Hazards in Operative Management of Patients with Systemic Mastocytosis

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During the past two years, six patients with systemic mastocytosis have required general or regional anesthesia for operative correction of various surgical problems. Mastocytosis constitutes an extremely difficult problem in diagnosis and management. A large experience with patients with mastocytosis in the Vanderbilt Medical Center in the last decade has enhanced awareness of this disorder and increased its early recognition. The hazardous problems of systemic mastocytosis and the difficulties of its diagnosis and management are summarized and focussed on the increased hazard of those patients with this disease who require various surgical operations. Close collaboration between anesthesiologists, surgeons, and internists in this medical center in the past two years has made it possible to carry six of these patients through anesthesia, operation, and the postoperative period safely and without fatality.

MASTOCYTOSIS is a disorder, characterized by an abnormal proliferation of the tissue mast cells, that can involve multiple organs of the body. Patients with mastocytosis frequently experience episodic attacks of flushing, palpitation, tachycardia, apnea, dyspnea, headache, pruritus, and occasionally nausea, vomiting, and diarrhea. Severe attacks are accompanied by syncope and profound hypotension, which can progress to refractory shock and death[1] (Table 1).

The symptoms of mastocytosis have been attributed previously to the release of histamine from mast cells, although antihistamine therapy has not been found generally to ameliorate the symptoms of this disease.[2,3] Recent work in this institution has documented overproduction of prostaglandin D2 in patients with mastocytosis and assembled evidence that prostaglandin D2 is an important mediator of the attacks in these patients.[3]

The attacks associated with mastocytosis result primarily from nonIgE-mediated mechanisms of mast cell activation. A number of provoking factors have been identified in these patients including emotional upsets, anxiety, physical exertion, heat, cold, occasionally alcohol ingestion, a variety of pharmacologic agents, and doubtless many other unidentified factors.

In consequence, various precautions must be taken to avoid known provoking factors and hazardous drugs in patients with mastocytosis who are required to undergo surgical procedures. In addition, specific consideration must be given to the immediate accessability of pharmacologic agents to reverse an acutely severe attack that may occur during anesthesia, operation, or the perioperative period. Most important in this regard is the availability of epinephrine for continuous intravenous infusion, which has recently been found to be uniquely effective in reversing severe episodes of hypotension associated with mastocytosis.[4]

In the past two years we have observed six patients with systemic mastocytosis who have required various operative procedures. Experience with these patients and their problems has prompted this report.

Clinical Cases

Case 1 (M.L.)

A 35-year-old white woman was admitted to Vanderbilt Hospital for the first time in October 1980 with a history of four syncopal episodes during the previous ten months. Each episode was accompanied by abdominal cramps, diarrhea, flushing, tachycardia, and well-documented profound hypotension. Previously well, she had her first syncopal episode in December 1979. Her periods of unconsciousness were for two to four hours—all having occurred at night—three while asleep and the last during sexual intercourse.

Previous work-up at another hospital had ruled out carcinoid syndrome, Cushing's syndrome, and thyroid abnormalities.

Physical examination on October 15, 1980, showed an obese white woman with temperature 98.6 F, pulse 80, respirations 20, and blood

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TABLE 1. *Episodic Attacks in Patients with Mastocytosis*

Flushing	Pruritus
Palpitation	Nausea
Tachycardia	Vomiting
Headache	Diarrhea
Dyspnea	Hypotension
Syncope	Cardiac arrest

pressure 130/80 mmHg. She breathed easily with no effort. Skin showed a positive Darier's sign with a wheal and flare after scratching the skin. The remainder of the examination was not remarkable.

Laboratory examination: An SMA-12 was within normal limits as was admission urinalysis.

Hospital course: Serial 24-hour urines were collected for prostaglandins and histamine. A skin biopsy showed an increase in mast cells in the dermis, both relative and absolute (10–15 mast cells per high power field).

Several 24-hour urines for catecholamines and cortisol metabolites were normal, but prostaglandins and histamine were elevated. A 24-hour urine for prostaglandin D2 metabolite (PGD-M) was found to contain 3526 nanograms (normal 238 ± 156). Urinary histamine was 113 μg/24 hours (normal <30 μg/24 hours).

The patient was discharged on Chlorpheniramine 8 mg by mouth (po) four times a day (qid), cimetidine 300 mg qid, and aspirin 3 tablets qid.

She was readmitted to Vanderbilt Hospital in March 1981 because of pregnancy and a wish for abortion and tubal ligation. In recent days, she had had moderate vaginal bleeding. Symptoms of mastocytosis had been obviated satisfactorily by medication. However, she had two healthy children and a fear of exacerbation of mastocytosis by pregnancy and delivery. Physical findings confirmed the uterus to be compatible with ten weeks gestational size with no adnexal masses.

Preanesthetic preparation was Valium 10 mg (po), aspirin 0.9 g (po), cimetidine 300 mg intravenously (IV), and atropine 0.4 mg intramuscularly (IM). General anesthesia was induced with ethrane, nitrous oxide, and oxygen. A therapeutic abortion by cervical dilatation, endometrial suction, and currettage was done and followed by laparoscopic tubal sterilization (Dr. Angus Crook). The patient withstood the procedure well.

Postoperative recovery was uneventful. No syncopal or hypotensive attacks occurred. Antihistaminics and aspirin were continued. A single mild episode of flushing and numbness of feet occurred on the day after operation, lasting about 15 minutes. She was discharged on the following day with continuation of aspirin, cimetidine, and chlorpheniramine.

The follow-up to November 1982 on this drug regimen has shown infrequent mild attacks of flushing, with occasional mild diarrhea and pruritus. No syncopal episodes have occurred.

Case 2 (R.B.)

A 32-year-old white woman was admitted to the Clinical Research Center of Vanderbilt Hospital in August 1981 because of "creepy, crawling" sensations, spreading from her feet to her thighs, with hot flushes of face and neck, accompanied occasionally by diarrhea. These symptoms have occurred episodically about once per month for the last two years, and each episode lasts for about 15 minutes. She was uncertain as to any provoking factors associated with these episodes. Until two years ago, she had been an extremely healthy woman with no significant medical problems, except for a hysterectomy in 1977 because of recurrent vaginal bleeding.

Physical examination showed a thin, nervous, 32-year-old white woman with normal vital signs. Darier's sign was positive. Breasts showed diffuse nodularity. Otherwise, general examination showed no significant abnormalities, except for a moderately severe scoliosis.

Laboratory studies on admission showed a normal blood chemogram and urinalysis. Twenty-four-hour uninary collections for histamine and prostaglandin D2 showed abnormal elevations of each (histamine 60 μg/24 hours and PGD2 metabolite 234 ng/24 hours). Skin biopsy showed 10–20 mast cells per high power field. Liver-spleen and bone scans and bone marrow biopsy showed no evidence of abnormalities.

Mammograms showed a cluster of microcalcifications in the superior mid portion of the left breast, thought by the radiologists to be very suspicious for malignancy. Upper GI series and small bowel follow-through showed no abnormalities of the gastrointestinal tract.

Throughout her hospital course, the patient had episodes of anxiety, with flushing and creeping sensation and a hot feeling two to three times per day without any changes in blood pressure or pulse. She was discharged on cimetidine 300 mg po qid., chlorpheniramine 8 mg po qid., and aspirin 0.6 g qid on August 12, 1981.

She was readmitted to the Surgical Service of the Vanderbilt Hospital on September 9, 1981, for biopsy of the left breast. History and physical examination showed no new findings. Because of the previous diagnosis of mastocytosis, the patient was seen in consultation before operation by Dr. Jackson Roberts, who outlined the hazardous factors and drugs to be avoided. She was continued on chlorpheniramine, cimetidine, and aspirin until the morning of operation when, at 6:30 am, she received Seconal 75 mg IM, Phenergan 25 mg IM, and Robinul 0.2 mg IM. At operation, anesthesia was induced with intravenous Valium and thiopental. Biopsy of the suspicious area of the left breast was carried out (Dr. Vernon Reynolds). Frozen section examination showed fibrocystic disease, with no evidence of malignancy. A penrose drain was left in, and this was removed the day after operation. She was discharged the following day with diagnosis confirmed by permanent sections.

The followup to November 1982 has shown that the patient has had infrequent episodes of mild manifestations of systemic mastocytosis and no severe episodes of syncope or hypotension, while continuing her maintenance program of cimetidine, Chlorpheniramine, and aspirin.

Case 3 (M.S.)

A 54-year-old white woman was admitted to the Clinical Research Center of Vanderbilt University for the seventh time in January 1982 because of gastric ulcer with recurrent bleeding episodes, hypothyroidism, and systemic mastocytosis.

She had been in good health until 1970, when she developed episodes of syncope, accompanied by palpitation, flushing, dyspnea, intense "burning" pruritus, and wheezing one to two times per week. Profound hypotension and, occasionally, diarrhea occurred with these episodes.

Eventually, she was referred to Vanderbilt Hospital and has had intensive evaluation over the previous decade in the Clinical Research Center under the direction of Drs. John Oates and Jackson Roberts. At an early admission, she was found to have elevated urinary histamine levels (149 μg/24 hours) and increased numbers of mast cells in biopsies of bone marrow. A diagnosis of mastocytosis was entertained and established subsequently. Despite treatment with antihistaminics, her attacks have persisted. Treatment has included cimetidine, cromolyn sodium, chlorpheniramine, and aspirin plus synthroid for hypothyroidism.

Failure of these medications to control her attacks led to measurements of other potential causes and resulted in demonstration of elevated levels of prostaglandin D2 metabolite in urine (909 ng/24

hours). During subsequent admissions, this was confirmed with consistency, and indomethacin was added to the treatment regimen.

Despite these medications, her severe syncopal attacks persisted and in July 1980 she was pronounced DOA (dead on arrival) in another hospital's emergency service, only to recover after resuscitative measures.

In July 1981, she had several melenotic stools and was readmitted to the Clinical Research Center at Vanderbilt Hospital. Endoscopy showed an active, antral ulcer on the lesser gastric curvature. Because of the ulcer, she was placed on antacids. Aspirin was withheld, and treatment with cimetidine, chlorpheniramine, and cromylin was continued. Later in the fall of 1981, she was re-evaluated, and endoscopy showed no change in the gastric ulcer. Multiple biopsies showed no evidence of malignancy. Skin biopsy showed 20–25 mast cells per high power field.

Surgical consultation was requested in December 1981, at which time gastric analysis was carried out, showing low basal gastric acid outputs—in no way compatible with the Zollinger-Ellison syndrome. Serum gastrin was recorded as 263 pg/ml. Vagotomy with resection of the gastric antrum and ulcer was recommended, but the patient elected to go home and return after Christmas.

Physical examination on readmission in January 1982 was unchanged. Blood pressure was 130/70 mmHg, pulse 80, and respirations 15. Head, neck, throat, and ocular examinations were normal. Darier's sign was positive, but skin was otherwise normal. Heart, lungs, and breasts were normal. Abdomen showed no tenderness or masses. Liver edge was felt 4 cm below costal margin. Pelvic and rectal examinations were negative except for surgical absence of the uterus. No adnexal masses were present.

Laboratory data showed no electrolyte abnormalities. Hematocrit was 37.5%. Prothrombin time and partial thromboplastin time were normal. Platelets were 390,000/ml.[3] X-rays of chest were normal. Electrocardiogram was normal except for nonspecific ST-T wave changes.

The patient was prepared for operation with full collaboration of our anesthesiologist (Dr. Winston Parris). Drugs to be used were selected by negative preoperative skin testing. At midnight on January 7, 1982, she received cimetidine 300 mg (po), cromylin sodium 140 mg (po), chlorpheniramine 4 mg (po), and indomethacin 50 mg (po).

On January 8, 1982, the patient was carried to the operating room. Preoperative preparation was indomethacin 50 mg (po), Valium 15 mg (po), Robinul 0.2 mg (IM), and Benadryl 25 mg (IV). Anesthesia induction was with halothane. There was no hypotension. Proximal gastric vagotomy was carried out with antral resection and anticolic Roux-en-Y gastrojejunostomy (Dr. William Scott). There were no untoward events during operation.

Early postoperative recovery was uneventful. Stadol was used for analgesia with satisfactory pain relief and Ancef as an antibiotic with no ill effects.

Pathologic examination showed fibrosis of antral mucosa and muscularis compatible with a healed gastric ulcer.

Postoperative course: The patient was instructed in and started on a postgastrectomy diet, increasing from liquids to solids after four days on nasogastric suction. Except for a single episode of hypotension, syncope, and flushing on the 12th postoperative day with rapid spontaneous recovery, her convalescence was free of complications.

She was discharged on January 23, 1982, on cromolyn sodium, cimetidine, chlorpheniramine and ferrous sulfate, with the plan of returning for inhospital (Clinical Research Center) evaluation in one month.

At her last admission in April 1982, she was doing well with no ulcer symptoms and good tolerance of postgastrectomy diet. The decision was made to put her back on Ascriptin with continuation of ferrous sulfate, cimetidine, chlorpheniramine, cromolyn sodium, and dessicated thyroid extract.

In follow-up to November 1982, she has had no recurrence of ulcer symptoms, and severe syncopal and hypotensive spells have been less frequent since institution of the multi-drug inhibiting program. However, careful monitoring will be continued.

Case 4 (K.C.)

A 23-year-old white woman was admitted to Vanderbilt Hospital in April 1982 because of systemic mastocytosis, multiple allergies, and a need for whole mouth dental rehabilitation. She had a long history of "allergies" manifested by hives and flushing. She had been initially hospitalized at Nashville Memorial Hospital in 1976 because of flushing, dyspnea, and chest pain. In July 1977, she was admitted to Vanderbilt Hospital and had an extensive evaluation of unexplained abdominal pain. Readmission to Nashville Memorial Hospital in 1979 demonstrated gallstones, for which cholecystectomy was done with severe postoperative flushing and dyspnea. She was referred subsequently to the Allergy Clinic of Vanderbilt Hospital, where it was determined that flushing attacks were precipitated by smoking, alcohol, stress, and narcotics, including morphine and codeine.

She was admitted again to Vanderbilt Hospital in December 1981, where a diagnosis of systemic mastocytosis was made on the basis of her history and the finding of 15 to 18 mast cells per high power field on skin biopsy and elevated plasma and urinary levels of histamine and prostaglandin D2 (plasma histamine 532 pg/ml; prostaglandin D2 metabolite in urine 3599/24 hours). During this admission, a severe flushing and hypotensive attack occurred after premedication for upper gastrointestinal endoscopy with Pontocaine and Valium. She was treated with an epinephrine intravenous drip and discharged subsequently on aspirin, cimetidine, and Maalox.

Readmissions to Vanderbilt Hospital were required twice in the next two months for resuscitation of severe attacks of flushing and hypotension induced by the drug Persantine on one occasion and failure to take her medications on the other.

In March 1982, after many mild reactions, she had a major attack of flushing and syncope while at work, and was resuscitated in the Emergency Service of Vanderbilt Hospital by intravenous epinephrine. This attack was associated with cramping abdominal pain, pruritus, and dyspnea.

Immediately prior to the admission to Vanderbilt Hospital in April 1982, she had a major flushing and hypotensive episode in the dental clinic of Vanderbilt Hospital after receiving a third injection of lidocaine, despite previous negative skin testing for this drug. After resuscitation with intravenous epinephrine in the dental clinic, she was admitted to the hospital.

Physical examination showed an obese young woman with temperature of 98.4 F, pulse 76, respirations 18, and blood pressure 120/80 mmHg. The skin showed dramatic dermographism, but without wheal or flare. She had several carious teeth. Cardiac size and rhythm were normal. There were no murmurs. Lungs showed no rales or wheezes. Breasts were large and pendulous and abdomen was obese, but otherwise normal. Remainder of examination was not remarkable.

Admission blood chemogram was normal, as were hematologic and coagulation studies and urinalysis.

She was seen in consultation by the anesthesiologists, and skin testing included the following drugs: butorphanol tartrate (Stadol), pancuronium bromide, Robinul, ephedrine sulfate, and control normal saline. She was reactive only to pancuronium with a mild allergic skin response. She tolerated oral Valium well the night before operation. Preoperative medication included cimetidine 300 mg (po) and Robinul 0.2 mg (IM).

She was taken to the operating room on April 14, 1982, and after preoxygenation she was given Benadryl 25 mg (IV). General endotracheal anesthesia was induced with halothane. A skin biopsy and a

bone marrow biopsy were done and followed by cleaning of teeth with application of fluoride. Composite restorations were placed in two molars and an amalgam filling in one other molar (Dr. Bruce Greenwood). She tolerated the procedure well with no untoward episodes during or after it.

After operation she was monitored in the Medical Intensive Care Unit for 24 hours. Stadol 1 mg, diluted in normal saline without preservatives, controlled her pain satisfactorily. Bone marrow and skin biopsies showed 15–18 mast cells per high power field. She was discharged April 16, 1982.

She has been followed to November 1982, exhibiting diminished severity and frequency of attacks and good compliance on indomethacin and antihistaminics.

Case 5 (H.P.)

A 51-year-old white woman was admitted to Vanderbilt Hospital in September 1982 with recurrent bouts of colicky right upper quadrant abdominal pain of 12 months duration. During a previous admission in May 1982, an oral cholecystogram had shown multiple gallstones.

Past medical history included multiple attacks of orthostatic weakness associated with diaphoresis, palpitations, and chest pain. She was first admitted to Vanderbilt Hospital in 1965 and evaluated for these complaints without specific diagnosis. Similar episodes required readmission in 1967, and again in 1969, without definitive diagnosis despite extensive evaluation. In 1970, a right radical mastectomy was done for infiltrating ductal carcinoma followed by radiation therapy.

In 1975, severe headaches prompted readmission to Vanderbilt Hospital, where x-rays of skull, electroencephalograms, and computerized axial tomographic scans of the head were negative.

In May 1982, she was admitted again to Vanderbilt Hospital with complaints of hot flushes, associated with diaphoresis, and weakness on standing of several months duration. Her work-up included measurements of catecholamines and metabolites, IgE, serum electrolytes, and hematologic indices, which were all normal. Oral cholecystogram was positive for gallstones. Electrocardiogram and echocardiogram were normal. Skin biopsy showed as many as 40 mast cells per high power field. She was discharged on cimetidine and doxepin.

Physical examination showed normal vital signs. She was a moderately obese white woman in no acute distress. Her skin had a reddish hue, but had no rashes or lesions. She was edentulous. Her head, eyes, ears, nose, and throat were otherwise normal. The right breast was surgically absent—no nodules in the mastectomy site. The left breast was normal with no palpable masses, and there were no palpable axillary or supraclavicular nodes. Her heart and lungs were normal. Abdominal examination showed deep tenderness in the right upper quadrant, but no masses or organomegaly. Pelvic and rectal examinations showed no abnormalities. Extremities and neurologic examination were normal.

Electrocardiogram and chest x-rays were normal. Hematocrit was 43%; white blood cell count was 5200; bilirubin 0.5 mg/dl; alkaline phosphatase 131; glucose 109 mg/dl; electrolytes and coagulation studies were normal. Liver enzymes, amylase, and creatinine were in the normal range. Urinary histamine and PGD2 metabolite measurements were not made.

The diagnosis of mastocytosis was made on history, skin biopsy (40 mast cells per high power field), and response to antihistaminic therapy. She was started on aspirin, cimetidine, and chlorpheniramine. An anesthesiologic consultant (Dr. Winston Parris) carried out skin tests for drugs to be used, and ascertained that she was allergic to pancuronium bromide.

She was taken to the operating room for cholecystectomy on September 22, 1982. Premedication included Valium 10 mg (po), Robinul 0.2 mg (IM) and cimetidine 300 mg (po). After preoxygenation, she was given Benadryl 25 mg (IV), and anesthesia was induced with Forane (iso-flurane).

Cholecystectomy was carried out through a right subcostal incision (Dr. Vernon Reynolds). The gallbladder was found to be filled with multiple small stones. An intraoperative cholangiogram showed a normal common bile duct free of stones. The patient withstood the procedure well with no hypotension, flushing, or other untoward events.

Postoperative pain was controlled satisfactorily with Stadol. She made an uncomplicated recovery and was discharged on September 28, 1982, on cimetidine 300 mg every 6 hours, chlorpheniramine 8 mg every six hours, and Darvocet N 100 for pain.

In follow-up to November 1982, she has made a satisfactory recovery with relief of abdominal pain and reduced frequency and severity of flushing spells.

Case 6 (F.G.)

A 32-year-old white woman was admitted to Vanderbilt Hospital for the sixth time in September 1982 because of acute, severe right upper quadrant abdominal pain of 24 hours duration.

Past medical history indicated that she was well until December 1979, when she had the first of an incredible series of syncopal episodes. In January 1980, she was admitted to Park View Hospital in Nashville for syncope and vomiting. Work-up was apparently unrevealing. During the next 10 months, she had one syncopal episode per month.

In late 1980, she had an extensive work-up at the National Clinical Center, Bethesda, Maryland, where she was found to have a neurogenic bladder and was taught to catheterize herself approximately six times per day. She returned to Bethesda for a repeat evaluation in early 1981.

In October 1981, she was hospitalized in a suburban hospital because of a syncopal attack with a scalp laceration. In the hospital, she had two syncopal attacks. Electroencephalogram was normal. Holter monitor demonstrated asymptomatic bradycardia and tachycardia.

In January 1982, she was admitted to Vanderbilt Hospital with continuation of her syncopal episodes more often than once per month. She also described at this time the presence of substernal aching pain of 2½ years duration and worse recently. In addition, she had arthralgias in many joints. Holter monitor showed asymptomatic alteration of sinus rate from tachycardia (up to 180) to bradycardia. Treatment with Inderal caused a skin rash and was discontinued. Two 24-hour urinary collections for histamine showed normal levels. Skin biopsy showed 6–10 mast cells per high power field. She was discharged on Theo-Dur, cimetidine, chlorpheniramine, and aspirin.

In February 1982, she was readmitted for syncopal attacks. When medications were discontinued she got worse—syncopal episodes became much more frequent. Urinary collections for PGD2 metabolites were not run.

She had several readmissions for adjustment of drug therapy in the spring of 1982.

In May 1982, she was readmitted to Vanderbilt Hospital for the fifth time because of recurrent syncope and right upper quadrant abdominal pain. She was nauseated but had no vomiting. There were no fever, chills, or icterus. Ultrasonograms showed multiple small gallstones. She refused operation on this admission. She was discharged on Aldactone, prednisone, cimetidine, and Synthroid.

The pain that initiated her sixth Vanderbilt Hospital admission on September 20, 1982, was severe and unrelenting for 24 hours. It was located in the right upper quadrant of the abdomen and radiated

through to her shoulder blade. She had nausea and vomiting, but no chills or icterus.

Physical examination on admission showed normal vital signs. She was an obese young white woman with acute abdominal pain. Her skin was normal in color and texture—no icterus or rashes. Darier's sign was negative. Her head, eyes, ears, nose, and throat were normal—except for a thyroidectomy scar and slight hoarseness. Her heart, lungs, and breasts were normal. On abdominal examination, she was tender in the right upper abdomen. No masses or organs were palpable. Remainder of examination was within normal limits.

She was seen in consultation by Drs. Jackson Roberts and Winston Parris. Skin tests of drugs to be considered for premedication and anesthesia were carried out. These included: normal saline control, pancuronium bromide, Robinul, ephedrine sulfate, and Marcaine. All tests were negative. She was started on amikacin, vancomycin, and metronidazole and prepared for cholecystectomy under epidural anesthesia (patient refused general anesthesia).

On September 27, 1982, she received premedication with Solu-cortef 100 mg (IV), Robinul 0.2 mg (IM), and Benadryl 25 mg (IV). In the operating room, epidural anesthesia was induced with 0.5% Marcaine and supplemented by Forane and nitrous oxide.

A right subcostal incision was made, and a small contracted gallbladder was visualized. Cholecystectomy was carried out (Dr. John Sawyers). Multiple small stones were contained within the gallbladder. An intraoperative cholangiogram was carried out, and the x-ray picture of the common bile duct outlined by contrast material was quite normal and free of stones.

The patient withstood the operative procedure quite well. There were no untoward intraoperative or early postoperative problems. She made an uneventful recovery. Nubain 1–4 mg (IV) was used to control postoperative pain with satisfactory results. Except for a generalized "burning sensation" over her whole body for several days, she had no complications after operation.

After operation, she was started back on prednisone 40 mg/day, rapidly reduced to 30 mg per day, Benadryl 50 mg/day, and Aldactone 25 mg three times daily.

She made an uneventful recovery from operation without complications and was discharged home on October 4, 1982.

Early postoperative recovery has been satisfactory.

Comment

The six patients with mastocytosis who required various surgical procedures under general or regional anesthesia represent only about 3% of the more than 200 patients with clinical and laboratory evidence of mastocytosis who have been studied by two of the authors (L.J.R., J.A.O.) at Vanderbilt University Hospital in the past decade.

These six patients were all white women whose ages ranged from 23 to 54 years; mean—38 years. Each patient had a history of recurring attacks of most of the symptoms listed in Table 1 as characteristic of mastocytosis. As seen in Table 2, the duration of symptomatic mastocytosis ranged from 15 months to 17 years, but diagnosis and pharmacologic treatment with antihistaminics and prostaglandin synthetase inhibitors had only been accomplished in the past 1 to 24 months.

TABLE 2. *Pre-operative Management in Mastocytosis*

Patient	Duration Mastocytosis	Duration Pre-op Rx	Results
1. M.L. 35, wf	15 Mos.	5 Mos.	Good
2. R.B. 32, wf	2 Yrs.	1 Mo.	Good
3. M.S. 54, wf	12 Yrs.	24 Mos.	Fair
4. K.C. 23, wf	6 Yrs.	3 Mos.	Poor
5. H.P. 51, wf	17 Yrs.	4 Mos.	Fair
6. F.G. 32, wf	3 Yrs.	9 Mos.	Fair

Four of these six patients had sustained many severe life-threatening episodes of syncope as a result of acute hypotensive attacks.

Roberts, Oates, and their co-workers have demonstrated that the most likely cause of these severe attacks is the secretion of prostaglandin D2 from the excessive number of mast cells.[3] In 1979, they had demonstrated that blockade of the flushing associated with metastatic gastric carcinoid could be accomplished successfully by administration of combined H_1 and H_2 receptor antagonists (chlorpheniramine and cimetidine).[5] Subsequently, in 1980, they observed lack of a satisfactory response to therapy with H_1 and H_2 receptor antagonists in two patients with systemic mastocytosis who had life-threatening attacks of flushing and hypotension. Studies in these patients in search for mediators of attacks of flushing and hypotension other than histamine led to the demonstration in each patient of an overproduction of prostaglandin D2 (PGD2).[3] In the past two years, additional supporting evidence has been accumulated by Roberts, Oates, and co-workers, establishing prostaglandin D2 as an important mediator of attacks in patients with mastocytosis.[4,6,7] The relative roles of histamine and PGD2 in the pathophysiology of mastocytosis, especially in patients with less severe disease, remain to be delineated.

Three of the four surgical patients with severe syncopal attacks of mastocytosis had abnormal elevations of PGD2 in plasma or of the metabolite (PGD2M) in urine. In one patient, PGD2 was not measured.

Difficulties in accurate measurements of histamine

TABLE 3. *Treatment of Mastocytosis*

Acute phase
Intravenous epinephrine 500 mcg bolus then 5–10 mcg/kg/min infusion
Subcutaneous 0.5 cc epinephrine 1:1000 self administered
Chronic phase
H_1 Receptor antagonist (chlorpheniramine)
H_2 Receptor antagonist (cimetidine)
Prostaglandin biosynthesis inhibitor (Aspirin, indomethacin)

TABLE 4. *Operative Procedures in Mastocytosis*

Patient	Anesthesia	Operation	Result
1. M.L., 35, wf	Enflurane	D & C; Tubal ligation	Good
2. R.B., 32, wf	Diazepam, pentothal	Breast biopsy	Good
3. M.S., 54, wf	Halothane	Partial gastrectomy	Good
4. K.C., 23, wf	Halothane	Dental rehabilitation	Good
5. H.P., 51, wf	Iso-flurane	Cholecystectomy	Good
6. F.G., 32, wf	Epidural (Marcaine) and iso-flurane	Cholecystectomy	Good

and the complexity of measurement of PGD2 and PGD2M restrict wide clinical application. It is probable that the most accurate method currently available for objective confirmation of the diagnosis of suspected systemic mastocytosis is the therapeutic response to a trial of H_1 and H_2 histamine receptor blockade and PGD2 synthetase antagonists (Table 3).

In 1960, Myers stipulated that more than 5 mast cells per high power field in a skin biopsy represented an abnormal excess of these cells.[8] By his criteria, all of the six patients with the combined problems of systemic mastocytosis and various surgical entities qualify for this diagnosis. In addition, these six patients also qualify for the diagnosis of systemic mastocytosis by their response to therapy with H_1 and H_2 antagonists and with PGD2 synthetase antagonists.

The difficulty of accurate diagnosis of mastocytosis is related to the fact that tissue mast cells may be increased in a patchy fashion in the skin and reticuloendothelial system and a biopsy can easily miss an abnormal accumulation of these cells. In addition, histamine and PGD2 may be elevated in plasma and their metabolites in urine during an acute attack in mastocytosis and immediately thereafter, but may be measured subsequently in normal ranges. This may occur also in the patients with milder manifestations of this disease.

We are pleased that in our medical center in the past two years, six patients with systemic mastocytosis, who have had various indications for general or regional anesthesia for various surgical procedures,[9] have been recognized before operation as having mastocytosis and have been managed successfully during the preoperative, intraoperative, and postoperative periods by surgeons working in close collaboration with anesthesiologists and internists (Table 4).

Systemic mastocytosis is an extremely hazardous disorder. Without knowledge of the idiosyncracies of patients with this disease, physicians, anesthesiologists, and surgeons can perpetrate, despite the best of intentions, catastrophic problems for patients, leading to acute episodes of mast cell degranulation with profound hypotension, refractory shock, and death as a result.

This study shows that clinicians, forewarned with knowledge of the hazards of mastocytosis and its management, can conduct patients through necessary surgical operations in safety.

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DISCUSSION

DR. MARK M. RAVITCH (Pittsburgh, Pennsylvania): I am sure we would all agree that this garden variety disease—arcane, abstruse, and esoteric—is exactly the kind of thing we would expect from anyone as erudite as Dr. Scott, and I wish I could tell you that I arise out of an overpowering desire to share with you my large fund of information on the subject.

I had seen such a patient—it was Patient 3—last year, at the time of a marvelous celebration of Dr. Scott's many achievements.

At that time, under the guise of conferring a certain privilege upon me, I was led into the pit of an amphitheatre as the presumed moderator of a clinical conference, and listened with popping eyes and mouth agape to a house officer presenting this sort of a story about things that I couldn't possibly conceive of. I had no clue as to what the disease was.

And I can only say that in that distinguished group was a large number of distinguished members of this organization—Presidents, ex-Presidents, future Presidents, some of them here today—and I offered each and all, separately and individually and together, the op-