

## Leading article

# What is the cause of the carcinoid flush?

Between 1952 and 1954 the constellation of clinical signs and symptoms in patients with carcinoid tumours became known as the carcinoid syndrome.<sup>1</sup> In 1953, Lembeck<sup>2</sup> isolated 5-hydroxytryptamine (5-HT, serotonin) from a carcinoid tumour. Initially it was thought that the carcinoid flush was the result of 5-HT which was known to have pharmacological vascular actions. But it is not as simple as that.

Clinical observation shows there are various types of flush<sup>1</sup>—namely, a diffuse erythematous flush affecting mainly the face, neck and upper anterior chest, but often spreading over the skin of the back and affecting the abdomen and palms. This flush is usually paroxysmal and short, lasting two to five minutes. Patients with this type of flush often look normal between flushes.

The second type of flush has a violaceous tinge to it. It affects the same areas, but lasts longer. The nose is often shining and purple during the flush, which frequently occurs on a background of permanent cyanotic flushing. These patients usually have a very high urinary 5HIAA output.

The third type of flush is usually associated with bronchial carcinoid tumours. The flushes often last several hours and may even last days. The skin becomes red and often slightly purplish and body areas other than the usual flushing areas are involved. There is profuse lacrimation and the conjunctivae are suffused. The facial skin swells and the normal facial creases become exaggerated into deep folds. This type of flushing is extremely distressing.

The fourth type of flush is bright red and patchy, the red flush is a particularly vivid red and the white patches seem particularly brightly white. Patchiness is most evident around the root of the neck. This type of flushing is usually associated with gastric carcinoid tumours and excess production of histamine.

These different types of flushing must have a different pharmacology and are likely to be because of different substances alone, or in concert affecting different parts of the vascular bed of the skin. Robertson *et al*<sup>3</sup> showed that 5-HT could not be the sole substance responsible for flushing. Quite simply 5-HT did not produce a true carcinoid flush when given intravenously, nor did its concentrations usually rise in arterial plasma during a flush. Oates *et al*<sup>4</sup> continued the search for the carcinoid flushing substance. In a series of investigations they found that the tumour contained kallikrein and that the hepatic venous blood draining carcinoid liver metastases contained a bradykinin like substance during an induced flush. They did, however, have some patients who did not release bradykinin into the circulation during flushing attacks.

At that time the bradykinin was isolated and identified by various extraction techniques and bioassays. My colleagues and I<sup>5</sup> measured arterial blood bradykinin concentrations during provoked carcinoid flush and in some patients the concentrations clearly increased, but plasma bradykinin

did not rise in all patients during the flushing. Nor did intravenous bradykinin reproduce qualitatively the spontaneous flush. The bradykinin flush is much pinker than the spontaneous flush and is associated with more marked tachycardia and hypotension. Bradykinin does not produce much hyperventilation, cyanosis, or any of the patchy skin discolouration sometimes seen in carcinoid flushing.

The paper by Gustafsen *et al* in this issue of *Gut* (p 1417) is an important contribution to this problem. Using a sensitive solid state immunoassay for bradykinin, bradykinin concentrations in peripheral venous blood during flushing, did not rise. There is one problem with their findings. It could be that plasma bradykinin is raised in arterial capillary blood and causing the flush, but that bradykinin is then inactivated, or taken up by tissues, producing normal concentrations of bradykinin in peripheral venous blood. This is a pedantic point which I hesitate to make, but it is just a possibility which cannot be excluded.

A valuable experiment would have been to inject bradykinin intravenously to produce a flush and then check that plasma concentrations of bradykinin are raised in peripheral venous blood. It seems, therefore that although the study by Gustafsen *et al* does not absolutely exclude bradykinin as the flushing substance in the carcinoid syndrome, it goes a long way towards it.

If 5-HT and bradykinin are not responsible, what is? How does one go about finding out? It is not sufficient to show that carcinoid tumours contain this or that substance which is known to be a vasodilator in various animal or tissue preparations. It is necessary to show that the suspect substance is present in plasma at concentrations known to produce flushing in normal volunteers, or patients with the carcinoid syndrome. Preferably the substance should be measured in arterial blood during the flush, and shown that its rise and fall coincides with the rise and fall of the flush. This is likely to be most easily examined in flushes provoked with iv noradrenaline, pentagastrin, or oral alcohol.

All sorts of potential flushing substances can be found in carcinoid tumours. The list is long and includes histamine (gastric carcinoids) substance P, prostaglandins and various tachykinins. Norheim and her colleagues<sup>6</sup> reported tachykinin immunoreactivity in carcinoid tumours, suggesting the presence of eledosin and kassinin peptides. It is possible that these are involved in flushing, but it has yet to be proved. Neuropeptide K has been found in plasma and tumour from patients with the carcinoid syndrome.<sup>7</sup> Apparently there is a  $\beta$ -pre-pro-tachykinin, a long peptide which contains the sequences of the tachykinins substance P, neuropeptide K and neurokinin A, while  $\alpha$ -pre-pro-tachykinin, contains only the sequence for substance P. Complicated radioimmunoassay techniques together with chromatographic separation have identified neuropeptide K, but we do not know definitely whether it produces the carcinoid flush. In fact a recent paper by Conlon *et al*<sup>8</sup> concluded that the circulating tachykinins cannot be solely responsible for the flush, particularly the meal induced flush. Nevertheless, basal concentrations of substance P and neurokinin A may be raised in a number of patients with the carcinoid syndrome, but no relationship is found between this and the degree of flush. In several patients tachykinins were not detectable in plasma in the basal state, or during flushing: again the blood analysed was venous. It is known that substance P

given iv will produce flushing in man, I do not know whether neuropeptide K, or neurokinin A cause flushing.

It has recently become apparent that 'direct vasodilatation' (direct relaxation of arterial smooth muscle), is not the only mechanism by which flushing might occur. 'Indirect vasodilatation', whereby endothelium derived relaxing factor (EDRF), an endogenous vasodilator produced by vascular endothelium,<sup>9</sup> can be released by, for example acetylcholine, substance P and vasoactive intestinal polypeptide, and can then in pharmacological sequence cause vasodilatation. Indeed, 5-HT released during platelet activation, can stimulate EDRF release *in vivo*.

Ought we to be looking for a substance that releases EDRF? If so, the model for detection will have to be rather special.<sup>10</sup> So the hunt for the flushing substance is still on. In the meantime what can we do therapeutically?

Flushing can be very severe and need treatment in its own right. Removal or destruction of secreting tumour mass either surgically, by partial hepatectomy, by embolisation of liver metastases, or by cytotoxic drugs, are aimed at the tumour. There are several pharmacological approaches to the treatment of flushing.<sup>11</sup> Flushes are often provoked by anxiety, excitement, exercise or alcohol and it is likely that the initial pharmacological trigger is either noradrenaline or adrenaline, acting on an  $\alpha$ -adrenoceptor on the tumour cell and releasing flushing substances. Phenoxybenzamine can be effective in controlling flushing by blocking  $\alpha$ -adrenoceptors. Other drugs which on occasions have been useful are propranolol (not in my hands), chlorpromazine and  $\alpha$ -methyldopa. Roberts *et al*<sup>12</sup> found that in a case of gastric carcinoid with histamine type flushing, a combination of H<sub>2</sub> and H<sub>1</sub> histamine antagonists was useful.

I have not been impressed by the effects 5-HT antagonists on the flush, either the non-specific ones like methysergide or pizotifen, or the newer specific 5-HT<sub>2</sub> antagonists like ketanserin. I doubt whether the new class of 5-HT<sub>3</sub> receptor antagonists will be helpful either – but clinical trials will have to be done. Prednisolone can be useful in the severe flushing caused by bronchial carcinoids and rarely in ileal carcinoids and I suspect it inhibits release of flushing substances.

Somatostatin has recently been shown to be dramatically effective in suppressing carcinoid flushing<sup>13</sup> and the new, more stable somatostatin analogue (Sandostatin) subcutaneously twice or three times a day, can be extremely effective in the suppression of flushing and other symptoms of the carcinoid syndrome.

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