

Flushing

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Flushing never killed anyone. Because flushing is a nuisance and not a life-threatening problem, and because the many kinds of flushing are seen by doctors in different branches of medicine, the subject has received scant attention. This review proposes a classification of flushing based mainly on the history and clinical examination and suggests that improved communication between medical specialties may help in our understanding and treatment of this symptom.

Flushing is a reddening of the skin caused by transient vasodilation. It may have a localised distribution (for example, the middle third of the face in rosacea, the post-prandial flushing of the pinna and cheek in Frey's syndrome) but here we are more concerned with flushing characteristically involving the blush area. The reddening usually begins in the cheeks and spreads to the ears and neck (Darwin, 1890), involving the V-shaped area of the lower neck and upper chest. The circumoral and circumorbital skin is spared, and the malar region reddens most (Lewis, 1927). However, the blush area varies from person to person, affecting a greater or lesser part of the neck and cheek.

Whereas blushing is always the result of emotional upset, flushing can be a response to physiological, pathological, pharmacological and psychological stimuli.

The smooth muscle of arterioles, pre-capillary sphincters and venules in the skin is influenced by nerves and vasoactive chemicals. Vasoactivity in the terminal part of the arterial tree is not under direct neural control but is dictated solely by chemicals that act on the endothelial cells. Vasodilation in the blush area produced by neural stimuli is predominantly an active process mediated through fibres running with the cutaneous nerves (Blair *et al.*, 1961; Fox *et al.*, 1962). The vasodilation is effected by cholinergic stimulation and, as the postganglionic fibres supplying the sweat glands are also cholinergic, neural flushing is associated with sweating. Direct acting vasoactive chemicals currently recognised are amines (such as histamine), polypeptides (such as kinins, which have a direct action and also an indirect action, via the release of catecholamines) and prostaglandins. The flushing produced by these agents acting on smooth muscle is not associated with sweating: the patient's skin is hot, dry and red.

This differentiation between neural and chemically mediated flushing is not absolute: certain amines and prostaglandins can act centrally on the heat control centre and may thereby effect neural flushing. However, this simple classification should help to clarify our understanding of the varieties of flushing.

Flushing Produced by Neural Activity

There are several clinical conditions characterised by sporadic episodes of flushing associated with perspiration. It seems likely that these symptoms, which are manifestations of cholinergic sympathetic overactivity, are a reflection of altered hypothalamic function. The hypothalamus may act inappropriately because of intrinsic abnormalities, but more often it does so as a result of chemical or physical stimulation.

Harvey Cushing (1932) introduced a variety of chemicals into the lateral ventricles of many patients, the majority of whom had undergone surgical removal of pituitary adenomata. Immediately after introduction of extract of posterior pituitary gland (pituirtrin), the patients noted a sensation of warmth, were seen to flush (the skin over the bone flap being spared) and broke out into a drenching sweat. Cushing noted a similar response when pilocarpine was introduced, but the effect was not produced by acetylcholine, or histamine, which causes dry flushing when given intra-muscularly. Cushing postulated a direct action of the chemicals on the hypothalamic nuclei by diffusion of pituitrin through the lining of the third ventricle.

A number of therapeutic agents can produce similar symptoms. Within half a minute of receiving thyrotrophin releasing hormone (TRH) some patients become flushed and perspire (Lauritzen, 1975). The same picture is occasionally seen in Parkinsonism: some patients with post-encephalitic Parkinsonism flush spontaneously (Pallis, 1971); Parkinsonian patients receiving bromocriptine may flush (Calne *et al.*, 1974) and some of those patients on L-dopa who develop the on/off phenomenon flush and sweat transiently one and a half to two hours after taking the drug (McDowell *et al.*, 1970). A variety of other drugs also cause flushing with sweating (Table 1).

Electrical as well as chemical stimuli may produce a similar picture: Penfield (1929) reported a 41-year-old woman with a tumour extending into the third ventricle who had attacks of diencephalic-autonomic epilepsy. During these attacks she had episodes of flushing and sweating similar to menopausal flushing.

The menopausal hot flush is the most common neurogenic vasomotor disorder. Flushes occur any time of the day or night, some women experiencing 20 to 30 each day, and they usually last a few minutes. Menopausal flushing may precede the cessation of periods by many months and, although it usually disappears after a year or two, it can persist for many years.

Although climacteric hot flushes are a reflection of sympathetic overactivity, there has been a tendency to concentrate on the endocrine imbalance thought to trigger off the flushes rather than to consider the autonomic mechanisms involved. It is widely accepted that hot flushes are a result of either oestrogen deficiency or gonadotrophin excess, but close scrutiny of these explanations has found them to

Table 1. Pharmacological agents that cause flushing.

	Dry flushing	Flushing with sweating
<i>Natural substances</i>		
short duration	PGE ₁ ATP	TRH
long duration	Histamine Nicotinic acid Calcitonin	
<i>Contrast media</i>	Conray	
<i>Gases</i>	Nitrous oxide	
<i>Therapeutic agents</i>	Alcohol Amyl nitrite Calcitonin Dextran Gold salts Hydrallazine Nicotinic acid and its derivatives Protamine sulphate Rifampicin Tamoxifen Triamcinolone	Antabuse Chlorpropamide Metronidazole Clomiphene Cyclandelate Danazol Isoprenaline L-dopa Metiamide

} flushing aggravated by alcohol

be inadequate (Mulley and Mitchell, 1976). The emphasis on endocrine aspects of the menopause has caused some fossilisation of thought and there has been little progress in our understanding of the mechanism of hot flushes. The study of those other conditions characterised by spontaneous episodic flushing and sweating may shed light on the pathophysiology of hot flushing and lead to alternative therapeutic approaches.

Flushing Produced by Chemical Agents Acting on Vascular Smooth Muscle

1. *Flushing as the Primary Symptom.* A large number of endogenous and exogenous chemicals produce flushing by direct action on the terminal vasculature. Different agents produce flushing of variable duration and intensity, and in some cases flushing extends far beyond the blush area.

Flushing of short duration can be produced by the injection of prostaglandin E₁, but whether this agent is responsible for the various forms of transient flushing is not known. A strong transient flush is seen in some patients receiving urographic contrast media (Witten *et al.*, 1973) and can also be produced by nitrites — when eaten in hot-dogs by susceptible subjects (Henderson and Raskin,

1972), or when inhaled as amyl nitrite, which produces a dramatic flush of head, neck and upper chest that may last several minutes (Aldridge, 1871). Amyl nitrite has been in use for over a century but its mode of action is still unknown.

Flushing of longer duration is produced by several chemicals including histamine and nicotinic acid. Intra-muscular injections of histamine result in a prolonged hot dry flush. Histamine release from the abnormal proliferation of mast cells causes the bright red flushing seen in urticaria pigmentosa (Sutter *et al.*, 1962). Agents that liberate histamine, such as codeine, aspirin and polymyxin B, provoke flushing in patients with this condition. A similar picture is seen in patients with gastric carcinoid who elaborate huge quantities of histamine (Oates and Sjoerdsma, 1962).

A complication of the treatment of hyperlipoproteinaemia by nicotinic acid is the pronounced dry flushing. Nicotinic acid is a component of Parentrovite and this probably explains why patients receiving this compound develop prolonged flushing. The flushing produced by the nicotinic acid derivative Perycit (pentaerythritol tetranicotinate) is said to be reduced by the administration of clonidine (Sigroth, 1974).

2. Flushing Associated with Systemic Symptoms. The carcinoid syndrome has been extensively studied but there is still no general agreement about the mechanism of the carcinoid flush; there are arguments for and against the role of serotonin, kinins and prostaglandins. Several writers have pointed out that agents may act synergistically to cause flushing. Synergism between serotonin and bradykinin (Grahame-Smith, 1972) and between serotonin and catecholamines (Demis and Zimmer, 1962) may cause vasodilation, whereas circulating levels of individual agents may be insufficient to produce flushing.

Progress in our understanding of carcinoid flush may improve if we correlate clinical symptoms with laboratory investigations, and initiate logical therapeutic trials. Grahame-Smith (1972) has described four clinically recognisable types of carcinoid flushing and, using his classification, it may be possible to deduce the possible active agent or agents involved in individual patients and suggest appropriate treatment.

Type 1. The patient has paroxysmal episodes of short-lived (2 to 5 minutes) flushing. The flushing is diffuse, erythematous and limited to the blush area. The short duration of these flushes suggests that kinins, whose half-life is about 30 seconds, may be involved. In many carcinoid patients there is a rise in arterial bradykinin during a flush, but few workers have commented on the clinical features of the flushing in these subjects. Many patients with carcinoid have flushing in response to emotional stress and to injections of catecholamines; these factors are known to stimulate the conversion of kallikrein to vasoactive kinins. Unfortunately, alpha- and beta-blockade have only produced mild and inconsistent amelioration of flushing and the kallikrein inhibitor Trasylol has not proved helpful. As yet there is no effective bradykinin antagonist. However, the possible

value of a vessel 'stabiliser' such as clonidine deserves evaluation in this group of patients.

A remarkably similar clinical picture is seen in patients with dumping syndrome and here, too, kinins are thought to be responsible.

Type 2. The patient has a cyanotic flush involving the blush area. The nose becomes purple and some patients have dilated facial veins. Flushing is slightly longer than in Type 1. The reason for the cyanosis is not clear: it may be that blood pools in the cutaneous capillaries because of contracted pre-capillary arterioles or closure of the vein sphincters. Robertson *et al.* (1962) found that the cyanotic flush was associated with a rise of serotonin. It would be logical to try to abolish this type of flushing with parachlorophenylalanine (PCP), an inhibitor of serotonin synthesis. So far this only appears to have been used in patients with Type 1 carcinoid flush and, not surprisingly, there was no improvement in symptoms (Engelman *et al.*, 1967).

Type 3. Distressing prolonged flushing is commonly associated with bronchial carcinoids (Melmon *et al.*, 1965). The flushing usually lasts hours or even days, and may be widespread. There is associated lachrymation, swelling of facial skin, explosive diarrhoea, nausea, vomiting, hypotension and fever. The chemical responsible has not been identified but steroid therapy may alleviate the symptom.

Type 4. Some patients with gastric carcinoid have vivid flushing with white patches in the reddened area, particularly around the root of the neck (Oates and Sjoerdsma, 1962). These patients have high levels of histamine. Avoidance of agents that stimulate histamine release seems appropriate in this group. As yet the role of antihistamines in the relief of these symptoms has not been established.

The Apud cell tumours occur in cells that are thought to arise in the neural crest (Apud = amine precursor uptake and decarboxylation). Tumours arising in these cells are able to elaborate and secrete vasoactive polypeptides and other chemicals. These tumours may present with flushing and a variety of other systemic symptoms.

Medullary carcinoma of the thyroid may occur in association with a variety of endocrine disorders. The disease is characterised by flushing and diarrhoea (Keynes and Till, 1971) and it is thought that the tumour produces a kinin polypeptide that acts on smooth muscle to produce these symptoms. However, the tumour may produce other vasoactive chemicals such as calcitonin (Cunliffe *et al.*, 1968) which can cause flushing. Some patients who receive calcitonin for Paget's disease experience extensive hot dry flushing which is said to be reduced by giving indomethacin (Barnett *et al.*, 1975). This suggests that calcitonin-induced flushing might be mediated by prostaglandins.

Ganglioneuromas and ganglioneuroblastomas also produce flushing, sometimes in association with diarrhoea and hypertension (Rosenstein and Engelman, 1963). These neural tumours secrete large amounts of catecholamines in addition to polypeptides. Other tumours, which secrete polypeptides and present with

general symptoms as well as flushing, include pancreatic tumours, pheochromocytomas and bronchogenic carcinomas.

CONCLUSIONS

Flushing is a common symptom which may be produced by a variety of stimuli. As a general rule, flushing produced by autonomic activity is associated with sweating, whereas vasoactive agents acting directly on vascular smooth muscle cause dry flushing. A number of tumours, including those arising in neuroectodermal tissue, may present with flushing and systemic symptoms.

A plea is made for detailed clinical observations of the different types of flushing. Documentation should be made of the extent and duration of the flush; whether or not there is sweating; and whether there are any precipitating or relieving factors. By obtaining this information from many branches of medicine, and correlating it with biochemical findings, we may be able to understand flushing better and treat the patient logically and effectively.

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