Diagnosis and Pathology of Carcinoidosis

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During the last 3-4 years the clinical picture characteristic of malignant argentaffinoma (carcinoidosis) has been worked out in Sweden and Switzerland. It was found that a peculiar type of flushing, either as a chronic cyanosis of the face somewhat resembling poly-cythemia, or combined with characteristic changing erythema on trunks and limbs was an important symptom. Combined with these attacks there was found hyperperistalsis with borborygmy, colics and diarrhoea and sometimes asthma. When the attacks had lasted for a long time there developed signs of pulmonary stenosis. The disease was often long drawn out (10-15 years). Post-mortem revealed the presence of carcinoid tumours in abdominal lymph glands and in the liver. The cardiac changes were usually quite peculiar, with shrinking of valves and chordae and sometimes also marked thickening of the endocardium on the right side of the heart. In some patients with the whole syndrome, Pernow and Waldenström demonstrated increased amounts of serotonin (5-hydroxy-tryptamine = 5-HT) in blood and urine. It was assumed that this substance was responsible for the changing picture and also the cardiac symptoms.

After these first publications we have been in a position to examine a large number of cases and samples of blood and urine from many more suspected or established instances of carcinoidosis. Our experience from Sweden is founded upon observations from more than 30 cases. Udenfriend and his group showed that 5-hydroxyindole-acetic acid (5-HIAA), a metabolite of 5-HT, was excreted in the urine of such a patient and pointed out that the presence of this substance in the urine might have considerable diagnostic importance. A Swedish group consisting of Hansson, Pernow, Thorson and the speaker have followed the excretion of 5-HIAA in the urine in a large number of cases and also in several patients daily for longer periods. It was found that the diagnostic importance is very great indeed and a

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number of patients have received a correct diagnosis this way. Positive evidence seems to be diagnostic but negative evidence may occur even in clearcut carcinoidosis. In two cases histamine in great quantities was found in the urine, a fact which seems to be of great physiological importance.

Proof that 5-HT is the direct cause of the vasomotor abdominal and cardiac symptoms has not been easy to furnish. Recent experiments by Roddick with intra-arterial injections of 5-HT have demonstrated that a flush is started similar to the flush in carcinoidosis. During the last weeks we have also been able to observe one patient in whom the chronic facial cyanosis completely disappeared after the extirpation of a huge teratoma containing large amounts of carcinoid tissue. No metastases were found. After the operation the excretion of 5-HIAA in the urine which had

previously been constantly elevated, came down to normal values. It therefore seems probable that 5-HT is the real cause of the symptoms.

The connection between 5-HT and valvular heart disease is a more difficult question. We have seen one patient, however, who suffered initially from flushes and had a high 5-HT content in the blood. After two years we could find no definite signs of pulmonary stenosis either clinically or on the roentgen picture. The postmortem revealed typical pulmonary stenosis.

To my mind it therefore seems highly probable that the characteristic clinical picture in widespread carcinoidosis is completely explained by the hyperserotoninemia. This malady should therefore be grouped together with insuloma and phaeochromocytoma as instances of endocrinologically active tumours.

One aspect of the disease might be purely metabolic however. Udenfrend has pointed out that both niacin and hydroxytryptamine are derived from the tryptophan pool. If 5-HT synthesis, as in carcinoidosis, is increased 50 or 70 times or perhaps more, niacin synthesis suffers and pellagra develops. Our last patient showed pellagrous changes in her skin that improved markedly on niacin treatment. After extirpation of the tumour there was further normalization and her plasma albumin also increased. This is so far a unique instance of a neoplastic condition, where the metabolism of the tumour cells leads to depletion of the body as regards essential metabolites. The importance of this condition for the understanding of tumour cachexia in general is evident.