MALIGNANT ARGENTAFFINOMA AND THE CARCINOID SYNDROME

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The term 'carcinoid syndrome' has been suggested to describe those cases where metastasizing argentaffinoma gives rise to systemic manifestations.[24] These consist of vasomotor disturbances (flushing and a peculiar cyanosis), increased bowel motility (diarrhoea and borborygmi), bronchial constriction ('asthma'), cardiac disturbances (pulmonary stenosis and tricuspid stenosis and incompetence, leading to heart failure[24]) and, less frequently, pellagra. Although isolated cases had been reported,[3,9,30] they were regarded as medical curiosities or as pulmonary stenosis with unusual features,[2,11] until Isler and Hedinger[16] recognized that the combination of right-sided cardiac lesions and metastasizing carcinoid tumours constituted a definite syndrome. In 1954 Thorson *et al.* collected all previously reported cases and added 5 of their own; they suggested that 5-hydroxytryptamine (5-HT, serotonin, enteramine) produced the systemic effects.[26] This was strongly supported by the isolation of 5-HT from an argentaffinoma,[22] and the concept has won general acceptance.[35]

Until the end of 1956, 57 cases had appeared in the literature;[24] 34 of these had endocardial lesions. Although the syndrome is uncommon, it is not as rare as has been thought, especially if incomplete cases are recognized. We have been able to collect 10 cases of malignant carcinoid from the records of this hospital since 1952, as well as one seen privately in 1942. Five had features of the carcinoid syndrome; the remaining patients showed evidence of malignancy, viz. local invasiveness or frank metastases, but none of the systemic components of the syndrome were present. As several patients had been studied before the recognition of the syndrome, their notes were not necessarily complete on this score.

Although carcinoids are most frequently found in the appendix, metastases from that site are rare,[24] and we are confining our report to extra-appendiceal cases. The next commonest site is the ileum, but the tumours may occur anywhere in the gastro-intestinal tract. In 3 cases bronchial adenomas of 'carcinoid type'[23] have been incriminated as sources of functioning metastases.[13] An argentaffinoma has even developed in an ovarian teratoma.[20] The sites in our cases are listed in Table II.

Carcinoid tumours are also known as argentaffinomas because of their staining affinity for silver but, as in several of our cases, this is not always well developed.[40] We have also encountered fibrosis around secondary deposits (as in case 1, and possibly in case 7), a feature that has previously been recognized.[5] Stimulation of fibrosis by 5-HT may explain the right-sided endocardial scarring sometimes found; oxidation in the lung to 5-hydroxy-indole-acetic acid (5-HIAA), which is physiologically inactive, explains the absence of left-sided lesions. None of our cases had valvular involvement; it would appear that cardiac manifestations occur relatively late in the disease.[33]

Since metastases appear to be an integral part of the syndrome, the ultimate prognosis is invariably poor. On the other hand the tumour and its metastases often grow very slowly and cases are recorded where more than 30 years elapsed between the appearance of gastro-intestinal symptoms and the establishment of the diagnosis.[11,30] Early diagnosis is of more than academic interest since we have evidence that radiotherapy has produced regression of metastases and remission of symptoms. The systemic effects can be very distressing, so that palliative measures become important and may in fact prolong life by delaying the appearance of cardiac lesions. From the literature we gather that the expectation of life is only about 2 years after the development of cardiac failure.

Our cases presented clinically in 3 main groups:

(*a*) With manifestations of the syndrome (cases 1 and 2);

(*b*) Because of ileal obstruction (cases 3-5);

(*c*) Accidental discovery of the tumour (cases 6-11).

Selected features are listed in Table I.

CASE REPORTS

Case 1

A 49-year-old European female was admitted on 23 March 1957 complaining of flushes, diarrhoea and nocturnal wheezing of 3 months' duration. The flushes occurred daily; the face and neck became hot and red for a few minutes; this was succeeded by a reddish-blue colour which lasted several hours. Latterly her face had developed a constantly high colour. The diarrhoea was painless and watery.

She had a reddish-blue complexion and looked well. The blood pressure was 170/100 mm. Hg. The cardiovascular, respiratory and nervous systems and the urine were normal. The liver was enlarged to 6 cm. below the right costal margin and was firm, nodular and slightly tender. Rectal examination was negative. There was a red, warm nodule 2 cm. in diameter in the skin of the right shoulder. Blood indices: Hb. 15·5 g.% ESR 10 mm. in the first hour (Westergren), WBC 8,000 per c.mm., smear and differential count normal.

Sigmoidoscopy, barium meal and barium enema were negative. An X-ray of the chest showed a nodular mass in the left parahilar region (Fig. 1); the heart and right lung were normal. Serum analyses: Albumin 5·4 g.%, globulin 3·6; van den Bergh reaction negative, bilirubin 0·5 mg.%; thymol turbidity 1, zinc turbidity 10; alkaline phosphatase 9·8 Bodansky-Shinowara units; prothrombin index 100. Urinary 5-HIAA: Ehrlich's aldehyde screening test negative; 201 μg. per ml., 156 mg. per g. of creatinine. Liver biopsy showed tumour tissue that took up Masson's silver stain equivocally, but had the features of carcinoid, with a papillary structure. The shoulder nodule showed similar features, with extensive surrounding fibrosis (Dr. A. H. Timme). Bronchoscopy was not permitted.

Cardiac catheterization (Dr. L. Vogelpoel and Dr. V. Schrire) showed a normal pulmonary resistance, normal pressures, no gradient between pulmonary artery and right ventricle, and a cardiac output of 5·7 l. per minute. A typical flush occurred when the catheter entered the hepatic vein. Other flushes could not be induced in hospital, in spite of manual compression of the liver, 3 oz. of brandy by mouth, intravenous histamine acid phosphate (0·02 mg.) and noradrenaline (4 μg)., enemas and a saline purge.

Little symptomatic relief was obtained from antispasmodics, kaolin and chlorpromazine. A 12-day course of deep X-ray therapy to the pulmonary deposit was given in June 1957 (tumour dose: 2,250 r.), with neither symptomatic nor radiographic response. In July a tumour dose of 2,700 r. to the whole of the liver mass over a 4-week period gave prompt relief: the diarrhoea and bronchospasm stopped and her complexion became normal. The liver did not shrink but lost its tenderness. Improvement

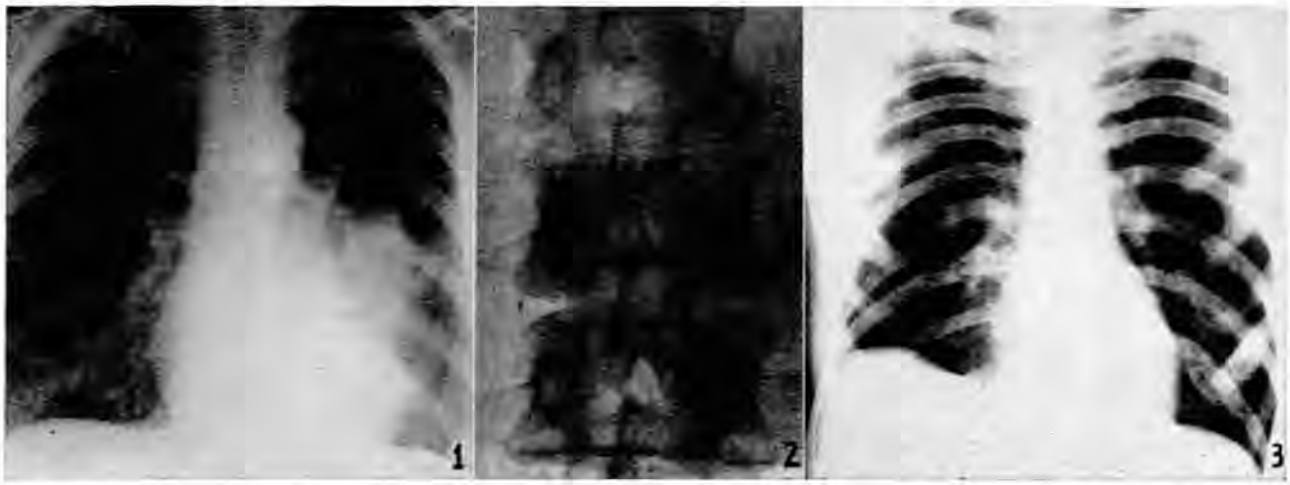

Fig. 1. Left para-hilar mass (case 1). *Fig.* 2. Osteosclerotic deposit, 2nd right lumbar pedicle (case 1). *Fig.* 3. Multiple deposits in the ribs (case 7).

has been maintained for 6 months at the time of writing, but there has been progressive osteosclerosis of the 2nd right lumbar pedicle (Fig. 2).

Comment. The syndrome was readily diagnosed on the basis of the clinical features, only pulmonary stenosis being lacking, and biochemical and histological confirmation was obtained. While the site of the primary has not been confirmed by bronchoscopy, it is probably a bronchial adenoma; the papillary structure of the hepatic metastasis favours a bronchial or rectal origin. However, an occult ileal primary with an unusual metastasis to the lung cannot be excluded. The presence of systemic metastases in the skin and spine is unusual. The cutaneous deposit looked 'flushed' and was surrounded, histologically, by considerable fibrosis, indicating that it secreted 5-HT. When she was first seen her flushes had apparently been superseded by a constant high colour. The response to irradiation of the liver was most gratifying. To our knowledge, this is the only case of the syndrome that has been well controlled for so long by any form of treatment.

Case 2

A 63-year-old European male was admitted on 17 March 1954 with abdominal cramps, flatulence and slight loss of weight of 2 months duration. He had suffered from persistent flushes of the face during the previous year, but not from dyspnoea or oedema.

He was ruddy-faced and looked well. The cardiovascular, respiratory and nervous systems and the urine were normal; the blood pressure was 120/70 mm. Hg. The liver was enlarged to 5 cm. below the right costal margin and was hard, irregular and non-tender. Rectal examination was negative. Blood indices: Hb. 14 g.%, VPC 46%, ESR 7 mm. (Westergren). The blood W.R. was negative. Blood urea 25 mg.%; serum albumin 4·5 g.%, globulin 2·0; van den Bergh reaction negative, bilirubin 0.5mg.%; phosphatase: alkaline 5 units, acid 0·16. Sigmoidoscopy to 15 cm. a plain film of the chest, barium meal, barium enema, oral cholecystogram, intravenous pyelogram and needle biopsy of the liver were all negative. The basal metabolic rate was +19.

Transient flushes were frequently observed in hospital, his face and neck becoming hot and red; they did not respond to testosterone and sedation. They were associated with striking pilomotor activity, which could be readily elicited by stroking the skin. Diarrhoea developed 1 month after admission— up to 4 watery stools a day; bacteriological studies were negative.

On 16 November he underwent laparotomy (Dr. H. Katz). There were numerous hard nodules in the liver, and the para-aortic and lesser-curvature nodes were infiltrated. A nodule was felt in the pancreas; the stomach was normal. *Histologically* a liver nodule showed the features of argentaffinoma (Dr. C. P. Retief).

The patient was discharged from hospital on 27 November 1954. His condition deteriorated progressively and he suffered from intractable flushes until his death in October 1955.

Comment. During life the flushes had been erroneously attributed to the male climacteric. The 'gooseflesh' elicited by stroking the skin has previously been noted in the carcinoid syndrome.[39]

Case 3

An 84-year-old European male was admitted on 15 October 1955 complaining of diarrhoea and loss of weight for 1 year and abdominal colic for 12 hours. For many years he had suffered from increased frequency of micturition. There had been no dyspnoea or oedema; flushing was not noted.

There were no signs of heart failure. The blood pressure was 240/130 mm. Hg. Scattered rhonchi were heard in the lungs. The liver and spleen were not palpable, but the bladder could be felt above the pubic symphysis and the prostate was diffusely enlarged. The nervous system and urine were normal. Sigmoidoscopy, bacteriological examination of the stools and a barium enema were negative. Blood urea 60 mg.%; serum phosphatase: alkaline 3·7 units, acid 0·46. An intravenous pyelogram showed gross hydronephrosis.

At laparotomy (Dr. P. C. W. Madden, 26 November 1955) a segment of small bowel 45 cm. long was found to be thickened, infiltrated and apparently strangulated; the mesentery was studded with small nodules, the lymph nodes were enlarged, and there was much free fluid. Definitive surgery could not be attempted and the patient died 3 days later.

Autopsy (Dr. S. J. Saunders) was performed 2 hours after death. *Gastro-intestinal system:* A polyp 2×1 cm. in size was obstructing the upper ileum; infiltration had extended through to the serosa. Secondary deposits were found in the liver (2 nodules), mesentery, and parietal peritoneum. Histologically the tumours had the features of argentaffinoma. *Lungs:* Bilateral basal bronchopneumonia. *Heart:* An old infarct; no endocardial lesions. *Urinary system:* Bilateral pyelonephritis and hydronephrosis; benign glandular hyperplasia of the prostate.

Case 4

A 65-year-old European female was admitted on 24 July 1953, complaining of abdominal cramps, diarrhoea and loss of weight for 6 weeks. There had been no dyspnoea or oedema; flushing was not noted. The blood pressure was 120/70 mm. Hg. The cardiovascular, respiratory and nervous systems and the urine

were normal. The abdomen was distended, with visible peristalsis, but there were no masses. Rectal examination was negative. Fluid levels were seen on a plain film of the abdomen.

At laparotomy (Prof. J. F. P. Erasmus, 26 July 1953) 120 cm. of lower ileum were resected because of obstruction, but the patient died 4 days later. There was no autopsy. *Pathology* (Dr. M. Sacks): Two tumours were found in the resected ileum: a polyp 2 cm. in diameter 30 cm. from the distal end, and an oval nodule, 2 × 1·2 cm., 7 cm. from the distal end. Both were carcinoids, the former having infiltrated the muscle coat. Tumour tissue was present in preformed vascular and lymphatic spaces, indicating that metastasis might have occurred.

Case 5

A 46-year-old Coloured female was admitted on 27 November 1957. Four months previously she had suffered from a 4-day bout of diarrhoea with cramps, passing partly-altered blood in the stools. This recurred 5 days before admission; in the interim there had been occasional melaena. Her most recent period had been scanty, and she had suffered from apparently typical menopausal hot flushes for 1 month.

She was very pale (Hb. 5 g.%). The blood pressure was 155/95 mm. Hg, and a soft systolic murmur was heard. The liver was palpable 4 cm. beneath the right costal margin and was smooth and non-tender. The respiratory and nervous systems and the urine were normal.

Sigmoidoscopy to 25 cm. was negative. A barium meal showed a sliding hiatus hernia; the stomach and small bowel appeared normal. An electrocardiogram was within normal limits.

After transfusion, a laparotomy was performed (Dr. W. G. Schulze, 5 December 1957). There was a small mass in the upper ileum, with blood in the bowel distal to it, and an infiltrated lymph node in the base of the mesentery. 13 cm. of ileum, and the node, were resected. The liver was enlarged but no tumour deposits were seen. In addition, the diaphragmatic hernia was repaired.

Pathological examination (Dr. W. B. Becker) showed an ulcerated argentaffinoma, with prominent intravascular spread, and lymph-node involvement. Post-operatively a 24-hour specimen of urine contained 3 mg. of 5-HIAA.

Comment. The interesting fact here is that the tumour ulcerated and bled, producing profound anaemia; this is an unusual occurrence with an argentaffinoma. The episodes of diarrhoea were associated with bleeding from the tumour and cannot be taken as evidence of the syndrome. The 5-HIAA excretion was measured after the resection and may well have been higher before the operation. There were no visible metastases in the liver, and the hepatomegaly is unexplained; however, the primary tumour showed significant invasion of blood vessels. Further 5-HIAA estimations may show whether hepatic metastases are developing.

Case 6

An 18-year-old European woman underwent appendicectomy for chronic pain in the right iliac fossa in 1952. At operation, which was done in a country town, a mass was removed from the caecum; it was sent to the University of Cape Town Department of Pathology and found to be an argentaffinoma invading the muscularis propria of the caecum (Dr. R. G. F. Parker).

The patient was traced through Dr. R. P. Dyer. She is quite well and has no diarrhoea, dyspnoea or oedema. She blushes easily but states that this is a family characteristic. The blood pressure was 120/70 mm. Hg and there was no evidence of heart disease. The liver was not enlarged. Her skin was normal. The urine did not contain albumin or sugar, and the Hb. was 16 g.%. The urinary 5-HIAA was 10·5 μg. per ml., 11.6 mg. per g. of creatinine.

Case 7

A 28-year-old European male first attended this hospital in February 1955. Part of his illness has previously been reported.[27] In 1948 he fell onto his sacrum; he consulted his practitioner several months later because of persistent pain. A tumour 1·5 cm. in diameter was found on the posterior wall of the rectum, 7·5 cm. above the ano-rectal ring; a biopsy was reported as carcinoma. At laparotomy enlarged nodes were found in the meso-rectum and there was a mass in the superior surface of the right lobe of the liver. Biopsies of a node and the liver were again reported as carcinoma.

In 1950 he consulted Sir Heneage Ogilvie. His general health was excellent and the primary was unchanged. On review of the histology the diagnosis was changed to argentaffinoma. In a series of operations in 1951 the pelvic colon, rectum and right lobe of the liver were resected, and the patient returned to South Africa. He remained well until 1952, when he developed pains in the legs. These became more and more severe; in November 1954 X-rays of the lumbar spine showed extensive osteolytic deposits. Radiotherapy relieved the pain, but it recurred several months later and he then came to this hospital.

There was no flushing, dyspnoea or diarrhoea. The cardiovascular system was normal and the blood pressure was 120/80 mm. Hg. An epigastric mass extended 7 cm. below the xiphisternum and appeared to be in the liver remnant. Digital examination disclosed a hard nodule 1·5 cm. in diameter on the anterior aspect of the lower sacrum. There was weakness of dorsiflexion of both feet and superficial sensory loss over both lower limbs. The peripheral blood picture and urine were normal. The blood W.R. was negative. Serum proteins: albumin 4·2 g.%, globulin 4·3. On X-ray, multiple deposits, showing both osteolysis and sclerosis, were seen in the ribs and spine (Fig. 3).

Initial treatment consisted of 4,000 r. (conventional deep X-ray therapy with H.V.L. 2·25 mm. Cu) to the dorso-lumbar and sacral regions over 28 days; there was complete relief of pain and regression of sensory changes in the lower limbs, and the sacral nodule disappeared. In May-July 1955 pain was relieved by 3,500 r. to the left ribs and both upper femora. However, the epigastric mass continued to grow and in October 1955, at the suggestion of Prof. A. Haddow, chlorambucil (kindly supplied by him) and busulphan were given for 1 month, in a dosage of 6 mg. of each a day, but there was no response. In January 1956 an upper abdominal X-ray bath, giving an estimated central tumour dose of 1,700 r., relieved his epigastric pain and caused the mass to regress. Two months later 2,400 r. given to the lower thoracic spine and the left 4th and 5th ribs relieved local pain.

In July 1956 he felt a dull pain in the right knee, and X-rays showed a vague sclerotic area in the distal right femur (Fig.4). The other deposits were unchanged, save for a pathological fracture in the right 9th rib posteriorly. On 3 occasions at this time asymptomatic blotchy erythematous macules were observed on the trunk; these were up to 10 cm. in diameter and faded within minutes.

Terminally the patient developed right hemiplegia, left facial paresis, herpes zoster of the right thigh and urinary incontinence. The epigastric mass increased considerably in size. He died at home in December 1956; there was no autopsy.

Comment. The ephemeral flushes constituted the only evidence of the syndrome. The extent and radiological appearances of the bony metastases were of interest. Radiotherapy provided significant palliation.

Case 8

A 50-year-old European male consulted Dr. Louis Mirvish (to whom we are indebted for the following notes) in February 1941 for a feverish cold. During the routine examination the liver was found to be enlarged to well below the umbilicus; it was hard, non-tender and nodular, and there was a mass in the right iliac fossa which appeared to be attached to it. Although the patient claimed that he was perfectly fit, it transpired that for the previous 6 months he had been aware of rumblings and occasional slight pains in the abdomen.

He had a ruddy colour, looked quite fit, weighed 215 lb. and showed no signs of weight loss. The blood indices were: Hb. 14 g.%, WBC 8,800 per c.mm., normal smear and differential count; ESR 54 mm. (Westergren) in March 1941 and 18 mm. in April. Barium meal and enema showed a very large filling defect involving the caecum and part of the ascending colon. The chest X-ray was normal.

His general condition remained good and he led an active life. In April large globular masses could be palpated on the surface of the liver, and in May ascites was detected. His bowels were still regular and he only occasionally experienced abdominal discomfort.

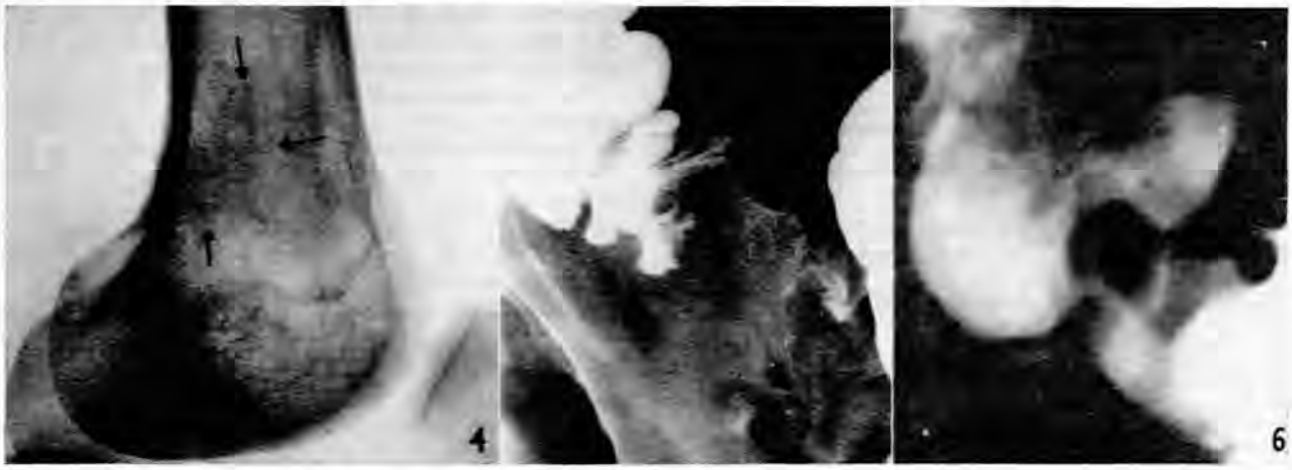

Fig. 4. Vague sclerotic area, right lower femur (case 7). *Fig.* 5. Irregular filling defect in the caecum, and polyp in the terminal ileum (case 9). *Fig.* 6. Carcinoid tumour in the base of the duodenum (case 11).

Eventually the patient was persuaded to undergo laparotomy (Prof. C. F. M. Saint, 20 June 1941). Free fluid was found in the abdomen. A large tumour involved the whole of the ascending colon save for the tip of the caecum. The liver was much enlarged and hard and contained many pearly-white fibrotic-looking areas which were obviously metastases. The omentum and bowel were studded with numerous secondary deposits. The ileum was enlarged, widened and thickened. An ileo-transverse colostomy was made. A biopsy of the infiltrated omentum showed the typical appearance of argentaffinoma (Prof. B. J. Ryrie).

The patient recovered well from the operation and was able to carry on with his usual activities. By November 1941, however, he had lost 30 lb. weight and was suffering from pain in the right iliac fossa, occasional diarrhoea and pyrexia. The diarrhoea became more troublesome, and by March 1942 his weight loss had totalled 60 lb., the liver was very large and hard, and the ascending colon was enormously wide, thick and immobile. There was some visible peristalsis on the left side of the abdomen.

In May 1942 he developed marked glossitis, the tongue being very red; this feature, as well as his considerable diarrhoea, resolved completely on 200 mg. nicotinamide a day, only for both to re-appear as soon as the medication was stopped. Ascites became severe and he developed oedema of the legs. He stopped work during August and died on 23 September 1942.

Comment. The diarrhoea appeared to be due to pellagra. In spite of widespread metastases, his general condition remained good for a long time. The naked-eye impression of fibrosis of the hepatic deposits is of interest.[5]

Case 9

A 69-year-old European male was admitted on 9 March 1957 for investigation of a mass in the right iliac fossa discovered accidentally at routine examination 2 months previously. He had suffered from hypertension and mild dyspnoea for 20 years; 6 months before admission he developed more severe dyspnoea and ankle oedema, which responded well to digitalis and mersalyl. Enquiry disclosed that he had experienced attacks of diarrhoea and borborygmi and had lost 12 lb. weight during the previous 6 months. There had been no flushing or wheezing.

He was a red-faced man, not in cardiac failure. The blood pressure was 240/125 mm. Hg, the heart was moderately enlarged, and a grade-2 systolic murmur and a pre-systolic triple rhythm were heard at the apex. The chest was slightly emphysematous. The lower border of the liver was felt 5 cm. below the right costal margin. There was a poorly-defined small irregular mass in the right iliac fossa. The nervous system and urine were normal.

An electrocardiogram showed severe left ventricular hypertrophy. A barium enema (Fig. 5) revealed an irregular filling defect at the infero-medial aspect of the caecum and a smooth rounded polyp just proximal to the ileo-caecal valve. At laparotomy (Prof. J. H. Louw, 15 March 1957) a hard mass was found in the caecum and right hemi-colectomy was performed. A single pearl-grey umbilicated nodule 3 cm. in diameter was seen in the anterior surface of the liver. *Pathology* (Dr. C. J. Uys): There were 2 argentaffinomas, viz. a 3-cm. mass in the wall of the caecum near the base of the appendix, and a pedunculated polyp just proximal to the ileo-caecal valve. Neighbouring lymph nodes were infiltrated.

Convalescence was satisfactory. The urinary 5-HIAA was only measured post-operatively, when it was 4·8 μg. per ml., 27 mg. per g. of creatinine. Attempts to provoke flushing by massage of the liver, the intravenous injection of 0·02 mg. histamine acid phosphate and the oral administration of 3 oz. brandy were unsuccessful.

Diarrhoea has persisted since the operation, and his complexion has remained abnormally high.

Comment. The syndrome was diagnosed on the basis of metastatic carcinoid tumours, diarrhoea, an unusually ruddy complexion and a slightly raised urinary level of 5-HIAA. The measurement was made after the primary tumours (with their secretory potential) had been removed. As in case 4 and many reported cases, the tumours were multiple.

Case 10

A 48-year-old Coloured male was admitted on 1 February 1956 complaining of postprandial epigastric pain for 18 months. For 3 months he had noticed intermittent melaena; in mid-January he vomited more than 2 litres of blood. Since then pain had not been relieved by alkalies and had been very severe on the day before admission.

He was pale and looked ill. The blood pressure was 125/75 mm. Hg, and the cardiovascular, respiratory and nervous systems and urine were normal. The liver, which extended 2 cm. below the right costal margin, felt normal; rectal examination was negative. Blood indices: Hb. 9·5 g.%, VPC 45%, ESR 32 mm. (Westergren), WBC 11,000 per c.mm., differential count normal and smear hypochromic. The blood WR was negative. Blood urea 38 mg.%. Plain films of the abdomen and chest were normal; barium meal revealed a huge penetrating ulcer bulging from the middle of the lesser curvature of the stomach.

At laparotomy (Dr. T. Schrire, 14 February 1956) a large gastric ulcer was found to be penetrating into the undersurface of the liver, which was studded with secondary deposits. The diagnosis of metastatic gastric carcinoma was made, and the ulcer was dissected free and sutured, after biopsies had been taken from it and a liver nodule. The patient died 3 days after the operation. There was no autopsy. *Pathology* (Dr. M. Sacks): The specimen

from the stomach showed an active benign peptic ulcer. The liver was infiltrated with carcinoid, which stained poorly by Masson's method.

Case 11

A 55-year-old Coloured male was admitted on 5 November 1955, complaining of post-prandial epigastric pain for 1 year. The blood pressure was 150/110 mm. Hg, and he had a left inguinal hernia; otherwise physical examination was negative. The urine and blood were normal (Hb. 14·5 g.%), but the stools contained occult blood.

Barium meal showed a high lesser-curvature gastric ulcer, and 'indications of duodenitis with ? mild prolapse of antral mucosa into the base of the cap' (Fig. 6). Billroth-I gastrectomy was performed (Dr. C. N. Barnard, 9 November 1955). *Pathology* (Dr. M. Sacks): The gastric ulcer was active and benign. In the duodenum, just distal to the pylorus, was a non-encapsulated submucosal nodule of carcinoid tissue.

It has not been possible to see the patient recently, but the manager of the farm on which he works reports that he is in good health and has no diarrhoea, wheezing or swelling. 'Intermittent flushing of the face and neck happens only if he is working in a stooped position'. At the time of that report the urinary 5-HIAA was 2·9 μg. per ml., 4·4 mg. per g. of creatinine.

DISCUSSION

The biochemical aspects of the carcinoid syndrome, and the properties of 5-HT, have recently been reviewed.[15,29] 5-HIAA, the inactive degradation product of 5-HT metabolism, is excreted in large quantities in the urine of patients with the carcinoid syndrome. The normal range of urinary 5-HIAA has been reported as 3·6±1·3 mg. per g. creatinine; in cases of the syndrome it was found to range from 22 to 1,230.[35]

TABLE I. LEVELS OF 5-HIAA

Case	*Urinary 5-HIAA (mg. per g. creatinine)*
1	156
5	3 (approx.)
6	11·6
9	27
11	4·4

We have been able to estimate the urinary 5-HIAA in 5 of our patients (Table I). In the 2 cases in whom the level was raised there was clinical evidence of the syndrome and metastases were found in the liver; the other 3 had low figures and there was not enough evidence to diagnose the syndrome. Although our normal range appears to be higher than Stacey's;[35] it did not encroach on the lowest figures reported as being diagnostic of the syndrome.

The finding of a high urinary level of 5-HIAA is strong presumptive evidence of metastasizing argentaffinoma and in our limited experience did not occur without at least one other sign of the syndrome. Only about 25% of cases of widespread carcinoid metastases show evidence of the syndrome;[24] in the remainder the tumor cells presumably secrete less 5-HT. The latter cases tend to present primarily as surgical problems.

Clinical Features (Table II)

The most suggestive symptoms of the carcinoid syndrome are attacks of flushing in the presence of diarrhoea; in the male these are practically pathognomonic of the condition. In the menopausal female flushing attacks are of less diagnostic value, unless set off by one of the known trigger mechanisms, e.g. a fatty meal,[4] food in general[8,10,26] or alcohol.[35] Attacks are occasionally precipitated by emotion[8] or defaecation.[10] They may be associated with other symptoms believed to be due to flooding of the circulation with 5-HT, e.g. palpitations, a fall in blood pressure, loss of consciousness and dizziness,[5,12,36] dyspnoea[30] and increased borborygmi.[36]

Flushing of the face occurred in 5 of our cases; in cases 1 and 2 this was due to the syndrome. In case 5 they were probably menopausal, in case 6 they seem to represent a familial tendency to blush easily, and in case 11 the significance of the phenomenon is not apparent. After a time, attacks of flushing may lead to a permanently high colour[6] (case 1). Transient macular flushes constituted the only indication of the syndrome in case 7. Cases 8 and 9 did not complain of flushing, but both had a ruddy complexion; they looked very well and the discovery of metastatic disease was most unexpected.

The diagnosis of metastasizing argentaffinoma must therefore be considered in any patient who looks 'extremely well' with a high colour, and who complains of diarrhoea or is found to have an enlarged and possibly irregular liver or an apparent abdominal malignancy. Anaemia is not a common finding, since most tumours arise beneath the lining epithelium and rarely ulcerate: case 5 is a significant

TABLE II. RESUME OF SIGNS AND SYMPTOMS

Case	*Age*	*Sex*	*Race*	*Primary*	*Syndrome*	*Skin Colour Change*	*Diarrhoea*	*Palpable liver*	*Hepatic Metastases*	*Systemic Metastases*	*Peptic ulcer*	*Anaemia*	*Pellagra*
1	49	F	E	Bronchus	+	+	+	+	+	+	−	−	−
2	63	M	E	?	+	+	+	+	+	−	−	−	−
3	84	M	E	Ileum ..	−	−	+	−	+	−	−	−	−
4	65	F	E	Ileum ..	−	−	+	−	−	−	−	−	−
5	46	F	C	Ileum ..	−	+(*b*)	+	+	−	−	−	+	−
6	18	F	E	Caecum ..	−	+(*c*)	−	−	−	−	−	−	−
7	28	M	E	Rectum ..	+	+	−	+	+	+	−	−	−
8	50	M	E	Caecum ..	+	+	+	+	+	−	−	−	+
9	69	M	E	Caecum (*a*)	+	+	+	−	+	−	−	−	−
10	48	M	C	?	−	−	−	+	−	−	+	+	−
11	55	M	C	Duodenum	−	+(*d*)	−	−	−	−	+	−	−

(*a*) In addition there was a non-invasive polyp in the ileum (Fig. 5).
(*b*) Probably menopausal.
(*c*) Familial blushing.
(*d*) ? significance.

exception. For this reason occult blood tests on the stool are usually negative until the terminal stages of the disease.[14,26] In this connection the association of peptic ulcer (which may bleed) with metastasizing carcinoid tumours is interesting and was found in cases 10 and 11 and in 8 of Macdonald's series of 21 cases of metastasizing argentaffinoma.[24]

In most cases the diarrhoea is due to the stimulant action of 5-HT on the smooth muscle of the bowel. This hormonal effect is independent of the site of the primary neoplasm (case 1), but local diffusion from a bowel tumour may conceivably play a part. Perhaps the diarrhoea in cases 3 and 4, who did not have the syndrome, may be explained on this basis. It is interesting that the diarrhoea of carcinoid syndrome may even simulate sprue.[38]

Pellagra may less commonly be a cause of the diarrhoea (case 8). 5-HT is derived from dietary tryptophan, which is also a precursor of nicotinic acid; in exception cases so much of the amino acid is diverted that pellagra results.[33,34]

None of our patients had cardiac manifestations. Pulmonary stenosis was excluded with certainty by cardiac catheterization in case 1. Ascites (cases 3 and 8) was due to peritoneal metastases. It is not necessary to invoke a cardiac aetiology for the oedema in case 8.

Metastases (Table II)

Although widespread metastases are the rule in the carcinoid syndrome, it has occurred with no more than a local lymph-node deposit[19] and with a tumour confined to its origin in an ovarian teratoma.[20]

The rarity of metastases from the appendix may be due to early diagnosis and consequent appendicectomy because of obstruction of the lumen. In a review of the literature Sinclair[32] found that 40% of ileal carcinoids had metastasized; in the rectum the figure is 9%.[25] Early attention may be drawn to the latter, as to any other rectal polyps, by intermittent bleeding.

The common situations of metastases are regional lymph nodes, liver and ovaries. Case 1 had a deposit in the skin: the rarity of this finding has been noted.[39] Cases 1 and 7 had bony metastases, which are also unusual, but have previously been reported.[13,18,28] Waldenström *et al.*[37] had a case in whom sclerotic deposits in the ribs remained unchanged for 3 years. Radiologically, the earliest feature of bone secondaries is ill-defined sclerosis (Fig. 4), perhaps accompanied by aching pain; this is followed by more obvious sclerosis, and then bony expansion (Fig. 3). Lytic areas are less common, and fractures appear to occur late.

TREATMENT

Resection of the primary growth and metastases offers the only chance of cure, and had been attempted in case 7.[27] Because of the relative slowness of tumour growth, this may be justified in fit young subjects. Manipulation of large growths during their removal may precipitate severe symptoms of excess of 5-HT;[34] pre-operative irradiation may prevent this.

Deep X-ray therapy seems to damp down both local and systemic effects of carcinoid metastases; e.g. the prompt and complete relief of bone pain from relatively small doses in case 7, and the amelioration of the syndrome and decrease in hepatic tenderness in case 1). Ariel's patient was alive and well 2½ years after treatment;[1] Klemperer[21] claimed success in both his cases. Adverse reports have also appeared.[7,35] In view of the relief obtained we feel completely justified in having given case 1 the desired tumour dose over the whole of the known tumour, even though this meant departing from some of the basic principles of palliation.

Reasonable dosage would appear to be about 3,000r. incidence dose over 10 days for bony deposits, 2,750-3,000 r. tumour dose over 4-5 weeks for hepatic metastases, and 3,000-3,500 r. tumour dose over 4 weeks for pulmonary tumours.

Radio-active colloidal gold (^{198}Au) is largely concentrated in the liver and should be useful for hepatic metastases; temporary improvement has been reported after its intravenous administration,[17] but the results seem inferior to ours with deep X-ray therapy.

Chlorambucil was of no help in case 6. Partial relief of hepatic pain has followed the injection of mustine into the hepatic artery,[16] but severe toxic complications are likely to occur.

Pharmacological control has not been successful. Antagonists of 5-HT are of little use at present: lysergic acid diethylamide[31] has unpleasant mental side-effects, and 2-brom-d-lysergic acid (BOL 148) has not proved effective.[34] Chlorpromazine was of little help in case 1. Conventional symptomatic measures may help to relieve the diarrhoea and bronchospasm. Pellagrinous symptoms may be controlled by nicotinamide.

SUMMARY

We report 11 cases of malignant argentaffinoma, of whom 5 showed evidence of the carcinoid syndrome. In none were there cardiac lesions. The importance of the incomplete syndrome is stressed. In one of our cases the primary tumour appeared to be in the lung. Attention is drawn to the occurrence of systemic metastases. The implications of fibrosis of tumour deposits are discussed. Diversion of tryptophan into the synthesis of 5-HT produced pellagra in one of our patients.

Treatment is discussed and the palliative value of radiotherapy is demonstrated.

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