BETA AMYLOID DEPOSITS AND HYPERPHOSPHORYLATION OF TAU IN THE PANCREAS IN TYPE 2 DIABETES

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INTRODUCTION

Strong epidemiologic evidence shows an association between Alzheimer disease (AD) and type 2 diabetes.

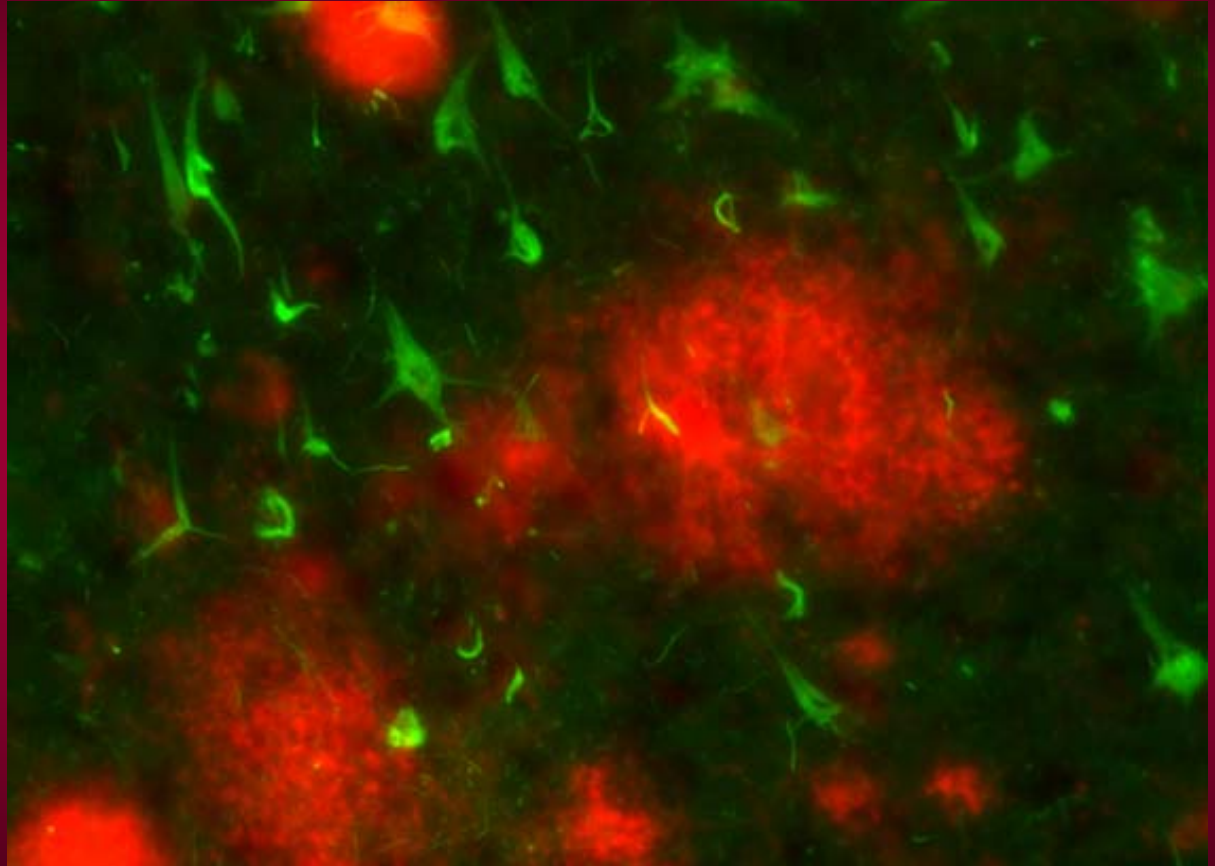These age related chronic disorders share several risk factors.

Both are associated with Down syndrome.

Amyloid formation is a key player in the pathogenesis of both.

INTRODUCTION

Alzheimer's disease:

4kDa $A\beta$ accumulates in senile plaques which is derived from a 120 kDa $A\beta PP$

Hyperphosphorylated tau is the major component of the paired helical filament in neurofibrillary tangles

INTRODUCTION

Type 2 diabetes:

Islet amyloid polypeptide (IAPP) amylin aggregates and accumulates in the Langerhans islets of the pancreas.
It derives from a larger 89-amino acid precursor protein called proamylin.

Islet β-cells produce both insulin and amylin and the degeneration of these cells will lead to decreased insulin and amylin deposits.
Cooper, 1987; Sanke, 1988.
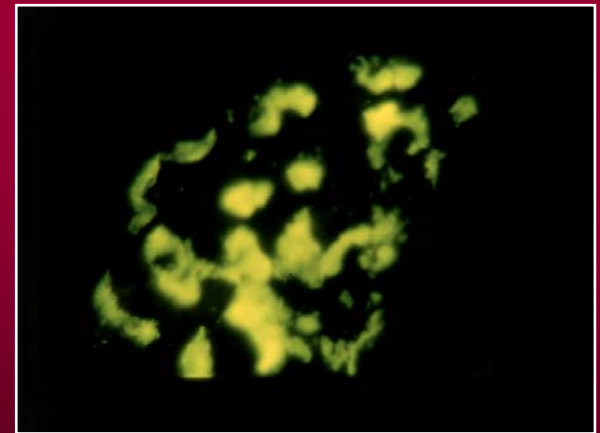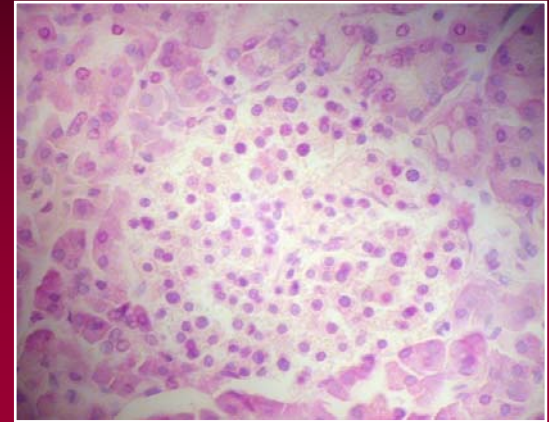
More than 80% of all diabetic patients: type 2 diabetes.

Aβ IN ISLET AMYLOID DEPOSITS

The pathogenesis of amyloid formation in AD and type 2 diabetes is still remains unclear.

Aβ and amylin aggregates are toxic to neurons and islet cells.

Aβ deposition in non-neuronal tissues was previously observed

Joachim, 1989, Askanas, 1994, Dentchev et al.; 2003; Goldstein et al., 2003

Pathological fibrillary lesions similar to paired helical filaments were also observed in various other organs than the brain, including the pancreas *Miklossy et al. JNEN, 1999*

Whether Aβ and phosphorylated tau may be associated with islet amyloid deposits in type-2 diabetes is not known.

Aβ IN ISLET AMYLOID DEPOSITS

Pancreas tissue of 36 autopsy cases was analyzed
        20 AD, and 16 controls
        10 clinically and pathologically confirmed
        type 2 diabetes

Ten anti-Aβ antibodies which recognized several epitopes, including Aβ 8-17 (6F/3D), Aβ17-24 (4G8), Aβ17-28 (2F9AF), Aβ40 (QCB1-40) and Aβ42 (QCB1-42, 21F12).

Five antibodies raised against tau protein, including AT8 and anti-p(409)Ser
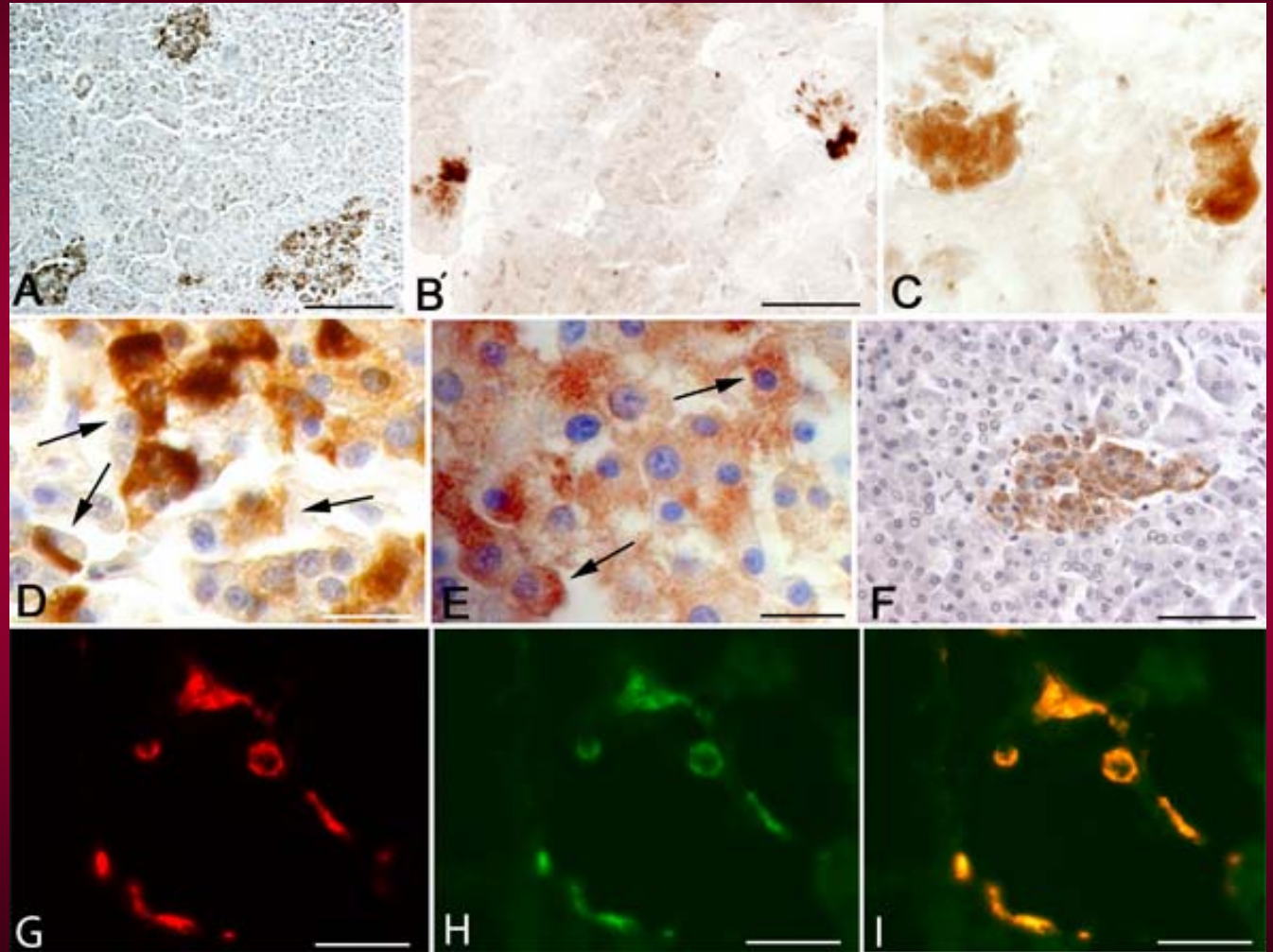
Ubiquitin. Apo-E, Apo-a, IB1, JNK

Two rabbit anti- human IAPP 1-37 (amylin) and a monoclonal antibody to aa. 29-37 synthesized peptide of human amylin were used

Aβ IN ISLET AMYLOID DEPOSITS

21F12 (A),
2F9AF (B)
4G8 (C)

Amylin (D)
21F12 (E)
Aβ 40 (F)
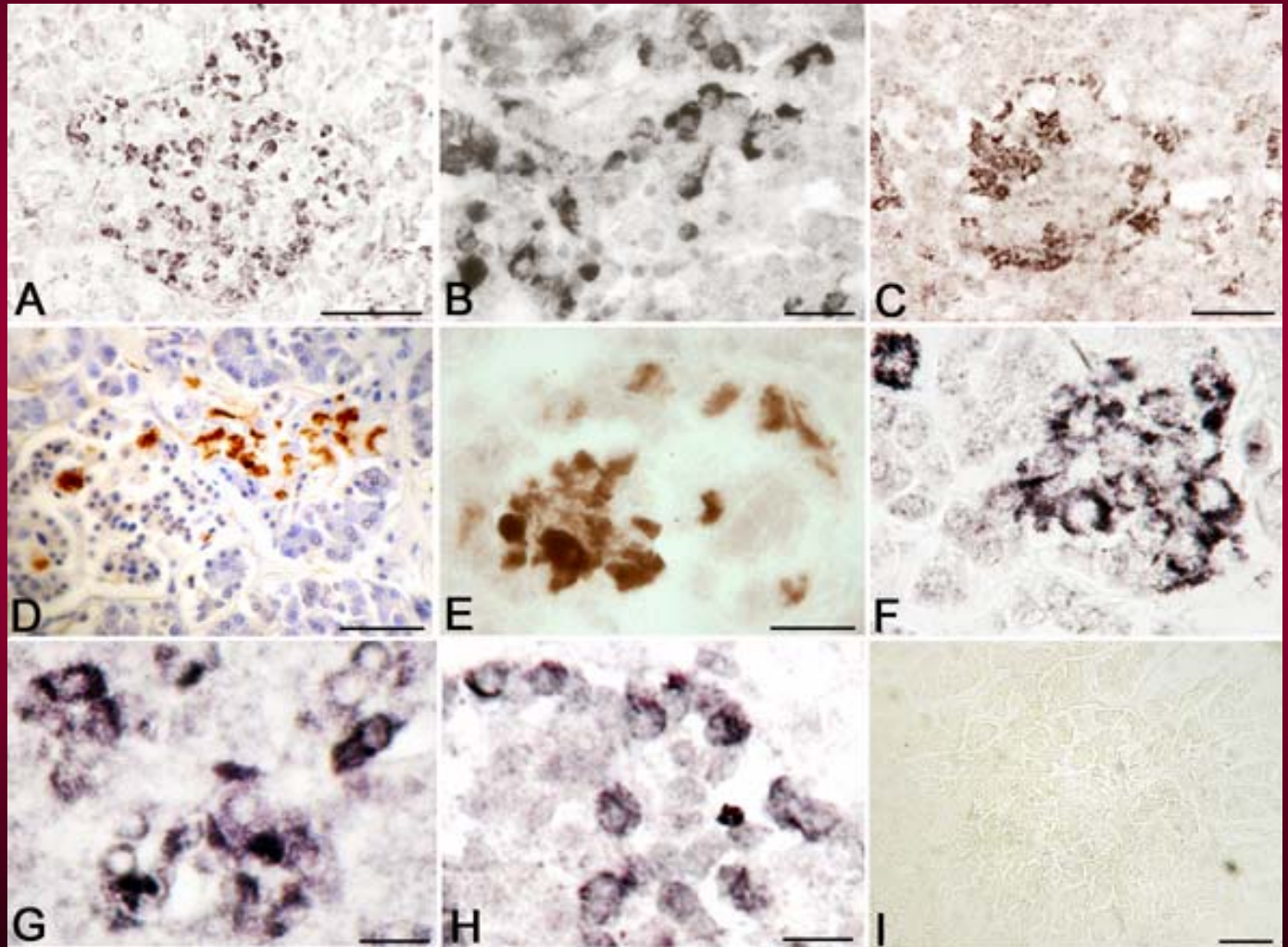
Aβ 40 (G)
Amylin (H)
Merged (I)

Hyperphosphorylated tau in the pancreas in type 2 diabetes

A0024 (A&B)
AT8 (C)

Ubiquitin (D)
Apo-E (E)
Apo-a (F)

IB1 (G)
JNK-1 (H)
Control

CHRONIC INFLAMMATION

The role of local inflammatory processes in AD is well established *McGeer, 2002 , McGeer and Rogers, 1992.*

Systemic indicators of inflammation have also been documented in type 2 diabetes *Kolb, 2005; Schmidt, 1999.*
Whether local inflammatory processes may also be present in the pancreas in type 2 diabetes is not known.

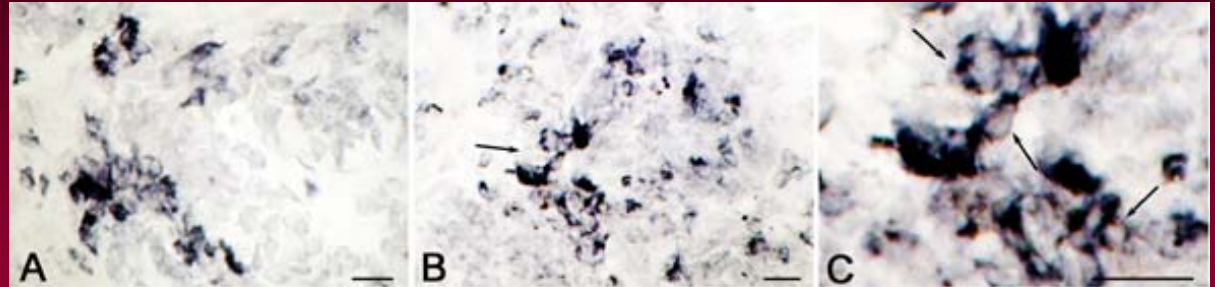7 autopsy cases: 5 type 2 diabetes and 2 controls

Anti-HLA-DR, DP, DQ (CR3/43) marker of activated macrophages.

Monoclonal antibodies directed against human complement proteins C3d, C4d and C5b9 (terminal attack complex) which detect bacteria marked for destruction.
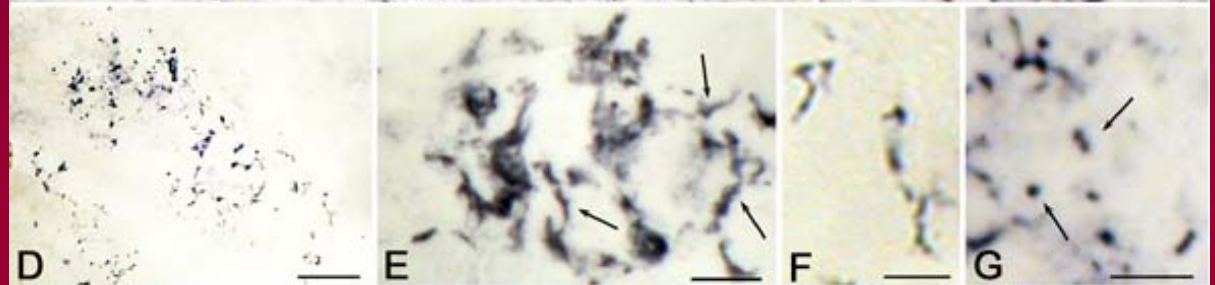
CD20, CD4 and CD8 antibodies to detect B, T4 and T8 lymphocytes.
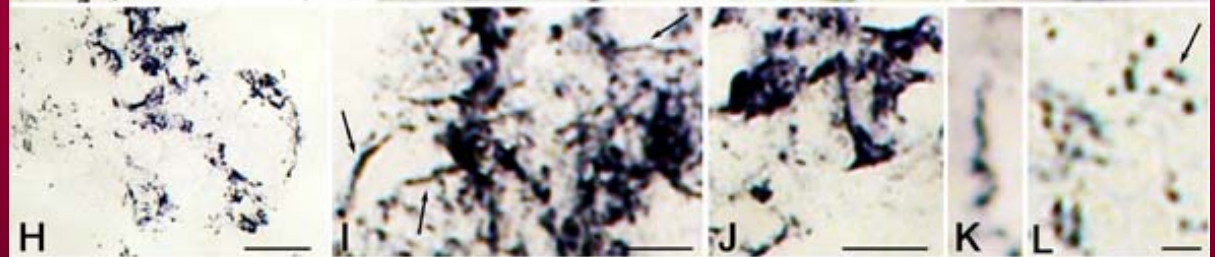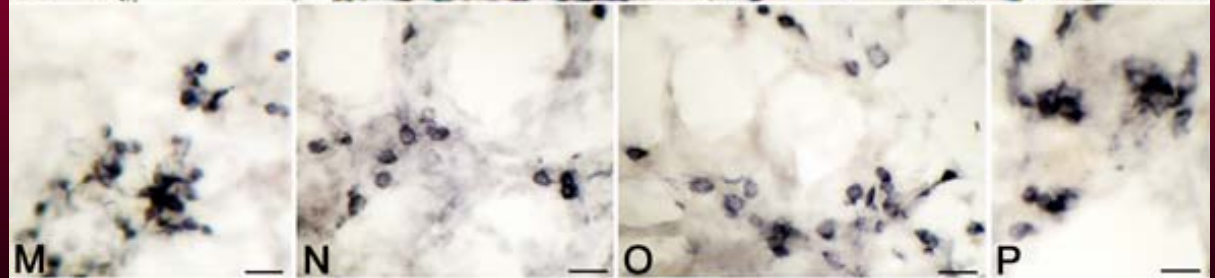
CHRONIC INFLAMMATION
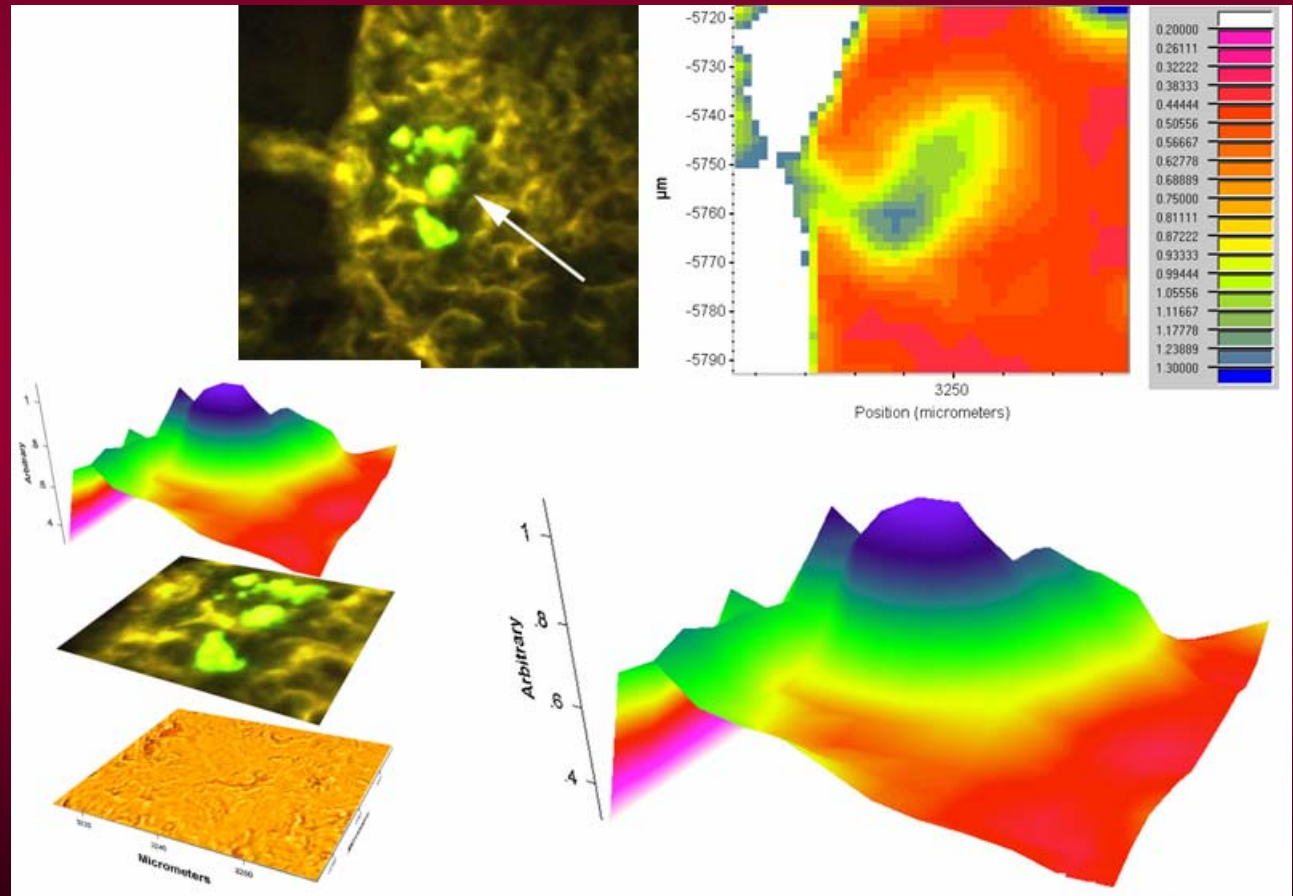
HLADR (A-C)

C3d (D-G)

C5b9 (H-L)

CD20 (M)
CD4 (N)
CD8 O,P)

In situ analysis of islet amyloid deposits by Synchrotron InfraRed MicroSpectroscopy (SIMRS)

The secondary structure of islet amyloid deposits was compared with Aβ deposits in AD using SIMRS)

Honore Daumier, 1808-1879/ Lithograph reproduced by the courtesy of the Museum of Fine Arts, Boston, Mass. Daumier's legend to this cartoon reads: "M. Babinet prevenu par sa portiere de la visite de la comete."

Periodontitis, a polymicrobial disorder is associated with type 2 diabetes.

The putative role of Gram negative bacteria and the indirect toxic effect of LPS were proposed to play a role in type 2 diabetes *Grossi, 1998*

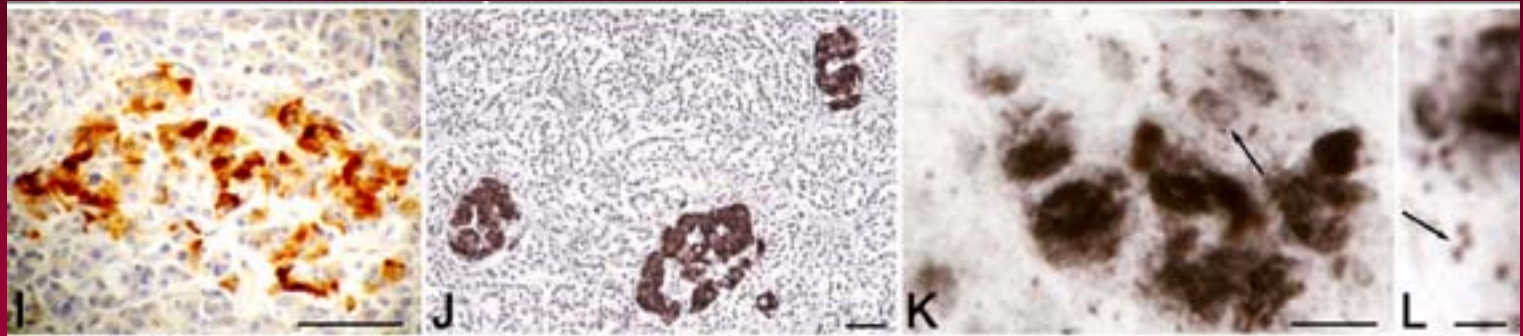Persistent bacterial debris are powerful inflammatory stimulators and are amyloidogenic
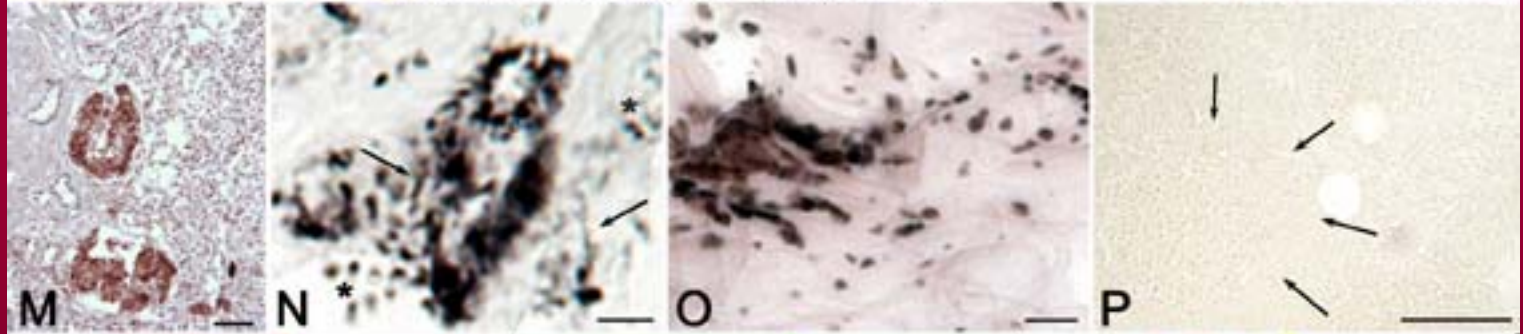
Fox et al., 1993

36 autopsy cases

Two antibodies, characterized for their specificities to recognize LPS and two antibodies to bacterial peptidoglycan (BPG) were used
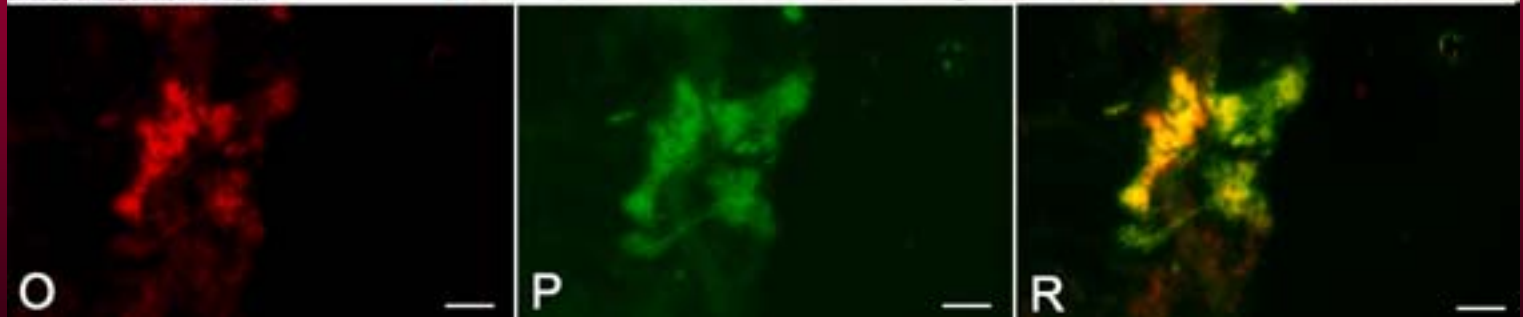
The role of bacteria or their toxins

Amylin (I)
LPS (J-L)

BPG (M,N)
LPS tonsil (O)
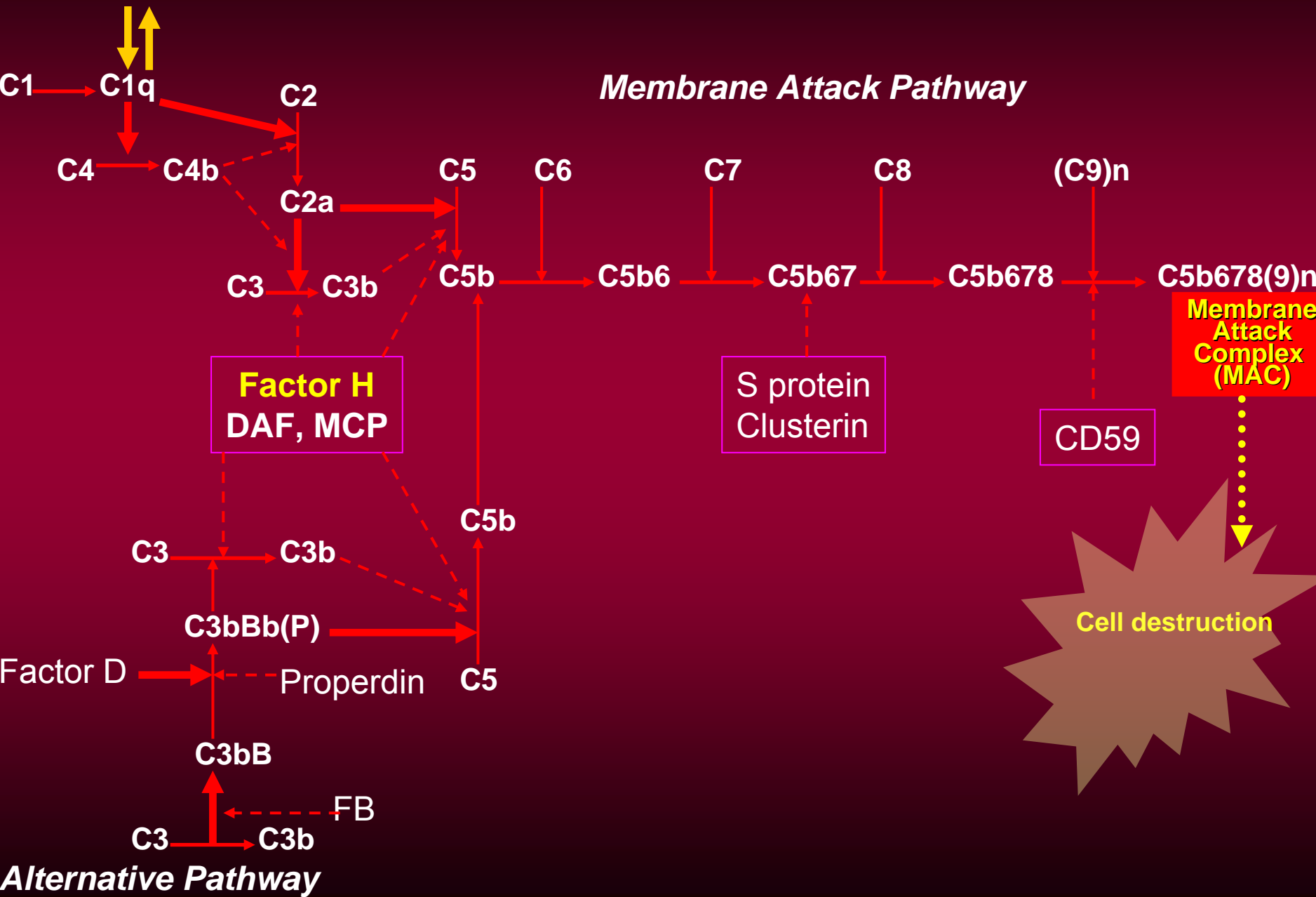Control (P)

Amylin (O)
LPS (P)
Merged (R)

Biological activities of bacteria or their toxins

- Apoptosis
- Chronic inflammation
- Free radicals – oxidative stress
- Increased proteoglycan synthesis
- Increased vascular permeability
- Amyloidosis

Classical Pathway

Persisting bacterial debris

C1 → **C1q** → **C2**

C4 → **C4b**

C2a

C3 → **C3b**

C5

Factor H
DAF, MCP

Membrane Attack Pathway

C5 **C6** **C7** **C8** **(C9)n**

C5b → **C5b6** → **C5b67** → **C5b678** → **C5b678(9)n**

S protein
Clusterin

CD59

Membrane Attack Complex (MAC)

C5b

C3 → **C3b**

C3bBb(P)

Factor D → Properdin

C5

C3bB

C3 → **C3b**

FB

Alternative Pathway

Cell destruction

Insulin, IGF-1 and LPS influence AβPP level in non neuronal cells

Western blot analysis was performed to analyze whether LPS, insulin and IGF-1 may also affect AβPP levels in non neuronal cells U87MG, TE671, fibroblasts)

The effect of IGF-1 on AβPP was also analyzed in fibroblast cell lines (R-, R503, R600) expressing different levels of IGF-1 receptor.

Bacteria and LPS induced increased ABPP and AB deposition

Insulin and LPS   Insulin   IGF-1
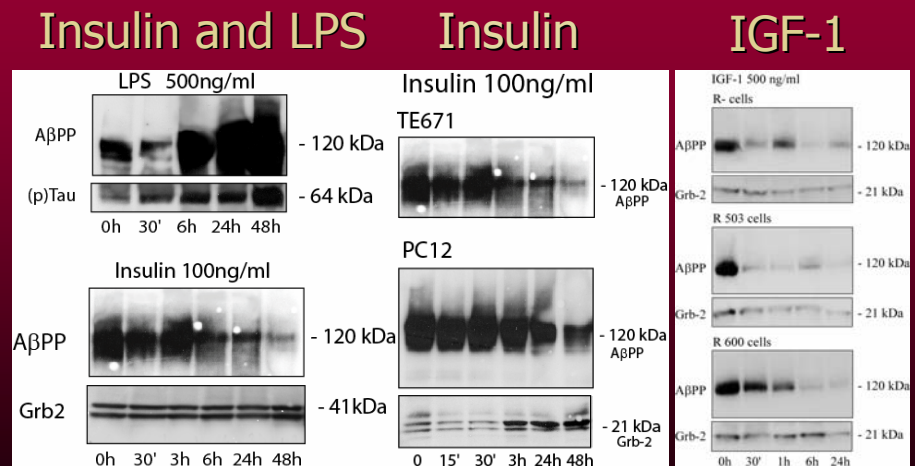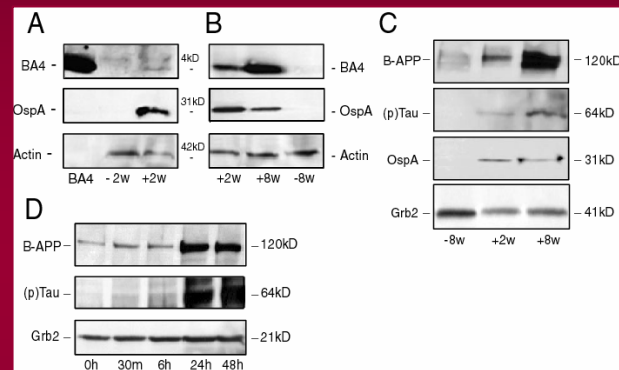
CONCLUSION

A host reaction similar to AD is also key player in the pathogenesis of type 2 diabetes

Local inflammatory processes, including complement activation, are also involved in the pathogenesis of type 2 diabetes.

The results also suggest that bacteria or their persistent debris may induce and sustain chronic inflammation and amyloid deposition in type 2 diabetes.

Further investigations are needed as a parallel antibacterial and antiinflammatory therapy may prevent or stop the degenerative process.

ACKNOWLEDGEMENTS