

A clinicopathologic study of ten patients with recurrent unexplained flushing

Beth S. Friedman, MD, Patrizia Germano, MD, Jose Miletti, RN, and
Dean D. Metcalfe, MD Bethesda, Md.

We describe the clinicopathologic features of 10 patients with recurrent unexplained flushing. These patients were referred to the National Institutes of Health with a diagnosis of mastocytosis or idiopathic anaphylaxis. Both diagnoses were eliminated after evaluation. Patients reported attacks of flushing lasting 15 minutes to 2 days and associated with such symptoms as anxiety, chest tightness, paresthesia, slurred speech, weakness, and pruritus. Abdominal pain was a constant feature, often associated with cramping and an increase in stool frequency. Attacks witnessed by physicians consisted of an exaggerated blush response of the face and upper part of the chest, and were sometimes associated with tachycardia, mild hypertension, and tachypnea. Hives, angioedema, wheezing, and hypotension were not observed. Routine laboratory studies and 5-hydroxyindoleacetic acid, vanillylmandelic acid, and plasma histamine levels were normal. Plasma histamine levels did not elevate during attacks. When performed, results of bone marrow examinations, skin biopsies, and bone scans were normal. Psychiatric examinations frequently revealed somatization disorders. Patients had often been prescribed a wide variety of medications including antihistamines, nonsteroidal anti-inflammatory drugs, and steroids, with little or no benefit. Despite the benign nature of the clinical and laboratory findings, patients had undergone repeated, often invasive, examinations for several years. Whether such patients have a prominent flush response exaggerated through a somatization disorder or a relatively benign flushing disorder associated with putative mediator release remains to be determined. Recognition of this category of patients with unexplained flushing will avoid subjecting such patients to unwarranted repeated examinations, procedures, and inappropriate therapy. (J ALLERGY CLIN IMMUNOL 1994;93:53-60.)

Recurrent episodes of flushing may be the presenting symptom of disorders including carcinoid syndrome, pheochromocytoma, medullary carcinoma of the thyroid, and mastocytosis. Flushing has also been associated with menopause and with consumption of alcohol. Finally, in some persons flushing may represent an exaggerated normal blush response.¹⁻³ In this article we describe a group of 10 patients referred to the National Institutes of Health (NIH) with the diagnosis of mastocytosis or idiopathic anaphylaxis, who had remarkably constant clinical features. Presenting complaints included recurrent episodes of cutaneous flushing associated with varying degrees of gastrointestinal, respiratory, and cardiac symptoms. After extensive observa-

Abbreviations used

S-HIAA:	5-Hydroxyindoleacetic acid
S-HT:	5-Hydroxytryptamine (serotonin)
NIH:	National Institutes of Health
NSAID:	Nonsteroidal anti-inflammatory drug

tion and evaluation, diseases in the different diagnoses, including mastocytosis, were eliminated as explanations for the flushing. Despite the apparently benign nature of the acute episodes, substantial disability was incurred by all patients. Confusion in diagnosis often led to an extensive medical evaluation before NIH referral and the unsuccessful use of medications including H₁ and H₂ antihistamines, calcium channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids. Clinical features, laboratory evaluation, and clinical prognosis are detailed.

METHODS

Patients

This report details the experience with 10 patients who were referred to the National Institute

From the Mast Cell Physiology Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

Received for publication Nov. 6, 1992; revised May 26, 1993; accepted for publication May 28, 1993.

Reprint requests: Dean D. Metcalfe, MD, Bldg. 10, Room 11C210, National Institutes of Health, Bethesda, MD 20892.

1/1/49026

of Allergy and Infectious Diseases for the evaluation and diagnosis of episodic attacks of flushing. The presenting diagnosis was either mastocytosis or idiopathic anaphylaxis. Four patients were examined in the outpatient clinic and six as inpatients, from January 1981 to April 1989.

Clinical assessment

A complete medical history was obtained from each patient. The patients were asked to describe a typical attack, including the frequency and duration of attacks; precipitating factors, including relationship to meals, menstruation, alcohol ingestion, and medications; and the presence or absence of throat tightness, hoarseness, chest tightness, cough, wheezing, pruritus, urticaria, dizziness, syncope, palpitations, chest pain, nausea, vomiting, diarrhea, and abdominal pain. All patients then underwent a physical examination during an asymptomatic period, and seven patients had a physical examination during an attack. Psychiatric examinations were performed by the Psychiatric Consultation Service of the National Institute of Mental Health for patients who were willing to be reviewed (patients 1, 3, and 6 through 10). Diagnosis was based on the criteria in the *Diagnostic and Statistical Manual of Mental Disorders (Third Edition—Revised)*.⁴

Laboratory studies

A comprehensive laboratory evaluation including a complete blood cell count and differential; urinalysis; and levels of serum electrolytes, fasting serum glucose, creatinine, blood urea nitrogen, calcium, phosphorus, total bilirubin, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, and total protein was obtained for all patients. Twenty-four-hour urine collections were analyzed for 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid on all patients. Posterior iliac crest bone marrow biopsy specimens and aspirates were obtained with standard techniques where clinically indicated for the evaluation of mastocytosis (patients 3 to 10). The biopsy specimens were fixed in formalin, embedded in paraffin, and sectioned, and slides were stained with hematoxylin and eosin, Giemsa, and toluidine blue to look for the characteristic lesions of mastocytosis.³ Skin biopsy specimens⁵ and technetium Tc 99m methylenediphosphonate bone scintigrams⁶ were obtained when clinically indicated, to find lesions representative of mastocytosis (patients 4, 6, 8 to 10).

Plasma histamine levels

Early-morning venous samples were collected in tubes containing ethylenediaminetetraacetic acid and placed immediately on ice. The samples were then centrifuged at 400g for 5 min. Plasma was separated with a pipette well away from the buffy coat. The fresh plasma was frozen in polypropylene tubes at -20°C

and stored until the time of analysis. It has been shown previously that plasma samples could be frozen and stored at -20°C without loss or increase in histamine content.⁷ Plasma histamine was measured by a modification of a single-isotope enzymatic assay involving extraction of [^3H]methylhistamine into chloroform with subsequent isolation by thin-layer chromatography.⁸ The plasma histamine determinations were performed by technicians who were unaware of the clinical diagnosis.

Skin prick tests

Skin prick tests with extracts obtained from the Walter Reed Extract Laboratories were performed on all patients. No subject had received antihistamines more recently than 72 hours before the study. No patients were receiving long-acting antihistamines. A drop of standard extract was placed on the volar surface of the forearm. An Amsco needle (1 mm tip) was used to prick through a drop of the extract. Controls were histamine, 10 mg/ml, and phenol saline solution. Thirteen airborne allergens were used: tree mix (ash, birch, elm, hickory, oak, poplar, sycamore, maple), grass mix (Kentucky, rye, orchard, timothy, Bermuda, meadow, fescue), mold mix I (*Alternaria*, *Helminthosporium*, *Phoma*, *Aureobasidium*), mold mix II (*Aspergillus*, *Penicillium*, *Mucor*, *Rhizopus*), dust mix (*Dermatophagoides farinae*), *Aspergillus*, cat and dog epithelia, mouse, cockroach, and feathers. Thirty-eight foods were tested. Positivity was rated as 1+ if the diameter of the erythematous wheal was less than 2 mm, 2+ if the wheal was at least 2 mm but less than 3 mm, 3+ if wheal was at least 3 mm, and 4+ if pseudopods with surrounding erythema were present.

RESULTS

Demographics

Characteristics of the patient population are presented in Table I. The group consisted of 10 patients, predominantly women (9:1) with a mean age of 29.7 years at the time of presentation. The age at which symptoms began ranged from 12 to 36 years (mean 26.5 years). Medical consultation and therapy were sought for an average of 3.2 years before referral to the NIH. Five of the patients (50%) worked in health-related fields, and none had a family history of flushing.

Lack of correlation between historical and physician-observed attacks

The patients' descriptions of their attacks, as obtained by history, are shown in Table II. Flushing was described by all patients and was predominantly but not exclusively of the face. Episodes of flushing, by history, lasted from 15 minutes to as

TABLE I. Patient demographics

Patient No.	Sex	Age (yr) at presentation at NIH	Age when symptoms began (yr)	Yr of medical treatment before referral	Occupation	Family history of flushing
1	F	16	12	4	Student	No
2	F	29	27	2	Receptionist in MD office	No
3	F	35	33	2	Homemaker	No
4	F	39	36	3	Homemaker	No
5	F	31	30	1	Nurse	No
6	F	32	28	4	Nurse	No
7	F	23	12	11	Secretary	No
8	M	38	36	2	Office worker	No
9	F	31	30	1	Psychiatrist	No
10	F	23	21	2	Cardiac rehabilitation student	No
Mean		29.7	26.5	3.2		

long as 2 days. Attacks were not temporally related to the menstrual cycle. One patient (No. 1) described these episodes of flushing as being painful. Half the patients described a prodrome with symptoms including anxiety, air hunger, chest tightness, paresthesias, slurred speech, weakness, and fatigue. Pruritus was present in five patients. Gastrointestinal symptoms were common (eight patients), and manifested in all eight patients as abdominal pain and as an increase in stool frequency (three to six) loose stools per day occurring from 1 hour to 1 week after a flushing episode) in six patients. Light-headedness and dizziness occurred in four and syncope in three of the 10 subjects. Palpitations were described by three patients. Urticaria was uncommon (two patients), as was headache (three). Respiratory symptoms were commonly described (six patients) as shortness of breath, throat swelling, and upper airway "congestion."

Attacks were observed by physicians in seven patients (Table III). Six patients had cutaneous vasodilation, predominantly of the face and chest; none had urticaria. Evaluation of vital signs demonstrated tachycardia in three patients, mild hypertension in three, and tachypnea in two (patients 7 and 8). The three patients (Nos. 6, 7, and 8) with tachycardia had confirmed sinus tachycardia on electrocardiogram. One patient (No. 6) subsequently had sinus arrhythmia documented on a 24-hour Holter monitor. No patient had wheezing or stridor. All five patients examined had normal blood glucose level during an attack.

Two patients (Nos. 7 and 8) became unresponsive during an attack.

Laboratory evaluation

All 10 patients underwent an extensive laboratory examination. Nine patients had completely normal serum electrolyte levels, renal and liver function, and urinalysis findings. One patient (No. 5) was found to have hypokalemia (mean K^+ 2.7 mEq/L) and hypochloremia (mean Cl^- 93 mEq/L), which was found to be the result of diuretic abuse. Patients 7 and 8 had arterial blood gases drawn during and 3 hours after an attack because of suspected hyperventilation. Respiratory alkalosis was demonstrated during the attack in both patients, with normalization on repeated analysis. All patients had plasma histamine levels measured during an observed attack. An elevated plasma histamine level (1570 pg/ml) was found in one patient (No. 10) during an attack; however, this was not reproduced during subsequent attacks. Plasma histamine levels were normal in all patients during asymptomatic periods (<619 pg/ml).⁹

All patients underwent multiple 24-hour urinary 5-HIAA measurements to rule out carcinoid syndrome. Urinary 5-HIAA levels were normal in all patients. In those persons (Nos. 5 and 9) where clinical suspicion warranted further evaluation for carcinoid tumor, computed tomography of the abdomen and chest was done, and no abnormalities were found. Twenty-four-hour vanillylmandelic acid and metanephrine values were obtained

TABLE II. Historical signs and symptoms during attack

Patient No.	Frequency of attacks	Prodrome	Flushing	Pruritus/urticaria
1	2-4/mo	None	Entire body, 1-2 days	Yes/no
2	2-3/mo	None	Face, arms; 3 hr	Yes/yes*
3	Weekly	Anxiety	Entire body, 1 hr	No/no
4	Daily	None	Face, palms; 1 hr	No/no
5	Daily	None	Face; 1 hr	No/no
6	Daily	None	Face; 1 hr	Yes/no
7	Daily	AH/CT/P	Face, chest, back, abdomen; 15-30 min	No/no
8	Daily	AH/CT/P	Face, arms, trunk; 20 min	Yes/no
9	Daily	T/W/SS	Face, chest; 20 min	Yes/no
10	Daily	W/SS	Face, neck, chest; 1-2 hr	No/yes

AC, Abdominal cramping; AH, air hunger; AP, abdominal pain; CT, chest tightness; D, diarrhea; ID, intermittent diarrhea; OUAC, occasional upper airway congestion; P, paresthesias; SB, shortness of breath; SS, slurred speech; T, tightness; UTS, unilateral throat swelling; V, vomiting; W, weakness.

*Urticaria never witnessed or rare.

in all patients and were within normal limits. To rule out mastocytosis, patients 3 through 10 underwent a bone marrow biopsy and aspiration, all of which were normal. Skin biopsies were performed on lesions that were suspected as urticaria pigmentosa in patients 4, 6, 8, 9, and 10. None had increased mast cell numbers. Bone scans were performed in patients 4, 6, 8, 9, and 10 and were not consistent with mastocytosis.

Frequency of associated atopic disorders

Half the patients had allergic rhinitis and/or asthma (Nos. 2, 3, 6, 9, 10). All patients were skin tested and four (Nos. 2, 3, 8, 10) responded to various airborne allergens; one patient (No. 2) had positive skin reactions to foods. Three patients had reported an anaphylactic episode: after a meal (No. 4) and to theophylline (No. 6) and fire ant (No. 9). One patient (No. 2) was suspected of having food allergies, but flushing episodes were not related to meals. Patients 6 and 10 reported drug and radiocontrast dye reactions. Patient 9 had insect sensitivity.

Referral versus NIH diagnosis

Prior diagnoses, referral diagnoses, NIH diagnoses, and psychiatric diagnoses are reviewed in Table IV. Patients were placed in the category of unexplained flushing if the diseases known to be associated with flushing were eliminated as diagnostic possibilities. In patient 1 systemic lupus erythematosus was originally diagnosed on the basis of a positive antinuclear antibody titer; however, after numerous repeated normal values and

in the absence of the clinical features of lupus, the diagnosis was changed to idiopathic anaphylaxis. After an extensive evaluation at the NIH, she was categorized as having unexplained flushing and a somatization disorder. Patient 2 was referred for the evaluation of idiopathic anaphylaxis. She was atopic, had multiple positive skin test results and abnormal pulmonary function test results; however, her attacks were not those of anaphylaxis and could not be associated with allergic stimuli, and she was therefore classified as having unexplained flushing. Patients 3 through 10 were referred for evaluation of mastocytosis. Mastocytosis was effectively ruled out in all patients. Patient 3 was judged to have a mood disorder in addition to flushing, and patient 5 was found to be abusing diuretics, although this could not be related to the facial flushing. Patient 6 had been diagnosed and treated for hereditary angioedema for 18 months without improvement in her symptoms. Reevaluation of her complement profile at the NIH led to the exclusion of this diagnosis. Before her NIH evaluation and after multiple attacks and emergency room treatments, she was given high-dose steroids to try to decrease the frequency of her attacks. She became dependent on steroids, and when a taper was attempted, she would report increasing attacks mimicking anaphylaxis. Steroid-induced hypertension and obesity developed, and she was referred to the NIH for evaluation of mastocytosis. Mastocytosis was ruled out, and she was categorized as having unexplained flushing. Psychiatric evaluation revealed a personality and somatization disorder. Patients 7 and 8 were re-

GI symptoms	Light-headedness/dizziness	Syncope	Palpitations	Headache	Respiratory symptoms
AP	No	No	No	Yes	No
AP/D	No	No	No	No	No
None	No	No	Yes	No	UTS
AP/ID	No	No	No	No	Hoarseness
AP/V/D	No	Occasional	No	No	OUAC
AC/ID	Yes	Occasional	Yes	No	Cough, SB
AP/D	Yes	Frequent, with or without flush	Tachycardia	Yes	SB
None	Yes	No	No	No	SB
AP/D	No	No	No	No	None
AP	Yes	No	No	Yes	None

ferred with the diagnosis of mastocytosis on the basis of clinical suspicion. Patient 7 had been treated with high-dose aspirin for presumed mastocytosis without improvement. Aspirin-induced gastritis and ulcers developed, which resulted in gastrointestinal hemorrhage and an exploratory laparotomy. Mastocytosis was ruled out. Both patients were shown to hyperventilate during flushing episodes. Patients 9 and 10 were also referred for evaluation of mastocytosis and had a similar constellation of symptoms, with attacks of facial flushing associated with a prodrome of tiredness and slurred speech. Both were categorized as having unexplained flushing and a somatization disorder.

Therapy

Various therapeutic modalities were unsuccessfully employed in these patients before referral to the NIH. These unsuccessful therapies are presented in Table V. Nine patients were treated with H₁ and H₂ antihistamines. All reported mild but unsatisfactory relief of their symptoms and continued to have frequent attacks. Therapeutic doses of NSAIDs were used in four patients (Nos. 4, 6, 7, and 10) without success. Systemic steroids were administered to one patient (No. 6), who reported a decreased severity and frequency of her attacks with high doses; however, with attempted tapering the attack frequency would increase. Calcium channel blockers were prescribed for two patients (Nos. 3 and 9), without success.

Follow-up

Follow-up evaluations were obtained from 1 to 6 years after the last NIH visit. Six of the 10 patients were contacted; four were lost to follow-

up. Two of the six patients contacted were too busy to discuss their condition. One patient (No. 2) had not had an attack for 1 year. The total duration of disease was 5 years. She did not receive psychiatric counseling. Patient 10 had significant improvement in the frequency and severity of her attacks after extensive psychiatric counseling both as an inpatient (2 months) and outpatient (10 months). This patient continued to take H₁ antihistamines and NSAIDs intermittently. Patient 3 sought further medical evaluation on discharge from the NIH and was told she had "idiopathic postprandial syndrome." She reported that her attacks were less frequent while she followed a strict hypoglycemic diet. Patient 6 had mild improvement in her disease, which she attributed to continued systemic steroid and H₁ and H₂ antihistamine use.

DISCUSSION

This article describes a group of 10 patients originally referred to NIH with the diagnosis of mastocytosis or idiopathic anaphylaxis. After an extensive evaluation these persons were discharged with the diagnosis of unexplained flushing. Characteristics of this group included a female predominance (female/male ratio 9:1), young age (12 years younger than those reported with idiopathic flushing),¹⁰ and long duration of symptoms (average 6.9 years) (Table I). The primary symptoms reported were flushing, abdominal pain, and frequent stools after flushing episodes (Table II). There was often an apparent exaggerated description of the attacks given by the patients, with few abnormalities found during physician-documented attacks (Table III). Routine laboratory studies and plasma histamine lev-

TABLE III. NIH physician-observed attacks

Patient No.	Flushing	Urticaria	Heart rate (beats/min)	Blood pressure (mm Hg)	Respiratory rate (breaths/min)	ECG changes	Wheezing	Syncope	Glucose level (mg/dl)
3	No	No	90	110/60	16	ND	No	No	ND
5	Face	No	76	90/60	20	ND	No	No	ND
6	Face	No	129	142/90	18	Sinus tachycardia	No	No	80
7	Face, chest	No	120	146/94	50	Sinus tachycardia	No	Yes	84
8	Face, chest	No	152 (during exercise)	176/86	40	Sinus tachycardia	No	Unresponsive*	101
9	Face, neck, chest	No	86	120/78	20	ND	No	No	90
10	Face, chest	No	80	122/80	16	ND	No	No	88

ECG, Electrocardiogram; ND, not done.

*Positive response to noxious stimuli.

els were almost always normal. There was a high percentage of underlying psychiatric abnormalities, with somatization disorder being the most prevalent, occurring in 86% (Table IV). Similarly, these patients were often diagnosed and treated for other disorders, most commonly mastocytosis and idiopathic anaphylaxis.

The erythema seen in these patients was consistent with that described in the literature in association with flushing.^{2, 11, 12} The distribution was in the "blush area," which includes the face, ears, and neck in most persons, the upper chest in some, and the epigastric area in a few.¹³ This distribution is seen with most flushing reactions despite the systemic nature of the provoking factors such as alcohol, when identified. One explanation for this is the greater vascular capacitance in the visible superficial cutaneous vasculature in the blush area.¹¹

Vasomotor symptoms are associated with declining estrogen levels during menopause. This possibility was considered, and in no instance could the recurrent flushing be attributed to declining ovarian function. Similarly, recurrent hives and even anaphylaxis have been associated with the menstrual cycle.¹⁴ However, no consistent temporal relationship was found between flushing episodes and the menstrual cycle.

Numerous attempts have been made in patients with carcinoid syndrome and flushing to try to elucidate the mediator responsible for flushing. It has been shown that 5-hydroxytryptamine (5-HT; serotonin) and bradykinin are not responsible.¹⁵⁻¹⁷ Other proposed flushing substances include hista-

mine, substance P, prostaglandins,^{18, 19} and various tachykinins, none of which has been shown to be the primary mediator.²⁰ The role of the vascular endothelium is not clear. It is known that vascular endothelium produces an endogenous vasodilator, endothelium-derived relaxing factor, which can be released by acetylcholine, substance P, vasoactive intestinal polypeptide, and 5-HT.¹⁷ Therefore the exact pathophysiology of flushing is still not understood, which explains the lack of effective therapy for patients with repeated episodes of flushing. Numerous therapeutic modalities have been attempted with minimal success, including propranolol, chlorpromazine, 5-HT antagonists, combination H₁ and H₂ histamine antagonists, and steroids.

The association of atopy in patients with unexplained flushing is slightly greater than in the general population; however, in none of these patients was an allergic stimulus found to provoke an attack, nor did the attack itself resemble anaphylaxis. Plasma histamine levels were normal between attacks, and plasma histamine levels were not elevated during flushing episodes. Thus the etiology of the flushing episodes does not appear to involve mast cell-dependent mediator release, as seen in mastocytosis, idiopathic anaphylaxis, and other disorders of mast cell dysfunction. This does not eliminate the possibility of a role for prostaglandin D₂, which may be elevated in the absence of evidence of mast cell involvement.¹⁹

It is interesting to note the high prevalence of psychiatric disorders in patients with unexplained

TABLE IV. Diagnoses before, at, and after referral to NIH

Patient No.	Prior Dx	Referral Dx	NIH Dx	Psychiatric Dx
1	Systemic lupus erythematosus	IA	UEF	Somatization disorder
2	IA	IA	UEF, food allergy, allergic rhinitis, extrinsic asthma	ND
3	None	Mastocytosis	UEF	Mood disorder
4	None	Mastocytosis	UEF	ND
5	None	Mastocytosis	UEF, diuretic abuse	ND
6	Hereditary angio-edema, IA	Mastocytosis	UEF	Personality and somatization disorder
7	Irritable bowel syndrome, thyro-toxicosis	Mastocytosis	UEF, hyperventilation syndrome	Psychiatric cause of hyperventilation
8	None	Mastocytosis	UEF, hyperventilation syndrome	Psychiatric cause of hyperventilation, somatization disorder
9	Carcinoid syndrome	Mastocytosis	UEF	Somatization adjustment disorder
10	None	Mastocytosis	UEF	Somatization and mixed personality disorder

Dx, Diagnosis; IA, idiopathic anaphylaxis; ND, not done; UEF, unexplained flushing.

flushing (Table IV). These patients often undergo repeated extensive evaluations in an attempt to diagnose a disease associated with flushing. It is unclear as to whether the confusion attendant to repeated medical evaluations contributes to the degree of patient complaints and/or that the patient has an exaggerated flushing response, which is then magnified in importance through the dynamics associated with an underlying psychiatric condition. In two patients hyperventilation contributed to the confusion, and, when identified, substantially reduced confusion; however, the association between flushing, abdominal pain, and psychiatric complaints suggests that many of these patients are reacting to the release of some mediator.

The focus of our referral pattern is mastocytosis. Interestingly, Aldrich et al.,¹⁰ examining patients for carcinoid syndrome, found a group of patients (predominantly women) who had flushing, sometimes associated with gastrointestinal complaints, but in which the diagnosis of carcinoid syndrome was ruled out. They referred to these patients as having idiopathic flushing. Although the patients we describe generally have similar features, our patients tended to be

TABLE V. Unsuccessful therapeutic modalities

	No. of nonresponders/No. receiving drug
H ₁ and H ₂ antagonists	9/9
NSAIDs	4/4
Systemic steroids	1/1
Calcium channel blockers	2/2
Danazol	1/1
Cromolyn sodium	1/1

younger. In addition, our report extends the observation made by Aldrich et al. by eliminating mastocytosis as a diagnostic possibility, in documenting duration of complaints and medication failures, in correlating historical complaints with physician-observed attacks, in demonstrating the morbidity associated with prolonged and unnecessary medical evaluations, and in diagnosing both allied medical and psychiatric associations. This being said, the observation that similar patterns of unexplained flushing are observed in separate

referral patterns documents the need to study this population of patients in an attempt to understand the underlying disorder, to approach better the diagnosis and treatment of these patients.

Despite the apparently benign nature of the disorder, patients had often undergone repeated evaluations in apparent excess to the degree of morbidity and nature of the attacks. It seems more appropriate that patients with unexplained flushing undergo an initial evaluation to rule out diseases including carcinoid tumor and mastocytosis. Attacks should be witnessed whenever possible by the physician, during which such diagnosis as hyperventilation could become apparent. Usually the attacks of flushing in the patients reported in this article were benign, did not resemble anaphylaxis, and were of no immediate threat to the well-being of the patient.

In our opinion, after the initial evaluation, patients should be reexamined every 6 to 12 months to determine whether symptoms are worsening, thus requiring further studies. If symptoms are not progressive, the patient may be spared needless studies. A psychiatric consultation is recommended. Known medications such as antihistamines, aspirin, and steroids are of minimal benefit.

We thank the medical staff fellows of the National Institute of Allergy and Infectious Diseases and the nursing staff of the Clinical Center for their help in caring for these patients, and Belinda Richardson for typing the manuscript.

REFERENCES

1. Medlin IM. Carcinoid syndrome. *J Clin Gastroenterol* 1980;2:349-54.
2. Mooney F. The flushing patient. *Int J Dermatol* 1985;24:549-54.
3. Travis WD, Chin-Yang L, Bergstrath EJ. Systemic mast cell disease: analysis of 58 cases and review of the literature. *Medicine* 1988;67:345-67.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed—revised. Washington, DC: American Psychiatric Association, 1987:261-64.
5. Garriga MM, Friedman MM, Metcalfe DD. A survey of the number and distribution of mast cells in the skin of patients with mast cell disorders. *J ALLERGY CLIN IMMUNOL* 1988;82:425-32.
6. Rosenbaum RC, Frieri M, Metcalfe DD. Patterns of skeletal scintigraphy and their relationship to plasma and urinary histamine levels in systemic mastocytosis. *J Nucl Med* 1984;25:859-64.
7. Shaff RE, Beaven MA. Increased sensitivity of the enzymatic isotopic assay of histamine: measurement of histamine in plasma and serum. *Anal Biochem* 1979;94:425-30.
8. Dyer J, Warren K, Merlin S, Metcalfe DD, Kaliner MA. Measurement of plasma histamine: description of an improved method and normal values. *J ALLERGY CLIN IMMUNOL* 1982;70:82-7.
9. Friedman BS, Steinberg S, Meggs WJ, et al. Analysis of plasma histamine levels in patients with mast cell disorders. *Am J Med* 1989;87:649-54.
10. Aldrich LB, Moattaci AR, Vinik AI. Distinguishing features of idiopathic flushing and carcinoid syndrome. *Arch Intern Med* 1988;148:2614-8.
11. Wilkin JK. Why is flushing limited to a mostly facial cutaneous distribution? *J Am Acad Dermatol* 1988;19:309-13.
12. Wilkin JK. Flushing reactions: consequences and mechanisms. *Ann Intern Med* 1981;95:468-76.
13. Wilkin JK. Flushing reactions. In: Rook AJ, Marbach HI, eds. Recent advances in dermatology; vol. 6. New York: Churchill Livingstone, 1983:157-87.
14. Meggs WJ, Pescovitz OH, Metcalfe DD, Loriaux L, Cutler GJR, Kaliner MA. Progesterone sensitivity as a cause of recurrent anaphylaxis. *N Engl J Med* 1984;78:9-14.
15. Robertson JIS, Pearl WS, Andrews TM. The mechanism of facial flush in the carcinoid syndrome. *Q J Med* 1962;31:103-22.
16. Gustafsen J, Boesby S, Nielsen F, Giese J. Bradykinin in carcinoid syndrome. *Gut* 1987;28:1417-9.
17. Grahame-Smith DG. What is the cause of the carcinoid flush? *Gut* 1987;28:1413-6.
18. Roberts LJ II, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D₂ in patients with systemic mastocytosis. *N Engl J Med* 1980;303:1400-4.
19. Morrow JD, Parsons WG III, Roberts LJ II. Release of markedly increased quantities of prostaglandin D₂ in vivo in humans following administration of nicotinic acid. *Prostaglandins* 1989;38:263-74.
20. Pernow B, Waldenstorm J. Determination of 5-hydroxytryptamine, 5-hydroxyindoleacetic acid, and histamine in 33 cases of carcinoid tumor (argentaffinoma). *Am J Med* 1957;34:18-25.