Excessive Urinary 5-Hydroxy-3-Indole Acetic Acid in the Absence of a Metastatic Carcinoid

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Considerable interest has been aroused in the diagnosis of the malignant carcinoid syndrome and the diagnostic reliability of increased urinary excretion of 5-hydroxy-3-indole acetic acid. The authors present observations important to this problem.

The colorimetric test allegedly specific for the malignant carcinoid syndrome was recently observed to be strongly positive in 2 patients who did not have this disease. Observation of excessive elevation of urinary 5-hydroxy-3-indole acetic acid (5-HIAA) by the qualitative chemical test of Udenfriend and co-workers has been considered a specific, simple, rapid, and reliable means of recognizing the presence of metastatic carcinoid tumors.1-3 This test of the urine of 1,023 patients selected at random by one investigator revealed uniformly negative results and prompted the conclusion that a false positive test due to drugs or other clinical conditions, if present at all, must be very rare.4 Recently 2 patients were observed who had symptoms prompting suspicion of the malignant carcinoid syndrome. The urine of both patients revealed well elevated levels of 5-HIAA by both the colorimetric test of Udenfriend and co-workers2-5 and the paper chromatographic test of Curzon.6 Subsequent investigations failed to demonstrate a carcinoid tumor in either patient. The exact specificity of this generally accepted colorimetric test for 5-HIAA is not known, and the reliability of the test in making a diagnosis of the malignant carcinoid syndrome is questioned.

The clinical features of the malignant carcinoid syndrome may be divided into the following groups: (1) cutaneous vascular lesions (paroxysmal or permanent erythematous flushing of the skin, intermittent patchy cyanosis and blanching), (2) gastrointestinal features (abdominal pain, diarrhea, hepatomegaly, and ascites), (3) cardiovascular manifestations (progressive exertional dyspnea, syncope, asthma, hypotensive states, right heart failure, and tricuspid and pulmonary valvular lesions), and (4) metabolic derangements (increased levels of serotonin in the blood, extreme elevations of 5-HIAA in the urine, peculiar personality changes, and definite psychotic episodes).

The excessive production of 5-hydroxytryptamine (serotonin, enteramine, 5-HT) from its dietary precursor tryptophan by the tumor tissue is allegedly the initiating step of the symptom complex.7-8 Tumors yielding as high as 2.5 mg. of 5-HT per Gm. of tissue have been reported.9 Subsequent metabolism of 5-HT results in the formation of 5-HIAA, which is excreted in the urine. The major chemical alterations in the malignant carcinoid syndrome therefore consist of elevated blood levels of 5-HT10 and greatly elevated levels of urinary 5-HIAA.11

The normal 5-HT in the serum ranges from 0.03 to 0.2 μg. per ml.12 and in the urine from 0.01 to 0.7 μg. per ml.13 The normal 24 hour urinary excretion of 5-HIAA ranges between 2.0 and 10.0 mg.2, 4, 5 In the malignant carcinoid syndrome the serum level of 5-HT has been found to range from 0.2 to 6.5 μg. per ml.12-14 and the urinary 5-HIAA from 60 to 2,000 mg. per 24 hours,8-15

Case Reports

Case 1. A 28 year old white salesman was admitted to Hermann Hospital January 4, 1958, with a long history of emotional disturbances, a 10 year history of diabetes mellitus, and a recent onset of intermittent dizziness, numbness of the left face, arm, and hand, weakness, nausea with emesis,
ataxic gait, and a sensation of "blacking out." He also experienced postprandial nervousness, accompanied by flushing of the face and neck. Three months prior to admission, he had been found hypertensive and given rauwolfa serpentina (Raudixin) 100 mg. twice daily with a subsequent exaggeration of symptoms. This medication had been discontinued after 2 weeks and had not been taken for the 2 months preceding hospitalization.

Physical examination revealed the patient to be 68 inches in height, to weigh 201 pounds, to have a blood pressure of 150/110, and a pulse 84 per minute. The heart was slightly enlarged without murmurs or thrills. The lungs were clear. The liver was not palpably enlarged. The genitalia were normal, and proctoscopic examination was not remarkable.

Laboratory studies revealed the patient to have a normal hemogram, serum cholesterol 504 mg. per cent, protein-bound iodine 5.4 μg. per cent, blood urea nitrogen 9.9 mg. per cent, phenolsulphonphthalein excretion 20 per cent in 15 minutes and 63 per cent in 2 hours, and a diabetic 3 hour glucose tolerance curve. The liver function tests included a cephalin-cholesterol flocculation 1 plus at 48 hours, thymol turbidity 2.6 units, alkaline phosphatase 3.5 Bodansky units, serum glutamic oxaloacetic transaminase 23 units, serum glutamic pyruvic transaminase 32 units, bromsulphalein retention 0 at 45 minutes, albumin 4.3 Gm. per cent, and globulin 2.7 Gm. per cent. The 24-hour urine specimen contained 1.5 μg. epinephrine, 31 μg. norepinephrine, 2.4 mg. 17-hydroxy corticosteroids, and 17.4 mg. 17-ketosteroids. The electroencephalogram revealed a poorly organized and regulated, moderately slow electrogram showing no focal or lateralizing signs. These findings were consistent with a moderate alteration of cerebral function of nonspecific etiology. Roentgenograms of the skull, chest, and upper gastrointestinal tract, small bowel, colon, and vertebral column were normal. The urinary 5-HIAA was reported strongly positive. On the basis of the latter test the patient was subjected to surgical exploration for a suspected malignant carcinoid tumor. At surgery, the contents of the abdomen were without note except for a slight asymmetry of the adrenal glands. The patient subsequently had a bronchosopic examination that was also normal.

Case 2. A 68 year old white male executive was admitted to Hermann Hospital January 3, 1958, because of weakness, nausea, and pain in the right upper quadrant of the abdomen and the right costovertebral angle. He had experienced a perforated duodenal ulcer in 1912, massive upper gastrointestinal hemorrhages in 1943 and 1951, and subtotal gastrectomy in 1956. Postoperatively, there was dehiscence of the duodenal stump with resultant shock; however he recovered under conservative management. Subsequently the patient developed a right upper quadrant pancreatic fistula that opened and closed 3 times prior to the last hospitalization.

Physical examination revealed the patient to be 74 inches tall and to weigh 180 pounds. The blood pressure was 120/80 and the pulse 84 per minute and regular. The patient appeared acutely ill. A draining right upper quadrant fistula was present. The liver was enlarged and palpable 3 to 4 cm. below the right costal margin. Tenderness on percussion was marked in the right upper quadrant. The remainder of the examination was not remarkable.

Laboratory examinations revealed a normal hemogram, corrected erythrocyte sedimentation rate 34 mm. in 1 hour, serum amylase 17 to 30 mg. per cent, serum lipase 1.5 mg. per cent, blood urea nitrogen 21 to 34 mg. per cent, and creatinine 2.6 mg. per cent. The liver function tests revealed cephalin-cholesterol flocculation 1 to 4 plus, thymol turbidity 0.9 to 2.0 units, alkaline phosphatase 10 to 24 Bodansky units, serum bilirubin 0.6 mg. per cent, serum glutamic oxaloacetic transaminase 32 units, prothrombin time 13 seconds with a 12 second control, and bromsulphalein retention of 5.0 per cent at 45 minutes. Roentgenograms of the chest, upper gastrointestinal tract, colon, and vertebral column were within normal limits.

Under observation the liver continued to enlarge, became very nodular, and the patient developed a peculiar type of erythematous flushing of the head and neck associated with paroxysmal episodes of respiratory distress prompting the determination of the urinary 5-HIAA. The laboratory examination by both of the previously mentioned methods was strongly positive for 5-HIAA. The patient deteriorated rapidly and died on March 3, 1958. Postmortem examination revealed a carcinoma of the body and head of the pancreas with metastasis to the liver. No evidence of a carcinoid tumor was found.

Discussion

In this communication the cases of 2 patients manifesting signs and symptoms prompting consideration of the malignant carcinoid syndrome in the differential diagnosis are reported. Both revealed high levels of urinary 5-HIAA determined by the 2 previously mentioned methods. Although extensive studies in these patients included bronchosopic examination and exploratory laparotomy in one and postmortem examination in the other, in neither was a carcinoid tumor found. The colorimetric test for the
detection of 5-HIAA is based on the appearance of a purple color on addition of 1-nitroso-2 naphthol, nitrous acid, and ethylene dichloride to the urine; the intensity of the color is directly proportional to the concentration of the 5-HIAA. Unfortunately, this test is not specific for 5-HIAA but is specific for 5-hydroxyindoles.\(^\text{2-5}\) Therefore, a positive test may be obtained in the presence of all the intermediary compounds of tryptophan metabolism having the 5-hydroxyindole configuration. Urine containing acetyl \(\alpha\)-aminophenol, the end-metabolic product of p-hydroxy-acetanilid, gives a positive test, as does the urine after excessive consumption of bananas.\(^\text{3-4}\) Under these circumstances, a false positive test for the malignant carcinoid syndrome may occur. Neither patient here considered received acetanilid or consumed bananas prior to their urinary tests for 5-HIAA. It is worthy of consideration that 5-hydroxyindoles may exist in elevated amounts in pathologic and physiologic states other than the malignant carcinoid syndrome.

Three cases of the malignant carcinoid syndrome have been reported in which 5-hydroxytryptophan was secreted by the tumor and excreted as such in the urine.\(^\text{16}\)

The only logical explanation for these 2 false positive tests in the absence of a malignant carcinoid must be that 5-hydroxyindoles other than 5-HIAA were present in the urine and resulted in a false positive test for 5-HIAA, or that elevated urinary 5-HIAA is common to conditions other than the malignant carcinoid syndrome. This report is given in the thought that it may prevent unnecessary surgery on the basis of this test, and in the hope of stimulating further investigation regarding the urinary excretion of 5-HIAA.

**Summary**

The cases have been presented of 2 patients, with strongly positive tests for urinary 5-HIAA, in which a malignant carcinoid tumor did not exist. From the observations made here, it would appear that the accepted test for urinary 5-HIAA may not be specific for this compound alone, and the presence of other 5-hydroxyindoles may result in a false positive test. It is also possible that high urinary concentration of 5-HIAA exists in pathologic and physiologic states other than the malignant carcinoid syndrome. The specificity of the commonly used test for urinary 5-HIAA in the malignant carcinoid syndrome needs further investigation.

**SUMMARIO in INTERLINGUA**

Es presentate le casos de 2 patientes con fortemente positive tests urinari pro acido 5-hydroxy-3-indole-acetic in le absencia de omne maligne tumor carciinoide. Super le base del observationes hic reportate, il pare que le currentemente acceptate test pro le presentia de acido 5-hydroxy-3-indole-acetic in le urina non es specific pro ille composito sole que le presentia de altere 5-hydroxy-indoles poter resultar in false positivitate. Il es etiam possibile que alte concentrationes urinari de 5-hydroxy-3-indole-acetic existe in statos pathologic e physiologic altere ille del syndrome de maligne tumor carciinoide. Le specificitate del commonemente usate test pro acido 5-hydroxy-3-indole-acetic in le urina in casos del syndrome de maligne tumor carciinoide require investigaciones additional.

**REFERENCES**


Medical Eponyms

By Robert W. Buck, M.D.

von Graefe’s Sign. This was described by Albrecht v. Graefe (1828-1870) at a meeting of the Berlin Medical Society on March 9, 1864, and was reported in the Deutsche Klinik 16: 158 (April 16) 1864, under the title “Basedow’s Disease” (Über Basedow’sche Krankheit . . .)

“When we cause the healthy person to look up and down, the upper eyelid moves correspondingly. In those suffering with Basedow’s disease, this motion is almost completely abolished or reduced to a minimum; that is, when the cornea is turned downward, the upper eyelid does not follow. This is not a direct result of the exophthalmos, because in the presence of tumors of the orbit or other causes of protrusion, the symptom is frequently absent, although in very marked degrees the motions of the lid are naturally interfered with. On the other hand, it is present in the mildest degrees of exophthalmos in Basedow’s disease . . . It is apparently to be regarded as a peculiar disturbance of the innervation of the muscles of the eyelid.”
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