Communications for this section will be published as space and priorities permit. The comments should not exceed 350 words in length, with a maximum of five references; one figure or table can be printed. Exceptions may occur under particular circumstances. Contributions may include comments on articles published in this periodical, or they may be reports of unique educational character. Please include a cover letter with a complete list of authors (including full first and last names and highest degree), corresponding author's address, phone number, fax number, and email address (if applicable). An electronic version of the communication should be included on a 3.5-inch diskette. Specific permission to publish should be cited in the cover letter or appended as a postscript. CHEST reserves the right to edit letters for length and clarity.

To the Editor:

I recently read the letter of Dr. Kirschner (November 2000).1 I would like to address some remarks and questions raised by Dr. Kirschner.

First, is the pathogenesis of catamenial pneumothorax recognized as the transdiaphragmatic passage of gas? If this is the case, then why does this disease occur in connection with menses?

Second, if the pore hypothesis is correct, then catamenial pneumothoraces seem to occur bilaterally due to the negative intrathoracic pressure.

Third, the subdiaphragmatic lymphatics communicate with the diaphragmatic pleura but not with the intrathoracic space. As a result, hydro- or pneumoperitoneum does not seem to develop hydro- or pneumothorax in a normal lymphatic state, even if fluid or gas are absorbed from the stomata. Furthermore, based on the fact that the absorption of intraperitoneal fluid is more extensive in the right hemidiaphragm, I think that the distribution of the peritoneal stomata may have a right-side predominance, and that diseases caused by such a physiologic function appear to have the same tendency.

Fourth, the article by Allen3 appears to have solved the controversy regarding whether peritoneal stomata represent normal open pores in the diaphragm, as well as blood, exudate, chyle, bile, and urine.

The right-sided predominance of the thoracic manifestations of this phenomenon is, I believe, the result of the anatomic difference between the two upper quadrants of the abdomen. In the right upper quadrant, the solid, more-or-less-fixed liver acts as a piston when the right hemidiaphragm contracts, raising the intraperitoneal pressure locally, trapping the offending substance (i.e., air, fluid etc.), and forcing substances through preexisting or acquired holes in the diaphragm. In the left upper quadrant, the relatively loose stomach, colon, and spleen are not mechanically likely to produce the same pressure changes as on the right side.

I cannot accept a lymphatic mechanism to explain these phenomena, nor can I consider the microscopic stomata to play any role in these porous diaphragm syndromes, as they are too small to permit such massive rapid fluid and/or gaseous shifts into the chest.

Kazuhiro Funatsu, MD
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To the Editor:

My comments to all of the remarks posed by Dr. Funatsu can be found in my paper entitled “Porous Diaphragm Syndromes.” In that article, I collected and documented the many disparate clinical syndromes, united by a common denominator, namely, gross diaphragmatic defects. This is the “gestalt” of this article.

These defects facilitate the phenomenon of peritoneopleural transphrenic passage of air (catamenial pneumothorax), other gases (CO2) in artificial pneumoperitoneum, and laparoscopy fluids (ascites from liver cirrhosis, and peritoneal dialysis fluid in treatment of renal failure), and possibly Meigs syndrome and tissue (endometriosis), as well as blood, exudate, chyle, bile, and urine.

The right-sided predominance of the thoracic manifestations of this phenomenon is, I believe, the result of the anatomic difference between the two upper quadrants of the abdomen. In the right upper quadrant, the solid, more-or-less-fixed liver acts as a piston when the right hemidiaphragm contracts, raising the intraperitoneal pressure locally, trapping the offending substance (i.e., air, fluid etc.), and forcing substances through preexisting or acquired holes in the diaphragm. In the left upper quadrant, the relatively loose stomach, colon, and spleen are not mechanically likely to produce the same pressure changes as on the right side.

I cannot accept a lymphatic mechanism to explain these phenomena, nor can I consider the microscopic stomata to play any role in these porous diaphragm syndromes, as they are too small to permit such massive rapid fluid and/or gaseous shifts into the chest.

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REFERENCE


Work-Related Inhalation Injuries

To the Editor:

I am writing with respect to the article by Valent et al (March 2002). This article is a very useful contribution to the literature.
Injuries, our referenced source of data. As one who has represented these victims for events within a single workday or shift. As heat or oxygen caused by a specific event, incident, or series of kinetic energy from a crash, or from the absence of such essentials resulting from acute exposure to energy, such as heat, electricity, or as any intentional or unintentional wound or damage to the body provided by the US Bureau of Labor Statistics: an injury. It might be useful, however, to report here the definition the medical and epidemiologic community about what constitutes of the article, as we clearly state throughout the abstract and the do not think that any misunderstanding could arise from the reading

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Correspondence to: Francesca Valent, MD, Università degli Studi
di Udine, Italy.

REFERENCE


To the Editor:

Mr. Kazan is right when interpreting that our article in the March 2002 issue of CHEST deals only with acute exposures. However, we do not think that any misunderstanding could arise from the reading of the article, as we clearly state throughout the abstract and the article that we focus on occupational injuries. There is a consensus in the medical and epidemiologic community about what constitutes an injury. It might be useful, however, to report here the definition provided by the US Bureau of Labor Statistics: "An injury is defined as any intentional or unintentional wound or damage to the body resulting from acute exposure to energy, such as heat, electricity, or kinetic energy from a crash, or from the absence of such essentials as heat or oxygen caused by a specific event, incident, or series of events within a single workday or shift. "This definition is available to anyone at the Web page of the Census of Fatal Occupational Injuries, our referenced source of data."2

Francesca Valent, MD
Gerald McGwin, PhD
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REFERENCES


Intraoperative Photodynamic Therapy After Pleuropneumonectomy for Malignant Pleural Mesothelioma

To the Editor:

We read with great interest the article by Schouwink et al (October 2001) about intraoperative photodynamic therapy after pleuropneumonectomy for the treatment of patients with pleural mesothelioma. In the series by Sugarbaker et al, pleuropneumonectomy has a low postoperative mortality rate (3.8%) and relatively satisfying long-term results. Their technique involves opening the pericardial cavity and resecting the diaphragm while preserving the peritoneum. However, mesothelioma is one of the most rapidly disseminating tumors. As recommended by Schouwink et al, it would seem preferable not to open the pericardium, as we were able to do in the five most recent pleuropneumonectomies that we have performed for the treatment of patients with mesothelioma. Similarly, it is often possible to leave diaphragmatic muscle and fibers in place in order to avoid tearing the peritoneum when detecting it. The high rate of peritoneal recurrences following pleuropneumonectomy reported by Baldini et al (26%) and Rusch et al (31%) may be due to seeding by transdiaphragmatic invasion before surgery or to peroperative tearing of the peritoneum or to secondary peritoneal necrosis.

To be sure, adjunct local treatment is essential to prevent intracavitary recurrence, which is otherwise inescapable. Radiotherapy is effective in treating mesothelioma. However, the local recurrence rate remained high (35%) in a series of 49 patients who underwent surgery in Boston between 1987 and 1993. Radiation therapy, which was performed in only 35 of these patients, consisted of a median dose of 30.6 Gy to the hemithorax and a boost dose of 50 Gy to areas with gross residual disease or localized positive resection margins. Higher radiation doses of up to 54 Gy to the entire hemithorax appear to significantly reduce the local recurrence rate (13%) in the series reported by Rusch et al. To decrease the liver and intestinal toxicity associated with high radiation doses to the diaphragmatic sinus, the abdominal organs may be lowered by reconstructing a taut prosthetic diaphragms during surgery. However, radiation doses of > 50 Gy to the heart remain potentially toxic, in particular doses delivered to the left side of the heart, and intraoperative photodynamic therapy, as suggested by Schouwink et al, seems to be an interesting alternative.

I was fortunate to be invited to Amsterdam and to obtain light dosimetry equipment there. For large pleural cavities, the potential complications associated with the technique are due to a narrow anatomic zone that includes in particular the esophagus, the bronchial and vascular stumps, and the myocardium. These anatomic structures are located very close to the light source that illuminates the cavity during intraoperative photodynamic therapy. We have studied the fluence (at the wavelengths that react with meso-tetra[hydroxyphenyl] chlorine) emitted by the surgical theater lights during resection. Although our calculations are approximate, fluence may be as high as 5 J/cm². We therefore decided to shield the esophagus, the bronchial and vascular stumps, and the pericardium. Conversely, the most difficult zone to illuminate was the pleural cul de sac. The diaphragm is lowered by running taut polyglactic acid sutures from one edge to the other, before illumination. Three patients received 0.15 mg/kg meso-tetra[hydroxyphenyl] chlorine and were operated on using these modified techniques.
while the cavity was illuminated with a 652-nm laser light and a fluence of 10 J/cm², except for the shielded zone. The large quantity of fluid drained postoperatively gave an indication of the effect of phototherapy on the pleural cavity walls. Slowing of esophageal motor activity was observed in all three cases.

Postoperative electrotherapy was performed in the first two patients on the thoracotomy scar and the pleural cul de sac. No recurrence was observed after 2 1/2 years in one patient (as determined by follow-up CT scan) and after 26 months in the other patient (as determined by follow-up CT scan and negative thoracoscopy findings at 12 months). The third patient developed an infection of the chest wall, which was complicated by an infection of the pneumonectomy cavity. Radiation therapy was impossible to perform. Thoracotomy was performed 9 months later and revealed a late esophageal fistula involving the upper one third of the esophagus (in an unshielded zone). The fistula was closed with a muscle flap. No recurrence was observed in the pleural cavity. Unfortunately, the patient eventually died.

In our limited experience, high-dose preoperative phototherapy therefore appears capable of destroying tumor residues but seems to require major precautions, such as shielding of the incision and the mediastinal organs. Consequently, its place among other techniques seems limited if future series confirm the low local recurrence rate reported by the New York team with the adjunction of high-dose hemithoracic radiation therapy and if the toxicity associated with radiation therapy remains low.

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REFERENCES


We thank Bonnette et al for the valuable comments on our study. In their reaction, they addressed the study of Sugarbaker et al using a trimodality approach of extrapleural pneumonectomy combined with chemotherapy and radiotherapy and some aspects of the use of photodynamic therapy (PDT) after resection. In this study, the perioperative mortality is only 3.8% and the median survival is 19 months. Although the survival was not calculated on an intention-to-treat basis, results were better than what is generally achieved with the combination surgery and PDT. At least three factors may have been responsible for the difference in treatment outcome. Firstly, the combination surgery, chemotherapy, and radiotherapy may have a better antitumor activity, leading to better tumor control with acceptable toxicity. Secondly, the use of histologic assessment to direct radiotherapy to locations of irradical tumor resection seems an elegant way to treat those locations at risk more effectively. Finally the use of MRI may have improved prediction of resectability, which is considered difficult by many investigators.

In the treatment protocol, with surgery and PDT used by Dr. Bonnette, which is comparable to ours, the esophagus, bronchial and vascular stumps, and pericardium were (partly) shielded from the laser light. This may have the advantage to avoid potential lethal complications (esophaged perforation, bronchial fistula, and myocardial infarction), which occurred in our study. However, organs shielded from light do not receive the additional PDT treatment, and may therefore be at risk for local tumor recurrence. In our opinion, the study of Bonnette et al is of particular importance because it can provide information on the risk of local recurrences.

Improvement of many issues of PDT in combination with surgery, such as patient selection and illumination of the diaphragmatic gutter, still seems possible. These improvements may better determine the exact place and indication of PDT-mediated therapy in malignant pleural mesothelioma.

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REFERENCES


End-of-Life Care: Data Supportive?

To the Editor:

I read with interest the article on ethics in end-of-life care by Kelly et al in CHEST (March 2002). Their objective was to...
Dr. Arnett charges statistical malpractice by the confusion of correlation with causation. In our study, we never claim to show any causation. We only report observations from our limited database. Our statistical significance does add greater clarity to these findings by suggesting they are not a result of chance. Additional findings that approached but did not meet significance are so disclosed with p values and statistical methods.

The specific differences that we found among medical subspecialties are consistent with the results of other reports in the medical literature. Dr. Arnett suggests that such references may be out of date (ie, references 10 and 11) but fails to note our citation of this same subspecialty bias in physician actions (reference 9) and in end-of-life publications over the subsequent 20 years (reference 18).

We propose that understanding and respecting subspecialty differences in end-of-life opinions may advance us toward more effective collaboration with colleagues and more effective communication with our patients. We hope that we have shed some light on these differences and invite readers to generate their own hypotheses about causation.

William F. Kelly, MD
Arn H. Eliasson, MD
Oleh W. Hnatuik, MD
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To the Editor:

I was recently consulted by a medical malpractice attorney who asked for assistance in the defense of his client, a board-certified pulmonologist who had been managing a patient with very difficult steroid-dependent asthma. The patient also smoked cigarettes. The man, age 41, had acquired aseptic necrosis in both femoral heads requiring total hip replacements.

The patient had suffered from asthma since the age of 6 months. He had had several hospitalizations for asthma and frequent trips to the emergency department for life-threatening attacks. He had been appropriately managed by this pulmonologist, with the use of inhaled short-acting as well as long-acting agonists, inhaled corticosteroids, leukotriene modifiers and, at times, bursts of systemic steroids to deal with exacerbations of asthma and/or associated acute and chronic sinusitis.

The major issue in the plaintiff’s strategy was the fact that this pulmonologist had never done spirometry at any time during the management of this patient. Accordingly, the plaintiff argued that the patient never had asthma, which was one of the contentions of the medical expert hired by the plaintiff, also a board-certified pulmonologist. Fortunately, however, numerous measurements of peak flow during exacerbations, which demonstrated increases from low values up to the “personal best” level of approximately 450 to 500 L/min while in remission following corticosteroid treatment had been recorded. But why a simple spirogram was not done by the pulmonologist, as well as other pulmonary function tests, is beyond me. It certainly would have helped in this physician’s defense. Later, an allergist did perform spirometry, which showed severe airflow obstruction and air trapping with a normal diffusion test result.

This is the fourth or fifth time I have been asked to defend a
What About the Role of the US Food and Drug Administration?

To the Editor:

As a professional couple with one half in the world of human subjects’ protection and the other half in the world of academic pulmonary medicine, we read the article by Miller and Shorr1 and the accompanying editorial by Perkins2 with great interest. The article, in the April 2002 issue of CHEST, elucidated the many challenges faced by all of us who conduct research involving human subjects. The authors have brought into focus the ethical challenges presented to the investigator, the institutional review board (IRB), and the sponsor. Although we agree with the authors regarding the problems that they have identified, we suggest that the responsibility for the problems is not limited to the three groups they have identified. We would like to point out some of the inherent and fundamental problems of industry-sponsored randomized clinical trials as they are currently conducted.

The current practice is that industry (with some input from expert consultants) designs clinical trials, the US Food and Drug Administration (FDA) reviews them, and then the sponsor then seeks sites for these trials. As Miller and Shorr point out, clinical trials have seen a tremendous change in recent times, moving away from academic medical centers and toward private practice settings. The scrutiny of IRB applications for these trials is different given the context of an independent IRB relative to the academic IRB. There is a potential and very real problem of “IRB shopping” with the obvious benefit that sponsors can have clinical trials conducted, unopposed and without modification. IRBs, both local and independent, are under extreme pressure to review protocols quickly and without requesting modification. By contrast, there is a strong tradition and clear need for local control of IRBs so that their actions reflect the communities that they serve. However, Miller and Shorr have pointed out the universal nature of the ethical dilemma confronting the investigators, the IRB, and the sponsor. Obviously, these groups did not meet this ethical challenge in the mometasone trial.

In this context, such review standards and, in fact, this level of review would be more appropriate at the level of the FDA. At the present time, the role that the FDA plays in the risk/benefit analysis for the subject is ambiguous. This realization leads to a variety of troubling questions. What was the role of the FDA in allowing a study such as the mometasone trial to proceed? In general, what kind of review does an investigational new drug application undergo? Is it reviewed by experts in the area of study? Does the FDA consider whether the protocol meets current guidelines for the treatment of the condition under study, or does the FDA see this as the responsibility of the sponsor or the local IRB?

Our local IRB is frequently told by sponsors that we are the only IRB that has issues with a particular protocol. These issues usually relate to the concerns with including a placebo arm, or with withdrawing or withholding proven treatment. Industry-sponsored clinical trials that do not pass ethical muster or put patients at unjustifiable risk should be stopped at the FDA review. They should be rewritten according to currently accepted guidelines for the treatment of the condition under study, and according to regulations meant to protect any vulnerable subjects who might be included.

At national IRB meetings last year (Public Responsibility in Medicine & Research), Robert Temple, MD, of the FDA...
suggested that the agency preferred to allow protocols to have broad inclusion and exclusion criteria so as not to limit multicenter trials. He saw narrowing of inclusion and exclusion criteria to make a study safe as the responsibility of the IRB. At the same IRB meeting, a representative of the pharmaceutical industry was quick to point out that academic IRBs were a problem for industry, and they would prefer that independent IRBs review all multicenter trials. The implications of this latter statement are obvious. However, the suggestion of the FDA that narrowing criteria should be done at the local IRB feeds this somewhat dysfunctional relationship. The federal government has now begun to realize that IRB shopping is a real phenomenon. Currently, proposed regulations to prohibit IRB shopping are available for public comment. However, prohibiting IRB shopping alone will not resolve the current problems involving the clinical trials industry that lead to conducting trials such as the one reviewed and analyzed by Miller and Shorr.1

Unquestionably, unethical clinical trials have been funded by sources other than industry, and have been approved by local IRBs, including academic IRBs. National Institutes of Health-funded studies have also failed the risk/benefit analysis.

In this time of heightened public awareness of the shortcomings of the human subjects’ protection process, we would argue that rigorous risk/benefit analysis should be applied before protocols reach the local IRBs. In this way, we can help prevent local conflicts of interest and ensure that research is conducted at a standard deserving of the public trust.

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REFERENCES

Errata

In the September 2002 issue, the book review of Cancer of the Lung: From Molecular Biology to Treatment Guidelines (CHEST 2002; 122:1108–1109), by Albert Miller, contained an error. On page 1109, the last sentence of the fourth paragraph should read “This is fortunate, since T3N0M0 is not included in the former, and stage IV is erroneously defined as any T, any N, M0.” Also the “important article by Henschke” is referenced as: Henschke CI, McCauley DI, Yankelovitz DF. Early Lung Cancer Action Projection: overall design and findings from baseline screening. Lancet 1999; 354:99–105.

In the August 2002 issue, the article, “IV Magnesium Sulfate in the Treatment of Acute Severe Asthma: A Multicenter Randomized Controlled Trial” (CHEST 2002; 122:489–497) by Silverman et al, contained editing errors in study site affiliations. The affiliations should read as follows:
*From the Department of Emergency Medicine (Drs. Silverman and Mancherje), Long Island Jewish Medical Center, New Hyde Park, NY; Department of Emergency Medicine (Dr. Osborn), Lincoln Hospital Medical Center, Bronx, NY; Department of Emergency Medicine (Dr. Runge), Carolinas Medical Center, Charlotte, NC; Department of Emergency Medicine (Dr. Gallagher), Jacobi Hospital Medical Center, Bronx, NY; Department of Emergency Medicine (Dr. Chiang), Bellevue Hospital Medical Center, New York, NY; Department of Emergency Medicine (Dr. Feldman), Boston City Medical Center, Boston, MA; Department of Emergency Medicine (Dr. Gaeta), St. Barnabas Medical Center, Bronx, NY; Department of Biostatistics (Dr. Freeman), Montefiore Medical Center, Bronx, NY; Department of Biostatistics and Epidemiology (Dr. Levin), Columbia University School of Public Health, New York, NY; and Division of Pulmonary and Critical Medicine (Dr. Scharf), Department of Medicine, Long Island Jewish Medical Center, New Hyde Park, NY.

The current affiliation information for Drs. Osborn, Runge, Gallagher, and Gaeta is correct.