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-

portunity to gain everlasting fame by telling us what the patient had, and they were all too modest to embarrass me by telling.

It cannot be a coincidence that all of this comes from Vanderbilt. A second ago, Dean Warren said he had never seen a case, and how many dozen had I seen?

There is an additional possibility, of course, and that is that they have extraordinarily sophisticated and astute clinicians, who could figure out that the wheals of the skin had something to do with histamine, and knew that you could find out whether there was histamine in the urine, and, for reasons that are absolutely beyond me, thought of prostaglandins, and then got skin biopsies, and put the whole thing together.

I think this is one of the most extraordinary examples of beautiful, sophisticated analytic clinical thinking carried to a conclusion.

And if Dr. Scott can tell us, it would be nice to know just exactly how this came about, and whether he had anything to do with it.

DR. JULIA SAWYERS (Nashville, Tennessee): As a practicing anesthesiologist, I believe that this paper will become a classic in defining this rare entity, with emphasis on early recognition and careful preoperative preparation of the patient.

I concur with his recommendations that the patient be treated before operation with histamine$_1$ and histamine$_2$ receptor antagonists and prostaglandin biosynthesis inhibitors. It has been reported in the literature that these attacks have been precipitated by a variety of anesthetic agents, including sodium pentothal and even lidocaine, used as intravenous regional technique.

Inhalation agents are considered the agents of choice, with Forane as the most satisfactory one.

In the preoperative workup, the importance of complete coagulation studies on these patients should be emphasized, since they are prone to severe hemorrhagic diathesis due to systemic heparin release and decreased synthesis of coagulation factors.

If blood transfusion is required, it should be monitored carefully for transfusion reactions, since they tend to be more severe than in a normal patient.

Secondly, further emphasis should be made on adequate but careful premedication of these patients, to avoid the anxiety reaction to surgery.

DR. JAMES C. THOMPSON (Galveston, Texas): The charge to discuss a condition of such preternatural rarity would inhibit an ordinary man, but in Academia, we are often called on to comment upon matters regarding that with which we have scant experience. The basis for this is the doctrine of metastatic competence. The successful professor handles this problem—this challenge—with alacrity, though, and reaches back into his past.

Mastocytosis, although rare in man, is slightly less rare in certain animals, and many veterinarians have experience with the problem.

I once assigned myself the task of studying mast cells, because I was interested in the physiology of histamine. We published a paper in the *Surgical Forum* on the significance of degranulation of mast cells in gastric secretion. The granules of mast cells are actually little pharmacopeias. They contain histamine and heparin, in a complex binding between the two, heparin is an acid, and histamine, a base. They contain serotonin and prostaglandins, and the lysis of these granules brings about the release of all these agents.

At times, the release is accompanied by local symptoms. For example, the itching of patients who have obstructive jaundice is thought by many to be due to local release of histamines by the detergent action of bile salts on the membranes of these mast cell granules.

The mechanism for general discharge of granule content in patients with systemic mastocytosis is, as far as I know, unknown. I have known of two patients who had this condition. They exhibited a Zollinger-Ellison-like syndrome at times; animals who have this disease also are troubled by problems of severe acid hypersecretion.

Now, the question I would like to ask Dr. Scott is that, having an opportunity to sit on the periphery of this vast gold mine that is operated by Drs. Roberts and Oates, I wonder if he knows whether any of these patients have had localized collections of mast cells that have been susceptible to excision and cure.

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): As a continuing student of Dr. Scott's, I found this a fascinating unfolding of a complicated condition. I have had an experience with a mastocytoma in a child.

I have seen two babies under a year of age who presented with this syndrome. I did not know what it was at the time, but the pediatric endocrinologist knew Dr. Oates, and contacted him, and they informed me that two trigger areas were present, one over the knee area in one of the babies, and the other in the upper thigh. The sites were slightly indurated and about 2 mm in size. When pressure was brought to bear on these areas during the changing of the diapers in these two babies, they became still, very pale, and then flushed. They asked if I would be willing to take out these trigger areas.

I did some reading, which, as you know, Dr. Scott, is not an extensive undertaking, because there is not much in this field that has been published. Under the type of anesthesia which Julia Sawyers has described to us this morning, we successfully removed both of these small areas which had accumulations of mast cells in them. Both babies have been free of any further attacks.

I would, therefore, like to ask you whether it is common in this generalized condition of mastocytosis to have a mastocytoma—I suppose, the appropriate term for this—and if so, whether this has been seen in your series, and how frequently Dr. Oates and his associates might think this occurs.

DR. ROBERT ZEPPA: I saw an infant twenty years ago with mastocytosis in a clinical research unit at UNC; there was some question about a surgical problem in this baby, and we were desperately frightened about doing anything, mainly because you could measure heparin-like activity in the serum.

I wonder if in this group of patients at Nashville there are any who demonstrate this particular problem.

Secondly, what are your recommendations, Dr. Scott—yours and your colleagues'—concerning the use of plasma expanders, if necessary, in these patients? Because most of the polymers are extraordinarily active on mast cell membranes, and might precipitate a crisis if, unknowingly, something like large-molecular-weight dextran, certainly, or the others—PVP, and so on—were administered to the patients.

DR. JAMES D. HARDY: (Jackson, Mississippi) I have a little relative, a boy, who lives in a foreign country and was born with a small lump in the skin over the left scapula. The overlying skin was slightly discolored and the mass was readily movable. As the boy got a little larger, the mass got a little larger, and then he began to have attacks.

What would happen would be that the lump, which now was about 2 cm in diameter and usually rather flat, would begin to enlarge periodically every few months. As it became larger in diameter and thickness, the overlying skin would become darker, and then gradually blisters would form over the surface and rupture. At about that time, he would begin to have attacks, just as Dr. Scott described. He would become fiery red, sleepy, and so forth every few hours. After some days, the activity and dimensions of the lesion would recede to the quiescent state.

My advice for immediate excision of this lesion was not accepted, because the pediatrician had consulted a dermatologist, and the dermatologist in this foreign country had said, "This is a fairly common thing, and let's not rush into an operation. We'll just watch this, and they generally will recede as the child gets older."

I talked to our pathologists about it, and they said this condition is not all that rare, but that it's the dermatologists who see it most often.

We were worried that his condition might be systemic in distribution, but only when this visible lump was changing and getting larger

and finally erupting did the baby have symptoms—otherwise he had none.

DR. H. WILLIAM SCOTT, JR. (Closing discussion): I want to thank all of the discussants, and let you know now that when we presented one of these patients to Dr. Ravitch last spring when he was the moderator of our grand rounds, the case was presented only as an ordinary, run-of-the-mill gastric ulcer, and we left it to him to dig out of the patient the problems of mastocytosis that she had been carefully studied for over the preceding several years, including all the prostaglandin data, etc.

But he did not get a fair shake on that, I must say. Dr. Ravitch, I apologize to you. Thank you very much for your comments.

I want to thank Dr. Julia Sawyers in particular for outlining the important items in management of these patients under anesthesia, which she described so well.

Dr. Thompson has asked a very good question; namely, did we have any patient with localized mastocytoma to excise? We have not. And I might say in answer to the other discussions about mastocytoma that there seem to be two categories of mastocytosis: (1) Cutaneous mastocytosis, which may be accompanied by a mastocytoma, a condition that occurs mainly in children and babies, and which may clear up with growth of the child; (2) Systemic mastocytosis, which we are talking about here, is usually unaccompanied by any skin disorder, excepting so-called Darier's sign, a wheal and flare on the scratching of the skin—dermographism with wheal and flare. But usually, there are no other cutaneous manifestations in these people, including the six that have come to operation, out of Dr. Oates' large series.

In answer to Dr. Zeppa's question about dextran, he is quite right that dextran is hazardous in this context, and is one of the drugs on the "no" list for people with systemic mastocytosis.

Dr. Oates has had an interest in the problem of carcinoid for many years, as many of you know, and he also, more recently, has been interested in prostaglandin metabolism, and all aspects of the prostaglandins. Back in 1979, Oates and Roberts demonstrated that blockade of the flushing associated with metastatic gastric carcinoid could be accomplished successfully by the use of combined H_1 and H_2 receptor antagonists, chlorpheniramine and cimetidine.

Subsequently, in 1980, they observed a lack of a satisfactory response to this therapy in two patients with systemic mastocytosis, who had very profound flushing and syncopal episodes, and in investigating the cause they discovered a prostaglandin metabolite in urine. First, they considered prostaglandin E_2, but subsequently found that this was not the source of the metabolite that they were looking at in urine. They subsequently demonstrated conclusively that prostaglandin D_2 was the factor causing these severe syncopal episodes, and they have substantiated that in a very sophisticated and careful scientific manner.