Increasing awareness Update on CVIDs

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Contents

- Awareness
  - How common are PADs ?
  - Why is diagnosis delayed ?
- Common variable immune deficiency disorders i.e. CVIDs
  - Who is affected and when ?
  - How do patients present ?
  - Single gene or polygenic disease ?
  - Management, including SCIg and home therapies

Why Awareness?

- EU conference on PIDs in June 2006
- Funded by EU Commission
- To produce a statement to be adopted by EU as a Consensus statement on these rare diseases
- To tell National Governments to provide funds for PID services
- 2007/14 is 7th EU Framework in which PIDs are a priority

Prevalence (in adults)

Diseases:	*Per 10^5 population*
Rheumatoid arthritis	1,000
Type I diabetes	200
Multiple sclerosis	60
Systemic lupus erythematosus	50
"CVIDs"	4
Scleroderma	1

Diagnostic delay - significant delay from onset of symptoms to diagnosis

Manchester UK 1989

Mean:

4 years in children

6 years in adults

Blore & Haeney

UK National audit *1995*

- **Mean 5 years**
- **Range [3.56 - 9.4 yrs]**
- **Varied with locality**
- **On type of antibody deficiency**
- **Mean 7.3 years for CVIDs** *Spickett, Askew & Chapel*

2005

Mean:

4.4 years

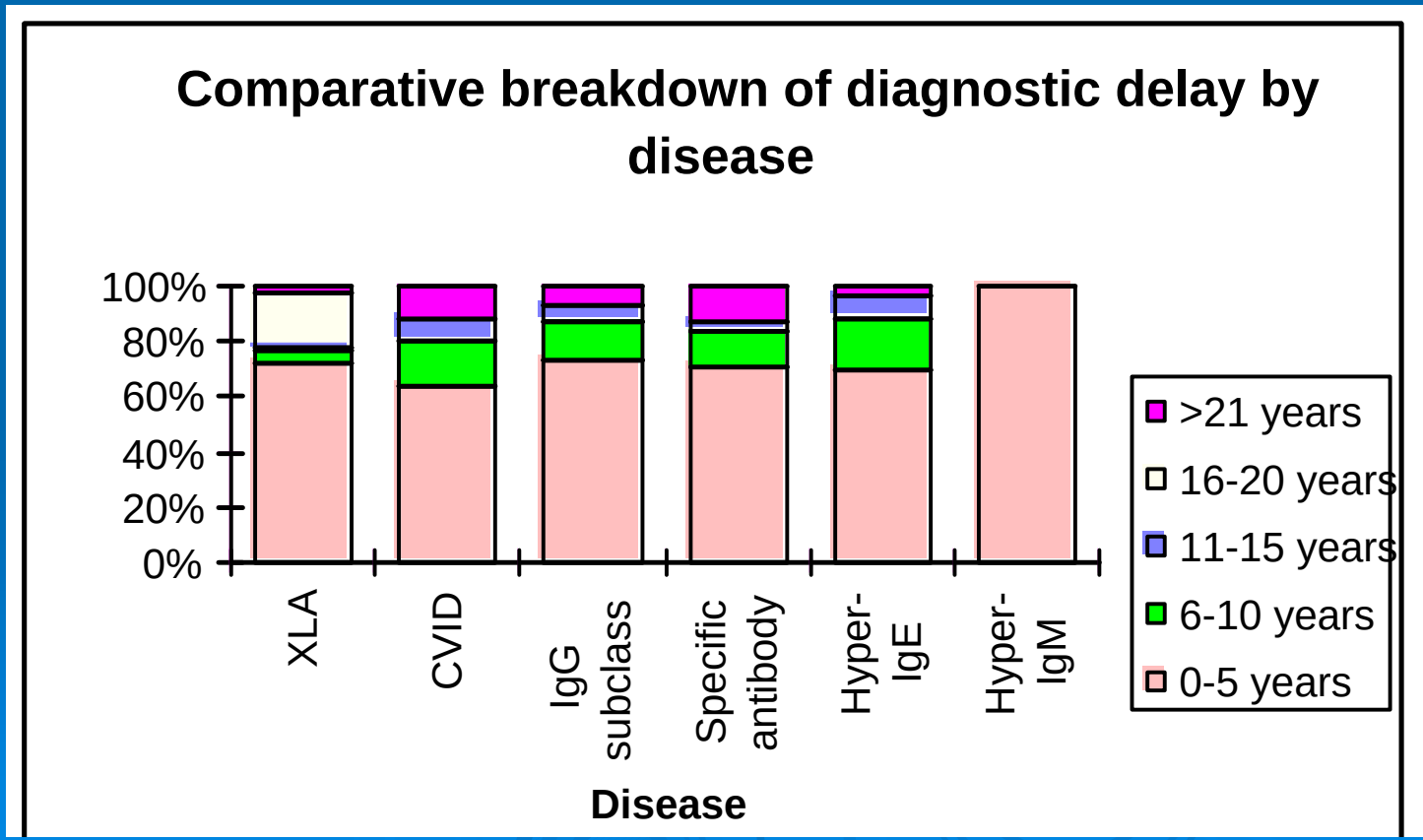
Median:

2 years

Seymour, Miles & Haeney

Evidence for diagnostic delay

(data from Spickett, Askew & Chapel 1995)



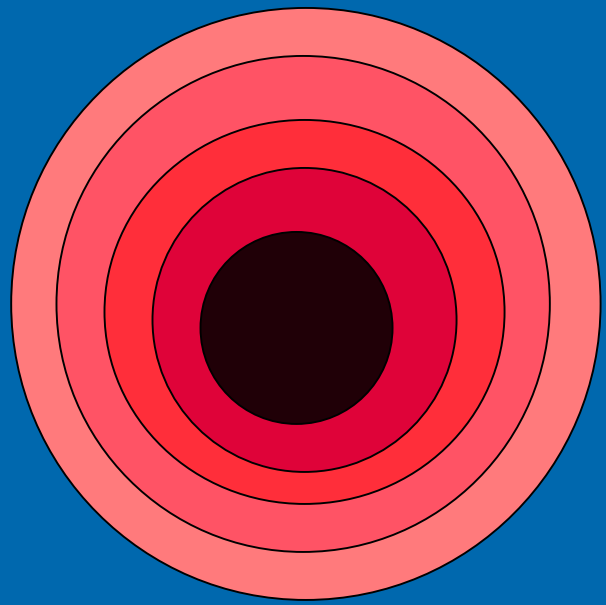
Reasons for delay

- **Patients may be seen by other specialists before coming to immunologists**
  - ***Which specialties in particular ?***
  - ***How can referral for diagnosis and treatment be speeded up ?***
- **General public awareness is low**
  - ***Encourage patient organizations to ensure general awareness, especially schools***
  - ***Education for physicians in primary care as well as hospital specialties***
  - ***Healthcare providers***

Public awareness

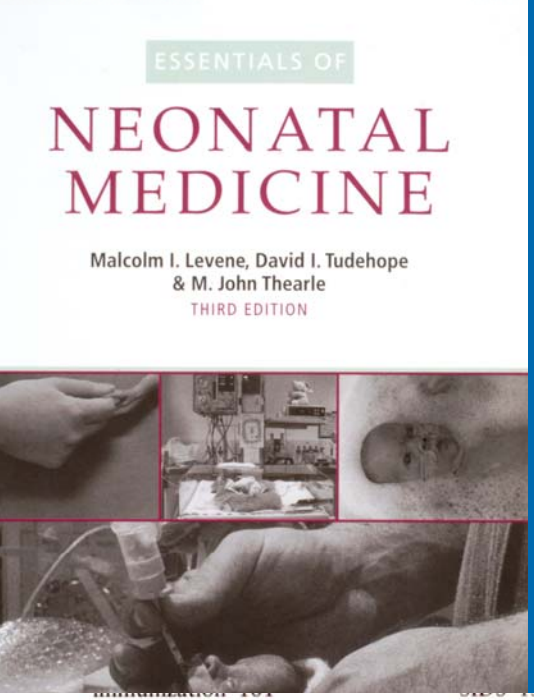
- **Potential patients - *Patient organisations***
  - Recurrent / unexplained infections
  - Loss of schooling/ time off work / visits to doctors
  - Unexplained granuloma, lymphoid infiltrations, atypical “lymphoma”, autoimmune cytopenias, splenomegaly, etc.
- **Healthcare providers - *Hospital managers***
  - Hospital laboratories and clinical services
- **Government agencies - *EU Commmission***
  - Provision of therapies, resources for diagnostic tests/centres
  - Comparison with other EU countries

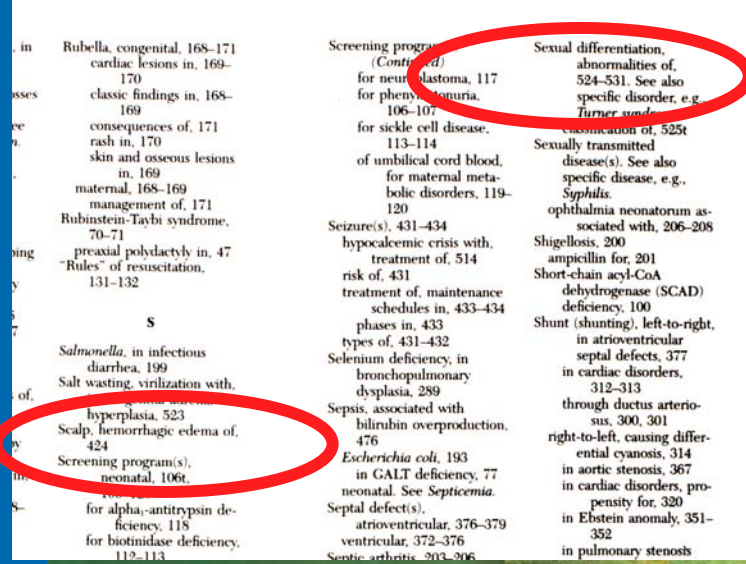
Primary care doctors - *from Rasa Duobiene*

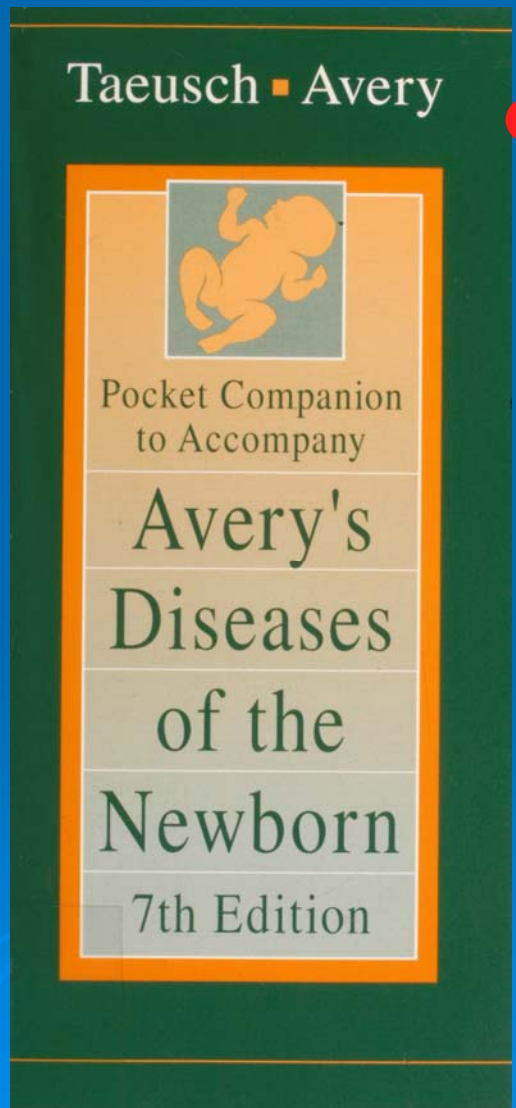


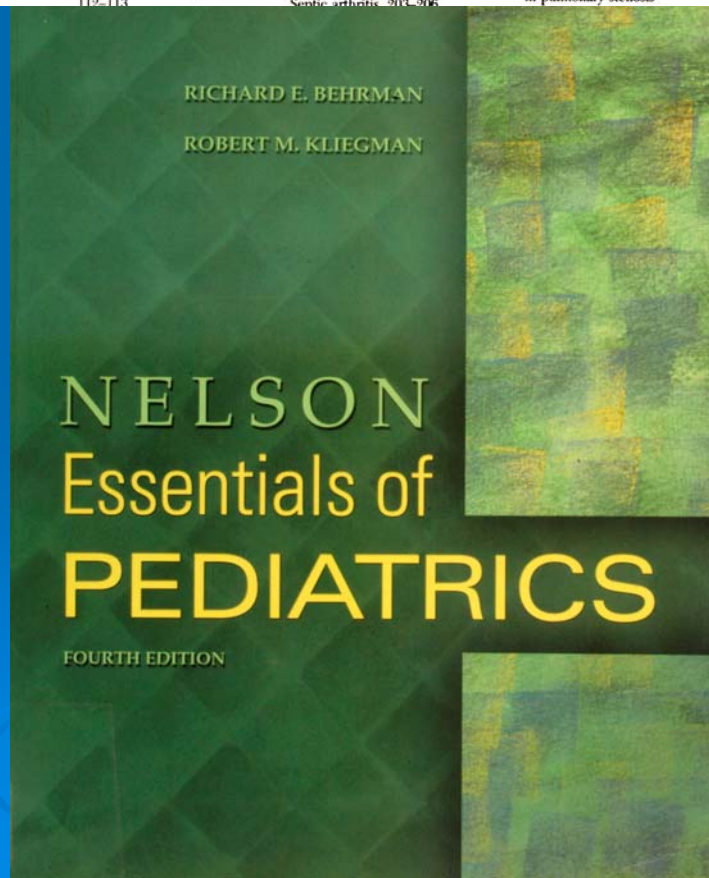
1. Six or more new documented ear infections requiring antibiotics < 1 year
2. Two or more unexplained documented sinus infections requiring antibiotics < 1 year
3. Two or more months on antibiotics without clinical improvement /resolution
4. Two episodes of pneumonia in any 2 year period in a non-smoker
5 Failure to thrive in an infant without an obvious explanation - Investigations for PID should be first line, as for sweat test and TTG / endomysial antibodies
6. Recurrent deep skin or organ abscesses in anatomical different sites
7. Persistent unexplained oral thrush or on skin after one year of age
8. Need for intravenous antibiotics to clear infections more than twice in life-time
9. Two or more deep seated infections in different anatomical sites in life-time
10. Family history of recurrent / severe/ persistent / unusual infections

Lack of awareness is no surprise…… if doctors don't know









Clinics presented with infections

(data from Spickett, Askew & Chapel. UK Audit of PIDs)

INFECTION	PERCENTAGE OF PATIENTS
Recurrent chest infections	67.5
Recurrent sinus infections	23.3
Infections in the gastrointestinal tract	10.8
Cutaneous infections	7.9
Bacterial meningitis	4.4
Septic arthritis	1.2
Recurrent conjunctivitis	1.4

DEPARTMENTS VISITED

Respiratory

ENT

Gastroenterology

Dermatology

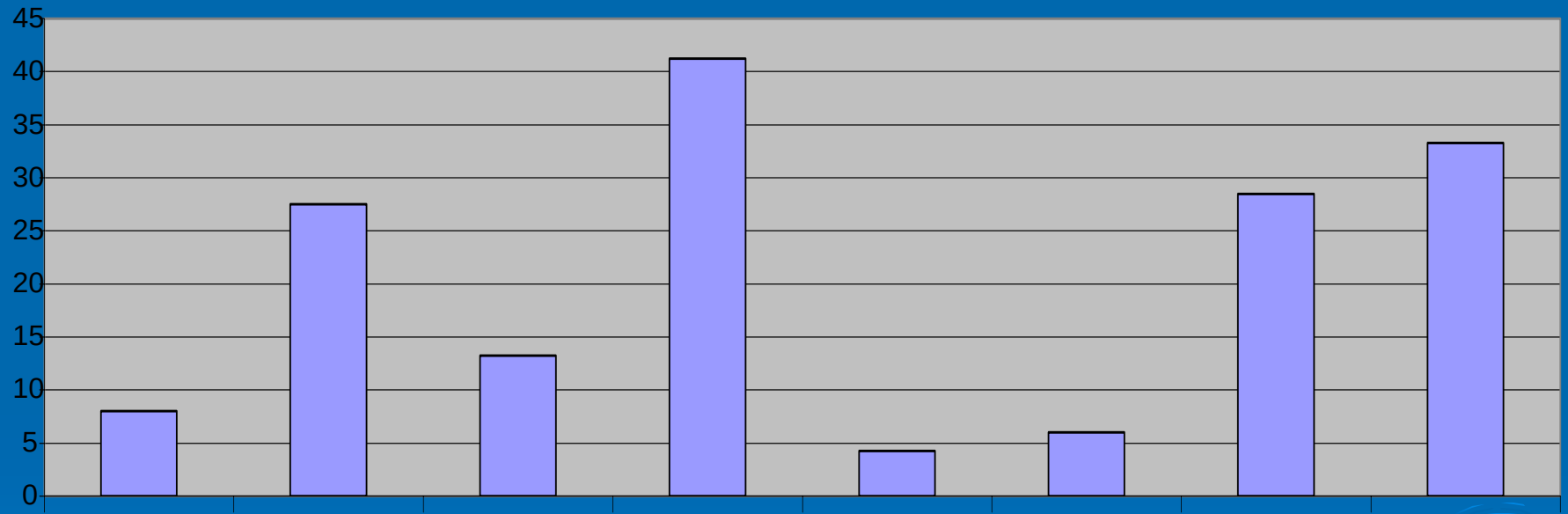
Neurology

Rheumatology

Ophthalmic

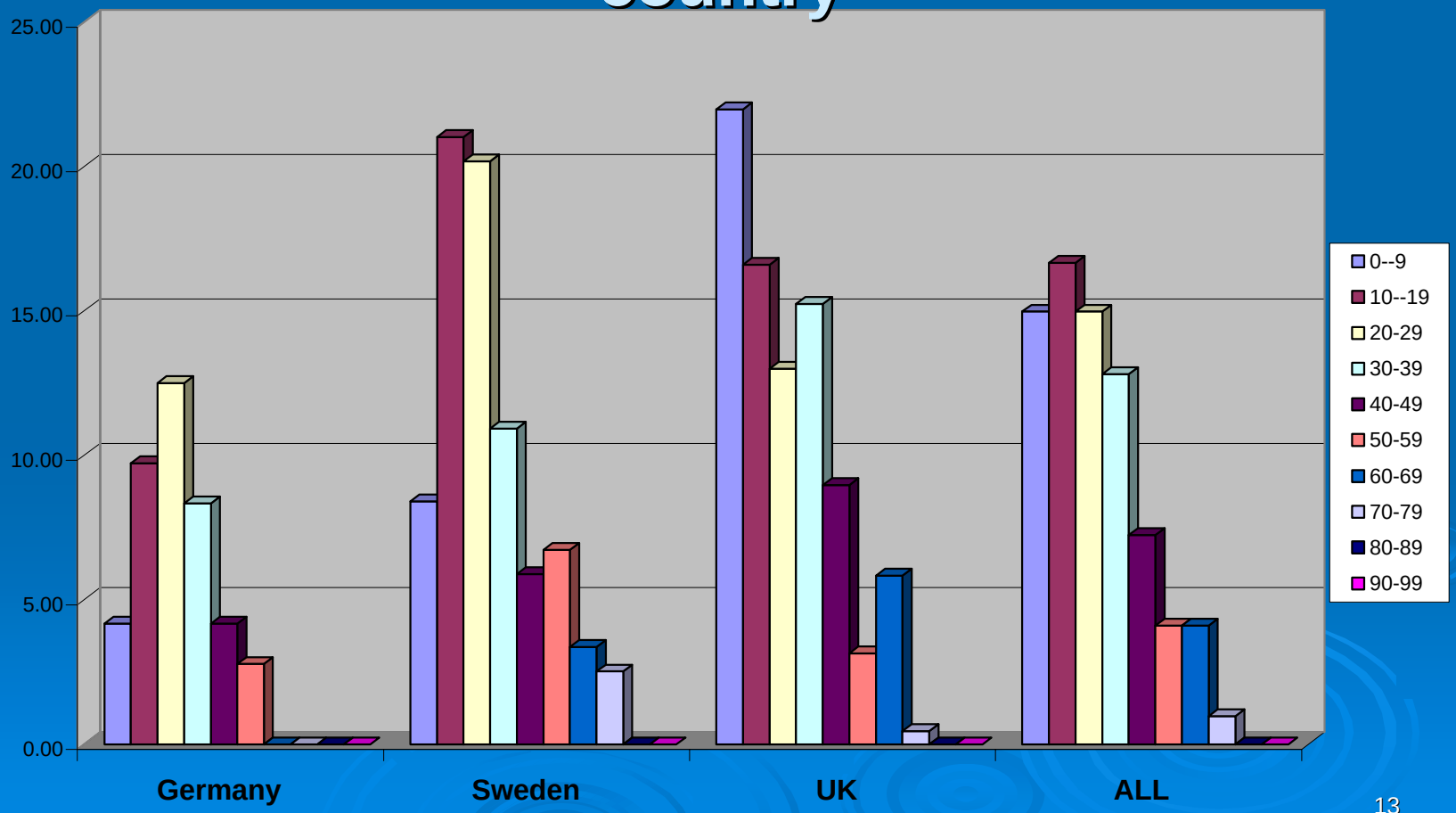
> 60% of diagnoses were NOT made in first three hospital visits, despite long histories & multiple depts.

Prevalence of Medical Sta
Patients Across Euro



Abnormal LFTs

Age of onset of symptoms in CVIDs as percentages in each country



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Criteria for diagnosis:

- **Agreed by ESID (*www.esid.org*)**
- **For clinical help & studies/registers etc**
- ***Definite* = 98% probability that same diagnosis in 20 years;*gene mutation & clinical features,* so not applicable to CVIDs**
- ***Probable* = 85% probability that same diagnosis in 20 years; *clinical & lab features as no known single gene defect* applicable to CVIDs**

Common Variable Immune Deficiency Disorders [CVIDs]

Probable: male/female patient with all of:

- **Aged > 4 years**
- **Serum IgG and IgA (probably not IgM) more than 2 SD below mean for age**
- **Poor response to all vaccines**
- **Causes of secondary antibody deficiencies excluded (eg lymphoma, medications)**

Presenting Infections

INFECTION	PERCENTAGE PATIENTS
Recurrent chest infections	67.5
Recurrent sinus infections	23.3
Gastrointestinal tract	10.8
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But infections are not everything….

Complicatons - Autoimmunity

Autoimmunity

- Arthropathy 6%
- IDDM 4.5%
- Hypothryoid 4.5%
- Pern. Anaemia 5%
- Vitiligo 4.5%
- *subtotal* *24.5%*

Cytopenias

- ITP 7%
- AHA 4.5%
- Neutropenia 3%
- *subtotal* *14.5%*

Complications:

Lymphoid infiltration

- Atrophic gastritis 6%
- Enteropathy 5%
- Granuloma 12%
- Idiopathic hepatomegaly 4%
- Lymphadenopathy 10%
- Splenomegaly 30%
- Lymphoid interstitial pneumonitis 10%

Others

- Iron deficiency
- Fat soluble vitamin deficiencies
- Gastric cancer
- NHL

- Bronchiectasis 30%

NONE 28%

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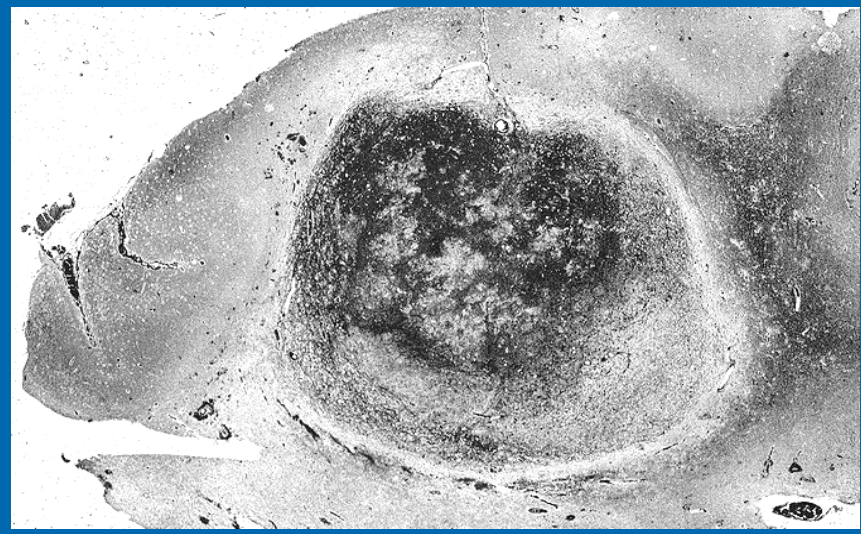
Granulomatous disease in CVID

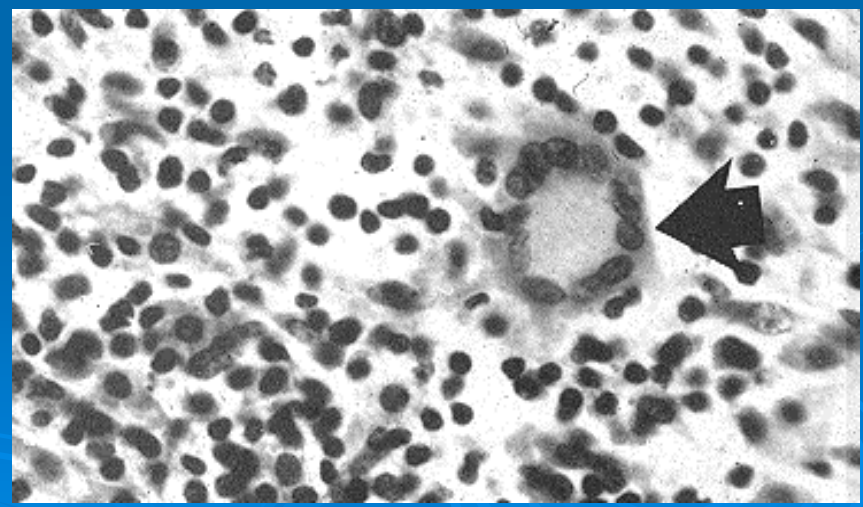
- 42% patients with lymphoproliferation
- of which 12% had granuloma
- Samples contained noncaseating granulomata
- Organ or tissue biopsy essential for confirmation & distinguish infection
- Respond to corticosteroids usually
- ? Infectious aetiology
- ? diagnostic delay contributed to severity

ESID CVIDs Registry 2006

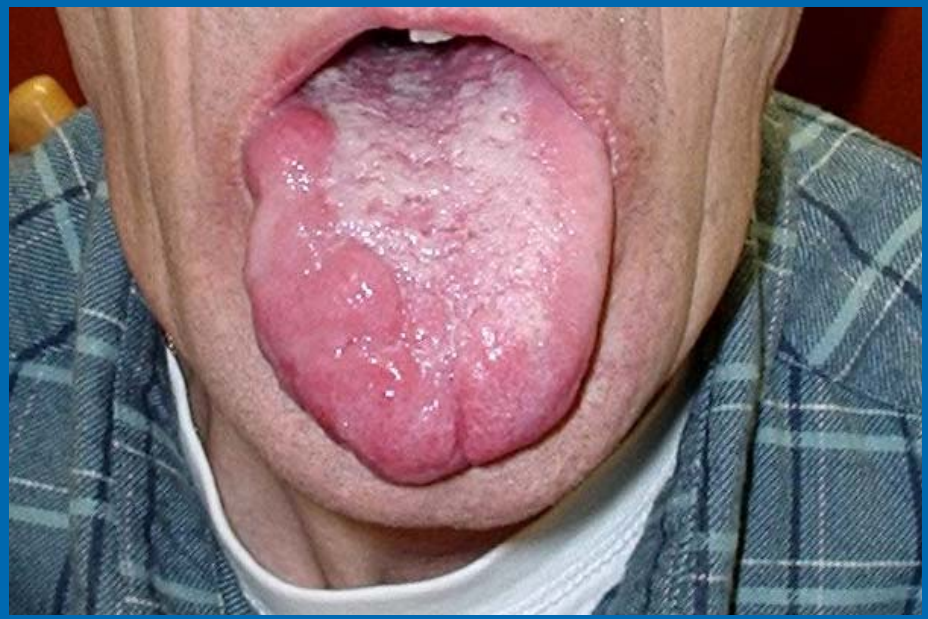
Cerebral granulomata

- Frontal lesion aged 10 yrs ? tumour
- 21 yrs symptoms raised pressure, temporal lesion - granuloma again at 40 yrs
- Panhypogamma IgG<1 g/l
- Few bacterial infections





Tongue & skin granulomata



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TIFF (Uncompressed) decompressor
are needed to see this picture.

Complications:

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Others

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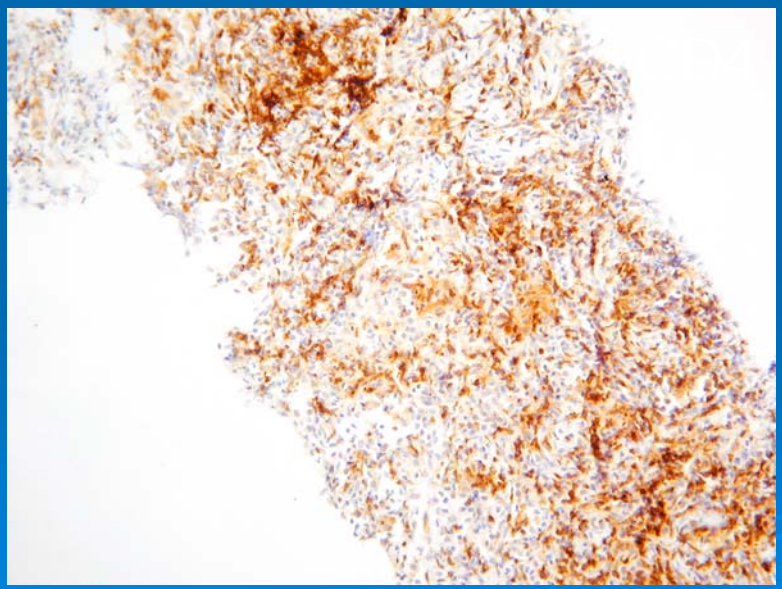
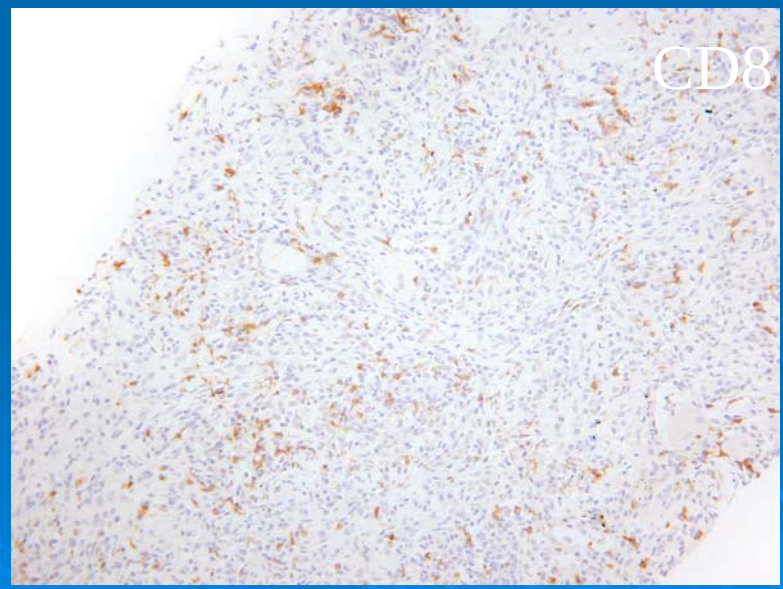
CVID lung syndrome – with SOB, fatigue & dry cough; CT ground glass areas

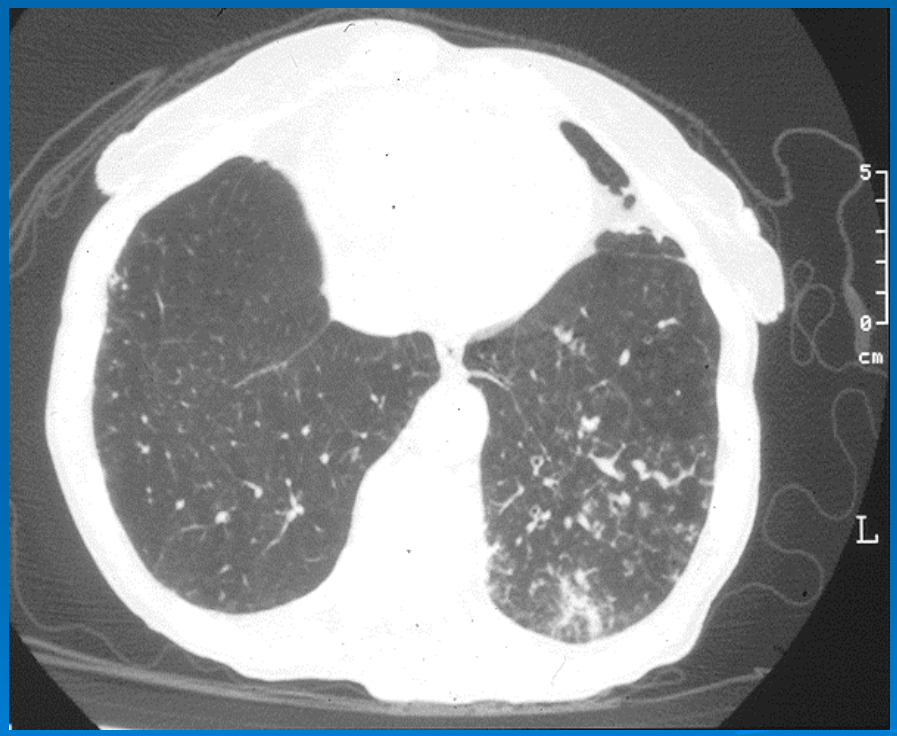
Needle core bx lung showing CD4 and CD8 proportions; few B cells (not shown) .No granuloma. **Diagnosis LIP**





Cyclosporin A + corticosteroids *Davies et al Thorax. 2000*

Bronchiectasis



- Silent progression of bronchiectasis in a few patients even on IVIg
- Trough IgG > 8 g/L
- ? related to:
  - diagnostic delay
  - dose of Ig
  - type of CVID

Complications:

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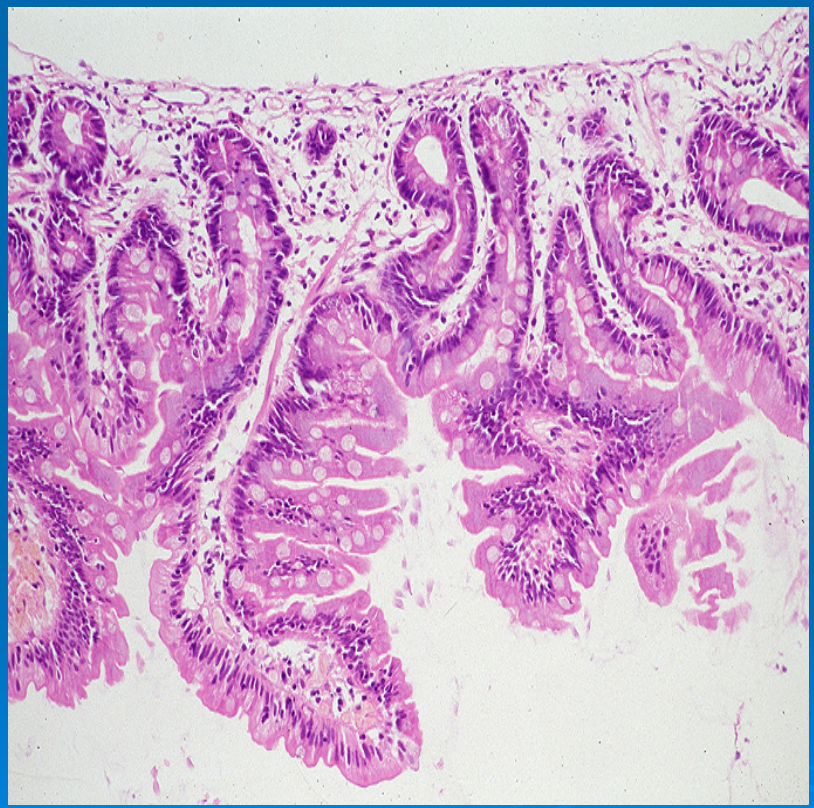
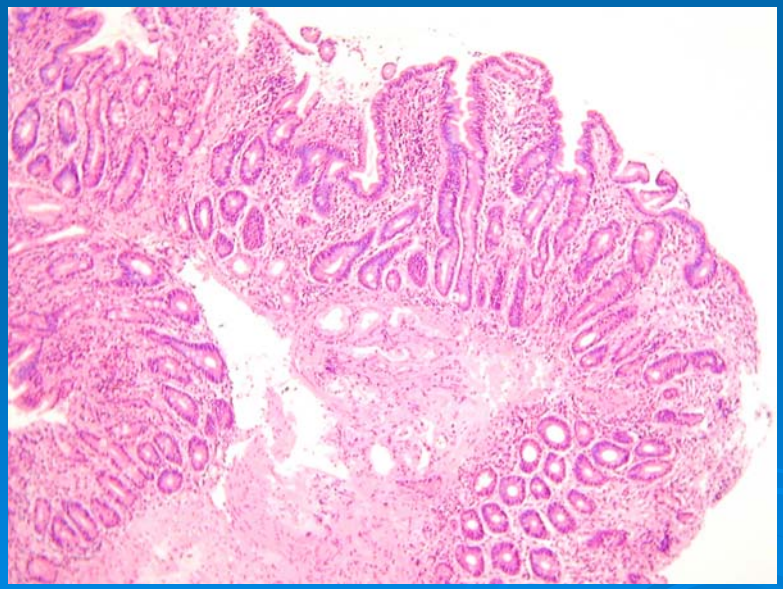
Enteropathy due to Giardia

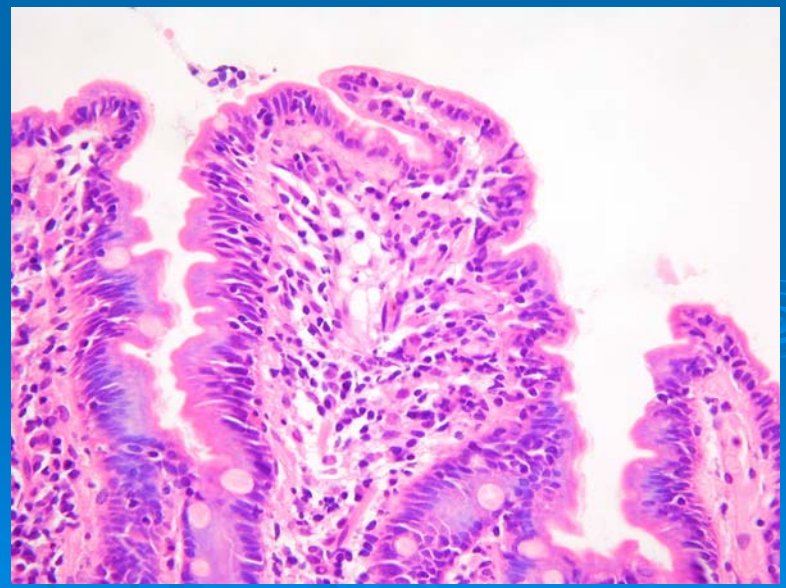


- Giardiasis missed repeatedly
- Not found on stool microscopy
- Resistant to Metronidazole
- “unexplained malabsorption
- Needed TPN

CVID Enteropathy syndrome:

- Duodenum with focal intraepithelial T lymphocytosis
- Responded to Budesonide
- Beware fat soluble vitamin deficiencies A,D and E





Case History -enteropathy

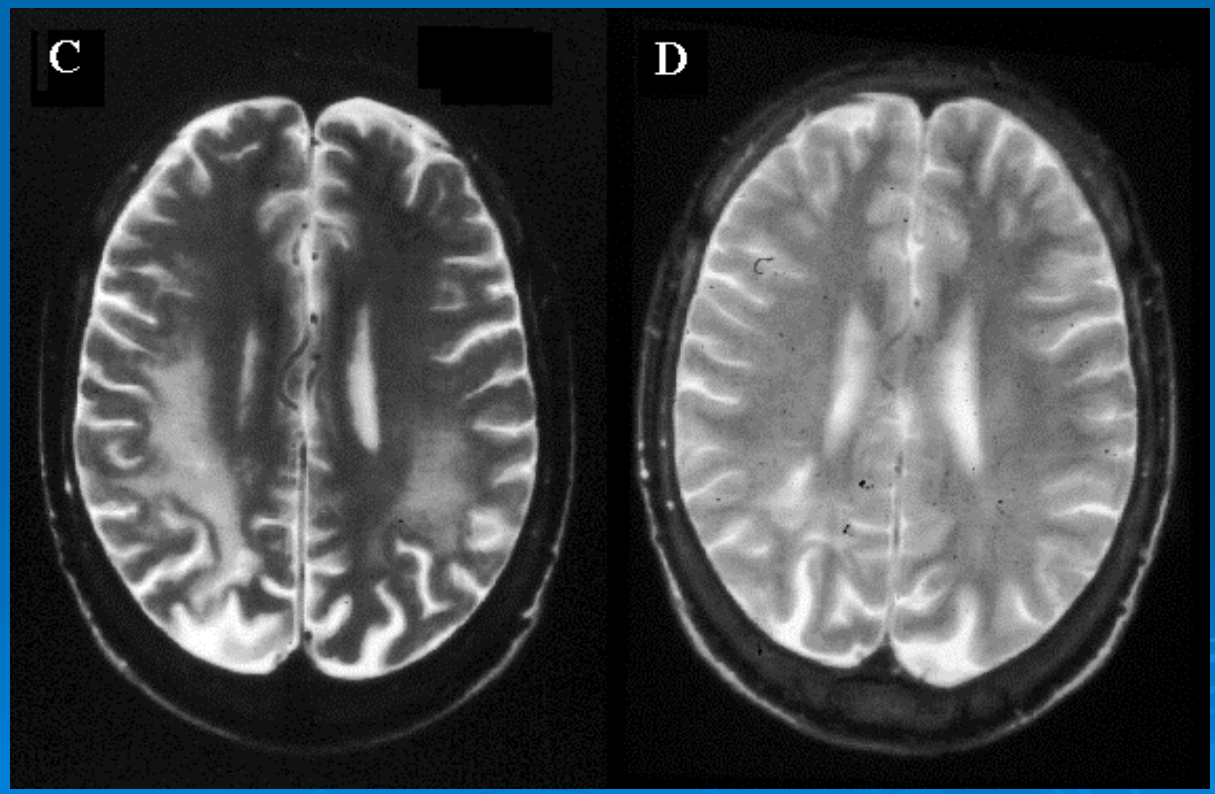
Previously
Night blindness - vitamin A deficiency on therapy
Retinitis pigmentosa

Now ataxia & tremors
low vitamin E = 2.75 mmol/L

- **CSF - normal**
- **MRI of the brain revealed extensive high signal change in the white matter**

Oral vitamin E (80mg/day) - asymptomatic+ MRI resolution

MRI diffuse high signal white matter changes in case pre-treatment (C) and improved after treatment (D).



Summary of clinical presentations in CVIDs

- **Childhood presentation** - not always FFT
- **Recurrent / severe infections** e.g. rec. otitis media or 2 episodes pneumonia - *not necessarily both*
- **Autoimmune disease** e.g. ITP, AHA, thyroid failure
- **Rarer lung, liver, GI features** should alert suspicion

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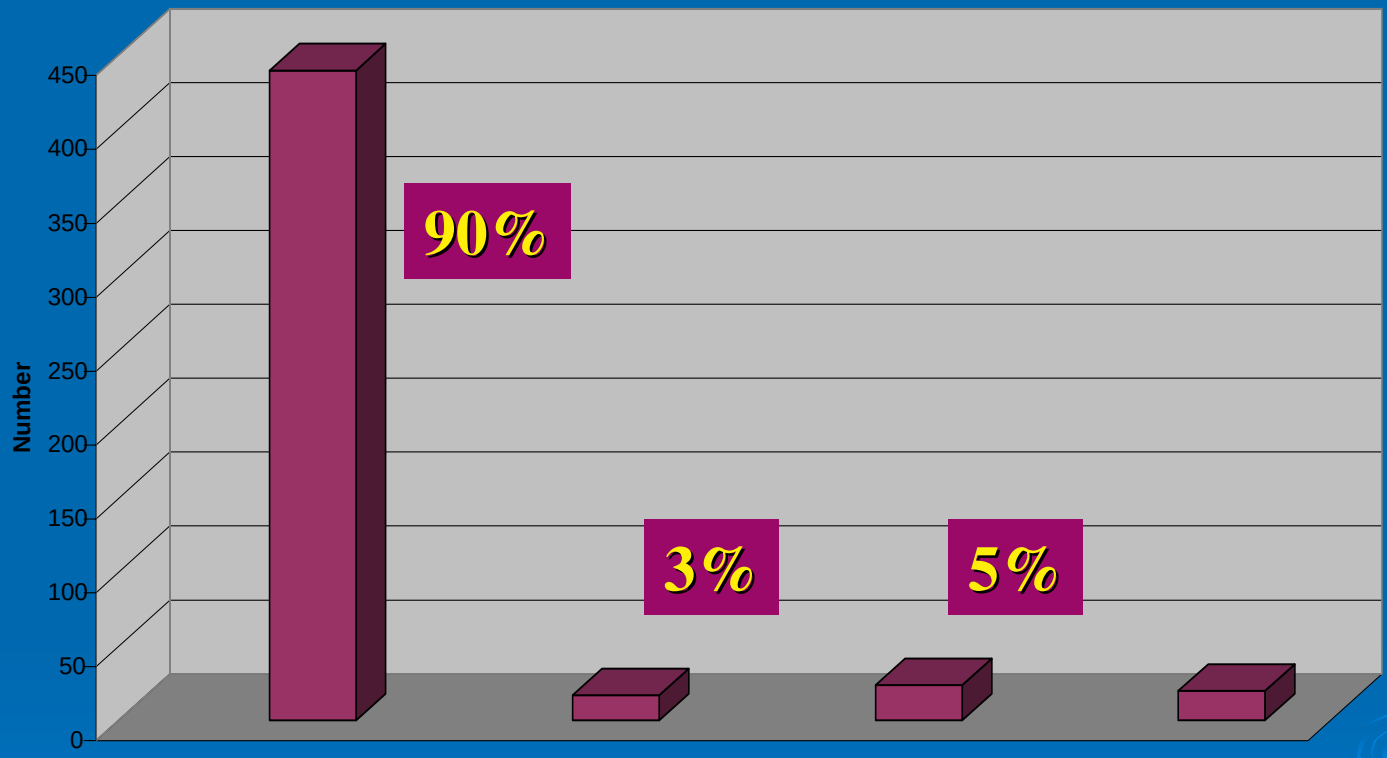
Positive family history: Unusual



European data

Not likely to be single genes involved

IUIS 2006

Disease	B cell numbers	Serum Ig	Associated Features	Inheritance	Genetic Defects/presumed pathogenesis
2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low numbers of B cells					
a) Common variable immunodeficiency disorders*	Normal or decreased	Decrease in IgG & IgA; IgM may be normal	May have autoimmune, lymphoproliferative and/or granulomatous disease	Variable	Unknown
b) ICOS deficiency	Normal or decreased	Decrease in IgG & IgA; IgM may be normal	Recurrent bacterial infections	AR	Mutation in *ICOS*
c) CD19 deficiency	Normal	Decrease in IgG & IgA; IgM may be normal	Recurrent bacterial infections	AR	Mutation in *CD19*
d) TACI deficiency	Normal	Decrease in IgG & IgA; IgM may be normal	May have autoimmune or lymphoproliferative disease	AD or AR	Mutation in *TACI*
e) BAFF receptor deficiency	Normal or decreased	Decrease in IgG & IgA; IgM normal	Recurrent bacterial infections	AR	Mutation in *BAFFR*

•This is a diagnosis of exclusion of other known primary antibody deficiencies. There are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogeneses.

New Molecular Defects in CVID

TACI deficiency (*Nat Genet* August 2005)

Ulrich Salzer et al

BAFF receptor deficiency (2006)

Klaus Warnatz et al

CD19 deficiency (*NEJM*, 2006)

Jose-Luis Franco et al

ICOS deficiency (*Nat Immunol*, 2003)

Grimbacher et al.

? Polymorphisms, disease causing, disease modifying ?

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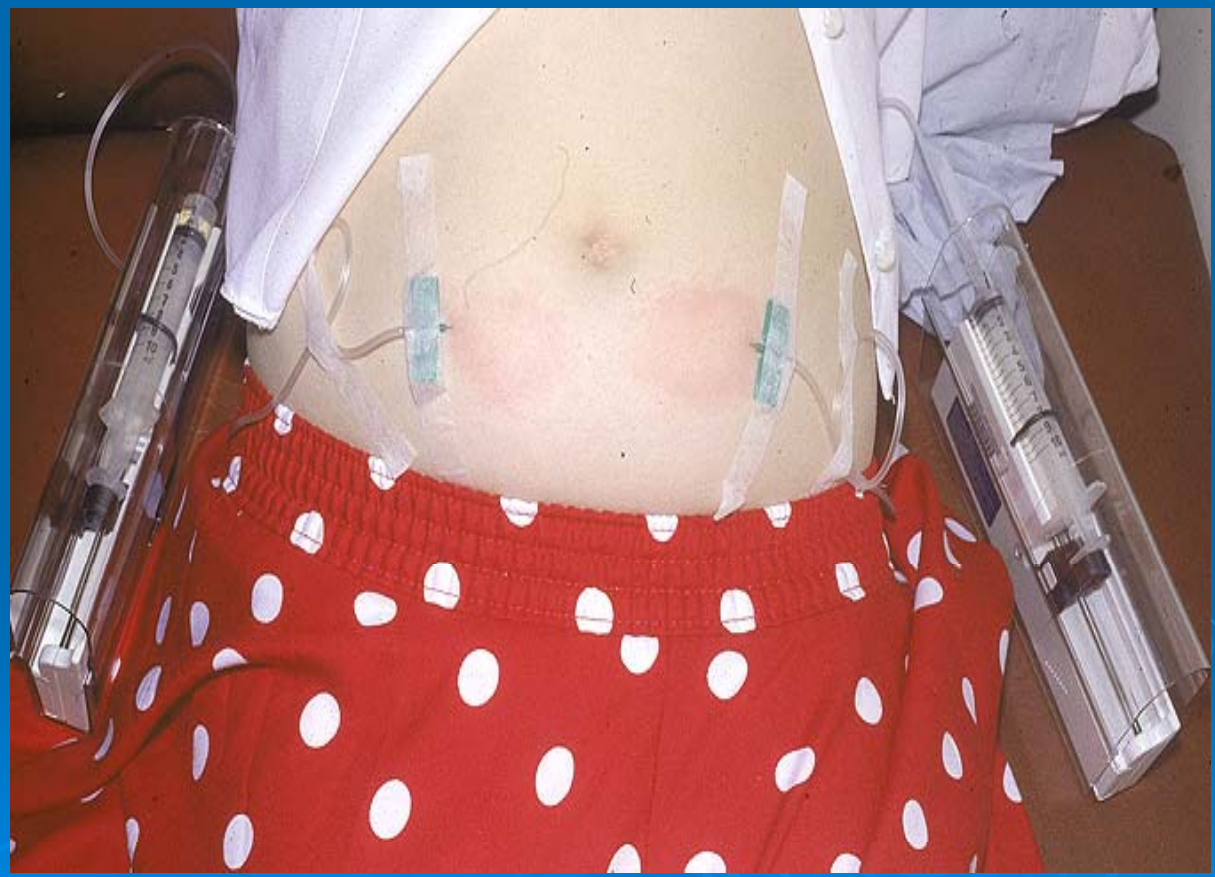
Subcutaneous Ig therapy

- Easy to use
- Safe
- Efficacious as IVIg in infection prevention

J-Clin-Immunol. 2000

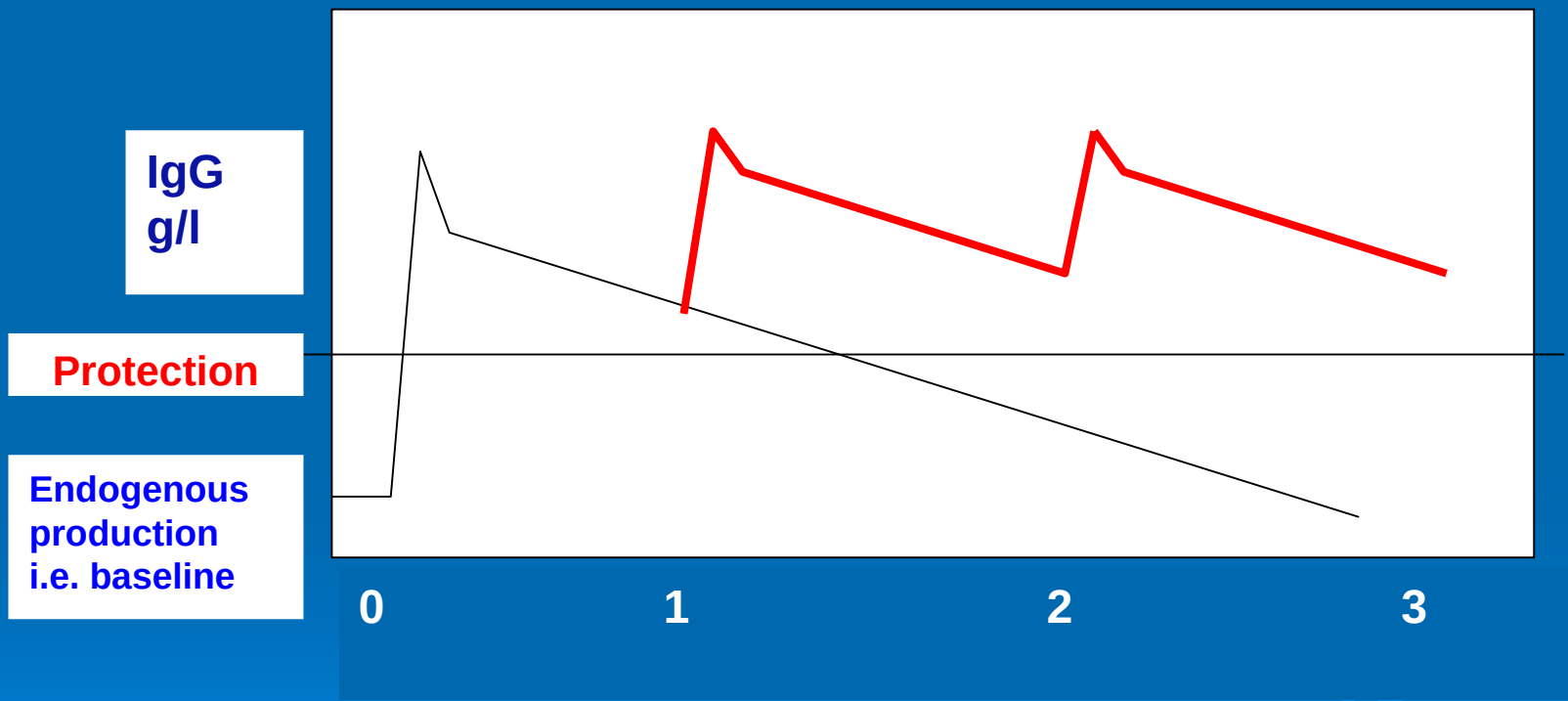


Efficacy of SCIg

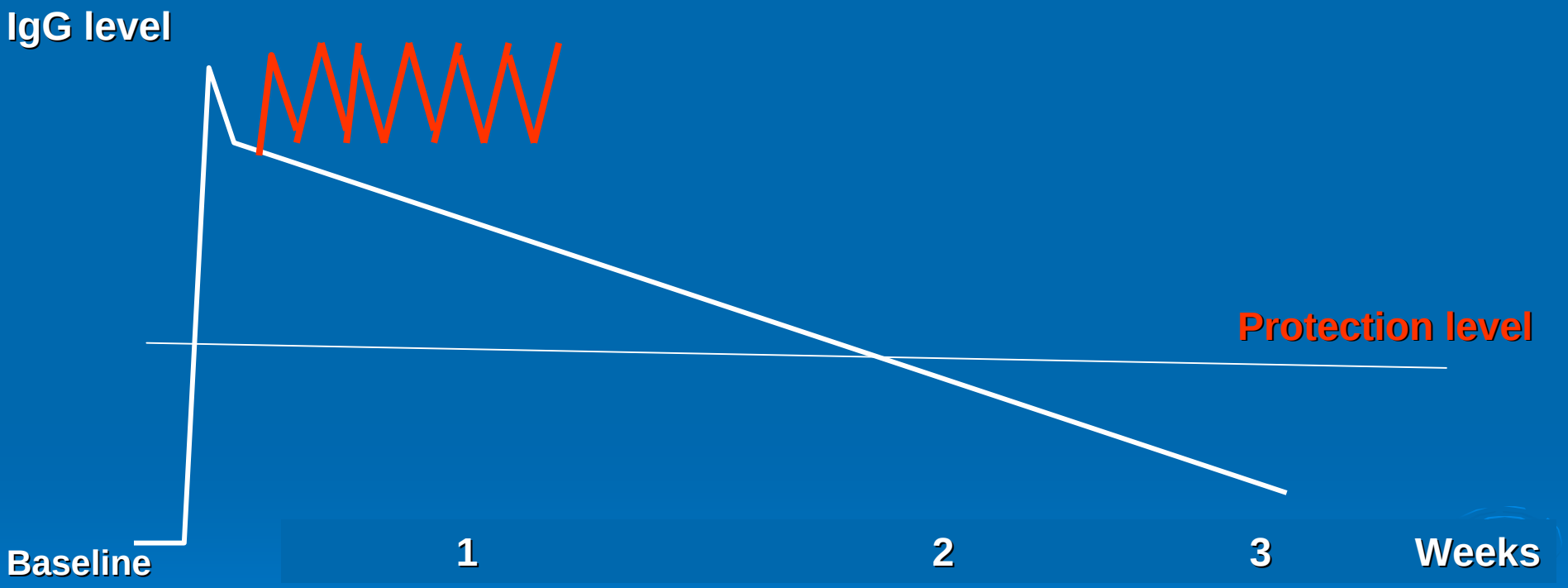
- Cross over trial in UK & Sweden
- 40 patients, 12 months of each
- 4 withdrawals in each arm
- Analysed for 9 months of each arm i.e. wash out
- Patient preference equal – most either
- Adverse reactions - mild & usually local

Chapel et al J-Clin-Immunol. 2000

IgG levels with shorter IVIg intervals



IgG levels with SCIg every 1-2 days

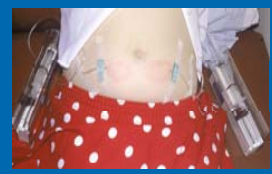


Route of Immunoglobulin therapy

IVIg for dose

Infants

SCIg in short bursts



Children

IVIg at longer intervals

Teenagers

SCIg for convenience

Adults

IVIg in clinic

Older folk

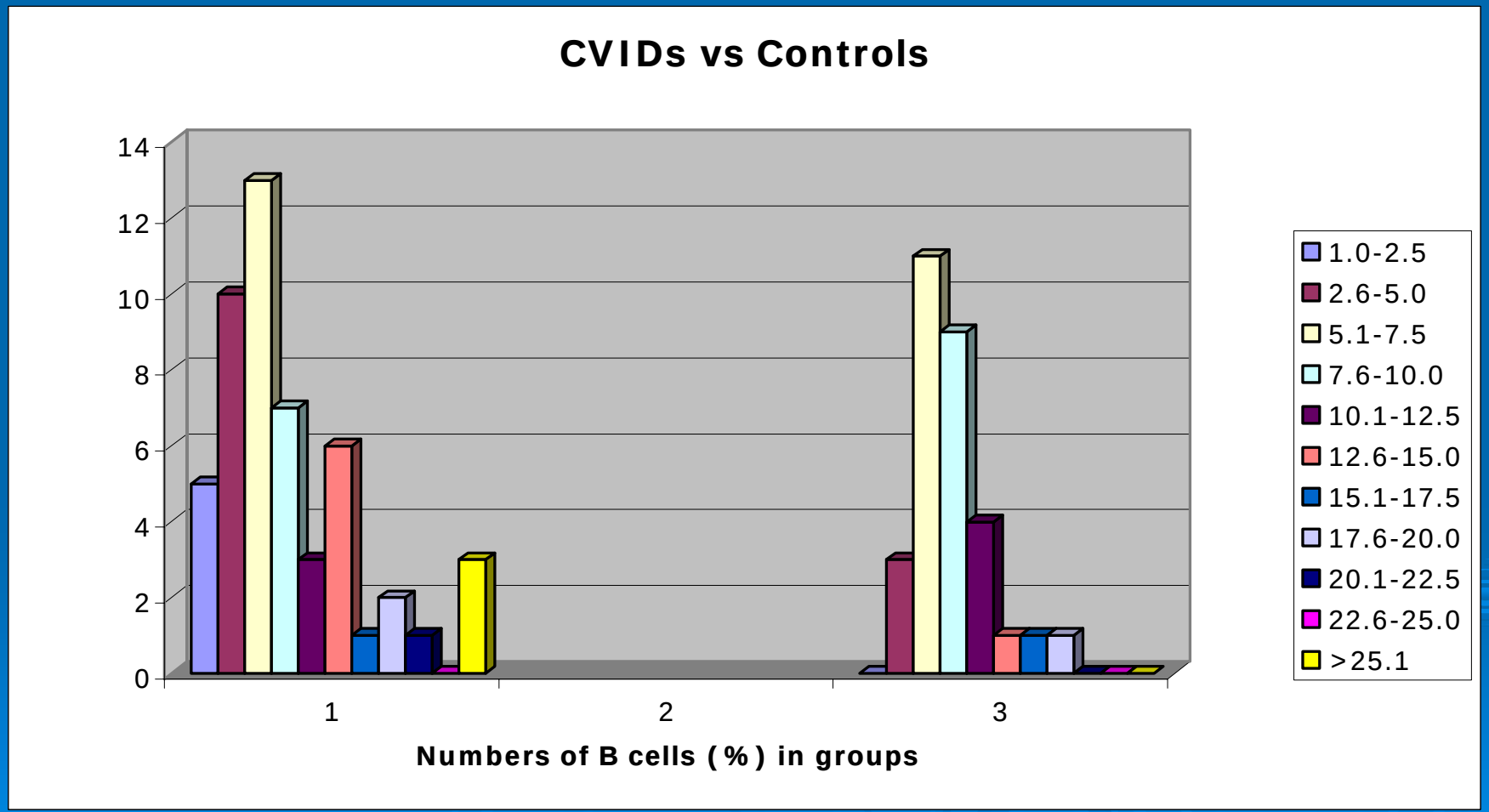
QuickTime™ and a Photo - JPEG decompressor are needed to see this picture.

My thanks to:

- Funding in Oxford from the 6th EU Framework EUROPOLICY, PiA Centre of Excellence Award PiA
- My colleagues in Immunology - Drs Misbah, Lopez-Grandados and Lortan, Sisters Janet Burton and Nicky Brennan
- **The Francouer foundation -Quebec**

ZLB-Behring

Numbers of B cells (%) : Variable



Immunoglobulin levels: Variable

Immunoglobulin isotypes at presentation in 1,294 "CVID" patients

Pan-European registry 1992 -2004