ARGENTAFFIN CARCINOMA ASSOCIATED WITH THE CARCINOID SYNDROME

JOHN B. PACE
B.PHARM., M.D., F.R.C.S.

and

ANTHONY P. JACCARINI
B.SC., B.PHARM., M.D., M.A. (OXON.),
B.SC. (LOND.), PH.D. (LOND.), A.R.I.C.

Departments of Surgery and of Chemistry,
Royal University of Malta

Argentaffin carcinomata or carcinoid tumours (Oberndofer, 1907) are not common neoplasms. The carcinoid syndrome (Thorson *et al.*, 1954), in which the systemic effects of excessive serotonin secretion by the tumour are demonstrable, is even rarer and occurs in 6% of all such tumours (Moertel *et al*, 1961).

Case report

A male labourer 42 years old was admitted to St. Luke's Hospital on 5th July, 1962. He gave a 5-year history of recurrent episodes of central abdominal colic, borborygmi and vomiting, without alteration of bowel habit. During the month prior to admission, these attacks had become worse and were accompanied by anorexia and loss of weight.

On examination, there were classical signs of intestinal obstruction, namely, abdominal distension, a "ladder pattern", visible peristalsis and augmented bowel sounds. No masses were palpable and the liver was not enlarged. The rectum was empty. A plain X-ray of the abdomen suggested small-bowel obstruction.

Laparatomy, on 6th July, 1962, revealed an annular neoplastic constriction, 2.5 cm. long, at the distal part of the jejunum causing almost complete obstruction. A 23 cm. length of small intestine, including the growth, was resected and bowel continuity was restored by end-to-end anastomosis.

Histological examination of the specimen showed an argentaffin carcinoma of the jejunum infiltrating through the muscle layers to the external tissues. The carcinoma consisted of well-defined solid clumps and strands of small closely-packed, polyhedral cells containing silver-stainable granules *(Fig. 1)*. No metastases were demonstrable in the mesenteric lymph nodes submitted for section.

The patient's recovery from the operation was uneventful and he was discharged from hospital on 7th August, 1962. When reviewed as an outpatient on 12th

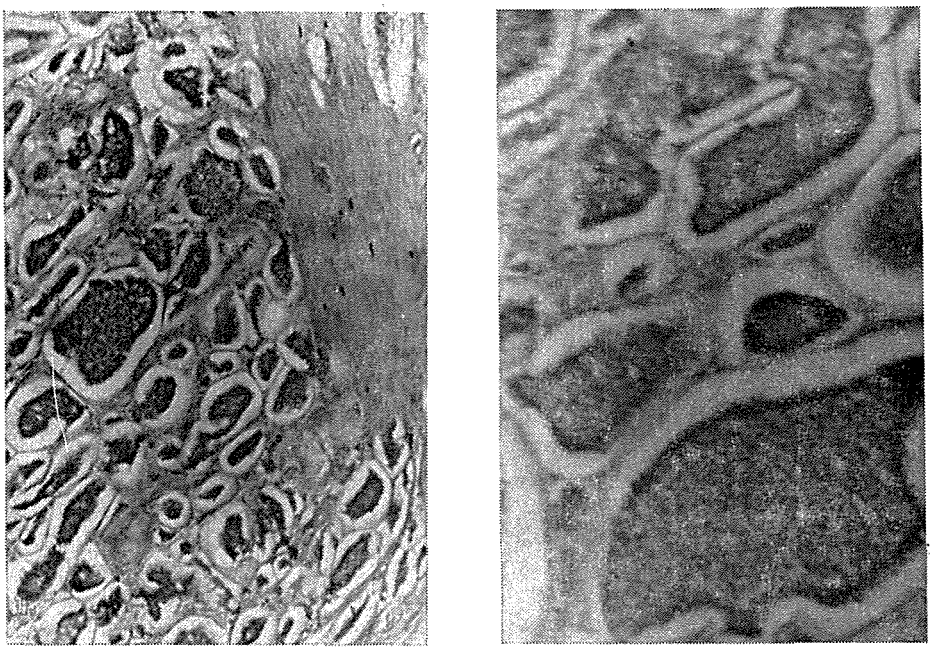

Fig. 1
Carcinoma of jejunum infiltrating muscle layers.

November, 1962, he was well and free from any evidence of recurrence or metastases. Thereafter he was lost to follow-up care for a period of 5 years.

He was re-admitted to hospital on 30th October, 1967, with a 7-month history of persistent watery diarrhoea and intermittent generalised abdominal pain radiating to the chest, accompanied by anorexia and loss of weight. He admitted to no symptoms between August 1962 and March 1967.

On admission, the patient was thin but did not look ill. His temperature was normal and his B.P. was 130/85 mm. Hg. The relevant physical signs were: a plethoric complexion, a regular tachycardia of 96/minute with occasional extrasystoles; a soft systolic murmur over the pulmonary area; and a hard, nodular enlargement of the liver to 3 inches below the right costal margin. The old right paramedian laparatomy scar was obvious; rectal examination was negative.

A provisional diagnosis of hepatic metastases from intestinal Carcinoid tumour was made. Haemoglobin was 11.1 gm/100 ml on 2. 12. 67, and gradually decreased to 9.0 gm/100 ml by 4. 4. 68, the stained films showing a normocytic hypochromic anaemia.

The W.B.C. count varied between 9,500/c.mm and 12,000/c.mm. Serum Agglutination tests against *Salm. typhi* were negative, and the faeces were found not to contain pathogens or abnormal constituents. Urinalysis (31. 10. 67) revealed a mild albuminuria but no associated abnormalities; the blood urea (15. 3. 68) was 43 mg./100 ml.

Serum protein electrophoresis gave a non-specific pattern, namely, an appreciable reduction in albumin with some absolute reduction in α^1-globulin and some increase in α^2-globulin, while the other fractions were within normal limits.

On 1st December, 1967, the 5HIAA urinary excretion was 286 mg/24 hours; serotonin and O-sulphate of 5HIAA were also detectable on urinary chromatograms. On 25th March, 1968, the 5HIAA excretion was 148 mg/24 hrs. and the serotonin and O-sulphate spots gave denser colours with Ehrlich's reagent; 5-hydroxytryptophan was also identified. Urinary histamine was 88 μg/24 hrs. and blood serotonin was 1.4 μg/ml.

Radiographic examination including

barium meal and "follow-through" examination, barium enema, and X-ray of the chest and the spine were not helpful. The only positive findings in these were a raised left dome of the diaphragm and osteoathritic changes in the spine.

Three weeks after admission the patient developed a severe burning pain in the anal region after defaecation. A rectal examination on 3rd December revealed a markedly tender, hard, craggy mass infiltrating the anterior rectal wall. This mass was observed to increase steadily in size, the patient's anorectal pain becoming more severe, with tenesmus setting in to add to his distress. The diarrhoea was gradually replaced by a tendency to constipation, with occasional rectal bleeding. The anorectal symptoms were not relieved by prednisone suppositories and local analgesics; they were slightly improved by Codeine compound tablets, B.P.; but their severity occasionally necessitated the use of pethidine.

On March 14th, 1968, a palliative colostomy was established in an attempt to relieve the severe rectal symptoms and to circumvent threatening intestinal obstruction. At operation the pelvic cavity was found "frozen" with massive growth and two litres of bile-stained ascitic fluid were removed.

During his 6-month stay in hospital, the patient's pulse rate varied between 80 and 120 per minute, and his temperature was usually normal. He was observed to develop attacks of facial flushing; during these episodes, each of which lasted a few minutes and apparently did not produce any subjective sensations, the patient's face and neck took on a dusky red colour. As the disease progressed, the facial discolouration became permanent and assumed a darker, slightly cyanotic, hue. These phenomena were not influenced by such drugs as cypro-heptadine hydrochloride ("Periactin"), chlorpromazine ('Largactil") or propantheline bromide ("Pro-Banthine").

The soft pulmonary systolic murmur noted on admission became clearer and louder during the first 3 months, and eventually assumed a harsh quality. During January, 1968, progressive jugular vein enlargement, lower limb oedema and ascites developed. The oedema responded only partially to diuretics and postural drainage, and gradually spread to the thighs and lower abdominal wall.

Dyspnoea occurred for the first time on 2nd May, 1968: it was associated with clinical signs of broncho-spasm. During the following 12 days, "asthma-like" attacks recurred with increasing frequency, severity and duration. The patient died on 14th March, 1968 after one of these respiratory crises, which failed to respond to bronchodilators and diuretics.

Comment

The typically slow growth of carcinoid tumours is shown in this case by the 10-year survival of the patient after the onset of sypmtoms. When resected, the small jejunal tumour had been causing symptoms for 5 years and had not yet overtly metastasised.

It has been shown that carcinoid of the small bowel is multiple in 50%, and already disseminated in 40%, of those cases coming to operation (Dockerty and Ashburn, 1943; Pearson and Fitzgerald, 1949; and Bowers and Cheek, 1952). It was impossible, in our case, to ascertain whether the hepatic and pelvic tumours were metastases from the jejunal primary tumour resected 5 years previously, or whether they were the result of one or more independent growths.

Tumours of the enterochromaffin or argentaffin cells are characterised by an increased production and metabolism of serotonin or 5-hydroxltryptamine (5-HT). Tryptophan *(Figure 2)* is initially hydroxylated to 5-Hydroxytryptophan (5-HTP) which is in turn decarboxylated to serotonin. The latter, under the influence of mono-amine oxidase (MAO — chiefly in the liver), is oxidised via the aldehyde to 5-hydroxindole-3-acetic acid (5-H.I.A.A.). 5-HIAA is the principal metabolite of serotonin and it is eliminated in the urine as such or as its phenolic sulphate ester.

It appears that in carcinoid patients with extensive liver metastases, MAO cannot cope with the increased production

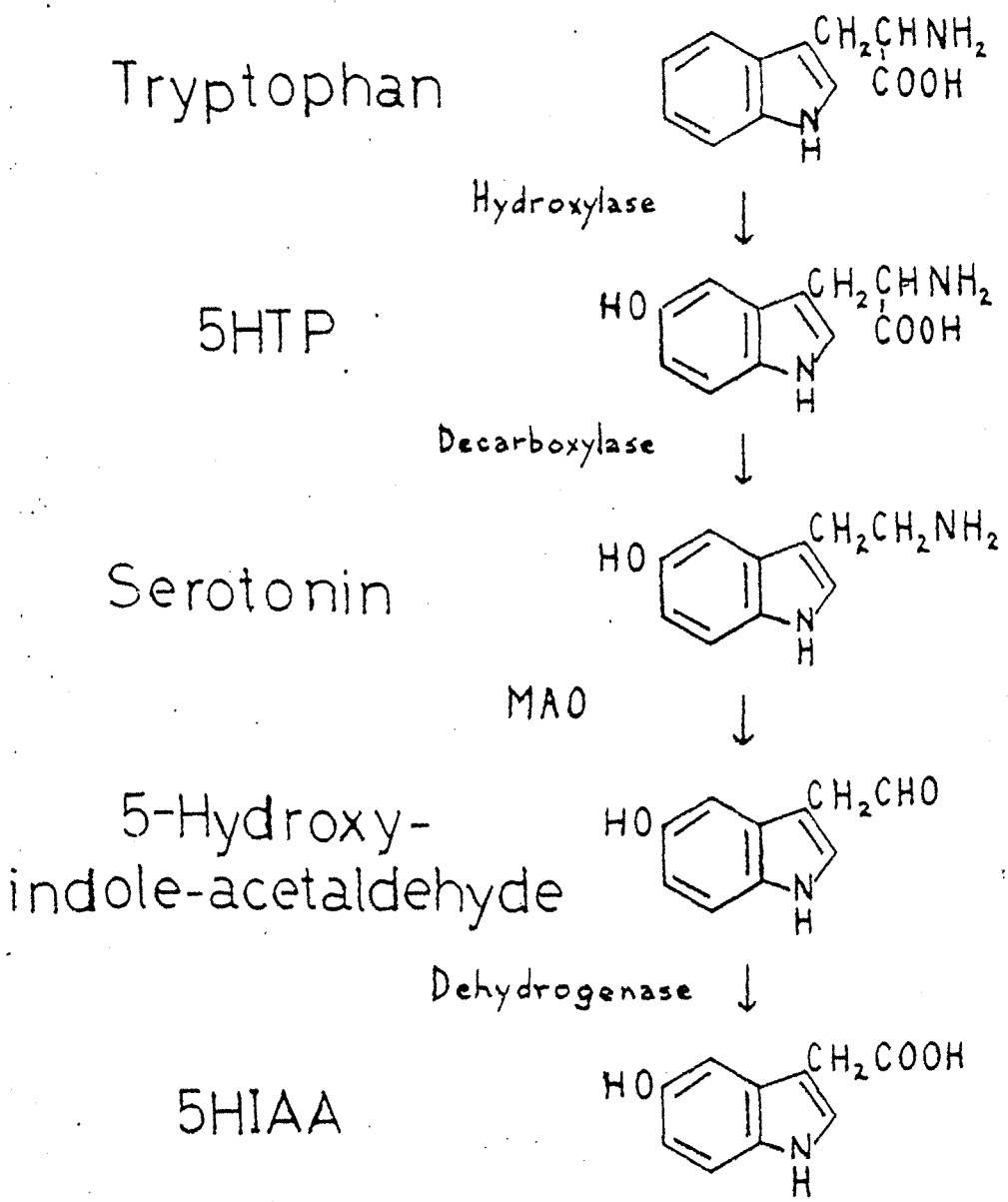

Fig. 2

Serotonin metabolic pathway

of serotonin and, in a third of such cases (Maertel *et al.*, 1961), the resulting high level of serotonin in the systemic circulation is responsible for the carcinoid syndrome. Against this is the evidence that patients on MAO inhibitors can still metabolise injected 5-hydroxytryptamine by a mechanism alternative to MAO. It would thus be reasonable to assume that this alternative and unknown mechanism fails to operate in carcinoidosis.

In the case reported here, the systemic effects became established only after definite clinical hepatic involvement. Indeed, two main phases of the disease could be distinguished: a period with an exclusively abdominal sypmtomatology and a later stage with the syndrome. The main clinical features of the latter (Snow, 1963) were demonstrable in this case, namely: (1) the facial flush, (2) the watery diarrhoea, (3) the abdominal colic, (4) the episodic bronchospasms, (5) the right sided heart lesion, and (6) the oedema.

The facial flushes were not associated, as is usual, with any subjective phenomena. Though serotonin releases histamine (Feldberg and Smith, 1953) attempts to correlate the occurrences of the "flush" with histamine levels have failed. Cases have been reported with increased urinary histamine (Oates and Spoerdsma, 1962; and Perrow and Waldenstrom, 1957). The level of the urinary histamine in the case reported here was in the higher range of normal. The watery diarrhoea persisted to the end, but the abdominal colic was overshadowed by the severe anorectal symptoms caused by the pelvic mass.

The advancing severity of the pulmonary stenosis could be followed clinically by the changing quality of the murmur and the evolution of the picture of right-sided heart failure. The oedema and ascites were part of this picture, but the antidiuretic effect of serotonin coupled, in later stages, with the osmotic changes due to hypoproteinaemia, probably also contributed to their persistence. On the other hand, the lower limb oedema was, no doubt, partly the result of venous compression by the tumour mass; and the ascites could be accounted for by the sheer

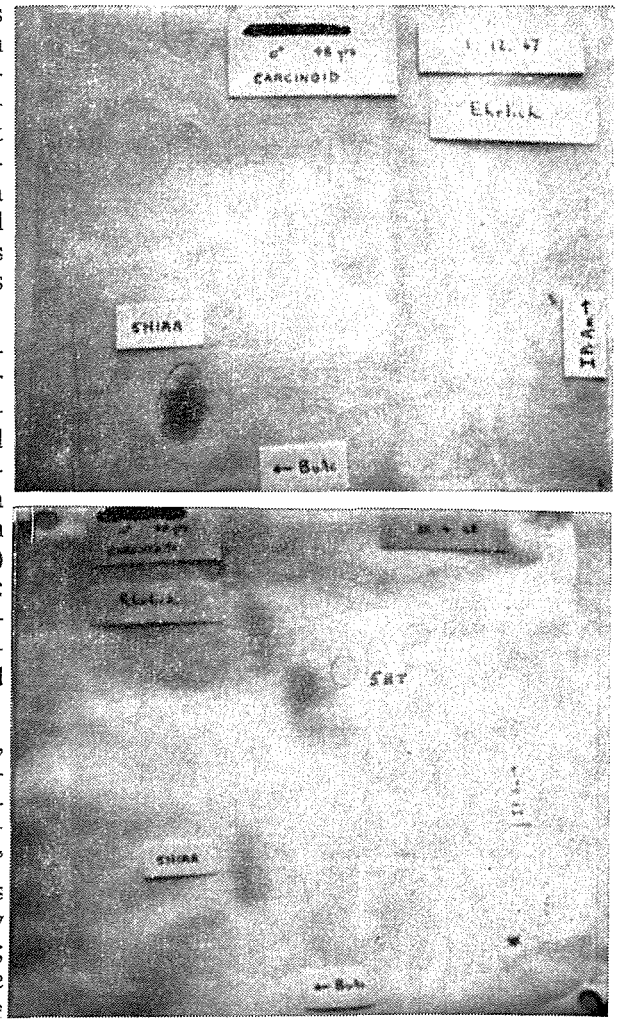

Fig. 3
Urinary indole paper chromatograms

presence of widespread intraperitoneal malignancy.

The figures for urinary 5-HIAA indicate that the production of serotonin was subject to fluctuation although high levels were maintained throughout. Moreover, the accentuation of the serotonin spot in later urinary indolic chromatograms *(Fig. 3)* might be accounted for by the swamping of MAO sites (especially in the liver) by tumour tissue as the disease progressed. However, mono-amino oxidases are widespread mitochondrial enzymes and it would not be unreasonable to postulate the endogenous production of some MAO inhibitor in the later stages of the disease.

The periodic estimation of urinary

5-HIAA excretion would seem to be a sensible procedure in the follow-up of patients who have had a primary carcinoid tumour resected. The test may not be sensitive enough to detect small quantities of metabolites secreted by small tumours (residual, metastatic or new primary); but the finding of a rising 5-HIAA excretion in consecutive tests carried out at reasonable intervals (say, every 3 months) would be significant, and should lead to the search, localisation and, where feasible, extirpation of the tumour. The more frequent use of the 5-HIAA excretion test in cases of obscure abdominal colic or bizarre pulmonary symptoms is bound to lead to the earlier diagnosis and more effective treatment of carcinoid tumours.

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