Clinical techniques

Cancer testing

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INTRODUCTION

Physicians and researchers have attempted to develop reliable screening tests for the early detection of cancer, the value of which has obvious benefits. Because of the nature of neoplastic disease and the variety of its presentation, no test has to this point been reliable for the detection of all cancer types.

Laboratory tests involving the presence of oncofetal antigens, hormone concentrations, enzyme and isoenzyme studies have been utilized with varying degrees of success. Each testing method has offered promise but many of these assays are limited by a decreased sensitivity and specificity and have not proven to be reliable as markers of early tumor growth. They have been of value for the detection of more advanced cancers and for the monitoring of therapeutic response. In some cases, they help to determine the patients prognosis.

Cytology studies as well as biopsy examination have proven to be more definitive for diagnosis of tumor type but suffers from difficulty in obtaining suitable material. Additionally, tumor masses which are of sufficient size in order to shed cells or be biopsied, mean the cancer has been present for some time. This makes for a greater likelihood of metastases.

An ideal biomarker should show enough sensitivity and specificity to detect early malignant transformation. Sensitivity is the number of positive results obtained in proportion to the actual number of true positives, while the specificity is the number of test negatives which are true negatives.Neoplastic cellulartransformation antigen and antibody detection hold promise forincreased sensitivity of early cancer growth. Monoclonal antibody detection methods also hold promise for earlier detection and provide a greater specificity (1).

This article is meant to be an over view of laboratory tests which the family practice physician can use when evaluating and treating cancer patients. It does not cover all the possible laboratory studies which are available, but rather, those useful for screening, obtaining a diagnosis, monitoring of therapy or determination of tumor recurrence.

Acid Phosphatase

Acid phosphatase is found primarily in the prostate gland, as well in smaller amounts in other tissues. Prostatic acid phosphatase (PAP) is produced by the epithelial cells and secreted into the glandular lumen. High amounts of PAP are found in seminal fluid. In benign hyperplasia (BPH) of the prostate, higher quantities of PAP are found in serum when compared to patients without BPH (2,3). Because of the prevelance of BPH in the population, it has been suggested that PAP (reference range = 2.5 to 3.7 ng/ml [RIA], method dependent) values be based on this population rather than normal subjects (3) . The increased serum PAP occurring with BPH is thought to be a function of increased prostatic mass and its effect on normal gland function. Serum values for CAP are also found to be higher, despite decreased prostatic tissue concentrations, when compared to levels found with BPH (3). This is felt to be due to due to spread of the tumor mass and a derangement of cellular function. A circadian variation is thought to exist in serum PAP levels in men with prostatic cancer (4). However, more sensitive and specific testing methods for PAP found the fluctuation to be unpredictable (2) .

A major limitation in the evaluation of prostate cancer is to be able to quantitate the extent and progression of the disease. PAP, while more specific than prostatic specific antigen (PSA) for cancer of the prostate, isn't as sensitive and is only increased if the tumor is a grade 3 or greater with metastases. Therefore, PAP is not utilized as often by clinicians.

The value of PAP lies in its ability to help determine tumor staging, monitoring of therapy and prognosis. While the majority of CAP are slow growing, those that aren't tend to metastasize quickly, especially once outside the prostate capsule. In general, a persistent decrease by 50% from the mean PAP value is suggestive of a favorable response to treatment. A return to the reference range of the PAP also indicates a favorable response to treatment and a better prognosis. Patients who had a normalization of PAP after therapy had a significantly longer survival rate than those who did not. Those who had a 50% reduction in PAP values, which showed no further reduction, did not significantly improve over those with elevated results (5). Persistent increases of 50% from the mean PAP value suggests a progressive disease and a poorer prognosis (2).

Alpha Fetoprotein

Alpha fetoprotein is a glycoprotein which is found in the yolk sac and later the gastrointestinal tract and liver of mammalian fetuses. It is the predominant protein in embryonic serum (6) with serum levels peaking by the 12th to 14th week of gestation and decreasing by term. Adult levels are reached by 2 years of age (6). It is thought that AFP serves as a transporter of various serum components and may have some immunoregulatory function as well.

Low levels are found normally in adults (Reference Range = 2 to 6 ng/ml but will vary slightly from lab to lab). Increases in serum values are associated with hepatocyte regeneration and hepatoma as well as with different germ cell derived tumors. In pregnancy, AFP elevations above the reference range may signify neural tube defect, abruptio placentae cenate, pre-eclampsia, esophageal atresia, oligohydramnios, myelomeningocele, anencephaly or fetal death. Low levels may be associated with Down's syndrome. The test is also of value in determining biliary atresia in newborns.

With primary hepatocellular carcinoma the AFP is elevated 90% of the time by radioimmunoassay (RIA), often showing values greater than 1,000 ng/ml.(15). Other germ cell tumors such as embryonal carcinoma, teratocarcinoma, entodermal sinus tumor and choriocarcinoma may also have associated rises in AFP. This occurs with metastases of these tumors as well. AFP levels may be elevated with hepatocellular regeneration or with destruction from viral insult or exposure to hepatic toxins or with active cirrhosis.

Higher positive rates are found in black and Chinese males (75%-90%) with hepatoma than in Caucasians (50%) (14). Children and young adults seem to have a greater likelihood of having increased AFP levels.

AFP monitoring is of primary value in following the course of the disease and/or the response to therapy. As with CEA, AFP should be monitored along with other tests, especially liver enzyme studies. In persons with primary hepatoma, lowered levels of AFP showed a better long term prognosis than those who did whose levels did not decrease (7).

Anti-Malignin Antibody

Anti malignin antibody (AMA) (Reference Range = O to 134 mcg/ml) is an IgM general transformation antibody (8) which is elevated in non terminal cancer, localizes on cancer cells and is cytotoxic (10). The antibody is produced in response to malignin which is found in malignant cells. Malignin appears to be non specific and is elevated regardless of the site or cancer type. It has been demonstrated in tissue culture of malignant cells (8). Unlike carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP), malignin is not an oncofetal antigen as it is not found in fetal tissues (8). It is thought to be associated with the cancer cells' anaerobic enzyme system which is common to all malignancies regardless of cell type. This may be the reason that there are increasing malignin levels found with tumor growth (8) .

Serum concentration of AMA correlates with survival rates in cancer patients, i.e. higher levels are a good indicator of longer survival rates whereas low levels have lower survival rates. Additionally, the test is more sensitive for detection of cancer and has shown to be a good screening test for most cancer types. A sensitivity and specificity of 95 % on a first determination and greater than 99 % on repeat determinations was found (9,ll).

An active cancer state is associated with elevated AMA levels. Levels below 135 mcg/ml during tumor growth indicates a poorer prognosis and higher mortality rate . A decrease of AMA from previously elevated levels, without signs of tumor remission also signifies a poorer prognosis, which usually is followed soon after by death. Lower levels in the absence of malignant disease are seen with successful therapy (8).

False positive rates were found to be statistically insignificant. They were slightly higher in medically ill patients as opposed to random samples. In one study, some persons who were positive in the medically ill category eneded up with a diagnosis of cancer within 19 months (8,10).

AMA is more reliable than CEA early on, as CEA levels are a function of tumor burden and dissloution, whereas the AMA is a measure of tumor growth. The AMA test appears to have the sensitivity and specificity for cancer detection needed for early diagnosis. Additionally, it offers a good measure of the body's immune response, so important in natural and immune enhancing therapeutics. Research has suggested that AMA would be an effective immunotherapeutic agent as it is available in monoclonal antibody form (10).

Anti T & Tn Antibody

Cancer cells have structures which are incompletely synthesized precursors of normal M and N blood group antigens as part of their surface protein makeup. The predominant incomplete precursor structures are the T (Thompson-Frederich) and Tn antigens which are the immediate precursors to the M and N antigens found on normal cells. The T and Tn antigens are therefore recognized as "foreign" by the immune system and thus stimulate the immune system to develop antibodies to them.

In healthy persons, no T or Tn antigen is present, but Anti T and Tn antibody is found in the serum and other body fluids. If cancer cells are present, the body begins antibody formation in stomach, liver and colorectal malignancies.

CA 125

Carbohydrate Antigen 125 (CA 125) (Referenee Ranges haven't been established) is a glycoprotein found in more than 80% of non-mucinous epithelial ovarian neoplasms and in smaller amounts in cancer of the endometrium, fallopian tubes, and endocervix. The highest levels are seen in ovarian cancer, making the test of value in monitoring ovarian germ cell tumors and epithelial ovarian carcinoma. Additionally, CA- 125 is found in tumors of the colon, pancreas, liver, breast and lung. It is also detectable in pregnancy, ovarian abscesses, endometriosis and benign teratomas. It is felt that the CA 125 is unable to distinguish between benign and malignant tumors (15).

Upon tumor resection, CA-125 levels decrease, provided all the tumor has been resected. If serum levels fail to normalize, there is a greater chance of tumor recurrence (16). Malignant pelvic masses were predicted by CA-125 elevations 80% to 90% of the time, making it somewhat reliable in distinguishing benign from malignant pelvic tumors (16). It is more sensitive in later stage ovarian cancers than early stages and is felt to be of greater value when combined with other diagnostic procedures (37) .

Because it is found with such a variety of cancers, CA 125 is not useful in the differential diagnosis of gynecological tumors (16). Therefore, CA 125 is not a good screening test but has some value in monitoring progression or recurrence of specific pelvic tumors once the diagnosis is made. Higher values make the likelihood of recurrence greater but lower values do not necessarily rule out recurrence.

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is an oncofetal glycoprotein present in tissues of embryonic origin, or in neoplastic tissue which has reverted to a primitive state. Primarily found in the fetal gastrointestinal tract, it as also present in small amounts in adult colon, stomach, pancreas and lung tissue. CEA is a chemically heterogenetic molecule which is responsible for the varying degrees of immunological specificity found. Because of this, CEA may vary in different tissues and between individuals.

Initially the CEA (Reference Range = 2.5 ng/ml for a non-smoker & <5 ng/ml for smokers) test was thought to be specific for adenocarcinoma of the colon but clinical experience showed that it could be elevated with other cancers as well, in particular cancers of the pancreas and stomach. In addition to cancer, CEA is also found to be elevated in smokers, inflammation due to infection, inflammatory bowel disease, and pancreatitis. An elevated test may also be seen in patients with cirrhosis of the liver and hypothyroidism.

CEA is not useful in detecting occult cancer, as a correlation between tumor size and antigen level is not linear. Many early cancers may not show a positive CEA until later on in the disease, while some colon cancers, even with metastases, may be negative. Poorly differentiated carcinomas also are not reliably followed by CEA testing.

CEA is most useful as a monitor of cancer therapy and recurrence of gastrointestinal carcinomas, in particular colorectal cancer. Additionally, it is useful for detection of locally recurring carcinomas with lung or liver metastasis, especially if the primary cancer is from

the colon. There is some evidence that CEA is the most sensitive for detection of colon cancers which have metastasized (17). Some of the highest CEA levels are found to occur with metastasis to bone or liver. Significant elevations may also be found with primary breast (45%-70%), lung (70%-90%) and ovarian cancers as well as medullary thyroid cancer.

Serum CEA values greater than 10 ng/ml are strongly suggestive of a tumor whereas results between 2.5 ng/ml and 10 ng/ml are usually associated with other causes such as gastrointestinal inflammation or smoking. There is a significant correlation with metastatic disease and CEA values greater than 20 ng/ml. Serial CEA levels are useful in determining the effects of therapy and eventual prognosis. But CEA may also elevate due to antineoplastic drug therapy and tumor necrosis. Thus, fluctuating values for CEA will be found if monitored often. Radiation may also contribute to transient rises. The return of CEA values into the reference range following surgery or successful therapy is a good indication that most of the tumor has been removed. However, small, transient rises in CEA may occur following treatment and may be d u e to causes other than tumor growth. Usually these rises are no more than 5 ng/ml and fluctuations may be seen for several months.

Progressive elevations of CEA may indicate a tumor recurrence 3 to 36 months before it manifests clinically. A sustained rise of at least 5 ng/ml on successive tests should be considered suspicious of tumor regrowth and the patient monitored closely. Small rises usually indicates local proliferation while a large rise, especially over a short period of time, often signifies hepatic metastases.

CEA by itself is not as effective for monitoring tumor recurrence and should be evaluated along with other laboratory tests. When coupled with gamma glutamyl transferase, alkaline phosphatase and CA 19-9, the reliability of CEA as a monitor for recurrent breast and colon cancers is enhanced (see GGTP and CA 19-9). Because of the variation in testing methods found in different laboratories, it is best to use a single laboratory for serial CEA determinations .

Cytology, Sputum

Sputum cytology examinations are useful for differentiation between small cell undifferentiated and bronchogenic carcinomas. As with urine cytology exam, there is an increasing probability of finding the cancer the more often a specimen is procured. However, there is a slightly lesser likelihood of finding cancerous cells when compared to urine cytology due to the paucity of materials obtained. A fresh early morning sputum sample over a 3 day period or sputum samples which have been induced or post-bronchoscopy specimens are valuable.

Sputum cytology examinations are also useful in obtaining a diagnosis of herpes virus, cytomegalic virus, fungal infection, and *Echinococcus, Paragonimus,* and *Strongyloides* infestations. Additionally, allergic reactions, asbestos infiltration and tuberculosis can also be found.

Bronchial lavage, endoscopy and biopsy have proven the most useful for diagnosis of bronchogenic carcinoma.

Cytology, Urinary

Urine cytology studies have been found to be highly reliable in the diagnosis of high-grade urinary tract tumors with a sensitivity of 94.2%. With primary bladder carcinomas in situ, the sensitivity was 100%. Poorer results occurred with grade I papillary tumors but are slightly higher in grade II tumors (33%). No false positives were found (18). A first specimen diagnosis was found on 79 % of patients tested, increasing an additional 14% on 2nd exam and another 7% with a 3rd examination. These results justify the recommended 3 successive first morning urine cytology exams (18).

Urinary cytology examination for the presence of a bladder or other urinary tract tumor is an easy to obtain, non invasive procedure of value as a cancer screening test. Urine cytology does have some limitations however, in that cellular deterioration makes it difficult to identify neoplastic cells. Therefore freshly voided urine which is quickly preserved makes the best specimen.

The most reliable diagnosis is obtained by cystoscopy and biopsy of the suspected tumor. Flow cytometry studies hold promise for the diagnosis of low grade differentiated tumors, which will enhance the procedure's sensitivity (15).

Estrogen & Progesterone Receptor Assays

Estrogen (ERA) and progesterone (PRA) receptor assays are performed on freshly obtained breast tissue from biopsy, lumpectomy or mastectomy. About 65 % of patients with primary breast cancer and 50% of metastasized breast cancer are estrogen receptor positive. Both tests are useful in predicting the patients response to hormone therapy. Patients who have positive estrogen receptor assays respond to anti-endocrine therapies such as androgens, tamoxifen or adrenalectomy. About 30% of breast cancer patients are ERA negative. Progesterone receptor assay is especially helpful in tumors whose estrogen response is low as therapy is enhanced if a positive PRA is found. Persons who are both ERA and PRA positive show a better response to therapy (70%-80%).

ERA and PRA tests may come with ploidy (diploid normal or aneuploid abnormal) and S phase analysis (synthesis phase, which estimates proliferative activity). Together they help in deciding which therapy is most effective and determining the degree of tumor virulence .

Increased survival times are noted in patients with high progesterone response levels as they showed a better response to treatment. Prognosis was good if the PRA remained positive on subsequent biopsy or with recurrence, but was poorer if it didn't. Some patients however, which are ERA and PRA responsive on testing, do not respond to hormone therapy.

If performing the analysis, your local laboratory should b e contacted prior to obtaining the specimen as preserving or delay in evaluating the tissue will affect the results.

Gamma Glutamyl Transferase

Gamma glutamyl transferase (GGTP) is a membrane bound enzyme responsible for the transport of amino acids. GGTP is highest in liver tissue and in smaller amounts in kidney, brain, pancreas, breast and prostate gland. Increases of serum levels can be seen either as a marker of cellular growth, or destruction due to inflammation or tumor burden/growth (14,20).

GGTP (Referenee Range = 10 to 32 U/L, will vary depending on the methodology) has been found to be a more sensitive marker of liver involvement than either SGOT/AST or SGPT/ALT. GGTP, as a measure for the presence of tumor involvement, is limited by elevations with non-malignant diseases such as systemic lupus erythematosus, rheumatoid arthritis and liver diseases such as hepatitis and obstructive jaundice.

GGTP is of value when it is elevated individually or along with alkaline phosphatase, as it may suggest some type of neoplastic process. Serum GGTP increases are found with progressive breast

cancer, melanoma, lung cancer and hypernephroma (20). GGTP, along with CEA and alkaline phosphatase measurements are found to be very useful markers to screen for breast cancer metastases (20). Patients with low or decreasing GGTP levels had no evidence of disease while those with high or increasing levels had clinical signs of progressive disease (20). Pronounced GGTP elevations are often seen with liver metastases from other organs (20,21).

Both GGTP and alkaline phosphatase are of little value in the preoperative diagnosis of hepatic involvement in persons with carcinoma of the rectum and colon without clinical evidence of hepatic metastases. There is a low prevalence of metastases combined with a high frequency of false positive results (21). A GGTP elevation should point the clinician to investigate further its source or cause of the elevation.

Serial (every 2-3 months) GGTP determinations which are in the reference range suggest that the patient is doing well and has no apparent disease or it has stabilized. Increasing values suggest an active or progressive disease (20).

Gastrin

Gastrin is produced by stomach mucosal cells primarily in the gastric antrum and stimulates hydrochloric acid, pepsin and intrinsic factor release by the fundic cells. Serum gastrin levels are elevated in up to 94 % of stomach cancers from gastrinoma.

Gastrin levels (Reference Range = up to 100 pg/ml, but will vary according to age and level of stimulation) may also be elevated with achlorhydria or hypochlorhydria associated with atrophic gastritis and pernicious anemia. Patients with vagotomy or with partial stomach resection (portions of the antrum remain), uremia or chronic hypercalcemia, or H2 - receptor blocking medication may also have elevated levels. A transient rise in serum gastrin occurs with eating, especially if the meal is high in protein (14).

Zollinger-Ellison syndrome, which is a gastrin producing non-beta islet cell tumor will show serum gastrin elevations up to 5 times the reference range values. This is diagnostic of this condition. About 2/3 of Z-E tumors are malignant (14,22).

The Secretion Stimulation test helps to differentiate gastrinoma from gastric ulcer in that persons with gastrinoma show greater than base line serum gastrin values whereas gastric ulcer patients do not.

Endoscopy and biopsy are the best methods for diagnosis of stomach cancer.

Human Chorionic Gonadotrophin

Human chorionic gonadotrophin (HCG) is a glycoprotein hormone produced by the developing chorionic villi of the placenta. HCG levels are elevated with germ cell neoplasm, gestational trophoblastic neoplasm, choriocarcinoma and hydatidiform mole, which has a high incidence of progression to choriocarcinoma.

The primary value of human chorionic gonadotrophin (HCG) levels (Reference Range +<3 mIU/ml) is in evaluation of testicular tumors in males and gestational neoplasm in women. With pregnancy, higher levels of HCG than expected for the period of fetal development should alert the physician to the possibility of a tumor. Upon delivery, HCG levels should return to normal in about 14 days. Because of the fast growing nature of germ cell tumors, high levels of HCG are often found. Normally negative, HCG levels can exceed 10000 Iu/ul. and is usually accompanied by elevations in alpha fetoprotein.

Suspicion of a testicular tumor should prompt the clinician to obtain a HCG level as soon as possible. A negative level however, may not rule out the presence of a germinal tumor (15). Positive results may also be found with conditions where there is a high rate of cellular proliferation (42). HCG, as well as AFP, is useful in monitoring therapy. A relationship between AFP and HGC was found upon histochemical examination of testicular tissue in testicular germ cell tumors. This correlates with the observed elevations in serum of both compounds (23).

Lactate Dehydrogenase

Lactate dehydrogenase (LDH) is an enzyme responsible for the breakdown of lactic acid and is found in almost all tissues. Because of its prevalence throughout the body and the variations in pH levels in which it must perform, 5 isoenzyme forms are found. LDH is thought to be elevated with tumor growth because of their high anaerobic metabolism.

Elevations in LDH (Reference Ranges are highly method dependent) are usually found along with other enzymes and help to determine the source of the disease. When found by itself without other enzyme elevations, high levels of serum LDH should alert the clinician to a possible malignancy, especially lymphoma (24). A predominance of LDH isoenzyme levels LD2 and LD3 is usually noted. An elevated LDH also can occur with myocardial infarction without creatine phosphokinase (CPK) or SGOT/AST elevation. In this case isoenzyme studies will show an LD1/LD2 inversion which confirms the infarction, provided there is no hemolytic or pernicious anemia present.

LD1 is high in concentration in normal colon mucosal cells while a predominance of LD5 is found in colon and breast cancer tissue (25,26). LDH is a fairly sensitive marker for solid tumor and may have some value as the only marker in seminoma detection (25,26). In this case the LD1 fraction is elevated (24).

The primary value of LDH and LDH isoenzymes is in alerting the physician to the possible presence of a tumor and in determining the source of the cancer. Levels will fluctuate considerably with therapy and/or tumor growth, making it less useful for monitoring the disease.

Leukocyte Alkaline Phosphatase

Leukocyte alkaline phosphatase (LAP) is a zinc dependent enzyme found in high amounts in white blood cells of the granulocytic series. As the white blood cell matures, increasing amounts of the enzyme is found. In primitive, immature or abnormally developing cells, smaller quantities are present. The primary value of the test is in the differential diagnosis of chronic granulocytic leukemia, chronic mylogenous leukemia and agnogenic myeloid metaplasia from leukemoid reaction (14,15). In these conditions the white blood cell count is elevated but the more primitive leukemic cells contain lower levels of LAP, where as with the leukemoid reaction, the cells contain normal levels (Reference Range =11 to 95, but may vary from lab to lab.).

LAP may be useful in screening prior to a bone marrow exam or in conjunction with it. A bone marrow aspiration will provide more definitive information. A Philadelphia chromosome test may also be obtained if chronic mylogenous leukemia is suspected as it will be present in up to 90% of CML patients. LAP also helps in the evaluation of polycythemia vera (90%) and myelofibrosis where it may be elevated significantly.

Elevated levels above the reference range are seen with polycythemia vera, myelofibrosis, leukemoid reactions, hairy cell leukemia, neutrophilia, aplastic anemia and Hodgkin's disease, making

the LAP a useful test for differentiation and monitoring of therapy with these conditions. Pregnancy, stress-induced leukocytosis or an increase in immature forms may cause elevated scores.

Lower levels are associated with chronic mylogenous leukemia, paroxysmal nocturnal hemoglobinuria, thrombocytopenia purpura and hereditary hypophoshatasia.

Generally LAP is considered a screening test which is used along with other examinations to aid in the differential diagnosis. It is not considered a definitive diagnostic test. There is increasing evidence that DNA analysis methods will provide a more specific diagnosis when sorting out the chronic myeloproliferative disorders (27).

Muramidase

Muramidase, or lysozyme, is present in monocytes and granulocytes but is generally found in higher amounts in leukemic cells. Elevated serum muramidase levels (Referenee Range = 2.8 to 8 meg/ml serum, < 2 mcg/ml in urine) are associated with myelogenous, monomylogenous and monocytic leukemias and is helpful with the differential diagnosis. Muramidase is also elevated in tuberculosis and sarcoidosis.

In patients with acute myelocytic leukemia, for those who have initially elevated serum muramidase levels, the prognosis was poorer than for those who do not. Of all persons with acute leukemia, those with acute monocytic leukemia had the highest pre-treatment muramidase values and the poorest prognosis (28). In general, patients with high pretreatment muramidase levels which do not return to the reference range following therapy, demonstarted a poorer prognosis.

The test is also used as a predictor of central nervous system involvement with myelocytic, monomyelocytic and monocytic leukemias (29), as higher levels are associated with CNS involvement. Bone marrow studies offer the best means of differential diagnosis for leukemias.

Prostatic Specific Antigen

Prostatic specific antigen (PSA) is a glycoprotein which is particular to prostatic epithelial cells. Increases are found with prostate cancer, benign prostatic hypertrophy (BPH), prostatitis and prostatic interepithelial neoplasia (30). With BPH and prostatitis, levels will vary from determination to determination depending on the degree of involvement or level of inflammation.

A correlation between prostate volume and increase in PSA has been demonstrated. With cancer of the prostate (CAP) a tumor burden of at least 1 ml. is necessary to raise serum PSA levels to a significant degree (31). This confirms other studies which show that an increase in PSA accompanies an increase of prostate mass (32). Tumor burdens greater than stage A1 in CAP is necessary to elevate PSA in most cases (30). In general, increased PSA levels (Reference Range = 0.0 to 4.5 ng/ml) without evidence of an enlarged prostate gland should be suspected to have at least a grade A2 CAP (30). PSA levels drop after prostatectomy or successful treatment of the cancer (33), prostatic hypertrophy or inflammation.

Prostatic specific antigen levels are elevated in 84.4% of patients with cancer of the prostate, 14.1% with BPH and 10% with other genitourinary cancers (32). It is not specific for CAP but is much more sensitive for prostate enlargement than acid phosphatase. Because of this it has become a good screening test, along with digital rectal examination, for prostate gland abnormalities.

TA-4

Tumor Antigen-4 (TA-4) is a purified protein associated with squamous cell carcinomas. In known squamous cell carcinomas of various organ systems such as the lungs and cervix, TA-4 levels (Reference Range = < 2.6 ng/ml) were found to be significantly higher than healthy controls. This was not true for patients with other, non-malignant diseases of the same organ systems (34).

TA-4 is a relatively specific marker of cervical squamous cell carcinoma and is useful in monitoring the disease (34). It is useful for obtaining a diagnosis of squamous cell carcinoma, especially if the disease is in the advanced stages (34). It has not proven to be as effective in detecting the early stages of the disease. A combination of pap smear, endocervical pap smear, colposcopy, endoscopy a n d biopsy (40), along with a TA-4 level are more reliable for cervical and lung squamous cell cancer detection.

Thyroglobulin

Thyroglobulin is a glycoprotein of high molecular weight which is secreted by thyroid follicular epithelial cells. It is involved with transport and storage of thyroid hormone. Thyroglobulin levels (Reference Range = up to 50 ng/ml, but will vary from lab to lab) are elevated with adenocarcinoma of the thyroid but also with thyrotoxicosis, iodine deficiency and benign thyroid adenomas.

Thyroglobulin is not a good test for detecting thyroid cancer as it is not sensitive or specific enough. It is of benefit however in following the course of the disease provided it is elevated because of the cancer. It will not be elevated with anaplastic or medullary carcinomas. However, thyroglobulin levels will correlate with thyroid tumor growth in most cases of tumor progression, even with changes in differentiation of the tumor (35). The test is useful in monitoring postoperative patients for tumor dissemination. It may be useful in persons with metastases to the bone if the primary site is known. A return of thyroglobulin levels to the normal range occurs with successful I-131 therapy but may take several months to occur (35) .

Thyroid scanning and fine needle biopsy of suspected nodes are the best methods for determining a diagnosis.

Vanylamandelic Acid

Vanylamandelic acid (VMA) is a major metabolite of epinephrine and norepinephrine which is found to be increased with an over production of catecholamines. VMA (Reference Range = 2 to 7 mg/day, variable depending on age) is of value for the evaluation o f pheochromocytoma and for hypertension. It will also be elevated with neuroblastoma, ganglioneuroblastoma and ganglioneuroma in about 80% of cases. For these conditions, up to 20-32% of persons with cancer will not have elevated VMA levels.

The test will be more sensitive for the detection of neuroblastoma if used along with homovanillic acid. VMA may also be elevated with hypothyroidism, hypoxia, hypoglycemia, diuretic therapy, myocardial infarction, Cushings syndrome, hemolytic anemia, lymphoma or severe renal disease (14). A 24 hour urine specimen is preferred as random samples can give false negatives.

CONCLUSIONS

Laboratory testing for the early detection of cancer is still in its infancy but holds promise with the further development of monoclonal and antibody assays. In particular, the anti malignin antibody, T & Tn antibody and to a lesser degree, CA 19-9 are the tests which offer the best chance of cancer detection while the tumor is in its early

growth phase. Both the AMA and T & Tn antibody tests also offer promise as potential immune therapies.

Enzyme assays, such as acid phosphatase, gamma glutamyl transferase, lactate dehydrogenase and muramidase, while somewhat nonspecific, are useful for the differentiation of cancer, and are a measure of metastases. Additionally, they are of benefit in following the patients response to therapy, and in the case of acid phosphatase, help in determination of patient prognosis.

Hormone assays such as human chorionic gonadotrophin, gastrin and progesterone and estrogen receptor assays are somewhat more specific for the type and origin of the tumor. ERA and PRA are valuable in assisting the clinician in deciding which course of therapy is most beneficial.

Proteins such as thyroglobulin and alpha fetoprotein are useful in following the course of treatment and in assessing metastases. Additionally, AFP is somewhat helpful in determining the origin of the tumor by virtue of its being present only with primitive cell growth.

Cancer antigen tests like CEA, CA125, TA-4 and prostatic specific antigen, are most valuable in monitoring the patient's response to treatment, recurrence of the cancer, and along with other tests, helpful in locating the source and extent of the tumor.

Cytology examination, be it PAP smear, sputum, serous fluid or urine still offers the clinician a direct method for the diagnosis of cancer based upon pathology examination. Additionally, tissue biopsy, bone marrow exam and to a lesser degree, colposcopy, sigmoidoscopy and endoscopy are still the most definitive procedures for obtaining a diagnosis of cancer.

Using the various laboratory tests and diagnostic procedures in conjunction with one another offers the clinician a broader capacity for the detection of cancer.

1. Schlom, J. Innovations in monoclonal antibody tumor targeting -Diagnostic and therapeutic implications. JAMA Vol 261: No 5744-6: Feb. 1989
2. Maatman, T. et al. The role of serum acid phosphatase as a tumor marker in men with advanced adenocarcinoma of the prostate. J. Urol. 132: 58-63 1984
3. Heller, J. Prostatic acid phosphatase: Its current clinical status J. Urol. 137 1091-103: June 1987
4. Doe, R. et al. Circadian variation of serum acid phosphatase in prostatic cancer. Metabolism 13:455 : 1964
5. Rohner, T, Sieber, P. Importance of acid phosphatase in response criteria for prostate cancer. Urology 30:316-7 1987
6. Bock, J. Current issues in maternal serum alpha-fetoproteinscreening. Am. J. Clin. Pathol. 97;541-54; 1992
7. Nomura, F. et al. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Cancer 64; 1700-7 1989
8. Bogoch, S. et al. Determination of anti-malignin antibody and malignin in 1,026 cancer patients and controls: Relation of antibody to survival. Journ Med. 13; 49-69: 1982
9. Bogoch, S. et al. Malignin antibody and early malignancy. The Lancet 237;977 : 1991
10. Bogoch, S. et al. Elevated levels of anti-malignin antibody are quantitatively related to longer survival in cancer patients Protides Biol.Fluids 31; 739-47: 1984
11. Abrams, M. et al. Early detection and monitoring of cancer with the anti-malignin antibody test. Cancer Detection and Prevention 18(1); 65-78: 1994
12. Springer, G. et al. T/Tn antigen vaccine is effective and safe in preventing recurrence of advanced breast carcinoma Cancer Detection and Prevention. 1993
13. Pleskow, D. et al. Evaluation of a serologic marker, CA 19-9, in the diagnosis of pancreatic cancer. Ann of Int. Med.110:704-09:1989
14. Ravel, R. Clinical Laboratory Medicine 5th Ed. Yearbook Medical Pub. Chicago 1989
15. Jacobs, D Ed. Laboratory Test Handbook 2nd Ed. Williams & Wilkins Baltimore 1990
16. Bast, R. et al. Pros and Cons of Gynecologic Tumor Markers Cancer; 60;1984-9 : 1987
17. Beart, R. et al.Postoperative Follow-up of Patients with Carcinoma of the Colon. Mayo Clin. Proc. 58;361-3 :1983
18. Koss, L., et al. Diagnostic Value of Cytology of Voided Urine Int. Acad. Cytol Acta Cytology 2 9: 810-6 :1985
19. Thornthwaite, J. et al. Determination of Antimalignin Antibody in Patients With Suspicious Mammograms Proc Annu Meet Am Assoc Cancer Res. 31;A1550: 1990
20. Sahm, D, et al. Gamma-Glutamyltranspeptidase Levels as an Aid in the Management of Human Cancer Cancer 52: 1673-78 :1983
21. Baden, H.etal. Diagnostic Value of Gamma-Glutamyl Transpeptidase and Alkaline Phosphatase in Liver Metastases Surgery, Gynecology & Obstetrics 133; 769-73:1971
22. Harvey, A .E. The Principles and Practice of Medicine. 21st Ed. Appleton-Century-Crofts Connecticut 1983
23. Morniaga, S. et al. Human Chorionic Gonadotropin and Alpha-Fetoprotein in Testicular Germ Cell Tumors An Immunochemical Study in Comparison with Tissue Concentration Cancer 52; 1281-89 :1983
24. Rotenberg, Z. et al. Elevation of Serum Lactic Dehydrogenase Levels as an Early Marker of Occult Malignant Lymphoma. Cancer 54; 1379-81 :1984
25. Stefani, M. Enzymes, Isoenzymes and Enzyme Varients in the Diagnosis of Cancer A Short Review. Cancer 55; 1931-36 : 1985
26. Van Lente, F. and Shamberger, R. Defining a Role for Enzymes in Cancer Diagnosis. Diag. Med. :June 1983
27. Krepe, H. et al. DNA Analysis to Aid in the Diagnosis of Chronic Myeloproliferative Disorders Am. J. Clin. Pathol. 98; 46-54: 1992
28. Wiernik, P. & Serpick, A. Clinical Significance of Serum and Urinary Muramidase Activity in Leukemia and Other Hematologic Malignancies Amer. Journ. Med. 46; 330-43 :1969
29. Peterson, B. et al. Central Nervous System Involvement in Acute Nonlymphocytic Leukemia Am. Journ. Med. 83; 464-70 :1987
30. Cohen, M. et al. Serum Prostate-Specific Antigen Levels in Stage A1 Prostatic Cancer Am. J. Clin Pathol. 100; 127-29 :1993
31. Brawn, P et al. Prostate-Specific Antigen Levels from Completely Sectioned, Clinically Benign, Whole Prostates Cancer 68; 1592-99 :1991
32. Stamey, T. et al.Prostate- Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate NEJM 317; 15 :1987
33. Barach, M et al. Evaluation of Prostate-Specific Antigen as a Marker for Adenocarcinoma of the Prostate J. Clin Lab Med. 29:810-6 :1983
34. Mino, N., et al., Availability of Tumor-Antigen 4 as a Marker of Squamous Cell Carcinoma of the Lung and Other Organs. Cancer 62:73 0-734 :1988
35. Bostch, H. et al. Long Term Follow-up Using SerialThyroglobulin Determinations in Pateints With Differentiated Thyroid Carcinoma. Cancer; 52;1856-9: 1983
36. Harderman, S. et al. Two New Techniques for Evaluating Prostate Cancer - The Role of Prostate-Specific Antigen and Transrectal Ultrasound. Postgrad. Med. 86;2 :1989
37. Piver, S. et al. Ovarian Cancer: Who Needs Screening? Patient Care Vol 27: No20 27-47: Dec.1993
38. Hollub, Fink & Murphy American Cancer Society Textbook of Clinical Oncology ACS, Atlanta: 1991
39. Rotenberg, Z. et al. Total Lactate Dehydrogenase and Its Isoenzymes in Serum of Patients with Non-Small Cell Lung Cancer Clin. Chem. 34; 668-70: 1988
40. Curry, S. et al. Colposcopy: When? Why? How? Patient Care 167;81 Mar. 94
41. Fechner R One Century of Mammary Carcinoma In Situ -What Have We Learned ? Am. Journ. Clin. Pathol. Vol 100; No 6 Dec. 1993
42. Tietz, N. Ed. Clinical Guide to Laboratory Tests. W. B. Saunders Co. Phila. 1983