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Intracardiac Thrombosis and Aortic Dissecting Aneurysms in Mustached Tamarins (*Saguinus mystax*) with Cardiomyopathy

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Spontaneous intracardiac thrombosis is rarely reported in animals, particularly nonhuman primates. The finding of 2 cases of intracardiac thrombi in mustached tamarins (*Saguinus mystax*) that died as a consequence of congestive heart failure prompted us to do a retrospective study to determine the frequency of this condition. Clinical records, necropsy reports, and tissues from 60 mustached tamarins that died or were euthanized between 1996 and 2009 were reviewed. Of the 60 monkeys whose cases were reviewed, 10 (16.6%) had intracardiac thrombi, and 4 (6.6%) had dissecting aortic aneurysms. Of the 10 animals with intracardiac thrombosis, 3 had left ventricular involvement alone; 4 monkeys had thrombi only in the right ventricle, and the remaining 3 animals exhibited thrombi in both ventricles. Myocardial fibrosis and chronic renal disease were common findings in affected animals. The causes of the intracardiac thrombosis in the tamarins in the present study are not known, but the clinical signs and gross and microscopic lesions suggest that congestive heart failure secondary to cardiomyopathy is the primary contributor. In addition, the cause of the aortic dissecting aneurysms in the tamarins in this study is not known. Further studies are required to determine whether factors including aortic curvature, genetic background, or hypertension—alone or in combination—play a role. To our knowledge, the current retrospective study is the first report of intracardiac thrombosis and aortic aneurysms in mustached tamarins.

Spontaneous intracardiac thrombosis and aortic aneurysms in animals are reported rarely. In domestic animals, arterial thromboembolism has been reported to occur in cats secondary to cardiac disease as a common occurrence.[32] In nonhuman primates, spontaneous intracardiac thrombosis has been reported in capuchin monkeys,[18] an owl monkey,[10] a woolly monkey,[3] a spider monkey, and a Formosan macaque.[14] Intracardiac thrombi are observed occasionally in SIV-infected rhesus macaques.[8] In humans, intracardiac thrombus formation is a relatively common complication after acute myocardial infarction.[13] Antemortem diagnosis in humans is achieved through ultrasound examination of the heart, and successful treatment, with thrombus resolution, has been reported with the use of oral anticoagulants.[13] Treatment of intracardiac thrombosis and aortic aneurysms in nonhuman primates has not been published; most cases of these abnormalities have been incidental findings during postmortem examination.

Aortic aneurysms have been reported in domestic animals, particularly horses.[28,30] In nonhuman primates, aortic aneurysms have been reported in squirrel monkeys,[33] owl monkeys,[5] gorillas,[15,22] a howler monkey,[21] a capuchin,[6] patas,[27] African green monkeys,[9] and a spider monkey.[7] In humans, aortic dissection is characterized by pooling of blood between and along the laminar planes of the vascular media, with the formation of a blood-filled channel within the aortic wall.[19] Hypertension is the chief risk factor in aortic dissection in humans and the most important clinical factor affecting aneurysmal growth.[19]

The finding of 2 cases of intracardiac thrombosis in mustached tamarins (*Saguinus mystax*) that died as a consequence of cardiac failure prompted us to do a retrospective study to determine the frequency of this condition. Here we report 10 cases of spontaneous intracardiac thrombosis and 4 cases of spontaneous aortic aneurysms in mustached tamarins.

Materials and Methods

Clinical records, necropsy reports, and tissues from 60 mustached tamarins (*S. mystax*) that died or were euthanized between 1996 and 2009 were reviewed. All animals were adults except for one monkey, which was 8 mo old at the time of death. Because most animals were wild-caught, exact ages typically were unknown. The colony was maintained as part of a viral hepatitis research project that was approved by the National Institute of Allergy and Infectious Diseases Institutional Animal Care and Use Committee, but not all animals were on study at the time of death. The monkeys were housed and cared for according to the *Guide for the Care and Use of Laboratory Animals*[16] and *Animal Welfare Regulations*.[4] Standard husbandry procedures included feeding commercial chow (New World Primate Diet 5040, Purina Mills, St Louis, MO; Marmoset Diet, ZuPreem, Mission, KS), diet supplements (bananas, apples, and marshmallows), and water ad libitum. The tamarins were housed in stainless steel 6.0-ft^2 biocontainment cages (Primate Products, Miami, FL) with PVC nesting boxes, 'nectar logs,' and other environmental enrichment objects for callitrichids. A 12:12-h dark:light photocycle was used. Room

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temperature was maintained at 24 ± 2 °C. Except while on study, tamarins were pair-housed (male–female) whenever possible. In addition, the colony was screened routinely for intestinal pathogens by using bacterial cultures and for parasites by using wet mounts and fecal flotation. At necropsy, tissues from all major organs were fixed in 10% neutral buffered formalin, embedded in paraffin sections, cut at 5 µm, stained with hematoxylin and eosin, and examined by light microscopy. In addition, selected slides of heart and aorta tissue were stained with Masson trichrome, Mallory phosphotungstic-acid–hematoxylin, and elastic Van Gieson stains. The various lesions were graded on arbitrary scale of 0 to 3+ (minimum to maximum).

Results

Of the 60 mustached tamarins that were retrospectively examined, 10 (16.6%) had intracardiac thrombosis, and 4 (6.6%) had dissecting aortic aneurysms. Clinical signs of congestive heart failure were present in 11 animals affected with intracardiac thrombi or aortic aneurysm and included cervical ventral subcutaneous edema, distended abdomen, exercise intolerance, dyspnea, lethargy, and, in one case, hindlimb paresis. At postmortem examination, the heart was enlarged with a rounded appearance. On section, the left ventricular free wall and interventricular septum were hypertrophic (maximum, 8 and 6 mm, respectively; normal range, 4 to 5 mm and 2 to 4 mm, respectively) with moderately decreased ventricular volume; the right ventricle appeared dilated with mild thickening of the free wall (maximum, 3 mm; normal range, 1.5 to 2 mm). In severe cases, the heart weighed as much as 5.9 g (normal range, 3.5 to 4 g). Thoracic, pericardial, and pleural effusion and lung congestion with or without atelectasis were observed. In severe cases, as much as 50 mL of a yellow-tinged to serosanguineous fluid was found in the thoracic cavity or abdominal cavity (or both). The liver was enlarged and congested, and the kidneys were pale or enlarged (or both). Cardiomyopathy was a common finding in the tamarin colony, affecting approximately 35% of the overall population.

Of the 10 tamarins with intracardiac thrombi, 3 had thrombosis only in the left ventricle, 4 had thrombi only in the right ventricle, and 3 animals developed multiple thrombi in both ventricles. Clinical, gross, and histologic findings in the animals with intracardiac thrombosis or aortic aneurysm (or both) are summarized in Table 1. Only the large intracardiac thrombi were noted macroscopically during necropsy and were characterized by a dark-red verrucous mass firmly attached to the endocardial surface of the ventricular free walls. In most cases, the point of attachment of the thrombus to the endocardium was the apical or anterolateral segment of the ventricle between the papillary muscles. On transection, thrombi were red with indistinct pale-gray layers. In 2 tamarins, the free section of the thrombus extended to the atrium. Histologically, the thrombi were composed of fibrin strands admixed with erythrocytes; inflammatory cells, which consisted mainly of neutrophils, some fibroblasts, and a few histiocytes; and cellular debris (Figure 1). In some cases, the surfaces of thrombi were overlaid with an extension of the endocardial endothelium denoting the chronicity of the condition. Some thrombi were well-organized, with multiple vascular channels lined by plump endothelial cells running throughout the thrombus. Well-organized thrombi often were characterized by deposits of alternating layers of erythrocytes (dark) and platelets with fibrin (pale); these layers are known as 'lines of Zahn.'[19] Mallory phosphotungstic-acid–hematoxylin staining confirmed the presence of fibrin in thrombi from 9 of the 10 tamarins.

Thrombi were adhered to the endocardium in 9 of the 10 tamarins. In each case, there was disruption or loss (or both) of the endothelium at the interface of the thrombus and endocardial surface; this interface was accompanied by a thin zone of inflammation containing a few neutrophils, macrophages, fibroblasts, cellular debris, and a thin layer of collagen fibers. The inflammatory response appeared to dissipate—and the thickness of the collagen deposition appeared to increase—with the level of thrombus organization. The entire surface of well-organized thrombi typically was overlaid by endothelium; whereas the endothelial covering of newer, less well-formed thrombi was incomplete, extending from the site of thrombus attachment at the endocardial surface toward the lumenal surface.

All tamarins exhibited varying degrees of myocardiocyte degeneration, necrosis, and fibrosis. The changes affected individual and small groups of cells and were characterized by intercellular edema, loss of cell membrane integrity, loss of sarcoplasmic detail, disruption and loss of striation, and increased presence of contraction bands. Nuclei in degenerate cells were often pyknotic or karyorrhectic. Degenerate myocardial cells were replaced by deposition of collagen, which was confirmed with Masson stains for fibrous connective tissue (Figure 2). Fibrosis affected the left ventricle, interventricular septum, right ventricle, and (to a lesser degree) the atria. Fibrosis was variable and random throughout the ventricular free walls and interventricular septa but was most pronounced in the subendothelial myocardium adjacent to attached thrombi. Cardiac fibrosis was graded according to increasing amounts of collagenous connective tissue separating or replacing cardiac myocytes in slides stained with hematoxylin and eosin and confirmed by collagen-specific stains. Higher-grade fibrosis often was associated with myocyte degeneration and cytoplasmic vacuolization. The media and adventitia of cardiac arterioles and small coronary arteries was expanded markedly by collagen deposition in 7 of the 14 hearts examined; Masson staining confirmed this finding, which suggested increased vascular resistance and hypertension.

Aortic aneurysms were characterized by dilation of the thoracic aorta, with dissecting margins filled with blood. Histologically, the dissecting aneurysmal wall had loss of elastic fibers, a thin smooth-muscle-cell layer, and collagen deposition. In the center of the lumenal blood, hematoidin and hemosiderin were surrounded by concentric layers of cell debris, fibrin, and histiocytes. In one case, the lumen of the aneurysm contained mostly fibrin and connective tissue. This same animal had a large atheroma associated with the aneurysm (Figure 3). Another tamarin with a thrombus of the left ventricular wall had an aortic atheroma. Aortic atheromas were characterized by thickening of the intima, due to a highly cellular fibrous cap composed of smooth-muscle cells, fibroblasts, macrophages, and collagen. The internal and external elastic membranes were absent, and the media of the artery was thinner under the fibrous cap.

One monkey with bilateral ventricular thrombosis had a focally extensive renal hemorrhagic infarct with arteriolosclerosis. Other renal lesions noted were multifocal interstitial lymphoplasmacytic nephritis, expanded glomerular mesangial matrix, and tubular proteinuria, which affected approximately 85% of the 60 tamarins evaluated in the current study. Enlarged livers were characterized by acute diffuse centrilobular congestion with hepatocel-

Table 1. Summary of clinical, gross, and histologic findings in 13 adult mustached tamarins with intracardiac thrombosis, aortic aneurysm, or both conditions

Sex	Experimental status	Clinical signs of congestive heart failure	Cardiomyopathy at necropsy	Myocardial fibrosis	Chronic nephropathy	Thrombosis				Aortic dissecting aneurysm
						Atrial		Ventricular		
						Left	Right	Left	Right	
Male	Unknown	+	++	++	+	—	—	+	++	++
Male	Hepatitis A virus	+	+	++	+	—	—	—	+	—
Male	Hepatitis A virus	++	++	+++	unknown	—	—	+	—	—
Male	Hepatitis A virus	+++	++	+	+++	—	—	+	++	—
Male	Hepatitis A virus	++	++	++	++	—	—	—	+++	—
Male	Unknown	++	+++	+++	+++	—	—	—	—	+
Female	Unknown	++	++	+++	+++	++	—	+++	—	—
Female	Naïve	unknown	unknown	++	unknown	—	—	—	++	—
Male	Hepatitis A virus	+	+++	++	++	—	—	—	—	+
Female	Unknown	—	unknown	unknown	unknown	—	—	—	—	+++
Female	Unknown	+++	+++	unknown	unknown	—	+++	—	+++	—
Male	Unknown	++	+++	+	+++	—	—	+++	—	—
Male	Naïve	+	+	+	+	—	—	++	+	—

–, negative; +, mild; ++, moderate; +++, severe

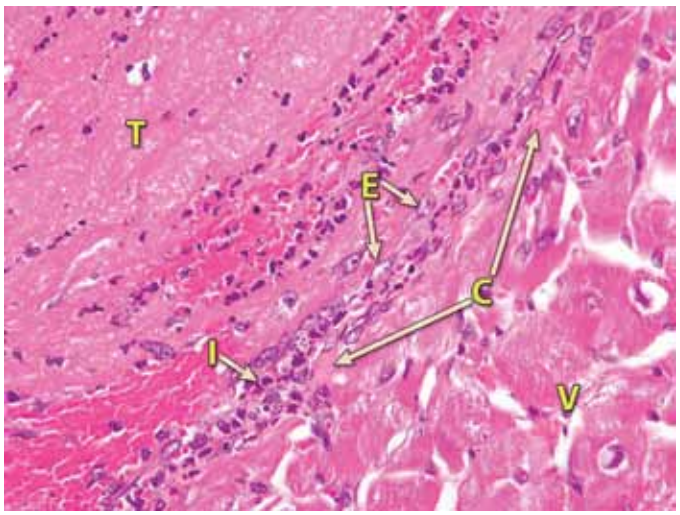

Figure 1. Intracardiac thrombus (T) attached to ventricular free wall (V). The thrombus consists of alternating layers of fibrin, erythrocytes, and inflammatory cells mainly neutrophils, macrophages, fibroblasts, and cellular debris. Note the thin line of inflammation (I) between the thrombus and the exposed subendothelial collagen (C) of the ventricular myocardium, characterized by neutrophilic infiltrates, cellular debris, and plump, discontinuous newly developing endothelial cells (E) lining the thrombus and the endocardial surface. Hematoxylin and eosin stain; magnification, ×400.

lular degeneration and necrosis and multifocal hemosiderosis. Lung lesions were characterized by diffuse airway histiocytosis, many of which were hemosiderin-laden (so-called 'heart failure cells'). The lesions noted (hydrothorax, ascites, ventral cervical edema, hepatic congestion, lung histiocytosis with heart failure cells) were all indicative of congestive heart failure. One tamarin with a large intracardiac thrombus had marked coronary hyaline arteriolosclerosis.

Of the 10 tamarins with intracardiac thrombosis, 4 had previously been infected with hepatitis A virus, and 2 were research-naïve; the experimental history was unavailable for the remaining 4 monkeys. Of the 4 tamarins with aortic aneurysms, 1 had been previously infected with hepatitis A virus, and 3 had no research history available.

Discussion

In humans, abnormal myocardial contraction due to arrhythmias, dilated cardiomyopathy, or myocardial infarction can lead to cardiac mural thrombi.[19]

A definitive cause of intracardiac thrombosis in the tamarins in the present study is unknown; however, concurrent clinical disease and microscopic lesions in all of the tamarins in the current study suggest that myocardial fibrosis and congestive heart failure as a consequence of dilated cardiomyopathy are the main causes. In humans,[19] cardiomyopathy and fibrosis change the muscular architecture and contractile rhythm of the heart, altering the normal laminar blood flow pattern of blood as it passes through the ventricular chambers, especially at the lumenal periphery within the papillary muscles. Degeneration or loss of hypoxemic endothelial cells adjacent to damaged myocardium exposes subendothelial collagen, specifically type III collagen. Platelets aggregate on the exposed collagen, releasing procoagulant constituents.[29] The complex coagulation cascade is triggered and thrombus formation occurs by fulfilling the Virchow thrombogenic triad:[19] (1) injury (resulting in endothelial damage) to the vessel wall; (2) changes (stasis or turbulence or both) in normal blood flow, and (3) abnormalities (hypercoagulability) of the blood. The final stage of the cascade, which distinguishes thrombi from simple blood clots, is the conversion of fibrinogen to fibrin. The polymerizing fibrin strands attach to the subendothelium and accumulate in alternating layers with blood cells. Sometimes difficult to distinguish from thrombi, postmortem clots (also known as 'chicken-fat clots') are not attached to the underlying endothelial surface and grossly fall into 2 layers: a yellow, upper one, and a darker, gelatinous, bottom one.

The presence of fibrotic cardiomyopathy in thrombotic and aneurysmal tamarins resembles the condition in humans. Myocar-

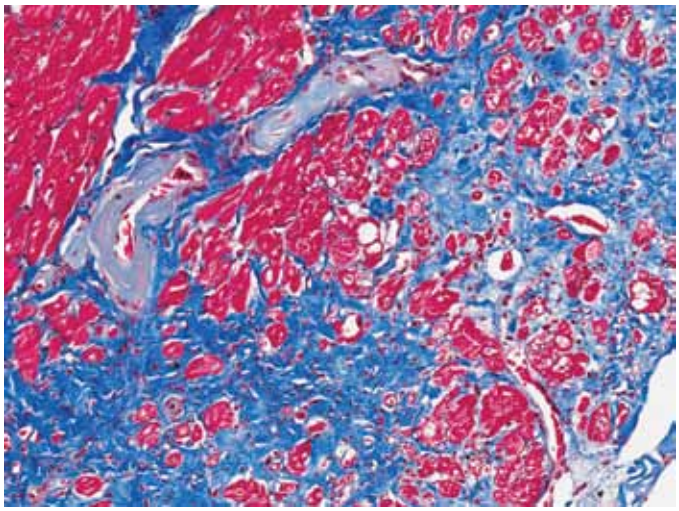

Figure 2. Trichrome stain of subendothelial myocardium adjacent to an organized thrombus, demonstrating isolated myocardiocytes in various degrees of degeneration with replacement by fibrous scarring and a small coronary artery with hyaline changes where collagen has replaced the media, a lesion known as hyaline arteriolosclerosis. Affected cells are isolated by intercellular edema and inflammatory infiltrates consisting of mononuclear inflammatory cells, occasional neutrophils, and cellular debris. Affected cells are fragmented; exhibit loss of nuclei and loss of striations. Masson trichrome stain; magnification, ×200.

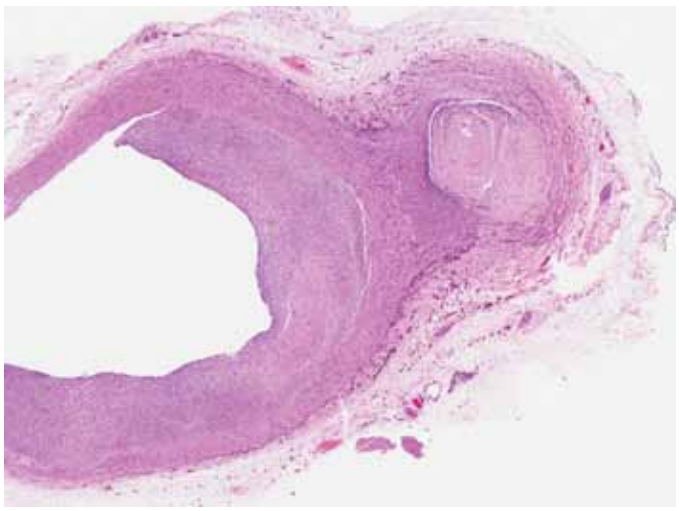

Figure 3. Image at low-power magnification showing an aortic dissecting aneurysm with thick atheroma development. Hematoxylin and eosin stain; magnification, ×15.

dial fibrosis is a common finding in humans with left ventricular hypertrophy due to chronic arterial hypertension.[25] Myocardial fibrosis and, more recently, arterial hypertension have been reported to occur in owl monkeys.[11,31] In addition, myocardial fibrosis is a common finding in chimpanzees and is suspected as the cause of arrhythmias and sudden death in this species.[20] In pressure-overload hypertrophy, continuous structural remodeling of the fibrillar collagen matrix is accompanied by an increase in heart weight. This remodeling is believed to be a compensatory mechanism that enhances tensile strength.[34,35] However, the increased stiffness of the myocardium has a detrimental effect on cardiac elasticity and contractility and predisposes to both atrial and ventricular arrhythmias.[34,35] Another possible mechanism for the development of myocardial fibrosis is thickening or vasospasm of small coronary arteries, with subsequent partial or momentary occlusion causing short periods of anoxia. These myocardial ischemic events are not severe enough to cause clinical signs.[1] One tamarin in the present study showed marked hyaline arteriolosclerosis of small coronary vessels, a well-known lesion in humans with moderate sustained arterial hypertension.[19] In humans, hypertension can lead not only to cardiac hypertrophy, and potentially heart failure, but also to aortic dissection and renal failure.[19] Repeated episodes of acute stress can contribute to the development of cardiac disease by triggering myocardial ischemia, ventricular arrhythmias, platelet activation, and increased blood viscosity.[26] All these are known contributing factors to the development of intracardiac thrombi.

It is interesting that despite the reports of hypertrophic cardiomyopathy and cardiac dilation in owl monkeys,[11] only one case of intracardiac thrombosis has been reported in that species.[10] Recently, several authors attempted to establish normal reference echocardiographic parameters in owl monkeys.[24] Similar studies should be conducted in mustached tamarins and might aid in the antemortem diagnosis of intracardiac thrombi.

Mustached tamarins may be genetically prone to thrombus formation, with environmental factors triggering the condition. Whatever the origin of the myocardial fibrosis in mustached tamarins, it may predispose them to development of intracardiac thrombosis. Although the cardiac lesions in the tamarins suggest arterial hypertension, we could not confirm this possibility because blood pressure was not assessed in these animals. Myocardial fibrosis in the tamarins might be an age-related condition, but it was not a common finding in a breeding colony in which animals where held for prolonged periods of time.[12] Unfortunately, because the current study is retrospective, it is not possible to obtain blood pressure or conduct echocardiographic studies in the study population. The cases of intracardiac thrombosis reported in a cebus monkey colony were thought to be associated with a previous experimental exposure to *Herpesvirus simplex* infection.[18] Although herpesviruses appear to infect human endothelial cells, intracardiac thrombi associated with herpesvirus infection have not been reported in humans. Similarly, the majority of the tamarins in the present report were used in hepatitis A virus research. To our knowledge, an association between hepatitis A viruses and intracardiac thrombosis or cardiomyopathy has not been described in humans or other species. Cebus monkeys relocated after the herpesvirus study were housed together, a situation that resulted in frequent fighting. Most animals showed fight injuries at necropsy, and at least one monkey had myocardial fibrosis.[18]

Aortic medial degeneration has been reported as a cause of aortic aneurysm and rupture in horses.[28,30] In humans, the most frequent risk factors for the development of aortic aneurysms are hypertension and atherosclerosis.[17] However, a recent study showed that aortic curvature is, potentially, a more important factor than are diameter, blood pressure, and cardiac output in regard to the forces on the aortic wall.[23] These same authors stated that the absolute increase in force becomes greater as the curvature of the ascending aorta increases, with a greater than 10-fold increase in the total force exerted on the ascending aorta as cur-

vature increases from straight to curved.[23] Aortic elasticity, which is important for compliance, is determined by the aorta's elastin and collagen contents. At high pressure (greater than 120 mm Hg), collagen is relatively inelastic and consequently increases the stresses experienced by the ascending aorta.[23] We do not know whether the tamarins in the present study suffered from arterial hypertension; however, the lesions noted on histologic examination of various organs suggest that they did. We also do not know whether aortic curvature is increased in mustached tamarins compared with other species. In any case, shear stress due to hemodynamic forces damages the aortic endothelium, resulting in increased permeability, leukocyte adhesion, and platelet aggregation.[19] Proteases released from a variety of cells, including inflammatory, mesenchymal, and endothelial cells, leads to destruction of the extracellular matrix of the aortic wall.[19] Smooth muscle cells contribute to aortic wall homeostasis against inflammation and proteolysis; however, once degradation of the wall starts, it is considered an irreversible terminal event[2] and, simultaneously, aneurysm may form due to a weakened arterial wall.

The definitive cause of the intracardiac thrombosis in the mustached tamarins in the present study is unknown; however, the clinical signs and gross and microscopic lesions suggest myocardial fibrosis and congestive heart failure as the main culprits. In addition, the cause of the aortic dissecting aneurysms in the tamarins in this study is unknown. Further studies are needed to determine whether factors such as aortic curvature, genetic background, and hypertension play a role. Investigation of heart and chronic renal disease in tamarins is necessary to determine the pathogenesis of these lesions and their relationship to the formation of intracardiac thrombi and aneurysms. To our knowledge, this is the first report of intracardiac thrombosis and aortic aneurysms in mustached tamarins.

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