To the Editor:

Insulin by Inhalation?

In his editorial, “Insulin Without Injections???” (December 1998), Dr. Misbin stated that type 1 diabetics would still need a daily insulin injection to maintain basal levels; therefore, optimism regarding the total elimination of injections was not warranted. I am pleased to refer him and your readers to an article by Edwards et al., which demonstrated inhaled insulin activity for up to 96 h in rats. The hope of insulin without injections is not a “pipe dream”; there is actually cause for substantial optimism in this area. There are at least three US companies that have research agreements with major pharmaceutical houses for inhaled insulin. Some are already doing phase 3 clinical studies. These companies are on the web: durapharm.com, aradigm.com, and inhale.com.

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Pulmonary Administration of Insulin as an Aerosol

To the Editor:

The work of Laube and colleagues (December 1998), which demonstrates the efficacy of the lung as an alternative route of delivery for insulin in controlling glucose levels in patients with type 2 diabetes mellitus, is an important contribution to clinicians dealing with this illness. I would, however, like to comment on the patient population that was studied. The patients included four obese subjects, and their average body mass index (BMI) was 30.74 ± 2.23 kg/m², which is significantly higher than the ideal BMI (22.4 kg/m²). It is now recognized that insulin resistance associated with diabetes in obese subjects is mainly caused by obesity itself. Tumor necrosis factor-α derived from adipose tissue provides a link between obesity and insulin resistance through its ability to block the insulin-stimulated tyrosine phosphorylation cascade, a mechanism that is very different from hyperglycemia-induced insulin receptor inhibition. It is also recognized that obese patients with diabetes should be treated with dietary therapy, exercise, and troglitazone to improve their impaired glucose tolerance. I do hope inhaled insulin therapy will become an alternative way to archive better glycemic control in diabetic patients. However, further comparative study about features of reaction to inhaled insulin between obese patients and nonobese subjects might prove to be interesting.

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REFERENCES


To the Editor:

Our study attempted to evaluate the efficacy of the lung as an alternative route for the delivery of insulin in controlling diabetes mellitus. For the study, we selected a small group of individuals having a type 2 diabetes mellitus diagnosis. These included men and women, individuals who approached ideal body weight, and those who were clearly overweight. The goal was to demonstrate that the lung is an effective route for the delivery of insulin for a broad spectrum of individuals with type 2 diabetes. At no time did we attempt to define the best route of therapy or the best mode of treatment for individual patients.

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CHEST / 116 / 2 / AUGUST, 1999
Herbalism for the Treatment of Asthma

To the Editor:

I read with great interest the editorial of Ernst (January 1999) regarding complementary/alternative medicine (CAM) for asthma. The author proposed that we advise our patients responsibly about the risks and benefits of CAM because there are still too few investigations into the effectiveness of these therapies for asthma. However, the traditional herbal therapy for the treatment of asthma has already been established in Japan. The Japanese Ministry of Health and Welfare authorized 161 complexes of traditional herbs for medical use. Of course, governmental health insurance covers the cost of treatments with these herbal complexes. These herbal medicines, which we call Kampo, originated in ancient China. They were modified and refined in Japan and were integrated into traditional Japanese medicine.

Herbal therapy for the treatment of asthma has been established a long time ago in Japan. Although traditional Japanese herbal therapy is very systemic, its theory is completely different from that of Western medicine. Doctors who want to use herbal medicine should learn how to evaluate patients' conditions and to choose the best herbal medicine to improve patients' illness, in addition to learning the theory of Oriental medicine. According to their expertise, doctors have to determine whether patients are responders or nonresponders before beginning herbal therapy. The fundamental rules that are used for choosing appropriate herbal medicines are based on the patients' constitutions, predispositions, stamina, and strength of response against illness. Six kinds of herbal complexes are included as recommended therapies in the Japanese National Guidelines for the Management of Asthma. For the acute phase of asthma, Mao is used along with several similar herbal complexes, including ephedrine, because patients' bronchodilation and sedation rapidly improve. On the other hand, the long-term administration of Saiko is performed to stabilize symptoms, since Saiko and its relatives have anti-inflammatory and immunoregulatory effects. In addition, Japanese doctors often prescribe herbal medicines to enhance nutrition and improve stamina. As mentioned above, herbal therapy is an effective strategy for the management of asthma in Japan. I wonder why such an established strategy has not been known to the world and is unavailable outside of Japan.

In the United States, patients have easier access to more kinds of CAM than do patients in Japan. At present, with the notable exceptions of certain herbs, some acupuncture therapies, and some homeopathic treatments, there is inadequate proof that most CAMs are more effective than the placebo. Moreover, such remedies are not always cost-effective, safe, or easy to incorporate into a patient's daily life. Each CAM should be reviewed and addressed with the most rigorous research design possible in order to get new strategies for the management of asthma.

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Sialyl Lewis X-i Antigen in Pleural Effusion

To the Editor:

We read with interest the report by Lee and colleagues (December 1998) on the usefulness of sialyl stage-specific embryonic antigen-1 (sialyl Lewis X-i antigen). We also have studied and published articles on the clinical utility of the antigen. The determination of the cutoff value for their study according to the mean ± SD seems inappropriate because confirmation of the “normal distribution” is not warranted. We believe that receiver operating characteristic (ROC) curve analysis is one of the suitable methods for determination of the cutoff value.

We can share the authors' observation that “pleural sialyl Lewis X-i antigen levels > 265 U/mL were considered to indicate a diagnosis of adenocarcinoma of the lung.” Our results showed, however, that levels ≥ 214 U/mL were found only in patients with adenocarcinomas that had been proven by cytologic examinations of pleural effusions. This level accounted for 95% specificity.
study included data from malignant pleural effusions resulting from metastatic adenocarcinomas of organs other than the lung.

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REFERENCES

To the Editor:

We would like to reply to the comments on our article (December 1998) by Satoh and colleagues. They suggest that the receiver operating characteristics (ROC) curve analysis appears to be one of the suitable methods to be used for the determination of a cutoff value, unless normal distribution of the data is confirmed.

To the best of our knowledge, there is no standard method for the determination of a cutoff value for a tumor marker. The selection of a cutoff point is dependent mainly on clinical significance. To avoid false-positive results, the highest value obtained from benign cases may be chosen as a cutoff point in this setting. The specificity appears to be 100%, but at the expense of sensitivity. To increase the sensitivity, a lower value may be used as the cutoff value, but at the expense of specificity.

In our study, the value given by the mean + 2SD of pleural fluid sialyl stage-specific embryonic antigen (SSEA)-1 was selected as a cutoff point because the data were found to be normally distributed in each subgroup (groups 3 to 6) of our benign cases.1 It is plausible that the data are normally distributed when these cases (groups 3 to 6) are pooled as one group. Unfortunately, the data are almost but not quite normally distributed. The ROC curve analysis is used as suggested to determine the cutoff value: 295 U/mL instead of 265 U/mL. When 295 U/mL is used as the cutoff point, the sensitivity and specificity are 64% and 95%, respectively. The sensitivity and specificity are 64% and 95%, respectively, when 265 U/mL is used as the cutoff point. In terms of sensitivity and specificity, the ROC curve analysis adds little value. This supports the notion that the method used in our study for the determination of the cutoff value is adequate.

The clinical significance of the cutoff values selected by either method, mean + 2SD or ROC curve analysis, is comparable in our study. However, we agree that the ROC curve analysis is one of the suitable methods to be used to determine the cutoff point of pleural fluid sialyl SSEA-1.

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REFERENCES

Fungal β-Glucan Can Yield False-Positive Results With the Limulus Amebocyte Lysate Endotoxin Assay

To the Editor:

We read with interest the study by Nelson and colleagues (January 1999).1 Using the limulus amebocyte lysate (LAL) method (E-Toxate; Sigma Diagnostics; St. Louis, MO) to measure endotoxin levels in saline aliquots infused through the bronchoscope and in BAL fluid, they reported detectable levels of endotoxin (range, 2 to 4 endotoxin units [EU/mL]) in both the saline aliquots and the BAL fluid. We wish to bring to the authors’ attention information concerning the specificity of the LAL assay that may affect their conclusions that endotoxin contamination of the lungs during bronchoscopy may contribute to BAL-induced lung inflammation.

The conventional LAL assay is not completely specific for endotoxin and may give false-positive results with other compounds.2 Particularly β-glucans react with the factor G-mediated coagulation pathway in the LAL system leading to activation of the LAL and thus, may yield false-positive results. This interaction between β-glucans and the LAL system is important to appreciate clinically. Nakao et al1 reported on the occurrence of false-positive endotoxemia following surgery. Using a conventional LAL test, transient elevations in blood endotoxin levels were noted in patients despite the lack of clinical evidence of endotoxemia. When the same samples were assayed using an endotoxin-specific assay (Endospecy; Associates of Cape Cod Inc/Seikagaku America; Falmouth, MA), endotoxin was not detected.

We have observed the same problem with false-positive results using the standard LAL assay in our laboratory when measuring endotoxin levels in samples contaminated with β-glucans. We washed sterile gauze with physiologic saline (under sterile conditions) and performed endotoxin determination on the saline using LAL assay (BioWhittaker Inc; Walkersville, MD) and a specific endotoxin assay (Endospecy; Seikagaku). The endotoxin levels measured by the LAL assay and Endospecy were 0.340 vs 0.114 EU/mL, respectively. The same sample was assayed in our institutional laboratory using the LAL assay and was reported as positive for endotoxin (lower limit of detection, 0.125 EU/mL).

Therefore, results of a standard LAL assay cannot definitively

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be attributed only to bacteria-derived endotoxin. Only with the use of specific endotoxin assays can the issue of potential endotoxin contamination during instrumentation of the airways be addressed.

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To the Editor:

Drs. Vassallo and Limper make the valid points that a positive result of an amebocyte limulus assay can be caused by the contamination of specimens with β-glucans rather than endotoxin and that the source of these β-glucans can be sterile materials, such as surgical gauze. Although BAL fluid specimens that we recovered from volunteers were passed through gauze prior to analysis, the specimens recovered after simply instilling fluid through the working channels of bronchoscopes were not passed through gauze; therefore, the gauze was not a source of contamination in these specimens. It is possible, however, that β-glucans derived from the cell walls of fungal organisms contaminated the working channels of bronchoscopes and that this material, rather than endotoxin, contributed to the positive results of the amebocyte limulus assays, which we noted. Certainly, both bacterial and fungal organisms could be potential contaminants in bronchoscopes, and, although the bronchoscopes may have been cleaned, cell-wall fragments of both types of organisms could remain within the working channel.

Although fungus-derived β-glucans are structurally distinct from bacteria-derived endotoxins, both of these microbial cell-wall products induce similar inflammatory responses within the lungs of experimental animals. It is uncertain, however, whether β-glucans induce the same intrapulmonary cytokine response as endotoxin. The cytokine response that we noted within the lungs after BAL is similar to the intrapulmonary cytokine response induced by inhalation of endotoxin in humans and after instillation in experimental animals, which supports the concept that endotoxin contamination contributes to BAL-induced pulmonary inflammation. View in the potential contamination with β-glucans, however, the conclusions of our study should be modified to indicate that intrapulmonary contamination with bacteria-derived endotoxin, fungus-derived β-glucans, or both may contribute to pulmonary inflammation induced by BAL in human subjects. We agree with Drs. Vassallo and Limper that further studies with more specific assays are indicated to assess endotoxin and β-glucan contamination and the relative roles of these microbial products in BAL-induced pulmonary inflammation.

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REFERENCES


Pleurodural Fistulas and Neurologic Manifestations

To the Editor:

In response to the article by Monla-Hassan et al (December 1998) regarding dural pleural fistulas, I bring up two cases of dural pleural fistula that I have encountered. In both cases, the patient presented with neurologic complications.

The first case was an elderly woman undergoing the removal of a non-small cell carcinoma involving the chest wall. The tumor was posterior medial in location, and extirpation required dissection in the vicinity of the dural reflection onto intercostal nerves. In the postoperative period, the patient developed hemiparesis. A CT scan of the head showed pneumoencephaly. The patient was returned to the operating room for re-exploration of the chest, at which time a dural rent was found and subsequently repaired. It was believed that the stroke occurred from cerebrospinal fluid (CSF) loss and caudal displacement of the brain with subsequent compression of the middle cerebral artery.

The second case involved a middle-aged man with underlying obstructive lung disease and pneumonia in the right upper lobe. The patient was treated long-term with antibiotics. However, the pneumonia failed to resolve, and a CT scan of the chest showed evidence of abscess formation/infective bullae in the upper lobe. The failure to resolve the process with antibiotics prompted a right upper lobectomy. The surgeon encountered dense adhesions, which made the dissection and extirpation difficult. In the postoperative period, the patient developed headache and meningismus. A lumbar puncture showed pleocytosis, hypoglycorrhachia, and elevated protein. Results of cultures were negative; however, the patient had been receiving antibiotics in the perioperative period. A pleural dural fistula and associated meningitis were clinically suspected, and the patient was started on broad spectrum antibiotics. While receiving antibiotics, the patient clinically improved. He subsequently underwent a right T6 costotransversectomy with repair of a dural rent.
collection of CSF in the pleural space was drained. Surgical specimens revealed fungal elements suggestive of Aspergillus. The patient subsequently received an extended course of orally administered itraconazole. Interestingly, approximately 1 year later, this patient developed a subarachnoid hemorrhage.

In summary, these two cases demonstrate dural pleural fistula as a postoperative complication of thoracic surgery involving dissection in the region of the dural reflection onto the intercostal nerve roots. These cases did not present with symptomatic effusion; rather, they presented with the neurologic sequela of the dural pleural communication.

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To the Editor:

We appreciate the addition to the literature that Dr. Zeller’s cases provided. However, there are substantial differences between the case that we reported (December 1998) and the two cases mentioned in Dr. Zeller’s letter. Pneumocephalus following thoracic surgery, such as lobectomy for lung cancer, has been reported in the literature. The reported cases were conditions temporally related to surgery, and the patients had presented with neurologic complications similar to the two cases mentioned in Dr. Zeller’s letter.

The case we reported represents an addition to the differential diagnosis of transudative pleural effusion. Our patient presented in Dr. Zeller’s letter.

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Research in Developing Countries

To the Editor:

The critical review on the biomedical investigation in developing countries by Selman et al (August 1998) suggests some comments on the subject:

1. What do the authors mean by “high-level research?” It may be thought that only the work comparable with the research done in developing countries could receive this nomination.
2. In spite of the complaints expressed in this paper, it is important to remark that the Mexican government provides, although scarce, almost the totality of funds for the scientific research in our country.
3. The investigators also have some problems because evaluations of their work are continuous, and they have a heavy burden of bureaucratic requisites and stressful requests, which involve a lot of time-consuming writing and sending of the concerning information.
4. Another difficult circumstance is the isolation of groups of investigators that remain in their “ivory castles,” without any contact and solidarity with their colleagues to put pressure on the government to increase the economical support for research programs, which is an important way to obtain more resources for a continuous scientific development.

In conclusion, the article of Selman and colleagues contains various points of view that must be taken into account by the authorities involved in biomedical investigations.

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REFERENCES

Low- vs High-Dose Inhaled Albuterol for the Treatment of Acute Asthma

To the Editor:

We read with interest the clinical trial recently published by Emerman et al (January 1999) comparing the administration of nebulized albuterol, 2.5 mg, to the administration of nebulized...
albuterol, 7.5 mg, in the treatment of acute asthma in the emergency department setting. The study was obviously conducted with scientific rigor, and the results cannot be disputed. However, we would like to offer an alternative explanation for the absence of a significant difference between these treatments. The choice of albuterol solution may have played a role in this study. The presence of benzalkonium chloride (BAC), a preservative that produces bronchoconstriction in a dose-dependent manner, may have antagonized the bronchodilator effects of albuterol. For example, a 2.5-mg dose of albuterol contains 50 µg BAC in the unsterile multidose dropper bottle and 300 µg BAC in the sterile unit-dose screw-cap vial, whereas the sterile-filled unit-dose vial contains no BAC. According to Dr. Emerman, the unsterile multidose dropper bottle (50 µg BAC/2.5 mg albuterol) was used in this study (personal communication; January 1999). Therefore, patients randomized to high-dose albuterol received 150 µg BAC every 20 min for a total of 450 µg. This is well within the range of BAC doses known to decrease forced expiratory volume by ≥ 20% in asymptomatic volunteers with asthma. It is unlikely that patients randomized to the low-dose regimen would be affected by the presence of BAC since they would have received a total dose of 150 µg, which is below the threshold dose. Thus, it is possible that the high-dose albuterol treatment did not provide greater bronchodilation because the effects were diminished by BAC-induced bronchoconstriction.

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To the Editor:

The work of Beasley and Hendeles,1 raises some interesting points about the presence of benzalkonium chloride (BAC) as a preservative in albuterol solution. As noted by the authors, previous work has indicated that benzalkonium chloride does act as a bronchoconstrictor when administered to patients who are also given inhaled histamine. The question for the clinician is whether or not the addition of BAC to albuterol solution in current clinical doses leads to paradoxical bronchial constriction. It is not at all clear from previous reports that this is the case. The response to histamine challenge is certainly different from judging the efficacy of a potent bronchodilator mixed with BAC. Furthermore, albuterol-free solution is not readily available in forms other than sterile unit dose vials. Unfortunately, the clinician would have to administer 9 mL of inhalation fluid in order to use standard albuterol-free unit dose vials to reproduce our study.

The effect of these considerations for the clinician is probably the same. Whether or not BAC limits the effectiveness of high-dose albuterol, or high-dose albuterol administered in repeated doses is more effective than repeated doses of 2.5 mg of albuterol, we confirm the conclusion of our article (January 1999).2 It would be interesting to repeat our study using BAC-free albuterol solution in a concentration that is consistent with the usual volumes of fluid used in nebulization. For the moment however, we again must conclude that there is not sufficient evidence to warrant giving repeated doses of high-dose albuterol in most asthmatic patients.

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Intentional Carbon Monoxide Poisoning

To the Editor:

In the case report by Vossberg and Skolnick (February 1999),1 it is stated that catalytic converters in automobiles have changed the clinical presentation of intentional carbon monoxide (CO) poisoning. As evidence, the authors describe a confused patient with a blood carboxyhemoglobin (COHb) level of 4.8% following 8 to 10 h of continuous exposure to exhaust from a running automobile in a closed garage. They point out that his maximum COHb level could not have been >10% because the sample was obtained 1 h after the patient was removed from the exposure and treated with 100% oxygen. It is suggested that even prolonged exposures of this type can result in only minimal increases in COHb levels.

The case raises several questions. It would be extremely unusual for an automobile to continue running for this length of time in a tightly enclosed space. At our regional referral facility for severe CO poisoning, we have treated >400 cases of intentional CO poisoning in the past 2 decades, 90% of which were due to automobile exhaust. The engine has typically stopped running when the victim is found, either because the vehicle runs out of fuel or because it stalls when the ambient oxygen is consumed to a sufficient degree. It should be noted that CO emission actually increases as oxygen availability decreases and combustion becomes less efficient. I would raise the possibilities that the patient’s exposure was not as long as was reported to the authors and/or that the garage was relatively well ventilated.

Although the authors are correct about the half-time of COHb clearance with oxygen (60 to 80 min), the subsequent level drawn 3.5 h later (three half-times) should have been significantly <3.0%. If the initial value was erroneous and the latter value correct, back extrapolating four half-lives would yield a predicted initial COHb >20%, which is more consistent with the history. Catalytic converters were introduced in the United States in the 1970s. Although the number of accidental CO deaths due to automobile exhaust have declined since that time,2 there are few data that demonstrate a decrease in intentional CO deaths. In fact, a study by the Centers for Disease Control and Prevention...
found that intentional CO deaths increased in the United States in the decade of the 1980s, thereby largely offsetting the decline in accidental CO deaths.2

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**Streptokinase for Endobronchial Blood Clots**

To the Editor:

Dr. Arney and colleagues (January 1999) reported their experience with the management of endobronchial blood clots. The authors also reviewed the literature concerned with this subject, including reports of the benefit of topical thrombolytic administration. Although examples of the recurrence of bleeding following the use of topical streptokinase were not uncovered within their library search, we indeed reported such a case 10 years ago. The patient had squamous cell carcinoma of the lung and required mechanical ventilation for massive hemoptysis associated with refractory hypoxemia. Following the use of a Swan-Ganz catheter to tamponade the left mainstem bronchus for hemorrhage, an endotracheal (ET) tube blood clot developed, resulting in life-threatening ventilatory failure. Although 100,000 IU of streptokinase was topically applied down the ET tube, thereby relieving the obstruction, later (4.5 h) the patient died of exsanguinating hemoptysis. Three hours after the patient’s death, the blood in the ventilator tubing remained unclotted.

It appears that streptokinase in a bolus of 100,000 U can be absorbed from the airway mucosa and result in a systemic lytic state. It is possible that a lower dose, diluted with saline solution and administered in small aliquots, can be safer, as mentioned by the authors. Time may not be on the patient’s side, however, if the airway clot is in the trachea or in the ET tube. We agree with Dr. Arney that extreme caution must be used when thrombolytic agents are instilled into the airway, and management needs should be considered, including cryoprecipitates in advance of administering these agents.

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**Reversible Unilateral Diaphragmatic Paralysis in Pulmonary Embolism**

To the Editor:

We observed a 28-year-old previously healthy male patient who was admitted to the Spinal Cord Injury Rehabilitation Center with fracture of the 12th corpus vertebrae and subsequent complete paraplegia 1 month after a road accident. The chest radiograph on admission was normal. Two months later, a few days after anticoagulant therapy cessation for ongoing mobilization, the patient developed sudden right-sided chest pain, tachypnea, and worsening of the clinical presentation. The chest radiograph showed an elevated right hemidiaphragm, which was highly suggestive of an acute pulmonary embolism (PE).
investigations, such as angiography or radionuclide imaging, were not available. On a video-assisted fluoroscopy, with the urologic examination equipment tilted in a 30° position, a poor mobility of the right hemidiaphragm was demonstrated, and the sniff maneuver showed a paradoxical movement (we were used to using this diagnostic tool in order to rule out posttraumatic phrenic nerve paresis). One month later, the patient still complained of a right-sided chest pain, and the fluoroscopy showed a pleural-based ill-defined opacity, a poorly moving right hemidiaphragm, and an ambiguous answer to the sniff maneuver. Two months later, while supported by a routine management with anticoagulants, antibiotics, and analgesics, the patient felt well, the chest radiograph returned to normal, and the answer to the sniff maneuver showed no impairment of the diaphragmatic mobility.

Palevsky et al. state that “one hemidiaphragm is occasionally elevated, presumably as a consequence of ipsilateral reduction in lung volume.” More than 30 years ago, the Encyclopedia of Medical Radiology mentioned the elevated hemidiaphragm as a common symptom of PE and suggested that it was a neural reflex mechanism with a subsequent “transient paralysis of the diaphragm.” But some 20 years later, the same encyclopedia only stated the fact that the elevated hemidiaphragm is an important diagnostic sign without further explanation. Reflex and humoral responses to PE were described, but the encyclopedia did not refer to an impairment of diaphragm function.

We demonstrated the transient palsy of the hemidiaphragm by fluoroscopy and sniff maneuver in acute PE. From a teleologic point of view, this phenomenon may correspond to a “plaster cast” of the affected lung; however, it induces poor ventilation and therefore, a higher risk of pneumonia, which should lead to an early administration of potent antibiotics.

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Clarification
In the June 1999 issue, the article “Assessment of Hazardous Dust Exposure by BAL and Induced Sputum” (CHEST 1999; 115:1720 –1728) by Fireman et al did not include the source of funding. This work was supported by the Committee for Research and Prevention in Occupational Safety and Health, Ministry of Labor and Social Affairs, Israel.