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Metastasising Carcinoid Tumours

By J. E. LENNARD-JONES and P. J. D. SNOW (Manchester)

(With Plate 1)

Thorson and his colleagues (1954) have recently shown that some metastasising carcinoid tumours are associated with a peculiar type of flushing, diarrhoea, an enlarged liver and sometimes with valvular lesions of the right side of the heart. The obscure relation of these curious features to the tumour has aroused interest and several case reports have since appeared. This paper presents some of the clinical and biochemical observations made on three such patients whom we have recently studied at Manchester Royal Infirmary (*Snow* et al., 1955).

The first patient was a woman of 58, who two years before she died began to have watery diarrhoea followed by loss of weight and breathlessness. Six months before death she began to experience flushing of the hands and face three or four times a day. On twelve occasions this flushing was followed in a few minutes by a feeling of weakness and a sensation of suffocation, which lasted for six to twelve hours and then gradually passed off. When observed in an attack, the face and extremities were intensely cyanosed while the rest of the skin was pale. No arterial pulsation could be felt even in the carotid arteries, but the heart sounds were normal at 100–120 per minute. During one attack an indwelling catheter was inserted and the patient was found to have anuria for four hours. Between attacks physical examination merely revealed a large, hard liver. A clinical diagnosis of malignant carcinoid tumour was made, and this was supported by the biochemical findings. Medical treatment was ineffective and, since *Thorson* and his colleagues reported that resecting a large mass of tumour tissue helped one of their patients, a laparotomy was performed but the only tumour tissue found was in the liver. The patient collapsed during the operation and died 24 hours later. At autopsy a small primary tumour was found in a Meckel's diverticulum. Histological examination of both the primary and secondary deposits showed a typical carcinoid structure.

The second patient was a man of 61 who, some nine months before he died began to flush after a glass of beer. Thereafter flushing of increasing intensity occurred

spontaneously and he gradually lost weight. When seen four months before he died watery diarrhoea had developed and the face was a permanent deep red colour (Fig. 1, Flate 1). This became accentuated and involved the whole body during episodes of flushing, which could be induced by as little as 10 ml. of 10% alcohol by mouth or intravenously. The only other abnormal finding on examination was a hard irregular enlargement of the liver. A clinical diagnosis of malignant carcinoid was made. This was supported by the biochemical findings, but post-mortem was refused.

The third patient, a man of 43, had had attacks of flushing for 20 years; these tended to be brought on by meals and invariably by taking alcohol in any form. At an examination made an account of dyspeptic symptoms one year before admission, a hard nodular liver was found which showed little change twelve months later when we saw him. At no time had there been any diarrhoea, and he had lost only 10 lbs. in weight. The flushing in this man was of a geographical type and could invariably be induced by giving 10 ml. of 10% alcohol by mouth or intravenously (Fig. 2). A diagnosis of malignant carcinoid was made and at laparotomy the liver

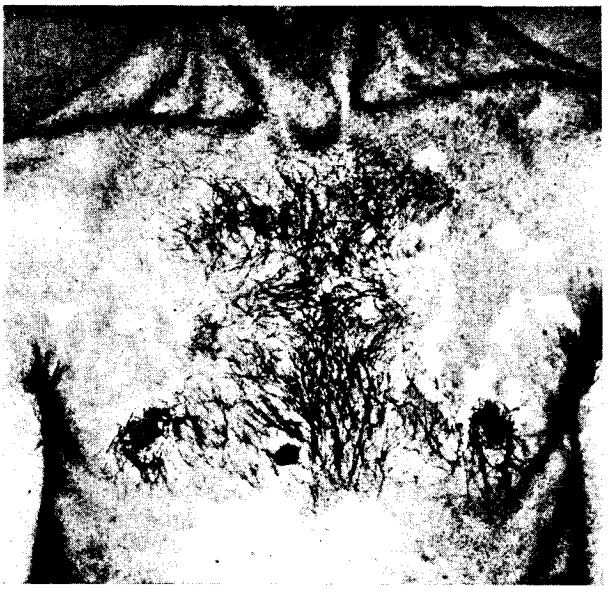


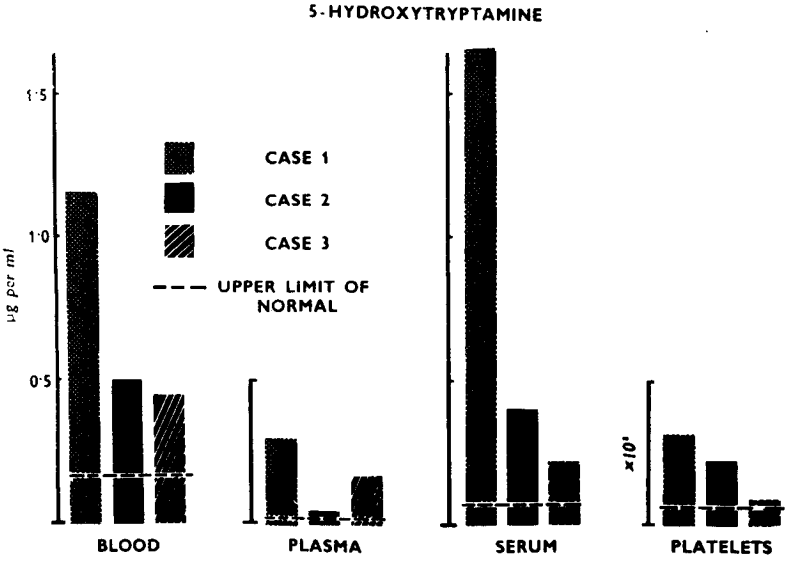
Fig. 2. Geographical erythema after alcohol (Case 3).

was found to contain numerous secondary deposits; the primary tumour was found on the anterior wall of the stomach. A chronic duodenal ulcer was also present. It proved impossible to remove a large bulk of tumour tissue, but the primary growth and a gland were exised and histological examination confirmed that the growth was a carcinoid. The patient's flushing was not affected by the operation.

None of our patients had either tricuspid or pulmonary stenosis. They showed two features which have not previously been described – the episodes of circulatory collapse seen in the first patient and the striking response of the second and third patients to alcohol.

One of the most interesting aspects of this condition is the mechanism by which the tumour causes symptoms. In 1953 *Lembeck* found a high content of serotonin in carcinoid tumour tissue and *Thorson* and his colleagues (1954) suggested that this substance might be responsible for the syndrome. Serotonin is the vaso-constrictor substance released when blood clots (*Rapport, Green* and *Page*, 1948) and has been identified chemically as 5-hydroxytryptamine (5-H.T.). It is probably secreted by the enterochromaffin cells of the alimentary tract, absorbed by the platelets and released when these are destroyed, to be excreted in the urine as 5-hydroxy-indole acetic acid. Its physiological role and pharmacological properties have not been fully established, but the effects of injection of the substance in animals and man resemble some of the symptoms of patients with metastasising carcinoids. The 5-H.T. content of blood, urine and tumour tissue from our patients was estimated by Dr. *R. S. Stacey*, and the results are summarised in Table 1.

TABLE 1

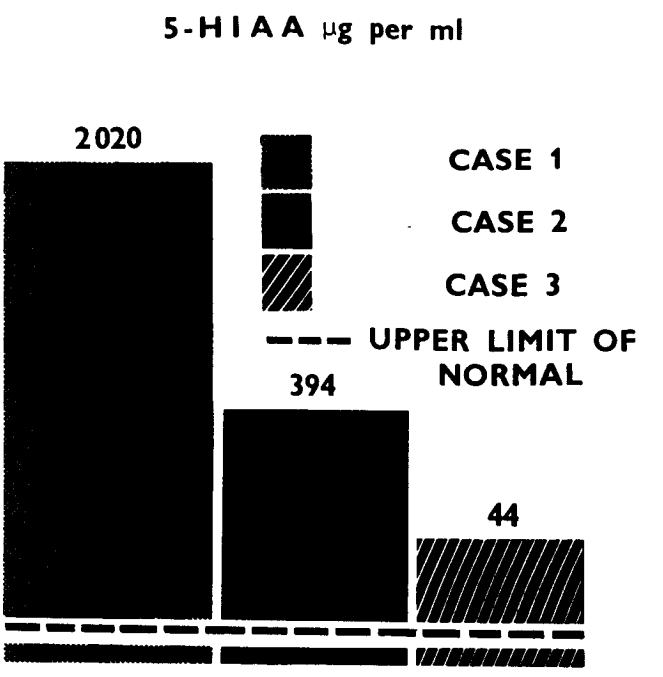


In all three patients all fractions of blood 5-H.T. were raised, the changes being greatest in the first patient in whom the symptoms

were most severe, and least in the third patient, in whom the symptoms were trivial. 5-H.T. was found in the tumour tissue from the first patient in a concentration of 0.6 mg/G. but only 0.33 ug/G. was found in that from the third patient. All three patients excreted considerable amounts of 5-H.T. in the urine.

5-hydroxy-indole acetic acid (5-H.I.A.A.) the urinary excretion product of 5-H.T. was estimated by Dr. *G. Curzon*, and the values obtained are shown in Table 2. All three patients had abnormally

TABLE II



high 5-H.I.A.A. excretion, the output corresponding with the clinical severity of the disease and with the blood 5-H.T. levels. In the first patient, day to day variation in the output of 5-H.I.A.A. expressed as mg-G. creatinine is shown in Fig. 3. One of the severe attacks was immediately followed by a marked increase in 5-H.I.A.A. excretion.

We were unable to modify the symptoms by the use of serotonin antagonists, including ergotamine tartrate, lysergic acid diethylamide, and BOL 148, a brominated derivative of L.S.D.

In summary, it may be said that large amounts of 5-H.T. were present in the blood of these three patients, and that there was a

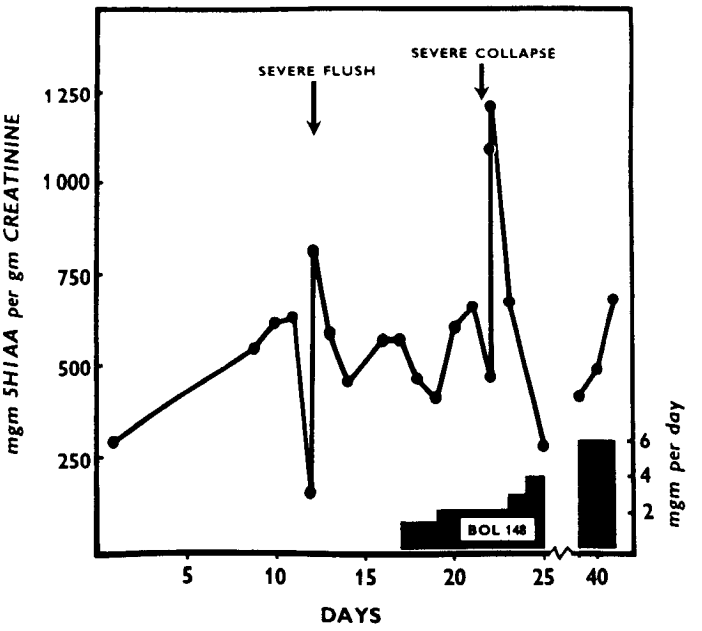


Fig. 3. Daily 5-H.I.A.A. Excretion showing increase after episode of circulatory collapse (Case 1).

rough correlation between the blood level and the severity of the symptoms. In the present imperfect state of our knowledge of the action of 5-H.T. in man, the participation of some other substance in the causation of the symptoms cannot be excluded, although we were unable to demonstrate the presence of any indoles other than 5-H.T., 5-H.I.A.A. and their conjugates in either tumour tissue or body fluids.

Acknowledgements. We wish to thank Professor *Robert Platt* and Dr. *H. T. Howat* for permission to publish details of their patients, and Sandoz Limited for supplies of B.O.L. 148 and lysergic acid diethylamide.

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Discussion

Dr. *Morson:* I would like to describe two cases of metastasizing carcinoid in which urinary estimations of 5-H.I.A.A. (5-hydroxy-indolyl-acetic acid) have been performed. In the first, the patient presented with a history of feeling tired but no other symptoms. A mass was felt in the right iliac fossa, which on rectal examination was attached to the uterus. At operation a tumour of ileo-caecal junction was found with secondary deposits over omentum, liver and pelvis. An ileo-transverse colostomy was performed. Biopsy of one of the secondary deposits showed a typical carcinoid tumour. Eight years later the patient remains alive and well, and clinically her secondary deposits are about the same size. She has no signs of the peculiar syndrome associated with metastasizing carcinoid despite an abnormally high level of 5-H.I.A.A. in her urine. This level approaches that expected in metastasizing carcinoid with flushing.

In the second case the patient presented with symptoms and signs of a malignant tumour of the rectum. A biopsy of this growth showed carcinoid of rectal type, but with cytoplasmic granules in the tumour cells which stained with the argentaffin and Diazo reactions. At operation secondary deposits were found in the liver and an abdomino-perineal resection of the rectum was performed. An examination of the specimen showed carcinoid of the rectum with many metastases in lymph glands. The urine both before and after operation showed a normal level of 5-H.I.A.A.

Here we have two cases of metastasizing carcinoid without the peculiar syndrome described by Dr. *Snow*. The first shows that patients with carcinoid metastases may live for many years and apparently not suffer much from the disease. It also shows that it is possible to have a high level of 5-H.I.A.A. in the urine without developing the typical carcinoid syndrome. It will be interesting to see whether this patient eventually gets the syndrome or gradually develops a tolerance to large amounts of 5-hydroxytryptamine in her circulation. The second case shows that despite the presence of a primary carcinoid tumour with lymphatic and liver metastases, the excretion of 5-H.I.A.A. is within normal limits. This may be a reflection of the peculiar histology of rectal carcinoids, although it was easy to find cytoplasmic granules typical of carcinoid in this case.

Lastly, I would like to point out that most of the cases of carcinoid so far reported which also have this peculiar syndrome, have had liver metastases. Further they have died very shortly after the syndrome has been discovered. This suggests that the syndrome is a terminal event.

I am grateful to Mr. *C. Naunton Morgan* and Mr. *W. B. Gabriel* for permission to refer to their cases.

Dr. *Sircus:* Microphotographs were shown and a case of a woman of 55 with diarrhoea and asthenia found to be due to a large malignant ulcer in the stomach and considered inoperable on clinical grounds was described. "She was discharged from hospital only to be readmitted with severe bronchial asthma and profuse diarrhoea a month later, and shortly died. Autopsy revealed that the large gastric ulcer was a carcinoid and metastases were present in the liver. It was suggested that the sudden onset of bronchial asthma in older people in association with diarrhoea must raise the possibility of a malignant sarcinoid. A large ulcer of the stomach as a presentation form of carcinoid had not apparently been described."

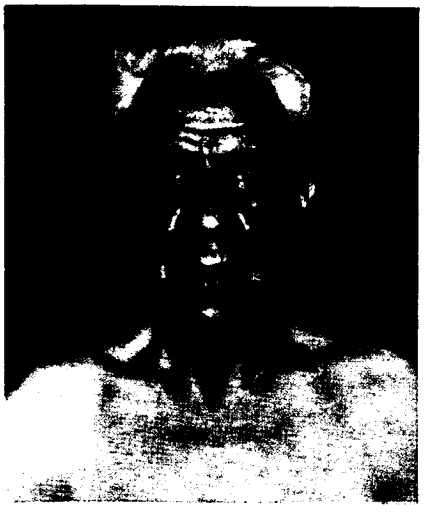

Fig. 1. The appearance of the second patient between attacks of flushing. (We are grateful to Sandoz Limited for a grant to enable this photograph to be reproduced in colour.)