REX HEALTHCARE

Laboratory Bulletin...

Updates and Information from Rex Healthcare and Rex Outreach

September 2001 *Issue Number 60*

Hemochroma -tosis and Blood Donations

In an exciting development for patients with hemochromatosis, the Food and Drug Administration (FDA) recently changed its policy on the suitability of their blood for donation. The Rex Blood Plan received approval from the FDA permitting hemochromatosis patients to become donors. Prior to the change in policy, no therapeutic phlebotomy units from hemochromatosis patients were accepted in the donor pool. Under the new regulations, if the patient meets all criteria for blood donation, the 500 ml. unit of blood may be used for transfusion. In order to implement this policy, the financial incentive to be less than truthful in answering the donor questionnaire (and thus avoid being assessed a fee for therapeutic phlebotomy) is removed. Effective September 5, 2001, no fee is charged to any hemochromatosis patient who comes to Rex Blood Plan for phlebotomy, regardless of their acceptability as blood donor. *

For years hemochromatosis patients could not understand why their blood could not be used to benefit someone who needed it. In fact, there was no medical reason why their blood could not be used.[1] In the 70's and early 80's, it was common practice to transfuse units collected from patients who fulfilled all other criteria for donation. . Later the FDA required specific labeling of all therapeutic phlebotomy units and mandated that informed consent be obtained from the recipient prior to transfusion. This essentially prevented the blood from being used. Through the continued efforts of Victor Herbert, MD (a New York City hematologist) and others, the FDA has relaxed these requirements and now permits use of this blood.

Physicians who direct their hemochromatosis patients to the Rex Blood Plan for therapeutic phlebotomy not only benefit the patient through phlebotomy but also may increase the blood supply. Most hemochromatosis patients in the early months of their treatment are phlebotomized once a week. Those in the maintenance phase are phlebotomized three or four times a year. This new FDA policy will help alleviate the constant shortage of donor blood. I would like to thank the Rex Blood Plan Staff and Dr. Timothy Carter (Blood Bank Medical Director) for making this possible.

Stephen V. Chiavetta, MD

1. Sanchez AM *et al*. Prevalence, Donation Practices and Risk Assessment of Blood Donors with Hemochromatosis. *JAMA* 286:1475-1481, 2001.

* This policy applies only to *hemochromatosis* patients referred for therapeutic phlebotomy.

Liquid Based Cytology Update

The Pap Smear has done an excellent job of reducing morbidity and mortality from cervical carcinoma during the last 45 years. Despite this, there are well-known sources of error involved with the collection, preparation and screening of traditional Pap Smears. These errors can include both false positive and false negative results. In an attempt to help reduce these limitations of the conventional Pap smear, liquid-based

cytology preparations have been developed. Two of these products, Cytyc ThinPrep and Autocyte Prep, are currently available. Each has been approved by the Food and Drug Administration (FDA) as replacements for the conventional Pap smear. The Cytyc ThinPrep was FDA-approved and introduced in May 1996 with the Autocyte Prep receiving FDA approval in June 1999. The Rex Healthcare Laboratory has been utilizing the Cytyc ThinPrep since May of 1998. The technique has been well received in our local gynecologic community, in large part due to Cytyc's aggressive direct marketing approach to clinicians and patients. The Autocyte Prep and the Cytyc ThinPrep utilize the exact same CPT billing codes and thus enjoy the same reimbursement. The Rex Cytopathology Department performed an in-house validation study on the new Autocyte Prep liquid-based cytology method. Rex now offers this new method as an alternative to the traditional Pap smear and to the Cytyc ThinPrep liquid-based methodology. Of note is that the term "liquid-based" cytology is considered synonymous with earlier terms such as "thin layer" or "monolayer".

The Autocyte Prep methodology differs significantly from that of Cytyc ThinPrep. The ThinPrep obtains a thin layer sample by using a membrane filter, which traps the cells of interest and allows them to be applied to a glass slide. Autocyte Prep obtains a thin layer sample using a density sedimentation method, producing an enriched cell sample which is then transferred to specially coated glass slides. The Autocyte Prep has a simple, uncomplicated collection method using the Rover Cervex-Brush. After the sample is collected by the clinician, the detachable head of the brush is simply popped off into the Autocyte preservative vial and sent to the laboratory. This process not only simplifies the collection process but also allows the **entire specimen** to be submitted for evaluation in contrast to both the traditional Pap smear method and the Cytyc ThinPrep in which the collection device is discarded after collection.

From a morphologic perspective, the Autocyte Prep and the Cytyc ThinPrep have much in common as each provides a superior preparation to the traditional Pap smear. Because of the density sedimentation procedure, the Autocyte Prep has been shown to have less "Unsatisfactory" or "Satisfactory but Limited" interpretations due to obscuring blood or absent endocervical cells. Please note that, despite what you may hear either stated directly or implied by sales representatives, there are currently *no published studies that directly compare the Autocyte Prep and the Cytyc ThinPrep*. **Preliminary** results from a study to be presented at the American Society of Cytology Annual Meeting in November 2001 indicate that the two methodologies are equivalent in detecting both low and high grade dysplasia, and that the Autocyte Prep has fewer "Unsatisfactory" and "Satisfactory but Limited" results due to blood or lack of endocervical cells. (Bolick DR, Personal Communication) The FDA recently issued a clarification statement, which states "There is no information in the labeling directly comparing these two devices in the same populations and no information on clinical follow-up because these studies had not been done to support approval… The FDA position is that both devices have been approved as safe and effective alternatives to the conventional Pap smear."(Acta Cytol 2000; 44:1120) The Cytyc ThinPrep collection medium has been approved by the FDA for use with the Digene Hybrid Capture II assay for the detection of HPV subtypes if the sample is collected with a broom device. However, off label HPV testing using this assay is available on either Cytyc ThinPrep specimens or Autocyte Prep specimens collected using either broom or brush devices through several reference laboratories.

Please contact Keith V. Nance, MD at 784-3286 if you have any questions regarding these relatively new Pap smear methodologies.

Keith V. Nance, MD

High Sensitivity C-Reactive Protein

Effective October 8, 2001, the Laboratory will offer a high sensitivity C-Reactive Protein (CRP) in place of the previous assay. As discussed in an earlier Lab Bulletin, CRP is an exquisitely sensitive marker of an "acute phase response" and therefore useful in excluding many inflammatory conditions (and enjoying greater precision and specificity than the venerable erythrocyte sedimentation rate in this regard). [1, 2] In recent years, there has been increasing interest in the use of CRP as a marker of systemic atherosclerosis, including coronary artery disease. Using more sensitive assays, several studies have shown patients with CRP levels in the upper quartile of the previous "normal range" are at increased (2 to 4X) risk of morbidity and mortality from coronary artery disease and peripheral arterial disease. [3-6] This risk is independent of (or additive to) the risk assigned by standard lipoprotein evaluation. These types of studies have supported the idea that there is an inflammatory component of atherosclerosis, in addition to a metabolic one. A prospective study of 543 presumably healthy men designed to assess the effect of aspirin on cardiovascular mortality (The Physician's Health Study) concluded that the reduction of risk for the first myocardial infarct associated with aspirin use was directly related to the latter's effect on CRP. [7] Another recent prospective study found that CRP levels declined by 13.1 - 16.9% in a group of patients treated with statin therapy, compared to a control group.[8] Finally, a large cohort study of 27,682 women (Women's Health Study) concluded that patients with CRP levels in the "highest quartile" had a relative risk of 15.7 of developing type 2 diabetes mellitus – suggesting inflammation is part of the pathogenesis of this disease. [9]

Thus, while clear guidelines are currently lacking, it appears that CRP will become an important test for risk stratification, in addition to its use as a measure of acute phase response. For rational use of this test, it is important to understand the difference between the two applications. In healthy individuals, CRP is normally present only in small amounts. CRP levels can increase 100 to 1000-fold within hours in response to trauma (including surgery), bacterial infection, non-infectious inflammatory disease, tissue necrosis, or neoplasia. With a half-life of 5-7 hours, levels generally fall quickly after the tissue insult, or as the inflammatory process resolves. As noted earlier, it is therefore an excellent test for serious inflammatory illness or tissue injury – and for monitoring response to treatment. It has utility in the initial evaluation of seriously ill patients in the emergency department, hospital or physician office. For this purpose, the traditional reference range **had been** 3 – 9 mg/L (0.3 –0.9 mg/dL).

The more recent studies described above were performed in patients who were considered "healthy" with regard to classic inflammatory disease. The studies found that within this "healthy" population, the concentration of CRP was not normally distributed, in that 75% of individuals had values less than 3.0 mg/L (0.3 mg/dL). The remaining 25% (upper quartile) had values between 3.0 – 9.0 mg/L (0.3 – 0.9 mg/dL). **As a result of the studies suggesting increased morbidity from vascular disease in this upper quartile, it has been suggested that an appropriate reference interval for true health should be less than 3 mg/L (0.3 mg/dL). Accordingly, we shall adopt this reference interval upon introduction of the more sensitive CRP assay. We will also convert the units of measurement from mg/L to mg/dL to reflect the units of measurement in many of the recent referenced publications.** *If CRP is to be used for risk stratification in apparently healthy patients, serial measurement may be necessary to establish a basal level (and exclude the possibility of another confounding inflammatory condition).* Obviously such testing is best performed in an

outpatient setting, when the individual is clinically stable.

John D. Benson, MD
Janet Johnson MT(ASCP)
Elaine Patterson, MT(ASCP)

1. Benson JD. C-Reactive Protein: the Lab Test that Medicine Forgot. *Rex Laboratory Bulletin* #20, May 1997.
2. Benson JD. ESR: Antiquated? Over-rated? Outmoded? *Rex Laboratory Bulletin* #10, April 1997.
3. Danesh J *et al*. Association of Fibrinogen, C-Reactive Protein, Albumin or Leukocyte Count with Coronary Artery Disease: Meta-analyses of Prospective Studies. *JAMA* 279:1477-1482, 1998.
4. Ridker PM *et al*. C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women. *N Engl J Med* 342:836-843, 2000.
5. Katritsis D *et al*. C-Reactive Protein Concentrations and Angiographic Characteristics of Coronary Lesions. *Clin Chem* 47:882-886, 2001.
6. Ridker PM *et al*. Novel Risk Factors for Systemic Atherosclerosis. A Comparison of C-Reactive Protein, Homocysteine, Lipoprotein(a), and Standard Cholesterol Screening as Predictors of Peripheral Arterial Disease. *JAMA* 285:2481-2485, 2001.
7. Ridker PM *et al*. Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men. *N Eng J Med* 336:973-9, 1997.
8. Albert MA *et al*. Effect of Stat Therapy on C-Reactive Protein Levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): A Randomized Trial and Cohort Study. *JAMA* 286:64-70, 2001.
9. Pradham AD *et al*. C-Reactive Protein, Interleukin 6, and Risk of Developing Type 2 Diabetes Mellitus. *JAMA* 286: 327-334, 2001.

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(unpaid political advertisement)

Due to an oversight on my part, a recent letter to members of the Medical Staff soliciting donations for the United Way neglected to include the address. Contributions may be mailed to Cindy Trussler, Rex Healthcare, 4420 Lake Boone Trail, Raleigh, NC 27607. Thank you for your support.

jdb

For further information, call the Laboratory (784-3040). Telephone extensions are: Pathologists' Direct Line (3201), Sharon Logue (Lab Director 2400), Robin Ivosic (Core Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396), Kori Horsley (Customer Service PM Manager 4340).