MALIGNANT CARCINOID
a new metabolic disorder

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by

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MALIGNANT CARCINOID

A NEW METABOLIC DISORDER

The clinical syndrome of malignant carcinoid of the small intestine with metastases to the liver has been described recently (1). It is manifest principally by peculiar cutaneous flushes and cyanosis, chronic diarrhea, respiratory distress, and valvular disease of the right heart. Suggestions concerning a mechanism whereby these manifestations are produced, are speculative.

Thorson et al. (1) were the first to suggest that the syndrome might be due to the production and release of serotonin (5–hydroxytryptamine) by the tumor. Erspamer (2) believes that serotonin is produced by the chromaffin cells of the intestinal tract. Since carcinoid tumors are derived from these cells, it is logical to assume that such tumors would be rich in serotonin. Lembeck (3) actually analyzed carcinoid tumor and found this to be true. The postulate of Thorson et al. (1) is further strengthened by the fact that serotonin has potent pharmacologic effects on the smooth muscle of blood vessels, bronchi, and intestine (2).

Previous studies (4) in the laboratories of the National Heart Institute have shown that serotonin is derived from the essential amino acid, tryptophan, and that the end product of this metabolic process is 5–hydroxyindoleacetic acid (5–HIAA). Five–HIAA is excreted in the urine and can thus serve as a quantitative index of this route of metabolism.

Recently, four patients with the "carcinoid syndrome" have been studied in the Clinical Center of the National Institutes of Health. Urine samples were obtained from two additional cases, as well as a specimen of tumor from one of these cases. The following is a summary of pertinent clinical and laboratory findings in these six patients.

CLINICAL MANIFESTATIONS

1. Essentially all the clinical manifestations reported by Thorson et al. (1) were observed. Cutaneous vasomotor phenomena and chronic diarrhea were present most consistently. "Asthma" and valvular heart lesions (pulmonic stenosis and tricuspid insufficiency) were present in half the cases.

2. Hypertension was not observed in any of the cases; in contrast, significant hypotension was observed during severe flushes.

3. Flushes could be induced in two cases by manual manipulation of the tumor.

4. Arthritic symptoms were noted in four cases, suggesting the possibility of a generalized connective tissue disorder.

5. Patients with malignant carcinoid live much longer than patients with other metastatic neoplasms.

CHEMICAL FINDINGS

1. Blood levels of serotonin were many times greater in carcinoid patients than in noncarcinoid individuals (see table, page 3).

2. Five–HIAA, a normal urinary metabolite of serotonin, was markedly increased in all the patients with malignant carcinoid (see table, page 3). A simple chemical test for 5–HIAA in urine has been devised and permits prompt diagnosis of this condition (see test, pages 3, 4).

3. Study of a carcinoid tumor revealed a high content of serotonin (0.8 mgm./gm.), and enzymes required for the formation and oxidation of this substance were found also to be present.

4. The precursor relationship of tryptophan to 5–HIAA and hence to serotonin was shown by a metabolic balance study and tracer studies using C^{14}–labelled tryptophan.

5. In normal individuals, approximately 1 percent of the daily tryptophan intake is utilized in the "serotonin pathway." In carcinoid patients, as much as 60 percent of the intake may be diverted by the tumor into this pathway leaving less of the amino acid available for the formation of niacin and protein (see figure, page 4).

Conclusion

Studies to date suggest that the manifestations of the "carcinoid syndrome" are due to an excess production of serotonin by the tumor and concomitant deficiency of tryptophan and its other metabolites.

Five–Hydroxyindole Compounds in Blood and Urine

	Blood Serotonin μgm./ml.	Urine 5–HIAA mgm./24 hr.
NORMALS[1]	0.1–0.3	2–9
CARCINOID I.	2.5	320–392
II.	0.5–1.5	240–280
III.	1.2–1.9	380–580
IV.	1.7–2.7	214–572
V.	----------	140
VI.	----------	76

[1] The range of values on about 40 noncarcinoid individuals.

A Simple Test for Malignant Carcinoid

This test is a simplification of the quantitative assay (5) for 5–hydroxyindoleacetic acid (5–HIAA) based on the development of a purple color specific for 5–hydroxyindoles on the addition of 1–nitroso–2–naphthol and nitrous acid.

Reagents

1–nitroso–2–naphthol—0.1 percent in 95 percent ethanol.

Nitrous acid—Prepare fresh by adding 0.2 ml. 2.5 percent $NaNO_2$ to 5 ml. 2N H_2SO_4.

Ethylene dichloride.

Procedure

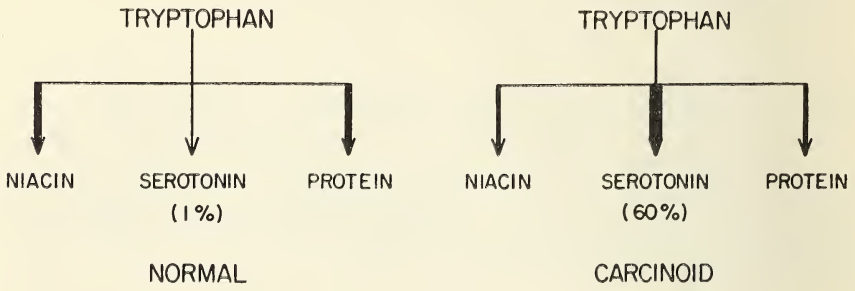
Run a normal urine for comparison.

Pipette into test tube:

0.2 ml. urine.
0.8 ml. water.
0.5 ml. 1–nitroso–2–naphthol. Mix.
0.5 ml. nitrous acid. Mix.

Let stand at room temperature for 10 minutes. Then shake with 5 ml. ethylene dichloride. If turbidity results, the tube should be centrifuged.

Interpretation: A positive test is indicated by a purple color in the top layer. No purple color will be seen with normal urine, though a slight yellow may be noticed. Assuming an average 24-hour urine volume of 1,000 ml., a purple color will be seen at levels of 5–HIAA excretion as low as 40 mgm. per 24 hours. At higher levels the color is more intense and is almost black at levels above 300 mgm. per 24 hours. Another substance, p–hydroxyacetanilid, reacts similarly but is found in urine only after administration of acetanilid or related drugs. The color formation may be inhibited in conditions resulting in the excretion of huge amounts of keto acids.



Comparison of tryptophan metabolism in normals and patients with malignant carcinoid.

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