Diagnostics Bulletin
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American Association for Respiratory Care

Notes from the Chair

by Carl Mottram, RRT, RPFT

If you can Dream it, you can Do it.
– Walt Disney

I just had the opportunity to spend a day with some of our pulmonary function colleagues at a National Emphysema Treatment Trial steering committee and coordinators meeting in Washington, DC. It never ceases to amaze me how much can be accomplished when we have the chance to sit down together and discuss techniques, methods, and equipment characteristics. From the experiences of others, we can learn the nuances of various manufacturers' equipment and their performance issues. It's also a great way to discover how others deal with laboratory operations, test performance, and networking options.

Through this process we are trying to establish a standard of testing for this multicenter research protocol, which utilizes numerous pulmonary diagnostic tests as the outcome measures. The Pulmonary Function Laboratory Registry being orchestrated by the American Thoracic Society (ATS) has the same goals in mind. This registry has been established to foster quality assurance and standards of practice between laboratories across the country. The same theme that has been developed by the ATS through its standardization statements and the AARC through its Clinical Practice Guidelines can now be utilized in a network of laboratories across the nation. The ATS cites various reasons for the establishment of this registry, including providing quality assurance guidelines, creating a network for exchange of information, and creating a voice to advance policies to administrators, regulators, and third party payers.

Although the registry will not act as an accreditation program, it should cultivate an atmosphere of quality improvement. There is a minor administration fee for participation, but I still encourage all laboratorians to join. You can take part in this registry by contacting the ATS at (212) 315-4374 to obtain an application form.

In the meantime, I hope you enjoy this issue and its focus on bronchoscopy, a clinical and diagnostic tool that continues to impact the lives of our patients. ■

New Techniques for Early Detection of Lung Cancer

by Steven C. Springmeyer, MD, pulmonary and critical care medicine, Virginia Mason Clinic, president and clinical director, Virginia Mason Research Center

I have been methodically guiding the bronchoscope for about five minutes when the first area catches our attention. "LB3 two," I say, and Andrea, the bronchoscopy assistant, records the site and classification for later biopsy. The room is completely dark except for the video screens, and Andrea works with a muffled pen light. Caroline, the RT and bronchoscopy assistant, and I have dark-adapted our eyes to improve our ability to see areas of dysplasia. These precancerous areas look rusty brown rather than the normal lime-green.

"New Techniques" continued on page 2

"New Techniques" continued from page 1

We're performing fluorescence bronchoscopy, the recent addition to bronchoscopy that lets us see bronchial cancers before they become invasive. This procedure has the potential to identify cancers when they can be cured without surgery, and will expand the number of patients who can benefit from fiberoptic bronchoscopy procedures.

We certainly have a lot of potential for improvement in lung cancer, the world's most common fatal cancer. The American Cancer Society predicts that in 1999, 170,000 new cases of lung cancer will be found, and 160,000 people will die of lung cancer. More people will die of lung cancer than the next three types of cancer combined (breast, prostate, and colon). Since 1985, more women each year have died of lung cancer than breast cancer. Although there is slowing in the rate of increase in men (smoking cessation effect), there are expanding numbers in women. Increasing numbers of former smokers of advancing age have added to an expanding at-risk population. Some estimate that there are 66 million people in the US who are at high risk for lung cancer. For example, a person about 65 years of age who smoked 1-2 packs per day for 20-30 years will have about a 2% risk of getting lung cancer per year. (Two people per hundred people in this group will get lung cancer each year.)

Lung cancer is the only major cancer that does not have a recommended screening test. In the 1970s there were several large trials that looked at CXRs and sputum cytology. These trials did not show improved survival figures, so neither test is recommended for screening. Now, however, many experts are recommending reevaluation of these tests, in addition to tests with newer technology.

The CXR is still the most common way today that curable lung cancer is found, so many specialists obtain yearly CXRs in their high risk patients. This approach is considered case finding rather than screening because it is done in patients with associated diseases like COPD. A former smoker with both COPD and a 40 pk/yr smoking history is in a group with a 4% risk of lung cancer per year. If a patient has severe bullous emphysema, the studies are showing an 8% prevalence of lung cancer. These are extremely high figures, and as these risk populations are identified, we should be able to develop testing strategies capable of finding their cancers at early stages.

The two new detection methods that look most promising are fluorescence bronchoscopy and lung pulmography. Fluorescence bronchoscopy was approved for clinical use in 1997 and is available in many areas across the country. Pulmography is in clinical trials at several sites around the country.

Pulmograms are done with newer helical (spiral) CT scanners, which are fast and specially adjusted for a low dose of radiation to the lung tissue. The dosage of radiation to the lung is estimated to be similar to breast mammography, so the risk of repeated scanning is anticipated to be low. Since these scanners take only about 10-15 seconds to acquire the images, scanning can be done with a single breath-hold. Single breath acquisition improves the image quality. Studies so far indicated that 3-5 mm nodules can be seen with this method. In contrast, a regular CXR can sometimes show a 10 mm nodule, but often the nodule has to be 20 mm to be observed.

Finding lung cancer nodules smaller than 10 mm should improve the cure rates with therapy. Nodules resected that are 20-30 mm (2-3 cm) have about a 70% cure rate, so we can hope to improve beyond that number. Results from studies in Japan indicate that the cure rates with resection of 5-10 mm nodules are in the range of 85-90%!

The current trials recruit patients who are at higher risk and without known lung cancer. These patients are former smokers and current smokers who have smoked for over 30 pk/years. The initial pulmograms show an abnormality in about four patients per 100 studies. Larger nodules are usually evaluated upon discovery, but the small nodules are sometimes observed for growth before diagnostic evaluation. If growth is observe then further diagnostic studies are initiated.

The data so far are preliminary, but this approach appears to have a

"New Techniques" continued on page 3

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"New Techniques" continued from page 2

good balance between removing lung cancers early and avoiding biopsy or removal of benign nodules. Patients are having repeat studies each year to assess the incidence of new nodules and the overall safety and yield of a pulmogram. As the results of these studies are made available, we should know which patients should get regular pulmograms, low-dose spiral CT, and how many lung cancers are cured when they're found very small.

Fluorescence bronchoscopy

The development of fluorescence bronchoscopy is an interesting story and shows the unanticipated benefits that may come from research. It turns out that the sputum cytology trials in the '70s generated a group of patients who had cancer cells in their expectorant but for whom the site of the cancer couldn't be found. They had bronchoscopic exams, but even with repeated exams the cancers couldn't be seen in about one-third of the patients. Several research groups began studying these patients by using photosensitizing agents and LASER-assisted bronchoscopy to improve visualization of these cancers.

Stephen Lam, MD, of the British Columbia Cancer Research Center, was one of these researchers. He found that he could use a low intensity laser with blue light at 442 nm and still see the early cancers without giving a photosensitizing drug. This is termed autofluorescence, and the instrument that has been developed is called LIFE-Lung. LIFE stands for "Light Intensified Fluorescence Endoscopy." The instrument is manufactured by Xillix Corporation and marketed in the US by Olympus.

Dr. Lam did the first trials himself in Vancouver, BC. He studied almost 100 patients and volunteers with over 300 biopsy sites. Compared to the standard white light exam, he found that fluorescence was 50% better in detecting dysplasia and CIS (73% vs. 48%). CIS stands for carcinoma-in-situ and means that cancer cells are still in the surface layer and haven't penetrated the boundary of the mucosa. Dysplasia is considered a precursor of CIS, and this has been shown in many tissues. Other findings showed that in patients with new lung cancer, there was a synchronous CIS in 15%. In ex-smokers, 25% had moderate dysplasia, 6% had severe dysplasia, and 13% had CIS.

Based on this experience, Dr. Lam and his team organized a multicenter trial, the results of which were published last year in volume 113 of CHEST. They studied 173 subjects suspected of having lung cancer, performing 864 random and directed biopsies. The mean age of those studied was 63, and they averaged 54 pk/yrs of smoking. The researchers found that 20% of the patients had moderate dysplasia or worse. There was a CIS in nine patients, or 1.2%. Of the cases of severe dysplasia, white light only found 9% of the abnormalities, while fluorescence found 56%. That translates to a 2.7 times improvement in the detection of these early lesions.

I began using the LIFE-Lung instrument in June of 1997 and now have examined over 100 patients. I keep track of my results, which essentially duplicate those of the multicenter trial.

Indications for fluorescence bronchoscopy include:

- All patients with prior lung cancer
- Anticipated Stage I, II, or IIIA lung cancer
- Patients with symptoms and high risk factors for lung cancer
- Patients with positive sputum cytology specimens

The fluorescence exam is done by attaching a very sensitive video camera to the bronchoscope eyepiece. The brochoscope's light attachment is changed from the white light source to the helium-cadmium laser, and the procedure can begin. With a very experienced bronchoscopist, a complete exam takes about 10-15 minutes. Patients with recent bronchial infections and prior radiation therapy may have altered findings.

The exam directs the bronchoscopist on the better areas to biopsy, but the determinations are based on pathology examinations. At present, the severity of the findings dictate the recommendations. CIS lesions warrant treatment, while dysplasic lesions are rechecked in 6 to 12 months. Progressive lesions will need treatment, but others will be followed. Treatment protocols are in development and will include cryotherapy, laser, and photodynamic therapy. It is hoped that lesions found earlier will be less likely to require surgical removal. Brachyradiation will be another alternative to surgery in selected patients.

New developments don't preclude prevention

These two procedures, fluorescence bronchoscopy and pulmography, should compliment each other in the search for early cancers. Bronchoscopy is best for examination of the airway mucosa, while pulmography will be best for the tissue tumors beyond the view of the scope. There will probably be a role for more sputum examination in the future, as well, and researchers are working with molecular biology techniques to find cancer cell markers, which should improve the detection of lung cancers. Blood and other body fluid tests, such as bronchoalveolar lavage, will probably also be used in lung cancer detection as markers are developed. All these techniques add hope that we will reduce lung cancer deaths by early detection of primary and secondary cancers.

Although these new procedures are exciting, primary prevention remains most important for patients at risk of lung cancer. We should continue to provide and support smoking cessation and smoking prevention initiatives. However, prior smokers who are interested in any foods, herbs, or medications that will reduce their risk of cancer should be advised to adhere to the

"New Techniques" continued on page 4

"New Techniques" continued from page 3

generally accepted diet of increased fruits and vegetables, especially the colored vegetables like carrots. There are trials going on with vitamin supplements, but we should be cautious about getting ahead of the research. A recent reminder comes from the beta-carotene trials. It was widely anticipated that beta-carotene pills would reduce lung cancer, but unfortunately, they increased the incidence 40%, and the effects have not decreased two years after stopping the trial. The Medical Letter emphasized this by recommending that *no one* should be taking beta-carotene vitamin supplements. ■

FYI . . .

FDA approves Xopenex for bronchospasm

The Food and Drug Administration has approved Sepracor Inc.'s Xopenex(TM) (levalbuterol HCl) inhalation solution in two dosage strengths for use with a nebulizer for the treatment and prevention of bronchospasm.

Xopenex is the therapeutically-active (R)-isomer of racemic albuterol. Racemic albuterol, an equal mixture of (R) and (S) isomers, is the world's leading bronchodilator for asthma. In Sepracor's clinical trials, Xopenex demonstrated excellent safety and efficacy and a duration of action that lasted up to eight hours.

"It appears the removal of the unnecessary (S)-isomer results in a purer and more potent drug," says Harold Nelson, MD, senior staff physician in the department of medicine at National Jewish Medical and Research Center and lead investigator in the Xopenex Phase III clinical trials. "For reasons that have not yet been clarified, the (S)-isomer, when exposed to the patient in racemic form, has been shown to interfere with the overall efficacy of the (R)-isomer."

In the Phase III, 362-patient, four-week study, patients treated with 0.63 mg of Xopenex demonstrated lung-function responses comparable to those treated with the standard clinical dose (2.5 mg) of racemic albuterol, both after the first dose and after four weeks of therapy. Patients on Xopenex generally reported a lower incidence and severity of beta-mediated side effects, such as nervousness and tremor, compared with those taking racemic albuterol.

Efficacy, as measured by the mean percent change from baseline in FEV1, was demonstrated for all active treatment regimens compared with placebo on day one and day 29. On both day one and day 29, 1.25 mg of Xopenex demonstrated the largest mean percent change from baseline in FEV1 compared to the other active treatments.

Hundreds of drugs on the market today are racemic mixtures with equal amounts of two isomers, an (R)-isomer and an (S)-isomer. In racemic albuterol, the (R)-isomer is exclusively responsible for the therapeutic effect and perfectly matches the human body's receptor. The (S)-isomer has been found to have no therapeutic benefit and poorly matches the body's receptor. Scientific data have suggested the (S)-isomer may cause detrimental airway hyperactivity. Xopenex is the optically pure (R)-isomer version of racemic albuterol.

"With the prevalence of asthma, especially in children, on the rise, there is a great need for rescue therapy with minimal side effects," says Jeffrey Drazen, MD, professor of medicine, Harvard Medical School. "Levalbuterol is the first real advance in rescue asthma therapy in over 20 years."

The first indication for Xopenex will be for the relief and prevention of bronchospasm. The drug will be available in solution formulation used in nebulizers.

Side effects from Xopenex, like other beta-agonists, may include dizziness, nervousness, tremor and dyspepsia. Patients with cardiovascular and convulsive disorders should use caution when administering the drug. (Sepracor)

Dehydration worsens exercise-induced asthma

University of Buffalo researchers have found that dehydration in people with exercise-induced asthma may induce bronchospasm even before exercise begins

The study involved eight young adults with exercise-induced asthma and eight persons of similar age without the condition. All participants were put through six minutes of high-intensity exercise on a cycle ergometer and/or treadmill. Each person's FEV1 was measured before and after exercise, both when fully hydrated and after 24 hours without fluids.

Results showed that among the non-asthmatics, hydration status had no effect on the FEV1 before, during, or after exercise. However, the FEV1 of the asthmatics was significantly lower both before and after exercise when they were dehydrated, compared to when they were completely hydrated. While the rate of respiratory decline remained the same in the asthmatics during exercise regardless of their state of hydration, they started out with less capacity when they were dehydrated. (University of Buffalo) ■