SARCOIDOSIS

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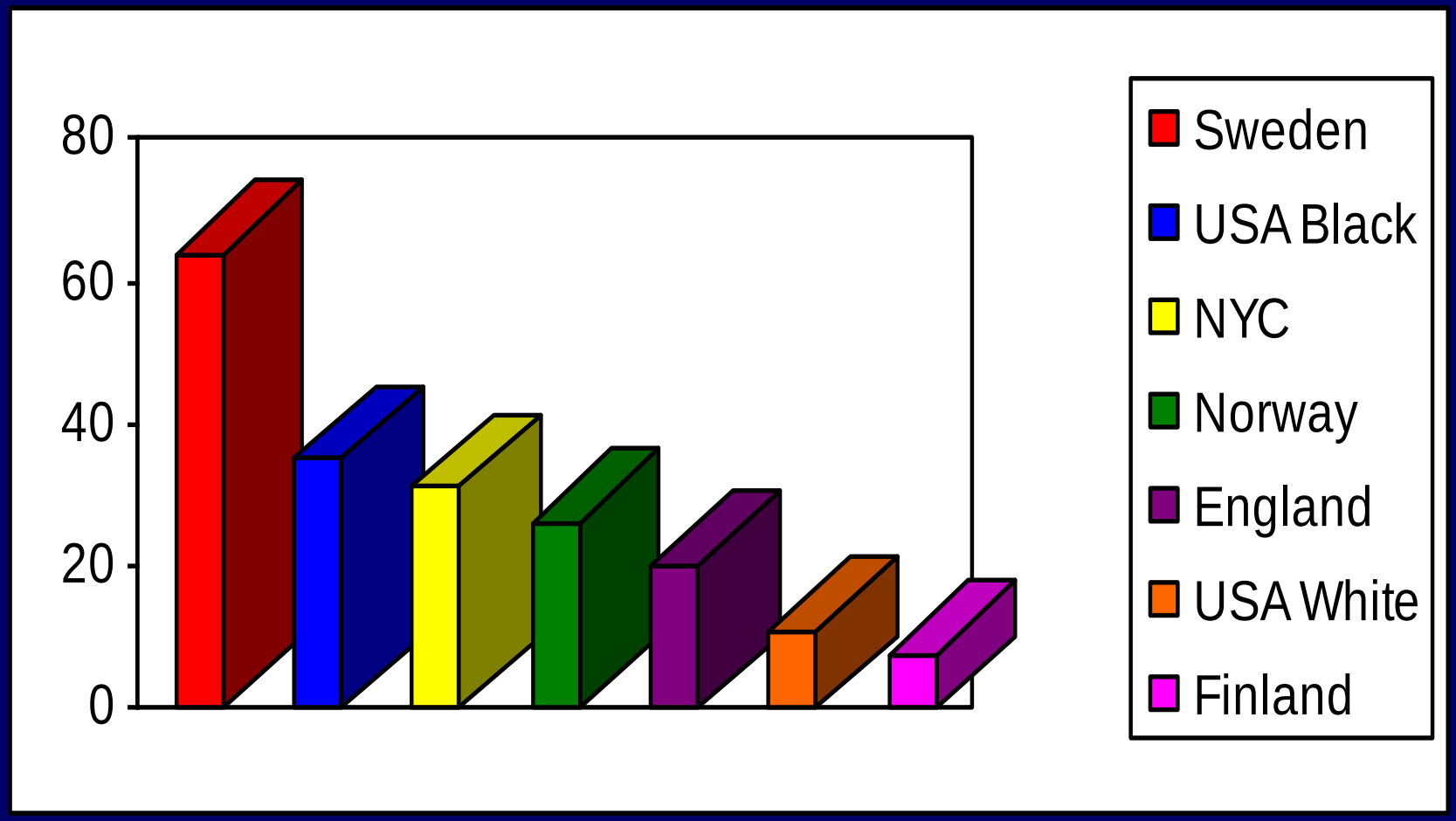
Definition

- Sarcoidosis is a granulmatous disease with multi-system organ involvement which is potentially reflective of a syndrome with different etiologies leading to similar histologic findings.
- Diagnosis is based upon:
  - **A compatible clinical presentation of at least two organ involvements**
  - **Supportive histologic evidence of non caseating granulomas**
  - **Reasonable exclusion of other granulmatous diseases**

Epidemiology

- World Wide Distribution
- All Ages and Sexes
- All Races
- Usually Below The Age of 40 yrs
- Second Peak – 50 yrs



Sweden 64 / 100,000
USA Black 35 / 100,000
NYC 31 / 100,000
Norway 26 / 100,000
England 20 / 100,000
USA White 11 / 100,000
Finland 7.5 / 100,000
Spain < .04 / 100,000

Incidence

- South East Asia
- Highest Incidence in Japan

Jindal, et al "Sarcoidosis in Developing Countries" Current Opinion Pulmonary Medicine, 2000

What About Incidence

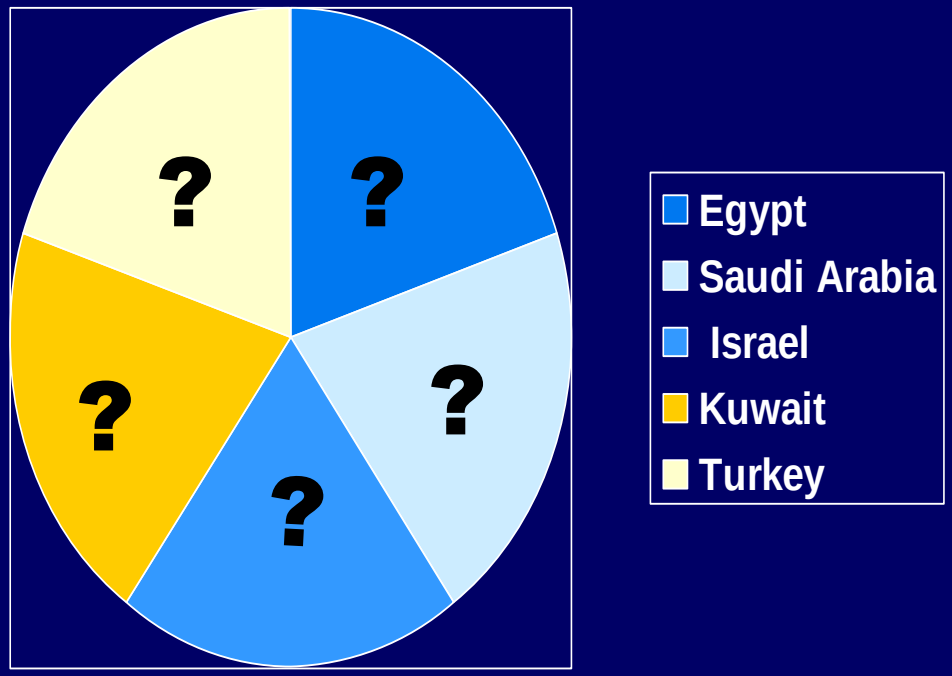
Egypt – 15,223 in 76.11 million

Saudi Arabia – 5,159 in 25.7 million

Israel -1,239 in 6.19 million

Kuwait – 451 in 2.25 million

Turkey – 13,778 in 68.8 million



Etiology – Controversial Controversy !!!

- Still Unknown – Genetic predisposition to environmental agent

  Epidemiological Study – suggests environmental agent

  ↓

  Inflammatory response in Sarcoidosis
- Infection - Virus, Herpes, Epstein Barr, CMV Coxackie, Retrovirus
- Propiniobacter Acne
- Mycobacterium - TBC VS Atypical Mycobacterial Disease
- Inorganic Dust – Aluminum, Zircium, Zinc, Beryllium
- Organic – Pine Tree - Pollen

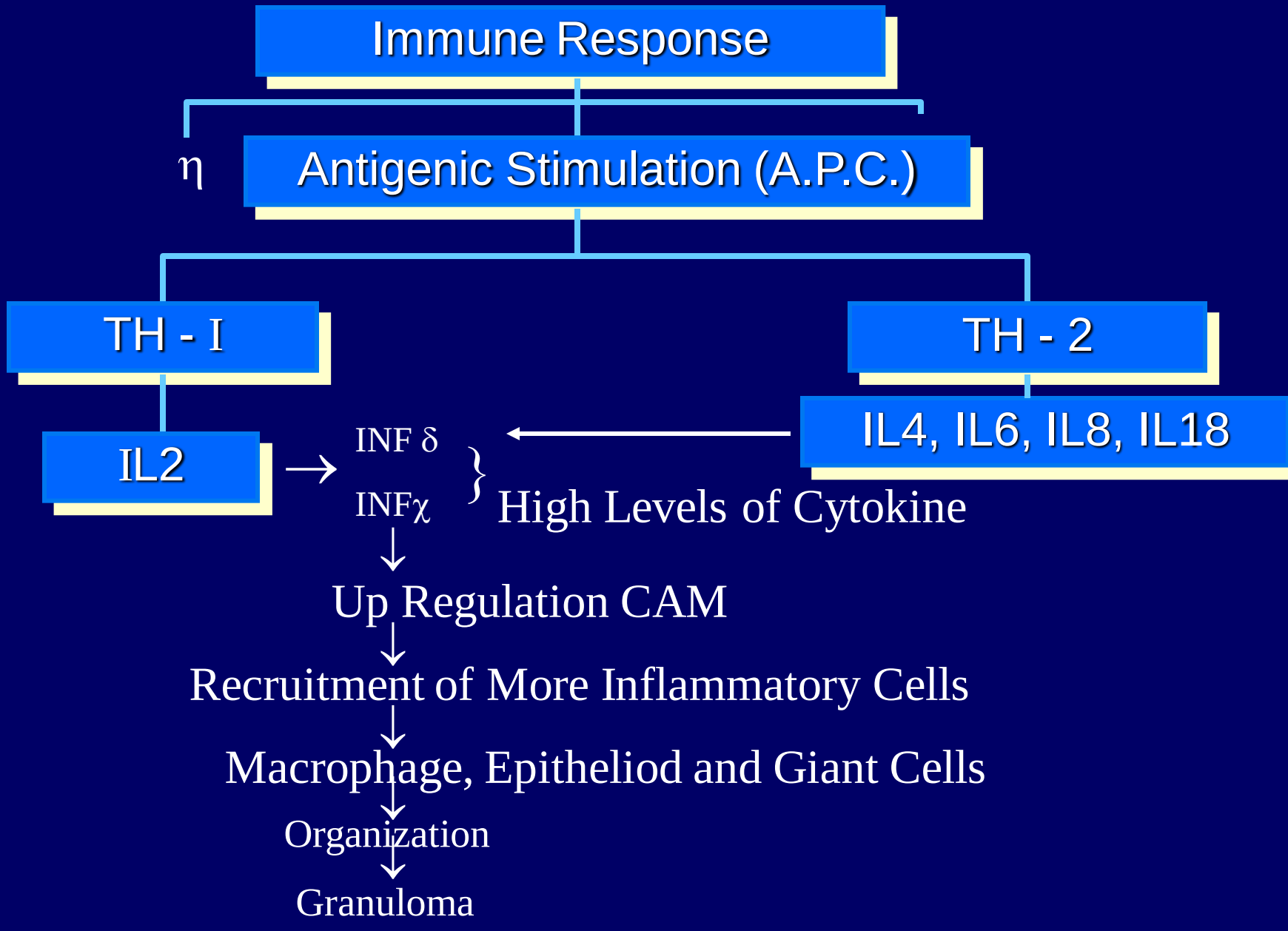
Genetic Predisposition

- Class I HLA – AI and B8
- Class II HLA – D12-3

Pathogenesis

- Basically it is an intense immune response to an antigen and does not occur as a result of anergy or impaired immune response

A.J.M.S. March 1995, Hunninghake



Clinical Presentation with Organ Involvement

- Lungs – Greater than 90%
- Symptoms
  - Maybe None
  - Abnormal Chest X-Ray
  - Dyspnea, nonproductive cough
  - Wheezing
  - Chest Pain
  - Haemoptysis

- SURT – Rare
  - Hoarseness of Voice
- Lymphatic System 30-35%
  - Cervical, axillary, epitrochler, mediastinal, retroperitenal
  - Character – Discrete, movable, non-tender, never ulcerative

** Mediastinal node – eggshell calcification

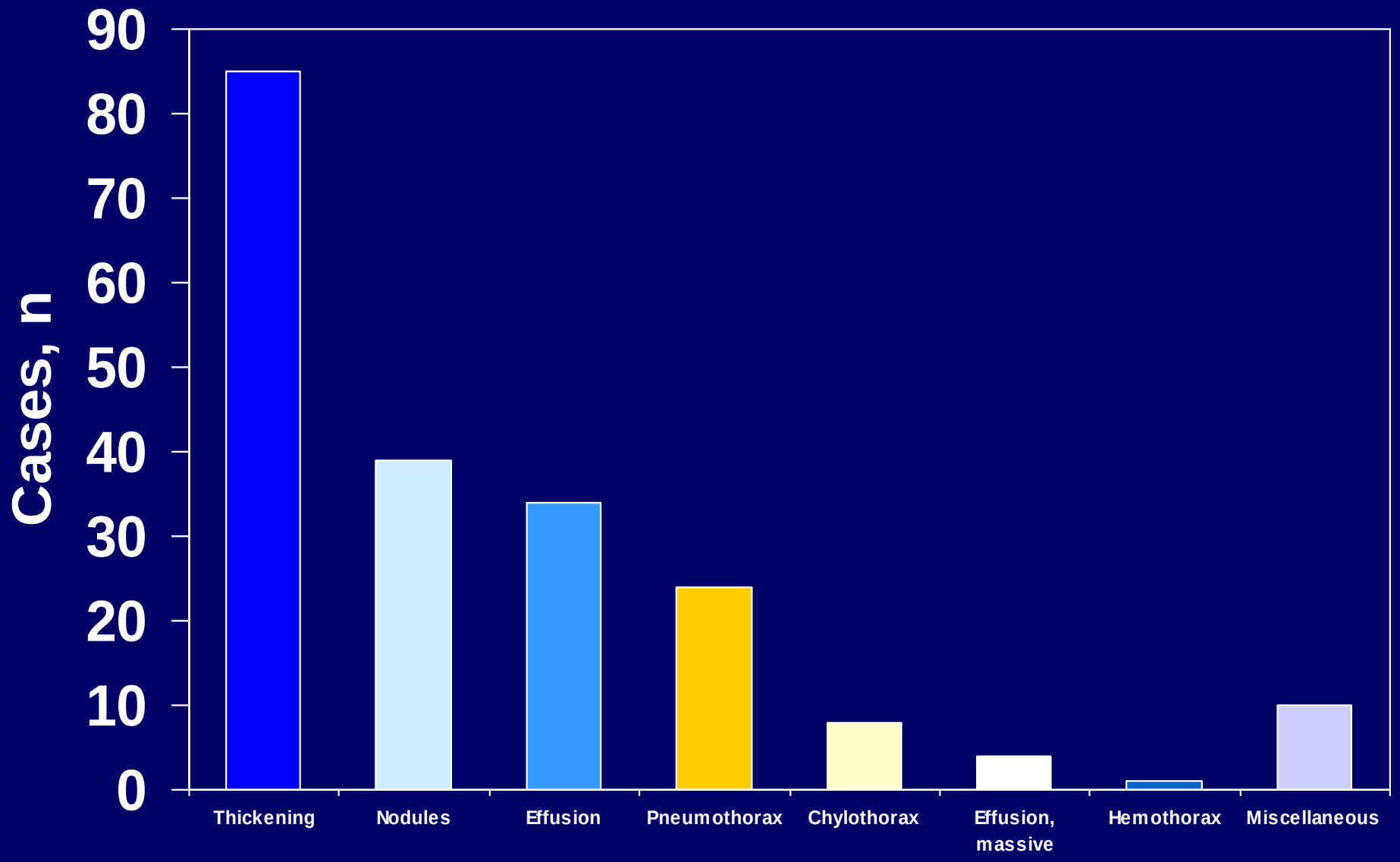
Lynch, et al “Pulmonary Sarcoidosis” 1997 Clin Chest Med
Baughman, “Clinics in Chest Medicine” 2004

Pleural Involvement In Sarcoidosis

- Incidence 3-7 % $\rightarrow$ 20% ??

Soskel, et al "Current Opinion in Pulmonary Disease" 2000

Pleural Types of Sarcoidosis



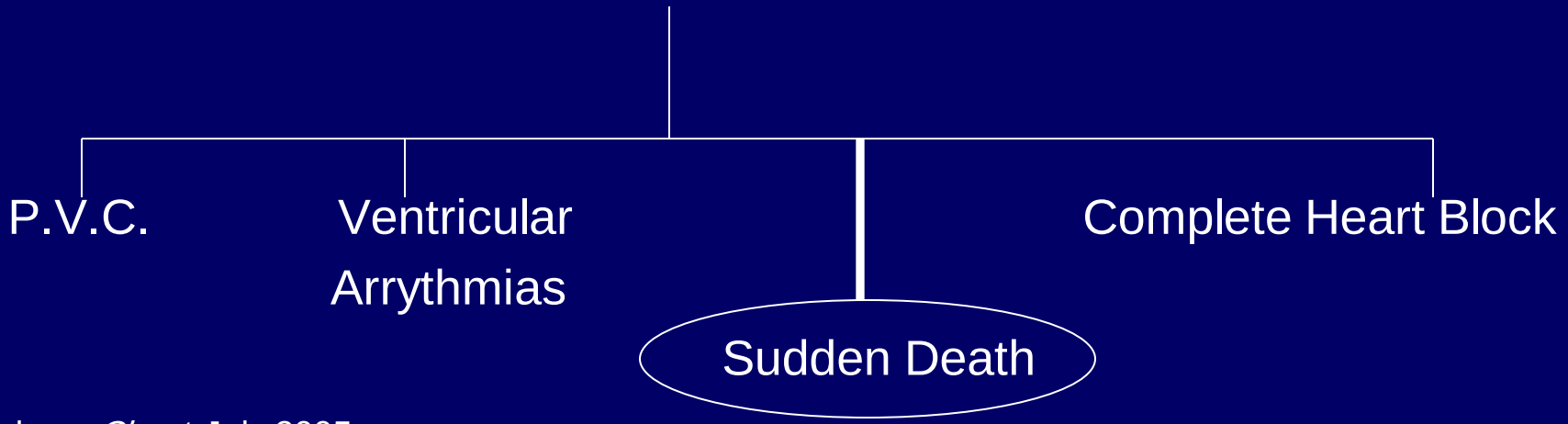
Cardiac Involvement

- **Incidence – overall – 5%**
- **Autopsy Evidence – 25%**
- **Biopsy Proven Sarcoidosis**
  - **Group A – Cardiac Symptoms - 84%**
  - **Group B – Screening for Cardiac Sarcoidosis – 4%**

Clinicopathology

- Massive Granulomatous Involvement of Myocardium → C.H.F.
- Granuloma involving papillary muscle → Mitral Regurgitation
  → Pulm. Hypertension
- Granulomatous Pericarditis
- Granulomas involving distal coronary arteries sparing proximal vessels
- Myocardial Scarring → Aneurysm

- Granulomas affecting conducting system



Judson; *Chest*, July 2005

Diagnostic Evaluation

- Electrocardiogram
- Echocardiogram
- Thallium Perfusion Scan
- Ga Scan
- CT (Spect)
- Cardiac – M.R.
- Ultrasonic Tissue Characterization
- Endomyocardial Biopsy

Liver

- Granuloma 50 – 80 %
- Abnormal Liver Function
- Granulomatous Hepatitis
- Portal Hypertension – Rare

Lynch,Sharma "Extrapulmonary Sarcoidosis" Seminar in Resp-Infn Vol 13, 1999

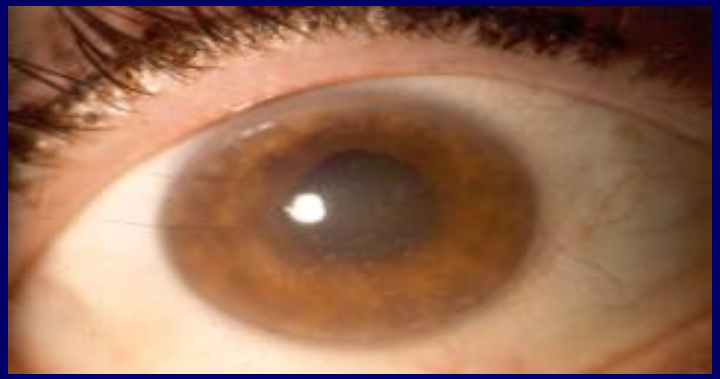
NeuroSarcoidosis

- Less than 10 %
- Involves Base of the Brain
- Cranial Nerves – Facial Nerve
- Mononeuritis Multiplex
- Headache – Mass effect
- Peripheral Neuropathy
- Horner's Syndrome
- Diagnosis
  - Ideally Tissue
  - CAT Scan
  - MRI
  - **Cerebrospinal Fluid**
    - Lymphocytosis
    - Elevated ACE
    - Increased β2 macrogolbulin
    - Increase CD4:CD8 Ratio

Sharma, "NeuroSarcoidosis" Chest 1997

Ocular Lesions

- 11 - 83%
- Anterior uveitis ***
- Chronic uveitis, glaucoma, blindness
  - Kerato conjunctivitis sica
  - Retinal Vasculitis

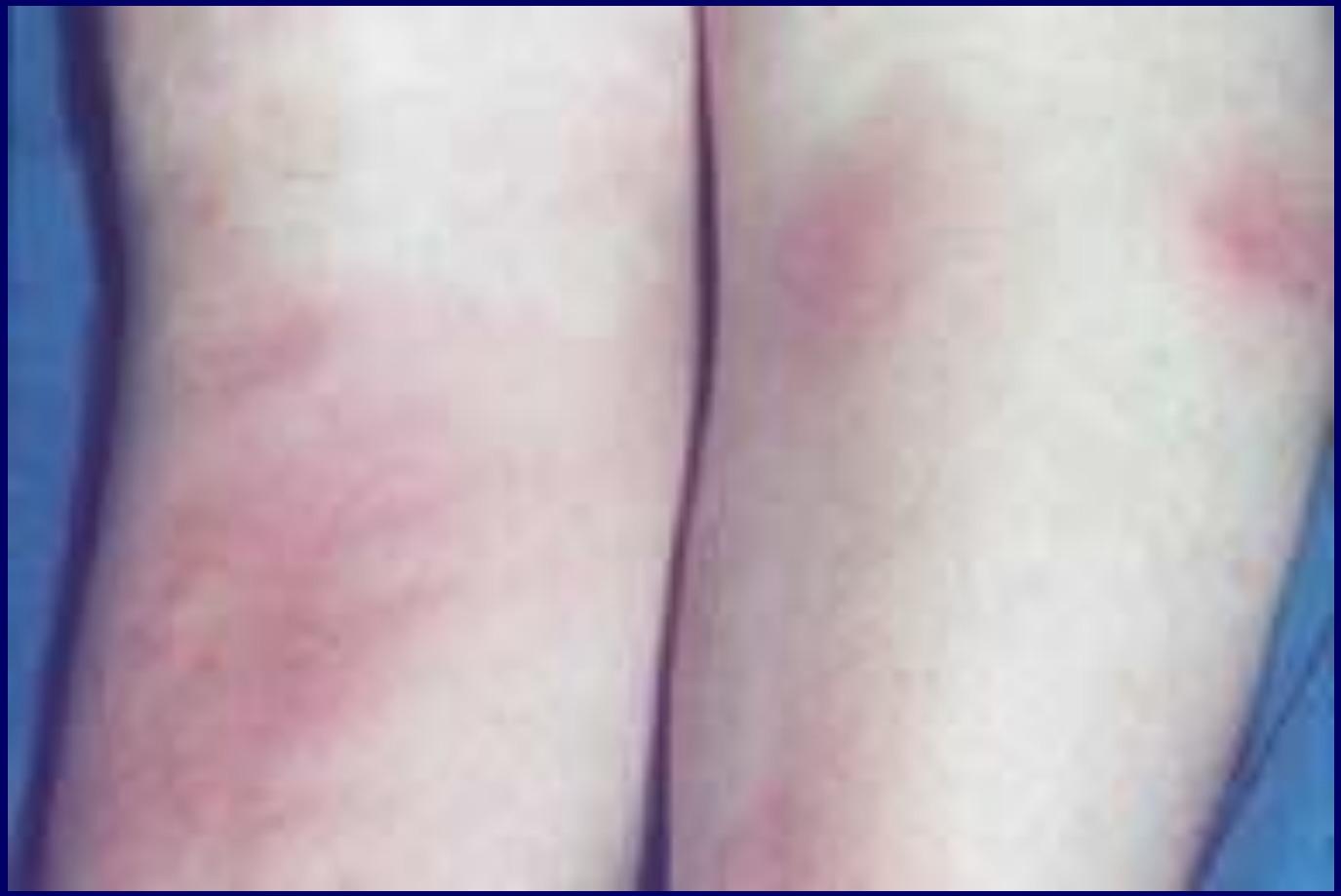


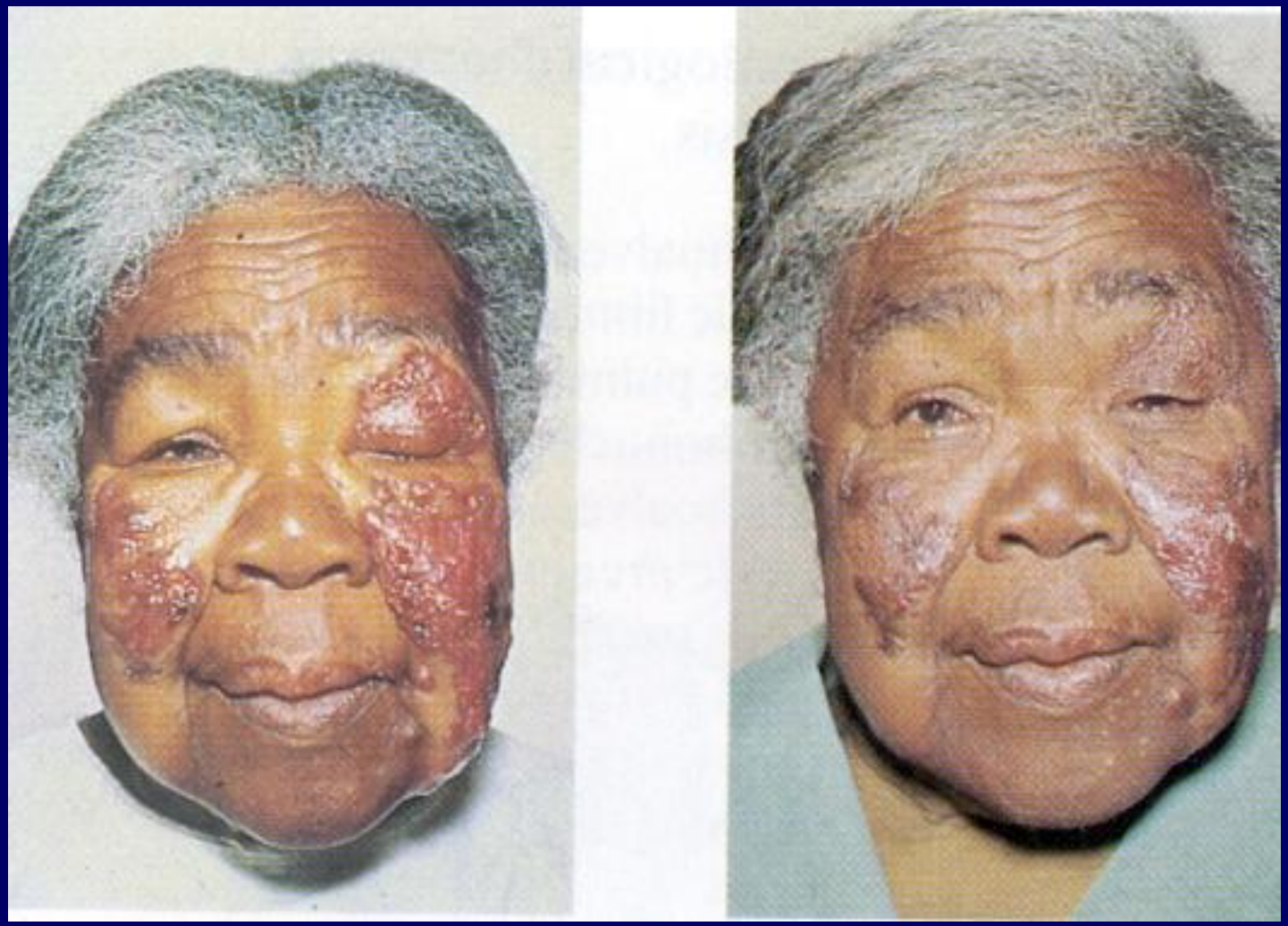
Lynch, Sharma "Extrapulmonary Sarcoidosis Seminar Resp-Inf" Vol 13 1999

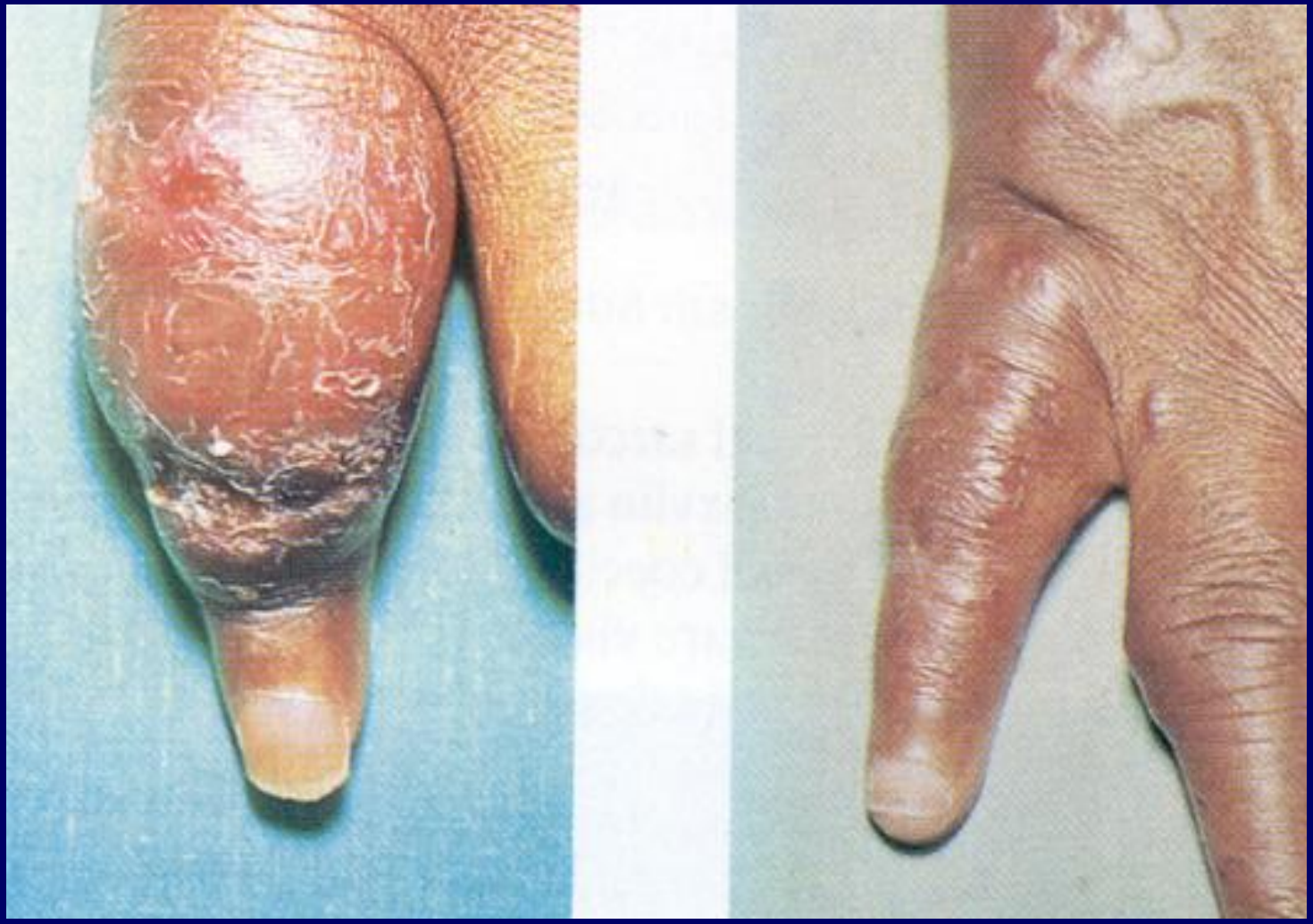
Skin

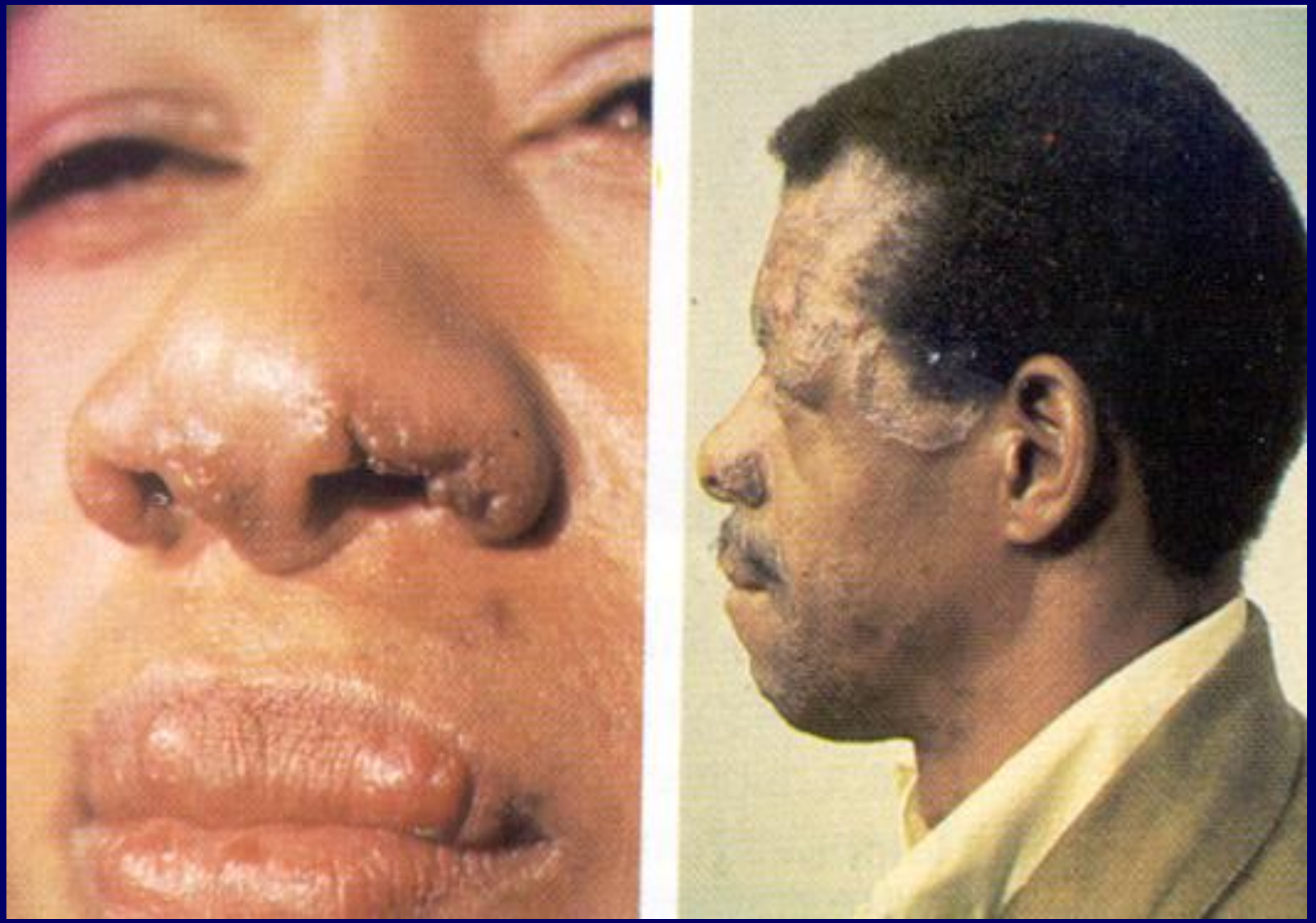
- 25 % of all patients
- Erythema Nodosum ***
- Lupus Pernio ***
- Maculapapular Rash
- Subcutaneous Nodule
- Hypo and Hyper Pigmented Area
- Alopecia

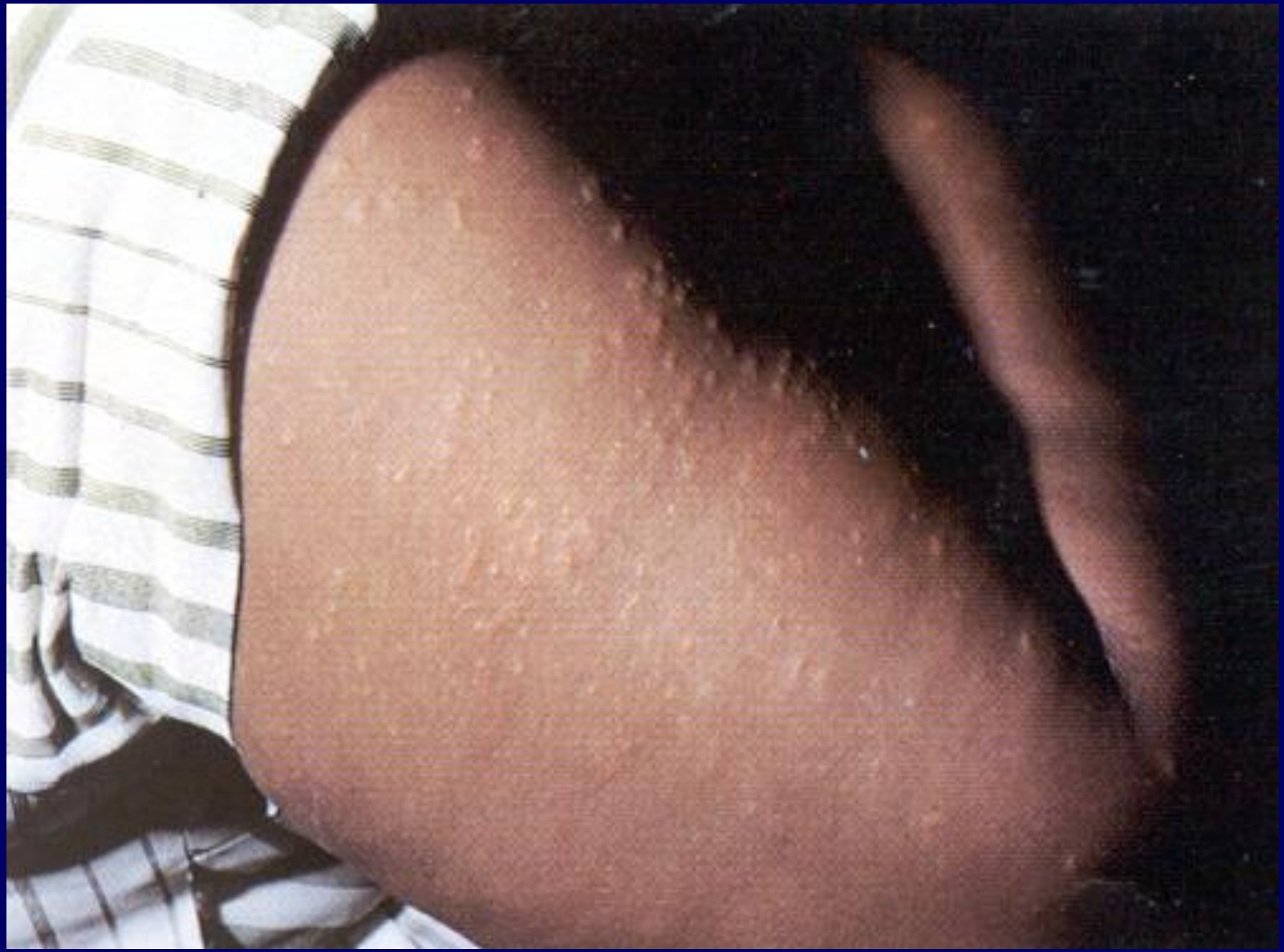
James “Sarcoidosis Skin” 1992 Resp Med 13











Musculoskeletal

- 25 – 40% of all patients
- Deforming Arthritis – Rare***
- Knee, Ankles, Elbow, Wrist
- Chronic Myopathy – Women
- Muscle Biopsy – Granuloma

Gran, "Acute Sarcoid Arthritis – A Favorable Outcome" Lit Review 1996 Scand J. Rheum

Parotid Glands

- 40% of all patients
- Self Limiting
- Symptomatic 6 %
- Uveo Parotid Fever

Endocrine

- Hypercalcemia 2 – 10%
- Hypercalciuria 6 – 30%
- Diabetes Insipidus 2%
  (Pituitary and/or Hypothalmas)
- Adrenal Suppression – Rarely

Sharma, "Calcium, Vit D and Sarcoidosis" Chest 1996

Gastrointestinal

- Very Rare Less Than 1% of all patients
- Stomach is the common site
- May mimic Crohn's Disease, Tuberculosis
- Pancreatic mass

Kidney

- Interstitial Nephritis - Rare
- Nephrocalcinosis and Renal Failure secondary to
  - Hypercalcemia & Hypercalciuria

Sato, “Renal Dysfunction in Patients with Sarcoidosis” 1996 Int Med - 35

Reproductive System

- Breast
- Uterus
- Testicle

Pregnancy and Sarcoidosis

- Treat Sarcoidosis as there is no Pregnancy
- Treat Pregnancy as there is no Sarcoidosis
- Symptoms May improve during Pregnancy
- Relapse may occur After Delivery

Johnson, John "Clinical Management of Sarcoidosis" Medicine 78, 1999

Haematological

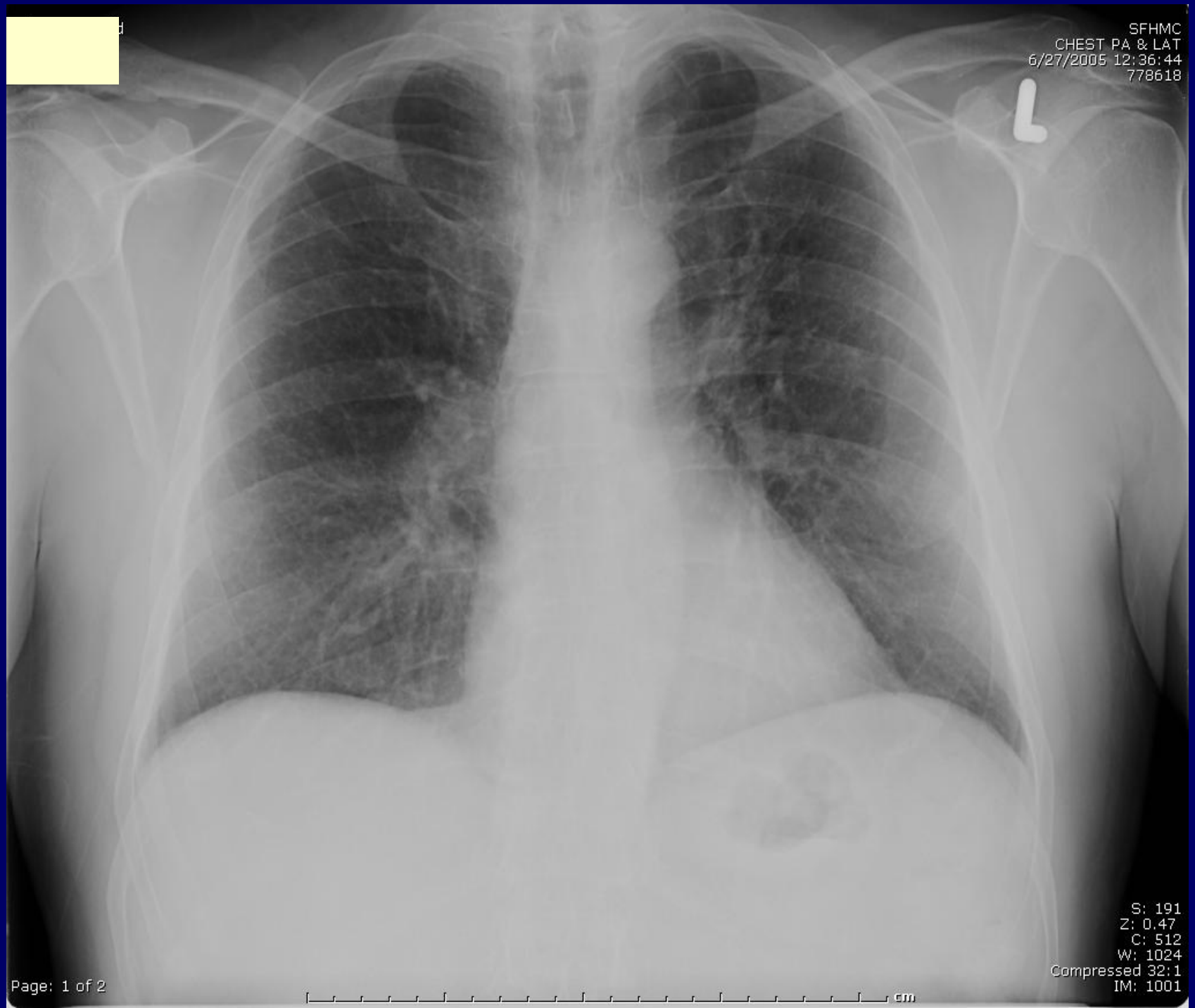
- Involvement of both white and red blood cells
- Anemia 4 – 20%
- Leukopenia 4 %
  - Bone marrow involvement
  - Redistribution of Blood T Cells to the Site of the Disease

Systemic Symptom

- Fever
- Fatigue
- Weight Loss
- Night Sweats

Classification

- Stage 0 Normal Chest x-ray
- Stage I Bilateral Hilar Adenopathy
- Stage II Bilateral Hilar Adenopathy & Parenchymal Infiltrates
- Stage III Parenchymal Infiltrates
- Stage IV Honey Comb or Fibro-Bullous Changes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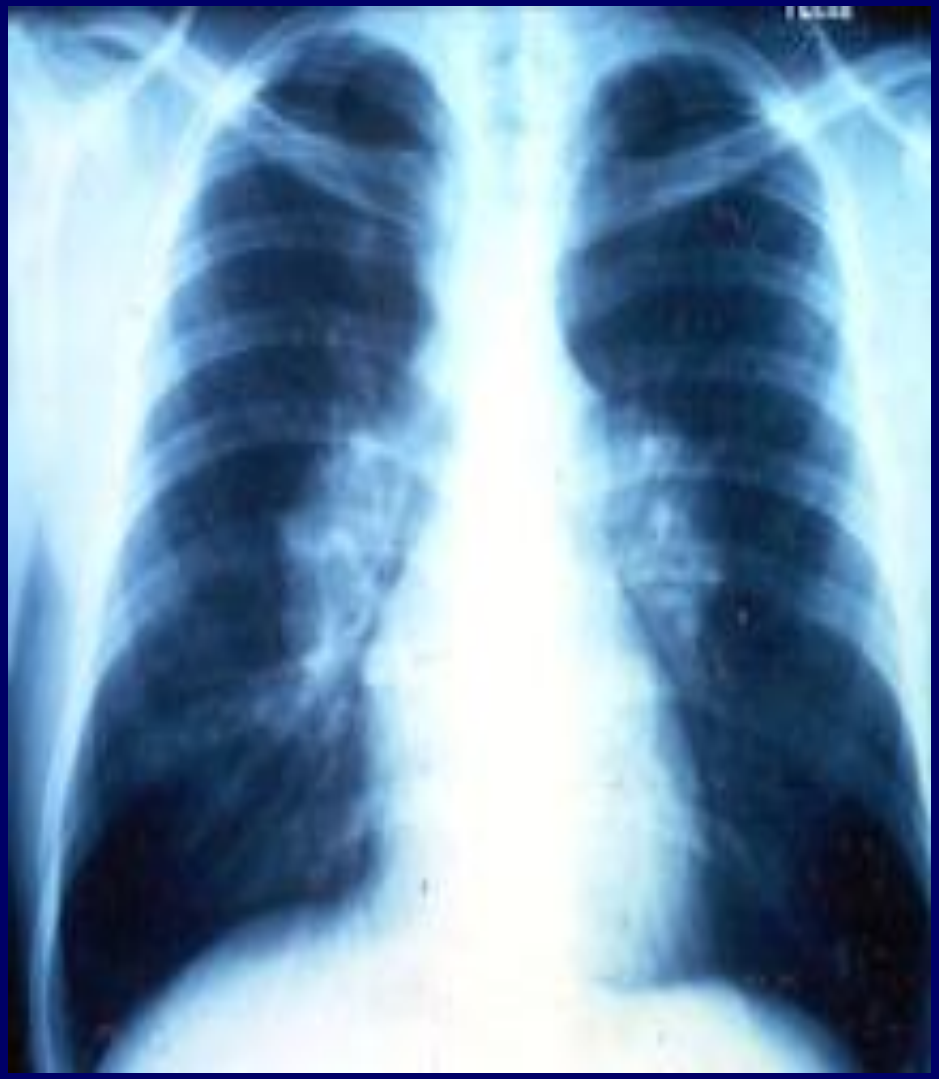

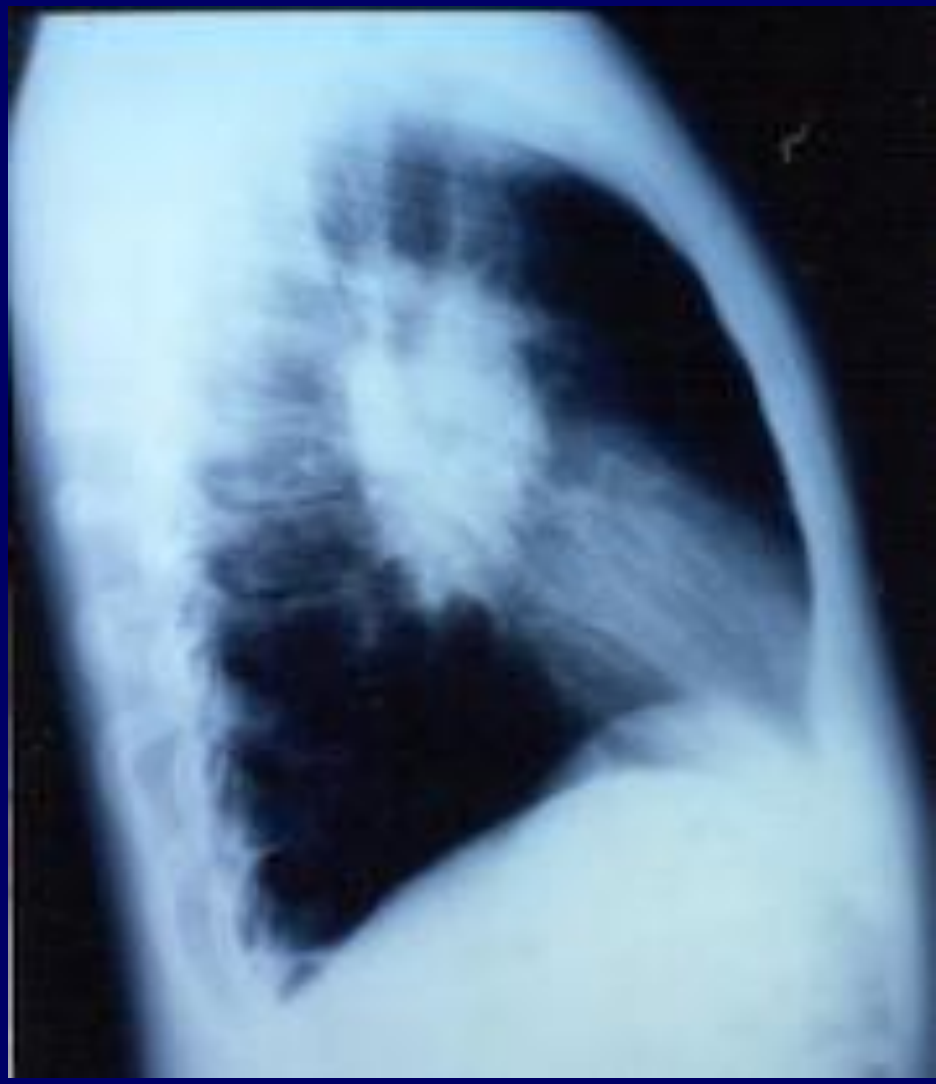

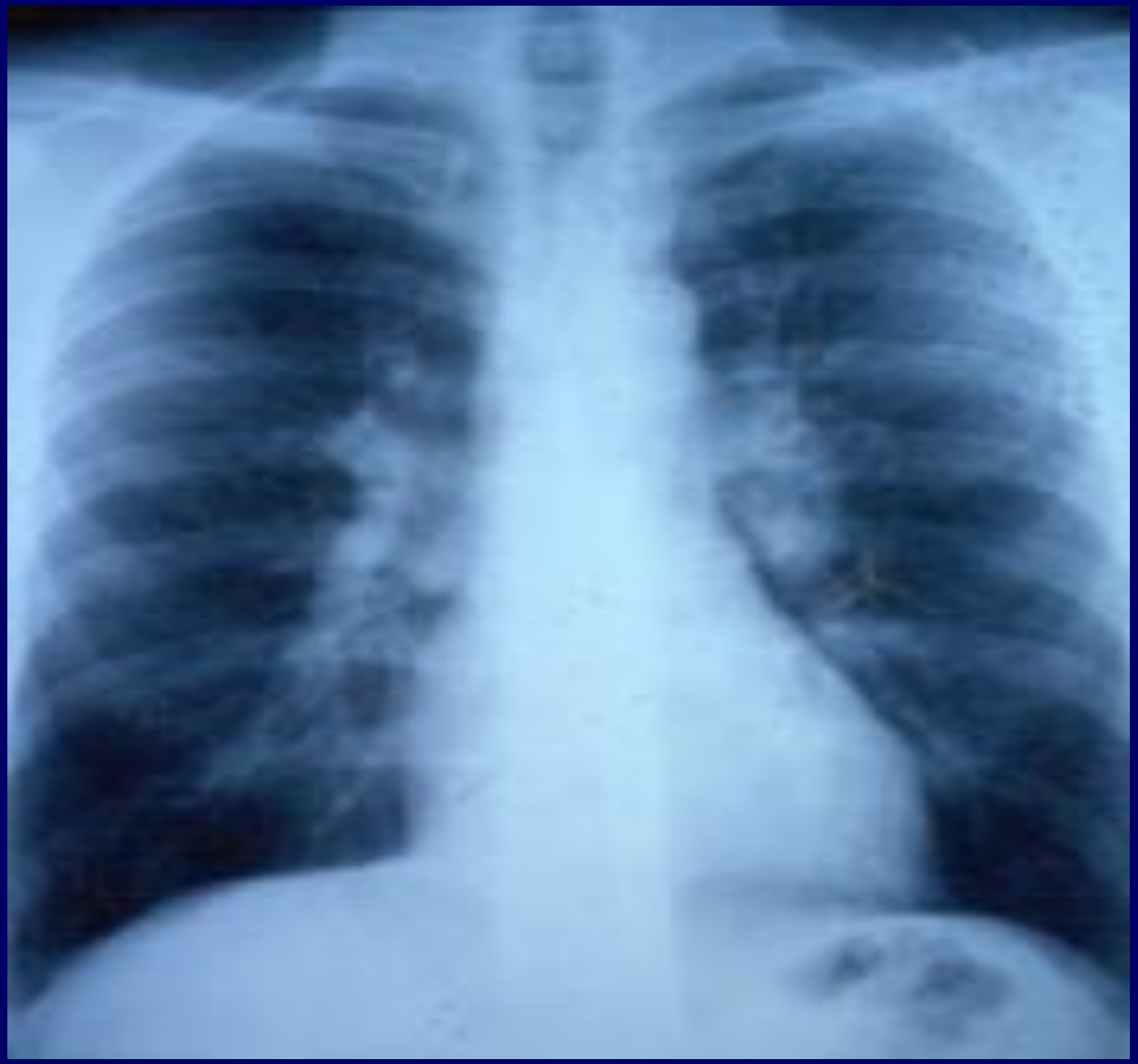

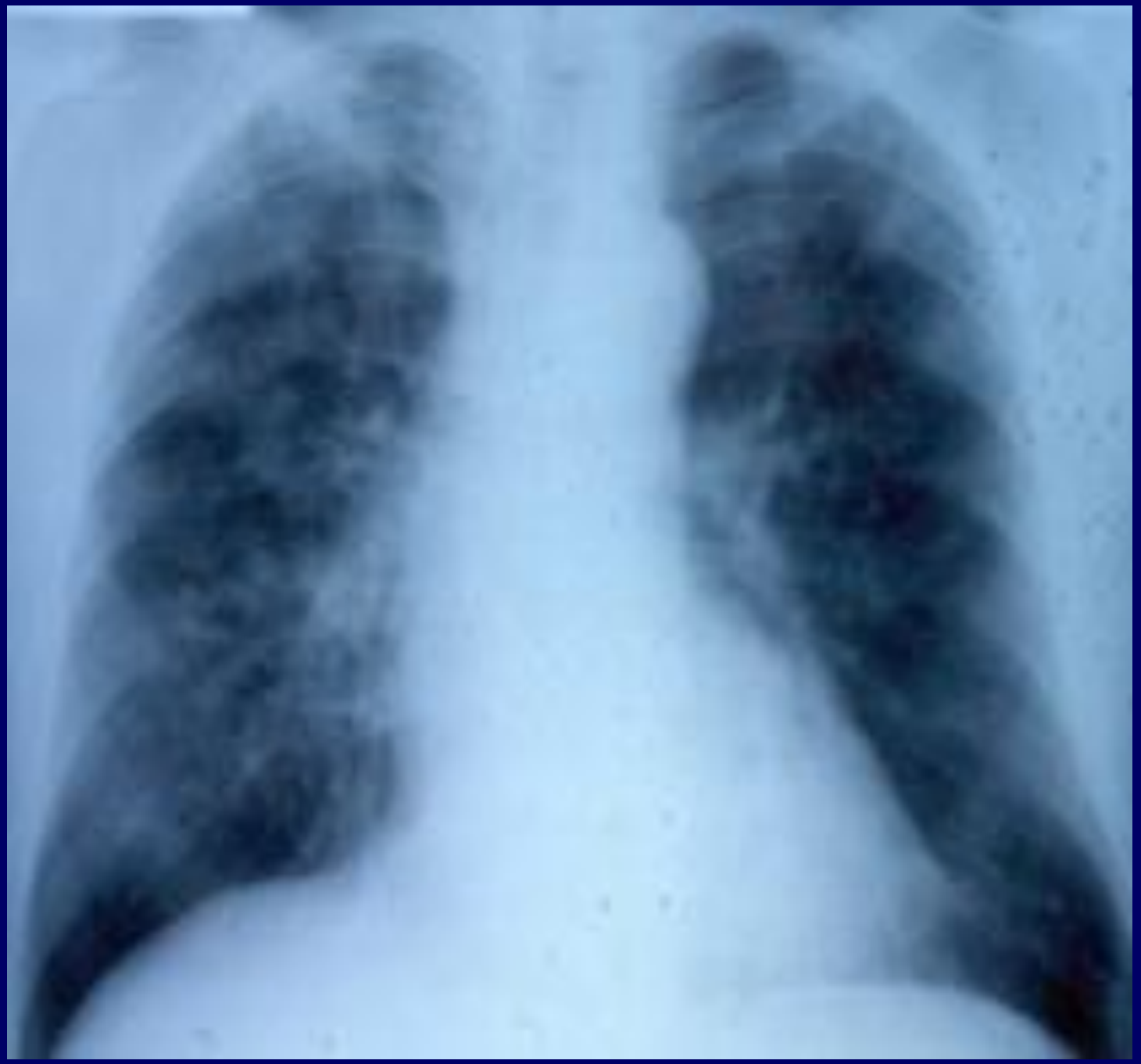

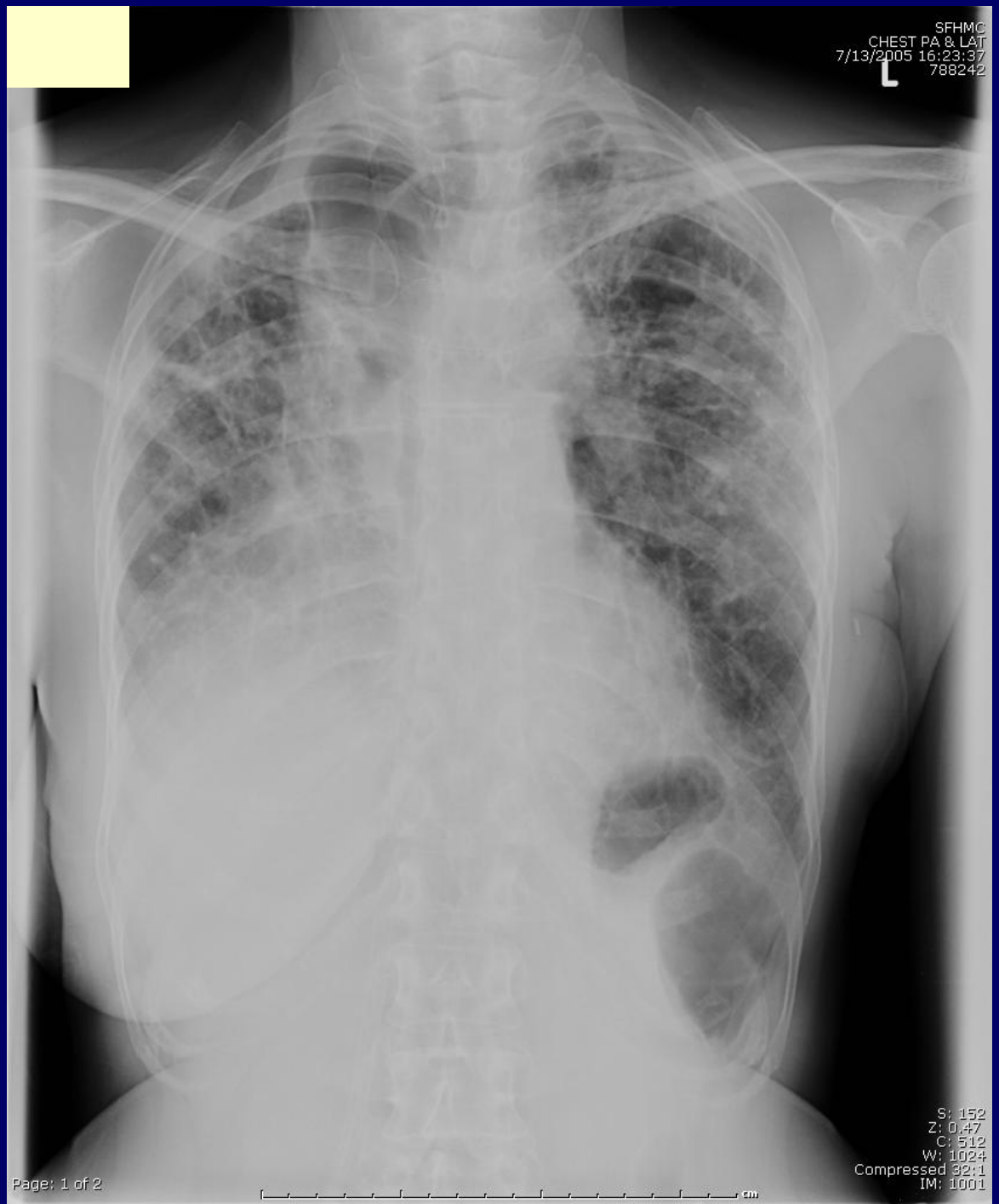
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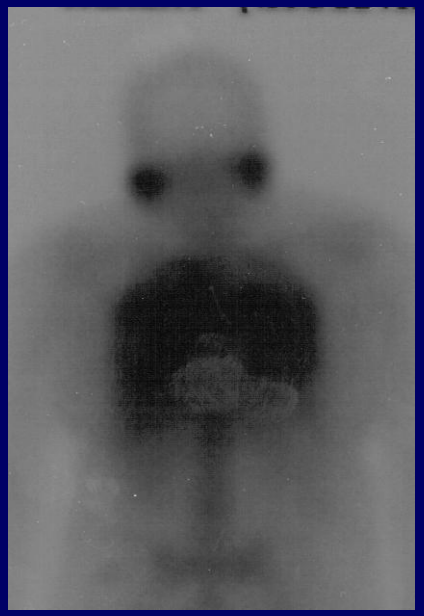
Diagnostic Evaluation

- History – including occupational and environmental exposure
- Physical Exam
- Chest X-Ray PA & Lateral Views
- Complete Pulmonary Function Studies with DLCO
- WBC, RBC, Hgh, Hct
- Serum Electrolytes Calcium
- Liver Function Test
- Urine Analysis Urine Calcium
- Electro Cardiogram
- Ophthalmologic Evaluation
- Anergy Panel – Tuberculan Skin Test
- CT Scan of Chest , HRCT
- Gallium Scan
- Kveim's Test
- Histology
- B.A.L.

Gallium Scan

- High Intensity Alveolitis
- Lambda-Panda Sign

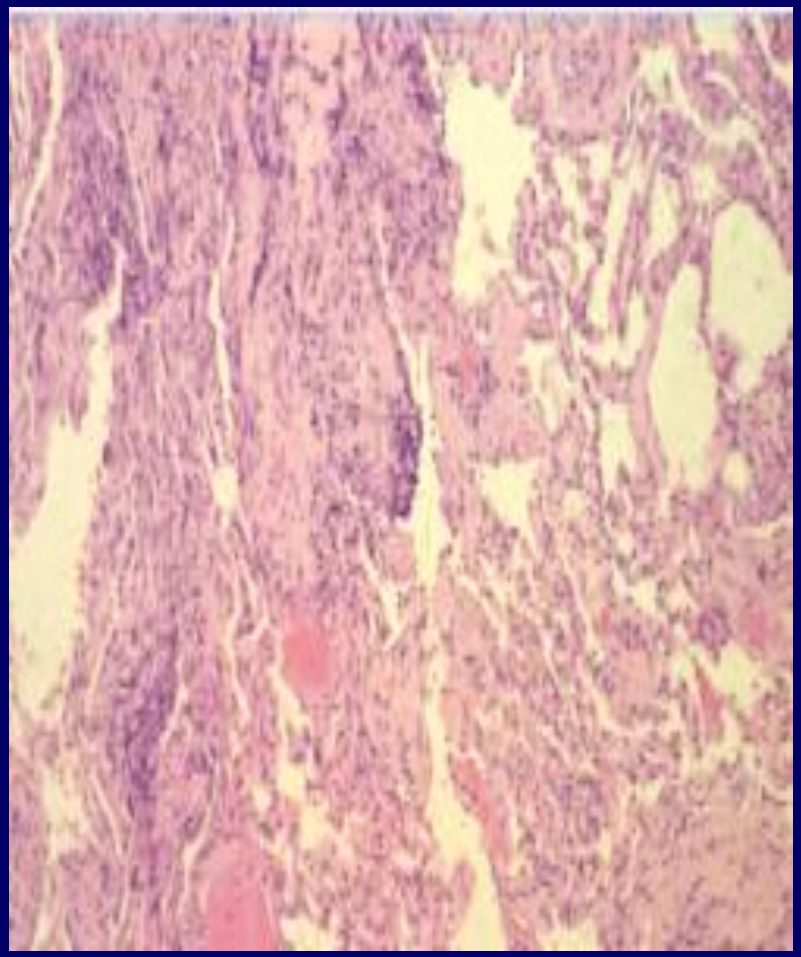


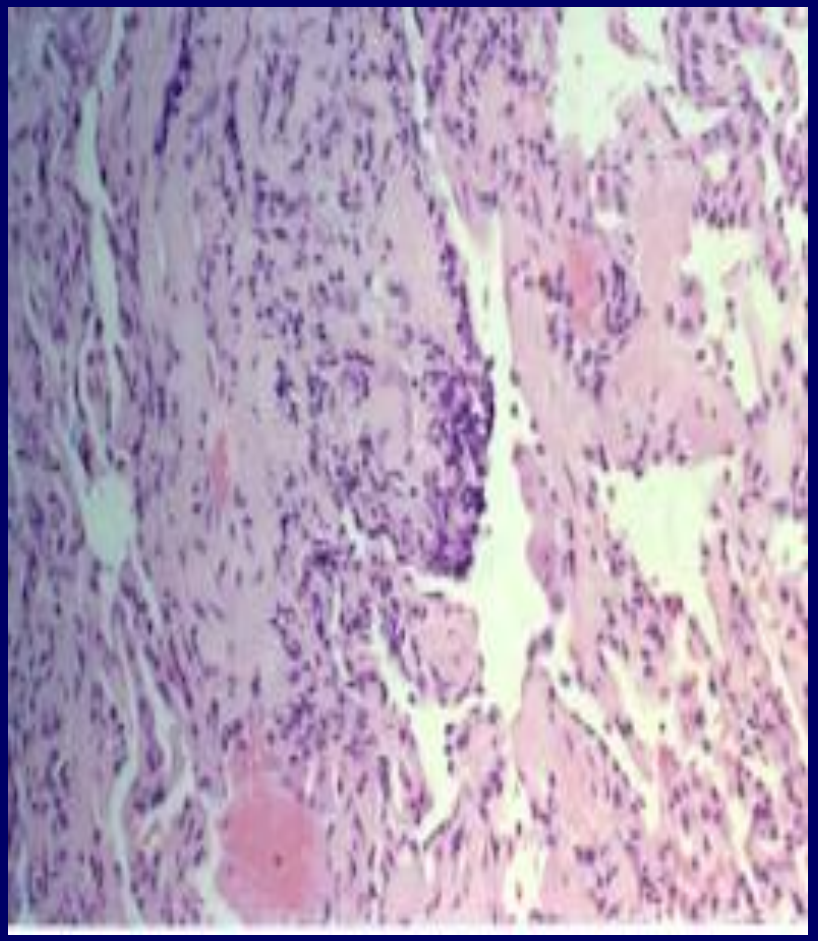
Mann “Nuclear Imaging in Sarcoidosis” Clin Chest Med 18 1997

Turner-Warwick Thorax 41 1986

Histology

- Transbronchial Biopsy 90 % +
- Lymph Node Biopsy
- Mediastinoscopy
- V.A.T.





Role of Bronchoalveolar Lavage in Sarcoidosis

- B.A.L. ***
- Total Cells 15-20 Million
- Macrophage 90%
- Lymphocyte 8%
- P.M.N. 2%
- Normal CD4:CD8 Ratio 2:1
- Sarcoidosis

↓

Lymphocytic Alveolitis
Increase CD4:CD8 Ratio
Increase Activated T Lymphocyte (HLADR)
CD4:CD8 Ratio > 3.5 – Consistent with Sarcoidosis

Lahiri, Schatz, et al "Clinical Specificity B.A.L. Cells" Chest Oct 1989
Costabel "Sensitivity and Specificity of B.A.L. " Sarcoidosis
Winterbauer "B.A.L. in Diagnosing Sarcoidosis" Chest 104 1993
Hung, ZuWallack, Lahiri "Sarcoidosis I.P.F. Hypersensitivity Lung Dis" Chest Oct 1996

Complications

- Pulmonary
  - Respiratory Failure
  - Chronic Pulmonary Hypertension
  - Pneumothorax
  - Haemoptysis 2° to Mycotoma
- Cardiac
  - Cardiomyopathy
  - High Degree Block
  - Sudden Death
- CNS
  - Hydrocephalas
  - Cranial nerve Involvement
- Eyes
  - Blindness
- Endocrine
  - Hypercalcimia
  - Nephrocalcinosis

Natural History and Prognosis of Sarcoidosis

- Wax and Wane
- Spontaneous Remission 70%
- Progressive Disease 16-30%
- Cardiac, CNS Involvement 4 – 7 %
- Mortality 1 – 5 %
  - Respiratory Insufficiency
  - Myocardial Involvement
  - CNS
- Corticosteroids Alter Natural Clinical Course!!!
- Relapse 16-74% Post Treatment

Grace, Lynch "Pulmonary Sarcoidosis" Clin Chest Med 18 1997

Management

Goals

- Primary – Patient Survival
- Secondary – Restoration of Organ Dysfunction

Questions

A. Treatment Alter Natural History
B. Alter Morbidity and Mortality !!!
C. Treatments Harmful !!!

Next Question

A. All patients with Sarcoidosis need to be treated !!!
B. Who and when treatment should be initiated
C. How To Treat These Patients

Jones, et al "Clinical Management of Sarcoidosis Medicine", 78, 1999
Gibson, et al "Effect of Long Term Steroids in Sarcoidosis", Thorax, 51, 1996
Fazzi, "Pharmacotherapeutic Management of Sarcoidosis", AmerJ. Resp Med
Moller, "Treatment of Sarcoidosis" 2003
Baughman, "Pulmonary Sarcoidosis" Clinics in Chest Medicine, 2004

Selection of the Patients

1. Systemic Symptoms – Fever, weight loss, night sweats
2. Progressive Respiratory Symptoms
3. Occular Sarcoidosis
4. Hyper calcemia, Hyper calciuria
5. Neurosarcoidosis
6. Myocardial Involvement
7. Granulomatous Hepatitis
8. Progressive Changes in Chest X-Ray ***
9. Lupus Pernio, Bone Involvement
10. Hypersplenism
11. SURT

Drugs

- Corticosteroid ***
- Hydroxychloroquine
- Methotrexate **
- Cyclophosphamide
- Azothioprime
- Cyclysporine *
- Bactrim DS !!
- Cytokine Modulators
  - Thalidomide
  - Pentoxifylline
- Infliximab
- Minocycline

- Combination Medication
  Corticosteroid
  Hydroxychloroquin
  Methotrexate

Pharmacotheraputic Management of Pulmonary Sarcoidosis; Amer J. Resp Med 2003

Corticosteroids - Systemic

- Inhibition of Lymphocyte and Mononuclear Activities
- Inhibits Release of IL I, IL II, IL III, TNFδ IFNχ
- Affects both T-Lymphocyte and Macrophage Function
- Reduces BAL Lymphocyte
- Prevents release of IL II by Blocking CD4 T Lymphocyte

Corticosteroids

- **Dose of Corticosteroids**
  - Prednisone - 40 mg daily x 2 weeks
  - 30 mg daily x 2 weeks
  - 25 mg daily x 2 weeks
  - 20 mg daily x 2 weeks
- **After 8 Weeks**
  - Prednisone – 15 mg daily x 3-4 months
  - Then maintain 10 mg daily
  - Complete 8 month therapy
- **Then**
  - Prednisone - 7.5 mg daily x 1 month
  - 5 mg daily x 1 month
  - 2.5 mg daily x 1 month
  - 2,5 mg every other day x 1 month
  - discontinue
- **Follow**
  - Clinical
  - Radiological
  - Physiological – PFT – Spirometry - DLCO
- **If relapse – initiate with 20 mg daily**

Inhaled Corticosteroids

Spiteri; “Inhaled Corticosteroids in Pulmonary Sarcoidosis” Post Grad Med J, 67, 1991

Milman, et al; “No Effect of High Dose of Inhaled Corticosteroid in Pulmonary Sarcoidosis” J. Int Med, 236, 1994

Albert, et al; “Inhaled Budesonide in Pulmonary Sarcoidosis Double Blinded Placebo Controlled Study” E.R.S., 5, 1995

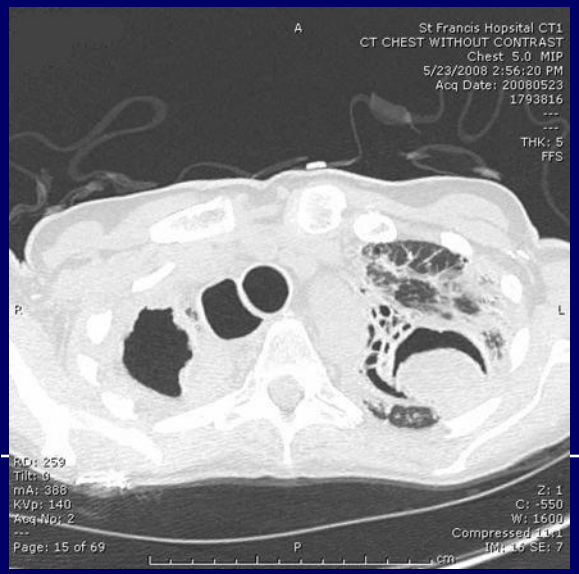
De Bois et al; “Randomized Trial of Inhaled Fluticasone Propionate in Chronic Stable Pulmonary Sarcoidosis – A Pilot Study”; E.R.S. 1999, 19, 1345-1356

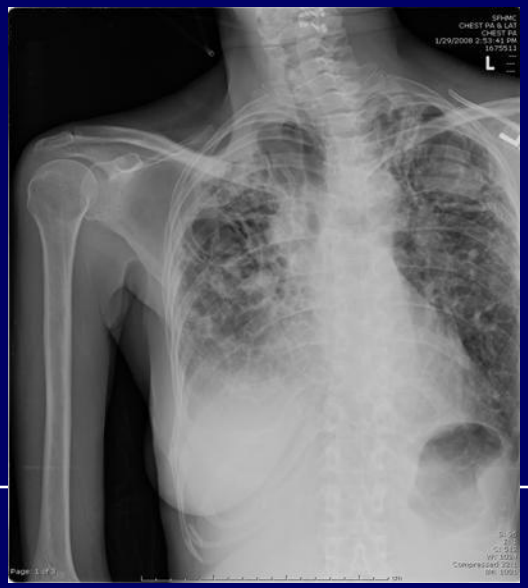
Conclusion

No Statistical Significance

Massive Haemoptysis

- Always Secondary to Mycetoma
- Conservative Treatment
- Bronchial Artery Embolization
- Lobectomy / Pneumonectomy
- Lung Transplantion



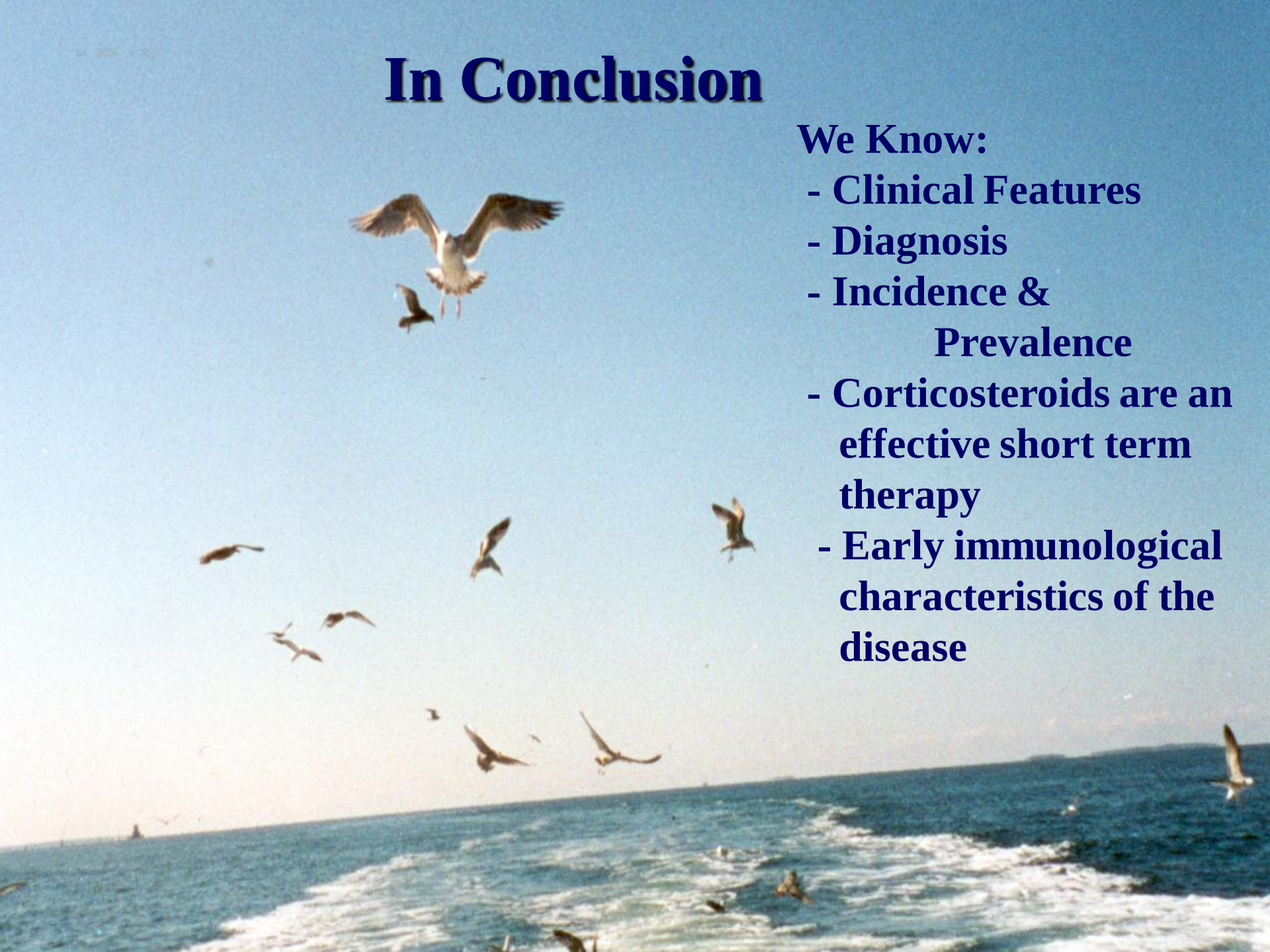


Surveillance

- Stage I - every 6 months
- Stage II, III & IV – every 3 months

- Following Discontinuation of Treatment
  - 3 Years Close Follow Up
- Relapsed Following Treatment
  – May Be Life Long

In Conclusion



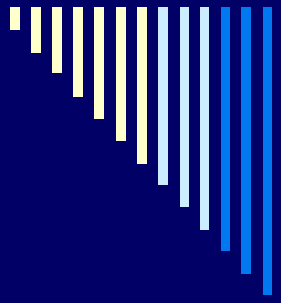
We Know:

- **Clinical Features**
- **Diagnosis**
- **Incidence & Prevalence**
- **Corticosteroids are an effective short term therapy**
- **Early immunological characteristics of the disease**

In the future

Would like to explore:

- The causes of Sarcoidosis
- Any marker to predict the progression of disease
- Do corticosteroids alter the natural history of the disease?
- Duration of corticosteroid therapy
- Any less toxic therapy !!
- Mechanism of lung injury and fibrosis
- Mechanism that results in persistent disease



Thank YOU