XXII World Congress of Neurology
Santiago - Chile 2015
Changing Neurology Worldwide

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WCN 2015

# AUTOIMMUNE PERIPHERAL NERVE DISORDERS
## Update in the Management of GBS

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Johns Hopkins University

2 November 2015

PNS
PERIPHERAL NERVE SOCIETY

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# Active Conflicts of Interest

- Consultant: Annexon Biosciences, Akros Pharma, Boehringer Ingelheim, Cigna Health Management, Inc., DP Clinical, Inc., Glenmark Pharma, INSYS Therapeutics, Inc, Octapharma AG, Pharnext SAS, ProPhase LLC, Sun Pharmaceuticals, Syntimmune, UCB Pharma Inc.
- Data Safety Monitoring Board: Acorda Therapeutics, Inc., Pfizer Inc., Johnson & Johnson, ISIS Pharmaceuticals, Novartis Corp., GlaxoSmithKline, Axovant Sciences Ltd.,
- Technology Licensing: Johnson & Johnson, Seattle Genetics, Inc., Genentech Corp., AstraZeneca, Glenmark Pharma, Acetylon Pharmaceuticals Inc.
- Board of Directors: GBS-CIDP Foundation International, Foundation for Peripheral Neuropathy, The Peripheral Nerve Society

# Guillain-Barré Syndrome

1859 Landry — Acute ascending paralysis

1891 Quincke — "Invention" of lumbar puncture

1916

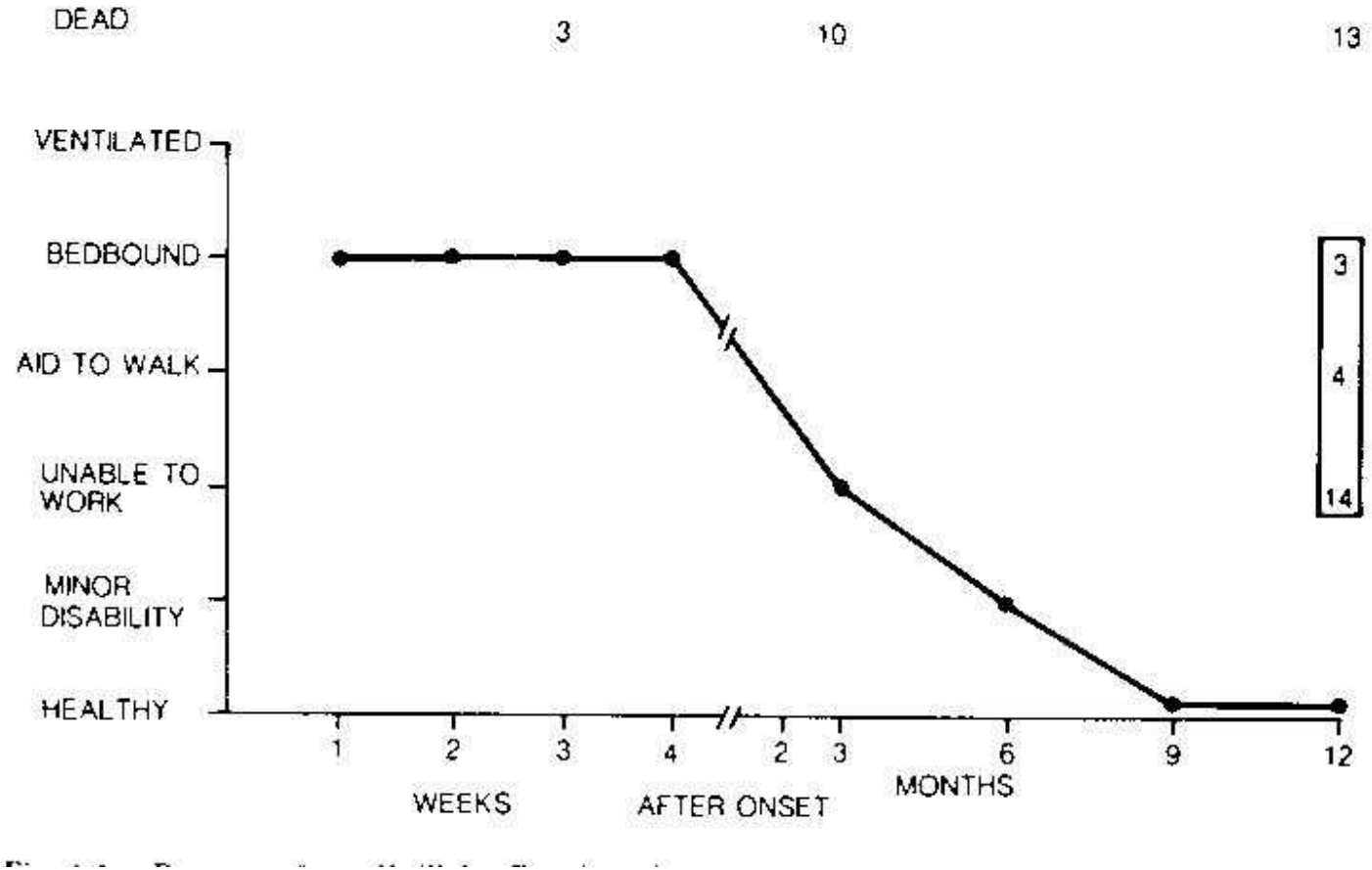
SUR UN SYNDROME DE RADICULO-NÉVRITE AVEC HYPERALBUMINOSE DU LIQUIDE CÉPHALO-RACHIDIEN SANS RÉACTION CELLULAIRE. REMARQUES SUR LES CARACTÈRES CLINIQUES ET GRAPHIQUES DES RÉFLEXES TENDINEUX,

par MM. GEORGES GUILLAIN, J.-A. BARRÉ et A. STROHL.

GEORGES GUILLAIN

FIGURE 1. *Photograph of Professor André Strohl.*

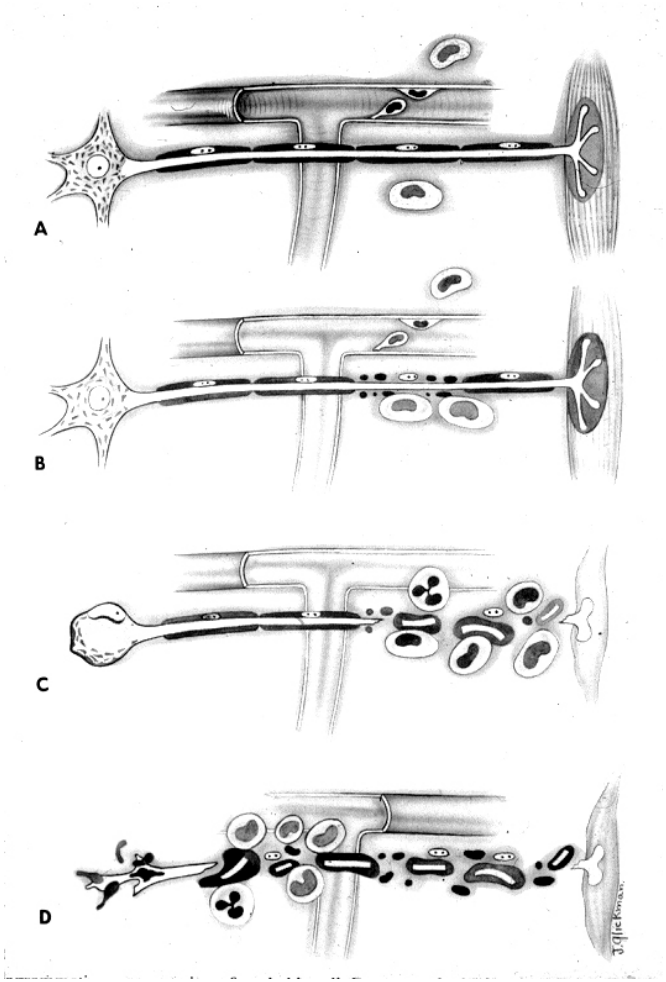
# Natural History of GBS



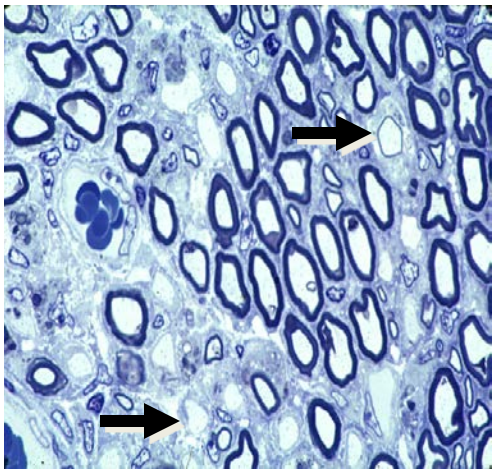

Adapted from Winer JB, Hughes RA, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988;51:605-12.

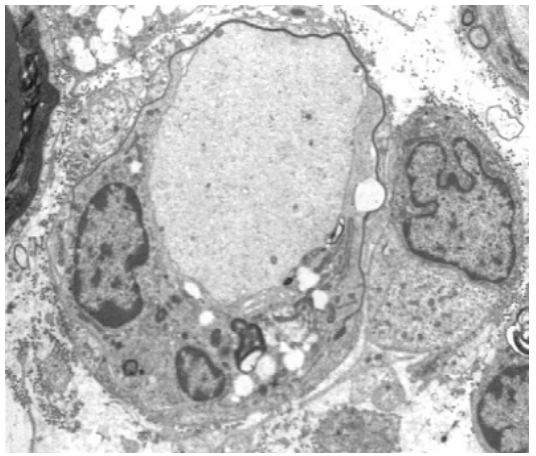

Arthur Asbury

# Pathogenesis of GBS




- Acute monophasic autoimmune attack on PNS myelin (demyelination with secondary axonal degeneration) usually post-infectious.

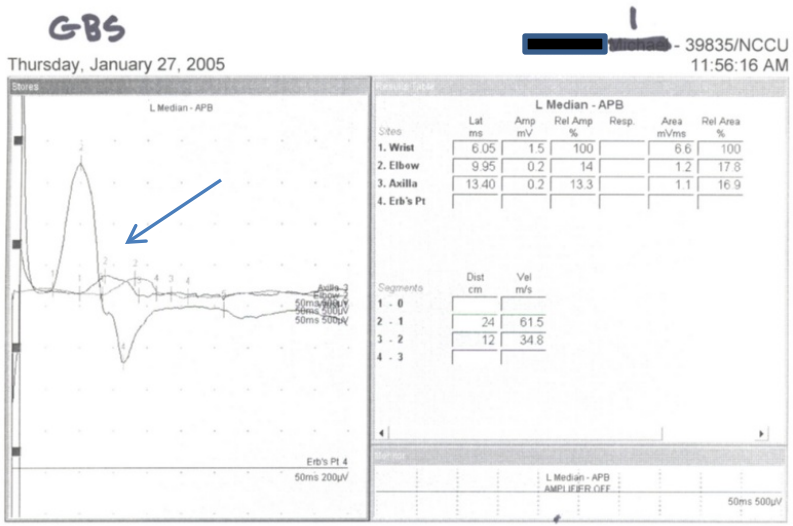




Courtesy J Griffin

Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. Medicine (Baltimore) 1969;48:173-215.

# Nerve Conduction in GBS




**L Median - APB**

| Sites | Lat ms | Amp mV | Rel Amp % | Resp. | Area mVms | Rel Area % | Dur ms | Rel Dur % |
|---|---|---|---|---|---|---|---|---|
| 1. Wrist | 6.05 | 1.5 | 100 | | 6.6 | 100 | 7.05 | 100 |
| 2. Elbow | 9.95 | 0.2 | 14 | | 1.2 | 17.8 | 8.85 | 126 |
| 3. Axilla | 13.40 | 0.2 | 13.3 | | 1.1 | 16.9 | 10.10 | 143 |
| 4. Erb's Pt | | | | | | | | |

**L Median - APB**

| Segments | Dist cm | Vel m/s |
|---|---|---|
| 1 - 0 | | |
| 2 - 1 | 24 | 61.5 |
| 3 - 2 | 12 | 34.8 |
| 4 - 3 | | |

- Features of acquired demyelination
  - Prolonged Distal and F-wave Latency
  - Reduced Conduction Velocity
  - Partial Motor Conduction Block
  - Abnormal Temporal Dispersion

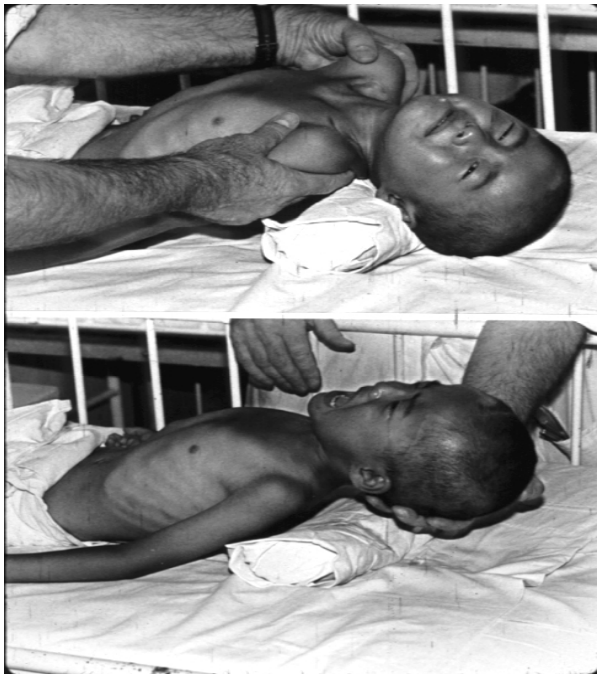
*Brain* (1986), **109**, 1115–1126

# AN ACUTE AXONAL FORM OF GUILLAIN-BARRÉ POLYNEUROPATHY

*by* T. E. FEASBY,[1] J. J. GILBERT,[1,2] W. F. BROWN,[1] C. F. BOLTON,[1] A. F. HAHN,[1,2] W. F. KOOPMAN[1] *and* D. W. ZOCHODNE[1]

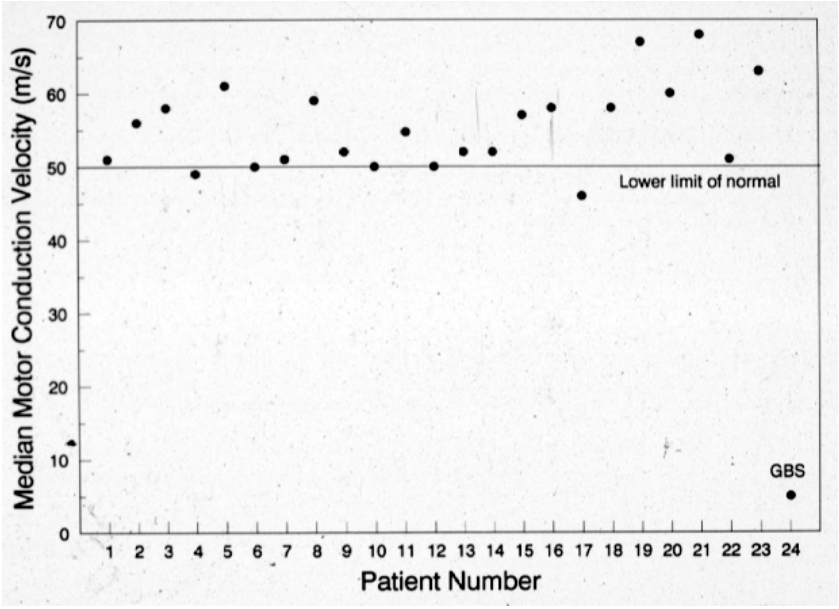
# GBS in China

- Mostly in children
- Mainly in summer
- Mainly rural children
- Clinically identical aside from normal sensation

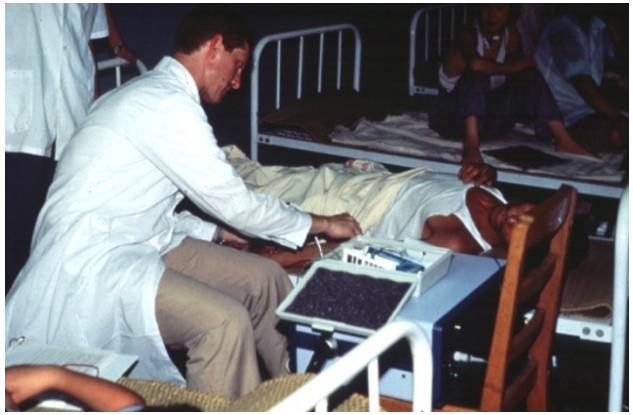


Hands of AK Asbury 1990

# Nerve conductions in GBS in China



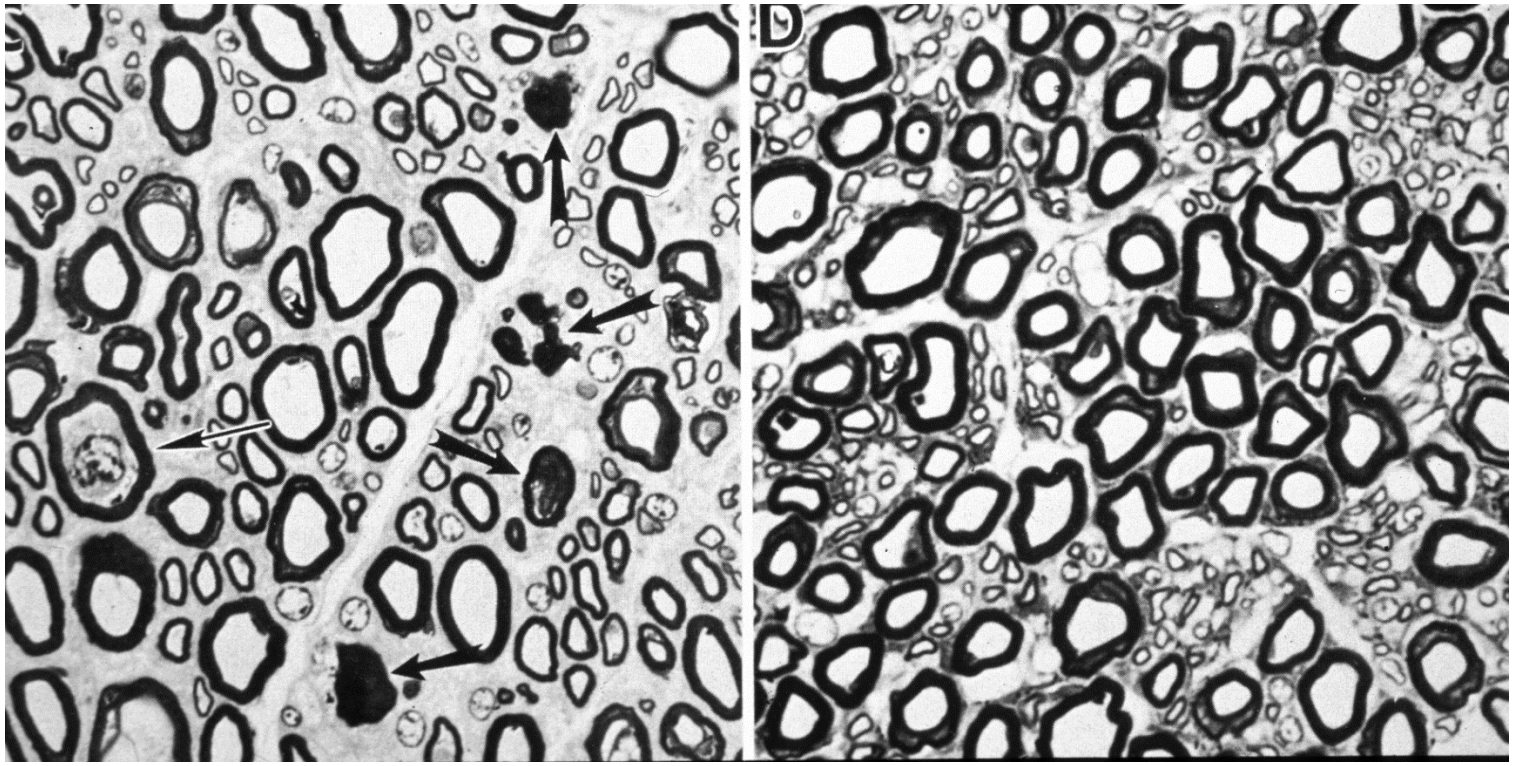

- No features of demyelination
- Normal SAP
- Low amplitude CMAPs
- EMG denervation
- Predicts pathology



McKhann GM et al. Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. Lancet, 1991;338:593-597.

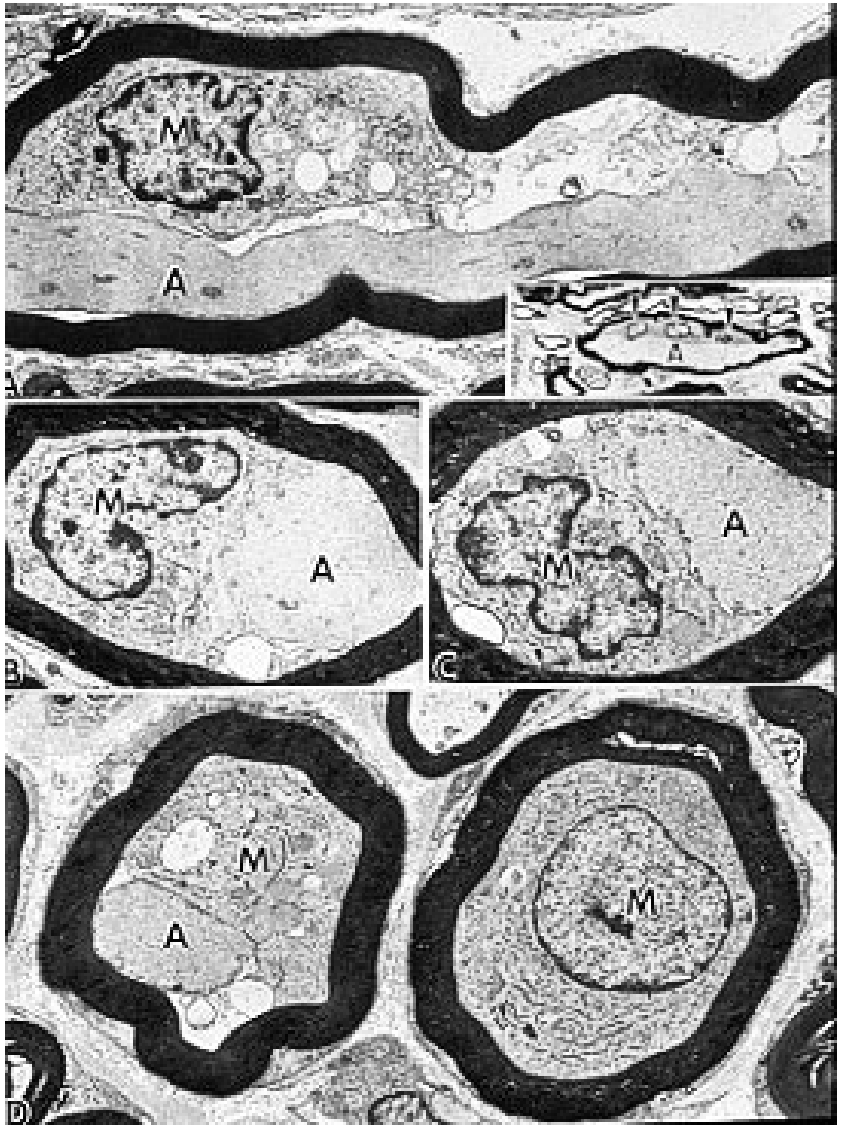
# Pathology from China

**Motor Root** **Sensory Root**



Griffin JW et al. Pathology of the motor-sensory axonal Guillain-Barre syndrome. Ann Neurol 1996; 39:17-28.

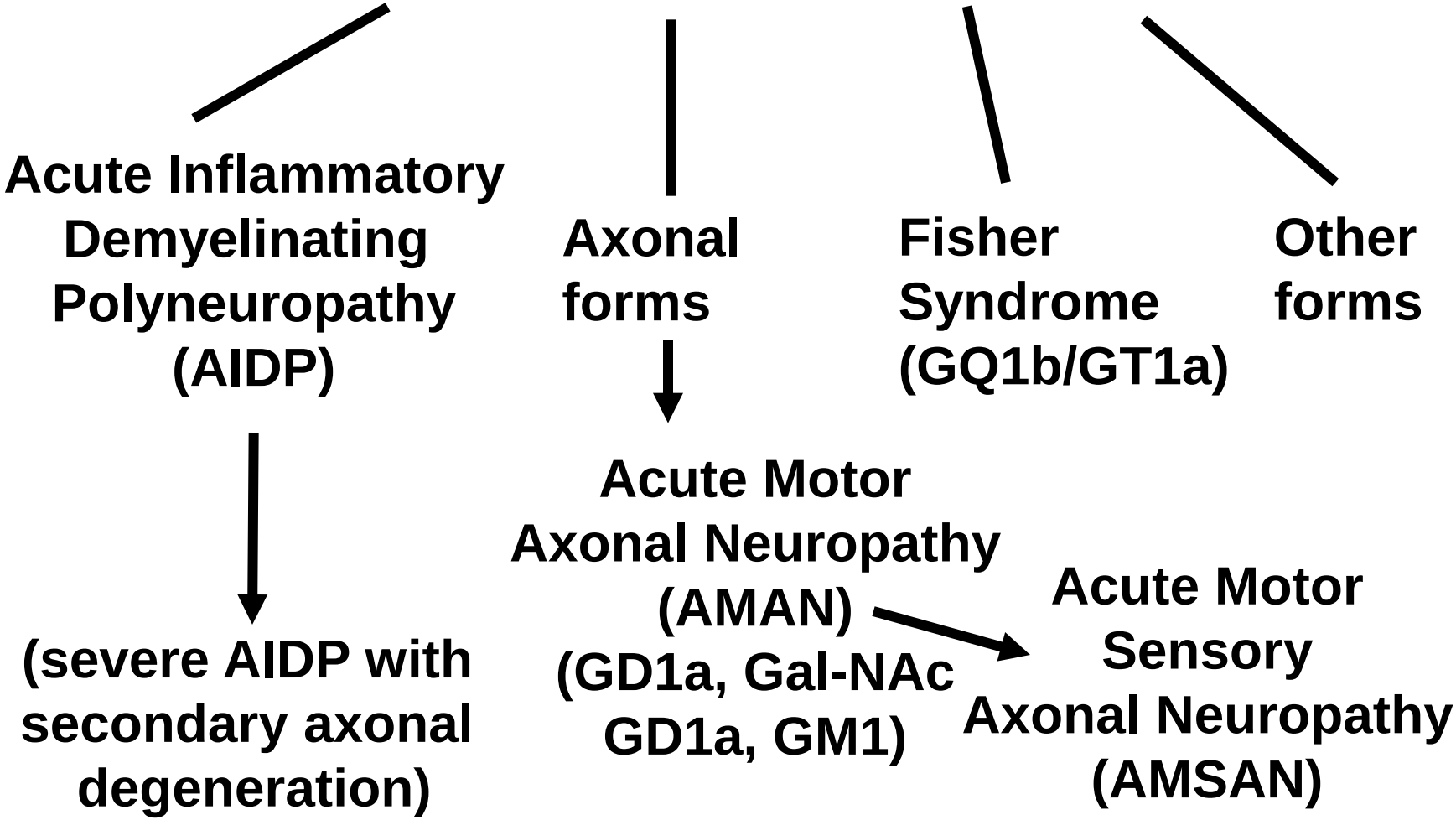
# Acute Motor Axonal Neuropathy



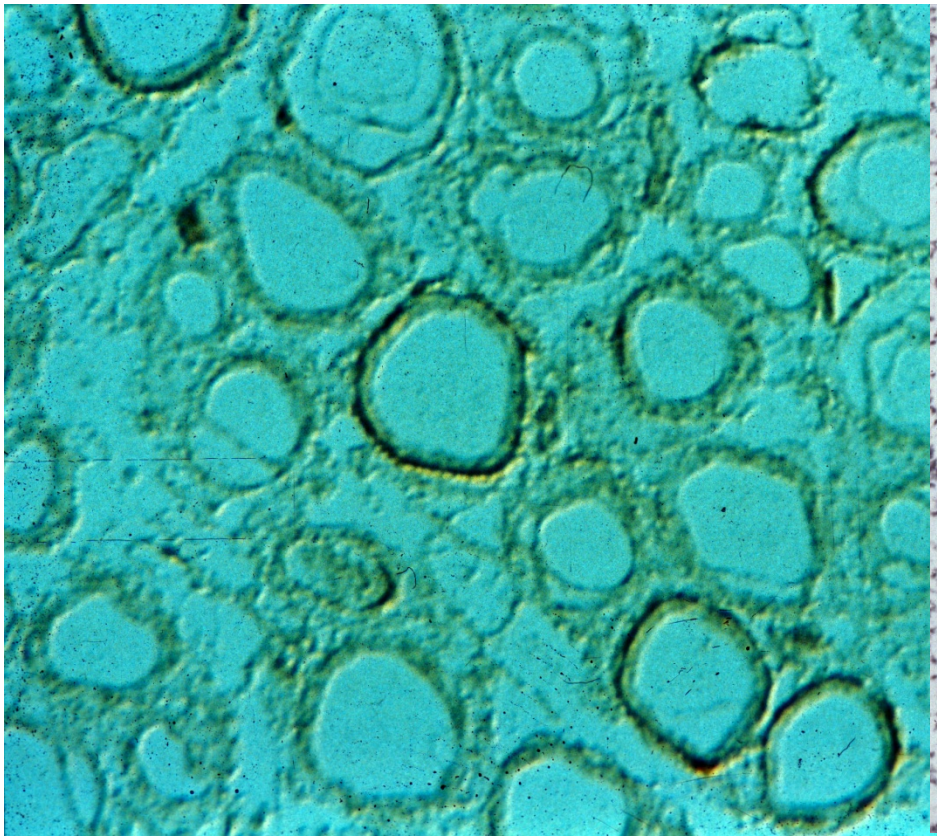

Macrophages dissect into the peri-axonal space of the internodes.

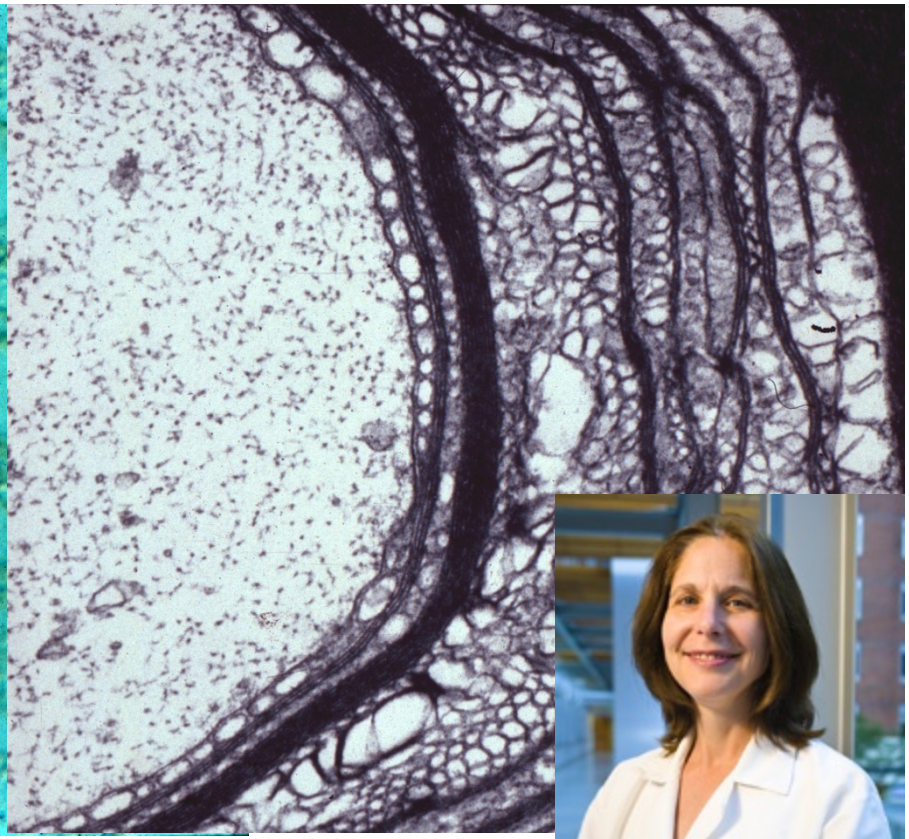
Griffin JW et al. Pathology of the motor-sensory axonal Guillain-Barre syndrome. Ann Neurol 1996;39:17-28.

# Guillain-Barre syndromes



# AIDP: Fibers with complement activation (C3d binding) undergo vesicular demyelination





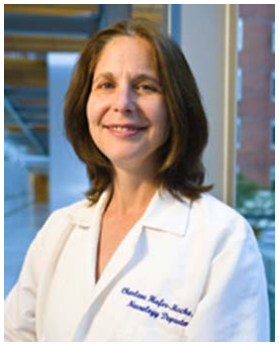


Hafer-Macko C et al. Immune attack on the Schwann cell surface in acute inflammatory demyelinating polyneuropathy. Ann Neurol 39:625-635, 1996.

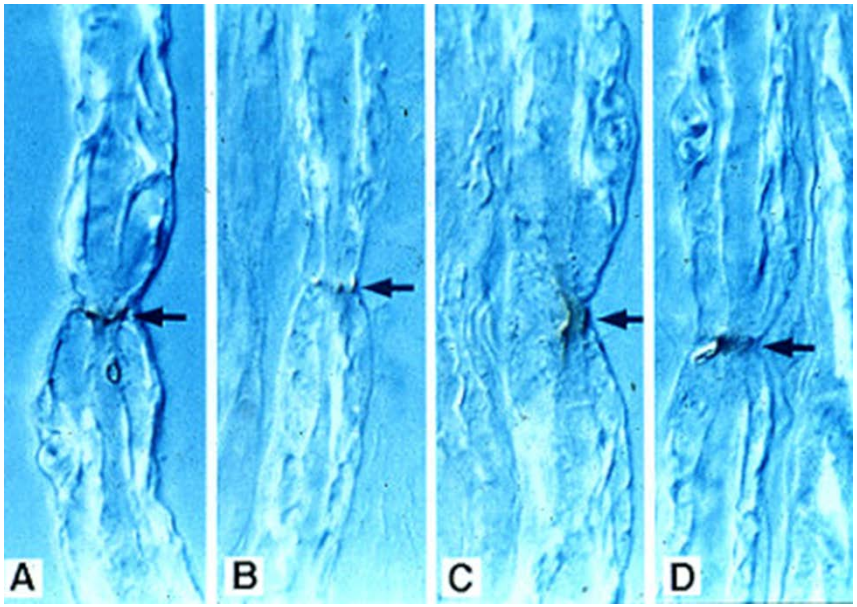
# Proposed Pathogenesis of AIDP

- Infection with a specific agent (may be *C. jejuni)*.
- Formation of cross-reacting anti-myelin or anti-ganglioside antibodies.
- Binding of these antibodies to epitopes on the Schwann cell plasmalemma.
- Complement activation and macrophage recruitment.
- Demyelination and conduction failure.
- In severe cases, secondary distal Wallerian-like degeneration.

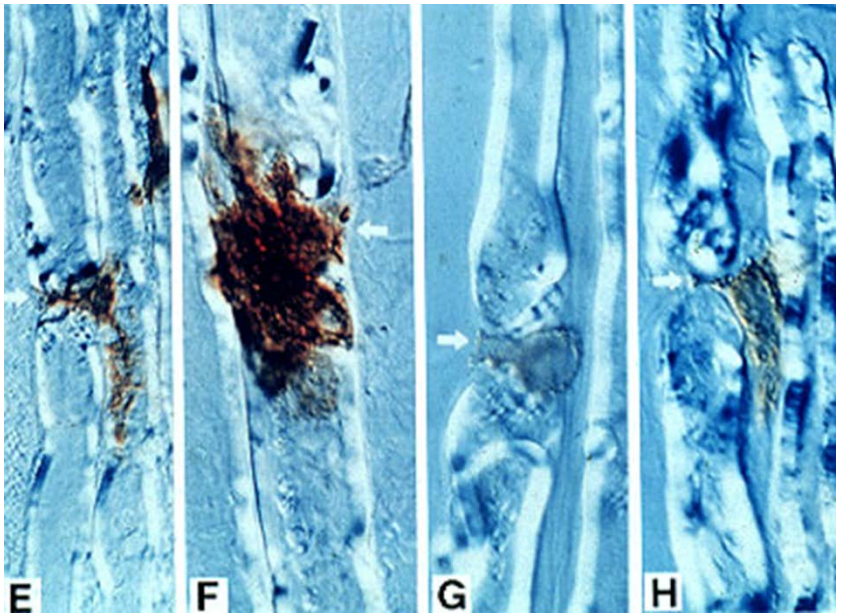
# Nodes in AMAN



**Complement**

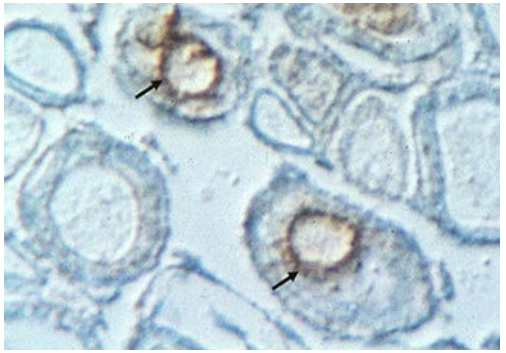


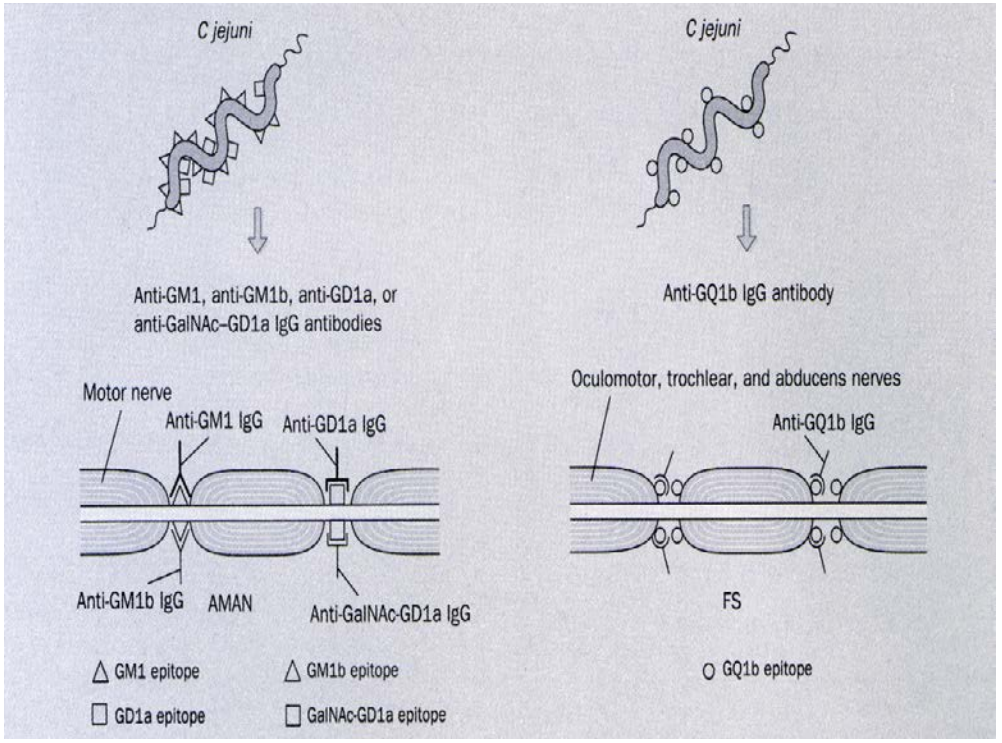

**Macrophages**



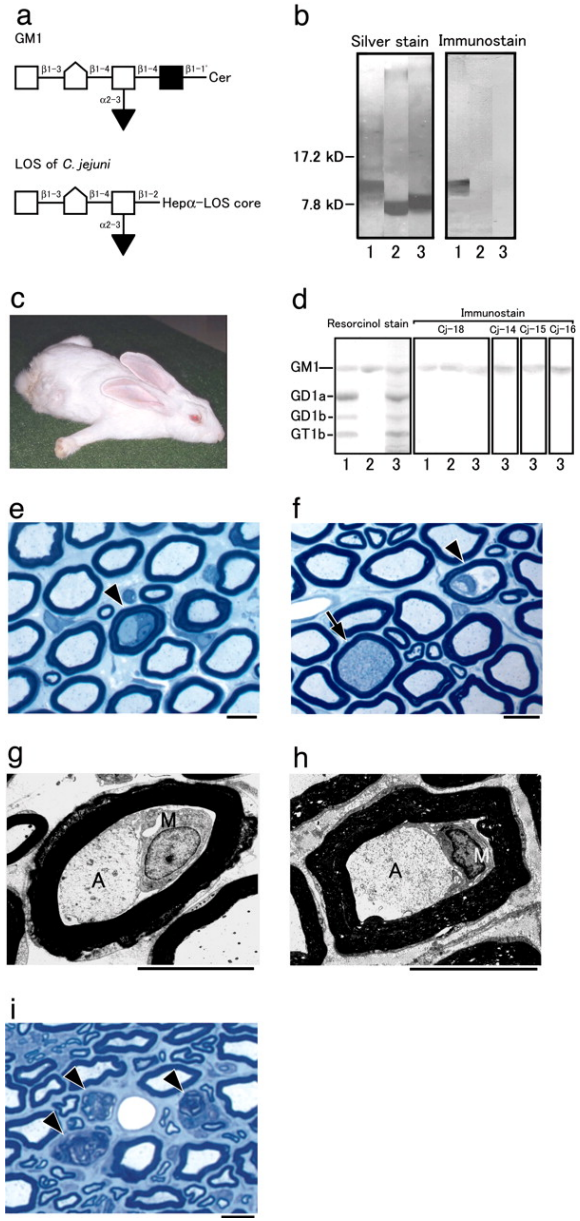

Hafer-Macko C et al. Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. Ann Neurol 1996;40:635-644.

Binding of IgG to internodal axolemma in AMAN

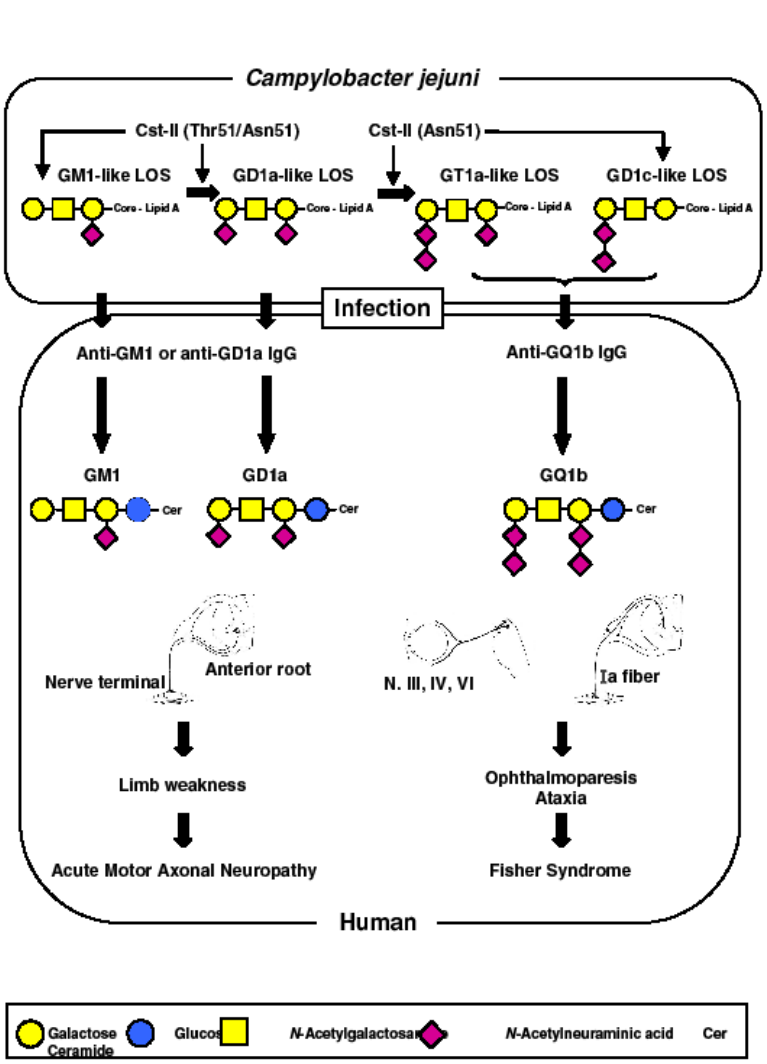


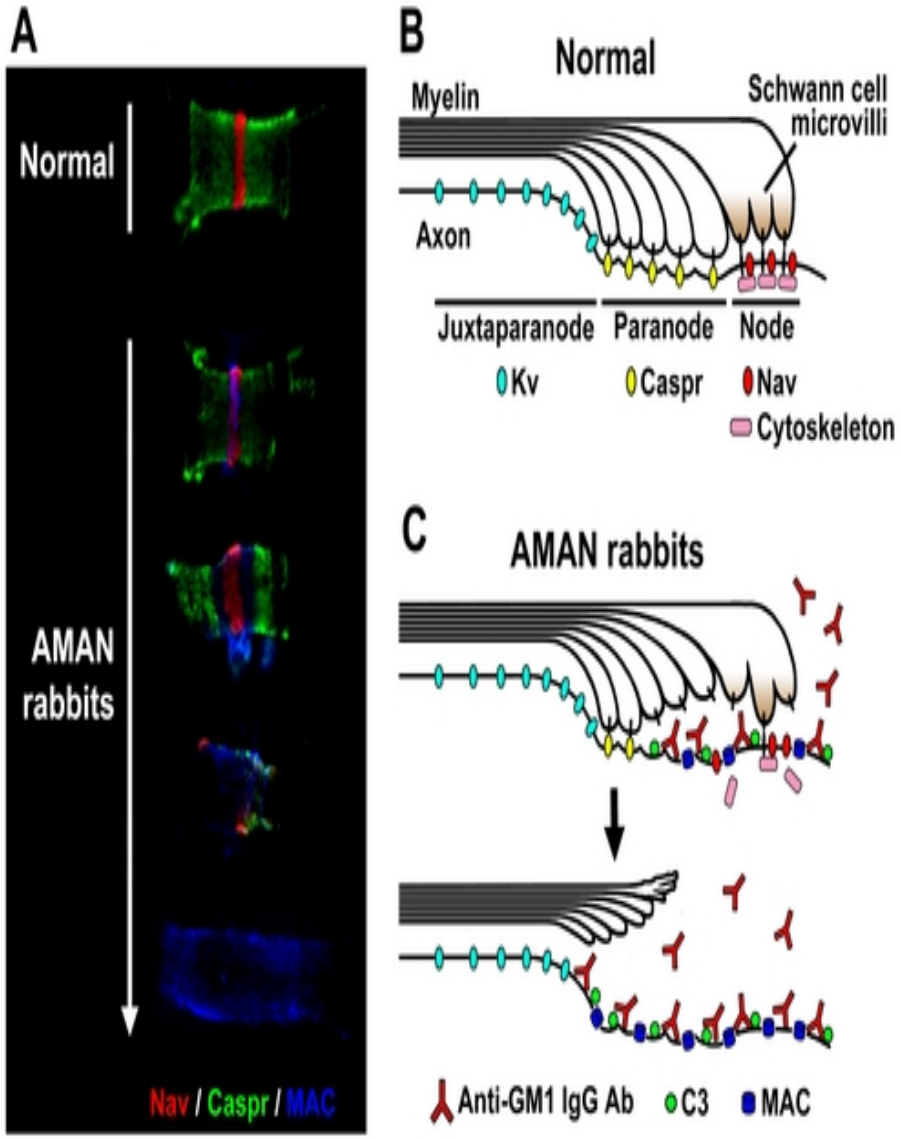



Yuki, Lancet Inf Dis 2001;1:29-37.




**Yuki N et al. Proc Natl Acad Sci USA 2004;101:11404-11409**



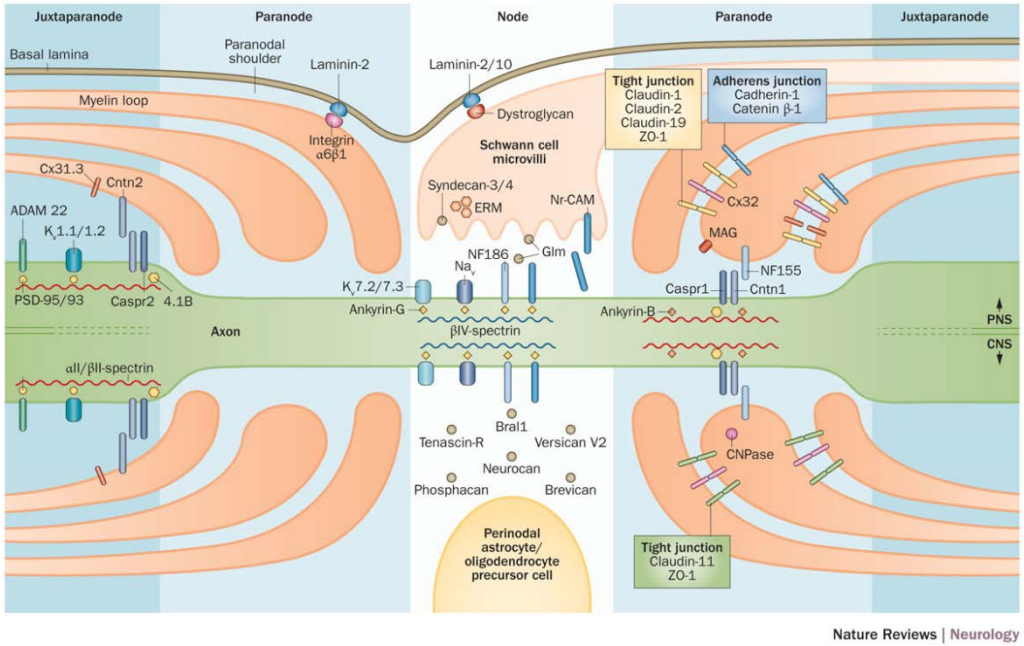

Yuki N and Kuwabara S. Axonal Guillain-Barré syndrome: carbohydrate mimicry and pathophysiology. J Peripher Nerv Syst. 2007;12:238-49.

# Proposed Pathogenesis of AMAN

- Enteric infection with a specific *C. jejuni* (usually Penner 0:19).
- Ganglioside-like epitopes in the LPS stimulate synthesis of complement fixing IgG anti-ganglioside (**GD1a**, GM1, GalNacGD1a, or GM1b) antibodies.
- Binding of these antibodies to Nav channels on the axolemma cause conduction failure and weakness.
- Recruitment of monocytes which help destroy the axon focally.
- Distal Wallerian degeneration follows.

# New Concepts

- The Node
- Conduction Failure
- Recovery



# Treatment of GBS

PE = IVIg = PE then IVIg

Supportive Care

Support Group Care (GBS-CIDP FI)

What to do after first treatment “fails”?

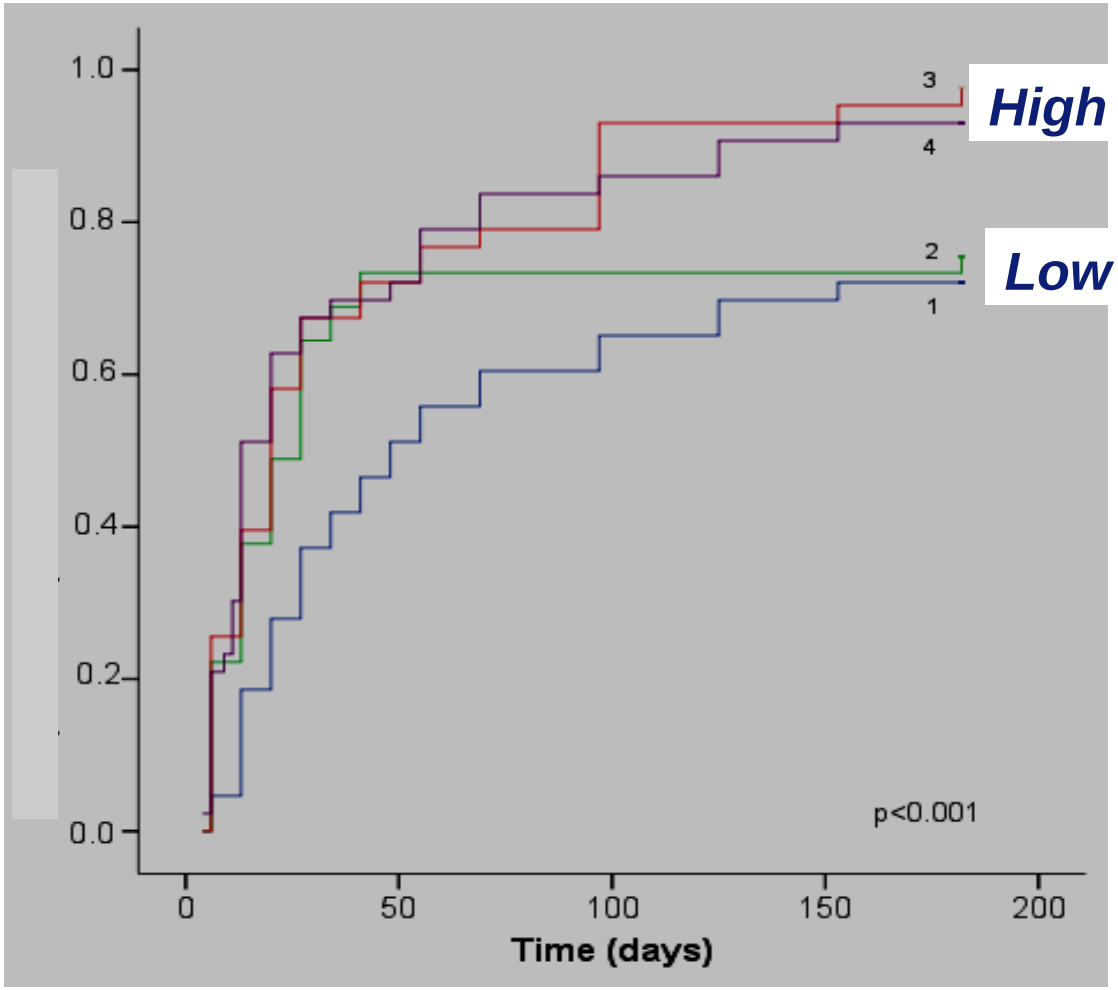
# IVIg pharmacokinetics and outcome in GBS

Kuitwaard K et al. Ann Neurol 2009;66:597-603.

## Serum ΔIgG after IVIg in 174 GBS patients in relation to recovery

Proportion of patients who walk unaided

From P van Doorn




***High* ΔIgG**

***Low* ΔIgG**

**Low ΔIgG** is associated with slower recovery

**All GBS Patients in IGOS (B Jacobs, lead)**

**Only those treated with IVIg 2 gram/kg (in 2-5 days)**

prognosis at day 7 after start IVIg

| Good prognosis (mEGOS 0-5) | Good prognosis (mEGOS 0-5) | Poor prognosis (mEGOS 6-12) | Poor prognosis (mEGOS 6-12) |
|---|---|---|---|
| NO Second IVIg course | Second IVIg course | NO Second IVIg course | Second IVIg course |

Primary endpoint: 4 weeks, follow-up 8, 12, 26 weeks

From P van Doorn

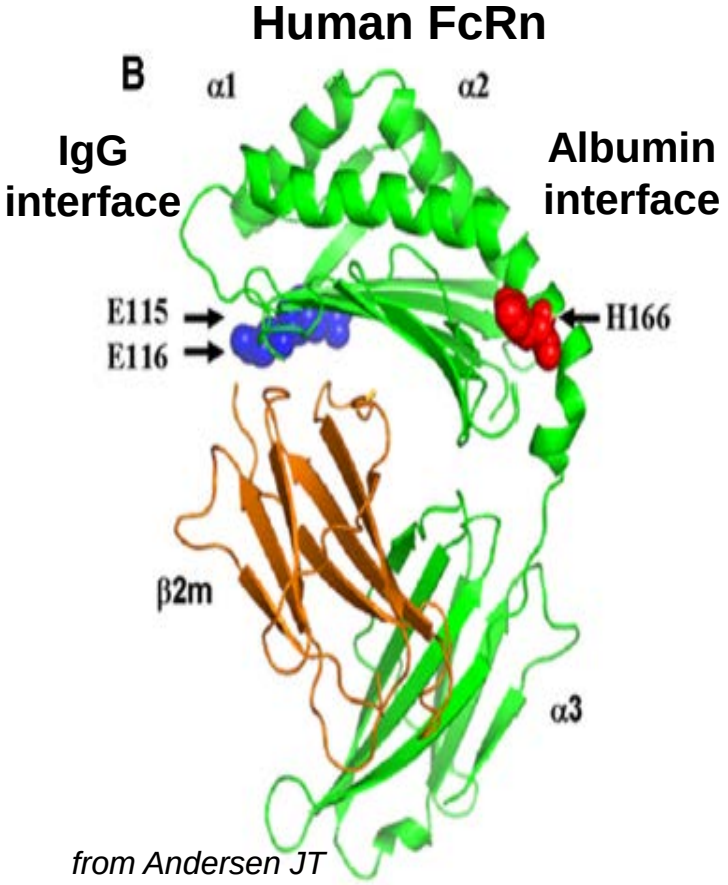
# Active and Upcoming

- Complement in GBS
  - Ongoing trial of eculizumab, a terminal complement inhibitor (Willison, Glasgow - PI)
  - Other complement drugs under consideration
- IgG-mimetics
  - Building on the Ravich observations
- Neonatal Fc receptor (FcRn)
- Monoclonal antibodies

# What is FcRn? It binds two ligands at non-overlapping sites: IgG and albumin

**IgG**

- Binds pH5, not pH7[1]
- 2:1 ratio[2]
- KDa = 25 nM[3]
- t½ = 21 days[4]




*from Andersen JT J Biol chem 2010*

**Albumin**

- Binds pH5, not pH7[5]
- 1:1 ratio[5]
- KDa = 4.5μM [3,5]
- t½ = 20 days[6]



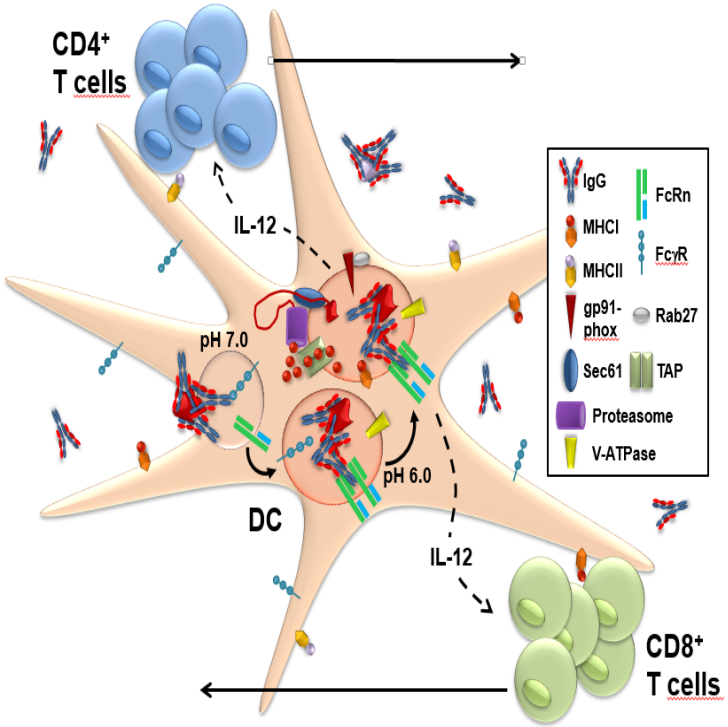
SYNTIMMUNE

# FcRn Is Widely Expressed in Adult Life

- Expression in numerous cell types
  - Parenchymal: hepatocytes, polarized epithelial cells, endothelial cells[1] (protect and transport IgG and albumin)
  - Hematopoietic: macrophages, dendritic cells (DC), neutrophils, B cells[1,2] (protect monomeric IgG and degrade multimeric immune complexes (IC)-IgG for antigen presentation)
  - Expression in a wide range of tissues
  - Lung, intestines, kidney, GU tract, brain, liver[1]
- Developmentally regulated[1]
  - High levels neonatal rodent intestinal epithelium
  - Placenta of humans

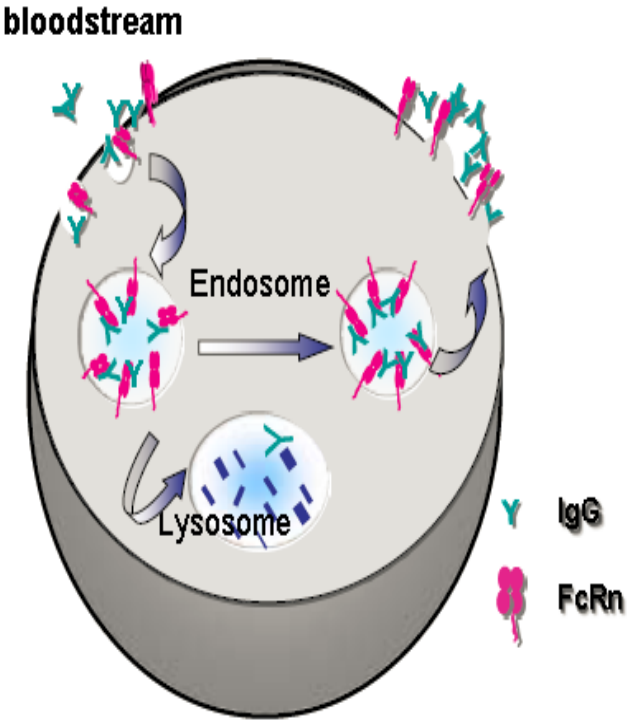
# FcRn has complementary roles in IgG biology by maintaining IgG levels and MHC Class I & II presentation: *Driving IgG mediated autoimmune disease*

FcRn within dendritic cells enables the presentation of IgG-complexed antigens to CD4 & CD8 T cells and production of innate cytokines (e.g. TNF, IL-12)




**Adapted from Blumberg, *J Immunol* 2015**

FcRn binds IgG and protects it from degradation by trafficking away from the lysosome and responsible for the long serum IgG half-life




*Brambell, Nature 1964; Junghans, PNAS 1996; Ghetie, EJI 1996; Roopenian, JI 2003; Akilesh, J Immunol 2007; Qiao, PNAS 2008; Liu J Immunol 2007; Ward PNAS 2008*

# Specific blockade of FcRn-IgG interaction in IgG-mediated autoimmune diseases will focus on the disease pathophysiology

- Promotes the degradation of pathogenic IgG antibodies (humoral immunity)
- Inhibits T cell activation stimulated by immune-associated antigen presentation (adaptive immunity)
- Blocks the production of cytokines including IL-12, INFγ, TNFα (inflammation)

SYNTIMMUNE

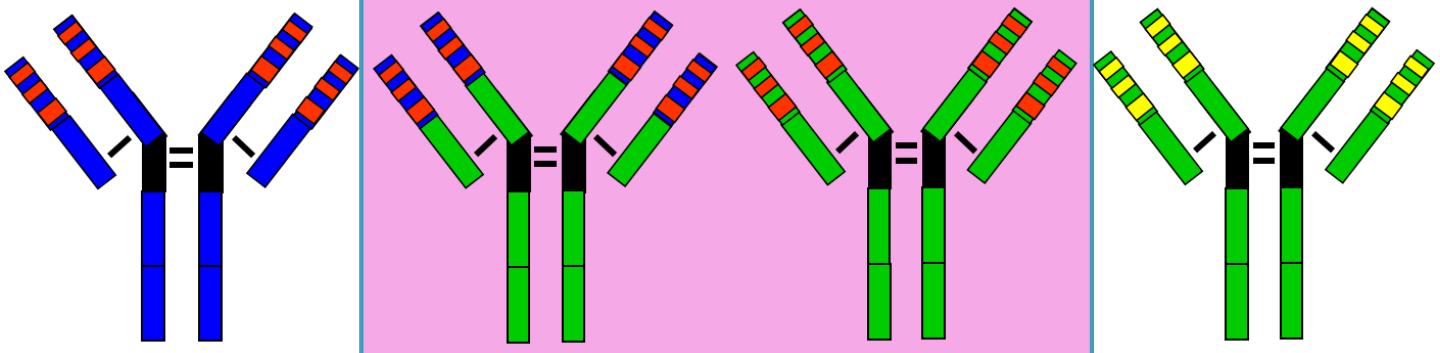
# Therapeutic recombinant antibodies

**murine**
monoclonal antibody
(highly immunogenic)

**chimaeric**
monoclonal antibody
CH+CL region human;
VH+VL region murine
(significantly less
immunogenic)

**humanised**
monoclonal antibody
CH+CL+FR region human;
CDR region murine

**human**
monoclonal antibody
entirely human

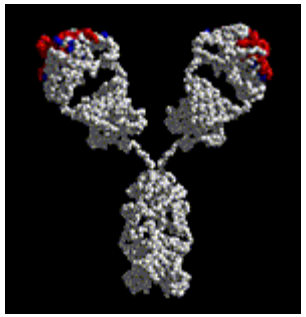


…momab | …ximab | …zumab | …mumab

**Rituximab**

**Natalizumab**
**Alemtuzumab**
**Ocrelizumab**
**Daclizumab**

**Ofatumumab**

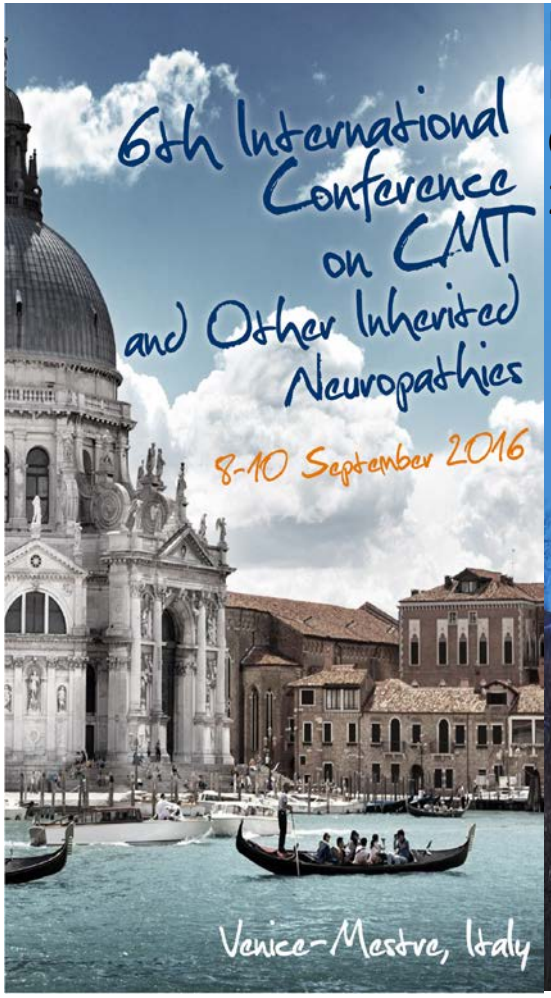


mouse | human | CDR-mouse | CDR-human

**Decreasing immunogenicity**

# PNS

PERIPHERAL NERVE SOCIETY




Inflammatory Neuropathy Consortium
21-5 June 2016