

# Baboons Affected by Hereditary Chronic Diarrhea as a Possible Non-Human Primate Model of Celiac Disease

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# Baboons Affected by Hereditary Chronic Diarrhea as a Possible Non-Human Primate Model of Celiac Disease

**Background:** Celiac disease (CD) represents a unique model of autoimmunity in which, in contrast to most other autoimmune diseases, a close genetic association with HLA genes (DQ2 and/or DQ8), a highly specific humoral autoimmune response (autoantibodies to tissue transglutaminase IgG, (tTG-IgG)), and, most importantly, the triggering environmental factor (gluten), are known. Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, CD could provide unique opportunities to tackle the pathogenic basis of autoimmune processes. However, the lack of an animal model of the disease represents a major limitation in reaching goals. **Aims:** To establish if the pedigreed colony of baboons with hereditary chronic diarrhea at the Southwest Foundation for Biomedical Research (SFBR), could be used as a possible non-human primate model for celiac disease. **Methods:** **Phase I:** The collection of the serum and biopsies samples to determined whether the chronic diarrhea experienced by these baboons could be secondary to gluten induced enteropathy. **Phase II:** Baboons admitted to the SFBR veterinary clinic with chronic diarrhea were placed on a Gluten Free Diet and monitored for 6 months. Blood samples and duodenal biopsies were collected at baseline, midway (3 months) and at the conclusion of the study. **Results:** All of the baboons have had a 10% weight gain and become free of diarrhea, within the first 4-6 weeks of starting the gluten free diet. Currently there are three baboons which have completed the study. These baboons are currently in the general colony on a regular baboon diet. Baboon 19656: Baseline: duodenal biopsies showed patchy villous blunting with an increase in intraepithelial lymphocytes, crypt hyperplasia, some signs of mitosis in the crypts, a decreased villous crypt ratio and a elevated tissue transglutaminase-IgG (tTG-IgG) and Zonulin levels. Midway (3 months): duodenal biopsies showed a normalization of the villous architecture number of intraepithelial lymphocytes, villous crypt ratio and tTG-IgG and zonulin levels. Conclusion (6 months): duodenal biopsies continued to show normalization of the villous architecture with a slight increase in the number of intraepithelial lymphocytes (as compared to 3 month biopsy) The tTG-IgG and zonulin levels continued to be normal. Baboon 16102: Baseline: duodenal biopsies showed a normal villous architecture with large increase intraepithelial lymphocytes focal inflammation, slight crypt hyperplasia, a positive tissue tTG-IgG and normal zonulin level. Midway (3 months): duodenal biopsy showed: a decrease in inflammation and a decrease in intraepithelial lymphocytes (as compared to baseline month biopsy). The tTG-IgG remained positive and the zonulin remained negative. Conclusion (6 months): duodenal biopsy continued to show a decrease in inflammation and a decrease in intraepithelial lymphocytes (as compared to 3 month biopsy). The tTG-IgG remained positive and the zonulin remained negative. Baboon 20008: Baseline: duodenal biopsies showed a moderate increase intraepithelial lymphocytes, crypt hyperplasia, deep crypts, inflammation in the lamina propria and a normal tTG-IgG and a elevated zonulin level. Midway (3 months): duodenal biopsy was unavailable. The tTG-IgG remained normal while the zonulin decreased to a normal level. Conclusion (6 months): duodenal biopsy showed a show normal villous architecture and villous crypt ratio. The tTG-IgG and zonulin levels remained normal. **Conclusions:** These preliminary observations suggest that a gluten-dependent enteropathy is present in the pedigreed baboon colony studied. The clinical, serological, and histological features suggest a similarity to human CD and, therefore, that the progeny of this sire can be potentially used as a primate non-human model of CD.

# Background



The Southwest Foundation for Biomedical Research (SFBR) in San Antonio, TX has a pedigreed baboon colony (population ~3000) that has had a problem of managing chronic diarrhea since the inception of the colony in 1972.

Infectious agents have been excluded and preliminary analysis of the distribution of diarrhea in the baboons at the SFBR, shows a concentration of the affected animals among the progeny of 4 sires that span 6 generations.

# Aims

To establish if the pedigreed colony of baboons with hereditary chronic diarrhea at the Southwest Foundation for Biomedical Research, could be used as a possible non-human primate model for celiac disease.

# Methods: Animal Selection

**4200**

Baboons were reviewed  
from 57 sires

4037  
Healthy

**163**

Chronic Diarrhea  
without an infection

112 (69%)  
From 53 sires  
(~2 cases/sire)

**51 (31%)**  
From 4 sires  
(~13 cases/sire)

**23 Controls**

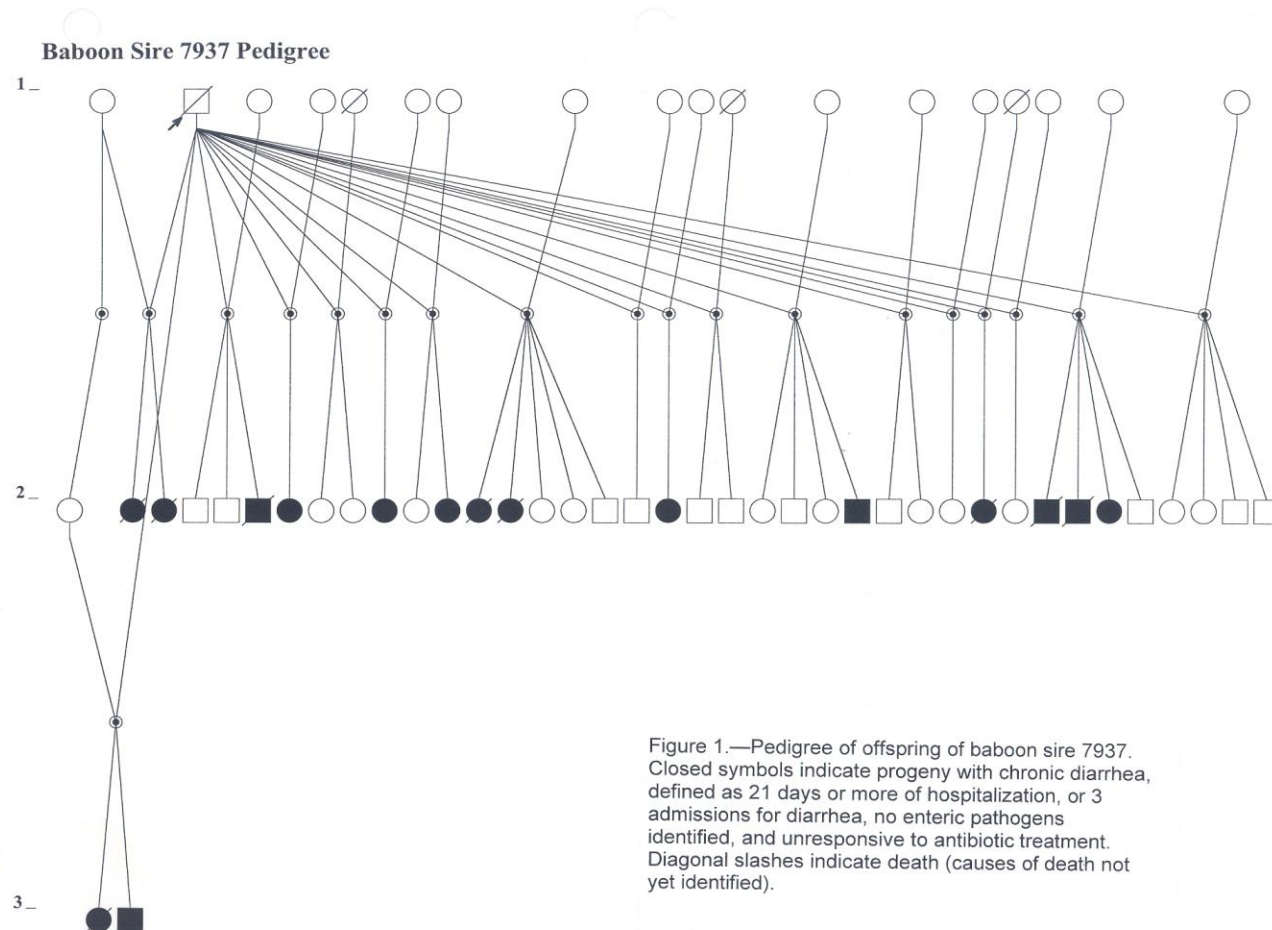
- tTG-IgG
- Zonulin
- Duodenal Biopsy and Necropsy specimens

**19 Chronic Diarrhea cases**

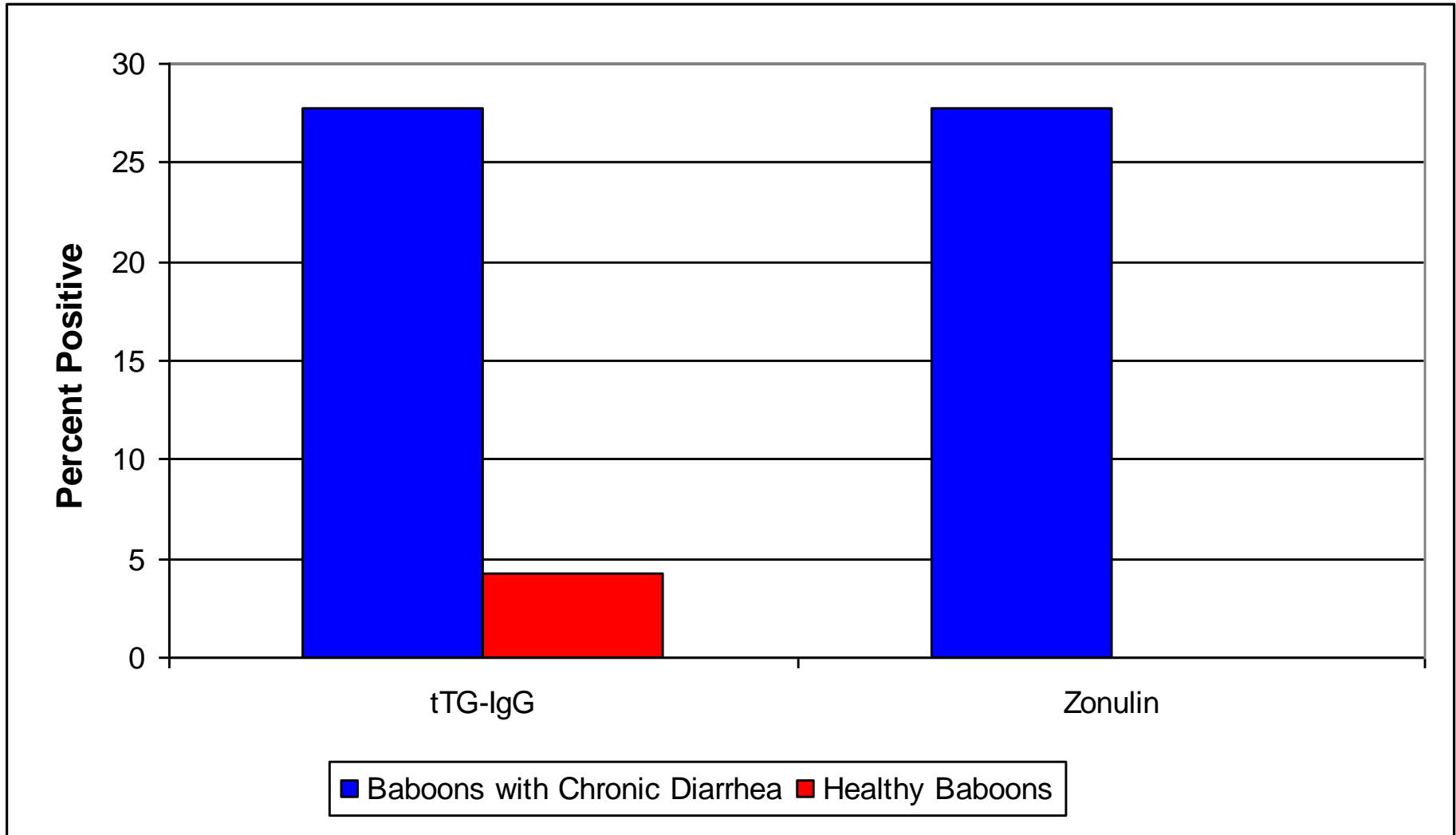
- tTG-IgG
- Zonulin
- Duodenal Biopsy and Necropsy specimens

# Presumptive Evidence that the Chronic Diarrhea Condition is Hereditary

40% of the off spring from one of the 4 original sires developed non-infective chronic diarrhea

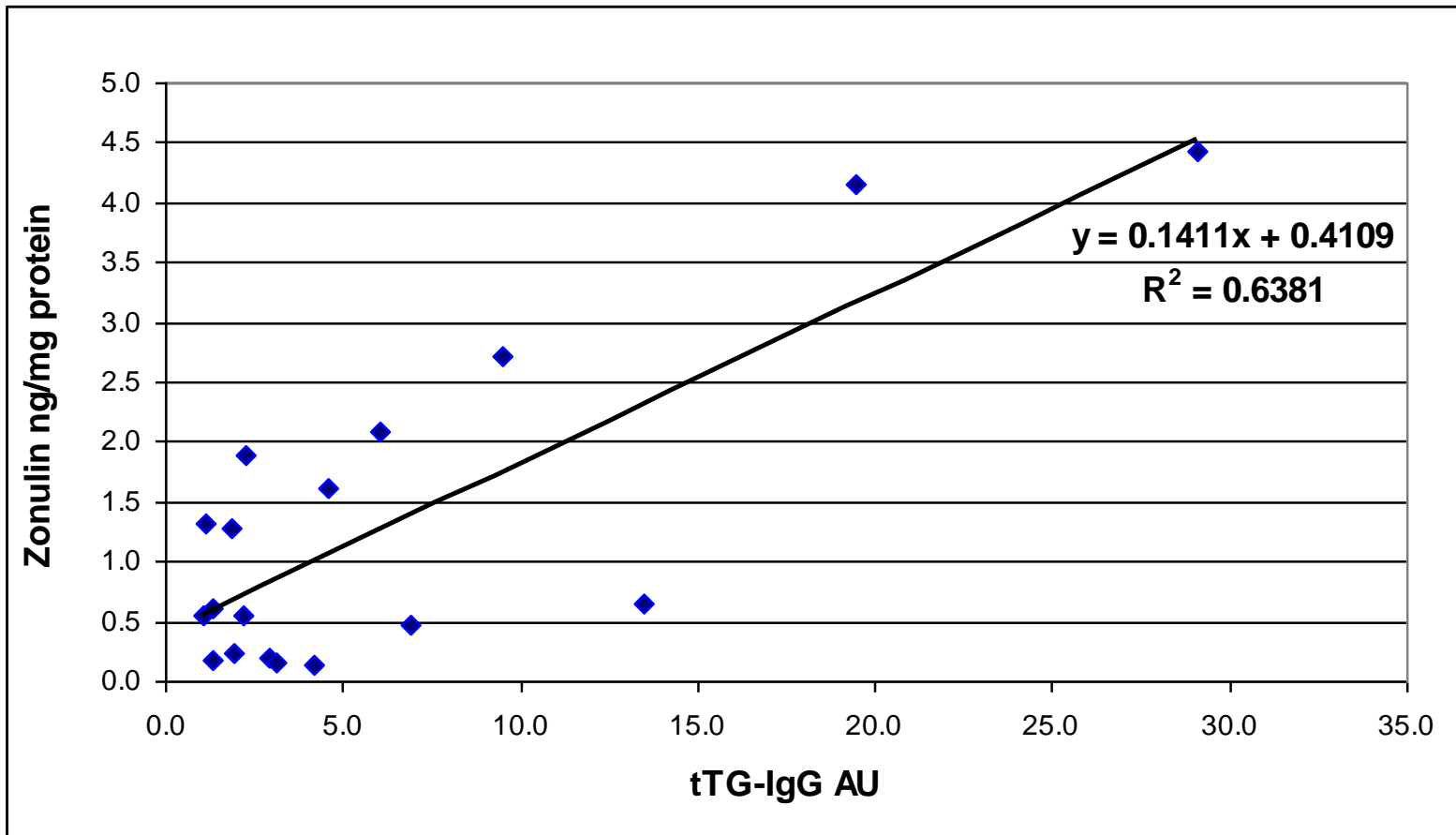


# Serology Results: Phase I



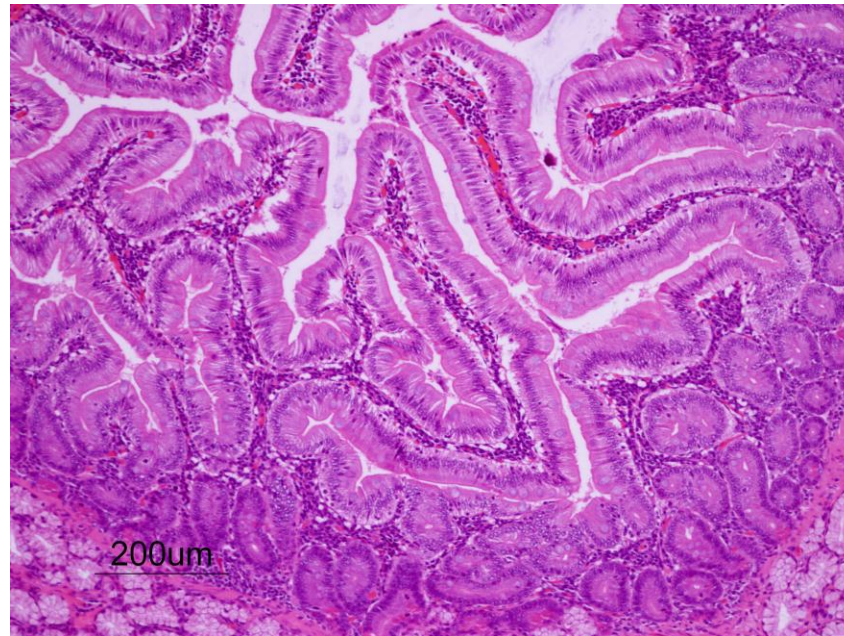
# Serology: Phase I

Correlation between positive tTG-IgG and elevated Zonulin levels



# Histology: Phase I

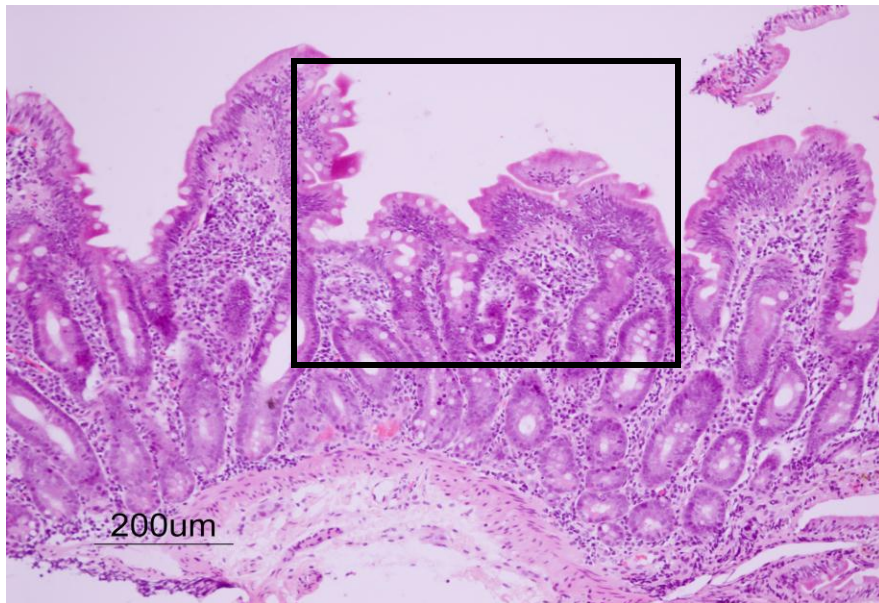
Duodenal tissues from a Healthy Baboon



**Normal Villous Architecture**

# Histology: Phase I

Duodenal tissues from Baboons with chronic diarrhea

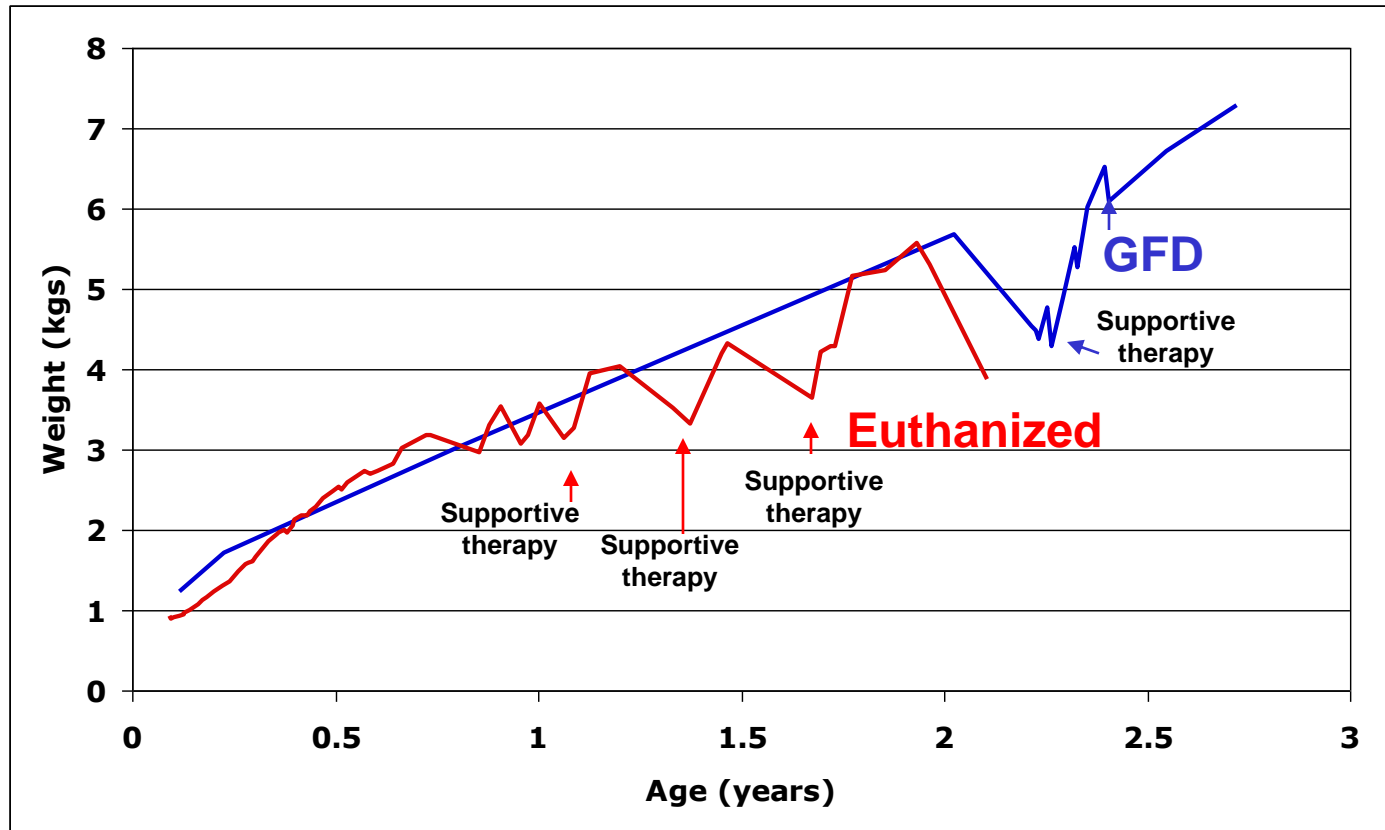


**Patchy Villous Blunting**

**Increased Intraepithelial lymphocytes**



# Intervention with the Gluten free Diet



Supportive Therapy: Gatorade, fruit and vegetables and the usual baboon (gluten containing) chow

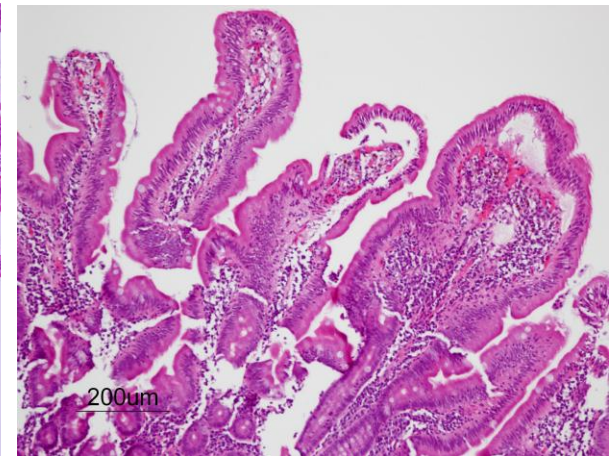
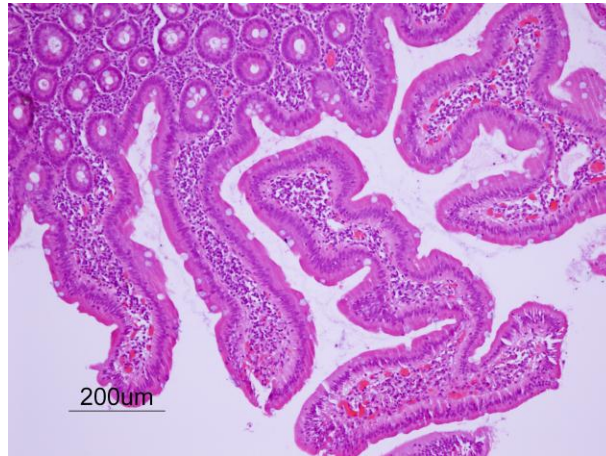
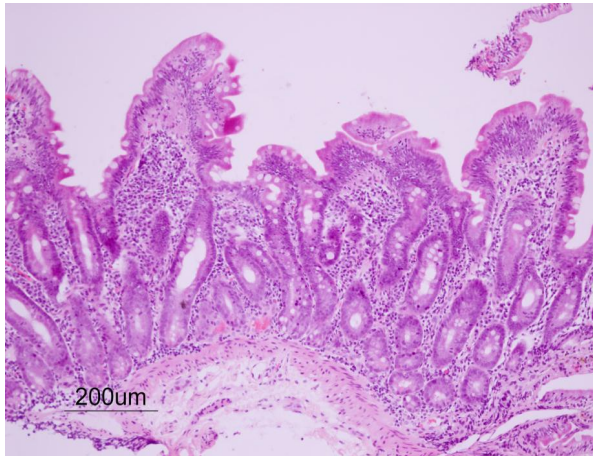
# Results: Phase II

## Baboon #19656, 2 years old

Baseline

3 Months on a GFD

6 Months on a GFD



**†TG-IgG** 9.1  
(Cutoff: 6.6AU)

1.8

5.3

**Zonulin** 6.32  
(Cutoff: 1.69ng/mg)

<0.02

0.03

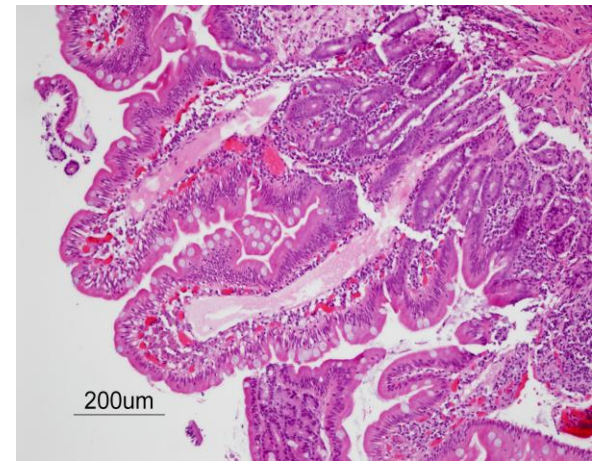
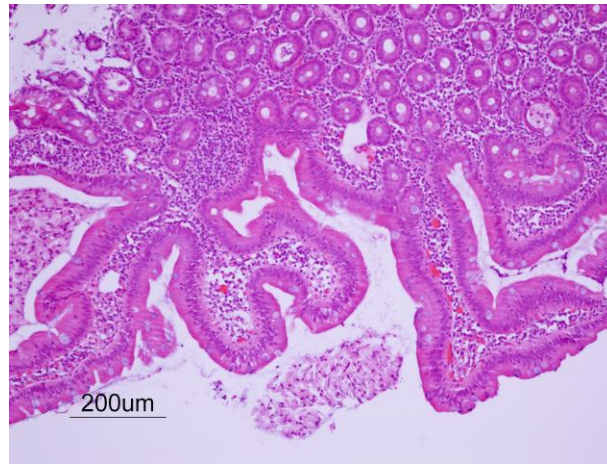
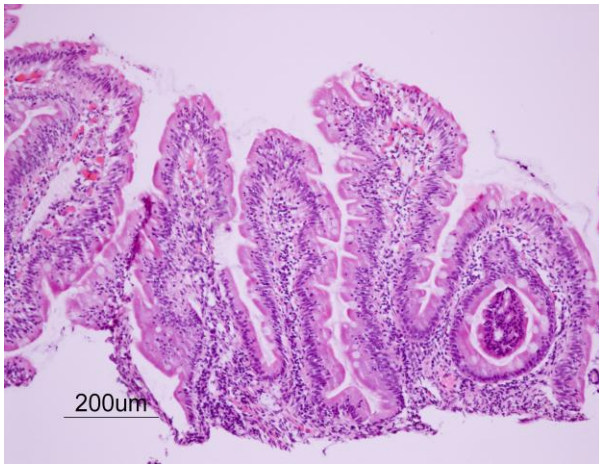
# Results: Phase II

## Baboon #16102, 6 years old

Baseline

3 Months on a GFD

6 Months on a GFD



**†TG-IgG** 6.9  
(Cutoff: 6.6AU)

9.9

13.5

**Zonulin** .047  
(Cutoff: 1.69ng/mg)

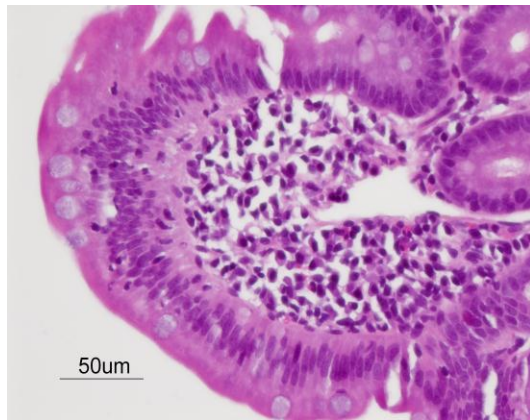
0.40

<0.02

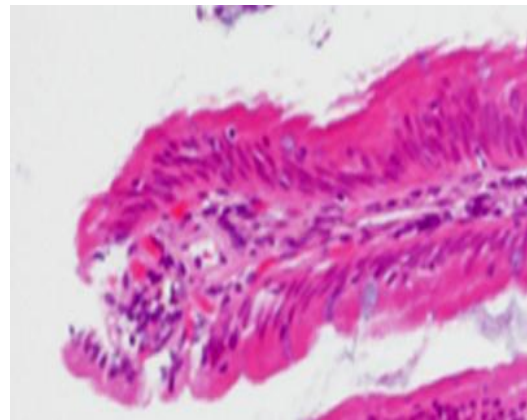
# Results: Phase II

## Baboon #20008, 3 years old

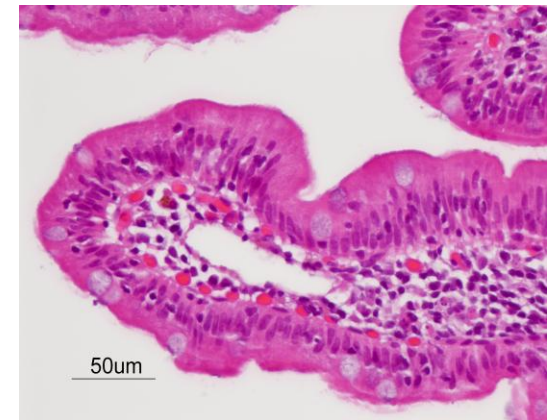
Baseline



3 Months on a GFD



6 Months on a GFD



**†TG-IgG** 4.2  
(Cutoff: 6.6AU)

4.1

5.9

**Zonulin** 7.04  
(Cutoff: 1.69ng/mg)

<0.02

<0.02

# Results: Phase II

All of the baboons have had a 10% weight gain and become free of diarrhea, within the first 4-6 weeks of starting the gluten free diet.

## Baboon 19656:

- **Baseline:** duodenal biopsies showed patchy villous blunting with an increase in intraepithelial lymphocytes, crypt hyperplasia, some signs of mitosis in the crypts, a decreased villous crypt ratio and an elevated tissue transglutaminase-IgG (tTG-IgG) and Zonulin levels.
- **Midway** (3 months): duodenal biopsies showed a normalization of the villous architecture, number of intraepithelial lymphocytes, villous crypt ratio, tTG-IgG and zonulin levels.
- **Conclusion** (6 months): duodenal biopsies continued to show normalization of the villous architecture with a slight increase in the number of intraepithelial lymphocytes (as compared to 3 month biopsy) The tTG-IgG and zonulin levels continued to be normal.

## Baboon 16102:

- **Baseline:** duodenal biopsies showed a normal villous architecture with large increase of intraepithelial lymphocytes, focal inflammation, slight crypt hyperplasia, a positive tissue tTG-IgG and normal zonulin level.
- **Midway** (3 months): duodenal biopsy showed a decrease in inflammation and a decrease in intraepithelial lymphocytes (as compared to baseline biopsy). The tTG-IgG remained positive and the zonulin remained negative.
- **Conclusion** (6 months): duodenal biopsy continued to show a decrease in inflammation and a decrease in intraepithelial lymphocytes (as compared to 3 month biopsy). The tTG-IgG remained positive and the zonulin remained negative.

## Baboon 20008:

- **Baseline:** duodenal biopsies showed a moderate increase in intraepithelial lymphocytes, crypt hyperplasia, deep crypts, inflammation in the lamina propria, a normal tTG-IgG and a elevated zonulin level.
- **Midway** (3 months): duodenal biopsy was unavailable. The tTG-IgG remained normal while the zonulin decreased to a normal level.
- **Conclusion** (6 months): duodenal biopsy showed normal villous architecture and villous crypt ratio. The tTG-IgG and zonulin levels remained normal.

# Results: Phase II

- **Currently there are three baboons which have completed Phase II of the study. These baboons are currently in the general colony on a regular baboon diet.**
- **The 3 baboons all had a 10% weight gain and no diarrhea after 4-6 weeks from starting the GFD.**
- **None of the 3 baboons have been readmitted to the clinic for diarrhea after completing the study.**

# Conclusions

- Within the first 4-6 weeks of starting on the GF baboon chow, the three baboons enrolled in the study continued to gain weight and their diarrhea resolved.
- The sire effect is presumptive evidence that the condition is hereditary.
- The clinical, serological, and histological features and the response to the GFD (both clinically and histological) suggest a similarity to human CD and, therefore, that the progeny of the 4 sires of this pedigreed colony can be potentially used as a primate non-human model of CD.