

Le syndrome autoimmun thyro-gastrique

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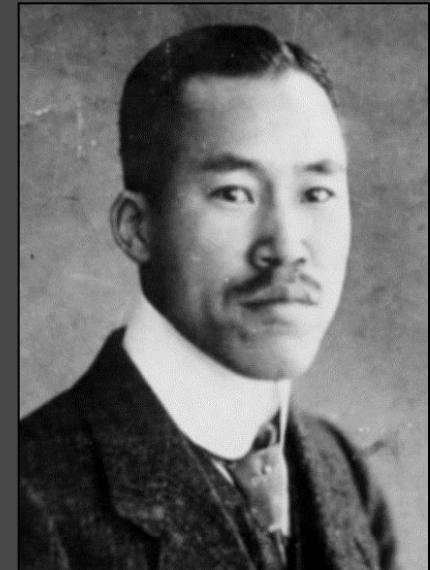
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Dr Thomas ADDISON
1793-1860



Dr Carl Von BASEDOW
1799-1854



Dr Hakaru HASHIMOTO
1881-1934

Itinéraire de notre Voyage

Le syndrome thyrogastrique autoimmun (STGA): Histoire

Le STGA: prévalence insoupçonnée

Le STGA: conséquences cliniques

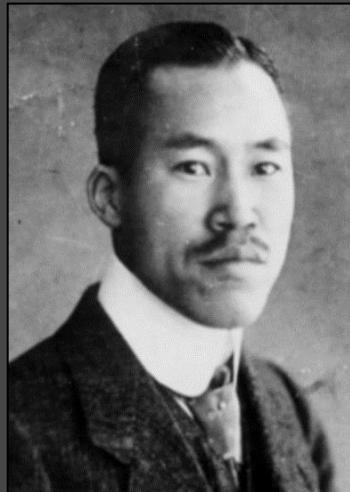
Le STGA: perspectives



Les maladies thyroidiennes autoimmunes



Dr Carl Von BASEDOW
1799-1854



*Dr Hakaru HASHIMOTO 1881-
1934*

Maladie de Graves – Basedow

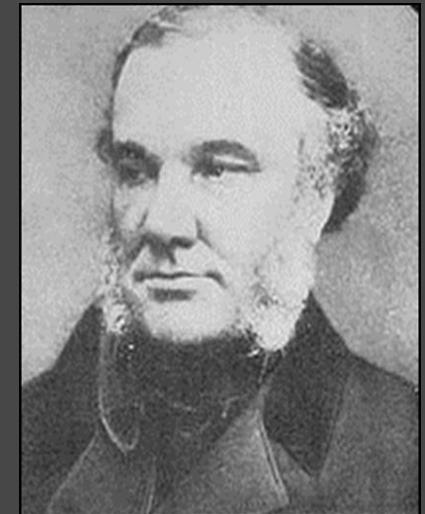
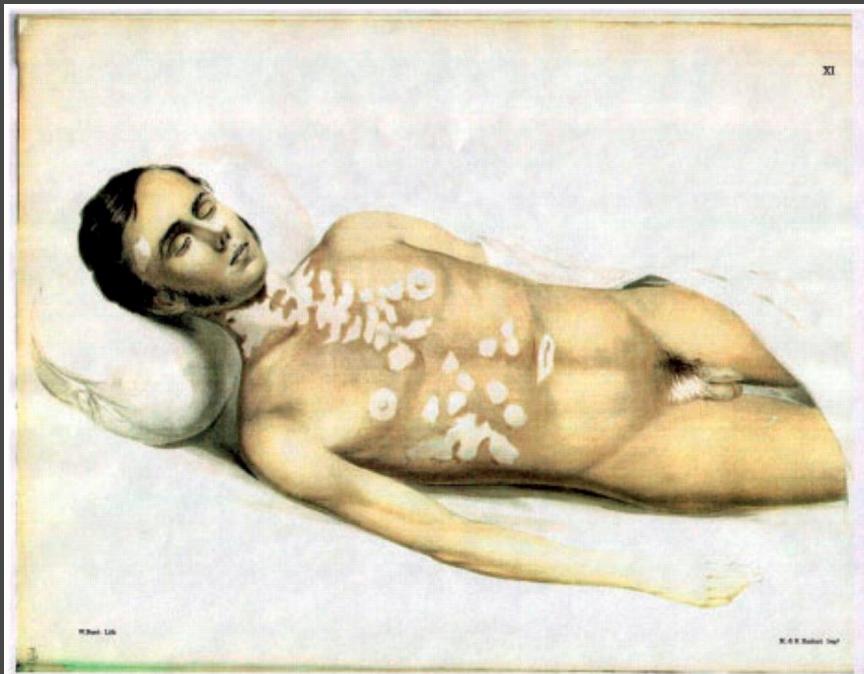
- Hyperthyroidie auto-immune
- Ophthalmopathie
- Dermatopathie
- Mécanisme autoimmun TH2
- Anticorps anti récepteur TSH
- (stimulation)

Maladie de Hashimoto

- Hypothyroidie autoimmune
- Encéphalite (très rare*)
- Mécanisme autoimmun type TH1
- Anticorps anti TPO
- Anticorps anti TG
- (destruction)

Une anémie pernicieuse...

- Thomas Addison (1793-1860)
 - Il décrit une anémie pernicieuse (fatale) 1849
 - À Londres



Ou anémie macrocytaire de Biermer-Addison...

- Anémie décrite:
 - « Über eine eigentümliche Form von progressiver, perniciöser Anaemie ». 1872
- Anémie macrocytaire sur carence en B12
- Associée à une myélite transverse.



Glossite sur carence en B12



Myélopathie transverse carencielle



Anton Biermer
(1827 - 1892)



The Nobel Prize in Physiology or Medicine 1934

George H. Whipple, George R. Minot, William P. Murphy



George H. Whipple

George R. Minot

William P. Murphy



for their discoveries concerning liver therapy in cases of anaemia

THYROID AUTO-ANTIBODIES IN PERNICIOUS ANAEMIA

BY

J. L. MARKSON, F.R.C.P.Ed., F.R.F.P.S.*Consultant Physician, Stobhill General Hospital, Glasgow*

AND

J. M. MOORE, M.B., Ch.B.*Bacteriologist, Stobhill General Hospital, Glasgow*

The reported impairment of vitamin B₁₂ absorption in three out of seven patients with hypothyroidism prompted Tudhope and Wilson (1960), working in Sheffield, to investigate the incidence of pernicious anaemia in 166 patients with hypothyroidism. They found that it was surprisingly high—7.8% in the whole series and 10.3% if those with previous thyroidectomy or with thyrotoxicosis treated with radioiodine or x-irradiation were excluded. The present investigation approaches this interesting association from a different aspect—namely, the incidence of thyroid disease in pernicious anaemia.

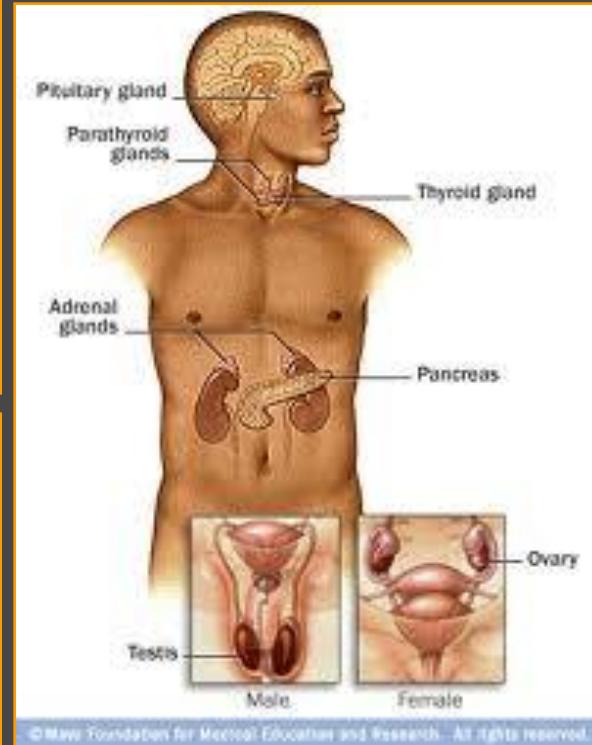
POLYGLANDULAR AUTOIMMUNE SYNDROME

PGS TYPE 1:

- ✓ Prevalence : 1/25.000 (Finland)
- ✓ Hypoparathyroidism or chronic candidiasis (1st manifestation)
- ✓ Adrenal insufficiency
- ✓ Hypogonadism

PGS TYPE 2:

- ✓ Prevalence 1/20.000
- ✓ Adrenal insufficiency
- ✓ AI thyroid disease (Schmidt sd.)
- ✓ Type 1 DM
- ✓ Hypopituitarism



PGS TYPE 3:

- ✓ Prevalence: Unknown
- ✓ 3A: AITD+ Type 1 DM
- ✓ 3B: AITD+ PA (circled in red)
- ✓ 3C: AITD+ Vitiligo ± Alopecia

Le syndrome thyrogastrique est-il sous diagnostiqué?

2ème PARTIE

Le syndrome thyrogastrique autoimmun (STGA): Histoire

Le STGA: une prévalence insoupçonnée

Le STGA: conséquences cliniques

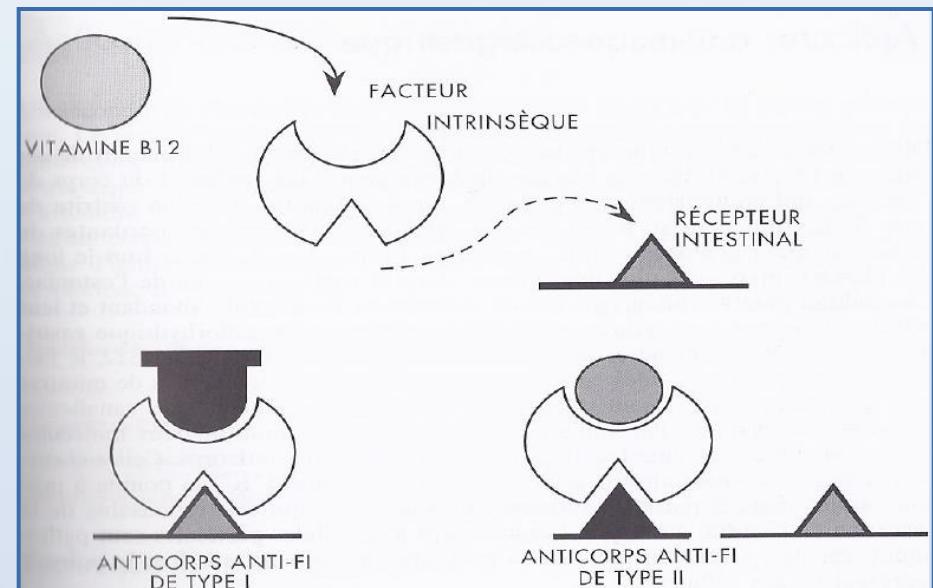
Le STGA: perspectives

*Je n'essaye pas de connaître les réponses,
j'essaye de comprendre les questions. (Confucius 孔夫子)*

Anti-facteur intrinsèque (AFI)

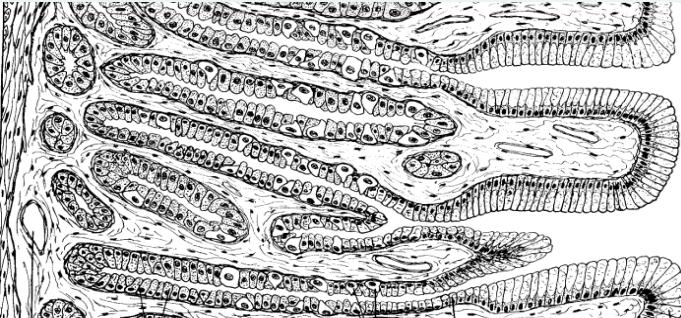
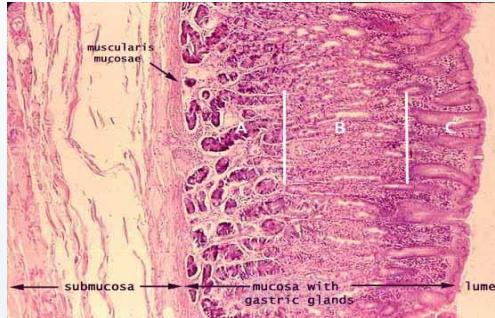
Auto-anticorps présents dans le sérum et/ou le liquide gastrique

- 2 types (mais même effet pathologique !):
 - Type I : bloquant : empêche la fixation du FI à la vitamine B12, empêchant ainsi son absorption.
 - Type II : liant/précipitant : bloque un autre site sur le FI qui intervient dans la fixation du complexe FI-Vit B12 sur le récepteur iléal.

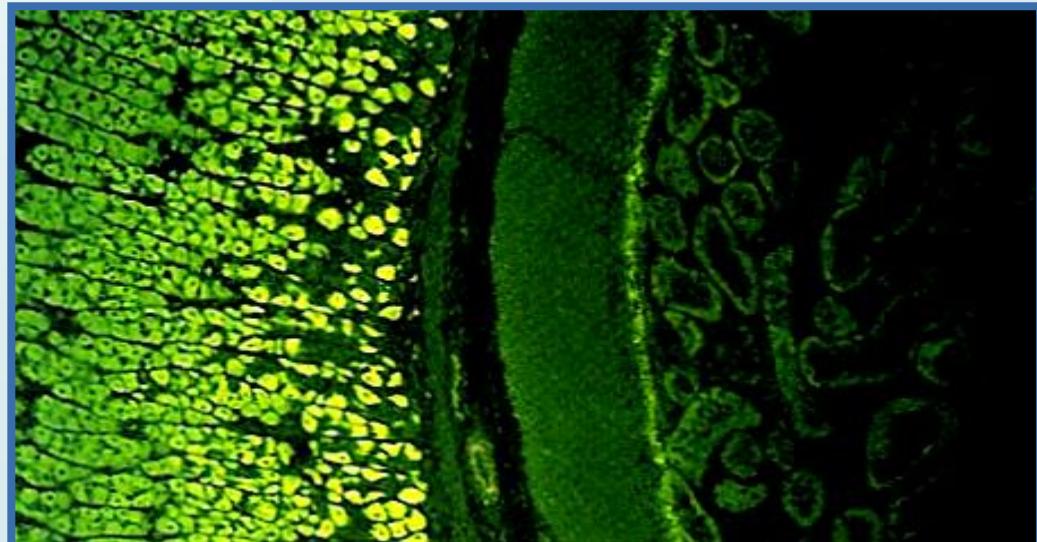


RL Humbel

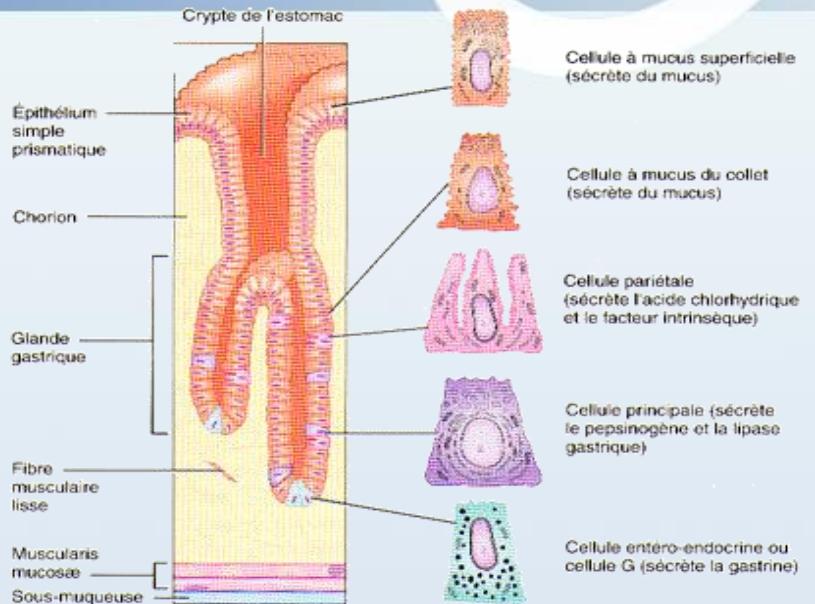
Anti-cellules pariétales gastriques (APCA)



Photos données par la firme Euroimmun



Slides du Dr Laurence LUTTERI.
Biologie Clinique. CHU de Liège



Détection : par IFI

Tissu de rongeur (souris): Estomac :
C.Pariétales :Aspect floconneux.
C.Principales –

NB : Titre d'AC non corrélé à la sévérité de la maladie

Cible : Anticorps anti-H⁺/K⁺ ATPase (enzyme responsable de la production d'HCl)

In vitro, destruction des cellules pariétales (in vivo : infiltration lymphocytaire) □ hypochlorhydrie et atrophie gastrique

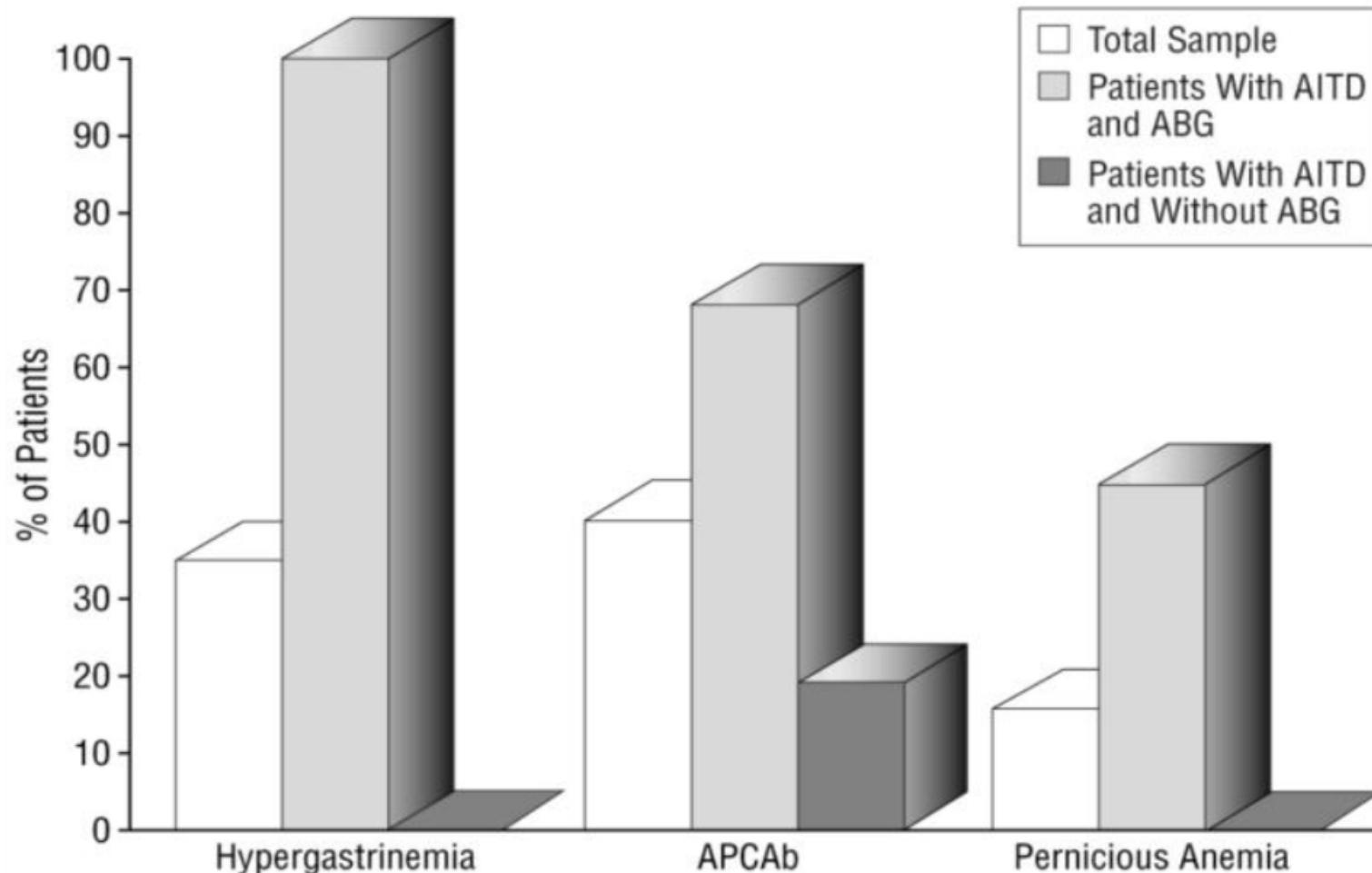
Atrophic Body Gastritis in Patients With Autoimmune Thyroid Disease

An Underdiagnosed Association

Marco Centanni, MD; Massimo Marignani, MD; Lucilla Gargano, MD; Vito D. Corleto, MD;
Alessandro Casini, MD; Gianfranco Delle Fave, MD; Mario Andreoli, MD; Bruno Annibale, MD

Conclusions: In the patients with AITD studied, about one third had ABG, which was diagnosed also in young patients; the measurement of gastrin levels represented the most reliable tool in the diagnosis of ABG; and the presence of anemia, even microcytic, was suggestive of undiagnosed ABG.

Atrophic Body Gastritis in Patients With Autoimmune Thyroid Disease: An Underdiagnosed Association



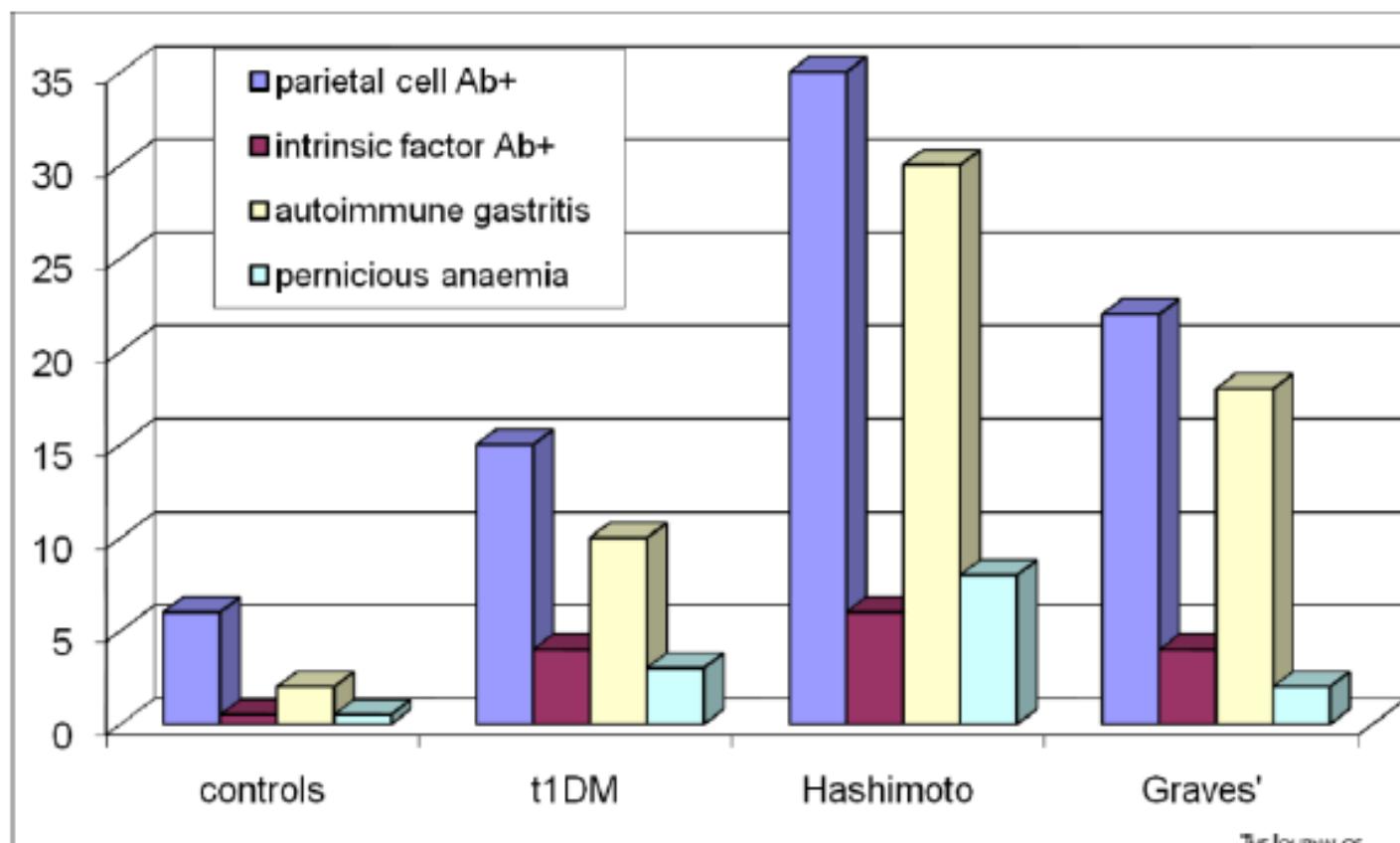
Reliability of different markers used in the diagnosis of atrophic body gastritis (ABG) in patients with autoimmune thyroid disease (AITD). APCAb indicates antiparietal cell antibodies.

Prévalence Anémie Pernicieuse/Thyroidite

Bolaert & al Am J Med 2010

Associated Autoimmune Disease	Hashimoto's Thyroiditis							
	Women N = 427	Mean Age ^a (y)	Mean Age ^b (y)	Men N = 68	Mean Age ^a (y)	Mean Age ^b (y)	Total N = 495	
Type 1 diabetes	5 (1.17%)	34.0	53.0	0 (0%)			5 (1.01%)	
Rheumatoid arthritis	20 (4.68%)	46.0	54.0	1 (1.47%)	64.0	64.0	21 (4.24%)	
Pernicious anemia	19 (4.45%)	39.0	51.0	0 (0%)			20 (4.04%)	
Systemic lupus erythematosus	3 (0.70%)	52.0	53.0	0 (0%)			3 (0.61%)	
Addison's disease	5 (1.17%)	42.0	55.0	2 (2.94%)	62.5	68.0	7 (1.41%)	
Celiac disease	5 (1.17%)	50.0	70.0	0 (0%)			5 (1.01%)	
Vitiligo	12 (2.81%)	37.5	49.5	1 (1.47%)	29.0	29.0	13 (2.63%)	
Multiple sclerosis	3 (0.70%)	44.0	45.0	1 (1.47%)	57.0	57.0	4 (0.81%)	
Myasthenia gravis	1 (0.23%)	29.0	34.0	0 (0%)			1 (0.20%)	
Inflammatory bowel disease	3 (0.70%)	55.0	62.0	1 (1.47%)	50.0	50.0	4 (0.81%)	
None	362 (84.78%)	41.5	46.0	62 (91.18%)	46.5	49.5	424 (85.66%)	

Prevalence of PCA, AIF, autoimmune gastritis, and pernicious anemia in the general population and endocrine diseases



De Block, C. E. M. et al. J Clin Endocrinol Metab 2008;93:363-371

THE JOURNAL OF
CLINICAL
ENDOCRINOLOGY
& METABOLISM

3ème PARTIE

Le syndrome thyrogastrique autoimmun (STGA): Histoire

Le STGA: prévalence insoupçonnée

Le STGA: conséquences cliniques

Le STGA: perspectives

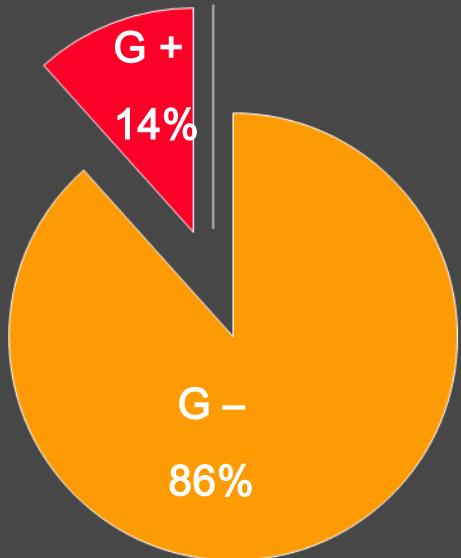
Ce que j'entends, j'oublie. Ce que je vois, je me rappelle. Ce que je fais, j'apprends
(Confucius 孔夫子)

SUBJECTS AND METHODS

A prospective series

of 410 patients:

- 360 patients with Hashimoto's Thyroiditis.
- 50 patients with Basedow's Disease.



Screening for gastrine, APC-Ab/IF-Ab

Fe , vit B12

56 G+

48 Hashimoto

8 Basedow

49 F / 7 M

age 51 ± 17 yrs

354 G-

45 G- Control subjects
matched for
age, sex and AIT type

SUBJECTS AND METHODS II

PROSPECTIVE AND MATCHED CONTROLLED STUDY
2 YEARS FOLLOW- UP



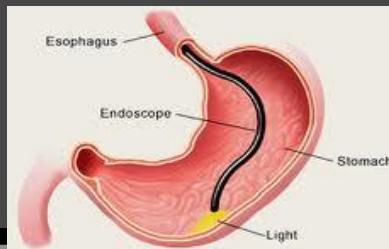
NO OTHER CLINICAL/BIOLOGICAL FEATURES OF AUTOIMMUNITY
(Diabetes, vitiligo, Addison, Candidiasis and celiac disease were screened and excluded)



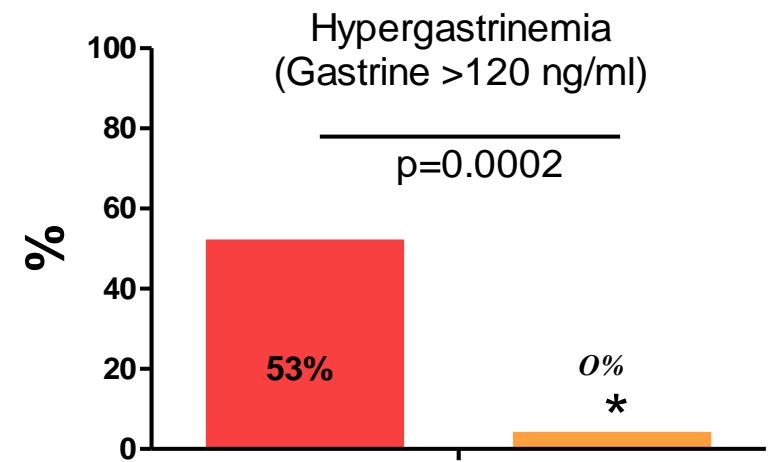
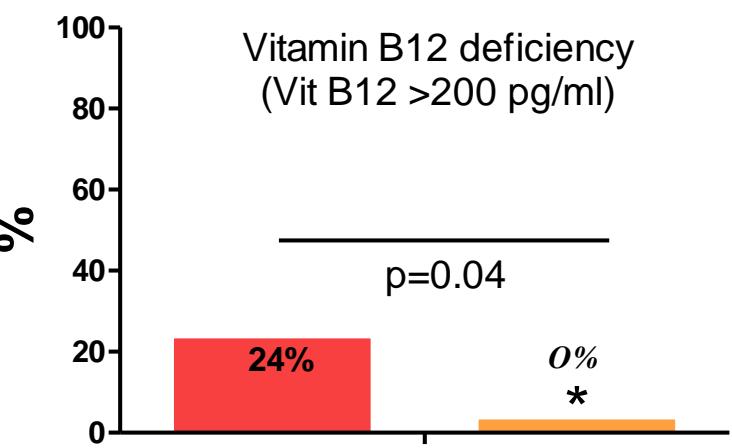
PATIENTS WITH POSITIVE MARKERS FOR GASTRIC AUTOIMMUNITY
WERE INVITED TO PERFORM GASTROSCOPY (ALL ASYMPTOMATIC)



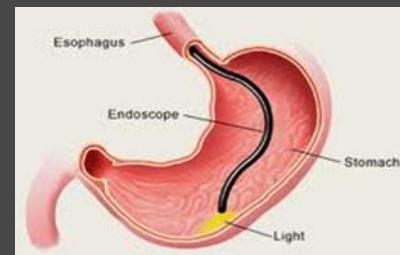
Statistical analysis was performed with SAS® version 9.2. Results were considered significant at the 5% level ($p<0,05$)
Prof Adelin Albert



RESULTS (II)

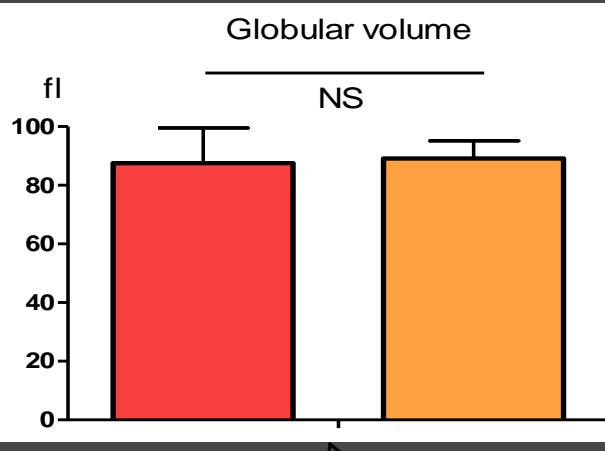
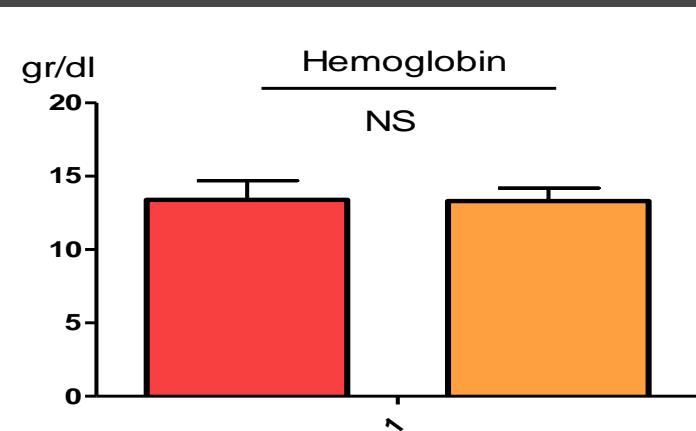


Positive gastric autoimmunity (N= 56)
Negative gastric autoimmunity (N= 45 controls)



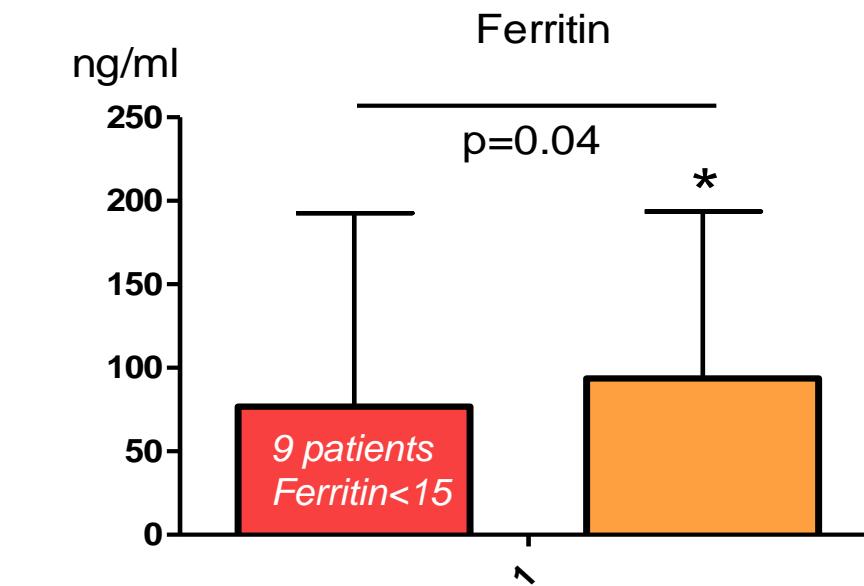
RESULTS

(III)



■ Positive gastric autoimmunity (N= 56)

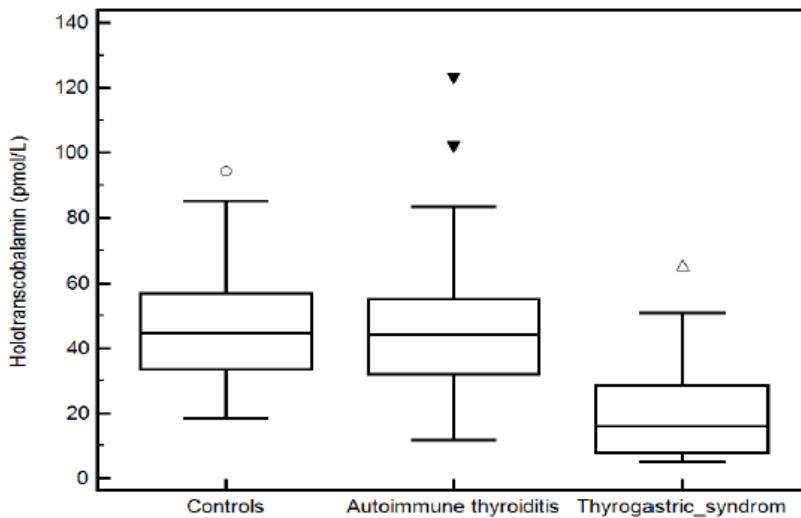
■ Negative gastric autoimmunity (N= 45 controls)



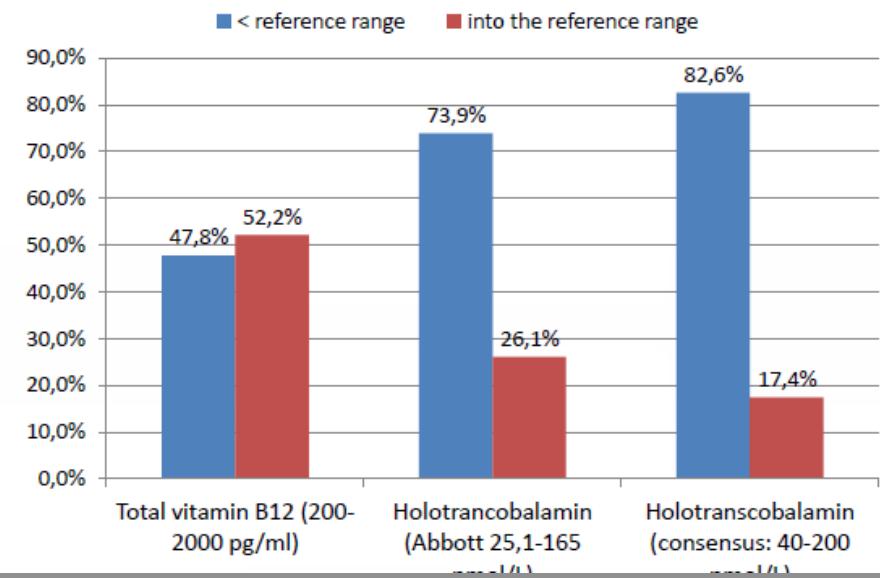
Holotranscobalamin versus Total Vitamin B12 as Indicators of Vitamin B12 deficiency in Thyrogastric Syndrome

L. VRANKEN¹, E. CAVALIER¹, H. VALDES-SOCIN² ;

The vitamin B12 concentration (both total and holotranscobalamin) was significantly lower in "thyrogastric syndrome" group ($p < 0,0001$) that confirms there is vitamin B12 malabsorption during gastritis.



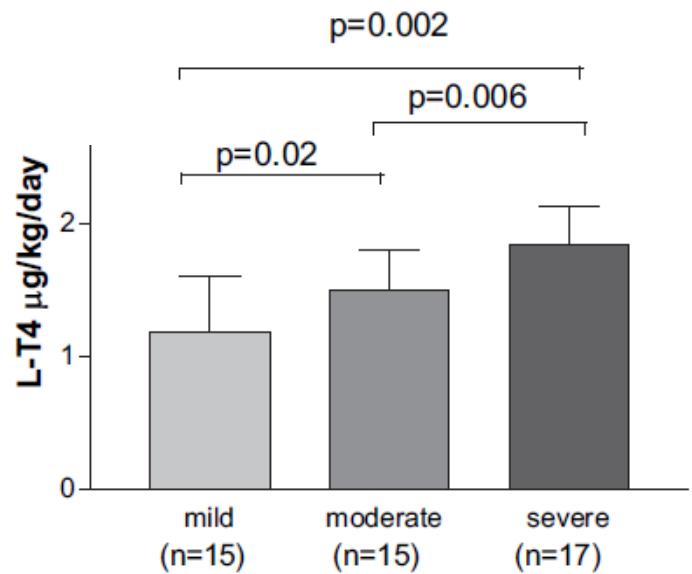
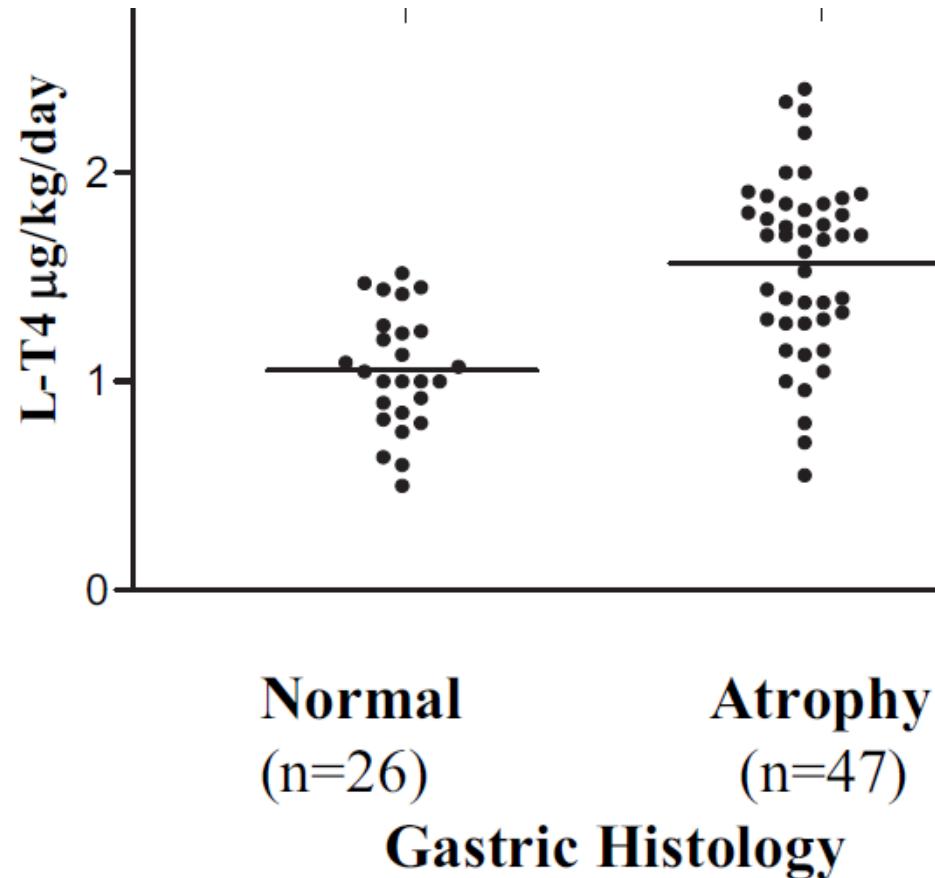
However, more patients were deficient using holotranscobalamin (73,9%) than with total vitamin B12 (47,8%) in the "thyrogastric syndrome" group.



Malabsorption de Thyroxine

L-Thyroxine Requirement in Patients with Autoimmune Hypothyroidism and Parietal Cell Antibodies

Serenella Checchi, Annalisa Montanaro, Letizia Pasqui, Cristina Ciuoli, Valentina De Palo, Maria Celeste Chiappetta, and Furio Pacini



Familial thyrogastric autoimmune syndrome: a study of 22 kindreds

Selim SID¹, Laurence LUTTERI¹, Yves BEGUIN¹, Edouard LOUIS¹, Albert BECKERS¹, Hernan VALDES-SOCIN¹
(1) : CHU de Liège, Liège, Belgium.

- **8 families** (Hashimoto = 7/Grave's disease = 1),
- 22 (19F/3M) kindred.

- Pedigrees included **brothers/sisters** (n = 6), **mother/children** (n = 1), and monozygotic twins (n = 1). Mean age at diagnosis was 39 + 12 years,

- Three patients had a **B12 deficiency** whereas **six other patients had iron deficiency only**. Familial cases had significant lower ferritin and higher gastrin levels than the control group ($p < 0,01$).

- **Antral and corpus gastritis** was confirmed in 13 patients. *Helicobacter pylori* was found in 6/13 gastroscopies. Two patients had gastric histological features of Biermer disease with gastrin >1000 ng/ml. B12 and iron malabsorption improved in HP+ treated patients.

Clinical, biochemical and histological features in atrophic gastritis with respect to thyroid status

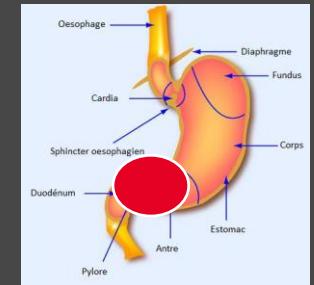
Table 1 Clinical, Biochemical, and Histological Features in Atrophic Body Gastritis (ABG) Patients with Respect to the Thyroid Status

	ABG Patients with Autoimmune Thyroid Disease n = 128	ABG Patients with Nonautoimmune Thyroid Disease n = 41	ABG Patients with a Healthy Thyroid Gland n = 150
Age, years, median (range)	54 (20-76) ^a	57 (30-80)	56.5 (17-95)
Female sex, %	83.6 ^b	85.4 ^b	55.3
Presence of pernicious anemia, %	48.4	41.5	49.3
Active smokers, present/absent	16.4	24.4	24.7
Fasting gastrin, pg/mL, mean ± SEM	631 ± 48	628 ± 83	606 ± 46
Pepsinogen I, ng/mL, mean ± SEM	17 ± 2	28 ± 9	19 ± 2
Positivity of intrinsic factor antibodies, %	39.8	31.7	46.7
Positivity of parietal cell antibodies, %	86.7 ^a	82.9	72.0
Presence of extrathyroid autoimmune diseases ^d , %	17.2 ^c	7.3	8.0
Presence of active <i>H. pylori</i> infection ^e , %	20.3	26.8	26.0

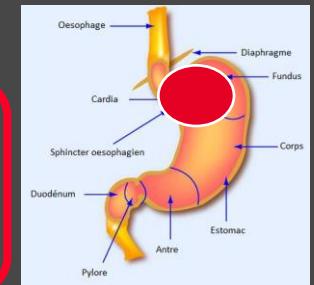
extrathyroid AI disease: vitiligo, T1DM

HISTOLOGICAL FINDINGS (I)

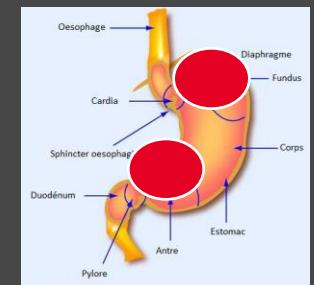
- **76% (25/33) Lymphocytosis**
- Antritis: **12% 4/33**
 - 1 Helicobacter/4



- Funditis: **9% 3/33**



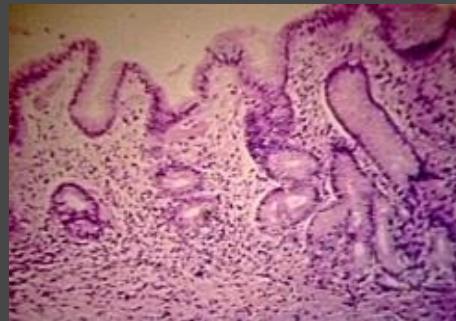
- Both: **54% 18/33**
 - 6 Helicobacter/18



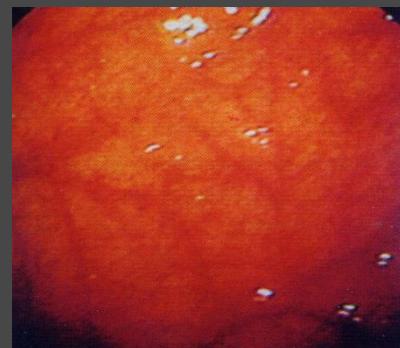
HISTOLOGICAL FINDINGS (II)

□ 28% (9/33)

GASTRIC ATROPHY



□ 33% (11/33) INTESTINAL METAPLASIA



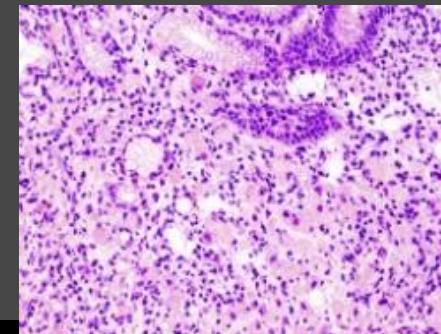
□ 21% (7/33)

HELICOBACTER PYLORI



□ 3% GASTRIC CARCINOID/CARCINOMA

Affter 3 Years of follow-up



LES DIFFERENTS ASPECTS DE LA GAI

	GAIT+ AIT	GAI + AIT+ Hp	GAI +Hp
Patients	33F/5H		
Age	53± 14	46 ±13 <i>P<0.01</i>	41 ±13
Anti MG	1/640	1/280 <i>P<0.01</i>	1/160
Anti FI	17%	5% <i>P<0.05</i>	0%
Gastrine (<120)	488	163 <i>P<0.01</i>	93
Métplasie	46 %	21%	10%
Atrophie	7 cas	0 cas	0 cas



Le syndrome thyrogastrique autoimmun (STGA): Histoire

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Le STGA: conséquences cliniques

Le STGA: perspectives

Si tu donnes un poisson à un homme tu le nourriras un jour.

Si tu lui apprends à pêcher il sera capable de se nourrir toute sa vie . (Lao-tzu 老子)

CAS CLINIQUE CHU NdB



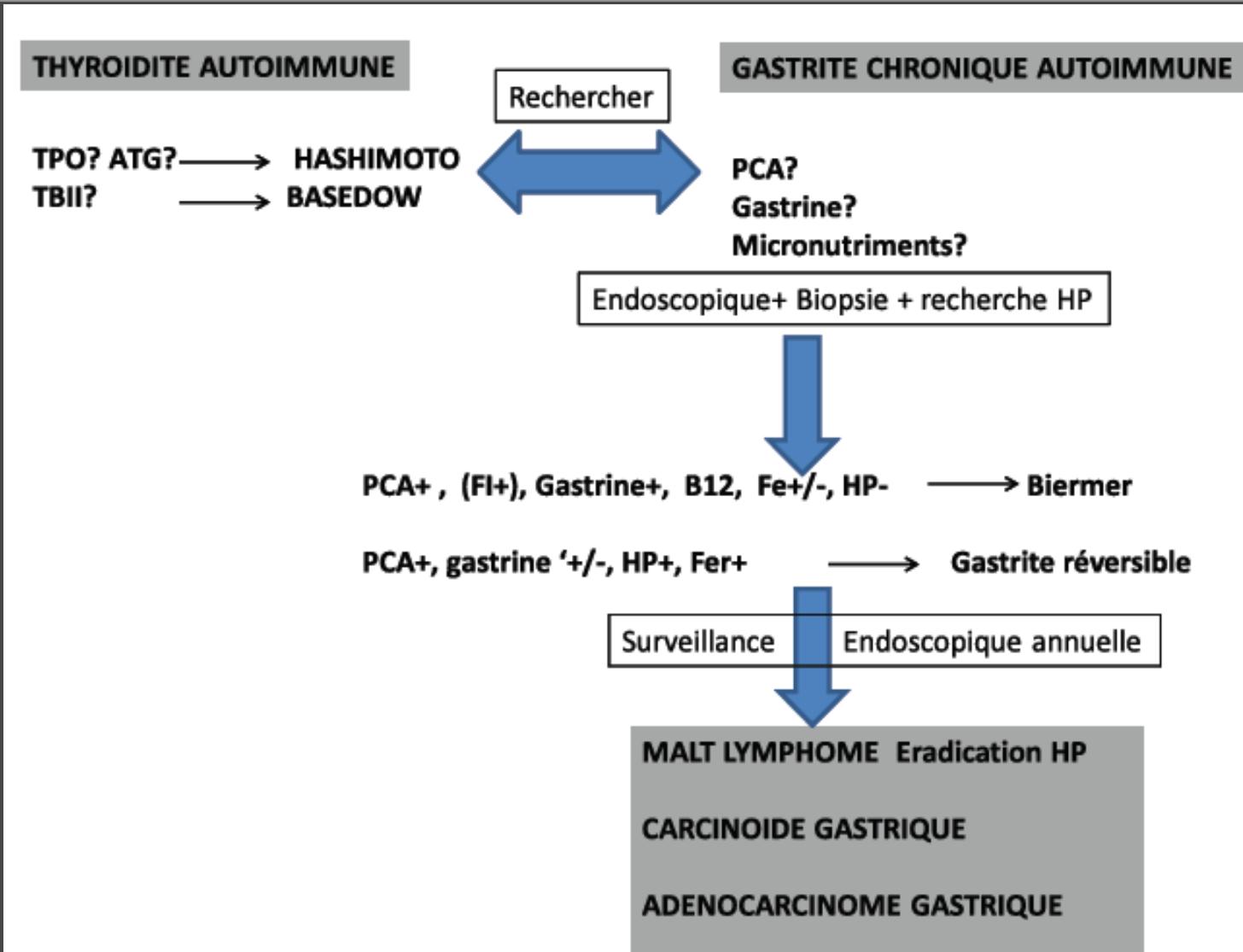
Aspect de Gastrite « nodulaire »

- Biologie 2012:
 - TPO+, MG+ 1/640, FI nég
 - Gastrine 45 pg/ml (>120)
 - Sérologie Hp +

- Biopsie muqueuse 2012 (Dr Mesureur):
 - Gastrite antrale sévère + Hp
 - Fundite modérée + Hp

- Biologie 2015 (3 ans après érradication)
 - TPO-, MG+ 1/160, gastrine 48
 - Breath test -

Comment diagnostiquer le SATG?



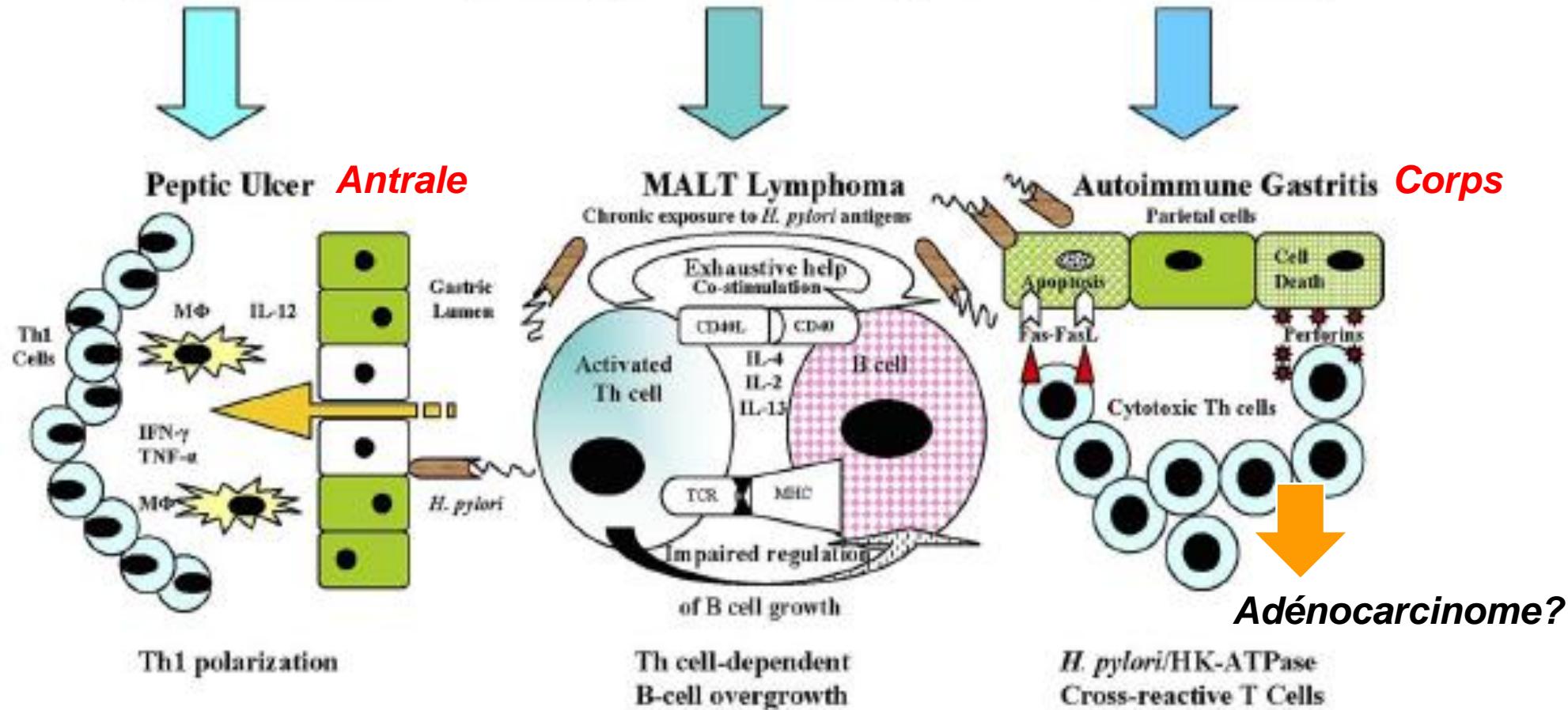
Valdes Socin & al .Le Syndrome Thyro gastrique auto-immun: ses conséquences sur les micronutriments et la tumorigenese gastrique. RmLg 2013

Helicobacter et Inflammation gastrique

M.M. D'Elios et al. / FEMS Immunology and Medical Microbiology 44 (2005) 113–119

117

Immunopathology of *Helicobacter pylori* infection



H Pylori & Atrophie du Corps Gastroïque

Auteurs	Patients avec ACG & Hp+	Méthodes Détection Hp
Annibale & al <i>Helicobacter</i> 2001	66% ont Hp+	Histologie- Sérologie
Annibale WJG 2005	62% Hp+	Sérologie
Annibale & al <i>Helicobacter</i> 2001	0%	Histologie-Serologie EIA Immunoblotting
Mini & al <i>Clin Chem</i> 2006	N=111 95% 0%	Immunoblotting Serologie EIA
Veijola & al WJG 2010	N=23 8/23	Histologie- Immunoblotting

Les rongeurs de Mongolie

Table 4 Gastric carcinogenesis in *Helicobacter pylori*-infected Mongolian gerbils

Histopathological findings	Mo			
	6	12	18	
Gastritis	5/5	4/4	5/5	10/10
Gastric ulcer	4/5	3/4	5/5	5/10
Atrophy	4/5	4/4	5/5	10/10
Intestinal metaplasia	2/5	3/4	5/5	10/10
Dysplasia	0/5	2/4	4/5	10/10
Gastric cancer	0/5	0/4	2/5	5/10
Gastric carcinoid	0/5	0/4	0/5	5/10

Data represent positive case /control. Uninfected control animals ($n = 5$ each) showed no abnormal findings.

p53 ?

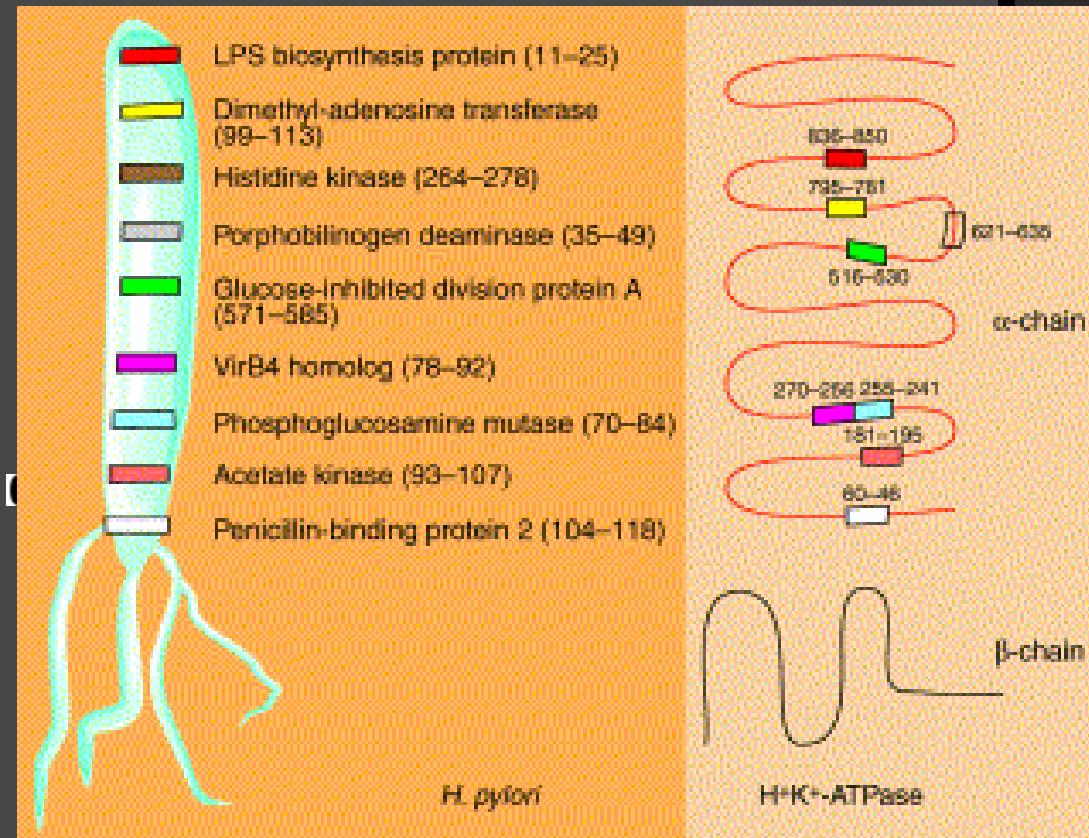
Kodama & al WJG 2005

Kagawa J, Honda S, Kodama M, Sato R, Murakami K, Fujioka T. Enterocromaffin-like cell tumor induced by *Helicobacter pylori* infection in Mongolian gerbils. *Helicobacter*. 2002 Dec;7(6):390-7

Molecular Mimicry between *Helicobacter pylori* Antigens and H⁺,K⁺-Adenosine Triphosphatase in Human Gastric Autoimmunity

Table II. Cross-reactive H⁺,K⁺-ATPase and *H. pylori* Peptides Recognized by Gastric T Cell Clones

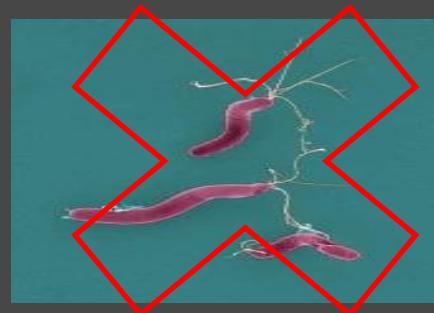
T cell clones (epitope)	Amino acid sequence recognized		<i>H. pylori</i> protein including the cross-reactive peptide (position)
	H ⁺ ,K ⁺ -ATPase bacterial peptide	MI ± SD	
1.C31 (α 621-635)	<u>IRVIMVTGDHPITAK</u>	79 ± 9	
	<u>VRVDVRRLDHLMNLI</u>	66 ± 5	Histidine kinase (264-278)
1.A04 (α 781-795)	<u>NLKKSIAAYTLTKNIP</u>	194 ± 16	
	<u>ISNLPPYYIATRLVLN</u>	108 ± 12	Dimethyl adenosine transferase (99-113)
2.P24 (α 46-60)	<u>KKEMEINDHQLSVAE</u>	23 ± 3	
	<u>LNNYQKENSLYNHNL</u>	27 ± 2	Penicillin-binding protein 2 (104-118)
2.R37 (α 836-850)	<u>KAESDIMHLRPRNPK</u>	50 ± 7	
	<u>NMRVFIIHLSEKTCK</u>	19 ± 2	LPS biosynthesis protein (11-25)
3.A30 (α 836-850)	<u>KAESDIMHLRERNPK</u>	49 ± 6	
	<u>NMRVFIIHLSPKTCK</u>	16 ± 1	LPS biosynthesis protein (11-25)
4.A15 (α 181-195)	<u>VIRDGDKFQINADQL</u>	39 ± 2	
	<u>VVQGGDKFHAPVLVD</u>	20 ± 1	Acetate kinase (93-107)
4.C32 (α 241-255)	<u>CTHESPLETRNIAFF</u>	87 ± 9	
	<u>VIQIGPMPTPATAEL</u>	75 ± 8	Phosphoglcosamine mutase (70-84)
4.C27 (α 256-270)	<u>STMCLEGTAQGLVVN</u>	137 ± 17	
	<u>ALDSLEKVARLVVK</u>	34 ± 2	VirB4 homologue (78-92)
4.C26 (α 516-530)	<u>VMKGAPERVLERCSS</u>	104 ± 9	
	<u>VFKGIPGLSLEAVEK</u>	47 ± 4	GidA (571-585)
4.A05 (α 621-635)	<u>IRVIMVTGDHPITAK</u>	99 ± 12	
	<u>IRIVKTTGDKILDAP</u>	51 ± 6	Porphobilinogen deaminase (35-49)



The important point of the present paper is the demonstration that all four *H. pylori*-infected AIG patients harbored in their gastric mucosa in vivo-activated T cells that reacted to both H⁺,K⁺-ATPase and *H. pylori*. The analysis of the sub-molecular specificity of T cell clones reactive only to

Mimétisme moléculaire entre urease B de *Helicobacter*/ β sous unité K+/H+ ATPase

- Mimétisme moléculaire HPylori/ATPase gastrique
 - De Luis 1998
 - Figura & al 1999
 - Raymond & al 2000
 - D'ELIOS. Trends Mol Med 2004.
- Prévalence augmentée de ATPO chez les patients avec sérologie *H Pylori+*: 10,4% vs 5,8% ($n=1621$)
 - Sterzl Physiol Res 2008
- Erradication *H Pylori* diminue les ATPO et les Anti MG
 - -Bertalot 2004. Diminution TPO
 - -Faller & al. De 26%---9% en 1 an.
 - Pathol Res Pract. 1999;195(4):243-6.



Helicobacter ►►► Gastrite ►► Biermer (?)

□ Virulence Hp

- Cag A: cytotoxine proinflammat
- Vac A: cytotoxine vacuolisante
- Sab A: recepeteur sialique

□ Mimétisme moléculaire

- K/H ATPase/Hp urease

□ Neutrophiles (polymorphismes)

- IL-6
- TNF alpha
- IL-1B

□ Macrophages M1 bactericides

- Ex souris KO M1 moins de gastrite

□ Peptides microbicides

- hB defensing
- Adrénomedulline
- Varis & al Scand J Gastroenterol. 1993 Aug;28(8):705-8.
- Is *Helicobacter pylori* involved in the pathogenesis of the gastritis characteristic of pernicious anaemia? Comparison between pernicious anaemia relatives and duodenal ulcer relatives.

Risque de NETs et Adénocarcinome

- Hypochlorhydrie
- Hypergastrinémie ($>1000 \text{ ng/ml}$)
- ECL hyperplasie
- Carcinoïde gastrique



Carcinoïdes:

8/71 (11%) patients avec
Anémie Pernicieuse
(moyenne 8 ans AP)

Kokkola 1998

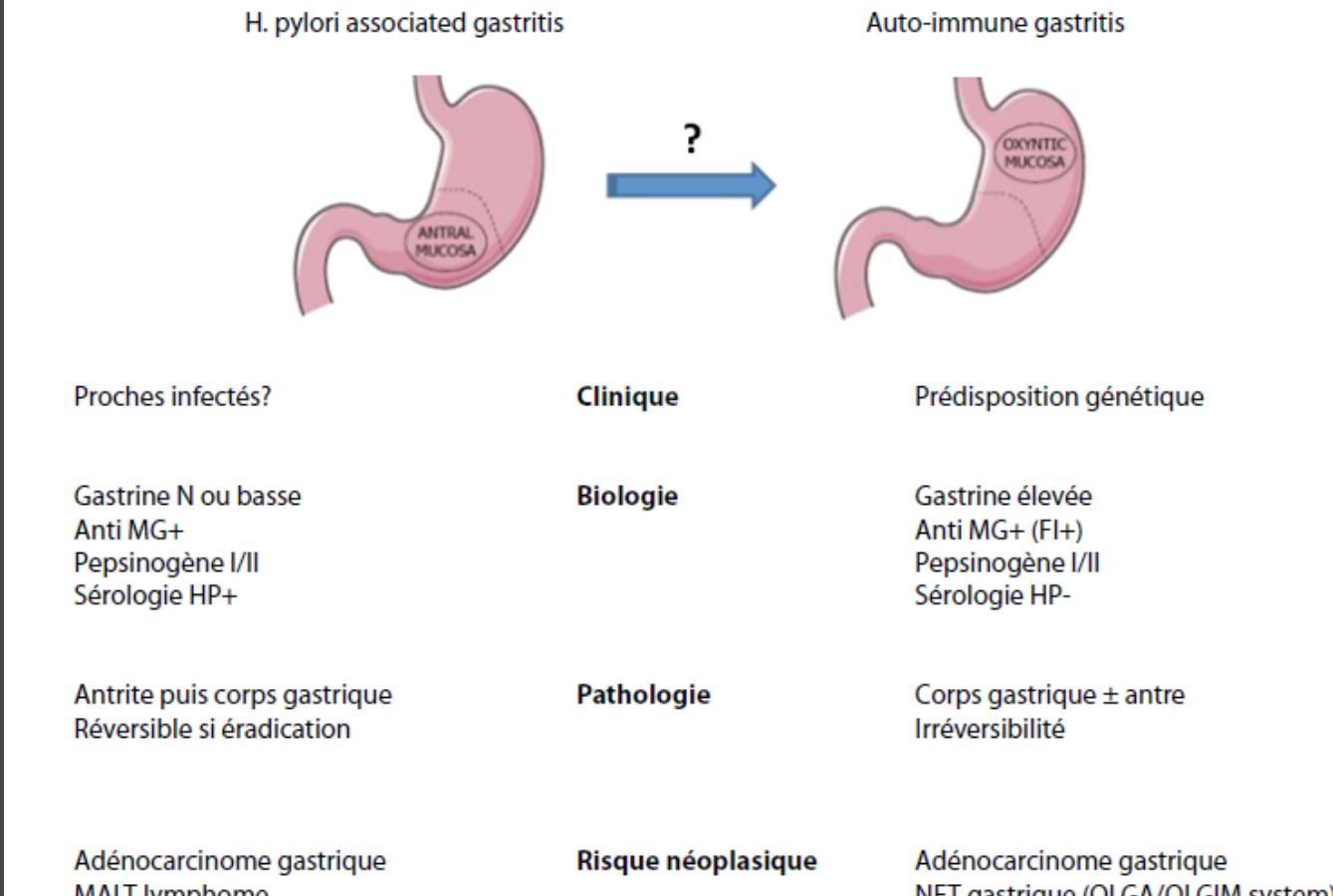
- Hypochlorhydrie
- Production de nitrosamines
- Diminution d' acide ascorbique
Anibale & al Gut 2003
- Activité carcinogénique



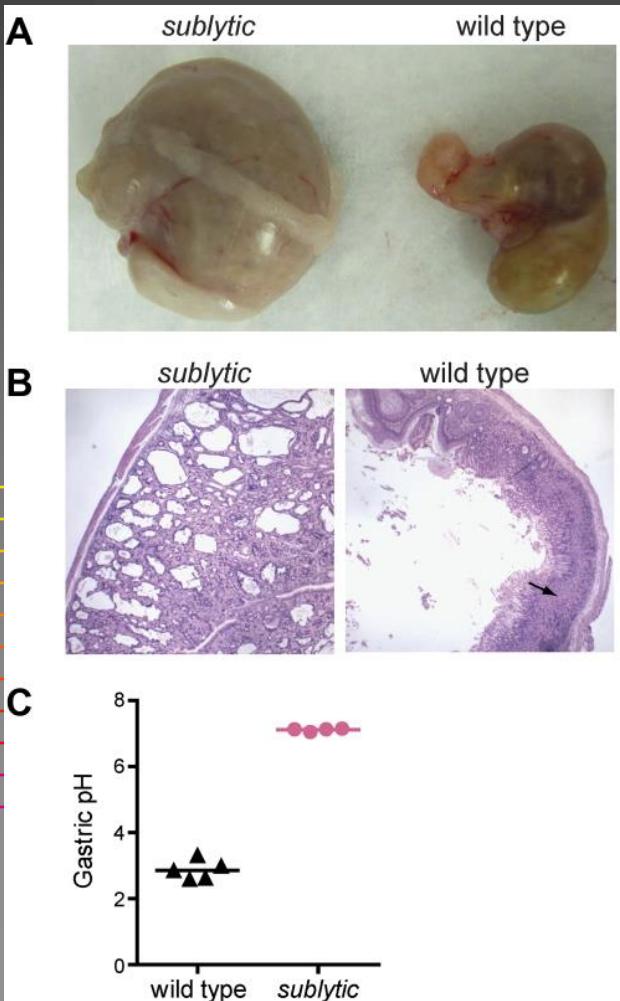
Sjöblomg 1998, Schafer 1985

adénocarcinome gastrique
incidence 0,1-0,5%

*Figure 2:
Les deux modèles physiopathologiques actuels de gastrite chronique auto-immune.*



Mutation of the gastric hydrogen-potassium ATPase alpha subunit causes iron-deficiency anemia in mice. Krieg L & al Blood 2011



Krieg, L., Milstein, O., Krebs, P., Xia, Y., Beutler, B. and Du, X. (2011) Mutation of the gastric hydrogen-potassium ATPase alpha subunit causes iron-deficiency anemia in mice. *Blood*, 118, 6418–6425.

doi: 10.1093/hmg/ddv054

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Original Article

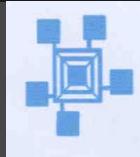
ORIGINAL ARTICLE

Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour

Oriol Calvete^{1,3}, Jose Reyes⁴, Sheila Zuñiga⁵, Beatriz Paumard-Hernández¹, Victoria Fernández¹, Luís Bujanda⁶, María S. Rodriguez-Pinilla⁷, Jose Palacios⁸, Damian Heine-Suñer⁹, Siddharth Banka¹⁰, William G. Newman¹⁰, Marta Cañamero^{2,†}, D. Mark Pritchard¹¹ and Javier Benítez^{1,3,*}

Krieg, L., Milstein, O., Krebs, P., Xia, Y., Beutler, B. and Du, X. (2011) Mutation of the gastric hydrogen-potassium ATPase alpha subunit causes iron-deficiency anemia in mice. *Blood*, **118**, 6418–6425.

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- Dr Potorac
- Dr Vroonen
- Dr Petrossians
- Prof Hennen

Quelques mots pour la fin...



*Prof Fuller ALBRIGHT
Massachusetts General Hospital*

- 1- Je vous ai dit plus sur le sujet que ce que je sais moi-même.
- 2- Ce qui a été dit, peut changer par la suite.
- 3- J'espère avoir soulevé plus de questions que de réponses.
- 4- En tout cas, comme toujours, plus de recherches sont nécessaires.

Fuller Albright (1900-1969)