HYPERBARIC MEDICINE AND RADIOTHERAPY: IS IT ‘DÉJÀ VU’ ALL OVER AGAIN?

by Dick Clarke CHT

One of the more promising new uses of hyperbaric medicine may well turn out to be an adjunct to radiotherapy. For the more senior members of the Respiratory Therapy discipline this just might ring a bell. To you, it would not seem that long ago that this was a fairly common combination.

The ‘holy grail’ of radiotherapy has long been the search for an effective method of overcoming tumor hypoxia. The therapeutic action of radiotherapy requires the presence of a certain critical intratumoral oxygen threshold. Many tumors are hypoxic and this diminishes radiotherapy’s effectiveness.

In the 1950’s, hyperbaric oxygen was identified as effective in overcoming hypoxia in certain types of tumor. Clinical trials quickly followed. Single person steel military diving chambers were converted to accommodate an acrylic window. Patients with tumors that anatomically corresponded with the window (breast, chest and lung) were placed into these chambers, usually after being paralyzed and mechanically ventilated. Once compressed to several additional atmospheres of oxygen pressure, these patients were irradiated using a radiation delivery device positioned directly above the window.

Preliminary results were encouraging and this lead to widespread adoption of this technique. Practioners quickly became frustrated, however, by the lack of anatomic visibility a single window afforded. Tumors elsewhere in the body could not be ‘reached’. Industry responded. Soon multiple windows were incorporated and by the early 1960’s the chamber’s hull was constructed entirely of acrylic. Now you know how today’s monoplace is hyperbaric chamber came about!

By the late 1960’s concerns were being expressed about the clinical effectiveness and safety profile of hyperbaric oxygen radiosensitization. Some felt that such exposure increased the incidence of new primary tumors and metastases in hyperbaric irradiated patients. It was also thought that survival advantage was not sufficiently different from conventional radiotherapy. Resulting interest waned and by the mid-1970’s had ceased together.

Then along came a modern review of these early clinical trials. Low and behold, and with the advantage of advanced statistical methodology, it became apparent that both head and neck and uterine cervix cancer patients had enjoyed a very clear and statistically significant survival advantage. Not so, cancers of the bladder. Why this might be so became somewhat evident in 2001. Great variability in degree of hypoxia was found to exist in different tumor types. Even within a particular tumor, oxygen levels were found to vary greatly.

Other hypoxic tumor radiosensitizers that came along after hyperbaric oxygen have not resulted in hoped for survival advantages. Attention has been re-focused, therefore, back on hyperbaric oxygen. Adding some measure of confidence to this direction has been a failure to substantiate a tumor initiator or enhancer action of hyperbaric oxygen exposure.

In this new era of hyperbaric oxygen radiation sensitization, brain tumors have received initial attention. Generally, such patients do very poorly, with most succumbing within two years of diagnosis. Another reason that these tumors are being studied is the fact that the hyperbaric centers in question have particularly strong neurosurgical involvement.

Initial results have demonstrated a prolonging of survival and improved quality of life. This time around, however, hyperbaric exposure was not employed concurrently as it had been in the 1960’s. Today, the patient receives hyperbaric oxygen immediately prior to radiotherapy. This should result in better radiation delivery (no scatter as the beam passes through the thick acrylic window) and reduced exposure of non-target tissues (fewer side effects).

What has emerged, however, is a critical and very brief window of hyperoxic opportunity. Studies, using both implantable oxygen electrodes and MRI, suggest that the time to begin radiation exposure must not exceed 15 minutes from exiting the hyperbaric chamber. This may sound like plenty of time but it is not quite as good as it looks. The ‘set-up’ time, in which a patient is positioned, alignment films are taken, developed and then read may consume up to 7-10 minutes. For this process to work, then, the hyperbaric chamber will need to be in or immediately adjacent to the Radiation Therapy Department.

In early 2007 a similar is scheduled to take place in the U.S. The tumor to be investigated is a squamous cell carcinoma of the head and neck, one that showed promise in the earlier men-

continued on page 82

The Complete Blood Count... *Continued from page 56*

rheumatoid arthritis, malnutrition, leukemia, or cancer. An important point for respiratory therapists to consider is that steroids modify the leukocytosis response. When healthy persons receive corticosteroids, the WBC count rises. However, when corticosteroids are given to a person with a severe infection, the infection can spread significantly without producing an expected WBC rises. The point to remember: leukocytosis, as a sign of infection, can be masked in a patient taking corticosteroids. In response to an infection, trauma or inflammation, WBCs release a substance called colony-stimulating factor, which stimulates the bone marrow to increase WBCs' production. The number of WBCs can actually double within hours when necessary, e.g., in an infection. A simultaneous increase in all of the five types of WBCs rarely occurs. However, when this does occur, dehydration and increased blood viscosity should be suspected before other considerations. Finally, hypoactive adrenal glands, thyroid pathologies or removal of the spleen may also increase WBC counts.

For those therapists working in neonatal/pediatrics, and labor and delivery, it is important to realize that babies on the day of birth have high WBC counts, ranging from 9,000-30,000. This number falls within two weeks. The percentage of neutrophils is high for the first few weeks after birth, but then an increase in lymphocyte count is seen. Until about 8 years of age, lymphocytes are more predominant than neutrophils in the child's blood circulation. Pregnancy results in leukocytosis, primarily due to an increased in neutrophils with a slight increase in lymphocytes.

Low white blood cell counts may occur in a number of conditions that therapists are familiar with such as chemotherapy, AIDS, viral infections. Other conditions include aplastic anemia (decrease in all blood cell lines), lupus, malaria, and alcoholism. Leukopenia is generally considered when the WBC count drops below 4,000 cell/cmm. Leukopenia may be caused by viral infections, overwhelming bacterial infections or bone marrow disorders. These patients are candidates for reverse isolation procedures by all health care provides who come in contact with them. These patients should be protected from anything that interrupts skin integrity, placing them at risk for an infection that they do not have enough white blood cells to fight. WBC counts less than 500 cells/cmm places the patient at risk for a fatal infection. It is also important to note that certain classes of drugs may produce leukopenia as well. These drug classes are: antimetabolitges, barbiturates, antibiotics, anticonvulsants, antithyroid drugs, arsenicals, antineoplastics, cardiovascular drugs, and diuretics.

The Differential

When considering WBCs, it is also important to discuss the relationship between the total WBC count and the absolute value for each of the cell lines. The "differential" is a separate component of the complete blood count and represents in a percentage fashion the distribution of WBCs in the blood. It will tell us out of 100 WBCs, what percentage of them are neutrophils, lymphocyste, monocytes, basophils or eosinophils. This is important because various pathologic conditions will alter the percentage of cells in predictable ways. In addition, one can determine the absolute cell count for each of the cell types. Depending on the laboratory setting, the absolute cell numbers are as follows:

- Neutrophils, 1500-7800 per cmm
- Lymphocytes, 1700-3500 per cmm
- Monocytes, 200-700 per cmm
- Eeosinophils, 50-500 per cmm
- Basophils, 0-200 per cmm

The normal distribution of WBCs is: neutrophils, 50%-70%; lymphocytes, 20%-40%; monocytes, 4%-12% eosinophils, 0-3%; basophils, 0-2%. These two parameters can be used together to help complete the differential diagnosis of the patient. As an example, take the WBC differential of 70 percent neutrophils. This is within normal limits, however, if the WBC count is 20,000, the absolute neutrophil count would be (70% x 20,000) an abnormally high count of 14,000 per cmm.

Another common use of the differential is to help in the identification of a bacterial infection as opposed to a viral one. Bacterial infections often cause an increase in the percentage of neutrophils (neutrophilia) whereas a viral infection often causes an increase in the percentage of lymphocytes (lymphocytosis). A "flip" (greater percentage of lymphocytes than neutrophils) would suggest a viral infection rather than a bacterial one. The differential is further used to visually confirm an increase or decrease in any of the blood cell types, presence of immature cells, platelet number estimation, and size variation of blood cell types.

"And I'll accomplish more than the other candidate. I'll spend less time in rehab."

Hyperbaric Medicine... *Continued from page 48*

tioned trials. This is a more common cancer (than those involving the brain), it is noted to have a high hypoxic fraction, (good potential for sensitization) and it carries approximately 50% survival at five years. So, it is hoped that the addition of hyperbaric oxygen as a radiosensitizer will be able to influence (improve) overall survival, something not observed in the brain tumor studies. This study will be placebo-controlled and double-blinded. Just a few percentage points change could mean a cure for a large number of patients who might not otherwise survive. Participating centers include The Mayo Clinic, in Rochester, Minnesota, Dartmouth-Hitchcock Medical Center, in Lebanon, New Hampshire, Norfolk General Hospital, in Norfolk Virginia, and Palmetto Health Richland Hospital, in Columbia, South Carolina.

Hyperbaric medicine has been considered by some to be a therapy in search of diseases. To some extent this is valid criticism. Some are quick to promote its use in otherwise refractory conditions that lack a cure, and do so without sufficient laboratory and reasonably high quality clinical trialing to suggest efficacy. Modern medicine demands higher levels of evidence in order to embrace a new diagnostic test or therapeutic procedure. Hyperbaric oxygen is now formal under study as a radiation sensitizer. It certainly faces competition from other agents in use or under investigation. However, it is moving along a pathway that will be scientifically robust enough to demonstrate whether or not hyperbaric oxygen is able to improve survival compared to today's standard of care. If it does, then it will represent a very good option as it lacks some of the very significant toxicity that characterizes some of the pharmacological agents in use or under review.