Peptides and Nutrients in "Difficult to Treat Cases"

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Disclosures

- **Member, Scientific Advisory Board**
  Designs for Health
- **Medical Consultant**
  CrohnsColitisLifestyle.com
- **No financial conflicts of interest to report**

- **Pictures used in this presentation are done with the express permission from the persons involved in the case studies**

OBJECTIVES

- To share actual cases centered around Gastro-Intestinal problems and demonstrate the power of healing with nutrients and the potential of the use of peptides in optimizing health

CASE #1

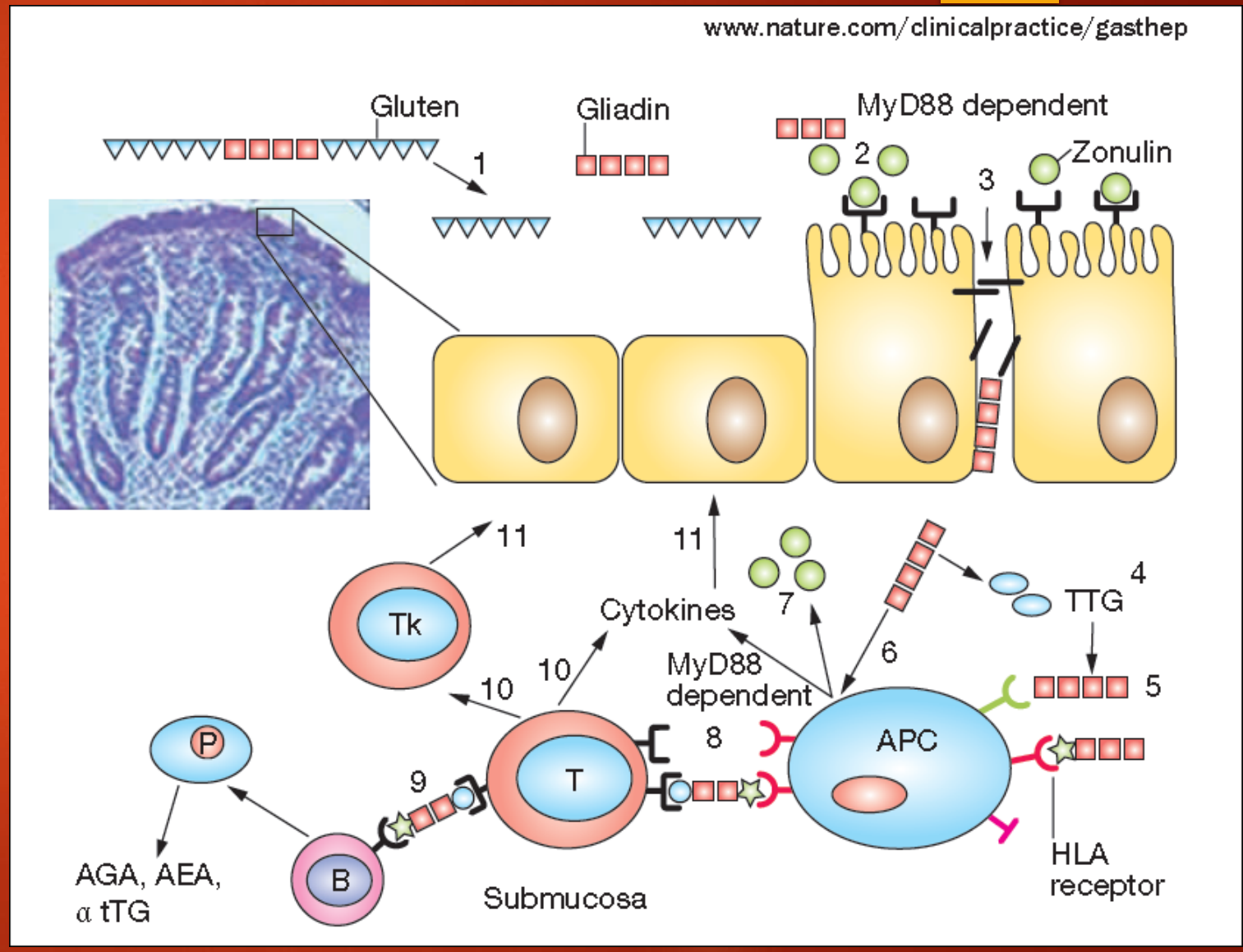
- Middle aged White Female → PCP for yearly PE
  -Medical Hx: Lyme Disease treated immediately with one month of antibiotics with no residual neurological deficiencies
- Diet: lean protein, vegetables, salad, yogurt, avoiding breads (to maintain BMI of 21)
- Exercise: Very active, excersies regularly at gym including cardio and resistance
- Review of systems:
  -fatigue
  -migraine headaches
  -food doesn't taste good anymore

CASE #1

- Labs:
  -CBC shows microcytic anemia
  -Ferritin level 7 (despite eating red meat on a regular basis
  -Chem profile WNL but FBS is higher than in the past (now98)
- Baseline DEXA: Osteopenia (to her surprise and the PCP)
- Had an episode of migraine headache, joint pain, and edema after eating bread at a restaurant

CASE #1

- New labs done:
  -Anti-gliadin Antibodies elevated
  -Negative for Tissue Transglutaminase
  -Zinc level low (????)
  -elevated CRP-hs
- Dx: Pre-Celiac with intestinal villi inflammation causing nutrient deficiencies (iron, calcium)



CASE #1

- Zinc levels low enough to cause a decrease in taste to this degree is not usually seen
- Further investigation: Patient had a silver amalgam removed within the past few months without protection from the mercury vapors
- Pathophysiology: mercury binds to zinc→overt zinc deficiency
- Zinc is a necessary micronutrient to make DiPeptyl Pepidase IV (DPP IV)
- DPP IV is the enzyme that cleaves the long proline tail off the gliadin molecule to make it "anallergenic"

CASE #1

- Genetic testing done:
  -HLA DQ-2 Positive
- Further labs done:
  -Fasting insulin >5, FBS 98
  -Total Cholesterol 202
  -HDL 90
  -Triglycerides 58
  -LDL 70

CASE #1

- Further labs done:
  -Positive for Glutamic Acid Decarboxylase-65 (GAD-65) AB
- GAD-65 AB: main antibody responsible for destruction of the beta cells in the pancreas causing “AUTOIMMUNE” Type 1 Diabetes

Predictive Autoantibodies

Horm Res 1999;52:119–124
(DOI:10.1159/000023447)

Autoantibodies Predicting Diabetes mellitus Type I in Celiac Disease

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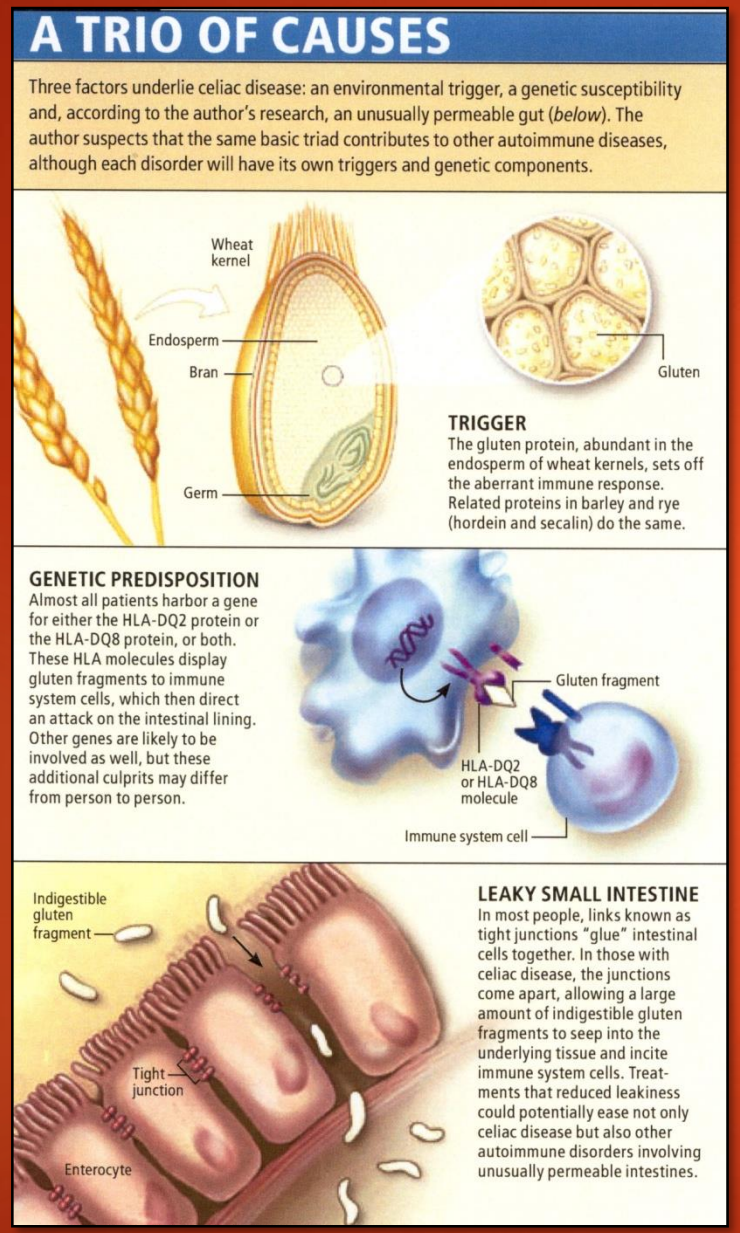
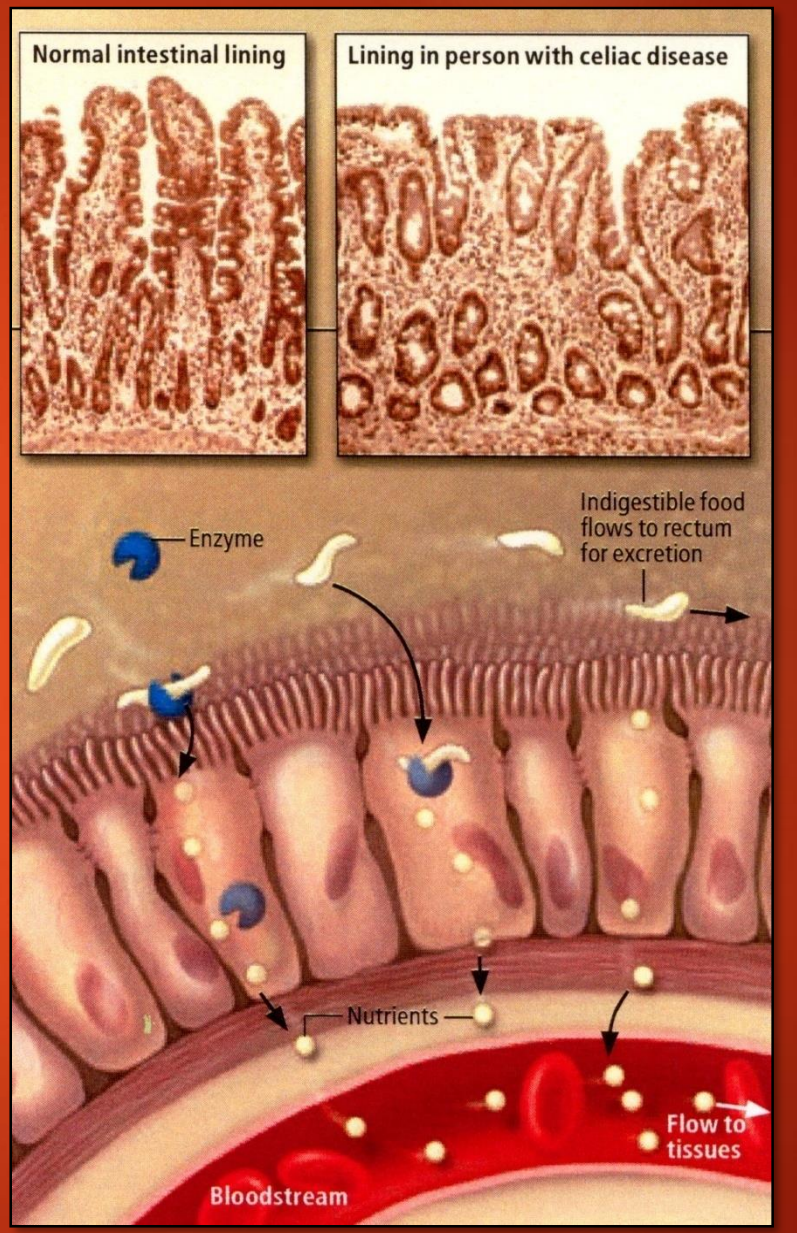
Type 1 DM and Celiac Disease

- In Endocrine clinics, GOLD STANDARD to check for markers for
  Celiac Disease after a diagnosis of Type 1 Diabetes
- PolyAutoimmune Syndrome (PAS): grouping of autoimmune diseases that are often seen together
  Celiac and Type 1 DM often seen together
- Concept of Molecular Mimicry: AGA AB are associated with GAD-65

CASE #1 (Putting the puzzle together)





Work of Dr. Allesio Fasano

Type 1 Diabetes Prevention Trial

Effects of Oral Insulin in Relatives of Patients With Type 1 Diabetes

The Diabetes Prevention Trial–Type 1

THE DIABETES PREVENTION TRIAL–TYPE 1
STUDY GROUP

OBJECTIVE — This randomized, double-masked, placebo-controlled clinical trial tested whether oral insulin administration could delay or prevent type 1 diabetes in nondiabetic relatives at risk for diabetes.

RESEARCH DESIGN AND METHODS — We screened 103,391 first- and second-degree relatives of patients with type 1 diabetes and analyzed 97,273 samples for islet cell antibodies. A total of 3,483 were antibody positive; 2,523 underwent genetic, immunological, and metabolic staging to quantify risk of developing diabetes; 388 had a 5-year risk projection of 26–50%; and 372 (median age 10.25 years) were randomly assigned to oral insulin (7.5 mg/day) or placebo. Oral glucose tolerance tests were performed every 6 months. The median follow-up was 4.3 years, and the primary end point was diagnosis of diabetes.

RESULTS — Diabetes was diagnosed in 44 oral insulin and 53 placebo subjects. Annualized rate of diabetes was similar in both groups: 6.4% with oral insulin and 8.2% with placebo (hazard ratio 0.764, $P = 0.189$). In a hypothesis-generating analysis of a subgroup with insulin autoantibody (IAA) levels confirmed (on two occasions) ≥80 nU/ml ($n = 263$), there was the suggestion of benefit: annualized diabetes rate 6.2% with oral insulin and 10.4% with placebo (0.566, $P = 0.015$).

CONCLUSIONS — It is possible to identify individuals at high risk for type 1 diabetes and to enroll them in a large, multisite, randomized, controlled clinical trial. However, oral insulin did not delay or prevent type 1 diabetes. Further studies are needed to explore the potential role of oral insulin in delaying diabetes in relatives similar to those in the subgroup with higher IAA levels.

Diabetes Care 28:1068–1076, 2005

jected 5-year risk of diabetes. Earlier we reported the results of the DPT-1 parenteral insulin trial, conducted in relatives with >50% projected 5-year risk of diabetes (1). This article reports the results of the DPT-1 oral insulin trial in relatives with a projected 5-year risk of diabetes of 26–50%. In both trials, relatives were studied because of their 10- to 20-fold increased risk compared with the general population (2,3).

Type 1 diabetes is a consequence of immune-mediated destruction of insulin-secreting pancreatic islet β-cells (4). A number of studies have suggested that oral administration of autoantigens induces protective immunity that has the potential to downregulate ongoing destructive immune reactions (5–7). Peptides derived from an orally administered antigen encounter the mucosal gut–associated lymphoid tissue, which serves both to protect the host from ingested pathogens and to prevent the host from reacting to ingested proteins. The concept is that low doses of orally administered autoantigens suppress autoimmunity by inducing antigen-specific regulatory T-cells in the gut, which act by releasing

The Diabetes Prevention Trial-Type1.Dabetes Care.2005;25:1068-76.

Type 1 Diabetes Prevention Trial

Table 1—*Baseline characteristics of randomly assigned subjects*

	Oral insulin group	Placebo group	*P* value
n	186	186	
Median age	11.0 (7–14)	9.5 (7–14)	0.3569
Average FPIR (μU/ml)	161.6 ± 72.4	158.9 ± 99.2	0.7672
Race			0.2807
White	164 (88.1)	163 (87.6)	
African American	5 (2.6)	2 (1.0)	
Hispanic	8 (4.3)	14 (7.5)	
Other	9 (4.7)	7 (3.7)	
Sex			0.1381
Male	119 (63.9)	105 (56.4)	
Female	67 (36.0)	81 (43.5)	
Relationship to index patient with diabetes			0.6552
Sibling	112 (60.2)	108 (58.0)	
Offspring	49 (26.3)	53 (28.4)	
Parent	11 (5.9)	7 (3.7)	
Second degree	14 (7.5)	18 (9.6)	
Antibody levels			
Median ICAs (JDF units)	80 (403–20)	80 (40–160)	0.9253
Mean IAAs (nU/ml)	382 ± 555	346 ± 436	0.4910
GAD antibodies			0.2908
Positive	144 (77.8)	136 (56.4)	
Negative	41 (22.1)	50 (43.5)	
ICA-512 antibodies			0.9567
Positive	97 (52.4)	97 (52.1)	
Negative	88 (47.5)	89 (47.8)	
Micro IAA			0.0551
Positive	39 (29.3)	28 (19.4)	
Negative	94 (70.6)	116 (80.5)	
HbA_{1c} (%)	5.35 ± 0.39	5.33 ± 0.34	0.5949
C-peptide area under curve			
During intravenous glucose tolerance test	34.8 (15.6)	35.1 (16.7)	0.8800
During oral glucose tolerance test	502.5 (201.1)	502.1 (207.2)	0.9858
During mixed meal tolerance test	383.1 (172.4)	381.0 (183.8)	0.9102

Data are means ±SD, n (%), or mean (interquartile range).

- Enrolled Non-diabetic relatives of patients diagnosed with T1DM
- Randomized to receive oral insulin or placebo
- Followed for 5-7 years to evaluate if oral insulin decreased the progression to T1DM

The Diabetes Prevention Trial-Type1.Dabetes Care;25:1068-76.

Type 1 Diabetes Prevention Trial

Oral insulin in relatives at risk for diabetes

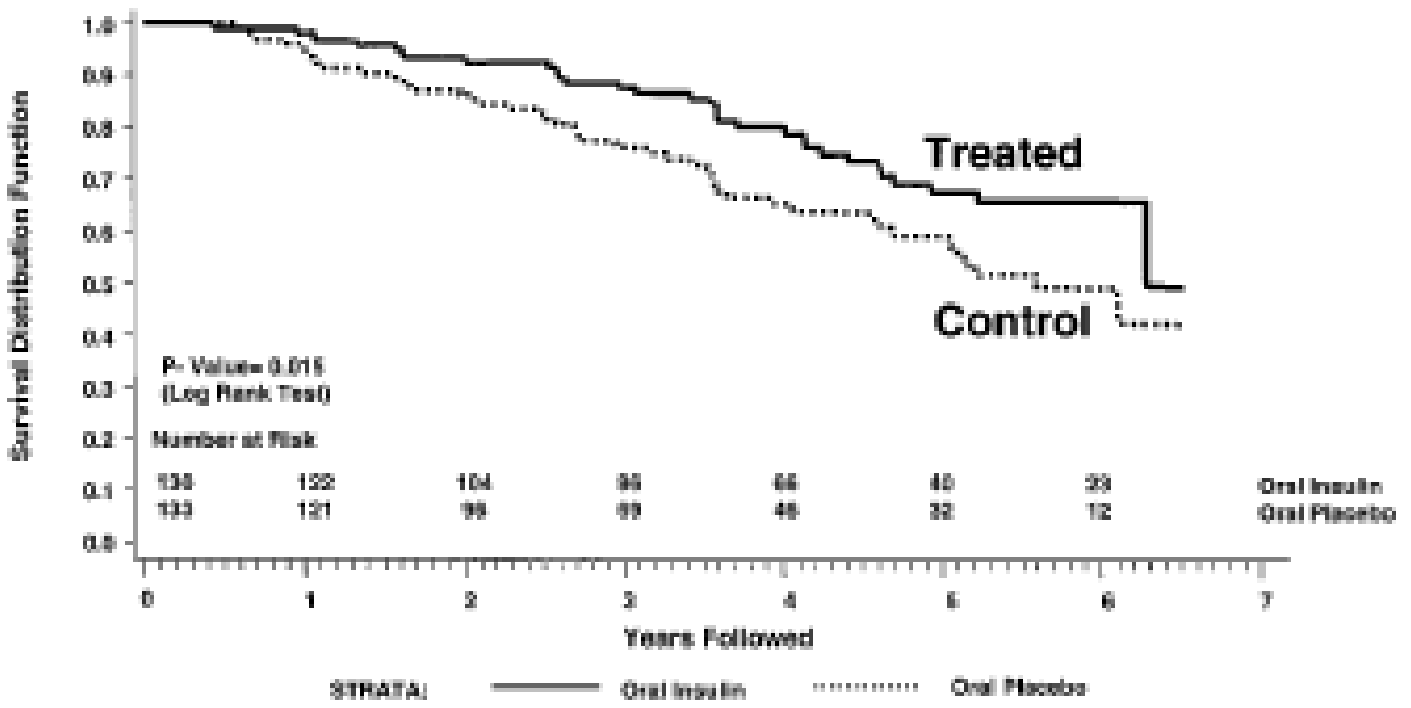


Figure 4—*Kaplan-Meier curves showing the proportion of subjects without diabetes during the trial by treatment assignment for subjects with baseline confirmed IAA ≥80 nU/ml. The number of subjects at risk in each group at each year of follow-up is enumerated at the bottom of the figure. The log-rank test was used for comparison between the groups, with the P values as indicated.*

The Diabetes Prevention Trial-Type1.Dabetes Care.2005;25:1068-76.

Autoimmune Biomarkers

- Predictive antibodies can be found in the blood up to 10 years before the onset of disease and up to 5 years before the onset of neurological autoimmunity
- Early detection means lifestyle changes can be implemented to stop the autoimmune process

Functional Medicine“4 R” Approach

- **Remove**
- **Replace**
- **Reinoculate**
- **Repair**

REMOVE

- **Remove or eliminate factors such as:**
  -Pathogenic microflora (fungi, bacteria, parasites)
  -Foods to which the person is allergic or sensitive
  -Environmental triggers (pesticides, heavy metals, drugs that have a negative effect, etc)
  -stressors that negatively affect the immune system
- **Functional medicine clinical approach**
  -Botanical antimicrobials or phytonutrients that are bacteriostatic/ bacteriacidal
  -Antigenic or elimination diet
  -Antibiotics/Antifungals as medically necessary

REPLACE

- **Replacement of beneficial factors that may be inadequate or totally deficient**
- **Functional medicine approach**
  -digestive enzymes
  -hydrochloric acid
  -fiber to aid in GI transit
  -macro- and micronutrients

REINOCULATE

- **Reinoculate or reintroduce the beneficial microflora to treat dysbiosis and/or balance the microbiome**
- **Stool testing helps to identify what bacteria is overgrown and what is deficient**
- **Functional medicine approach may include:**
  -Bifidobacteria strains
  -Lactobacillus strains
  -Saccharomyces boulardii
  -Soluble fiber
  -Prebiotics

REPAIR

- **Repair and support regeneration of the gut mucosa by providing the necessary nutritional support**
- **Functional medicine approach may include nutrients to "self-repair:**
  -L-glutamine,
  -Vitamin C,
  -zinc
  -curcumin,
  -EPA and DHA
  -Vitamin D
  -Berberine

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AMERICAN JOURNAL OF PHYSIOLOGY
Gastrointestinal and Liver Physiology

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Am J Physiol Gastrointest Liver Physiol. 2012 Mar 1; 302(5): G504–G514.
Published online 2011 Dec 15. doi: 10.1152/ajpgi.00312.2011

PMCID: PMC3311435

Berberine promotes recovery of colitis and inhibits inflammatory responses in colonic macrophages and epithelial cells in DSS-treated mice

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Berberine: Anti-inflammatory Effect

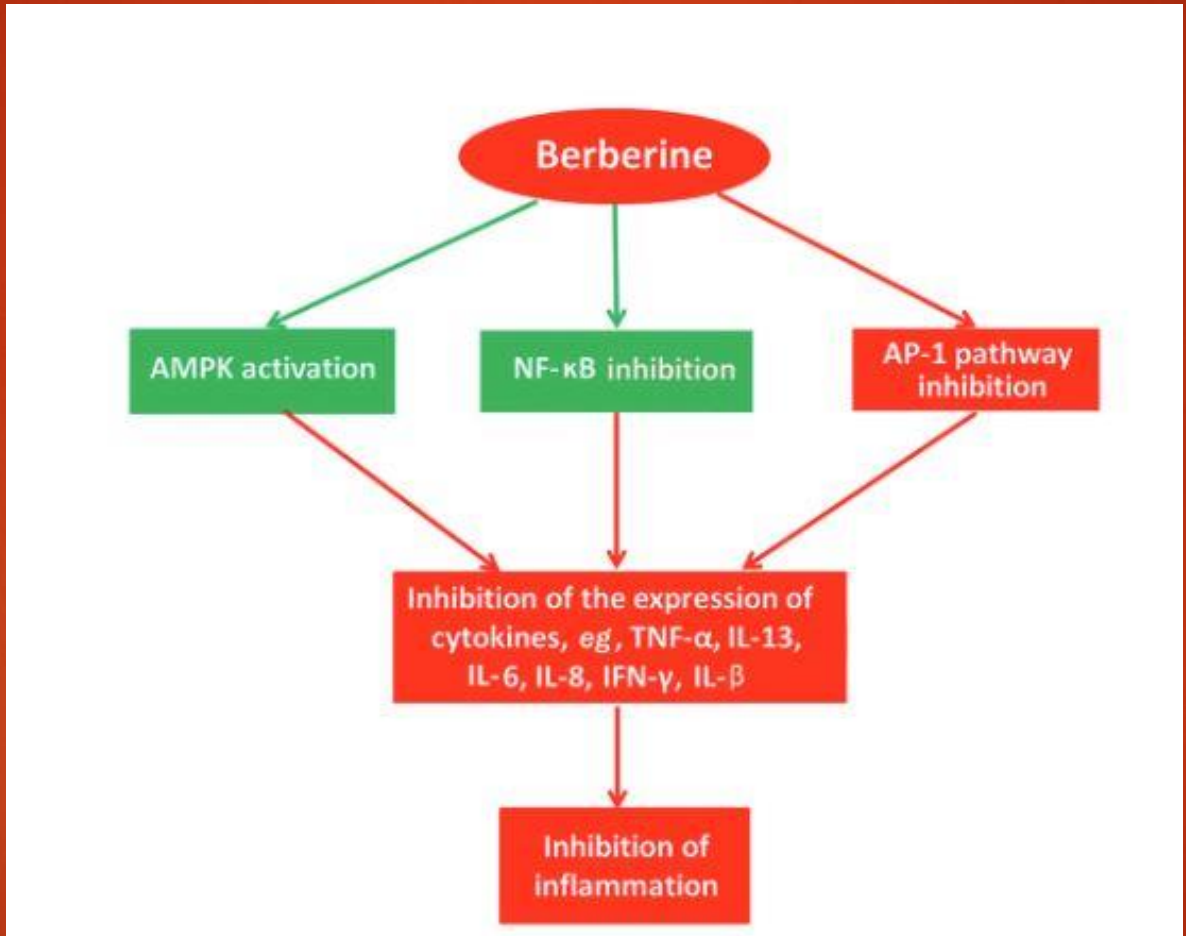

Figure 3. Summary of the anti-inflammatory effect of berberine.

Yan F, et al. Berberine promotes recovery of colitis…Am J Physiol Gastrointest Liver Phys.2012;302(5):G504-14

Vitamin D

Am J Physiol Gastrointest Liver Physiol 294: G208–G216, 2008.
First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.

Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

Juan Kong,[1] Zhongyi Zhang,[1] Mark W. Musch,[1] Gang Ning,[2] Jun Sun,[3] John Hart,[4] Marc Bissonnette,[1] and Yan Chun Li[1]

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Submitted 31 August 2007; accepted in final form 23 October 2007

Case study: Hannah

- 17 yo white female
- Presentation of weakness/nausea after class trip
- ER visit for "dehydration"
- Lab results: New onset Type 1 Diabetes (+GAD-65)
- Additional testing revealed:
  -Pre-Celiac Disease
  -C-peptide 0.7 (nl 0.8-1.4): shows good pancreatic reserve
- Suggested Tx by hospital:

Case study: Hannah

- Intervention:
- Long term benefits: Has not lost beta cell function over past 5 years

Case Presentation: Kurt

- Patient profile: 20 yo WM with progressive inability to flex hands and pain in bottom of feet when walking
- Presentation: progressive thickening of palms of hands and soles of feet
- Diagnosis: Palmar-Plantar Keratosis with the only recommeded Tx of high dose steroids for life
- Evaluation/Testing: HLA DQ-2 positive (traced to dad) and + AGA AB, neg tTg AB
- New Diagnosis: Positive AB titer to gliadin
- Results: skin on hands and feet normalized after 1 yr on gluten free diet (Hx of F/U: problem reoccurred after going off gluten-free diet)

Case Presentation: Brian

- Patient profile: 14 WM referred to office for counseling regarding diet and blood sugar monitoring due to new Dx of T1DM while in ER for Tx of refractory asthma attack (waiting to get appt at Yale Pedi Endo in 6 weeks)
- Presentation: thin, pale, ht of 11 yo, tanner 1, sullen
- Diagnosis: T1DM, severe asthma, short stature,
- Evaluation/Testing:

Case Presentation: Brian

- New Diagnosis:
- Results: 4 yr F/U: graduated the tallest boy in his class (was the shortest), top honors,
- **NO DX OF T1DM or Asthma**

Case study: Hailey

- Patient profile: 14 yo WF with severe Rheumatoid Arthritis with Hx of high dose prednisone, methotrexate (liver damage), DMARD meds (excision of excessive growth of lymphoid tissue) and still remains in pain
- Presentation: thin, frail, guarded due to pain in lower extremities
- Diagnosis: Severe Juvenile Rheumatoid Arthritis
- Evaluation/Testing:

Case study: Hailey

- New Diagnosis: +Antigliadin AB and Casein AB IgG
- Results within one year:
  -off methotrexage,
  -prednisone down to 2 mgm,
  -weaning off DMARD,

Case presentation: Katie

- 26 yo white female Police Officer with c/o fatigue
- Routine chem labs: Severely elevated LFTs, non drinker and neg for all studies looking for infectious disease. Liver biopsy done.

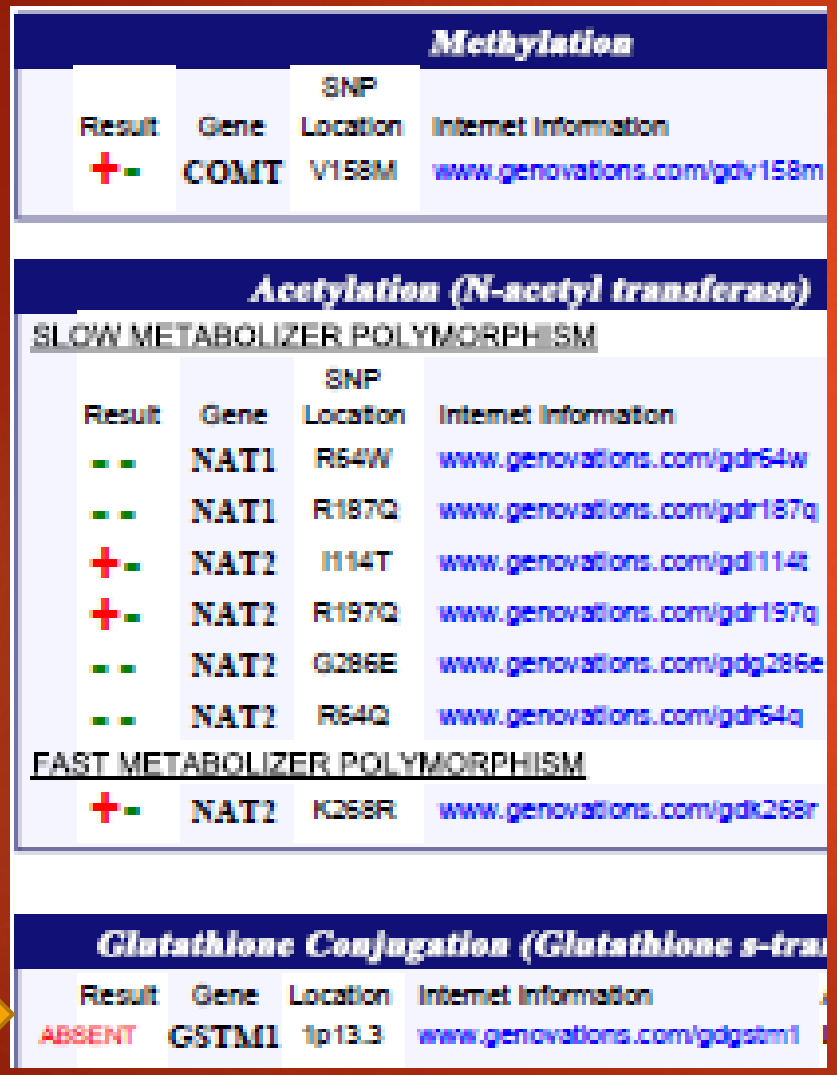
Case presentation: Katie

- **Final Dx: Autoimmune Hepatitis**
- Prescribed Tx: Immune suppressing drugs (told she might die early from cancer and would not be able to have children)
- Was engaged and wanted to have children
- Second opinion at my office
- **Standard lab testing: NEGATIVE for Antigliadin AB IgG and IgA**
- Tumor Necrosis Factor a (TNFa):

Case presentation: Katie (con't)

TEST	RESULTS				
ANTIBODY ARRAY 3	**Normal**	**Equivocal***	**Out of Range**	**Numeric Value**	**Reference** (ELISA Index)
Wheat/Gluten Proteome Sensitivity & Autoimmunity					
Wheat IgG			X	3.86	0.3-1.3
Wheat IgA			X	4.18	0.4-2.4
Wheat Germ Agglutinin IgG		X	.	1.27	0.3-1.5
Wheat Germ Agglutinin IgA	X			1.55	0.9-1.9
Alpha Gliadin 33 MER IgG			X	3.73	0.3-1.4
Alpha Gliadin 33 MER IgA			X	4.52	0.6-1.8
Alpha Gliadin 17 MER IgG			X	1.66	0.3-1.5
Alpha Gliadin 17 MER IgA			X	3.68	0.6-2.0
Gamma Gliadin 15 MER IgG	X			1.21	0.4-1.7
Gamma Gliadin 15 MER IgA		X	.	1.74	0.7-1.9
Omega Gliadin IgG	X			1.03	0.5-1.6
Omega Gliadin IgA			X	1.98	0.6-1.8
Glutenin IgG		X	.	1.14	0.2-1.5
Glutenin IgA			X	1.83	0.5-1.7
Gluteomorphin IgG			X	1.64	0.3-1.5
Gluteomorphin IgA		X	.	1.66	0.6-1.8
Prodynorphin IgG	X			1.22	0.4-1.7
Prodynorphin IgA		X	.	1.76	0.6-1.8
Gliadin-Transglutaminase IgG	X			0.98	0.4-1.6
Gliadin-Transglutaminase IgA			X	2.37	0.6-1.6
Transglutaminase IgG		X	.	1.11	0.5-1.4
Transglutaminase IgA			X	2.00	0.6-1.5

Katie: DetoxiGenomics



Methylation

Result	Gene	SNP Location	Internet Information
+-	COMT	V158M	www.genovations.com/gdv158m

Acetylation (N-acetyl transferase)

SLOW METABOLIZER POLYMORPHISM

Result	Gene	SNP Location	Internet Information
- -	NAT1	R64W	www.genovations.com/gdr64w
- -	NAT1	R187Q	www.genovations.com/gdr187q
+-	NAT2	I114T	www.genovations.com/gdi114t
+-	NAT2	R197Q	www.genovations.com/gdr197q
- -	NAT2	G286E	www.genovations.com/gdg286e
- -	NAT2	R64Q	www.genovations.com/gdr64q

FAST METABOLIZER POLYMORPHISM

Result	Gene	SNP Location	Internet Information
+-	NAT2	K268R	www.genovations.com/gdk268r

Glutathione Conjugation (Glutathione s-tra

Result	Gene	Location	Internet Information
ABSENT	GSTM1	1p13.3	www.genovations.com/gdgstm1

- GF Detox (28 days)
- Antioxidant support
- N-AcetylCystiene 4 caps BID
- Milk Thistle 3 daily
- Glutathione support
- L-5-MTHF 1 mg BID (also had the MTHFR +677 and +1298)
- CLEAN WATER/GF diet
- Results:

Case Presentation: Anna

- Hx of progressive Multiple Sclerosis
  -wheel chair bound at age 26
  -almost legally blind
- Treatment obtained in Russia: Excising her own stem cells, then treating with powerful chemotherapy, high dose steroids, multiple antibiotics, re-infusting her own stem cells
- Results: able to walk and see BUT left her
  -COMPLETELY STEROID DEPENDENT
  -Dysbiosis
  -Irritable Bowel Disears
  -Severe MicroNutrient Deficiency



Picture used with permission

Case Presentation: Anna's Tx Plan

- Weaning off steroids: tedious as want to avoid cortisol withdrawal syndrome
  -ACTH level "non-existant" refects TOTAL HPA axis shutdown
  -Adrenal support including DHEA supplementation
- Treat the dysbiosis with prebiotics and probiotics
- Treat the Leaky Gut
- Treat the nutrient deficiencies
  -intra-nasal route
  -sublingual route (i.e. Vit D SL due to inability to absorb fat soluable vitamins

Case Presentation: Anna after Tx



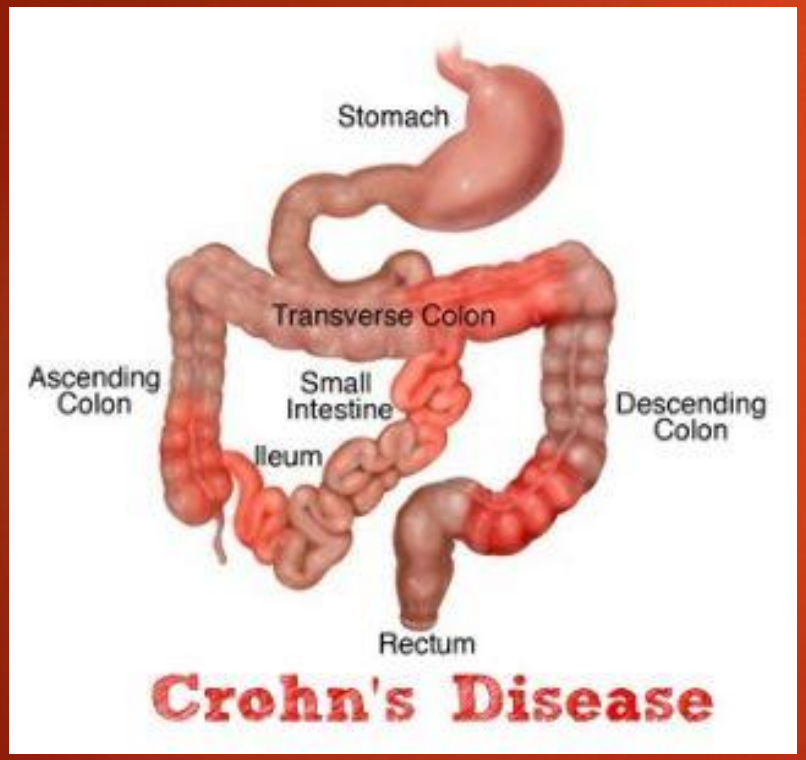
Case Presentation: Dane

- Healthy college student into body building
- Started to have intermittent episodes of abdominal pain but were self-limiting
- Graduated from college
- Very stressful high powered job
- Abdominal symptoms more severe and more frequent
- Interfered with his job and life in general
- Dx: Ulcerative Colitis → Crohn's Disease



Picture used with permission

Crohs's Disease: Autoimmunity GI





Case Presentation: Dane

- Hospitalized for treatment
- Bowels movements up to 30 time in 24 hours
- High dose steroids
- Total Parenteral Nutrition
- Methotrexate
- Immune Modulating Drugs (DMARD drugs)
- Down to 128 pounds (6 foot 2 inches)
- Only recourse was to do a "TOTAL COLECTOMY"
- Signed himself out of the hospital to seek other Tx options

Case Presentation: Dane

Started his **SHIELD** program

- **S**upplements
- **H**erbs
- **I**magination
- **E**xercise
- **L**ifestyle
- **D**iet
- Gained over 60 lbs Muscle



Picture used with permission

Peptide Therapy for GastroIntestinal Problems:

BPC 157

- J Appl Physiol (1985). 2011 Mar;110(3):774-80. doi: 10.1152/japplphysiol.00945.2010. Epub 2010 Oct 28.
- **The promoting effect of pentadecapeptide BPC 157 on tendon healing involves tendon outgrowth, cell survival, and cell migration.**
- Chang CH1, Tsai WC, Lin MS, Hsu YH, Pang JH.

- Molecules. 2014 Nov 19;19(11):19066-77. doi: 10.3390/molecules191119066
- **Pentadecapeptide BPC 157 enhances the growth hormone receptor expression in tendon fibroblasts.**
- Chang CH1, Tsai WC2, Hsu YH3, Pang JH4.

BPC 157

- Curr Pharm Des. 2011;17(16):1612-32.
- **Stable gastric pentadecapeptide BPC 157: novel therapy in gastrointestinal tract.**
- Sikiric P1, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicek R, Radic B, Drmic D, Ilic S, Kolenc D, Vrcic H, Sebecic B.

BPC 157

- Curr Pharm Des. 2017 Feb 20. doi: 10.2174/1381612823666170220163219
- **Stress in gastrointestinal tract and stable gastric pentadecapeptide BPC 157. Finally, do we have a solution?**
- Sikiric P, Seiwerth S, Rucman R, Drmic D, Stupnisek M, Kokot A, Sever M, Zoricic I, Zoricic Z, Batelja L, Ziger T, Vlainic J, Rasic Z, Bencic ML.

BPC 157

- Curr Med Chem. 2012;19(1):126-32.
- **Focus on ulcerative colitis: stable gastric pentadecapeptide BPC 157.**
- Sikiric P1, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicek R, Radic B, Drmic D, Ilic S, Kolenc D, Stambolija V, Zoricic Z, Vrcic H, Sebecic B.

BPC 157

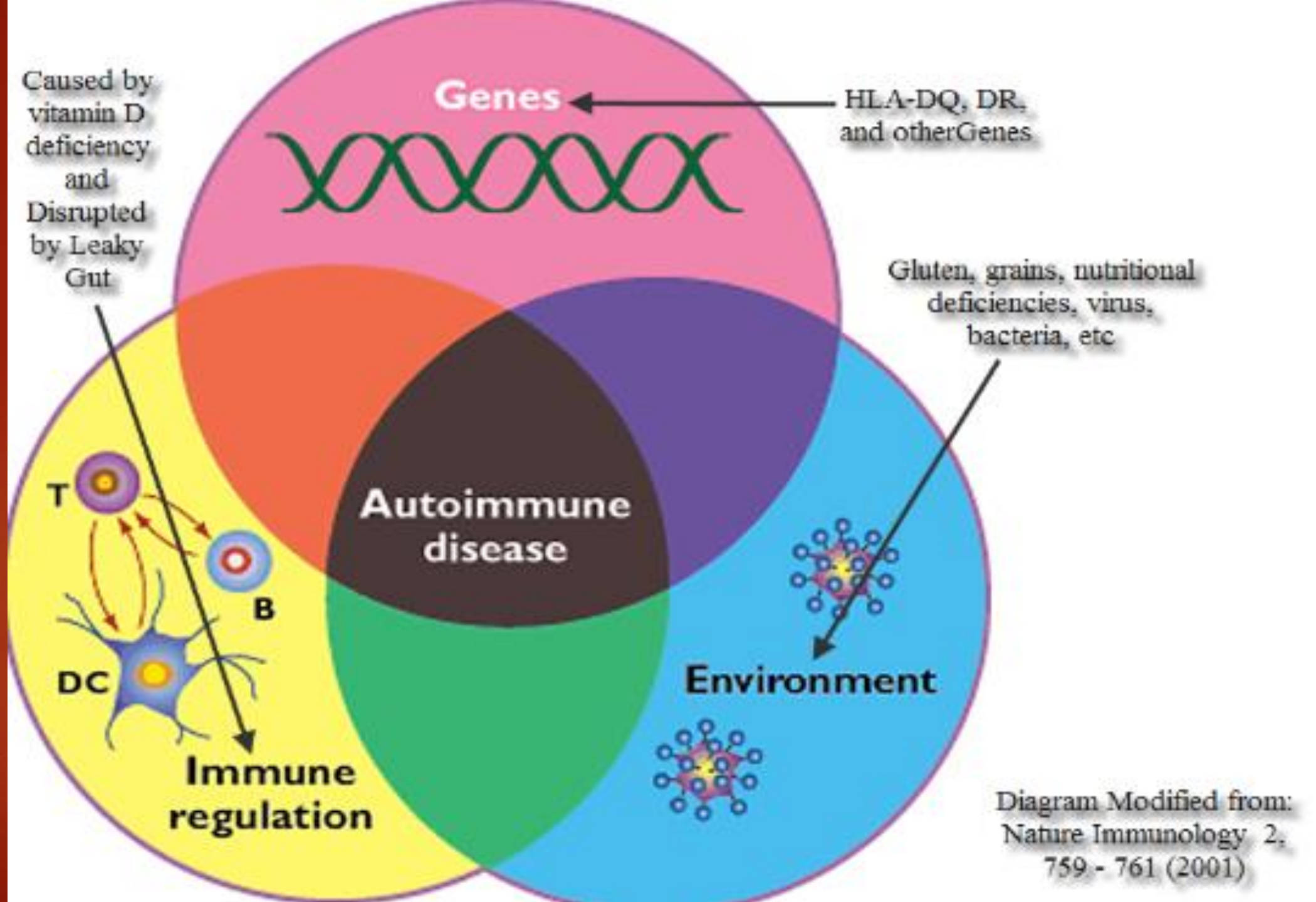
- Curr Pharm Des. 2013;19(1):76-83.
- **Toxicity by NSAIDs. Counteraction by stable gastric pentadecapeptide BPC 157.**
- Sikiric P1, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicek R, Radic B, Drmic D, Ilic S, Kolenc D, Aralica G, Safic H, Suran J, Rak D, Dzidic S, Vrcic H, Sebecic B.

BPC 157

- Curr Pharm Des.2014;20(7):1126-35.
- **Stable gastric pentadecapeptide BPC 157-NO-system relation.**
- Sikiric P, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicek R, Radic B, Drmic D, Ilic S, Kolenc D, Aralica G, Stupnisek M, Suran J, Barisic I, Dzidic S, Vrcic H, Sebecic B1.

BPC 157

- Curr Pharm Des. 2014;20(7):1121-5.
- **BPC 157 and blood vessels**
- "BPC 157 was concluded to be the most potent angiomodulatory agent, acting through different vasoactive pathways and systems (e.g. NO, VEGF, FAK) and leading to optimization of the vascular response followed, as it has to be expected, by optimization of the healing process. Formation of new blood vessels involves two main, partly overlapping mechanisms, angiogenesis and vasculogenesis. "


Genes
HLA-DQ, DR, and otherGenes
Caused by vitamin D deficiency and Disrupted by Leaky Gut
Gluten, grains, nutritional deficiencies, virus, bacteria, etc
T
B
DC
Autoimmune disease
Environment
Immune regulation
Diagram Modified from: Nature Immunology 2, 759 - 761 (2001)