Original Article

The Incidence of Lymphoplasmacytic Gastritis in the Fundus and Antrum of Cynomolgus Monkey (*Macaca fascicularis*) Stomachs

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Abstract: Lymphoplasmacytic gastritis is a concern for toxicological pathologists reading preclinical, non-human primate toxicity studies because subtle gastric changes which could be treatment-related may be masked and gastritis lesions may be confused with treatment-related effects and thus a gastric finding may be incorrectly assigned as a treatment-related lesion. This paper discusses the incidence of lymphoplasmacytic gastritis in cynomolgus monkeys at a contract research organization. The incidence of lymphoplasmacytic gastritis in the fundus and antrum of control cynomolgus monkeys on 18 non-gastric compound studies, was scored. The average fundus score ranged from 0.3 to 1.5 and the average antral score ranged from 0.9 to 3.5 in the cynomolgus monkey stomachs examined. The number of affected control animals in a study ranged from 0 to 5 control animals. No correlation between the route of vehicle administration and the severity or incidence of the lesions was noted. The percentage incidence of affected animals ranged from 0 to 100%. An increased incidence lymphoplasmatic gastritis from 2000 to 2004 was noted. The implications of lymphoplasmacytic gastritis in cynomolgus monkeys used for acute toxicity studies are discussed. (DOI: 10.1293/tox.25.249; J Toxicol Pathol 2012; 25: 249–256)

Key wods: cynomolgus monkey, stomach, gastritis, lymphoplasmacytic

Introduction

Gastritis has been reported in non-human primate species. In 1998, Rubio and Hubbard[1] reviewed the histology of the stomachs of 215 baboons and demonstrated that seven had chronic gastritis, two had hyperplastic foveolar gastropathy (resembling Menetrier's gastropathy in humans), three had hyperplastic foveolar lymphocytic gastritis, one had an adenocarcinoma and 200 had normal mucosa[1]. These workers also identified hyperplastic foveolar gastropathy and hyperplastic foveolar gastritis in three baboons[2]. In 2008, Rubio and co-workers (2008)[3] demonstrated gastritis in 92 well-preserved gastric specimens taken from baboons dying of natural causes. The gastritis was subdivided into acute, superficial, chronic, atrophy in corpus, atrophy in antrum, follicular and lymphocytic subtypes[3]. In all of these cases of gastritis in 92 baboons, no *Helicobacter pylori* organisms were noted in the gastric mucosa, thus suggesting that causes other than *Helicobacter* species were responsible for the disease entity[3]. In humans, focally enhanced gastritis has been associated with the presence of idiopathic colitis,

however in a study by Sonnenberg and co-workers (2011)[4], there was an absence of gastritis noted in conjunction with idiopathic colitis in rhesus macaques (*Macaca mulatta*).

In a review of background findings in cynomolgus monkeys (*Macaca fascicularis*) from three different geographical origins published in 2006[5], the authors state that subacute gastritis was observed in 65 out of 90 cynomolgus monkeys and is characterized by a diffuse, lymphoplasmacytic infiltration of the lamina propria of the stomach. The gastritis is marked and more diffuse in the antral mucosa, it is moderate, more superficial and often patchy in the fundic mucosa. In addition, multifocal haemorrhage, neutrophils within gastric glands, prominent lymphoid aggregates, glandular cystic dilatation, glandular atrophy and intestinal metaplasia are also observed[5]. Vidal and co-workers (2008)[6] demonstrated that the fundus and antrum of the cynomolgus monkey stomach contains scattered, variably sized, lymphoid aggregates and lymphofollicular foci present within the lamina propria and occasionally extending through the muscularis mucosae and into the underlying submucosa. Ito and co-workers (1992)[7] described mononuclear cell infiltration into the stomachs of 81 out of 221 male cynomolgus monkeys and 44 out of 221 female cynomolgus monkeys. Shimoi and co-workers (1998)[8] noted the presence of gastritis in laboratory-bred cynomolgus monkeys accompanied by atrophy of epithelial cells, but without the presence of ulceration and haemorrhage. Mucosal atrophy, inflammatory cell infiltration and dilatation of gastric glands were noted

in the stomachs of a small number of marmosets in a study in 1996[9]. Reindel and co-workers (1999)[10] state that at necropsy, red areas and rarely erosions/ulcers are observed in non-human primates. Upon histopathological examination, the disease demonstrates a minimal to moderate lymphoplasmacytic infiltration into the lamina propria of the antrum and fundus of the non-human primate stomach[10].

Lymphoplasmacytic gastritis is primarily a concern for toxicological pathologists reading preclinical, non-human primate toxicity studies because subtle gastric changes which could be treatment-related (such as a decrease in parietal cells) may be masked by the presence of the lymphoplasmacytic gastritis. Lesions are thus not recorded as treatment-related findings. In addition, lymphoplasmacytic gastritis lesions may be confused with treatment-related effects and thus a gastric treatment-related finding (such as superficial erosions) may be incorrectly assigned to a compound. For these reasons, we examined the fundus and antrum of control cynomolgus monkeys used in studies for compounds that caused no gastric toxicity, retrospectively, in order to assess the prevalence and incidence of lymphoplasmacytic gastritis in this animal species and to ascertain whether the route of vehicle administration affected the severity of the lesions.

Materials and Methods

Adolescent cynomolgus monkeys originating from the Philippines were kept in individual cages. All the cynomolgus monkeys were serologically negative for Herpes virus simiae, simian retrovirus, simian immunodeficiency virus and simian T-lymphotropic virus-1. Clinical evidence of gastric disease was not detected in cynomolgus monkeys before or during the study periods. The cynomolgus monkeys were approximately 2.5 to 3.5 years old at the time of necropsy. Animal room temperature and relative humidity controls were generally maintained at 18-23ºC and 40 to 70% respectively. The cynomolgus monkeys had free access to tap water in bottles with sipper tubes. Drinking water and diet were routinely monitored for contaminants. Studies commenced after an acclimatization period of 14 days, during which animal health was monitored by a veterinary officer. All studies were conducted using protocols approved by the United Kingdom Home Office.

This study is based on the evaluation of control cynomolgus monkeys derived from 18 separate studies. A total of 136 cynomolgus monkey stomachs were examined retrospectively by the same pathologist. The cynomolgus monkeys were euthanized with pentobarbital using intravenous infusion, exsanguinated and necropsied. The stomachs were rapidly removed from the cases, stapled onto cardboard and fixed in 10% buffered formalin. Following fixation, samples of the pylorus/antrum and fundus/corpus were taken and processed in paraffin. The sections were cut and stained with hematoxylin and eosin. In the event of spiral bacteria being detected on hematoxylin and eosin sections, Warthin Starry staining was then performed for the detection of the spiral bacteria.

Hematoxylin and eosin sections of both the fundus and antrum of each cynomolgus monkey stomach were scored for lymphoplasmacytic gastritis severity and distribution. The scoring criteria used for evaluating the gastric lesions included mononuclear cell infiltration, proliferative epithelial changes, presence of neutrophils, reduction in parietal cells and surface epithelial damage. The above criteria were scored for intensity and distribution from 0 to 4 (0 = absence of findings, 1 = minimal; 2 = slight, 3 = moderate, 4 = marked) similar to the Sydney and updated Sydney scoring systems[12,13]. A grade 1 score included minimal mononuclear (lymphoplasmacytic) cell infiltrate in the lamina propria of antrum and fundus. A grade 2 score included mononuclear cell infiltrate in the lamina propria, with some lamina propria expansion and separation of glands and occasional intraepithelial lymphocytes. A grade 3 score included a mononuclear cell infiltrate in the lamina propria, with moderate lamina propria expansion and separation of glands. As well as intraepithelial lymphocytes, decreased mucus content, minimal epithelial hypertrophy and hyperplasia in the glands, antral gland karyomegaly and reduced numbers of parietal cells were also present. A grade 4 score demonstrates the same elements as grade 3, but also includes minimal neutrophil infiltration, mucosal erosions, haemorrhage, cell debris on the surface epithelium and mucosal and submucosal lymphoid follicles. A total fundus or antrum score (i.e. sum of all fundus or antrum scores of control animals in the study) was calculated. The total fundus and antrum score was calculated in order to summarise the findings of one study. This allowed for the comparison of studies between one another. Then an average fundus and antrum score for control animals in a study was determined by dividing the total score by the number of control animals in a study. A total affected fundus and antrum score was then calculated (sum of fundus or antrum scores for affected animals only). An animal was considered affected when it had a fundic score of 2 or more (with an antrum score of 1 or more). An antrum score of 3 alone was considered to indicate gastritis. So, possible fundus/antrum combinations in affected animals were 2/1; 2/2; 2/3; 0/3; 1/3. An average affected fundus and antrum score was calculated by dividing the total affected score in a study by the number of affected animals in the study (for fundus and antrum separately). The incidence of affected animals was then calculated by dividing the number of affected animals in a study, by the total number of animals in the study and converting this figure to a percentage.

Results

Table 1 displays the study number, year of study, total number of control animals in study, route of vehicle administration, number of affected animals and incidence of affected animals total fundus score i.e. sum of all fundus scores in study, average fundus/antrum score, range of fundus/antrum scores, total affected fundus/antrum score and

Table 1. The Study Number, Year, Number of Control Animals in Study, Route of Vehicle Administration, Number of Affected Animals, Incidence of Affected Animals (%), Total Fundus and Antrum Score i.e. Sum of All Scores in Study, Average Fundus and Antrum Score (i.e. Total Fundus or Antrum Score Divided by Number of Animals in Study), Total Affected Fundus and Antrum Score i.e. Sum of Fundus or Antrum Scores for Affected Animals in Study and Average Affected Fundus and Antrum Score (i.e. Total Affected Fundus or Antrum Score Divided by the Number of Affected Animals in the Study)

Study number	Year	Route of vehicle administration	Number of control animals in study	Number of affected animals	Incidence of affected animals (%)	Fundus Nonaffected and affected animals — Total score[1]	Average fundus score	Range of fundus scores	Fundus Affected animals — Total affected fundus score[2]	Average affected fundus score	Antrum Nonaffected and affected animals — Total score[1]	Average score	Range of scores	Antrum Affected animals — Total score	Average score
L	1987	O[a]	10	0	0	6	0.6	0-1	0	0	10	1	0-2	0	0
R	1988	O	12	0	0	3	0.3	0-1	0	0	12	1	1	0	0
N	1990	S.C.[b]	6	0	0	3	0.5	0-1	0	0	6	1	1	0	0
P	1990	O	8	0	0	3	0.4	1	0	0	7	0.9	0-1	0	0
O	1991	O	8	1	13	8	1	0-2	2	2	7	1	0-1	1	1
Q	1993	O	6	0	0	4	0.7	1	0	0	8	1.3	1-2	0	0
M	1994	O	4	0	0	2	0.5	0-1	0	0	8	2	2	0	0
I	1999	O	8	0	0	8	1	1	0	0	8	1	0-2	0	0
J	1999	O.G[c]	8	1	13	6	0.8	0-2	2	2	14	1.8	1-2	2	2
H	2000	O.G.	12	1	8.3	11	1	1	2	2	7	1.2	1-2	0	0
G	2000	O.G.	6	0	0	6	1	1-2	0	0	20	1.7	1-2	2	2
F	2001	I.V.[d]	6	5	83.3	9	1.5	1-2	8	1.6	14	2.3	1-3	13	2.6
D	2003	I.V.	10	2	20	11	1.1	1-3	3	1.5	11	1.83	1-3	9	1.8
C	2003	O.C.[e]	6	2	33	7	1.2	1-2	2	1	16	2	1-3	3	1.5
A	2003	O	6	5	83.3	9	1.5	1-2	8	1.6	10	1.7	1-3	3	1.5
B	2003	O.G.	8	2	40	9	1.13	1-2	2	1	13	1.3	1-3	3	1.5
E	2004	O.G.	2	2	100	6	3	3	6	3	7	3.5	3-4	7	3.5
K	2004	N.G[f]	10	3	30	15	1.5	1-4	10	3.3	23	2.3	2-4	11	3.7

[1] Sum of all scores in study. [2] Sum of fundus scores for affected animals in study. a– oral, b– subcutaneous, c – oral gavage, d – intravenous, e – oral capsule, f – not given.

average affected fundus/antrum score. The histopathology of the fundus included mononuclear cell infiltrate, proliferative epithelial changes, occasional neutrophilic infiltrates and a reduction in parietal cells and these lesions were incorporated into the gastritis score. The histopathology of the antrum included lymphoplasmacytic infiltrates (lamina propria), proliferative epithelial changes and occasional neutrophilic infiltrates (incorporated into the gastritis score), as well as lamina propria expansion, gland separation, intraepithelial lymphocytes, decreased mucous content, cell debris on the surface epithelium, mucosal and submucosal lymphoid follicles and occasional mucosal erosions and haemorrhage. Figure 1 demonstrates gastritis scores of 0, 1, 2, 3 and 4 in the fundus. Figure 2 demonstrates gastritis scores of 0, 1, 2, 3 and 4 in the antrum.

The average fundus score ranged from 0.3 to 1.5 and the average antral score ranged from 0.9 to 3.5. The number of affected animals in a study ranged from 0 to 5 animals. The percentage incidence of affected animals in a study ranged from 0 to 100%. No correlation between the route of vehicle administration and the severity of the lesion was noted.

Helicobacter organisms were visible in two animals in one study (study E) and the antrum of these animals were stained with hematoxylin and eosin (Fig. 3a) and stained with Warthin Starry silver stain (Figs. 3b and c). The silver stain revealed two morphologically distinct, spiral bacteria i.e. *H. pylori* and a *Helicobacter heilmanni*-like organisms (HHLOs). The smaller comma-shaped bacteria were considered to be *H. pylori* (Fig. 3b). The larger organisms with 6 to 8 spirals were considered to be HHLOs (Fig. 3c).

Discussion

Individual animal results were added together to give a total score for a study to allow different studies to be compared to one another. The presence of lymphoplasmacytic infiltrations in both the fundus and antrum of the cynomolgus monkey stomach is in agreement with Vidal and co-workers (2008)[6] who demonstrated that the fundus and antrum of the cynomolgus monkey stomach contains scattered, variably sized, lymphoid aggregates. A review of background findings in cynomolgus monkeys (*Macaca fascicularis*) from three different geographical origins published in 2006[5], states that subacute gastritis is observed in 65 out of 90 cynomolgus monkeys and is characterized by a diffuse lymphoplasmacytic infiltration of the lamina propria of the stomach. Shimoi and co-workers (1998)[8] noted the presence of gastritis in laboratory-bred cynomolgus monkeys accompanied by atrophy of epithelial cells, but without the presence of ulceration and haemorrhage. Finally, Ito and co-workers (1996)[7] noted the presence of mononuclear cells and dilatation of gastric glands in cynomolgus monkeys in a study in 1996.

The gastritis scores for the antrum were consistently higher than the scores for the fundus in our study. The reason for this antral predisposition to more severe lesions is not

known, however it is possible that the antrum is susceptible to environmental antigens. Drevon and co-workers (2006)[5] report that the gastritis noted in cynomolgus monkeys was marked and more diffuse in the antral mucosa and it was moderate, more superficial and often patchy in the fundic mucosa. A similar finding of greater antral severity of gastritis lesions was noted by Katsuta and co-workers (2001)[11].

The percentage incidence of affected control animals ranged from 0 to 100% in a study and the numbers of affected control animals in a study ranged from 0 to 5 animals per study. In some studies, such as study A, E and F, the scores of the animals were high and the number and percentage incidence of affected control animals was high. This indicates that the lymphoplasmacytic gastritis in cynomolgus monkey stomachs is a constant problem with no apparent reduction in lesions over a period of 18 years and with an increase in severity from 2000 to 2004.

The cause of lymphoplasmacytic gastritis in cynomolgus monkeys is not known and it is possible that environmental antigens such as food antigens may cause an immunological reaction within the lamina propria of the stomach. One of the proposed causes of the lymphoplasmacytic gastritis lesions in non-human primates is thought to be *Helicobacter* spp. infection. *Helicobacter* spp. has been recorded in cynomolgus monkeys (*Macaca fascicularis*)[10,11], rhesus monkeys (*Macaca mulatta*)[14,15], baboons (*Papio anubis*)[16], squirrel monkeys (*Saimiri sciureus*)[17] and marmosets (*Callithrix jacchus*)[18,19]. Early maternal transmission to neonatal non-human primates may occur within 48 hours, however, Solnick and co-workers (1999)[20] demonstrated that isolation of newborn rhesus monkeys during the first 24 hours after birth appears to be a reliable method for producing pathogen (*Helicobacter* spp.)-free animals in most instances. Dubois and co workers (1994)[21] demonstrated that a gastritis score of 1.5 was noted in animals uninfected or infected with *Gastrospirilium hominis*-like organisms and a score of 2 or greater was noted in all *H. pylori*-infected animals.

Helicobacter spp. organisms were only demonstrated in hematoxylin and eosin-stained stomach sections in one study out of the 18 studies examined in our study. The examination of all stomach sections stained with Warthin Starry may have increased the number of *Helicobacter* spp. organisms observed, however, hematoxylin and eosin is considered to be an adequate stain for the identification of *Helicobacter* spp. organisms[13]. Drevon-Gaillot and co-workers (2006)[5] reported that the lymphoplasmacytic infiltration grades varied significantly from one anatomic region to another and according to the source of the monkeys. The antral mucosa was more severely infiltrated than the fundic mucosa, especially in monkeys from the Philippines or Vietnam and the *Helicobacter* organisms were noted in the fundus of most cynomolgus monkeys whereas they were less common in the antral mucosa. The mononuclear cell infiltration grade of the stomach was significantly lower in the Mauritian monkeys than in those from other countries[5]. These differences may be related to geography or they may be related to environmental factors such as nutrition or hous-
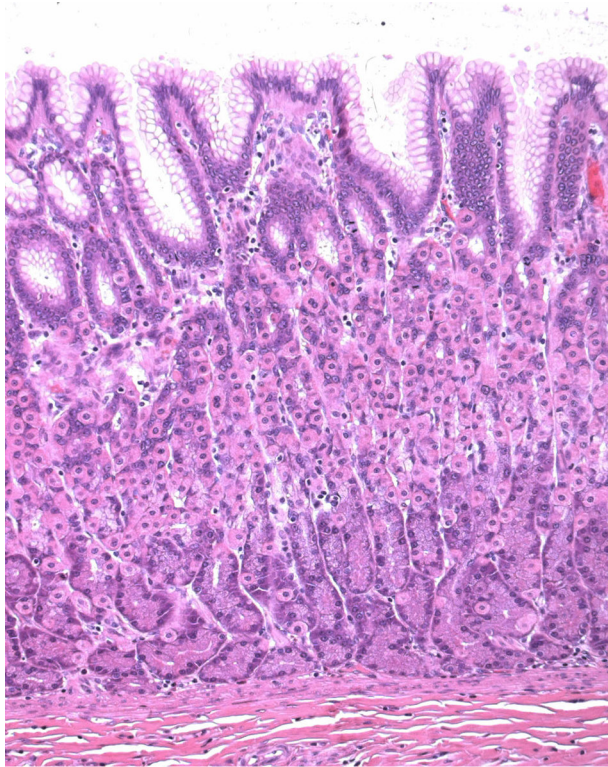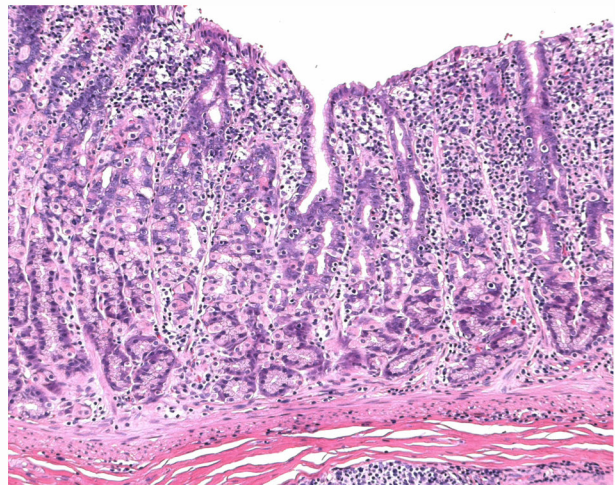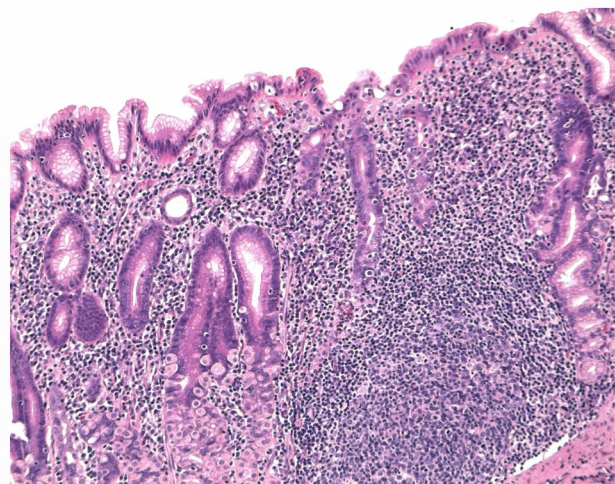
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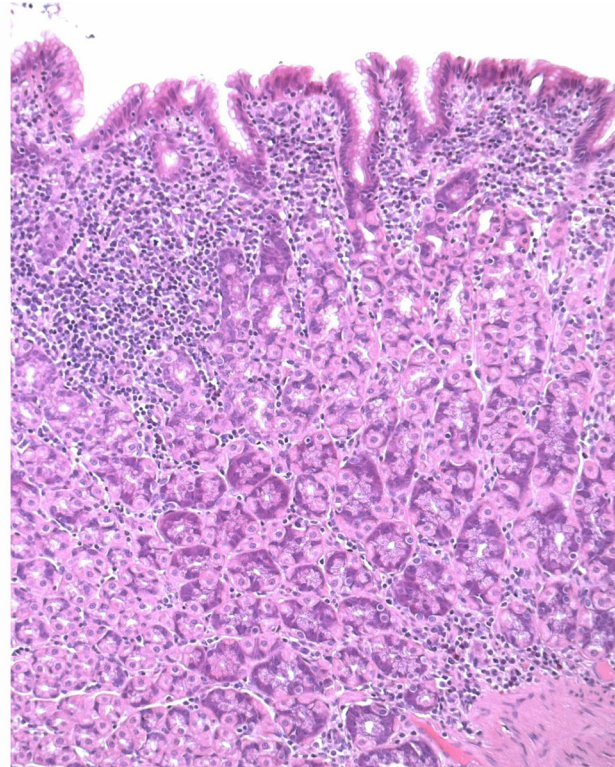
Fundus score 2
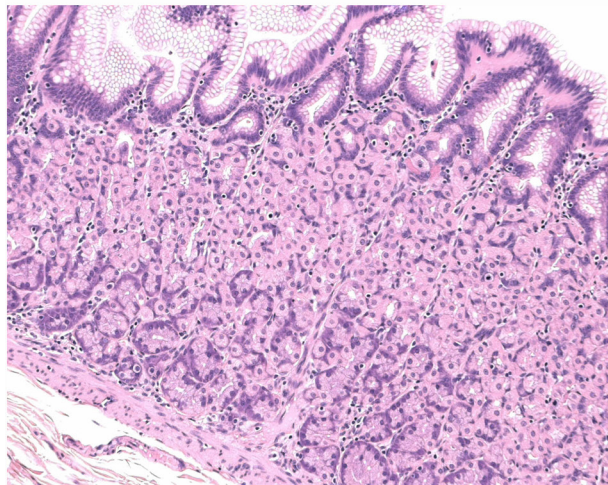
Fundus score 1

Fundus score 3

Fig. 1. Gastritis scores 0, 1, 2, 3 and 4 demonstrated in the fundus of a cynomolgus monkey. Hematoxylin and eosin. Fundus gastritis score 0 demonstrates unremarkable mucosa, lamina propria and submucosa. Fundus gastritis score 1 demonstrates minimal mononuclear cell infiltration into the lamina propria. Fundus gastritis score 2 demonstrates a slight to moderate mononuclear cell infiltration into the lamina propria as well as a reduction in parietal cells. Fundus gastritis score 3 demonstrates a marked mononuclear cell infiltration into the lamina propria as well as a reduction in parietal cells and proliferation of epithelial cells. Fundus gastritis score 4 demonstrates a severe mononuclear cell infiltration into the lamina propria, a reduction in parietal cells and surface epithelial damage.
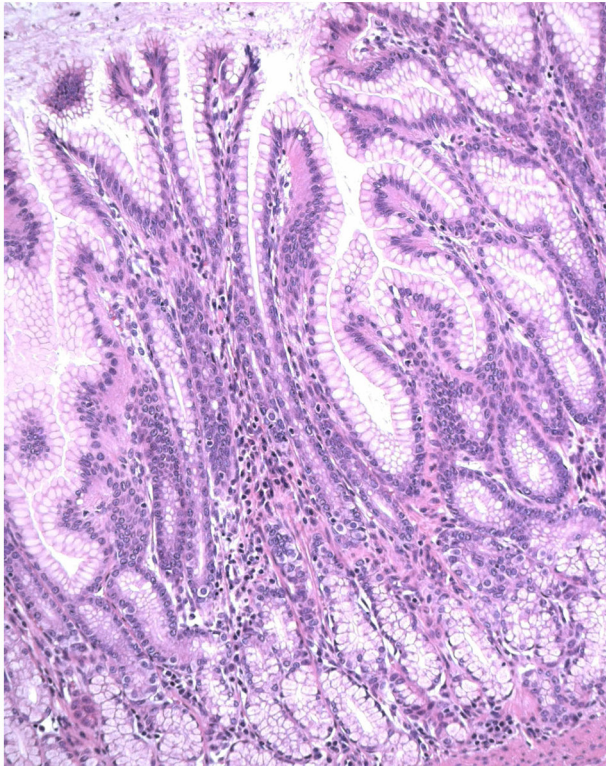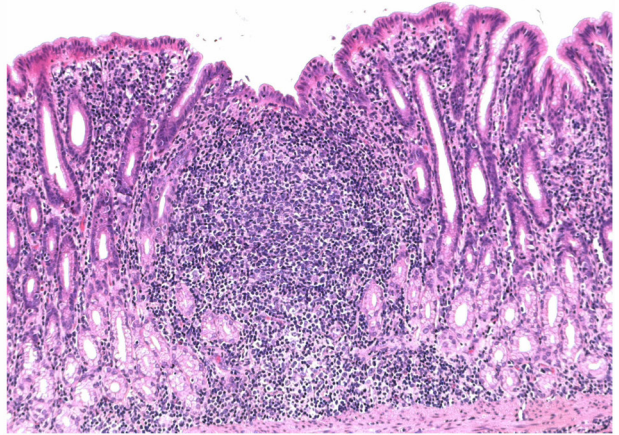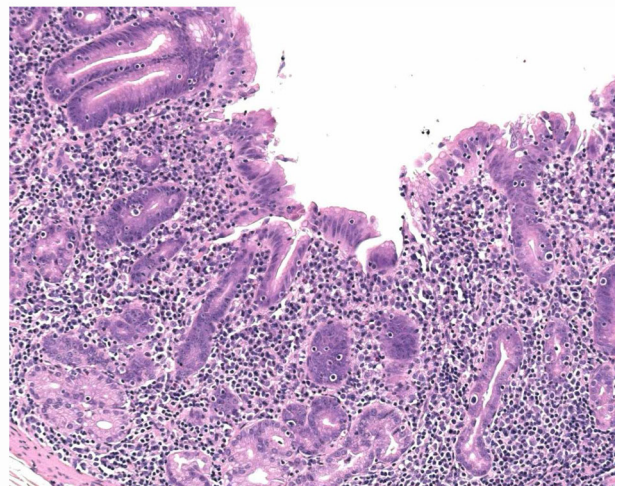
Fundus score 4
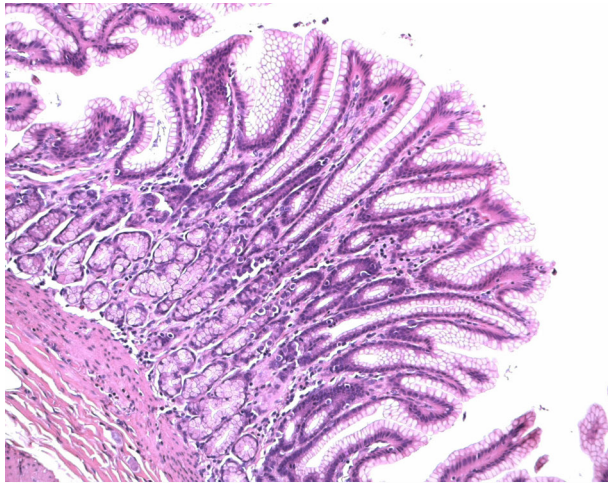
Antrum score 0
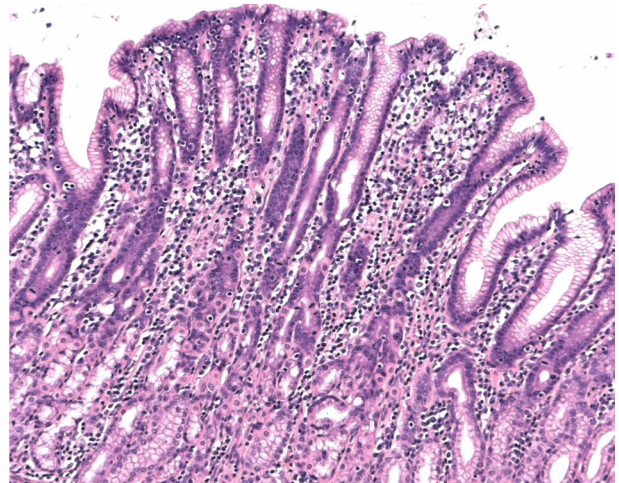
Antrum score 2

Antrum score 1

Antrum score 3

Antrum score 4

Fig. 2. Gastritis scores 0, 1, 2, 3 and 4 demonstrated in the antrum. Hematoxylin and eosin. Antrum gastritis score 0 demonstrates unremarkable mucosa, lamina propria and submucosa. Antrum gastritis score 1 demonstrates minimal mononuclear cell infiltration into the lamina propria. Antrum gastritis score 2 demonstrates a moderate mononuclear cell infiltration into the lamina propria as well as surface epithelial damage. Antrum gastritis score 3 demonstrates a marked mononuclear cell infiltration into the lamina propria as well as proliferative changes in the gastric mucosa. Antrum gastritis score 4 demonstrates a severe mononuclear cell infiltration into the lamina propria as well as proliferative changes in the gastric mucosa, intraepithelial lymphocytes and surface epithelial damage.
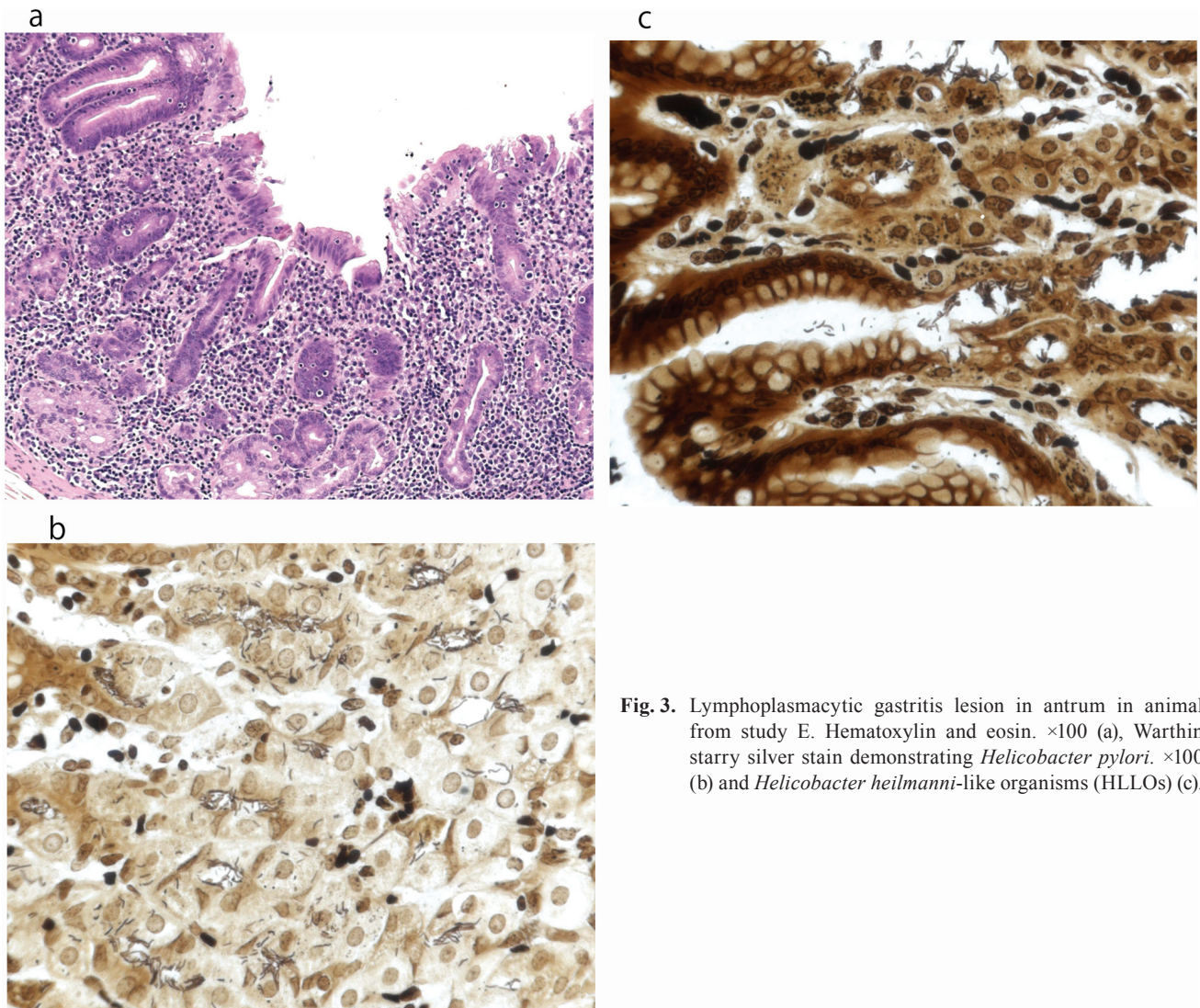
Fig. 3. Lymphoplasmacytic gastritis lesion in antrum in animal from study E. Hematoxylin and eosin. ×100 (a), Warthin starry silver stain demonstrating *Helicobacter pylori*. ×100 (b) and *Helicobacter heilmanni*-like organisms (HLLOs) (c).

ing conditions. Lowenstine (2003)[22] believes that outdoor monkeys have more lymphocytes and plasma cells in the gastrointestinal tract lamina propria than indoor-housed primates. Katsuta and co-workers (2001) demonstrated a high incidence of *Helicobacter pylori* gastritis in the antrums of cynomolgus monkeys from the Philippines with a lower incidence of *Helicobacter pylori* gastritis in animals originating from Japan and a zero incidence of gastritis in animals originating from Indonesia. These authors state than *Helicobacter* spp. transmission can readily occur in colony-bred cynomolgus monkeys and in addition, inadequate sterilization of gastric gavage tubes is likely to be a significant route of transmission in oral administration studies. However, we have presented the evidence that the route of administration of the vehicle (oral, gavage, intravenous and oral capsule) did not influence the incidence or the severity of the lymphoplasmacytic gastritis lesions.

Lowenstein (2003)[22] reports that lymphocytic gastritis with intestinalization of the mucosa or atrophy appears to be increasing in non-human primate centres and she also states that conversely, in some colonies, colonisation with *Helicobacter* spp. is ubiquitous, however the lesions are absent. Taken together these data indicate that the exact cause of lymphoplasmacytic gastritis in non-human primates has not been elucidated and that *Helicobacter* spp. may or may not play a role in this lesion.

We were able to demonstrate an increased incidence of the gastritis lesion from over a period from 2000 to 2004. The reasons for this trend are not known, but may include that possibility that stress, antigenic stimulation or changes in geographical sourcing of cynomolgus monkeys has increased over the years resulting in a greater incidence of gastritis in cynomolgus monkeys used in toxicity studies as well as the possibility that the higher incidence of the *Helicobacter* sp. infections in human populations has resulted in spread of the bacterium from human handlers to cynomolgus monkeys in contract research laboratories. Although inadequate sterilization of gastric lavage equipment is likely to be a significant route of transmission in oral administrations studies, we suggest that the oral gavage route is not

necessarily a factor in the high incidence of lymphoplasmacytic gastritis in our study. The causes of the increasing incidence of lymphoplasmacytic gastritis are many and varied and include the possibility that cynomolgus monkeys are genetically predisposed to develop gastritis.

These findings indicate that the presence of lymphoplasmacytic gastritis with or without the presence of *Helicobacter* spp. organisms continues to be a problem. The lymphoplasmacytic gastritis lesion has the potential to interfere with the interpretation of experimental and toxicity studies because the lesion can be confused with a treatment-related effect (such as a decrease in parietal cells) or the lesion can mask an underlying treatment-related effect (such as ulceration or erosion). In conclusion, ongoing monitoring of lymphoplasmacytic lesions in the stomachs of cynomolgus monkeys is necessary to establish the background levels in cynomolgus monkeys used in all contract research and pharmaceutical environments. Toxicological pathologists need to know about the incidence of this lesion in order to avoid incorrectly attributing the lesion to a treatment-related finding caused by the compound currently being tested.

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