Urinary Excretion of 5-Hydroxyindole Acetic Acid, A Serotonin Metabolite, in Hypertensive Renal-Vascular Disease.* (22802)

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The recent literature has called attention to the syndrome of metastatic carcinoid, manifested by vascular cutaneous flushing, respiratory distress and chronic diarrhea associated with right sided valvular disease of the heart (1-2). The work of Lembeck(3) and Udenfriend(4,6) has resulted in the demonstration of high concentrations of 5-hydroxytryptamine (5HTA, serotonin) in carcinoid tumors and the detection of the 5HTA metabolite, 5-hydroxyindole acetic acid (5HIAA), in urine(5). Sjoerdsma and Udenfriend(6) in their excellent study of patients with the "carcinoid syndrome" have demonstrated high titers of 5HTA in blood and high concentrations of 5HIAA in urine of such patients.

Several authors(2,10) have called attention to the fibrous tissue proliferation present in many of the patients with long standing "carcinoidosis." They have particularly noted the unusual and extensive distribution about the right heart (fibrous thickening of the endocardium with pulmonic and/or tricuspid stenosis) as well as fibrous tissue proliferation in the pelvis and about the abdominal viscera. In some instances evidence of previous inflammatory lesions was noted as indicated by the microscopic description of new blood vessels and occasional round cell infiltration. Because of the vasomotor disturbances, fibrous tissue proliferation and the apparent role of 5HTA metabolism in patients with the "carcinoid syndrome," it seemed worthwhile to study 5HTA's metabolite, 5HIAA in patients demonstrating the severe arterial lesions, which are found in the acute fibrinoid necrosis of malignant hypertension(7,8).

Methods and materials. Twenty-four hour urine specimens were obtained in all instances mentioned in this report with 10 cc of toluene as a preservative. 5HIAA was determined by the procedure of Udenfriend, Titus and Weissbach(5). Normals were obtained on 15 adults and 2 children. Six patients were classified as malignant hypertension because they demonstrated necrotizing arteriolitis and/or papilledema. One of these (J.S., wt. 16 kg) had received Serpasil, 17.80 mg orally in 48 days after which her initial urinary 5HIAA was determined. She then received 19.9 mg of Serpasil I.M. in 8 days with subsequent 5HIAA determinations. Also included are 2 patients presenting the late phase of chronic glomerular nephritis and 2 patients on whom 5HIAA exertion was determined after removal of early carcinoid tumors of the intestinal tract. There has been no reference in the literature concerning the effect of proteinuria on the determination of 5HIAA. The following experiment was performed to rule out the possibility that protein might interfere, since all our patients with hypertension and diminished excretion of 5HIAA had proteinuria. Aliquots of urine from patients with proteinuria (5 to 10 g/day) were analyzed and mixtures were made with known normal urines.

The *results* are summarized in Table I. The average daily excretion of 5HIAA in normal adults was 4.4 mg (ranges 2.3 to 6.3) and for 2 normal children 2.7 and 3.4 mg. Low levels (less than 2.) were found in 3 patients with malignant hypertension and 2 patients with advanced changes of chronic glomerular nephritis. One patient (E.P.) with a markedly elevated blood urea nitrogen (81 mg %) had urinary 5HIAA levels in the normal range. Sjoerdsma(9) and his group call attention to low values in patients with collagen vascular disease (lupus erythematous disseminatus). No mention is made of renal involvement in these patients. Conceivably the low values were in patients with renal vascular involvement. Moreover these investigators confined their description of "low val-

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TABLE I. Urinary Excretion of 5-Hydroxyindole Acetic Acid.

Diagnosis		Comment	No. of patients	Age	Bun. at time of analysis (mg %)	Avg 24 hr urine vol (cc)	Urinary excretion (mg/24 hr)
Normal subjects	Adults		15	18 to 56		1410	2.3 to 6.3, avg 4.4
	Children		2	11		1140	2.7, 3.4
Malignant hypertension	C.L.	Papilledema; autopsy; necrotizing arteriolitis in kidney	1	53	27	1120	1.08
	E.P.	Papilledema	1	40	81	2800	5.4
	E.S.	Papilledema; autopsy; necrotizing arteriolitis of kidney with minimal fibrosis and lymphocytic infiltration	1	29	48	900	2.5
	J.D.	Papilledema; renal biopsy, chronic pyelonephritis with severe arteriolar sclerosis	1	38	38	785	4.8
	G.R.	Papilledema; autopsy, severe arteriolar sclerosis with no inflammatory reaction	1	37	108	200	0.5
	J.S.	Papilledema; autopsy, chronic pyelonephritis with necrotizing arteriolitis	1	7	104	653	1.5 after 17.8 mg Serpasil
					72	797	1.7 } after 1.9 mg
					104	715	0.96 } Serpasil I.M.
Chronic glomerular nephritis	M.S.		1	16	94	1970	1.6
					100	1455	1.9
	W.H.		1	5	88	410	1.4
					20	800	1.2
Carcinoid	E.C.		1	59			2.4, 2.8, 4.0
	S.W.		1	27			3.2

ues" to patients with "collagen vascular disease," while disregarding normal to high levels in such allied collagen disorders as rheumatic fever, rheumatic heart disease and scleroderma (ranges 5.1 to 7.1 mg). Further recording of 5HIAA excretion in patients with proliferative arterial lesions with and without renal involvement will be necessary before any concrete conclusion may be drawn. It must be noted that proteinuric renal disease itself might possibly lead to diminished 5HIAA excretion, although the proteinuria *per se* does not interfere with the determination as indicated by an 82 to 100% recovery of 5HIAA in mixtures of normal urine and the urine from patients with proteinuria.

The reported low values(9) in several cases of malignant disease might also be attributable to concurrent vascular renal disease.

The low excretion of 5HIAA in patients with hypertension might be due either to a poor amine oxidase activity of the diseased kidney, or, more possibly to a retention of serotonin in the blood. These possibilities are presently under investigation in our laboratory.

The 2 patients with early carcinoid tumors excreted normal amounts of 5HIAA, analysis being performed 2-3 weeks after removal of the tumors. Patient S.W. had a small (.5 cm diameter) rectal polyp removed which on microscopic examination revealed a well circumscribed carcinoid tumor. Patient E.C. presented with acute intestinal obstruction, relieved by resection of 45 cm of ileum containing a carcinoid tumor (5 x 6 cm) with metastasis to the accompanying regional lymph nodes. No liver involvement was noted and there were no associated cardio-vascular abnormalities other than fluctuating blood

pressure of 190/110 to 160/100, soft aortic systolic murmur, and electrocardiographic changes suggesting diffuse non-specific myocardial disturbance.

Summary. The urinary excretion of 5-hydroxyindole acetic acid in patients with malignant hypertension and chronic glomerular nephritis is reported. Low levels were recorded for 3 patients exhibiting the malignant phase of hypertensive cardiovascular disease and in each patient with chronic glomerular nephritis. All patients exhibited extensive renal involvement and 5 of the 6 patients with malignant hypertension had severe arterial lesions. The 2 patients on whom determinations were made after removal of early carcinoid tumors did not show abnormal urinary 5-hydroxyindole acetic acid levels. Recovery studies show that proteinuria does not interfere with the determination of 5HIAA in the urine.

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Distribution of C^{14}-Labeled Aminoacetonitrile in Tissues of Rat, Metabolism and Mode of Elimination.* (22803)

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Several recent studies(1,2,3) have dealt with the effects of aminonitriles on rats. The remarkable ability of these substances to produce the characteristic skeletal lesions of lathyrism in young animals suggests the investigation of the metabolism of the aminonitriles, with the aid of the isotopic labeling technic. Very recently isotopically-labeled β-amino-proprionitrile has been reported synthesized and a study of its metabolism begun (4). For the present work, aminoacetonitrile (AAN) labeled with C^{14} in its cyanide group was employed. It has been previously established(1) that this compound resembles closely in its action, but is more potent than the higher homolog, β-aminoproprionitrile, or β-(γ-L-glutamylamino)-proprionitrile, the active principle of Lathyrus peas. Besides determining the distribution of the radioactivity in the animal organism and the modes of elimination, experiments were designed to explore the possible incorporation of the cyanide carbon atom into major body constituents, including protein, lipid, and carbohydrate. One possible route would be via hydrolysis of the cyanide radical to yield a carboxyl group, *i.e.* the transformation of AAN into glycine.

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Methods. Synthesis of $(H_2N\text{-}CH_2C^{14}N)_2 H_2SO_4$. The following modification was employed of the method given in Organic Syntheses(5): A solution of NaCN (1 g, 20 mM, containing 1 millicurie of C^{14}) in 1.7 ml water was added slowly to a mixture of 1.1 g of NH_4Cl (20 mM) and 3 ml of 37% formaldehyde (40 mM). When half the NaCN had been