

# THE CLEVELAND CLINIC DISEASE MANAGEMENT PROJECT

**TITLE:** FLUSHING  
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### DEFINITION

Flushing describes episodic attacks of redness of the skin together with a sensation of warmth or burning of the face, neck, and less frequently the upper trunk and abdomen. It is the transient nature of the attacks that distinguishes flushing from the persistent erythema of photosensitivity or acute contact reactions. Repeated flushing over a prolonged period of time can lead to telangiectasia and occasionally to classical rosacea of the face.<sup>1</sup>

Flushing can be an exaggeration of a physiological process or a manifestation of a serious condition that needs to be identified and treated. A biochemical work-up of every case of flushing is neither practical nor cost-effective; in this chapter, the author will present guidelines that will help determine when a work-up is warranted.

### PREVALENCE

The prevalence of flushing has not been determined.

### PATHOPHYSIOLOGY

Redness of the skin may be due to an increased amount of saturated hemoglobin, an increase in the diameter or actual number of skin capillaries, or a combination of these factors.<sup>2</sup> Flushing is due to increased blood flow through the skin, causing warmth, and because of engorgement of the subpapillary venous plexus, redness. The vasodilatation of flushing may be due to a direct action of a circulatory vasodilator substance, for example histamine, or it may be caused by changes in the neurological control of the cutaneous vasculature in the affected areas. In the face, neck, and upper trunk, where flushing is most frequent, the neurological control of vascular tone is predominantly exerted by autonomic vasodilator nerve fibers. These fibers are found in somatic nerves supplying the affected skin, including the trigeminal nerve. Since autonomic nerve fibers also supply eccrine sweat glands, neurally activated flushing is frequently associated with sweating (wet flushing) as opposed to flushing due to circulating vasodilator mediators which frequently does not involve sweating (dry flushing). The presence or absence of sweating has therefore been proposed as a clinical guide to the mechanisms of flushing, although in practice this is not always reliable. Examples of wet flushing are physiological flushing and menopausal flushing. An example of dry flushing is niacin-provoked flushing.<sup>1</sup>

The diameter of the blood vessels of the cheeks is wider than elsewhere, the vessels are nearer to the surface, and there is less tissue thickness obscuring them. This may explain why flushing occurs in that limited distribution.<sup>3</sup> Polycythemia produces the characteristic ruddy complexion, but it may also cause a peculiar coloration termed "erythremia," which is a combination of redness and cyanosis. The tongue, lips, nose, earlobes, conjunctivae, and fingertips especially demonstrate this coloration. Erythremia results when there is a combination of increased amounts of saturated hemoglobin and desaturated hemoglobin.

In some carcinoid tumors, fibrosis of the right side of the heart may lead to a combination of stenosis and regurgitation at the tricuspid valve as well as pulmonary stenosis. If cyanosis occurs, the combination of flushing and cyanosis may produce the reddish cyanotic erythremia.<sup>2</sup>

## FLUSHING SYNDROMES

### Physiological Flushing:

Embarrassment or anger may cause flushing in some individuals in whom the threshold for this response may be low or the reaction itself unusually intense; this is also known as blushing.<sup>1,2</sup> Explanation and reassurance are usually sufficient. If necessary, propranolol or nadolol may be used to alleviate the symptom.<sup>1</sup>

Heat causes flushing in many patients, and overheating can lower the threshold to flushing due to other causes such as menopause.<sup>3</sup> Overheating such as after exercise or sauna can cause physiological flushing due to the effect of the rise in blood temperature on the thermoregulatory center in the anterior hypothalamus. A similar mechanism is responsible for facial flushing due to hot drinks, which cause a rise in temperature of blood in the oral cavity in turn leading to a rise in temperature of blood perfusing the hypothalamus. The temperature of hot coffee rather than its caffeine causes flushing.

A useful maneuver for patients faced with a brief thermal exposure is to suck on ice chips carried in an insulated cup. This will attenuate flushing for the first 20 to 30 minutes.<sup>3</sup>

### Menopausal Flushing:

About 80% of postmenopausal women experience flushing associated with sweating. A similar syndrome may also occur in men with prostate cancer receiving treatment with gonadotropin-releasing hormone analogs such as buserelin. About 65% of post-menopausal women have hot flushes for 1 to 5 years, 26% for 6 to 10 years, and 10% for more than 11 years. There is considerable variation in the frequency, intensity, and duration of hot flushes within and among individuals. A typical hot flush begins with a sensation of warmth in the head and face, followed by facial flushing that may radiate down the neck and to other parts of the body; it is associated with an increase in temperature and pulse rate and followed by a decline in temperature and profuse perspiration over the area of flush distribution. Visible changes occur in about 50% of women. Each hot flush lasts for 1 to 5 minutes. The primary role of estrogen deficiency has been questioned and a deficit of thermoregulation has been proposed. Rapid estrogen withdrawal rather than a low estrogen level by itself is likely to induce hot flushes.<sup>4</sup> Synchronous with the onset of each hot flush is the release of a pulse of luteinizing hormone; this does not seem responsible for the hot flush since flushing can occur after hypophysectomy. The anterior hypothalamus has estrogen and progesterone receptors, and both hormones can be used effectively to treat hot flushes through binding with their respective hypothalamic receptors. Neurotransmitters that may be involved in the pathogenesis of hot flushes include norepinephrine and other noradrenergic substances. The central noradrenergic system in the hypothalamus triggers the hot flushes via  $\alpha_2$ -adrenergic receptors on the noradrenergic neurons. Thus, clonidine—an  $\alpha_2$ -adrenergic agonist—effectively alleviates hot flushes through reduction of noradrenergic release.<sup>4</sup>

Pharmacologic menopause with flushing can be induced by a variety of drugs: 4-hydroxyandrostenedione, danazol, tamoxifen, clomiphene citrate and leuprolide. Certain characteristics suggest the diagnosis of climacteric flushing: drenching perspiration, a prodromal sensation of overheating before the onset of flushing and sweating, and waking episodes at night with the typical symptoms. Alcohol can enhance a menopausal flush.<sup>5</sup> Veralipride, an antidopaminergic drug, can cause a reduction in the frequency and intensity of menopausal flushing in premenopausal women pretreated with goserelin (gonadotropin-releasing hormone agonist) for endometriosis.<sup>6</sup>

### Flushing Caused by Drugs:

Other medications that can cause flushing are corticotropin-releasing hormone, doxorubicin, and niacin (**Table 2**). Flushing is a side effect of sildenafil citrate in 12% of patients.<sup>7</sup> Systemic administration of morphine can cause flushing of the face, neck, and upper thorax, which is thought to

be histamine-mediated.<sup>5</sup> Patients can develop facial flushing and/or generalized erythema after epidural or intra-articular administration of glucocorticoids. The exact pathophysiology is unclear but it could be related to distention of the joint capsule.<sup>8</sup>

### **Flushing Associated with Alcohol Intake:**

Certain oriental genotypes show extensive flushing in response to low doses of alcohol. They have been found to have higher plasma levels of acetaldehyde. This abnormality is probably related to a deficiency of an isoenzyme of liver aldehyde dehydrogenase. This population can be detected by using an ethanol patch test which produces localized erythema. A special type of alcohol flush is also associated with chlorpropamide, the oral anti-hyperglycemic agent. Even small amounts of alcohol provoke intense flushing within a few minutes of ingestion. This flushing is not associated with sweating, but in some cases tachycardia, tachypnea, and hypotension may be seen. The flush is mediated by elevated acetaldehyde plasma levels and possibly by release of prostaglandins.

Alcohol ingestion can trigger flushing in carcinoid tumors, mastocytosis, medullary thyroid carcinoma, and certain lymphoid tumors.

Trichloroethylene, a chemical that has been abandoned in recent years because of carcinogenic potential, can cause flushing. When inhaled following ingestion of alcoholic beverages, a striking cutaneous reaction results, consisting in the sudden appearance of erythema of the face, neck, and shoulders—a reaction that has been termed "degreaser's flush." Nausea and vomiting may also occur.<sup>5</sup>

### **Flushing Associated with Food:**

Eating spicy or sour foods can cause facial flushing. This gustatory flushing is due to a neural reflex involving autonomic neurons carried by the branches of the trigeminal nerve. The flushing may be unilateral.

The flushing of monosodium glutamate (MSG) is controversial. Oral challenge with MSG failed to provoke flushing in volunteers with a history of MSG flushing. Patients should be encouraged to look beyond MSG at other dietary agents, such as red pepper, other spices, nitrites and sulfites (additives in many foods), thermally hot foods and beverages, and alcohol.<sup>5</sup> Scromboid fish poisoning (tuna and mackerel) is due to the ingestion of fish that was left in a warm temperature for hours. In addition to flushing, patients with scromboid fish poisoning have sweating, vomiting, and diarrhea. These symptoms are due to intoxication with histamine, which is thought to be generated by histidine decarboxylation by bacteria in spoiled fish.

### **Carcinoid Syndrome:**

"Carcinoid syndrome" describes the manifestations of carcinoid tumors: flushing, bronchoconstriction, gastrointestinal hypermotility, and cardiac disease. Carcinoid tumors are neuroendocrine tumors that derive from a primitive stem cell that may differentiate into any of a variety of adult endocrine-secreting cells, producing a variety of peptides, hormones, and neurotransmitters. The annual incidence is 1.5 per 100,000 population.<sup>9</sup> The average age of patients is 50 years, and there is no gender predominance.<sup>10</sup>

Carcinoid syndrome occurs in about 10% of patients with these tumors.<sup>10</sup> In 75% of patients, episodes of severe flushing are precipitated by exercise, alcohol, stress, and certain foods (spices, chocolate, cheese, avocados, plums, walnuts,<sup>1</sup> red sausage, and red wine). With time the flushing may appear without provocation.<sup>9</sup> The character of the flush differs depending upon the site of origin of the tumor (**Figures 1 and 2**). Tumors of the foregut (stomach, lung, pancreas) are associated with a bright-red "geographic" flush of a more sustained duration, as well as lacrimation, wheezing, sweating, and a sensation of burning. In ileal tumors, the flush is patchier and more violaceous,

intermingled with areas of pallor, and does not last as long. Flushing of either type may be associated with facial edema that may persist and lead to telangiectasia and even facial rosacea. With extensive disease, one can also see pellagra-like skin lesions. (These result from excessive utilization of tryptophan by the carcinoid tumor, leaving little for the daily niacin requirement). These lesions include hyperkeratosis; xerosis; scaling of the legs, forearms, and trunk; angular cheilitis; and glossitis (**Figure 3**). Seventy percent of patients also have watery diarrhea, and 35% develop right-sided endocardial fibrosis leading to congestive heart failure. Diarrhea and other gastrointestinal manifestations may precede or coexist with the flushing.<sup>5</sup>

Ninety-five percent of all carcinoids are found in the appendix, rectum, or small intestine.<sup>9</sup> The remainder arise outside of the intestinal tract (ovary, testis). In general, the larger the primary tumor, the greater the likelihood of metastasis, which provides prognostic implications.<sup>9</sup> Carcinoids of the appendix and rectum rarely present with the carcinoid syndrome. Forty to 50% of patients with carcinoids of the small intestine or proximal colon have manifestations of the carcinoid syndrome.<sup>10</sup> Tumors that secrete their hormonal product into the portal venous system do not cause flushing because the released amines are inactivated by the liver. In contrast, liver metastases may escape hepatic inactivation and deliver their product directly into the systemic circulation and hence cause flushing.<sup>9</sup> Pulmonary or ovarian carcinoids release pharmacological products directly into the venous circulation, bypassing the portal system, and can therefore cause symptoms without metastasizing to the liver.<sup>1,10</sup>

### Pathophysiology

The flushing seen with foregut carcinoids is due to release of histamine. Flushing seen with ileal carcinoids cannot be explained solely by the production of serotonin.<sup>1</sup> Serotonin may or may not be released into the circulation during flushing, and intravenous infusion of serotonin does not cause flushing. Foregut carcinoids do not generally secrete serotonin but, instead, its precursor, 5-hydroxytryptamine. Screening should therefore seek this product if the other metabolites are not elevated.<sup>9</sup> Other mediators that have been proposed include prostaglandins and tachykinins. Tachykinins are believed to be mediators of the flushing in tumors of the midgut. They exert vasodilation and contraction of various types of smooth muscle. These peptides include substance P, substance K, and neuropeptide K. Urine excretion of histamine is usually increased in patients who have gastric carcinoid (**Table 3**).<sup>9</sup>

### Diagnosis

Clinical diagnosis is not difficult in patients with flushing episodes associated with systemic symptoms (diarrhea, wheezing, and weight loss) and hepatomegaly. It is more difficult in patients who have occasional flushing and no associated symptoms.<sup>1</sup> Only when there is reasonable clinical suspicion should biochemical testing be done, and localization studies must be reserved for those cases proven biochemically.<sup>10</sup> When in doubt, a carcinoid flush can be provoked by alcohol ingestion (4 mL of 45% ethanol) or the infusion of 6  $\mu$ g noradrenaline, an effect that can be blocked by phentolamine (5 to 15 mg intravenously). Calcium gluconate, 10 to 15 mg/kg, administered intravenously over 4 hours, may produce a flush mimicking a spontaneous attack.<sup>5</sup> Epinephrine reverses flushing in patients with mastocytosis but provokes flushing in patients with the carcinoid syndrome. The procedure should only be performed in a controlled environment. A 1  $\mu$ g/mL solution of epinephrine in normal saline is administered by intravenous bolus beginning with an initial dose of 0.05  $\mu$ g. The dose is doubled at intervals of 10 minutes until flushing appears or until a maximum of 6.4  $\mu$ g is given. When flushing occurs, it usually begins within 60 seconds after epinephrine administration and dissipates after 3 or 4 minutes.<sup>10</sup>

The diagnosis should be confirmed by determining urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, which is normally 2 to 10 mg (10 to 50  $\mu$ mol) per 24 hours.<sup>5</sup> A value of more than 150  $\mu$ mol/24 hours (30 mg/24 hours) usually confirms the diagnosis, and in carcinoid syndrome it is often above 40 mg per day.<sup>5</sup> This test has a sensitivity of 75% and a specificity of up to 100%. The degree of elevation of 5-HIAA does not always correlate with the severity of flushing.<sup>9</sup> Excretion fluctuates, so that repeated measurements may be necessary. Some patients with carcinoid may lack the metabolic machinery to convert serotonin to 5-HIAA, so they

have high blood levels of serotonin but normal urinary 5-HIAA.<sup>5</sup> Dietary factors may cause confusion; the patient should therefore receive a diet free of the culprit items (**Table 4**) for 3 days before the urine collection is made. Although the levels of serotonin in patients with tumors usually far exceed those found after food ingestion, this precaution helps to exclude carcinoid in individuals with borderline-high 5-HIAA levels.<sup>9</sup> Measuring blood serotonin is helpful when urinary 5-HIAA is equivocal. Patients with carcinoid syndrome have very high blood levels of serotonin. Measurement of serotonin and its metabolites permits the detection of 84% of neuroendocrine tumors. Even carcinoids that predominantly secrete 5-hydroxytryptophan are associated with increased urinary excretion of 5-HIAA because the released 5-hydroxytryptophan is converted to serotonin in other tissues and is subsequently metabolized to 5-HIAA.<sup>9</sup> Chromogranin A, a peptide co-secreted with serotonin, is elevated in most patients with carcinoid tumors. In the evaluation of flushing with an equivocal 24-hour urinary 5-HIAA, a normal plasma chromogranin A value suggests nonendocrine causes. This test is sensitive but not specific, and its predictive value in carcinoid is still uncertain.<sup>10</sup> Flushing was associated with a rise in circulating substance P in 80% of patients with gastric carcinoid. Neurokinin A levels are elevated in certain patients (**Tables 4 and 5**).<sup>9</sup>

### Management

Corticosteroids, phenothiazines, and bromocriptine have been effective in the treatment of patients with bronchial carcinoid tumors. The mechanism of action of these agents is unknown. Cyproheptadine, a serotonin antagonist, may control the flushing. Methysergide can control the diarrhea but has no effect on flushing. Combined administration of H<sub>1</sub> and H<sub>2</sub> receptor antagonists may prevent attacks of flushing in patients with foregut carcinoid tumors that produce histamine.<sup>10</sup> Alpha-interferons may control symptoms of carcinoid syndrome and produce objective biochemical responses (greater than 50% suppression of 5-HIAA) that have a median duration of about 4 weeks.<sup>10</sup> Since catecholamines are known to precipitate attacks, a trial of clonidine is worthwhile. Somatostatin is a potent antagonist of the flushing reaction associated with both gastric and ileal carcinoid tumors but has a short half-life. The somatostatin analogue octreotide has a much longer half-life, making subcutaneous therapy possible. It must be given by subcutaneous injection one to three times a day and should be titrated in increments of 50 µg every 8 hours.<sup>10</sup> Octreotide lowers plasma levels of serotonin and tachykinins and relieves both flushing and diarrhea. Amelioration of these manifestations is accompanied by a marked reduction in the urinary excretion of 5-HIAA.<sup>10</sup> Lanreotide, a long acting analogue of somatostatin administered intramuscularly every 14 days, is effective at controlling the flushing of carcinoids.<sup>11,12</sup> A depot form of octreotide (Sandostatin LAR) has been shown to control flushing at a dose of 20 mg intramuscularly every month.<sup>13</sup> Flushing may relapse with continued treatment.<sup>9</sup> The patient should receive an adequate niacin supplement (nicotinamide rather than nicotinic acid, since the latter causes flushing) and should avoid foods, agents, and activities that precipitate symptoms.<sup>5</sup>

In some patients, failure of medical treatment may necessitate carrying out hepatic artery embolization. This treatment is based upon the dependence of metastatic malignant tissue but not healthy liver parenchyma on an intact hepatic arterial blood supply. Anti-tumor chemotherapy remains experimental. Alpha-interferon causes symptomatic relief accompanied by lowering of urinary 5-HIAA. (For more discussion on the treatment of carcinoid tumors, see Carcinoid Tumor.)

### Prognosis

About one-fifth of patients with the carcinoid syndrome undergo a protracted course. In the remainder, deterioration can be rapid. The mean survival is about 8 years with some surviving up to 20 years. Mean survival is 36 months after the first flushing episode.<sup>9</sup>

### Mastocytoses:

#### Etiology

Mastocytoses are benign proliferative disorders of the reticuloendothelial system and familial cases have been reported. Mastocytoses are due to a hyperplastic rather than a neoplastic process. They are often self-limited, especially in childhood (**Table 6**). Mast cells possess the enzyme histidine decarboxylase which enables them to synthesize and store histamine. Other preformed mediators

include tryptase, chymase, and carboxypeptidase. Serotonin has not been detected in human mast cells.<sup>14</sup>

### **Histopathology**

There are increased numbers of normal-looking mast cells in the dermis. These cells may be predominantly perivascular or may show a nodular distribution. The epidermis is normal, apart from increased melanization.<sup>14</sup>

### **Biochemical Markers**

Symptoms of mastocytosis are mainly the result of release of products of mast-cell activation. Plasma histamine levels are frequently raised in patients with systemic symptoms, and elevated urinary excretion of histamine and its metabolite methyl imidazole acetic acid (MIAA) can also be seen. Plasma tryptase levels can also be elevated. Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is another product of mast-cell activation. Urinary excretion of this substance and its major metabolites can be elevated several-fold in patients with mastocytoses. Urine should be collected within a few hours of an attack.<sup>14</sup>

### **Clinical Presentation**

Episodic bright-red flushing occurs either spontaneously or after rubbing the skin or exposure to alcohol or mast-cell degranulating agents. Flushing attacks may be accompanied by headache, dyspnea and wheezing, palpitations, abdominal pain, diarrhea, and syncope and may closely resemble the flushing episodes of the carcinoid syndrome, especially the foregut variety, which are also mediated by histamine. Rosacea may develop rarely. PGD<sub>2</sub> might be associated with the symptoms of flushing and diarrhea.<sup>14</sup> The flushing of cutaneous mastocytosis typically lasts more than 30 minutes, unlike the typical carcinoid flush which lasts less than 10 minutes.<sup>5</sup> In urticaria pigmentosa, the diagnosis is established by demonstrating that gentle rubbing of the lesional skin causes local itching, redness, and whealing (Darier's sign). This reaction is due to local histamine release. Darier's sign may also be demonstrated in nonlesional skin. Confirmation of the diagnosis is obtained by skin biopsy. In patients with systemic symptoms, bone-marrow biopsy and liver and spleen scans are usually performed. Bone scans should only be carried out in the presence of localized bone symptoms.<sup>5,14</sup>

### **Treatment**

Treatment of nonlocalized forms of mastocytosis is mainly symptomatic. Patients should avoid known histamine-degranulating agents. Antihistamines remain the preferred treatment for most patients with uncomplicated urticaria pigmentosa. Human skin blood vessels possess H<sub>1</sub> and H<sub>2</sub> receptors, which are involved in both vasodilation and increased vascular permeability evoked by histamine. Thus, combination treatment with an H<sub>1</sub> antihistamine (hydroxyzine, 10 to 20 mg) and H<sub>2</sub> antihistamine (cimetidine, 200 to 500 mg) is logical and sometimes effective at controlling the flushing episodes. Oral administration of the mast-cell stabilizing agent disodium cromoglycate has proved effective in some patients. The drug does not decrease urinary excretion of histamine and the histamine metabolite MIAA. Some experts recommend using this agent only in patients with systemic mastocytosis suffering from gastrointestinal symptoms. Photochemotherapy has been reported to cause symptomatic relief as well as objective reduction in the population of mast cells and the urinary excretion of MIAA.<sup>14</sup>

### **Medullary Thyroid Carcinoma:**

The range of substances secreted by medullary carcinoma of the thyroid is considerable, whether sporadic or familial. Flushing is the most common symptom after diarrhea. Occurring in one-third of the patients with diarrhea, there is pronounced episodic flushing, which as in the carcinoid syndrome may be induced by alcohol ingestion. Calcitonin-gene related peptide, which is an extremely powerful peripheral vasodilator, is the most likely mediator that causes flushing.<sup>5</sup> The other possible explanation is that calcitonin stimulates prostaglandins which in turn cause the symptoms.<sup>12</sup>

## Harlequin Syndrome:

This describes hemifacial flushing and sweating sometimes associated with warmth and anhidrosis of the contralateral arm and leg (**Figure 4**). This may be induced by exercise. The suggested etiology is a lesion involving both preganglionic or postganglionic cervical sympathetic fibers and parasympathetic neurons of the ciliary ganglion.<sup>15</sup> Harlequin syndrome has been described in patients with a contralateral lung cancer invading the spine, Pancoast's syndrome, and Horner's syndrome.<sup>5</sup>

## Auriculotemporal Nerve Syndrome (Frey's Syndrome):

This syndrome usually manifests as immediate unilateral or bilateral flushing and/or sweating in the distribution of the auriculotemporal nerve in response to gustatory or tactile stimuli. In adults, this syndrome is a well recognized sequela of parotid surgery, trauma, or infection. It occurs rarely in children, most often noted after the introduction of solid food. The flushing is often attributed erroneously to food allergy. It typically begins at 2 to 6 months of age when solid foods, mostly fruit, are introduced. Occurring within a few seconds of eating, it has a peculiar distribution in a triangular area that extends from the tragus of the ear to the midpoint of the cheek. It is not associated with sweating and persists for 20 to 60 minutes. The flushing continues to occur for up to 5 years. In adults, gustatory sweating is the predominant feature of auriculotemporal nerve syndrome; flushing happens less often. Half of the pediatric patients with this symptom were delivered with forceps assistance which possibly causes trauma to the nerve. The likely mechanism is misdirection of parasympathetic fibers along sympathetic pathways during the nerve regeneration that follows trauma. This may account for erythema when eating. The emergence of symptoms several months after the proposed trauma (usually 3 to 6 months) is probably related to the time required for nerve regeneration, and it is possible that vigorous chewing causes intense stimulation of the parotid gland. Auriculotemporal nerve syndrome is benign in infants and does not tend to worsen. Furthermore, the severity of the flushing tends to diminish with age in most patients. The physician can reassure parents and avoid unnecessary testing and maneuvers<sup>16</sup> (**Figure 5**). A similar syndrome can develop after facial herpes zoster.<sup>17</sup>

## Flushing with Pseudocarcinoid Syndrome in Secondary Male Hypogonadism:

A series of three male patients with secondary hypogonadism has been described where flushing was associated with elevated 24-hour urine 5-HIAA. Flushing disappeared and 5-HIAA levels normalized after starting testosterone enanthate treatment. Male patients with flushing and increased urinary 5-HIAA levels should undergo assessment for hypogonadism after screening for carcinoid tumor.<sup>18</sup>

Treatments that lower serum testosterone, such as orchiectomy or luteinizing hormone-releasing hormone analogs, cause hot flushes in over half of men. Lack of regulatory feedback in the hypothalamus from circulating serum testosterone is the presumed mechanism. Most often, hot flushes are only mildly bothersome and can be tolerated without the need for treatment. However, if flushes are particularly annoying or problematic, treatment should be offered. Small doses of diethylstilbestrol are effective in relieving hot flushes but cause gynecomastia. Megestrol acetate, at a dose of 20 mg bid, completely eliminates hot flushes in most men, and the dose can be progressively lowered in some.<sup>19</sup>

## Other Diseases Causing Episodic Flushing:

Cheung et al<sup>20</sup> have described a family with monoamine oxidase deficiency causing episodes of flushing affecting the face and chest precipitated by emotion or certain foods, followed by diarrhea, headaches, and sometimes palpitations. Blood serotonin levels in this family were elevated secondary to decreased activity of monoamine oxidase. Sertraline hydrochloride controlled the symptoms by depleting platelet serotonin.

Flushing is rare in patients with pheochromocytoma. If flushing occurs at all, it is seen after a paroxysm of hypertension, tachycardia, palpitations, chest pain, severe throbbing headaches, and excessive perspiration. Pallor is typically present during the attack, and mild flushing may occur after the attack as a rebound vasodilation of the facial cutaneous blood vessels.<sup>5</sup> Facial flushing and headache can happen along with sweating of the face, neck, and upper trunk in patients with spinal cord lesions above T-6. This may occur as an exaggerated response to bowel or bladder distention.<sup>1</sup> Other causes are certain pancreatic tumors, insulinoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinemia, and skin changes). Transient flushing of the face, chest, or arms has been noted after neurological deterioration secondary to rapid rise in intracranial pressure.<sup>21</sup>

## ROSACEA

Persistent flushing from whatever cause may eventually lead to rosacea. The lesions of rosacea that initially occur in the central convex areas of the face consist of papules and pustules against a background of erythema, telangiectasia, edema, and eventual permanent induration or thickening of affected skin.<sup>2</sup> Patients with severe flushing due to mastocytosis can develop rosacea in less than a year after the onset of flushing episodes.<sup>5</sup>

## EVALUATION OF THE PATIENT WITH A FLUSHING DISORDER

It is important to consider the clinical characteristics of the flushing before embarking on expensive laboratory evaluation.<sup>5</sup> The physician should consider four clinical characteristics in the initial evaluation of a patient with flushing: 1) provocative and palliative factors, 2) morphology, 3) associated features, and 4) temporal characteristics.<sup>2</sup>

**Provocative or palliative factors:** Certain agents that trigger the flush suggest an underlying systemic disease as the cause for the flushing, eg, mastocytosis and carcinoid syndrome.

**Morphology:** Is there a basic feature that comes and goes? Is the redness patchy or confluent? What is the color of the flush? Is there cyanosis? Is the flushing preceded or followed by pallor?<sup>2</sup> The morphology of the flushing may suggest not only the cause of the flushing but also, in the case of carcinoids, the anatomic origin of the disorder.<sup>5</sup> **Associated features:** These may include respiratory symptoms, gastrointestinal symptoms, headache, urticaria, facial edema, hypertension, hypotension, palpitations, or sweating. **Temporal characteristics:** These are the frequency of the flushing and the timing of the specific features during each flushing reaction. Important information can be obtained from a 2-week diary in which the patient records qualitative and quantitative aspects of the flushing event and lists exposure to all exogenous agents.<sup>2</sup> When the diagnosis remains obscure after evaluation of the 2-week diary, the patient is given an exclusion diet listing foods high in histamine, foods and drugs that affect urinary 5-HIAA tests, and foods and beverages that cause flushing. If the flushing reactions completely disappear, restoring the excluded items individually can identify the causative agent. If the flushing reactions continue unchanged, then further metabolic work up may be undertaken.<sup>5</sup>

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