. E. Eckenhoff: Causes of Death Among Anesthesiologists: A 20-Year Survey, Anesthesiology **29**: 565, 1968.

(8) *Renal Toxicity*

There appears to be a dose-relationship between methoxyflurane and renal pathology following exposure to clinically significant concentrations. Case reports have been well documented.[17]

There are no known reports of high output renal failure in anaesthetists. However, it is interesting that Bruce and colleagues[48] reported a two-fold increase in chronic renal disease as a cause of death among anaesthetists in the period from 1957 to 1966 over the period from 1947 to 1956. It was during the later ten-year period that the fluorinated anaesthetic agents were introduced.

(9) *CNS Alterations*

It is of some concern that the incidence of *suicides* (Table VII) were 1.5 times as frequent in the A.S.A. as in the U.S. male population in general, and 2.73 times the rate of Metropolitan male policy holders.[48] Admittedly, it is known that the suicide rates among physicians in general exceeds that of the population as a whole but evidence indicates that anaesthetists have a relatively high suicide rate as compared to other specialty groups. The high death rate from this cause among anaesthetists below the age of 45 years is of special concern. There are no known reasons for associating suicidal depression with chronic exposure to trace concentrations of anaesthetics in the operating room.

Three reports in the European literature suggest *headaches and irritability* in anaesthetists as occupational hazards[36,38,52] possibly attributable to the direct effects of the agent on the brain or the cerebral vessels. A survey of Russian anaesthetists indicates an increase in "functional disturbances of the central nervous system" following prolonged exposure to poorly ventilated operating rooms.[36]

(III) REPORTED METHODS FOR REDUCING THE ANAESTHETIC CHRONIC EXPOSURE RISK

Now that it is clearly established that operating room personnel and patients can be exposed to inadvertent trace concentrations of anaesthetics and that there

TABLE VIII

METHODS FOR REDUCING CHRONIC EXPOSURE RISK FROM ANAESTHETICS

(1)	Decrease Operating Room Pollution
	Adequate ventilation
	Gas traps
	No open techniques
	No "tent" draping
	Threshold limit values
(2)	Decrease Anaesthetic Machine Residues
(3)	Analyze Solvent-Preservative Composition
(4)	Radiation Control
(5)	Patient and O.R. Personnel Control

are theoretical potential hazards associated with this exposure, it seems prudent, even in the absence of more information, to get as much anaesthetic out of the operating room as possible. There are several ways of doing this. These are summarized in Table VIII.

(1) *Decreasing Operating Room Pollution*

(*a*) *Adequate ventilation*

It is a fair question to ask what is the safe level for anaesthetic gases in the operating room atmosphere. This is difficult to define.

(*b*) *Threshold limit values* (TLV) have been established at the present time for only two anaesthetic agents (chloroform, 50 ppm; diethyl ether, 400 ppm (established by the American Conference of Government Industrial Hygienists (A.C.G.I.H.) in 1967). These levels do not take into consideration recent information about metabolism, enzyme induction, or teratogenicity. In the face of a potential hazard, and with only limited data available, it would seem imperative to establish these levels at minimum values for the new fluorinated anaesthetics, and possibly revise downward those previously established for the older anaesthetics.

Current studies suggest the practicability of maintaining ambient halothane in the operating room atmosphere below a concentration of 1 ppm.[5] Reduction of this contamination to the lowest possible level should be attempted. Present recommendations are that operating rooms be air-conditioned with non-recirculating systems capable of providing minimal total air exchange rates of at least ten times per hour[5] (14 times per hour at Vancouver General Hospital). Such systems may be expected to significantly reduce, although not totally eliminate, the contaminating anaesthetic gases. P.A.R.'s should be similarly controlled.

(*c*) *Scavenging Equipment (Gas Traps)*

When high-flow anaesthetic systems are employed, arrangements should be made for closed-system venting of all excess gases to the outside through the use of appropriately designed scavenging equipment. The wall suction system used for most of these units has the disadvantage of being intermittently needed for patient care. Whitcher and colleagues[5] recommend fun-

nelling excess anaesthetic gases directly into the exhaust ducts of the room ventilating system without recirculation and a low-resistance (¾ inch) wall outlet. Such an arrangement has another important advantage, in that it eliminates the hazard present in certain commercial scavenging systems which may transfer maximum wall suction pressure directly to the patient's lungs.

Scavenging systems have been demonstrated and are capable of reducing mean concentrations of halothane in the operating room atmosphere by 91 per cent with the non-rebreathing system and by 85 per cent with the semi-closed circle system.[5]

A variety of scavenging systems or gas traps have been presented varying from the most simple type in design[53,54] to more sophisticated units.[55–58]

All these scavenging systems have common objectives. They are attached to the expiratory valve of the anaesthesia machines; adaptable to a wide variety of expiratory valves; protect the patient from the extremes of positive and negative pressure which could be applied to the patient's airway if the wall or operating room outlet pressure was interrupted or incorrectly applied. However, not all units have safeguarded against these problems.

Additional precautions to reduce operating room pollution should be the discouragement of open, high flow anaesthetic techniques, particularly when in conjunction with inadequately ventilated operating rooms and/or the use of surgical "tent draping." High concentrations of anaesthetics may build up.

(2) *Minimize Anaesthetic Machine Residues*

The time required for elimination of a given amount of anaesthetic from anaesthetic rubber tubing, soda lime or baralyme, metal and plastic parts of the circuit of the anaesthetic machine is considerably longer than its corresponding period of absorption.[7] One consequence of this slow process of elimination is the transfer of a given anaesthetic used for one patient to subsequent patients anaesthetized with the same equipment.[7,8] Some authors recommend that in cases of suspected *hypersensitivity* to a particular inhalation agent, the entire circuit should be replaced with unexposed tubing and unexposed carbon dioxide absorbent, if exposure to trace concentrations of the anaesthetic agent is to be avoided.[7,8] This will undoubtedly reduce the concentration of anaesthetic but does not always eliminate it.[8] In fact, on the basis of one study,[8] by removing all rubber from the anaesthetic circuit and replacing the soda lime, a washout time of 90 minutes would still be required to arrive at a non-detectable concentration, in the case of halothane.

From a practical point of view, exchanging rubber parts and soda lime and flushing for two hours would be difficult. Possible alternatives have been suggested:[8] disposable anaesthetic machines, one machine per agent, a cut-off between flow meters and volatile liquid vaporizers, or a different machine circuit from each vaporizer to the patient. On existing machines a selector switch could move gas from the flow meters directly to the patient thus excluding the halothane or methoxyflurane exposed circuit but, however, necessitating two different sets of tubing.

(3) *Analyze Solvent-Preservative-Propellent Compositions*

Until more information becomes available for these products care should be taken to avoid a direct concentrated exposure. The composition of every solvent – preservative used in conjunction with intravenous agents should be known.

(4) *Radiation Control*

The wearing of dosimeters by operating room personnel in areas where radiological equipment is consistently employed, is recommended.

(5) *Patient and Personnel Control*

Some idealists have gone so far as to recommend a fresh operating room for every surgical procedure and the segregation of patients in the recovery room!

However, it does seem reasonable that precautions be taken for patients and operating room personnel with regard to screening for hepatitis, hypersensitivities and pregnancies and appropriate allocation of their assignment accordingly.

Résumé

Des informations bien documentées indiquent qu'à l'heure actuelle, il existe des traces de concentrations d'agents anesthésiques par lesquelles, les patients, le personnel de la salle d'opération, de la salle de réveil peuvent être exposés, par inadvertence à longue échéance – Les sources établies sont les suivantes :

(1) Pollution de l'air ambiant de la salle d'opération.
(2) Résidus dans l'équipement anesthésique.
(3) Contaminants préservatifs – solvant – propulsant – et la radiation en combinaison avec les sources précitées.

La question maintenant est de savoir si cette exposition à long terme à cette concentration basse d'agents anesthésiques est préjudiciable. Des dangers potentiels théoriques ont été suggérés – Ce sont :

(1) Un effet toxique direct.
(2) Une formation accrue de métabolites toxiques.
(3) Développement d'une hypersensibilité.
(4) Une cause d'hépatite postopératoire.
(5) Suppression de la division cellulaire prédisposant aux effets embryotoxiques et tératogéniques.
(6) Immunosuppression avec les implications possibles de prédisposition à la malignité du système lymphoïde réticulo-endothélial.
(7) Suppression hémostatique par inhibition de l'aggrégation plaquettaire.
(8) Toxicité rénale.
(9) Et altération dans l'activité du S.N.C. comme prouvée par les tendances à la dépression suicidaire et de l'instabilité fonctionnelle (céphatés, fatigue anoréxie, nausée, perte de mémoire).

Même en l'absence d'information, voire de confirmation en regard à ce problême potentiel, il semble impératif d'éliminer le plus d'agents anesthésiques possible de la salle d'opération.

Les moyens recommandés pour y parvenir :

(1) Diminuer la pollution de la salle d'opération par
   (a) Une ventilation adéquate.
   (b) En établissant un seuil de valuers limités d'agent anesthésique.
   (c) Installation d'un équipement d'évaluation des gaz anesthésiques.
   La conclusion des item (*a*) et (*b*) a prouvé une réduction acceptable dans la pollution de l'air ambiant de la salle d'opération.
   (d) Décourager les techniques utilisant des systêmes anesthésiques par circuit ouvert et à grand débit, particulièrement en association avec toute mise en place de champ opératoire sous forme de tente.

(2) Minimiser les résidus de la machine d'anesthésie en réduisant ou en enlevant l'opportunité pour l'absorption d'anesthésiques par la machine d'anesthésie, les circuits, les absorbeurs et les tubes de caoutchouc. Ceci peut comprendre des variations dans l'utilisation du matériel anesthésique disponible ; installation d'un (CUT OFF) entre les délimiteurs et les vaporisateurs de liquide volatile, ou un systême de circuit différent partant de chaque vaporisateur se rendant au patient.

(3) Maintenir une vigilance, une surveillance quant aux ingrédients, des compositions intraveineuses, solvant, préservatif, propulseur et éviter toute exposition directe dès que possible.

(4) Le port de dosimètres de radiation par le personnel de la salle d'opération dans les endroits ou les équipements radiologiques sont utilisés de routine.

(5) Se montrer vigilant quant au choix et à l'emploi du personnel de la salle d'opération et de la salle de réveil qui présentent une histoire d'hépatite, d'hypersensibilité ou de grossesse ; une assurance raisonable peut être donnée, à savoir que dans les salles d'opération ou une ventilation adéquate et des mesures appropriées pour l'élimination de substance anesthésique des machines aient été entreprises, que les risques possibles découlant du fait que patients et personnel soient exposés aux agents anesthésiques, sont négligeables.

De plus les études sur l'exposition chronique aux concentrations minimes d'agent anesthésique ont de façon paradoxale indiqué que les anesthésiques avec hydrocarbonne halogène peuvent avoir une marge de sécurité plus grande qu'on l'a eue jusqu'ici, et que l'évidence suggérée d'hépatite postopératoire présumément attribuée à l'halothane peut être beaucoup trop élevée.

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