September 10, 2007

LETTER OF MEDICAL NEED AND EXPLANATION FOR UNUSUAL BLOOD TESTS BEING USED ROUTINELY

Dear Sirs,

My practice is a highly specialized one devoted entirely to consultations regarding diagnosis and management of neuroendocrine tumors and their associated endocrine syndromes. This group of diseases is rare. There are very few specialists devoting full time to these conditions. The most frequent of them is carcinoid of which new cases are reported in the United States in 3 – 4 individuals per 100,000 of the general population per year at the present time. Much rarer are nonfunctioning neuroendocrine tumors of the pancreas (islet cell tumors), insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas, ectopic ACTH-producing tumors, medullary thyroid carcinomas and various exceedingly rare other peptide hormone producing neuroendocrine cancers. These tumors most often arise in the gastrointestinal tract or the pancreas but can also appear in the lung, ovary and very rarely in a wide assortment of other tissues.

Even those neuroendocrine tumors which do not cause clinical endocrine syndromes because of not producing large amounts of bioactive amines or peptide hormones, do nonetheless usually produce more than is normally generated in the body and these biochemical "markers" can be measured as confirmatory findings for the diagnosis and also indicators of prognosis, progression of the tumors and response to treatment. None of these substances for which I test are considered experimental or part of a purely investigative undertaking.

The most common marker measured is chromogranin-A which is increased in the blood in approximately 90% of all neuroendocrine tumors and can be viewed as a "SED rate" for these neoplasms. (Ref 1. Oberg K, Kvols L, Caplin M, et al: Consensus report on the use of Somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Annals of Oncology 15:966-973, 2004. Ref 2. Nehar D, Olivieri S, Claustrat B, et al: Interest of chromogranin-A for diagnosis and follow up of endocrine tumors. Clinical Endocrinology (OSF) 60(5):644-652, 2004).

Serotonin. Measurement of this substance in the serum is essential for confirming the presence of carcinoid tumor and indicating its degree of function. (Ref 3. Donaldson D: Carcinoid tumours-The carcinoid syndrome and serotonin (5-HT). A brief review. Journal of the Royal Society Health 120(2):78-79, 2000).

Insulin. This and C-peptide are important to be measured in suspected cases of insulinoma. There are almost innumerable references available concerning this in the literature. (Ref 4. Chevenne D, Crivin F, Porquet D: Insulin assays and reference values. Diabetes Metab 25(6):459-476, 1999.)

Pro-Insulin. This substance can have greatly increased levels in patients with insulinoma and may be the only positive marker found in such a case. (Ref 5. Shetty MR, Boghassian HM,

Duffell D, et al: Tumor-induced hypoglycemia: a result of ectopic insulin production. Cancer 49: 1920, 1982.)

C-Peptide. (Ref 6. Corn C. C-peptide and autoimmune markers in diabetes. Clinical Laboratory 49(1-2):1-10, 2003).

Gastrin. This substance is produced by gastrinomas and is the cause of Zollinger-Ellison syndrome. Its measurement is essential for diagnosing these conditions. (Ref 7. Mignon M: Diagnostic and therapeutic strategies in Zollinger-Ellison syndrome associated with multiple endocrine neoplasia Type 1 (MEN-1): Experience of the Zollinger-Ellison Syndrome Research Group: Bichat 1958-1999. Bull of Academic NAT Med 187(7):1249-1258, 2003).

Vasoactive Intestinal Polypeptide (VIP). This substance is produced in excess by VIPomas and causes the syndrome of WHA (pancreatic cholera). (Ref 8. Gozes I, Furman S: Clinical endocrinology and metabolism. Potential clinical applications of vasoactive intestinal peptide. A selected update. Best practices Res. Clinical Endocrinology and Metabolism 18(4):623-640, 2001.)

Calcitonin. This substance is produced in excess by medullary thyroid carcinoma and occasionally ectopically produced by many neuroendocrine tumors. (Ref. 9. Pacini F, Fontanelli M, Fugazzola L, et al: Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. Journal of Clinical Endocrinology and Metabolism 78:826-829, 1994.)

Glucagon. This substance can be produced by glucagonomas arising in the pancreas and cause a specific syndrome characterized by rash, glossitis, anemia, weight loss, diabetes, deep vein thrombosis, depression and deficiency in amino acids. (Ref 10. McGavran MH, Unger RH, Lecant L, et al: A glucagon-secreting alpha-cell carcinoma of the pancreas. New England Journal of Medicine, June 22:274(25);1408-1413, 1966).

Histamine. This substance is produced in excess from mast cells in a variety of conditions including allergies and mast cell disease. In the latter an excess of tryptase is also found in the blood. Some neuroendocrine tumors, particularly those arising from the lung and the stomach, can produce histamine as well as other active substances and its measurement is important to help both diagnose and explain the source of symptoms. (Ref 11. Roberts LJ II, Bloomgarden ZT, Marney SR Jr, et al: Histamine release from a gastric carcinoid: provocation by pentagastrin and inhibition by somatostatin. Gastroenterology 84:272-275, 1983.)

Tryptase. This substance is produced in excess by mast cells in the presence of mast cell disease and its measurement is critical for the diagnosis of that condition. (Ref. 12. Schwartz LB, Metcalf DD, Miler JJ, et al: Tryptase levels as an indicator of mast cell activation in systemic anaphylaxis and mastocytosis. N Eng J Med 316:1622-1626, 1987.)

Substance-P. This peptide is often produced in excess by neuroendocrine tumors and its measurement can confirm a diagnosis. (Ref. 13. Norheim I, Theodorsson-Norheim E, Brodin E,

et al: Tachykinins in carcinoid tumors: use as a tumor marker and possible role in carcinoid flush. Journal of Endocrinology and Metabolism 63:605-612, 1986.)

Neurokinin-A. This substance also is sometimes produced in excess by neuroendocrine tumors and its measurement can corroborate a diagnosis. (Ref. 14. Theodorsson-Norheim E, Norheim I, Öberg K, et al: Neuropeptide-K: a major tachykinin in plasma and tumor tissues from carcinoid patients. Biochemistry Biophysiology Res Commun131(1):77-83, 1985.)

Pancreatic Polypeptide. This substance is often produced in excessive amounts by neuroendocrine tumors of the pancreas as well as those arising elsewhere regardless of whether they produce other hormones, and though it is nonspecific it is a very helpful confirmation of the presence of such tumor and must often be measured routinely. (Ref. 15.)

Neurone-Specific Enolase (NSE). NSE is a nonspecific substance which is often increased in the circulation of individuals with neuroendocrine tumors and is a helpful corroboration of the diagnosis. (Ref. 16. Baudin E, Gigliotti A, Ducreus M, et al: Neurone-specific enolase and chromogranin-A as markers of neuroendocrine tumors. The Journal of Cancer 78:1102, 1998.)

Pancreastatin. This split product of chromogranin-A is sometimes exceedingly elevated in the blood whereas chromogranin-A may not be, and is therefore a very useful indicator of the presence of neuroendocrine tumor disease in those cases which have normal chromogranin-A. (Ref. 17. Feldman J, O'Dorisio TM: Role of neuropeptides in serotonin in the diagnosis of carcinoid tumors. American Journal of Medicine 81:41, 1986.)

Prostaglandin D2, E2 and F2. These are bioactive substances which are sometimes overproduced by foregut or hindgut neuroendocrine tumors and can be the only abnormality found in obscure cases to explain flushing or diarrhea. (Ref. 18. Nets SA, McRae JR, Robertson RP: Prostaglandins as mediators of paraneoplastic syndromes: Review and update. Metabolism 30:299, 1981.)

Peptide YY. This substance is occasionally measured when a carcinoid or other neuroendocrine tumor of the hindgut is suspected because it is sometimes the only marker produced by such a lesion. (Ref. 19. Adrian TA, Bacarese-Hamilton AJ, Savage AT, et al: Plasma PYY concentrations in gastrointestinal diseases. Digestive Diseases Science 29:35, 1984.)

Beta Naturetic Peptide (BNP). This substance is increased in the blood in the presence of dilatation of the atrium and is a strong marker to support a diagnosis of carcinoid heart valve disease with tricuspid regurgitation. It is measured whenever that diagnosis is suspected. (Ref 20. Dokainish H, Zoghei WA, Lakkis MM, et al: Incremental predictive power of β-type naturetic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. Journal of American College of Cardiology, April 19;45(8):1223-1226, 2005).

Urinary 5-HIAA. This metabolic product of serotonin is elevated in 50-80% of carcinoid

cases dependent upon the site of origin of the tumor. (Ref 21. Feldman JM: Urinary serotonin and the diagnosis of carcinoid tumors. Clinical Chemistry 32:840, 1986.)

Alpha subunit of HCG. This marker is abnormally elevated in a significant number of neuroendocrine tumor cases and is useful therefore as an indicator. (Ref 22. Grossman M, Trautmann ME, Poertl S, et al: Alpha-subunit and human chorionic gonadotropin-beta immunoreactivity in patients with malignant endocrine gastroentero-pancreatic tumours. European Journal of Clinical Investigation 24:131, 1994. Ref 23. Nobels FR, Kwekkebom DJ, Coopman SW, et al: Chromogranin-A as serum marker for neuroendocrine neoplasia: comparison with neurone-specific enolase and the alpha-subunit of glycoprotein hormones. Journal of Clinical Endocrinology and Metabolism 82:252, 1997.)

A good summary of most of these markers measured in the blood for neuroendocrine tumors is written by Ardill and Erikkson and specifically deals with urinary 5-HIAA, calcitonin gene-related peptide, gastrin releasing peptide, PP, PYY, somatostatin, alpha subunit of HCG, N-peptide-K and neurokinin-A, chromogranin-A and pancreastatin, as well as other circulating products. They provide relatively up to date references for the literature. (Ref 24. Ardill JES and Erikkson B: The importance of the measurement of circulating markers in patients with neuroendocrine tumors of the pancreas and gut. Endocrine-Related Cancer 10:459-462, 2003.)

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