Anesthesiology
62:325–330, 1985

Health Experiences of Operating Room Personnel

Julie E. Buring, Sc.D., Charles H. Hennekens, M.D.,† Sherry L. Mayrent, Ph.D.,‡ Bernard Rosner, Ph.D.,§ E. Robert Greenberg, M.D.,¶ Theodore Colton, Sc.D.***

In an attempt to evaluate health experiences of operating room personnel using previously published reports, the authors calculated summary relative risks (RRs) for each outcome under investigation by combining data from six studies. For each summary RR, they also calculated 95% confidence limits; when the range of the confidence interval excludes 1.0, the increased risk is statistically significant at the 0.05 level. The most consistent evidence was for spontaneous abortion among pregnant physicians and nurses who work in operating rooms, where the RR was 1.3 (95% confidence limits from 1.2 to 1.4). For liver disease there were statistically significant increased RRs among both men (1.6, 1.3–1.9) and women (1.5, 1.2–1.9), but these were based on smaller numbers of studies. Although the results of pooled analyses are suggestive, most studies of this issue have relied on voluntary responses and self-reported outcomes, so that response and/or recall bias could explain these findings. In addition, these investigations generally have examined working in operating rooms rather than actual exposure to anesthetic gases. Finally, there have been considerable improvements in operating room scavenging systems during the last decade. Thus, prospective cohort studies are needed to determine whether there is a relationship between current levels of occupational exposure to anesthetic gases and adverse outcomes, particularly spontaneous abortion and liver disease. (Key words: Anesthetics, gases. Anesthetics, volatile. Operating rooms: contamination; personnel. Toxicity: fetal; hepatic.)

This article is accompanied by an Editorial. Please see: Mazze RI, Lecky JH: The health of operating room personnel. ANESTHESIOLOGY, 62:226–228, 1985.

* Instructor in Preventive Medicine and Clinical Epidemiology, the Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital.

† Associate Professor of Medicine, the Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital.

‡ Research Associate in Medicine (Epidemiology), the Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital.

§ Associate Professor of Preventive Medicine and Clinical Epidemiology, the Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital.

¶ Associate Professor of Medicine and Community and Family Medicine, Dartmouth Medical School.

** Professor and Chief, Epidemiology and Biostatistics, Boston University School of Public Health.

Received from the Departments of Medicine and Preventive Medicine and Clinical Epidemiology, the Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, the Departments of Medicine and Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, and the Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts. Accepted for publication August 15, 1984. This study was supported in part by a contract from the American Society of Anesthesiologists.

Address reprint requests to Dr. Hennekens: 55 Pond Avenue, Brookline, Massachusetts 02146.

IN RECENT YEARS, concern has grown regarding the possible occupational hazards to medical and dental personnel exposed to anesthetic gases. The public health impact of any adverse effects is potentially great, as over 200,000 individuals have occupational exposure each year in the United States alone.[1] At present, however, there are conflicting interpretations[2–8] of the numerous published retrospective cohort studies that relate to this issue.[9–25]

Since no single epidemiologic study can definitively establish a cause–effect relationship due to the potential for chance, bias, or confounding to explain the result, a judgment of causality is strengthened when different investigators, using various methods in a number of populations, find consistent results.[26] One statistical method to estimate more precisely the overall relative risks from several studies is to pool the data from all those with similar populations, exposures, and endpoints. By this method, a true increase in risk could emerge that otherwise might appear to be due to chance because it does not achieve statistical significance in one study due to small sample size. We therefore have estimated pooled relative risks of various health experiences of operating room personnel, based on all currently available relevant information, identified aspects of this issue on which information is deficient, and suggested areas for future research.

Materials and Methods

Although it is clearly inappropriate to compare individual subjects in any one study directly with those in another, combining the relative risks (RRs) from all relevant studies for each outcome of interest would decrease the likelihood that chance would explain a particular health experience of operating room personnel. We accordingly reviewed 17 published reports.[9–25] We excluded from further consideration four analyses[9–12] of overall mortality, which showed no relationship with prior occupational exposure and did not present data on the specific endpoints under evaluation. Five addi-

TABLE 1. Retrospective Cohort Studies Included in Pooled Analyses: Reproductive Outcomes

	Cohen *et al.*[20]	Knill-Jones *et al.*[21]	Rosenberg and Kirves[22]	Axelsson and Rylander[23]	Ad Hoc Committee[24]
Groups compared	Operating room nurses *vs.* general duty nurses; female anesthesiologists *vs.* other female MDs	Female anesthetists *vs.* other female MDs	Operating room *vs.* other nurses	Operating room and anesthesia department RNs *vs.* other RNs	Operating room MDs and RNs *vs.* other MDs and RNs
Response rates	77%	81%	72%	84%	55%
Pregnancies: exposed/nonexposed	MDs = 37/58 RNs = 36/34	MDs = 737/2,150	RNs = 257/150	RNs = 139/573	MDs = 486/308 RNs = 4,607/1,948
Spontaneous abortions: exposed/nonexposed	MDs = 14/6 RNs = 10/3	MDs = 134/315	RNs = 50/17	RNs = 21/63	MDs = 80/27 RNs = 852/294
RR	MDs = 3.7* RNs = 3.2*	MDs = 1.2*	RNs = 1.8*	1.4	MDs = 2.0* RNs = 1.2*
Live births: exposed/nonexposed	—	MDs = 599/1,817		RNs = 114/434	MDs = 384/276 RNs = 3,690/1,629
Congenital malformations: exposed/nonexposed	—	MDs = 39/89	—	RNs = 5/9	MDs = 27/7 RNs = 312/124
RR	—	1.3	—	2.1	MDs = 2.8* RNs = 1.1

* Statistically significant at $P = 0.05$.

tional studies were excluded because they used noncomparable control groups,[13,14] looked at reproductive outcomes among wives of exposed men,[15] or presented data in a form we could not interpret.[16,17] We also chose to exclude data from two studies among dentists and dental assistants,[18,19] because their exposure to anesthetic gases differs substantially from that of operating room personnel. Using data from the six remaining reports,[20–25] we then tabulated results among women for reproductive outcomes,[20–24] as well as for chronic diseases including total malignancies; breast, uterine, and cervical cancer; and liver and kidney disease.[24] Among men we evaluated total malignancies as well as liver and kidney disease.[24,25] Each tabulation included only those studies that reported comparable study populations; for example, for reproductive outcomes, data from exposed women were not pooled with data from wives of exposed men.

We used the relative risk (RR) as a descriptive measure of the strength of association between exposure and disease. We calculated the RR as the ratio of the rate of disease among those exposed to the comparable figure among those not exposed. We treated the results of each study as individual strata to obtain summary point and interval estimates of RR.[27] In this method, we pooled individual RR estimates and weighted them according to their sample sizes; thus, the greater the sample size, the greater the contribution of that study to the overall pooled estimate. For each summary RR estimate we then calculated 95% confidence limits. The range of the confidence limits gives an estimate within which the true RR is likely to lie; when this range does not include 1.0, the RR is statistically significant at the 0.05 level.

Results

Tables 1 and 2 summarize the six retrospective cohort studies that fulfilled the aforementioned eligibility criteria for the pooled analyses.[20–25] Data from the remaining seven studies of nonfatal endpoints[13–19] are presented in tables 3 and 4, with reasons for their exclusion from the analyses. We found statistically significant increased RRs of spontaneous abortion among both female physicians (1.4, 95% confidence limits 1.2–1.6) and female nurses (1.3, 1.1–1.4), with an overall RR for all exposed women of 1.3 (1.2–1.4) (table 5). For congenital abnormalities, the increase was of borderline statistical significance and only for exposed physicians (1.4, 1.0–2.0). For nonreproductive outcomes (table 6), for which the results all were based on only one or two studies, there were significantly increased RRs for liver disease among both men (1.6, 1.3–1.9) and women (1.5, 1.2–1.9). For kidney disease, there was an increased risk (1.3, 1.1–1.6) only among women. For total cancer, there was no significant increased risk among men (1.1, 0.8–1.5). Among women, however, the increase was significant (1.4, 1.1–1.7) but due wholly to an increase in risk of cervical cancer (2.8, 1.5–5.0), which did not take into account any other predictive variables, such as sexual history or possibly cigarette smoking. Analogously, there was a decreased risk of breast cancer of borderline significance (0.7, 0.5–1.0), which did not consider other potential confounding variables, such as family history or age at first full-term delivery.

Discussion

Our pooled analysis of six published studies indicates that an increased risk of spontaneous abortion for women

working in the operating room during pregnancy is the health experience for which the evidence is most extensive and consistent. The magnitude of the increased risk for spontaneous abortion is approximately 30% among women working in the operating room. For congenital abnormalities the data are somewhat less consistent. Similar conclusions have been suggested in most,[2–7] but not all,[8] previous reports.

For nonreproductive outcomes the data are much less consistent. This may be due to fewer studies that examined the endpoint, random fluctuation in subgroups, or uncontrolled confounding variables. For example, there was an increase in risk of liver disease among both males (RR = 1.6) and females (RR = 1.5), but these findings were based on only two studies in men and one for women. For kidney disease, in addition to a small number of studies of this endpoint, we noted an effect in the subgroup of females but not among males. Breast cancer risk was lower (RR = 0.7), a finding of borderline significance, but in these studies no information was available on other risk factors. Cervical cancer was increased significantly among exposed women (RR = 2.8), but the 95% confidence limits were wide (1.5–5.0), and we could not control for important confounding variables from the data available. Thus, sexual variables such as age at first intercourse and number of partners as well as possibly cigarette smoking may account, at least in part, for this result, which in turn could explain the observed significant increase in risk of total malignancies for women but not for men.

These pooled analyses must be interpreted with caution. First, none of the studies published to date has quantified level of exposure. Most have employed a simple dichotomy of "exposed–unexposed," and in many this status was derived solely from job classification or membership in a professional society. Even for spontaneous abortion, where the adverse effect of working in an operating room seems most consistent, data on nature, degree, and length of exposure often are lacking and may not be comparable between studies. It is also possible that some other uncontrolled confounding variables may be associated with working in the operating room, such as occupational stress or exposure to contaminated blood or aerosol sprays. Consequently, we cannot be certain that waste anesthetic gases are responsible for the observed effects, let alone assess dose–response trends and threshold levels or identify particularly hazardous anesthetic gases. The epidemiologic evidence currently available seems to us insufficient for developing standards for operating rooms or setting exposure limits. Moreover, it is very likely that exposure levels have decreased generally during the last decade due to improvements in operating room scavenging systems. Thus, it may be that the results from this pooled analysis are relevant to past practices but might not apply to current operating room conditions.

Second, the studies published to date share many weaknesses, including low response rates among potential

TABLE 2. Retrospective Cohort Studies Included in Pooled Analyses: Nonreproductive Outcomes

	Ad Hoc Committee (24)	Spence and Knill-Jones (25)
Groups compared	Operating room MDs and RNs *vs.* nonoperating MDs and RNs	Anesthetists *vs.* other male MDs
Response rates	55%	70%
Total malignancies		
No. men exposed/no. nonexposed	8,942/2,604	1,407/4,069
Cancers: exposed/nonexposed	75/17	22/69
RR	1.3	0.9
No. women exposed/no. nonexposed	19,258/5,966	—
Cancers: exposed/nonexposed	469/104	—
RR	1.4*	—
Breast cancer		
No. women exposed/no. nonexposed	19,258/5,966	—
Cancers: exposed/nonexposed	134/56	—
RR	0.7	—
Uterine cancer		
No. women exposed/no. nonexposed	19,258/5,966	—
Cancers: exposed/nonexposed	47/16	—
RR	0.9	—
Cervical cancer		
No. women exposed/no. nonexposed	19,258/5,966	—
Cancers: exposed/nonexposed	107/12	—
RR	2.8*	—
Liver disease		
No. men exposed/no. nonexposed	8,025/2,423	1,407/4,069
No. diseased: exposed/nonexposed	347/65	44/85
RR	1.6*	1.5*
No. women exposed/no. nonexposed	15,843/5,024	—
No. diseased: exposed/nonexposed	447/92	—
RR	1.5*	—
Kidney disease		
No. men exposed/no. nonexposed	8,108/2,420	1,407/4,069
No. diseased: exposed/nonexposed	330/108	31/100
RR	0.9	0.9
No. women exposed/no. nonexposed	16,084/5,056	—
No. diseased: exposed/nonexposed	473/115	—
RR	1.3*	—

* Statistically significant at $P = 0.05$.

TABLE 3. Retrospective Cohort Studies of Reproductive Outcomes Excluded from Pooled Analysis, with Reasons for Exclusion

	Askrog and Harvald[13]	Ericson and Kallen[14]	Knill-Jones *et al.**[15]	Pharoah *et al.*[16]	Corbett *et al.*[17]	Cohen *et al.*[18]	Cohen *et al.*[19]
Groups compared	Female anesthetists, wives of male anesthetists and anesthetic nurses *vs.* selves before employment	Women working in operating rooms *vs.* all female health care workers in Sweden who delivered babies	Male MDs working in operating rooms *vs.* other male MDs	Female MDs holding anesthetic appts. *vs.* those with other hospital and nonhospital appts.	Female nurse anesthetists *vs.* Connecticut Tumor Registry rates	Male dentists exposed to anesthesia *vs.* unexposed dentists	Heavily exposed *vs.* unexposed male dentists (M); heavily exposed and unexposed female dental assistants (F)
Response rate	76%	—	70%	72%	85%	48%	M = 74% F = 70%
Pregnancies: exposed/ unexposed	MDs: 8/26 Wives: 119/137 RNs: 85/229	—	5,891/7,296	670/8,374	—	887/1,541	M = 1,328/5,709 F = 400/3,184
Spontaneous abortions: exposed/ unexposed	MDs: 0/7 Wives: 9/28 RNs: 10/38	—	657/795	92/1,120	—	142/139	M = 89/582 F = 76/258
RR	MDs: Wives: (not given) RNs:		1.0	1.0	—	1.8†	M = 1.5† F = 2.4†
Live births: exposed/ unexposed	MDs: 8/18 Wives: 108/110 RNs: 75/185	494/19,127	5,175/6,442	578/7,317	— —	765/1,393	M = 1,177/5,277 F = 316/2,882
Congenital malformations: exposed/ unexposed	MDs: 0/0 Wives: 1/3 RNs: 0/1	22/986	235/233	16/130	—	36/57	M = 57/259 F = 16/104
RR	MDs: Wives: (not given) RNs:	(not given)	1.3†	1.6†	—	1.2	M = 1.0 F = 1.4
Reason for exclusion	Noncomparable control group	Noncomparable control group	Wives of exposed men	Inadequate exposure information	Data not analyzable	Dentists	Dentists and dental assistants

* This study is actally part of the same study as that reported in Spence and Knill-Jones[25] (table 2).

† Statistically significant at $P = 0.05$.

TABLE 4. Retrospective Cohort Studies of Nonreproductive Outcomes Excluded from Pooled Analysis

	Corbett *et al.*[17]	Cohen *et al.*[18]	Cohen *et al.*[19]
Groups compared	Female nurse anesthetists *vs.* Connecticut Tumor Registry rates	Male dentists exposed to anesthesia *vs.* unexposed dentists	Heavily exposed *vs.* unexposed male dentists (M); heavily exposed and unexposed female dental assistants (F)
Response rate	85%	48%	M = 74% F = 70%
Cancers			
No. men exposed/unexposed	—	1,631/1,326	4,517/8,387
No. cases exposed/unexposed		11/7	38/61
RR		1.4	1.1
No. women exposed/unexposed	621 nurses	—	2,740/6,926
No. cases exposed/unexposed	33 malignancies	—	29/50
RR	1,333/100,000 observed 403/100,000 expected	—	1.5
Liver disease			
No. men exposed/unexposed		1,528/1,249	4,517/8,387
No. cases exposed/unexposed		90/29	145/159
RR	—	2.6*	1.7*
No. women exposed/unexposed		—	2,740/6,926
No. cases exposed/unexposed		—	44/71
RR	—	—	1.6
Kidney disease			
No. men exposed/unexposed		1,481/1,273	4,517/8,387
No. cases exposed/unexposed		39/38	129/202
RR	—	0.9	1.2
No. women exposed/unexposed		—	2,740/6,926
No. cases exposed/unexposed		—	113/165
RR	—	—	1.7*

* Statistically significant at $P = 0.05$.

study subjects and inadequate information on nonrespondents; lack of details on amount, duration, and nature of exposure; lack of confirmation and verification of reported adverse outcomes; lack of information on many possible confounding variables; the possibility of response bias both through the nature of the questionnaires or the respondents' prior beliefs regarding adverse effects; and the possibility of biased recall of events and exposures that occurred in years past. Response bias is of particular concern in assessing the relationship with spontaneous abortion. In one study among hospital personnel in Sweden, 30% of all miscarriages among women in the nonexposed groups were not reported on the questionnaires, while all miscarriages were reported in the exposed group.[23] Thus, the magnitudes of the increased risks seen in this pooled analysis, even for spontaneous abortion, are well within the range that might be due to bias or uncontrolled confounding variables. However, the consistency of the effects noted among many different studies increases the belief that these relationships are causal.

One further issue relates to the small number of studies appropriate to include in the pooled analyses. The fact that for some of the outcomes of interest,

TABLE 5. Summary Relative Risks for Reproductive Outcomes among Women

	Spontaneous Abortions		Congenital Abnormalities	
	RR	95% CL	RR	95% CL
Physicians	1.4	(1.2–1.6)	1.4	(1.0–2.0)
Nurses	1.3	(1.1–1.4)	1.1	(0.9–1.4)
Total	1.3	(1.2–1.4)	1.2	(1.0–1.4)

TABLE 6. Summary Relative Risks for Nonreproductive Outcomes

	Males		Females	
	RR	95% CL	RR	95% CL
Total cancer	1.1	(0.8–1.5)	1.4	(1.1–1.7)
Cervical cancer	—	—	2.8	(1.5–5.0)
Breast cancer	—	—	0.7	(0.5–1.0)
Uterine cancer	—	—	0.9	(0.5–1.6)
Liver disease	1.6	(1.3–1.9)	1.5	(1.2–1.9)
Kidney disease	0.9	(0.8–1.1)	1.3	(1.1–1.6)

particularly nonreproductive, only one study provided data certainly precludes the possibility of pooling. On the other hand, this strongly supports the need for additional investigations of these endpoints, as no single epidemiologic study, however well designed and executed, can provide definitive evidence.

Although pooling of data from several studies decreases the likelihood that chance explains a particular finding, such analyses have no effect upon uncontrolled sources of bias or confounding. We therefore believe the most plausible interpretation of the existing data to be that prospective cohort studies are needed before firm conclusions can be reached. Additional retrospective studies are unlikely to produce more useful or detailed information on either the type of risk or the nature and extent of relevant exposures. Because the exposed population is already well aware of possible hazards, further studies relying on historic information and self-reported disease outcomes would be so prone to bias that we see little merit in their undertaking. Similarly, studies that are incapable of achieving near total participation and complete follow-up of exposed and unexposed subjects selected for study will have little value. In this regard, the ongoing study by Spence and Knill-Jones[28] of risks among operating room personnel will provide useful information. In addition, prospective studies are needed that permit the accurate recording, classifying, and quantifying of type, degree, and intensity of exposure; these studies should define rigorously the adverse outcomes of interest, and their occurrence should be confirmed by investigators unaware of the exposure status of the individual. If results of these prospective studies support the findings of the pooled analyses, they then could lead to development of recommendations for special exposure groups such as pregnant women or those with hepatic dysfunction.

References

1. Cohen EN: Anesthetic Exposure in the Workplace. Littleton, PSG Publishing, 1980
2. Vessey MP, Nunn JF: Occupational hazards of anaesthesia. Br Med J 281:696–698, 1980
3. Cohen EN: Inhalation anesthetics may cause genetic defects, abortions and miscarriages in operating room personnel, Controversy in Anesthesiology. Edited by Eckenhoff JE. Philadelphia, WB Saunders, 1979, pp 47–57
4. NIOSH: Occupational Exposure to Waste Anesthetic Gases and Vapors. Washington, D. C., U. S. DHEW, 15–76, 1977
5. Ferstandig LL: Trace concentrations of anesthetic gases: A critical review of their disease potential. Anesth Analg 57:328–345, 1978
6. Vessey MP: Epidemiological studies of occupational hazards of anesthesia—a review. Anaesthesia 33:430–438, 1978
7. Spence AA, Cohen EN, Brown BW: Occupational hazards for operating room-based physicians. JAMA 238:955–959, 1977
8. Walts LF, Forsyth AB, Moore JG: Critique; Occupational disease among operating room personnel. ANESTHESIOLOGY 42:608–611, 1975
9. Bruce DL, Eide KA, Linde HW, Eckenhoff JE: Causes of death among anesthesiologists. A 20-year survey. ANESTHESIOLOGY 29:565–569, 1968
10. Bruce DL, Eide KA, Smith NJ, Seltzer F, Dykes MHM: A prospective survey of anesthesiologist mortality, 1967–1971. ANESTHESIOLOGY 41:71–74, 1974
11. Doll R, Peto R: Mortality among doctors in different occupations. Br Med J 1:1433–1436, 1977
12. Doll R, Peto R: Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 2:1525–1536, 1976
13. Askrog V, Harvald B: Teratogen effekt of inhalationsanaestetika. Nord Med 16:498–500, 1970
14. Ericson A, Kallen B: Survey of infants born in 1973 or 1975 to Swedish women working in operating rooms during their pregnancies. Anesth Analg 58:302–305, 1979
15. Knill-Jones RP, Newman BJ, Spence AA: Anaesthetic practice and pregnancy. A controlled survey of male anaesthetists in the United Kingdom. Lancet 2:807–809, 1975
16. Pharoah PDD, Alberman E, Doyle P: Outcome of pregnancy among women in anesthetic practice. Lancet 1:34–36, 1977.
17. Corbett TH, Cornell RG, Leiding K, Endres JL: Incidence of cancer among Michigan nurse-anesthetists. ANESTHESIOLOGY 38:260–263, 1973
18. Cohen EN, Brown BW, Bruce DL, Cascorbi HF, Corbett TH, Jones TW, Whitcher CE: A survey of anesthetic health hazards among dentists. J Am Dent Assoc 90:2191–2196, 1975
19. Cohen EN, Brown BW, Wu ML, Whitcher CE, Brodsky JB, Gift HC, Greenfield W, Jones TW, Driscoll EJ: Occupational disease in dentistry and chronic exposure to anesthetic gases. J Am Dent Assoc 101:21–31, 1980
20. Cohen EN, Bellville JW, Brown BW: Anesthesia, pregnancy and miscarriage: A study of operating room nurses and anesthetists. ANESTHESIOLOGY 35:343–347, 1971
21. Knill-Jones RP, Rodrigues LV, Moir DD, Spence AA: Anaesthetic practice and pregnancy. Controlled survey of women anaesthetists in the United Kingdom. Lancet 1:1326–1328, 1972
22. Rosenberg P, Kirves A: Miscarriages among operating theatre staff. Acta Anaesthesiol Scand (Suppl) 53:37–42, 1973
23. Axelsson G, Rylander R: Exposure to anaesthetic gases and spontaneous abortion: Response bias in a postal questionnaire study. Int J Epidemiol 11:250–256, 1982
24. American Society of Anesthesiologists Ad Hoc Committee: Occupational disease among operating room personnel. ANESTHESIOLOGY 41:321–340, 1974
25. Spence AA, Knill-Jones RP: Is there a health hazard in anaesthetic practice? Br J Anaesth 50:713–719, 1978
26. Hennekens CH, Buring JE. Epidemiology in Medicine. Boston, Little Brown and Co, 1985 (In press)
27. Katz D, Baptista J, Azen SP, Pike MC: Obtaining confidence intervals for the risk ratio in cohort studies. Biometrics 34:469–474, 1978
28. Spence AA, Knill-Jones RP: Health problems of anaesthetists and their families. Br Med J 1:114, 1979