Progress Report: The carcinoid syndrome

'As a rule disease can scarcely keep pace with the itch to scribble about it'
(John Mayow)

The carcinoid syndrome is just about keeping pace. Since its recognition in the 1950s, the clinical picture has proved to be variable¹, this variation reflecting either differences in the humoral secretions of the causative tumour or differences in host response. The major manifestations of the syndrome remain flushing, diarrhoea, wheezing, and cardiac valvular lesions, the variability occurring in regard to qualitative differences in flushing, the presence of other minor manifestations and the diversity of the combinations of the major components of the disease spectrum^{2,3}. Certain features need to be emphasized. By the time the syndrome presents, in the presence of primary tumours, draining their venous effluent into the portal circulation (eg, gastric, ileal, pancreatic) hepatic metastases are invariably present. Conversely, primary tumours draining directly into the systemic circulation (eg, bronchial, ovarian) may cause the syndrome without metastatic spread. It is necessary to determine whether hepatic metastases are present or not, and if not, the whereabouts of the primary tumour, since removal of a primary without metastases will cure⁴.

The clinical picture and urinary excretion pattern of 5-hydroxyindoles help in diagnosis. Atypical flushing patterns and the presence of an excess of 5-hydroxytryptophan and 5-hydroxytryptamine (5HT) in the urine besides the usual excess of 5-hydroxyindole acetic acid, suggests a bronchial, gastric, or pancreatic tumour⁵. Generally diagnosis is not difficult, but two situations are worth noting. First, the differentiation of flushing not due to the carcinoid syndrome. The carcinoid flush is usually provoked by intravenous administration of adrenaline (1 to 5 micrograms) or noradrenaline (5 to 15 micrograms)⁶. Noncarcinoid flushing is not so provoked. Secondly, where for some reason other than flushing the carcinoid syndrome is suspected (eg, unexplained diarrhoea, unexplained tricuspid or pulmonary valvular disease, or the incidental finding of carcinoid tumour at laparotomy). Here provoking flushing is useful because carcinoid flushing can sometimes be provoked in patients with the syndrome who have no spontaneous complaint of flushing. The estimation of the urinary 5HIAA excretion is essential in diagnosis and although occasionally this may be normal in the presence of the true syndrome such an occurrence is very rare⁷.

Many problems remain to be solved as regards the mechanisms by which the various clinical manifestations are caused. Kallikrein release from the tumour and subsequent increase in circulating bradykinin is undoubtedly a major factor causing the flush in most but not all patients⁸. Occasionally 5HT is paroxysmally released during flushing, but this is unusual⁹. It should be suspected when the flush is markedly cyanotic and is accompanied by obvious hyperventilation. Histamine release from gastric carcinoids has been reported. Recently prostaglandin F₂ was found in a bronchial carcinoid and an unidentified hydroxy fatty acid, perhaps a prostaglandin, was present in two ileal carcinoids¹⁰. The role which prostaglandins have to play in the diarrhoea and flushing has yet to be determined.

The cause of the diarrhoea is not yet fully understood. Its improvement with methysergide¹¹, a 5HT antagonist, and with para-chlorophenylalanine¹², an inhibitor of 5HT synthesis, and the similarity of gut motility patterns in the carcinoid syndrome and after 5HT infusion¹³ suggest a causative role for 5HT. The cause of the wheezing which affects a minority of patients has not been adequately investigated. Likewise the cause of the cardiac valvular lesions is unknown. Undoubtedly a circulating substance, released by the tumour and largely inactivated by the lungs, will prove responsible but the nature of such a substance is at present a mystery. Of interest is the remarkable improvement in the cardiac state which may occur when unmetastasized ovarian primaries are removed¹⁴. How much this improvement is due to haemodynamic change and how much to true resolution of the valvular disease it is not possible to say.

Dependent oedema is common in the carcinoid syndrome and on occasion this is not adequately explained by carcinoid heart disease, liver involvement with tumour or obvious metabolic abnormalities such as hypoproteinaemia. The oedema responds to conventional diuretic therapy and if resistant, spironolactone may be very effective.

The functional behaviour of the neoplastic enterochromaffin cell composing carcinoid tumours varies with the tumour site. The clinical and biochemical syndromes produced by bronchial, gastric and ileal tumours cell differ, while rectal carcinoids do not produce the syndrome at all⁵. In addition ectopic hormone production may occur in the carcinoid syndrome. Cushing's syndrome (ACTH)¹⁵ and hypoglycaemic attacks (insulinlike material)^{16,17} have been reported associated with the carcinoid syndrome usually caused by tumours of foregut origin. It has been suggested recently that the bronchial carcinoid is the 'benign' form of the oat cell carcinoma of the bronchus and that the cell of origin of both is a bronchial Kultschitzky cell¹⁸. Of course oat cell carcinomas of the bronchus are notorious for their tendency to produce ectopic hormones; less well known is their occasional production of the carcinoid syndrome¹⁹. The recognition of an association between particular stem cell types, their tumour offspring, and their propensity to produce ectopic hormones implies that there is some biological organization at a cellular level allowing these functions to occur and speaks strongly against haphazard, chance, and disorganized production of hormonally active substances. Williams²⁰ has suggested that the stem cells of tumours producing ectopic hormones contain certain types of DNA which are more easily derepressed. If this is true then the enterochromaffin cell seems particularly prone to this derepression.

Treatment of the carcinoid syndrome involves destruction or removal of the functioning tumour mass or drug therapy aimed at preventing the synthesis, release or pharmacological actions of the various substances produced by the tumour. Removal of the primary growth is important, first when no metastases are present (bronchial and ovarian tumours) and second when it is causing local mechanical effects. The surgical treatment of metastatic growth is worth serious consideration in each individual case. If abdominal exploration is undertaken then removal of involved lymph nodes, metastatic ovarian tumours, and peritoneal deposits can improve symptoms. But the main problem is that of hepatic metastases. First it is necessary to investigate the site, size and number of hepatic metastases by liver scanning and coeliac artery angiography. If metastases are mainly confined to one lobe then massive hepatic resection should be considered²¹. Such resection can lead to great symptomatic improvement return of urinary 5HIAA excretion to normal and complete disappearance of flushing even resisting provocation tests¹⁷. Such resection should be considered early in the course of the disease to avoid the development of the cardiac lesions. Anaesthesia can cause severe hypotension, best treated by volume repletion and avoidance of noradrenaline as a

pressor agent (using angiotensin or metaraminol if necessary), and also severe bronchoconstriction best treated by IV methysergide 1 to 4 milligrams.

There have been a bewildering number of drugs used in the treatment of the carcinoid syndrome but only a very few are worth considering. Methysergide, a 5HT antagonist, is very useful as treatment for the diarrhoea¹¹ and its efficacy outweighs its toxic effects of vasospasm and retroperitoneal fibrosis. Parachlorophenylalanine, a potent inhibitor of tryptophan 5-hydroxylase²², the rate-limiting enzyme in the synthesis of 5HT²³, has been shown to diminish diarrhoea and on occasion can dramatically improve the patient's appetite, vigour, and wellbeing^{12,17}. Alpha-methyldopa is on occasions definitely useful in diminishing flushing. Its action is unlikely to be due to the slight inhibition of 5HTP decarboxylase in the tumour but perhaps to some interference with the mechanism by which endogenous catecholamines trigger flushing²⁴. Based upon the observation that certain catecholamines may trigger flushing by releasing kallikrein from the tumour⁸, phenoxybenzamine, 10-30 mg daily, may diminish flushing by preventing kallikrein release^{24,25}. Phenoxybenzamine may also partially alleviate the diarrhoea and wheezing. Propranolol seems to be equivocally effective in diminishing flushing²⁶, and I have not observed benefit from it so far. Chlorpromazine and promazine may on occasion help partially to control flushing. Prednisone is useful in controlling the severe flushing and facial oedema produced by bronchial carcinoids. Overall, though, drug treatment of the flush is not very effective. The wheezing usually responds to an isoprenaline aerosol, which does not provoke flushing.

Cytotoxic drug therapy has not proved very successful so far. Oral cyclophosphamide can definitely diminish liver size and cause biochemical improvement but long term symptomatic improvement is not forthcoming²⁷. This has been the experience too with oral 5-fluorouracil²⁷ and intravenous vinblastine¹⁷. I am not very optimistic about regional hepatic perfusion with the cytotoxic agents presently available, but long term results with this technique are awaited.

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