ACQUIRED HEART DISEASE WITH ARGENTAFFIN CARCINOMA

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Argentaffin tumours are not uncommon and have been known for over half a century—Oberndorfer called them carcinoid tumours‡ in 1907. It is surprising, therefore, that the relationship between the malignant variety of tumour and acquired heart disease was not recorded until Biörck and his colleagues published their observations in 1952. This was followed by a full description by Thorson *et al.* (1954) of a syndrome characterized by cutaneous flushing, asthma, and diarrhœa and by lesions of the tricuspid and pulmonary valves in association with metastasizing argentaffin carcinoma.

Although 23 probable cases have now been reported, very few have been diagnosed in life, so that there is a lack of precise information concerning the clinical state of the heart.

The purpose of this paper is to present the findings in a case that was unusually well-documented. For the first time, clinical examination was supplemented by phonocardiographic studies and by cardiac catheterization, which enabled one of us (M. S.) to demonstrate the removal of the excess of serotonin (5-hydroxytryptamine) from venous blood by the lungs (Goble *et al.*, 1955). Surgical exploration revealed the presence of a primary tumour with hepatic metastases and necropsy examination demonstrated the lesions in the heart and other organs.

CASE REPORT

A 33-year-old housewife, who had been well until 1953, started to experience facial flushing and blotchy red patches on the forearms shortly after meals. Some months later she developed mild breathlessness and wheezing attacks, and at the end of 1954 a systolic murmur was noticed. She attended the National Heart Hospital for Dr. Paul Wood's opinion, and was admitted under his care in May, 1955, for further investigation, with a provisional diagnosis of pulmonary stenosis.

On admission, she was thin and confessed to having lost 21 lb. (9.5 kg.) in weight in the past two years. There was some painless diarrhœa, which had developed six weeks previously; on some occasions there had been up to ten loose motions a day, without blood or mucus. Menstruation had been irregular for the past six months. It was noted that, after most meals she became flushed, and later on, wheezy: sometimes the flushing was induced by emotion. During an attack, a diffuse erythema spread over her face from the neck, and small red patches, separated by blanched areas, appeared on the forearms. About 15 to 45 minutes after a meal, she also developed typical asthmatic wheezing, with audible sibilant rhonchi and marked retraction of the sternum, which lasted for one to two hours. Occasionally she had fleeting pains in the chest and lower abdomen.

There were telangiectases over both malar regions, and a persistent "gooseflesh" appearance of the skin. There was no cyanosis, clubbing, œdema, nor ascites. The pulse was regular with a reduced volume

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‡ These tumours are more properly known as argentaffin or Kulchitzky-cell carcinomas. This is because, as Masson showed, the tumour-cells often possess the same affinity for silver stains as the Kulchitzky-cells normally scattered in the mucosa of the small intestine and elsewhere, and also because the tumours are by no means as innocent as the term carcinoid would imply (Willis, 1948).

and the blood pressure 110/90 mm. There was a small dominant *a* wave in the jugular venous pulse. The right ventricle was not palpable but a slight systolic thrill was felt in the pulmonary area. At all areas there was a loud ejection-type systolic murmur, maximal in the second and third left interspaces, where the second heart sound was single. An atrial sound was heard but no diastolic murmur. The liver was enlarged to the level of the umbilicus. It was firm and slightly tender, and several large irregular nodules could be palpated on its surface. There was a mild hypochromic anaemia.

Radiography showed no enlargement of the heart nor dilatation of the pulmonary trunk or its main branches. There was slight reduction of the peripheral arterial shadows in the lungs. Barium-meal examination by Dr. Peter Kerley showed displacement of the stomach to the left, rapid emptying of the small bowel with disturbance of the mucosal pattern, and filling of the rectum in two to three hours.

Electrocardiography (Fig. 1) showed normal P waves, a vertical heart with clockwise rotation, slight right ventricular preponderance with dominant R waves in V4R and moderately deep S waves in V6.

Phonocardiography showed an ejection-type systolic murmur beginning late after the first sound and continuing up to a single second sound. An atrial sound was recorded at the apex and at the left sternal edge.

FIG. 1.—Electrocardiogram (28/6/55), showing slight right ventricular preponderance.

Cardiac catheterization was performed while the patient was fasting, and later after she had had a meal of tea and toast. This induced flushing within 15 minutes and an attack of wheezing within 45 minutes, so that observations were made at both of these times. The intrathoracic pressure-swing during the wheezing attack was recorded by an intra-oesophageal tube. The significant findings were as follows.

(a) Under fasting conditions, the pulmonary artery pressure on expiration was 9/4 mm. Hg, and the right ventricular pressure 56/–3 mm., indicating a pressure-gradient of 47 mm. across the pulmonary valve.

(b) There was no evidence of an intracardiac shunt. The blood samples from the superior vena cava, right atrium, right ventricle, and pulmonary artery had an oxygen saturation of 50–55 per cent. Those from the brachial artery were only 86 per cent saturated under fasting

conditions but the patient was asleep at this time. During the flushing and wheezing attack, however, the oxygen saturation rose to 90 per cent (the lower limit of normal for this laboratory).

(c) The cardiac output while fasting was 3.5 litres a minute, rising to 4.8 during flushing and falling to 3.1 litres a minute during the wheezing attack.

(d) The pulmonary vascular resistance remained normal throughout, being 69 dynes sec. cm.⁻⁵ (0.9 unit) while fasting, 50 (0.6 unit) during flushing, and 78 (1.0 unit) while wheezing.

(e) The intrathoracic respiratory pressure-swing rose from 9 mm. Hg whilst fasting to 16 mm. during flushing and to 27 mm. during the bronchospasm. These changes were reflected in the pulmonary capillary venous pressure tracing, the last figure of which, recorded while holding the breath, was 8 mm. Hg, corresponding with a respiratory pressure-swing of 25 mm. Some respiratory pressure-swing was reflected in all pulse tracings. The findings indicated that there was some bronchospasm even when the patient was free from symptoms.

(f) Paradoxical pulse was revealed in the change in the left brachial artery pressure from 89/64 mm. Hg on inspiration to 109/76 mm. on expiration.

(g) There was a small pressure gradient of 3–5 mm. Hg. across the tricuspid valve.

Biochemistry. The history and clinical findings strongly suggested the diagnosis of argentaffin carcinoma with hepatic metastases and pulmonary stenosis. Biochemical confirmation of this was obtained by the finding of a raised serum level of 5-hydroxytryptamine and by the increased output of its excretion product, 5-hydroxyindoleacetic acid in the urine (Goble *et al.*, 1955). No abnormality was found in the serum electrolytes, the tests of liver function and the Kepler test, but the urinary excretion of 17-ketosteroids was 2.4 mg. in 24 hours.

Treatment. Although ergotamine tartrate, phentolamine, and dibenylene have some action as serotonin anti-metabolites under experimental conditions, their administration produced no clinical improvement in this patient. It was considered, therefore, that removal of the primary tumour with some of the metastatic deposits might alleviate the distressing symptoms and Sir Russell Brock undertook this at the Brompton Hospital in July. A small primary tumour 1.5 cm. in diameter was located in the ileum after careful search, together with three enlarged glands in the mesentery. Sir Russell resected the tumour with a triangle of mesentery bearing the glands, and performed an end-to-end anastomosis. He also removed a large metastasis from the liver (which was studded with them), and a hardened gland from the vicinity of the portal vein.

Unfortunately, there was no improvement following operation, and on the advice of Professor D. W. Smithers it was decided to try direct irradiation of the liver metastases with radioactive gold. Eighty millicuries of colloidal ¹⁹⁸Au was infused by slow intravenous drip in August. A temporary alleviation of symptoms followed, but a severe neutropenia developed. This subsided, however, after thirty-three days.

Progress. In September, a fresh cardiac murmur was noticed at the lower left sternal border. It was a moderately loud, late diastolic murmur which increased in intensity and length during inspiration, and it was recorded phonocardiographically. There was also a marked increase in the *a* wave of the jugular venous pulse to 6 cm. above the sternal angle, and an additional diagnosis of tricuspid stenosis was therefore made. Slight sacral and ankle oedema had now appeared.

In October, 1955, the patient was readmitted to the Heart Hospital for the last time. She was now in a sad state of mental and physical deterioration, hallucinated, depressed, emotionally labile, difficult to manage, and doubly incontinent. Sedatives and chlorpromazine afforded little relief. Oedema of the forearms developed and she sank into coma. Death ensued in November, 1955, two and a half years after the onset of symptoms.

PATHOLOGICAL FINDINGS

Surgical Biopsies. We are indebted to Dr. R. C. Hallam for his report on the primary tumour and on a liver metastasis removed at operation. The primary tumour (Fig. 2) was a solitary rounded nodule, 1.5 cm. in diameter projecting into the lumen of the ileum. Its cut surface was firm, fibrous, and pale yellow, and showed nodular thickening of the submucous layer, with an intact mucosa. Microscopically, the tumour was an argentaffin carcinoma, lying mainly in the

FIG. 2.—The primary tumour in the ileum. The mucosal surface is intact over the tumour ($\times 2$).

FIG. 3.—Low-power photomicrograph through the primary tumour. The dark-staining masses of tumour cells can be seen in the submucosa and mucosa (Hæmatoxylin-eosin; $\times 13$).

submucosa (Fig. 3), although some clumps of tumour cells were found in the mucosa and traced through the muscle and serosal coats. Fontana's silver staining revealed argentophil granules in an occasional tumour cell.

Metastatic deposits were identified in the mesenteric lymph nodes and in the liver.

Necropsy examination was made by one of us (R. H.) about eight hours after death.

The subject was a woman of small physique, considerably emaciated. There was slight bronzing of the skin, most noticeable on the lower limbs, and there was a goose-flesh appearance of the skin over the shoulders. There was some œdema of the hands but none elsewhere, and there was no jaundice or cyanosis.

The *pericardium* contained about 5 ml. of clear fluid and was free of adhesions.

The *heart* was of normal size, weighing 250 g. The tricuspid valve orifice was moderately stenosed, the cusps being much thickened at their free edges and the chordæ tendineæ grossly thickened and shortened (Fig. 4). Histologically, the cusp itself showed a great increase of fibro-elastic tissue, and its borders could be followed in continuity with the elastic of the atrial and ventricular endocardium. Superimposed on both surfaces of the cusp proper were masses of rather poorly-staining fibrous tissue.

The right atrium was of normal size, with a fragment of clot adherent in the apex of the auricular appendage. The wall was a little thickened, and microscopically showed some patchy thickening of

FIG. 4.—Tricuspid valve after cutting open. The cusps are much thickened at their free margins, and the chordæ tendineæ greatly thickened and shortened. There is also slight hypertrophy of the right ventricle (about natural size).

the endocardium. The right ventricle showed early hypertrophy, measuring up to 0.5 cm. in thickness; otherwise it was normal.

The pulmonary valve was more affected than the tricuspid. The orifice was stenosed to a triangular shape, and the cusps were grossly thickened, shrunk and made rigid by tough fibrous tissue which extended down to the endocardium of the infundibulum. The sinuses of Valsalva were greatly reduced. Fig. 5 is a view of the intact valve from above comparing the pulmonary valve on the right with the aortic valve on the left. Fig. 6 shows the pulmonary valve after cutting, and illustrates how the valve site forms a constricting waist between the pulmonary trunk and the infundibulum of the right ventricle. Microscopically, the appearances were similar to those of the tricuspid valve. The cusp proper showed extensive fibroelastosis, the elastic being in continuity with that in the pulmonary trunk. The borders of the cusp were sharply demarcated from the masses of fairly acellular fibrous tissue covering both surfaces of the cusp (Fig. 7). There were some areas of more active fibrosis, and a few lymphocytes in places.

The left atrium was of normal size, but showed some thickening of the endocardium due to fibroelastosis, which was associated with some degeneration of the plain muscle. The myocardium showed an increase of interstitial tissue. The left ventricle was up to 1.3 cm. thick, but not dilated. Microscopically, there was some increase of interstitial tissue with one or two areas of more extensive replacement fibrosis, and the epicardium showed a few scattered round cells, as it did in the other heart sections.

The mitral valve appeared normal, but histological examination revealed what appeared to be a fairly recent thrombotic lesion on one of the cusps. The aortic valve was normal apart from a little thickening in the extreme bases of the cusps: this can be seen in the top, left cusp of Fig. 5.

The foramen ovale was sealed and the ductus arteriosus closed. The coronary arteries were virtually free from atheroma (although the left circumflex artery was smaller than usual). There was minimal atheroma in the aorta and in the pulmonary arteries, and the great veins were normal.

FIG. 5.—Intact pulmonary valve viewed from above to show the greatly thickened cusps, the small sinuses of Valsalva, and the stenosed triangular orifice. On the left are two aortic cusps for comparison. There is some thickening visible in the base of the upper aortic cusp (about natural size).

FIG. 6.—Pulmonary valve after cutting open. The cusps are shrunk and greatly thickened by tough fibrous tissue which is spreading down into the infundibulum of the right ventricle. Note how the valve site forms a constricting waist between the pulmonary trunk and the infundibulum (about natural size).

FIG. 7.—Pulmonary valve cusp. The cusp proper shows much fibroelastosis (at bottom of picture). Superimposed on it is a mass of fibrous tissue. Note the sharp boundary (Elastic van Gieson; $\times 92$).

The *peritoneum* showed numerous strong adhesions at the operation site, but no free fluid. The liver was enlarged to 2200 g. and was partly adherent to the anterior abdominal wall. Its surface was studded with scattered, neatly-rounded, raised, creamy-white metastases, and on slicing, these were seen to be concentrated in the right lobe (Fig. 8) to form a mass measuring 7×12 cm., partly necrotic in the centre. Elsewhere, the liver parenchyma was pale. Microscopically, the tumour showed the structure of an argentaffinoma, the tumour cells being in neat, well-defined masses, with numerous blood sinuses in direct

FIG. 8.—Slice of liver, showing the argentaffin carcinoma metastases concentrated in the right lobe (about $\times \frac{1}{2}$).

FIG. 9.—Lung metastasis (H&E; $\times 76$). FIG. 10.—Lung. Group of tumour cells in a capillary in centre of picture (H&E; $\times 290$).

contact with tumour cells. There was some attempt at fibrous encapsulation of the metastases. The argentophil reaction (Masson-Fontana) was negative.

The *lungs* showed moderate congestion only and appeared well aerated, but on histological examination numerous microscopic metastases were seen in all areas. The largest one seen is illustrated in Fig. 9 while Fig. 10 shows a group of tumour cells, possibly an embolus, in a lung capillary. There were also

widespread bronchitis, and patches of early bronchopneumonia in all areas, with a little emphysema. The vessels showed no lesion.

Other Viscera. There was no tumour in the abdomen apart from the liver metastases. The ileal anastomosis, situated about 50 cm. from the ileo-cæcal valve, was perfectly healed. Silver methods failed to reveal any excess of argentophil cells at the site of the operation, or in sections from other parts of the intestine. The *spleen* weighed only 80 g. but showed no lesion. The *kidneys* showed congestion only, each weighing 120 g. The *brain* weighed 1400 g. and showed no lesion. The *lymph-nodes* were inconspicuous: sections of abdominal and thoracic nodes revealed no metastases microscopically.

DISCUSSION

The physiological studies showed only a moderate degree of pulmonary stenosis, which is in agreement with the slight degree of right ventricular hypertrophy demonstrated cardiographically and at necropsy. In several of the cases described by Thorson *et al.* (1954), however, there was moderate right ventricular hypertrophy at necropsy although there was only slight pulmonary stenosis. Signs of tricuspid stenosis developed while the patient was under observation, although cardiac catheterization had earlier demonstrated a small diastolic pressure gradient across the tricuspid valve. The finding of normal pulmonary vascular resistance during flushing, when circulating serotonin was increased, refutes the suggestion by Thorson *et al.* (1954) and Jenkins and Butcher (1955) that the pulmonary stenosis is in some way the result of increased pulmonary vascular resistance due to vasoconstriction of pulmonary arterioles by serotonin.

The necropsy findings in this case agree with those in the 18 already reported: in 15 of these there was pulmonary stenosis, in 10 some tricuspid abnormality, and in 4 minor changes, such as we have described, in the mitral and aortic valves (Rosenbaum *et al.*, 1955; Jenkins and Butcher, 1955; Bean *et al.*, 1955). The patchy thickening that we found in the endocardium of the right atrium was reported in three cases (Thorson *et al.*, 1954; Branwood and Bain, 1954). The gross changes in the tricuspid and pulmonary valves correspond in general with the description of others—sclerotic thickening of the cusps, often with fusion of the commissures. In our case, there was almost no inflammatory reaction, though Biörck *et al.* (1952) reported round cell infiltration in one case.

There is increasing evidence (Pernow and Waldenström, 1954; Page *et al.*, 1955; Sjoedsma and Udenfriend, 1955) that the various features of the syndrome are related to the presence of large amounts of circulating serotonin, which is secreted by the primary tumour and its metastases. This was clearly demonstrated in our case (Goble *et al.*, 1955). Similar mental changes to those in our case were observed once by Jenkins and Butcher (1955). It is believed by Woolley and Shaw (1954) that certain psychoses, such as schizophrenia, may be related to disturbed serotonin metabolism.

The pathogenesis of the cardiac lesions remains obscure. It was shown (Goble *et al.*, 1955) that the serotonin content of pulmonary artery blood was higher than that of blood in the brachial artery or superior vena cava. It was suggested that this was due to removal of serotonin by the enzyme mono-amine oxidase, which is known to be present in lung tissue in high concentration and to have the property of inactivating serotonin (Bradley *et al.*, 1950). The high concentration of serotonin in right-heart blood may alter the endothelium, by increasing cellular permeability (Pickles, 1955) and allowing platelet deposition on the valve cusps, with subsequent fibrosis. In this connection, the minor changes found in the aortic and mitral valves in our case are of interest in view of the presence of lung metastases.

SUMMARY

A case is reported of argentaffin carcinoma of the ileum with hepatic metastases, pulmonary and tricuspid stenosis, flushing, asthma, and diarrhœa.

Cardiac catheterization studies, reported for the first time in this condition, confirmed the presence of pulmonary stenosis, indicated a slight degree of tricuspid stenosis, and showed normal

pulmonary vascular resistance during fasting, flushing, and wheezing. It also permitted original observations on serotonin metabolism which throw some light on the pathogenesis of the syndrome.

Removal of the primary tumour did not relieve symptoms, but temporary improvement followed the administration of radio-active colloidal gold.

The pathological findings in our case are described and the pathogenesis of the syndrome discussed.

We wish to thank Dr. Paul Wood, under whose care the patient was admitted, for permission to publish this case and for his valuable criticism. We are indebted to Sir Russell Brock for the findings at operation, to Dr. R. C. Hallam for his report on the surgical material, and to Mr. D. F. Kemp for Fig. 2 and 3. Finally, we express our gratitude to Professor R. A. Webb for his interest and kindness in providing laboratory facilities, and to Dr. D. N. Baron and Dr. J. C. Leonard for their constructive criticism.

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