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Spontaneous Lesions of the Cardiovascular System in Purpose-Bred Laboratory Nonhuman Primates

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ABSTRACT

This retrospective study was performed to determine the range, occurrence and incidence of spontaneously arising histopathological findings of the cardiovascular system in purpose-bred laboratory nonhuman primates. Data were collected from 84 controlled toxicological studies with equal numbers of male and female animals and full tissue lists. Attempts were also made to standardize pathological terms used by various original pathologists. Tissue sections from 2464 animals, which included 2050 cynomolgus monkeys (*Macaca fascicularis*), 284 common marmosets (*Callithrix jacchus*) and 130 rhesus monkeys (*Macaca mulatta*) were examined. The most common cardiac finding was focal myocardial inflammation, subcategorized as either "inflammatory cell infiltration" (339) or "focal myocarditis" (131). Other cardiac findings included mineralization (29), endocarditis (16), pericarditis (10), squamous cysts (6) and ectopic thyroid tissue (5). Perivasculitis/vasculitis in the kidney, lung, meninges, sciatic nerve, and other tissues (206) was the most common vascular lesion. Focal myocarditis was more common in male (60%) than female (40%) animals. Cardiac mineralization and extramedullary hematopoiesis were more common in marmosets than other species while ectopic thyroid tissue was present in marmosets and cynomolgus monkeys. To our knowledge, this is the first study to demonstrate the range and incidence of spontaneous cardiovascular lesions in laboratory nonhuman primates.

Keywords. Cardiovascular; spontaneous pathology; nonhuman primate; cynomolgus; rhesus; marmoset.

INTRODUCTION

In preclinical toxicology studies, drug-induced cardiovascular lesions continue to be an important area of concern, in particular with respect to assessment of cardiovascular safety of drugs intended for human use. In the course of such studies, it is not uncommon to encounter drug-induced histopathological lesions in the heart and blood vessels that are similar to those that may arise spontaneously in control animals. Since this can considerably hinder the evaluation of toxicological compounds, it is important for pathologists to be able to recognize such background changes in control animals of a test species. Although nonhuman primates are widely used in preclinical toxicology studies due to their phylogenic relationship to humans, specific information on the range of background findings is not readily available. This review was conducted in order to report and characterize the range and incidence of spontaneous background microscopic cardiovascular lesions in young, healthy cynomolgus monkeys (*Macaca fascicularis*), rhesus monkeys (*Macaca mulatta*) and common marmosets (*Callithrix jacchus*) purpose-bred for laboratory use.

MATERIALS AND METHODS

Animals

Cynomolgus monkeys (*Macaca fascicularis*), common marmosets (*Callithrix jacchus*), and rhesus monkeys (*Macaca mulatta*) were obtained for use in toxicological studies. The animals were purpose-bred for laboratory use and came from accredited suppliers (Charles River, USA; Harlan, UK; Guanxi Grandforest Primate Company, China; and Bioculture, Mauritius). All animals were between 12 and 30 months of age, and had body weights ranging between; 1.6–2.5 kg for cynomolgus monkeys; 250–400 g for common marmosets, and between 1.9–3.4 kg for rhesus monkeys. They were housed in groups of 2 to 3 animals of the same sex and dose group in custom-designed Home Office approved primate cages (Chapter 14, section 21, UK Animals (Scientific Procedures) Act of 1986). The temperature and humidity were automatically controlled at 21°C ± 4°C and 55% ± 10% respectively, with a minimum of 15 air changes per hour. An automatic light cycle of 0700–1900 (12-hour cycle) was maintained. Each individual gang pen had drinking water and food hoppers and animals were fed a commercial primate diet (Mazuri diet, Special Diet Service Ltd, Witham, Essex, England) which in the case of marmosets, was moistened with water and condensed milk ("Mazuri marsh"), and supplemented with vitamin D_3 and other multivitamins (Abidec) twice weekly. Twice weekly fruit supplements were also offered to all animals.

All studies were conducted in accordance with the UK Animals (Scientific Procedures) Act 1986, which conforms to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, Council of Europe).

Clinical Examination and Clinical Pathologic Evaluation

A thorough clinical examination that included physical examination, ophthalmology and electrocardiography was carried out on each of the animals by a veterinary surgeon. The number of electrocardiographs recorded for each animal varied depending on the study but recordings were generally

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taken pretrial, at regular intervals during the trial and at the end of the trial. Complete hematology and clinical chemistry evaluations of blood samples collected from the animals were also carried out pretrial, at regular intervals during the trial and at the end of the trial.

Pathological Evaluation

Animals were humanely euthanized by intravenous injection with sodium pentobarbitone and exsanguinated via femoral veins. A detailed necropsy was performed under the supervision of a veterinary pathologist who was present throughout the necropsy sessions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin wax, sectioned to a 4–5 μm thickness and stained with hematoxylin and eosin. They were examined histopathologically and the findings entered directly onto a computerized database (PLACES 2000 Instem, Apoloco Limited Systems, Pennsylvania, USA).

Heart Collection and Trimming

During necropsies, hearts were dissected following the direction of blood flow and the various chambers, valves and major blood vessels examined. Entire hearts were collected and fixed in 10% neutral buffered formalin. At trimming, the following sites were collected from fixed sections of cynomolgus and rhesus monkey hearts;

(a) A section of the left ventricle and atrium, which included the dorsal papillary muscle and the left atrioventricular valve.
(b) A section of the interventricular septum, which included the right atrium, aortic valve and the right atrioventricular valve.

A section of the right ventricular free wall including the right atrium and right atrioventricular valve was collected from cynomolgus and rhesus monkey hearts at trimming in slightly less than half of the studies. For marmosets, 2 parallel longitudinal sections of the heart from the base to the apex were made at trimming and a saggital section exposing all four chambers collected for all studies.

Study Design

A search for pathological findings involving the cardiovascular system was made on all nonhuman primate studies evaluated over a period of 5 years, from 2000–2005, using the electronic software (PLACES 2000 Instem, Apoloco Limited Systems Pennsylvania, USA) used by the pathology department. From this pool of material, histopathology slides for re-evaluation were selected from studies with:

(a) At least one control or untreated group (controlled studies).
(b) Methods of drug administration other than continuous intravenous infusion.
(c) Equal distribution of male and female animals.
(d) No treatment related pathology findings (following histopathological evaluation by veterinary pathologists).
(e) Good Laboratory Practice (GLP) compliance and evaluation of a full tissue list.

Archival histopathology slides were retrieved and sections were re-evaluated by a veterinary pathologist to ensure consistence in grading and nomenclature. Data was available from a total of 2,050 cynomolgus monkeys, 284 common marmosets and 130 rhesus monkeys, which included control as well as treated animals from studies with no treatment related findings.

Statistical Analysis

For each species, the incidence of each finding was compared between male and female animals using Fisher's 2-sided Exact tests (SAS version 8.2). A p value of less than 0.05 was considered statistically significant.

RESULTS

Clinical Signs and Necropsy Findings

One animal which was later diagnosed with spontaneous bacterial endocarditis and renal arterial thrombosis had exhibited clinical signs of depression, subdued demeanor and a hunched posture, and was euthanized on humane grounds. Necropsy findings for this animal included an abscess on the leg, a bite wound on the tail and pale foci on the heart and kidneys. With the exception of this one animal, clinical signs including electrocardiography and clinicopathologic abnormalities were absent in animals in which histological lesions were documented in the cardiovascular system. Rare gross lesions were reported at necropsy, and included raised foci or nodules and pale or dark foci on the pericardium or endocardium. These findings were subsequently confirmed histopathologically as squamous or epithelial cysts, pericarditis and endocarditis, respectively.

Histopathology Findings

Heart. Spontaneous pathological findings in the cardiovascular system of cynomolgus monkeys, common marmosets and rhesus monkeys over a period of 5 years were evaluated. Those lesions that met the criteria for incorporation into the study, and their incidence, are documented in Table 1. Focal inflammatory cell infiltration of the myocardium was the most common cardiac lesion in all 3 species examined, with variable involvement of the epicardium or endocardium. The finding was predominantly graded minimal to mild (grades 1 to 2 on a scale of 1–5) and was characterized by focal infiltration of the myocardial interstitium, perivascular spaces or subepicardial or epicardial fat by variable amounts of fairly uniform mononuclear cells, mostly lymphocytes, with little or no evidence of myocardial degeneration or necrosis (Figure 1a). In most cases, this finding was difficult to differentiate from focal myocarditis, which was the second most common finding in the heart in all three species. Focal myocarditis was characterized by a mild to moderate accumulation of a mixture of inflammatory cells, predominantly monocytic, in association with variable degrees of myocardial degeneration or necrosis or some other evidence of inflammation such as edema or fibrin deposition (Figure 1b). This finding was generally more severe than inflammatory cell infiltration. It was quite common for both lesions to occur together in the same heart section, and in such cases the most severe lesion (usually focal myocarditis) was recorded.

Both inflammatory cell infiltration and focal myocarditis were more common in the subepicardial and subendocardial areas of the heart including the base of the dorsal papillary

TABLE 1.—Histological findings of the cardiovascular system in cynomolgus monkeys, marmosets and rhesus monkeys and their corresponding incidences in male and female animals

Findings	Cynomolgus (*Macaca fascicularis*)			Marmosets (*Callithrix jacchus*)			Rhesus (*Macaca mulatta*)			
	Male 1025	Female 1025	Total (%) 2050	Male 142	Female 142	Total (%) 284	Male 65	Female 65	Total (%) 130	Total (%) 2464
	Species and incidences									
Inflammatory cell infiltration	145	135	280 (13.0)	21	14	35 (12.3)	15	9	24 (18.5)	339 (13.8)
Perivasculitis/vasculitis	65	57	122 (6.0)	27	33	60 (21.0)	11	13	24 (18.5)	206 (8.4)
Focal myocarditis	62[a]	40[a]	102 (5.0)	8	5	13 (4.6)	18[a]	8[a]	26 (20.0)	131 (5.3)
Mineralization	5	6	11 (0.5)	8	10	18 (6.3)	0	0	0 (0)	29 (1.2)
Endocarditis	5	4	9 (0.4)	2	3	5 (1.8)	1	1	2 (1.5)	16 (0.6)
Pericarditis	2	1	3 (0.1)	5	2	7 (2.5)	0	0	0 (0)	10 (0.4)
Myocardial fibrosis	2	1	3 (0.1)	6	1	7 (2.5)	0	0	0 (0)	10 (0.4)
Hematopoiesis	1	2	3 (0.1)	3	5	8 (2.8)	0	0	0 (0)	11 (0.4)
Squamous cysts	2	4	6 (0.3)	0	0	0 (0)	0	0	0 (0)	6 (0.2)
Ectopic thyroid	1	2	3 (0.1)	0	2	2 (0.7)	0	0	0 (0)	5 (0.2)

[a] Significant difference between male and female animals ($p < 0.05$).

muscle, with no apparent differences in the involvement of the 4 chambers of the heart. In cynomolgus and rhesus monkey species, focal myocarditis was more common in males ($p < 0.05$) compared to female animals and was mostly graded minimal to mild.

Other less common findings included mineralization of the myocardium and heart vessel walls, endocarditis (Figure 2), pericarditis, myocardial fibrosis, extramedullary hematopoiesis, squamous cysts and squamous epithelial cysts (Figure 3) and ectopic thyroid tissue (Figure 4). Endocarditis and pericarditis were largely macroscopic diagnoses which were supported by histological evidence of localized or extensive mild to severe fibrinous or purulent inflammation with varying degrees of fibrosis.

Mineralization of vascular walls and the myocardium (Figure 5), and extramedullary hematopoiesis around blood vessels or in the epicardium were more common in marmosets than other species and were associated with the occurrence of similar lesions in other body organs.

Ectopic thyroid tissue in the heart and its associated blood vessels, and squamous cysts (keratinized cyst) or squamous epithelial cysts (nonketinized cysts) were present in cynomolgus monkeys and common marmosets. In most cases encountered in this study ectopic thyroid tissue were present as well-defined large colloid-filled follicles (Figure 4a), but 2 cases of smaller, ill-defined and multifocally located follicle-like structures occupying both epicardial and mid-myocardial areas were also seen, prompting the original evaluating pathologists to call such findings "ectopic thyroid follicle-like structures" (Figure 4b and 4c). The most common areas occupied by ectopic thyroid tissue were the subepicardial areas at the base of the heart including atrial appendages and walls of the great vessels.

Squamous cysts, which were alternatively recorded as keratinized cysts, were characterized by cystic structures lined by a thin layer of flattened epithelium and filled with concentric layers of keratin. In some cases, the epithelial wall of the cyst appeared to be broken, inciting a foreign body inflammatory reaction where the keratin was in direct contact with adjacent tissues (Figure 3a). Squamous epithelial cysts on the other hand were composed of stratified squamous epithelium around a central lumen filled with a few inflammatory cells, an amorphous cellular debris or eosinophilic colloid-like material (Figure 3b). The base of the epithelia wall was usually surrounded by a layer of fibrous connective tissue of varying thickness. Local to these structures were often found variably sized squamous epithelial plaques with no central lumen; which were thought to represent tangential sections of walls of adjacent squamous epithelial cysts. As with ectopic thyroid tissue, squamous epithelial cysts were only found in

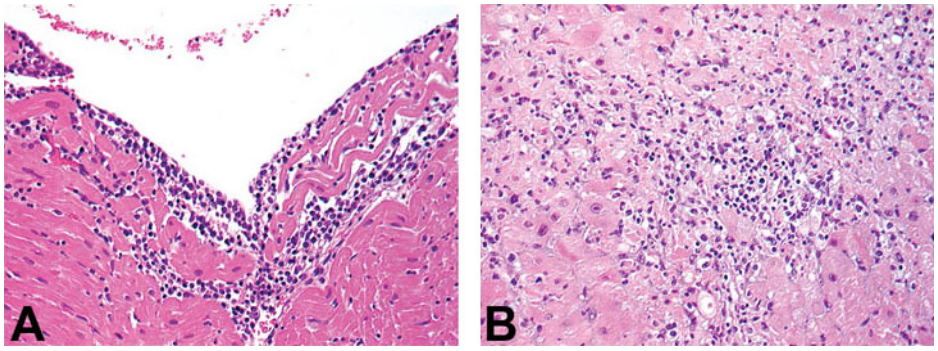

FIGURE 1.—(a) Inflammatory cell infiltration in the subendocardial areas of the left ventricle of the heart by predominantly lymphocytic and plasmacytic cells. Young female cynomolgus monkey (*Macaca fascicularis*); (b) Focal myocarditis in the left ventricular subepicardial area in a young male rhesus monkey (*Macaca mulatta*).

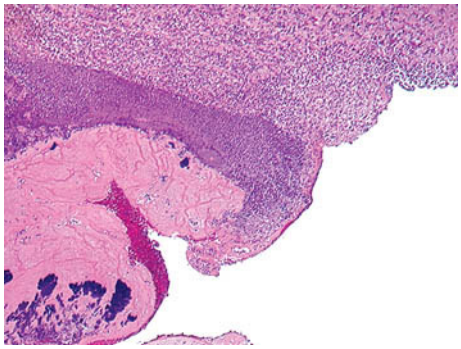

FIGURE 2.—Sponaneous bacterial valvular endocarditis in a young male cynomolgus monkey (*Macaca fascicularis*).

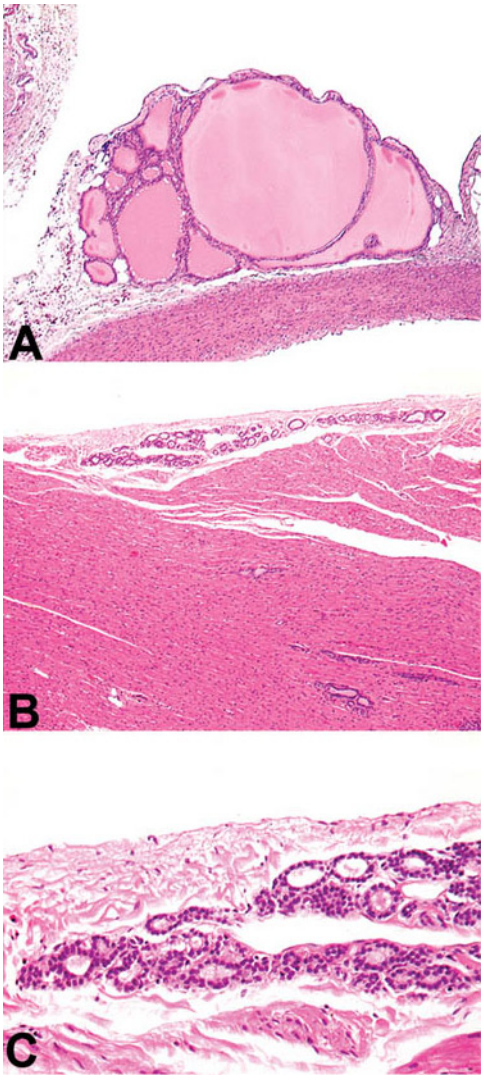

FIGURE 3.—Ectopic thyroid tissue at the base of the aorta in a young female marmoset (Callithrix jacchus); (b) Ectopic thyroid tissue or thyroid follicle-like structures embedded in the epicardial and deeper subepicardial areas of the midsection of the heart in a young female cynomolgus monkey (*Macaca fascicularis*); (c) A higher magnification of 3b, showing the follicular structures in the epicardial areas.

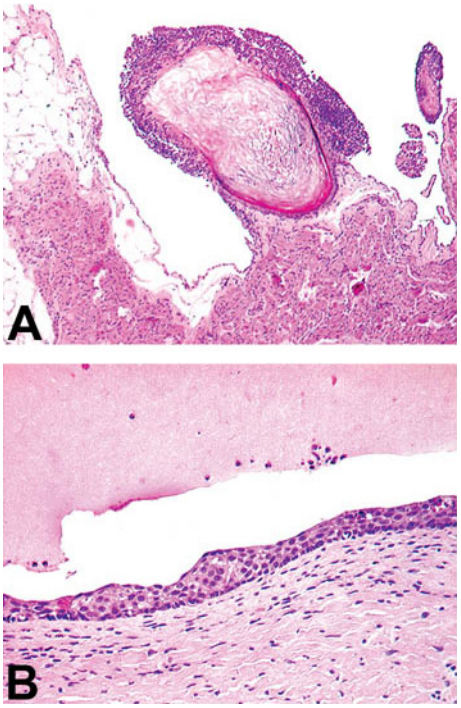

FIGURE 4.—(a) Squamous cyst or keratinised cysts associated with a foreign body inflammatory reaction affecting the epicardial surface of the right atrium in a young female cynomolgus monkey (*Macaca fascicularis*); (b) The wall of a squamous epithelial cyst surrounding a central lumen filled with colloid-like material and scattered cellular debris, affecting the epicardial area of the right atrium. There is a layer of fibrous connective tissue surrounding the wall of the cysts. Young female cynomolgus monkey (*Macaca fascicularis*).

the subepicardial areas at the base of the heart, while squamous cysts were found throughout the heart surface or just under the heart surface at the base, middle and apex of the heart.

Blood Vessels. Perivasculitis and vasculitis were the most frequently encountered lesions affecting blood vessels. These were largely localized lesions characterized by perivascular or vascular wall infiltration with lymphocytes without fibrin deposition or extensive necrosis of the tunica media. The most commonly affected organs in decreasing order of frequency were: kidney, lungs, meninges (brain and spinal cord), heart (Figure 6a), urinary bladder and sciatic nerve. The findings were relatively more common in marmosets and rhesus monkeys than cynomolgus macaques. However, perivasculitis of the meningeal blood vessels, a relatively common finding in cynomolgus monkey studies (Figure 6b) was only reported in this species. Vascular mineralization was invariably associated with aortic, coronary artery or myocardial mineralization and was thus not considered separately from cardiac mineralization.

Some degenerative changes such as myofiber hypertrophy, karyomegaly/polyploidy were not diagnosed in the original studies. Since the present study was focused on re-evaluation of previously recorded lesions, the incidence of such lesions in this study was not investigated.

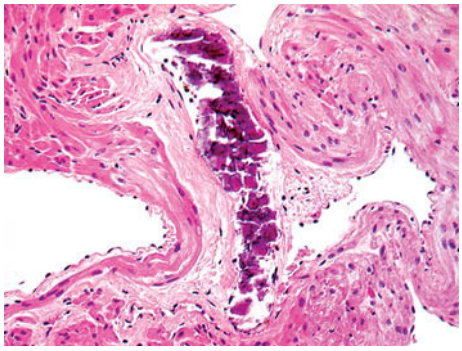

FIGURE 5.—Focal mineralization in the right atrial appendage of a young male marmoset (*Callithrix jacchus*).

DISCUSSION

New pharmaceutical agents are occasionally withdrawn from the market or severely restricted to specific indications due to unexpected adverse events. Fatalities and cardiac abnormalities are among the major causes of withdrawal of drugs or restriction in their labelling (Gussak et al., 2004). Drug-induced cardiovascular injury therefore continues to be an area of concern, especially arterial injury since there is currently no unequivocal biochemical marker of such injury or toxicity in man or animals (Brott et al., 2005). Consequently in laboratory animals used for preclinical toxicology studies a precise description of cardiovascular lesions in terms of morphology, location and distribution is necessary for correlation between structural damage and derangement of specific cardiovascular functions.

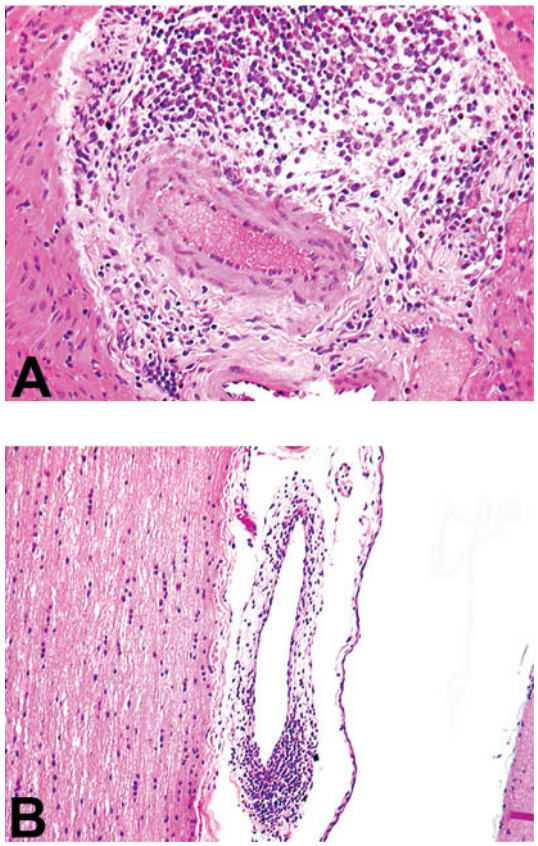

FIGURE 6.—(a) Spontaneous perivasculitis and myocarditis around a coronary artery in a young female cynomolgus monkey (*Macaca fascicularis*); (b) Spontaneous perivasculitis of a meningeal vein in a young male cynomolgus monkey (*Macaca fascicularis*).

This study highlights the range and incidence of spontaneous findings of the cardiovascular system likely to be encountered in young purpose-bred nonhuman primates involved in toxicological studies. There is currently limited documentation in the literature of such lesions in these species for comparison with this study, although some reports on cardiovascular pathology of nonhuman primates from zoos, or wild-caught animals (Ayers and Jones, 1978; Schulman et al., 1995) and laboratory-kept primates (Quereshi, 1979; Kaspareit et al., 2003; Porter et al., 2003) have been published. This is in contrast to other laboratory animal species such as dogs and rodents in which spontaneous lesions of the cardiovascular system are well documented.

Of the lesions affecting the heart, idiopathic inflammatory cell infiltration of the myocardium with little or no evidence of myofiber necrosis was the most commonly reported finding. It was not associated with any clinical sign or grossly visible lesions, and no etiological agent was isolated or demonstrated. Similar findings have been described in several nonhuman primate species (Ayers and Jones, 1978; Quereshi, 1979; Scott, 1999) and various terms such as myocarditis (Ayers and Jones, 1978), chronic interstitial myocarditis (Quereshi, 1979) and idiopathic lymphocytic interstitial myocarditis (Scott, 1999; Lowenstine, 2003) have been used. Such inflammatory lesions have, in the absence of an obvious cause, been attributed to stress precipitated by capture of the animals, and therefore reported incidences in such wild–caught animals are higher than those presented in this study (Quereshi, 1979).

Focal myocarditis, the second most common lesion of the heart in this study, was characterized by some evidence of myocardial fiber necrosis and often associated edema or fibrin deposition. It was similarly not associated with any clinical signs, infectious causal agent or necropsy findings, and was more common in male than female animals in cynomolgus and rhesus monkeys. This sex difference has not been reported in the literature. Similarly, focal myocarditis has not been reported separately from idiopathic inflammatory cell infiltrations, and we also found that original study pathologists used varying terminology to report these 2 findings. It is the opinion of these authors that to a large extend the two represent the same pathological entity, which differs only in the severity and the involvement of adjacent myocardial tissue and the nature of the cellular infiltrates. Therefore umbrella terms such as "focal idiopathic myocardial inflammation" or "focal myocardial inflammatory cell infiltration" could be applied and graded according to the presence or absence of degenerative or inflammatory changes in the adjacent myocardial tissues.

The role of stress in the pathogenesis of these idiopathic inflammatory lesions of the heart in purpose-bred nonhuman primates remains unclear. Natural infectious causes of myocarditis are uncommon in nonhuman primates (Scott, 1999), but include viral, bacterial and protozoal causal agents such as encephalomyocarditis virus (Ayers and Jones, 1978; Baskin, 1993), *Streptococcus pneumoniae* (Ayers and Jones, 1978; Baker, 2003) and *Toxoplasma gondii* (Ayers and Jones,

1978), respectively. All these organisms are unlikely to occur in purpose-bred and laboratory-housed animals.

Findings such as endocarditis, pericarditis, mineralization and extramedullary hematopoiesis also occurred at low incidences in our study. Even though only one case of bacterial endocarditis was associated with clinical findings in this study, other cases of endocarditis and pericarditis were usually evident at necropsy as pale or dark foci, unlike focal myocardial inflammations that were not observed at necropsy. Vegetative valvular endocarditis originating from a suppurative lesion in the body has been reported in nonhuman primates (Ayers and Jones, 1978) and *Staphylococci* are the most commonly implicated bacteria.

Mineralization and extramedullary hematopoiesis were more common in marmosets than other species. Both dystrophic and metastatic mineralization of the myocardium and vascular walls do occur uncommonly in nonhuman primates (Scott, 1999). However, the increased incidence of this lesion in marmosets could be linked to a vitamin D_3 oversupply, since marmosets have a special requirement for dietary vitamin D_3 (Lowenstine, 2003), and the presence of minimal mineralization in other organs such as adrenal glands is also suggestive of metastatic calcification. Similarly, myocardial extramedullary hematopoiesis in this species, which was associated with increased occurrence of the same lesion in other organs, could be related to the naturally occurring extramedullary hematopoiesis in the common marmoset (Zühlke and Weinbauer, 2003). This finding should not be confused with myocardial inflammatory cell infiltration.

Squamous cysts, squamous epithelial plaques and ectopic thyroid tissue in the heart have been reported in cynomolgus monkeys (Kaspareit et al., 2003), and the B6C3F1 mouse (Elwell and Mahler, 1999). It has been suggested that squamous cysts and epithelial plaques could be of foregut origin while ectopic thyroid tissue could be of thyroglossal duct origin (Ewell and Mahler, 1999; Kaspareit et al., 2003). Similar structures were present in the heart and the great vessel walls of cynomolgus monkeys and marmosets in the present study and there was an increased incidence of ectopic thyroid tissue than reported previously. The distribution of squamous epithelial cysts and plaques in relation to the areas of the heart and the presence of a colloid-like material in the central lumen suggested a common origin with ectopic thyroid tissue than squamous keratinized cysts. To the authors' knowledge, this study is amongst the first to document the occurrence of ectopic thyroid tissue in the myocardial tissue in marmosets and cynomolgus monkeys, as well as to highlight the incidence of cardiac mineralization and extramedullary hematopoiesis in the hearts of marmosets.

The most common vascular lesion in our study was localised perivasculitis and vasculitis in various organs. It was considered distinct from polyarteritis nodosa (PAN) since the latter presents as a systemic necrotizing vasculitis of small to medium sized blood vessels often accompanied by clinical and necropsy findings. Polyarteritis nodosa has been described in cynomolgus macaques (Albassam et al., 1993; Porter et al., 2003), and other laboratory species such as dogs, rats and pigs (Walvoort et al., 1987; Mitsumori, 1990; Kerns et al., 2001).

Although vascular and perivascular inflammatory lesions were relatively common in our study, there were no clinical signs associated with these lesions, and evidence of fibrinoid necrosis was absent. However, vasculitis and perivasculitis of meningeal blood vessels in cynomolgus monkeys, even though graded minimal to mild, affected several meningeal blood vessels of the brain and spinal cord.

It is not clear whether the absence of more severe and chronic lesions of both the heart and blood vessels was due to the young age of the animals examined or the "cleanliness" of modern reared purpose-bred laboratory nonhuman primates. It is likely that both factors played a role. Other factors likely to cause variation between our findings and any such past and future studies include individual variations among pathologists evaluating the lesions, the differences in the species of nonhuman primates analyzed, their ages, source and background, as well as their management and experimental conditions prior to sacrifice. We deliberately did not include continuous intravenous infusion studies in order to avoid the large number of background vascular changes associated with this method of drug administration (Lilbert and Burnett, 2003).

To our knowledge, this is the first report to specifically document the occurrence of spontaneous cardiovascular lesions in nonhuman primates. Adequate care should be taken when interpreting these findings in toxicological studies.

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