REX HEALTHCARE

Laboratory Bulletin. . .

Updates and Information from Rex Healthcare and Rex Outreach

October/November 1998 *Issue Number 35*

Free T4 Reference Range

An improved free thyroxine (free T4 or FT4) assay will be introduced in early December. The new immunoassay has superior clinical correlation with the reference dialysis method compared to our current method. Both may be affected by nonthyroidal illness or medication. (Anticonvulsant therapy may decrease FT4, while heparin may increase it.) TSH remains the preferred test for initial evaluation of thyroid disease. FT4 is helpful to confirm hyperthyroidism (where TSH is much less than 0.1 mIU/L) or hypothyroidism (where TSH is > 10 mIU/L). It can also be helpful in evaluating patients with nonthyroidal illness ("euthyroid sick syndrome"). A more detailed review of thyroid function testing is planned for a future issue of the bulletin.

The new FT4 assay will necessitate a change in the reference range from 0.90 - 1.60 ng/ml to 0.58 - 1.65 ng/ml.

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

FROZEN SECTION OF THE THYROID? JUST SAY NO

Recently the role of frozen section evaluation of nodular thyroid disease at the time of surgery has come into question due to the increased use and documented accuracy of preoperative fine needle aspiration biopsy.

Dr. Keith Nance reviewed five years of thyroid fine needle aspiration results at Rex, and found a sensitivity of 92%. This data coincides with the general impression that fine needle aspiration is considered more sensitive for diagnosis of thyroid malignancy than frozen section. As a screening tool, fine needle aspiration interpretation provides the highest level of sensitivity at the expense of specificity. Frozen section evaluation has greater specificity and can be used to plan the extent of surgery.

Fine needle aspiration is not always definitive due to suboptimal specimens from primarily cystic colloid nodules or insufficient cellular material. Both fine needle aspiration and frozen section evaluation are limited in their ability to separate follicular adenoma from follicular carcinoma. It is well recognized that fine needle aspiration can rarely if ever diagnose a follicular carcinoma, as this requires demonstration of capsular or vascular invasion. Frozen section evaluation can assess only small portions of the tumor capsule during the time of surgery. Thorough sampling of the capsule requires multiple permanent sections.

The diagnosis of papillary thyroid cancer can be made by frozen section, but there is generally no need for the frozen section process since fine needle aspiration is accurate in diagnosing these lesions preoperatively. In fact, fine needle aspiration may be superior to frozen section diagnosis of papillary thyroid cancer because the

frozen section processing often masks the characteristic nuclear features which are enhanced by formalin fixation. These nuclear changes on the other hand are well visualized in the fine needle aspiration material.

So where does all of this lead us? An algorithm for stratifying fine needle aspiration and frozen section evaluation into the diagnostic process of thyroid lesions is suggested. For a patient who has a large thyroid nodule that will ultimately come to surgery, a fine needle aspiration is not warranted. A frozen section at the time of surgery can assist in excluding a malignant process. For smaller nodules, the fine needle aspiration process should be used as a screening tool to select patients for surgery. This process will attempt to minimize false negative diagnoses at the expense of false positive results. In this way, carcinoma of the thyroid will not be missed. For fine needle aspiration diagnoses of follicular neoplasms, a frozen section analysis is unnecessary since a diagnosis of follicular carcinoma cannot be objectively made in the vast majority of cases. For papillary, medullary, and anaplastic carcinoma, a frozen section evaluation of the thyroid mass is recommended to plan for the extent of surgery. Some authorities may argue with the need for frozen section evaluation for papillary carcinoma, since a formal diagnosis of papillary carcinoma by fine needle aspiration is an accurate and specific diagnosis. However, completion thyroidectomy is a substantial surgical procedure, and a conservative approach with frozen section confirmation of the primary diagnosis seems prudent and necessary to avoid the error of a false positive diagnosis that may occur with the nuclear changes associated with Hashimoto's thyroiditis.

John P. Sorge, M.D.

DeMay R. Frozen Section of Thyroid? Just Say No. Am J Clin Pathol 110:423-424,1998.

New C. difficile toxin A/B test offered at Rex.....

After treatment with antibiotics, some patients develop gastrointestinal problems ranging from mild diarrhea to severe pseudomembranous colitis. Many cases of the milder forms of gastrointestinal illness and most cases of pseudomembranous colitis are caused by *Clostridium difficile*. This opportunistic bacterium grows in the intestine where the normal flora has been altered by the antibiotic use. The organism produces toxins which damage the intestinal mucosa.

Initially, a bioassay tissue culture system that detected toxin B was used. Subsequently, an enzyme immunoassay was developed that detected toxin A. A new test is now available at Rex that detects both toxin A and B. This test has been shown to be more sensitive in detecting toxin producing strains of *C. difficile*.

The *C. difficile* toxin A/B test has replaced the current test. If you have any questions or would like more information about this test please do not hesitate to contact the laboratory.

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Elaine Patterson, Manager (3054)
Eloise Clark, Tech Specialist (3040)

THE SCHILLING TEST STEPS

Introduction:
The Schilling test, long considered the gold standard in the diagnosis of pernicious anemia, is no longer necessary, but will be available at Rex Lab for special circumstances. . Through the efforts of Dr. Virgil Fairbanks from the Mayo

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Clinic and Dr. Robert Schilling (for whom the test is named) from the University of Wisconsin, a cascade of tests from a single serum sample has been established to make the diagnosis. Not only is it more convenient for the patient, but also much cheaper. The Medicare fraud police permit reflex testing provided the series of tests are understood by the ordering physician when the test is requested and provided it is medically necessary. Mayo Medical Laboratories now offers a diagnostic algorithm to expedite the identification of patients with vitamin B_{12} deficiency (see diagram next page).

Clinical Signs and Symptoms:

Vitamin B_{12} deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. This is one neurologic disorder that is easily treatable and should not be missed.

Biochemical Rationale:

Serum vitamin B_{12} assay does not detect all cases of vitamin B_{12} deficiency at the cellular level and a decreased level is not specific for pernicious anemia. This algorithm takes into account the following:

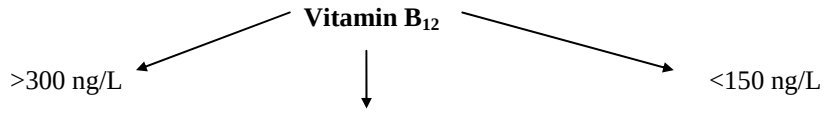
1) the most sensitive test for vitamin B_{12} deficiency at the cellular level is the assay for methylmalonic acid (MMA),
2) nearly half the cases of pernicious anemia can be unambiguously identified if the serum test for intrinsic factor blocking antibody (IFBAB) is positive (and this is a simpler and less expensive test than the MMA), and
3) the serum gastrin is usually markedly increased in pernicious anemia (as a result of gastric atrophy) and this test can be used as a substitute for the more complicated and more expensive Schilling test of intestinal absorption of vitamin B_{12}.

This algorithm is similar to one published by Green, et al in 1995 except that the serum gastrin assay is performed in place of the Schilling test.

Economic Considerations:

A significant decrease in laboratory costs can be realized by using the algorithm rather than individually ordering all of the tests for a patient suspected of having B_{12} deficiency. All the tests of the "Pernicious Anemia Cascade" are performed on a single serum specimen. An interpretive report from the Mayo Clinic is included with the test results completed in approximately 5-7 days. The following are the individual charges: vitamin B_{12} and folate $52.00, intrinsic factor blocking antibody $54.00, methylmalonic acid $66.00 and gastrin assay $36.00. The Schilling test costs $223.00. Medicare only reimburses $ 70.53 for the Schilling test. The total charge by Mayo Reference Lab for the pernicious anemia cascade is $99.50.

Pernicious Anemia Algorithm:



(no further testing) (low)

150 - 300 ng/L
(borderline)

Intrinsic Factor Blocking Antibody Test

MMA Assay

<0.4 umol/L (normal)	>0.4 umol/L (abnormal)	Positive*	Negative

Gastrin Assay

>200 pg/mL* (elevated)	<200 pg/mL (normal)

*Consistent with pernicious anemia.

SPECIMEN REQUIRED:

The test should be ordered as the "Pernicious Anemia Cascade"(Reference) . Draw blood in either plain, red-top tube(s) or SST tube(s). Spin down and divide serum into 3 plastic vials, 1 containing 1.0 mL, 1 containing 2.0 mL, and 1 containing 3.0 mL. Band specimens together and send frozen on dry ice.

PRECAUTIONS:

This test should not be ordered on patients who have received a radioisotope (either diagnostically or therapeutically), or a vitamin B_{12} injection within the pervious week.

REFERENCES:

- Green R, Kinsella KJ: Current concepts in the diagnosis of cobalamin deficiency. Neurology 45:1435-1440, 1995
- Personal communication with Dr. Virgil Fairbanks
- Mayo Clinic Laboratory Reference Manual

Stephen V. Chiavetta, M.D.

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