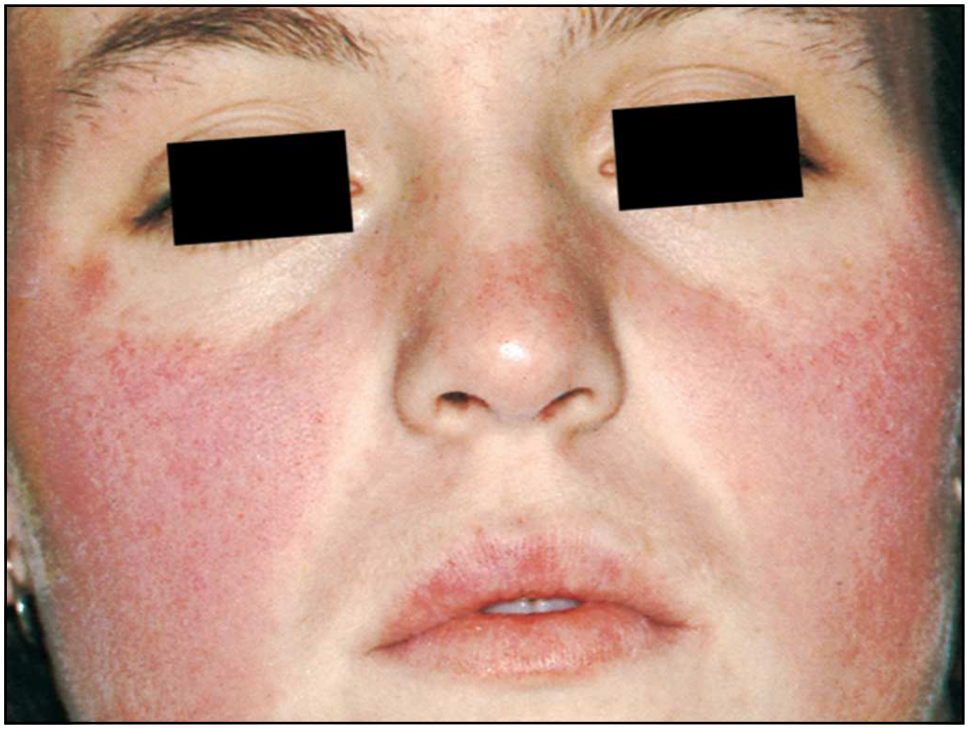
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)



Other Types of "Lupus"

Discoid Lupus Erythematosus

Lupus Pernio --- Sarcoidosis

Lupus Vulgaris --- Tuberculosis of the face

Manifestations of SLE

- **Fever**
- **Rashes**
- **Arthritis**
- **Fatigue**
- **Weight loss**
- **Lung**
  - **Pleurisy, pneumonia**
- **Heart**
  - **Pericarditis, heart failure**

Kidneys

- **Nephritis**

- **Nervous system**
  - **Stroke, cerebritis**
  - **Seizures**
- **Blood count**
  - **Anemia**
  - **Thrombocytopenia**
  - **Abnormal clotting or bleeding**

American College of Rheumatology Criteria

- 1. Malar rash
- 2. Discoid rash
- 3. Photosensitivity
- 4. Oral/nasal ulcers
- 5. Nonerosive arthritis
- 6. Pleurisy/pericarditis
- 7. Renal abnormalities
- 8. Seizures, psychosis
- 9. Blood count abnormalities
- 10. Antinuclear antibody
- 11. Other abnormal antibodies (e.g., anti-DNA antibodies)

Manifestations of SLE

- Fever
- Rashes
- Arthritis
- Fatigue
- Weight loss
- Lung
  - Pleurisy, pneumonia
- Heart
  - Pericarditis, heart failure

Kidneys
- Nephritis

- Nervous system
  - Stroke, cerebritis
  - Seizures
- Blood count
  - Anemia
  - Thrombocytopenia
  - Abnormal clotting or bleeding

Anti-Cardiolipin Syndrome (Anti-phospholipid Syndrome, Lupus Anticoagulant)

- Occasional feature of Lupus, or occurs alone
- Frequent miscarriages
- Tendency to form blood clots
  - Stroke
  - Blood clots in legs or lungs

- **INCIDENCE (FREQUENCY) –**
  - **Number of new cases in a given population over a certain period of time, usually a year**
- **PREVALENCE –**
  - **Number of active cases in a given population at a certain point in time (cross-section)**

Annual Incidence per 100,000

- US –1.0
- US—2.0
- US – 7.6
- US – 4.6
- US – 1.8
- Curacao – 4.6
- US – 2.4
- US – 5.6
- Brazil – 8.7
- Sweden – 4.8
- UK – 6.5
- Sweden – 4.8
- Denmark – 2.5
- UK – 2.5
- Finland – 0.37
- Norway – 2.6

Gender – Age of Onset
F:M

Children = 1:1

Teen/Middle Age = **9:1**

65 & Older = 1:1

NATURE (GENETICS)

–Overall likelihood = **0.04 - 0.1?**

–Sister = **2-5%**

–Fraternal twin = **2-5%**

–Identical twin = **24-58%**

NURTURE (ENVIRONMENTAL)

Drugs
- Hydralazine

Foods
- Flaxseed?

Viruses
- Epstein-Barr Virus

Toxins
- Sunlight

Mechanisms – How does SLE develop?

- Autoimmunity – Failure of the immune system to recognize “self”.
- Genetic background
- Triggered by ?

SLE -- Diagnosis

- Symptoms
  - Fatigue, joint pain, fever, etc.
- Physical findings
  - Rashes, swollen joints, etc.
- Laboratory findings
  - Antinuclear Antibody (ANA), Abnormal urinalysis, etc.

Antinuclear Antibody (ANA)

- We've all got some
- Screening test – Very sensitive
- Most individuals with a positive ANA test do not have SLE
- May lead to over-diagnosis

Other antibodies – Less sensitive but more specific for SLE

Anti-DNA Antibodies***

Anti-Smith (Sm) Antibodies***

SSA, SSB, RNP antibodies

MARKERS OF DISEASE ACTIVITY

- Depressed complement levels
- Elevated anti-DNA levels
- Elevated erythrocyte sedimentation rate
- Elevated C-Reactive Protein
- Urine abnormalities
  - Protein
  - Blood cell casts

Complement

- A system of proteins normally involved in healthy immune reactions, e.g., killing bacteria
- Over-activated in Lupus, results in abnormal immune reactions, e.g., destroying red blood cells or damaging the kidneys.
- Levels are below normal in active Lupus, complement is used up, or “consumed”.

Anti-DNA Antibodies

- Abnormal antibodies directed against a person's own body tissues.
- Anti-DNA antibody levels frequently parallel Lupus disease activity, particularly kidney inflammation.
- Rising levels can help to predict a flare.
- Anti-DNA levels can be used to monitor response to treatment

Treatment

- Aspirin, Non-steroidal anti-inflammatory drugs (NSAID's)
- Cortisone
  - Prednisone
  - Medrol
  - Etc.

Anti-Malarial Drugs

- Chloroquine
- **HYDROXYCHLOROQUINE (PLAQUENIL)**
- Quinacrine

Treatment

- Immunosuppressants
  - Cyclophosphamide (Cytoxan)
  - Azathioprine (Imuran)
  - Mycophenylate mofetile (CellCept)
- Biologic agents
  - Belimumab
  - Rituximab

Treatment - Biologic agents

Belimumab (Benlysta)

Rituximab (Rituxin)

Morbidity – Early Phase

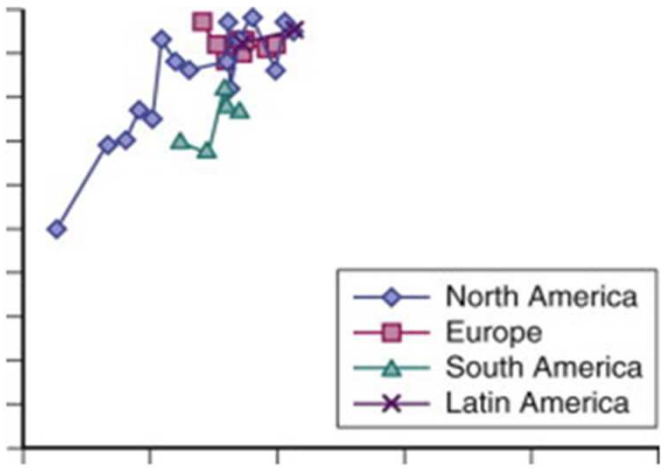
- Severe Lupus flare
- Renal failure
- Brain disease (Cerebritis, stroke)
- Vasculitis, gangrene
- Myocarditis
- Pneumonitis
- Bleeding/Thrombosis
- Infection

Morbidity – Late Phase

"Disease Burden" "Treatment Burden"

- "Metabolic Syndrome"
  - Diabetes
  - Hyperlipidemia
  - Arteriosclerosis, myocardial infarction, stroke
- Fracture complications
- Infections
- Malignancy

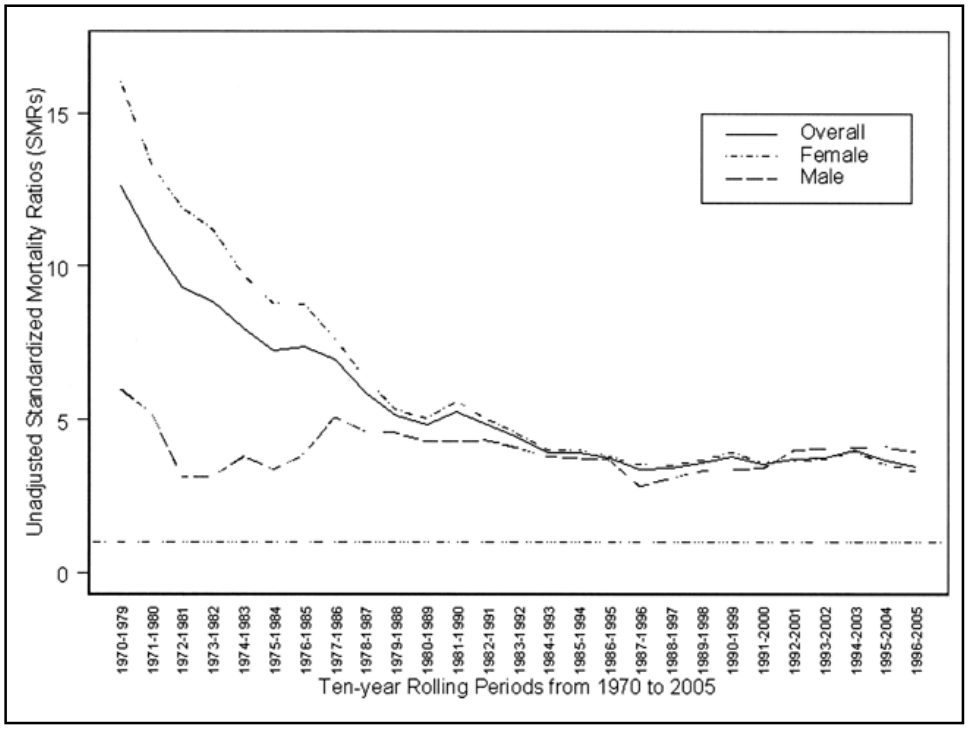
Five Year Survival Rates 1950-2011



Changing Patterns of Mortality

Journal of Rheumatology 2008

- 1241 Subjects
- Standard Mortality Ratio (SMR)
- Cohorts
  - 1970-1978
  - 1979-1987
  - 1988-1996
  - 1997-2005



Why improved outlook?

- Increased awareness
- More sensitive screening – earlier diagnosis
- Improved management of first phase
  - Immunosuppression
  - Improved treatments for complications (e.g., infections)
- Improved management of second phase
  - Blood pressure control, statins, etc.

Mortality in SLE

Bertansky S et al 2006

- 9,547 subjects
- Overall Standard Mortality Rate 2.4
- "Relative High Risk"
- High Mortality for
  - Circulatory disease, infections, renal disease, non-Hodgkin's Lymphoma, lung cancer
- Highest Risk
  - Female sex, younger age onset, SLE duration <1 year, African-American

Medicine (2003)

- 1000 subjects followed for 10 years
- 10 year survival
  - Overall 92%
  - Renal 88%
  - Non-renal 94%
- Causes of death
  - First 5 years -- Active Lupus, Infection 29% each
  - Second 5 years -- Thrombosis, ASCVD 26%

Kasitanon et al.
Medicine (2006)

- 1378 subjects
- Medial follow-up 6.1 years. 8.6% died
- Probability of survival
  - 5 years – 95%
  - 10 years – 91%
  - 15 years – 85%
  - 20 years - 78%
- Worse prognosis
  - Onset >50 years old
  - M>F
  - Annual income <$25,00

Prognostic Factors

Cervera r, et al. (2003); Seleznick MS, et al. (1991), Kasitanon N, et al. (2006)

- Renal Disease
- Hypertension
- Male sex
- Young age
- Poor SE status
- Cerebritis
- Cerebrovascular disease
- AA (SE?)
- Antiphospholipid antibodies
- Hemolytic anemia
- Thrombocytopenia
- Pulmonary hypertension
- Pulmonary hemorrhage

Lupus Nephritis

- Class I -- Normal or minimal change
- Class II -- Mesangial nephritis
- **Class III -- Focal membranoproliferative**
- **Class IV -- Diffuse membranoproliferative**
- **Class V -- Membranous glomerulonephritis**
- **Class VI -- End-stage**

PROGNOSIS OF VARYING SEVERITY

Worse	Better
• 18 year old presents with glomerulonephritis • 36 year old with pulmonary hemorrhage • 28 year old with organic brain syndrome, early dementia • 40 year old presents with stroke	• 40 year old presents with rash and arthritis • 38 year old with chronic stable thrombocytopenia • 32 year old with extreme fatigue and muscle aches • 58 year old with pleurisy

MALIGNANCY

- Non-Hodgkins Lymphoma
- Hodgkins Lymphoma
- Lung Cancer
- Breast Cancer
- Squamous cell skin cancer
- Cervical cancer
- Vulvar/Vaginal cancer

Non-Hodgkins Lymphoma

Annals of Rheumatic (Diseases 2005)

- 42 cases over 76,948 patient years
- Mean age at diagnosis 57 years
- Females 86%
- Diffuse Large B=cell type, i.e., aggressive
- 22/42 died within 1.2 years

Non-Hodgkins Lymphoma

Archives of Internal Medicine (2005

- Standardized Incident Rate (SIR) 7.4
- Considered “moderate”

Non-Hodgkins Lymphoma

Annals of Rheumatic Diseases (2007)

- Swedish study
- 16 subjects identified over 30 year period
- Conclusion:
  - Chemotherapy (cyclophosphamide, azathioprine) no increased risk
  - Hematological, pulmonary or sicca features higher risk

Breast Cancer

Rheumatology (2004)

- 871 subjects
- 15 breast cancers vs. 7.2 predicted (SIR 2.1)
- No relation to family history or hormone use

Skin Cancer

Lupus (2003)

- Icelandic SLE Registry
- 238 subjects 1957-2001 (44 years)
- 39 malignancies in 36 subjects (16%)
- Odds Ratio (OR)
  - Squamous cell cancer **6.43** (p=0.012) – Significant
  - Lymphoma **5.48** (p=0.052) – "Not significant"
  - Uterine cancer **2.46**
  - Ovarian cancer **2.0**
  - Lung cancer **1.72**
  - Breast cancer **1.6**