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ALTITUDE ILLNESS

- High altitude disease can be divided into acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). AMS is essentially a benign and limited disease, while HAPE and HACE can be potentially lethal. The most common form of altitude disease is acute mountain sickness.

ACUTE MOUNTAIN SICKNESS

- The incidence of AMS is about 25% at 9,000 ft and 67% at 14,000 feet.

SYMPTOMS

- Symptoms usually consist of headache, nausea, vomiting, anorexia, weakness, fatigue, light headedness, dizziness, difficulty sleeping, chilliness, irritability, difficulty in concentration, tinnitus, visual and auditory disturbances, dyspnea, palpitations, tachycardia, weight loss and Cheyne Stokes breathing.
- **HEADACHES**. Headache is usually the first manifestation and may be mild to severe, bitemporal, throbbing, worse at night and on awakening. These symptoms may occur at altitudes as low as 6500 feet (2000 m). The more common symptoms are usually attributable to cerebral edema and occur within the first 24 hours of rapid ascent, and tend to improve over 3-7 days in the majority of patients.
- **EDEMA**. Some patients may develop peripheral and visceral edema, weight gain, proteinuria and oliguria. As individuals ascend to high altitude, there is a shift of fluid from the intravascular space into the interstitial or intracellular space, and a tendency toward
- a decrease in diuresis.

TREATMENT

- **MILD SYMPTOMS**. Treatment of AMS is descent. However, mild symptoms can be treated with rest, acetaminophen, ibuprofen, and acetazolamide (250 mg BID).
- **MODERATE SYMPTOMS**. Moderate symptoms can be treated with rest, dexamethasone (4 mg q6h for 1-3 days, tapered over 5 days), and acetazolamide 250-500 mg BID-TID.

- **SEVERE SYMPTOMS**. Severe symptoms must be treated with oxygen, dexamethasone (8 mg followed by 4 mg q6h PO or IM), and acetazolamide up to 1.5 grams daily. Acetazolamide functions by increasing ventilation, preventing periodic breathing, improving oxygenation, increasing diuresis, and creating a metabolic acidosis by urinary loss of bicarbonate, potassium and sodium.
- **PREVENTION**. Prevention of AMS may be effected by common sense measures such as avoiding alcohol, sedatives, excessive exertion on the first day, and slow ascent. Individuals should eat frequent small meals that are high in easily digested carbohydrates such as jams, fruits, and starches. Extra salt should be avoided, but drinking more water than usual is important in preventing water loss created by over breathing the dry air at high altitudes. If ascending to 6-7000 feet (2,000 m), take 2-3 days to ascend to this level. Above 10,000 feet (3,000 m) ascend 1,000 feet per day.
- **ACETAZOLAMIDE**. Acetazolamide may be started the day before the ascent at 250-500 mg and taken every h.s. for 3-5 days.
- **NIFEDIPINE.** Nifedipine may be started 2 days before the ascent at 20 mg daily, followed by 20 mg q8h starting on the day of ascent and continued for 3 days.
- **DEXAMETHASONE**. Dexamethasone may also be started on the day of ascent at 2-4 mg q6h and continued for 3 days, and then tapered over 5 days.
- **PENTOXIFYLLINE**. Pentoxifylline has been used in some countries to improve cerebral function, and prochlorperazine at 10 mg PO q6h has also been used as a preventive measure in some countries. These latter two drugs have not been widely used in the USA.

CHRONIC MOUNTAIN SICKNESS

- This illness is also known as Monge's disease. It is uncommon and results from chronic alveolar hypoventilation in residents of high altitude settlements. It resembles alveolar hypoventilation (Pickwickian syndrome). It apparently is due to a loss of ventilatory acclimatization. The hallmarks of the disease are a low or absent ventilatory response to hypoxia, excessive hypoxemia, pulmonary hypertension, secondary polycythemia and cor pulmonale.
- It was first described in 1928 as an illness occurring in indigenous Quechua Indian residents in the Andes.

SYMPTOMS

- It is characterized by hypoxemia, cyanosis, somnolence, mental depression, clubbing of the fingers, polycythemia, and right ventricular failure.

LABORATORY

- **HEMATOCRIT**. The hematocrit commonly is greater than 75%.
- **ECG.** The ECG may show right axis deviation, right atrial and ventricular hypertrophy.
- **CHEST X-RAY**. Chest x-ray will show right heart enlargement and central pulmonary vessel prominence.
- **HEART CATHETERIZATION**. Heart catheterization may show pulmonary hypertension.
- **PULMONARY FUNCTION TESTING**. Pulmonary function testing will show alveolar hypoventilation and elevated PCO2.

TREATMENT

- The treatment of CMS is simple. Descent to lower altitudes causes a rapid improvement in the symptoms and reversal of the abnormal physical findings and laboratory abnormalities. Patients that are unable to move to lower altitudes may be treated with medroxyprogesterone and other respiratory stimulants. Phlebotomy may be used, but is not the treatment of choice.

HIGH ALTITUDE PULMONARY EDEMA (HAPE)

- HAPE usually occurs after a rapid ascent to above 9000 feet (2700 m).

CONTRIBUTING FACTORS

- Contributing factors include strenuous exercise and exposure to cold. Long term residents at high altitude may develop reentry pulmonary edema when they return to high altitude after a short visit at lower altitudes. Patients that have a congenital absence of one pulmonary artery are particularly at risk for HAPE, and tend to

develop the syndrome at altitudes as low as 5000 feet (1500 m). There is also an increased incidence of HAPE in individuals that have a previous history of HAPE.

SYMPTOMS

- The symptoms begin after about 6-96 hours after arriving at the high altitude level. The symptoms consist of a dry irritating cough that may become bloody and frothy, dyspnea, substernal pain, wheezing, orthopnea, cyanosis, tachycardia, weakness, ataxia, and coma. The incidence of HAPE varies from .01-2%. It is uncommon, but potentially much more serious than acute mountain sickness. Most of the complicated cases occur at altitudes beyond 10,000 ft. It is not unusual to see 1-2 deaths from HAPE at Colorado ski resorts annually.

LABORATORY

- **CHEST X-RAY**. Chest x-rays will show unilateral or bilateral alveolar infiltrates with enlargement of the pulmonary arteries. The pulmonary edema is a noncardiogenic form of pulmonary edema, and cardiomegaly and Kerley B lines are not seen in HAPE. Recurrent episodes of pulmonary edema usually do not show the same radiographic distribution of infiltrates. The atrial pressure is normal, but there is elevation of the pulmonary artery pressure. The pulmonary wedge pressure is normal, while the pulmonary vascular resistance is elevated.
- **BLOOD TESTS**. The white count is occasionally elevated, but the
- sedimentation rate is usually normal. Patients with HAPE have a
- relative thrombocytopenia and prolonged prothrombin time.
- **ECG**. ECG findings may reveal right ventricular strain. The mortality of HAPE ranges from between 0-50% depending on several factors.

TREATMENT

- Treatment of HAPE consists of oxygen, descent to a lower altitude,
- and rest.
- **OXYGEN**. By administering 100% oxygen, the pulmonary artery pressure will drop, arterial oxygen saturation will increase, and respiratory rates will decrease. High flow rates should be given by

mask to maintain arterial oxygen saturation greater than 90% in patients with severe HAPE.

- **DESCENT**. Descent of about 1500-3000 feet is usually effective.
- **REST.** Exertion should be kept to a minimum.
- **EPAP**. Expiratory positive airway pressure (EPAP) up to 10 cm H2O will improve the hypoxia, increase tidal volume and decrease the respiratory rate without a change in the minute ventilation.
- **DEXAMETHASONE**. Dexamethasone at 8 mg initially, followed by 4 mg q6h PO may be useful, but its effectiveness has not been established.
- **ACETAZOLAMIDE**. Likewise acetazolamide may be helpful by increasing diuresis and stimulating ventilation, but its efficacy has not been established.
- **FUROSEMIDE**. Furosemide should not be given, as it has no benefit, and may lead to pulmonary embolism.
- **NIFEDIPINE**. Nifedipine has been shown to lower pulmonary hypertension and improve oxygenation. It is initially given as 10 mg sublingually plus 20 mg PO, followed by 20 mg PO q6h. Nifedipine may be used as a prophylactic agent for HAPE.

HIGH ALTITUDE CEREBRAL EDEMA

- High altitude cerebral edema (HACE) is the least common of all of the syndromes, but can be potentially severe. HACE usually occurs with HAPE, but can occur by itself.

SYMPTOMS

- After about 1-3 days at altitudes greater than 8250 feet (2500 m), the patient will develop severe headaches, confusion, staggering gait, truncal ataxia, seizures, hallucinations, mental confusion, slurred speech, nausea and vomiting, which can progress to coma. The development of cerebellar ataxia is a sensitive symptom, prompting immediate treatment. Retinal hemorrhages may be seen in about 50% of patients. They are very common at altitudes greater than 16,000 feet (5000 m). They usually are of no concern unless they appear in the macular area. Nosebleeds are rare, but subungual splinter hemorrhages are occasionally seen at altitudes greater than 16,000 feet (5000 m).

TREATMENT

- The most effective treatment is high flow oxygen and descent.

ATRIAL FIBRILLATION

CAUSES

- **HEART**. Mitral valve disease, hypertensive heart disease, acute ischemia, left atrial myxoma, and constrictive heart disease.
- **LUNG**. COPD, acute pulmonary emboli, and pneumonia.
- **METABOLIC**. Hyperthyroidism, and pheochromocytoma.

ACUTE RATE CONTROL

- If the patient is hemodynamically compromised, electrical cardioversion may be attempted.
- Class Ia drugs, such as procainamide, quinidine, and disopyramide, should not be used unless the AV node is first blocked, as this can increase the ventricular rate
- Digoxin is not the drug of choice, unless there is CHF. In this setting, digoxin may convert the atrial fibrillation to a sinus rhythm by increasing the left ventricular ejection fraction which can cause a decrease in left atrial size and pressure.
- In the absence of CHF, the drugs of choice are diltiazem, verapamil, metoprolol and esmolol.
- Patients with WPW syndrome and atrial fibrillation should not be given AV nodal blockers as this can increase the ventricular rate to dangerous levels by acceleration of conduction through the accessory pathway. These patients should be treated with procainamide. Lidocaine may also be used, but is less effective. In an emergency, or failure of procainamide and lidocaine, electrical cardioversion may be used
- **DILTIAZEM** is given as 0.25 mg/kg IV over a 2 minute period. If, after 15 minutes, an additional dose of 0.35 mg/kg given over 2 minutes may be repeated. The maintenance IV dose is 5-15 mg/hour. The oral maintenance dose is 120-360 mg/day.
- **VERAPAMIL** is given as 5-10 mg IV over 2 minutes. If needed, 10 mg given over 2 minutes may be repeated in 30 minutes. The oral maintenance dose is 240-480 mg/day.
- **METOPROLOL** is given as 5 mg IV every 5 minutes x 3 doses. The oral maintenance dose is 25-100 mg bid.

- **ESMOLOL** is given as 500 ug/kg IV over 1 minute. The maintenance IV dose is 50 ug/kg/min. However, if needed, repeat the loading dose and increase the maintenance dose by 25-50 ug/kg/min every 5-10 minutes. The half life of esmolol is only 9 minutes.

CHRONIC RATE CONTROL

- **BETA BLOCKERS, DILTIAZEM AND VERAPAMIL**. In the absence of left ventricular dysfunction, the drugs of choice are beta blockers, diltiazem or verapamil. If the patient has CHF, or left ventricular dysfunction, digoxin is the treatment of choice.
- **DIGOXIN**, traditionally, has been the drug of choice. It can be effective in controlling the ventricular rate at rest, but fails during exercise. The addition of an oral beta blocker or diltiazem, or verapamil can control the rate during exercise. Diltiazem may be a better choice, as diltiazem doesn't increase the digoxin levels, as does verapamil.
- Beta blockers that cause severe bradycardia may be treated with a beta blocker that has intrinsic sympathomimetic activity, such as pindolol.
- **REFRACTORY CHRONIC RATE CONTROL** that does not respond to pharmacologic therapy can be treated with radiofrequency ablation of the AV node, (anteriorly and posteriorly on the tricuspid annulus), and implantation of a VVI pacemaker. Alternatively, radiofrequency may be applied by catheter to the posterior or midatrial septum near the ostium of the coronary sinus which will slow the ventricular rate without the need of a pacemaker.

CONVERSION OF ATRIAL FIBRILLATION TO SINUS RHYTHM

- Justification for electrical cardioversion of atrial fibrillation to a sinus rhythm includes the loss of the atrial kick when the patient has left ventricular decompensation.
- Also, if the patient still is symptomatic after rate control, cardioversion may be attempted. However, if the patient has had atrial fibrillation for more than a year, it is unlikely that the patient will maintain the sinus rhythm for longer than 6 months following electrical cardioversion.
- Prior to electrical cardioversion, it is recommended that patient receive warfarin for 3 weeks prior to the conversion and 4 weeks following cardioversion to prevent embolization. If the patient is hospitalized and needs immediate cardioversion, IV heparin may be used for 2 days

prior to cardioversion followed by oral warfarin afterwards. The use of transesophageal echocardiography prior to electrical cardioversion is problematic at the present time, because some patients have experienced emboli following cardioversion in the absence of a demonstrated left atrial clot or left atrial spontaneous echo contrast.

- Patients that have atrial fibrillation secondary to pneumonia, postoperative states and hyperthyroidism should not be cardioverted.
- Drug maintenance of sinus rhythm following electrical cardioversion is indicated if the patient has conditions predisposing to atrial fibrillation such COPD and those with severe left atrial enlargement. *QUINIDINE* has ben used in the past, and studies have shown that patients receiving quinidine were more likely to be in sinus rhythm 1 year after cardioversion (50% versus 25%). However, sudden death from quinidine, may be greater in this group. Likewise, flecainide and propafenone, although effective, may result in increased mortality with an increase in ventricular tachycardia and fibrillation. *SOTALOL*, a class III agent, is effective for AF, but has an increased incidence of torsades de pointes. Low doses of *AMIODARONE* (less than 300 mg/day), another class III drug, is also effective in AF, but can produce a fatal pulmonary fibrosis.
- **THE MAZE PROCEDURE** may also be used to convert a patient from atrial fibrillation to a sinus rhythm. This is a surgical or catheter radiofrequency procedure consisting of atrial incisions that are used to interrupt the conduction pathways for the most common reentrant circuits and direct the sinus wave to the AV node. While some of these patients will be helped, some patients will require a dual-pacing DDD-R pacemaker for sick sinus syndrome.

PREVENTION OF EMBOLISM

- In the absence of contraindications, all patients under the age of 65 with risk factors (hypertension, previous stroke, hypertension) and all patients over the age of 65 should receive oral anticoagulants. Low intensity warfarin therapy, with a target INR of 1.4-2.8 is as effective as higher intensity warfarin, and has a lower complication rate.
- Lone atrial fibrillation, which is defined as those patients who have no structural heart disease, diabetes, hypertension, or thyrotoxicosis do not require prophylaxis with warfarin or aspirin.
- Aspirin, although not as effective as warfarin, may be used at a dose

of 325 mg/day to prevent ischemic stroke in those patients who are unable to take warfarin. Low dose aspirin of 75 mg/day is not effective in reducing the incidence of stroke.

CEREBRAL ABSCESS

OVERVIEW

- **HEMATOGENOUS SPREAD**. Hematogenous-caused brain abscesses tend to be multiple and multiloculated as opposed to the contiguous-spread brain abscesses which tend to be solitary.
- **AGE.** The average age of brain abscesses is 30-40 years of age, but ultimately depends on the cause. About 25% of brain abscesses occur in children that are less than 15 years of age.
- **MORTALITY.** There has been considerable improvement in the mortality rate over the last few years due to advances in CT and MRI scanning resulting in earlier diagnosis and treatment. At the present time, the mortality rate is about 5-10% which is considerably improved over the previous mortality rate of 40-60%

CAUSES

- Brain abscess can be caused by a contiguous focus of infection from otitis media, calvarial osteomyelitis, dental infection, sinusitis, hematogenous dissemination from a distant area such as cardiac valves, lung, skin, bone, abdomen and pelvis, or head trauma and post-neurosurgery.

ORGANISMS INVOLVED

- **STREPTOCOCCI**. About 60-70% of brain abscesses are caused by aerobic, microaerophilic and anaerobic streptococci which normally live in the oral cavity, female genital tract and appendix.
- **STAPHYLOCOCCI.** Staphylococcus aureus accounts for about 10-15% cases of brain abscess, especially those that originate from bacterial endocarditis and head trauma.
- **BACTEROIDES**. Bacteroides species can be isolated in about 20-40% of cases.
- **PROTEUS, KLEBSIELLA, PSEUDOMONAS, AND ESCHERICHIA**. Patients that have otitis media cause brain abscesses that harbor Proteus species, Klebsiella, Pseudomonas species and Escherichia

coli.

- **FUNGI**. Fungi can also cause brain abscess in immunocompromised patients. Patients that have neutropenia may develop Aspergillus, Candida and Rhizopus cerebral abscesses.
- **CRYPTOCOCCI**. Cryptococcus neoformans may cause brain abscesses, but more likely cause meningitis.
- **MYCOBACTERIUM.** Mycobacterium tuberculosis can cause tuberculomas.
- **ACTINOMYCES**. Actinomyces species causes brain abscess from odontogenic and pulmonary foci.
- **NORCARDIA AND LISTERIA**. Listeria monocytogenes and Nocardia asteroides cause brain abscesses in immunocompromised patients.
- **TOXOPLASMA**. AIDS patients can cause Toxoplasma gondii brain lesions.
- **CYSTICERCOSIS AND ENTAMOEBA**. Other causes of brain abscess are cysticercosis and Entamoeba histolytica.

CLINICAL

- **SYMPTOMS**. Brain abscesses occur between the ages of 30-40, whereas cerebral tumors and cerebral metastasis occur between the ages of 55-60. Patients present with headache, fever and focal changes mainly, but there may also be seizures and mental changes. Seizures occur in about 25% of patients. Fever only occurs in 50% of patients and in elderly patients fever is characteristically absent. About 20% of brain abscesses have no source of infection.
- **LOCATION OF ABSCESSES**. Most cerebral abscesses occur superficially in the frontal and parietal lobes and about 75% are solitary. Toxoplasma gondii, however, tends to occur in the basal ganglia. Frontal lobe abscesses usually arise from the sinuses and temporal lobe or cerebellar abscesses from otitis infections.

LABORATORY

- **BLOOD CULTURES**. Blood cultures are only positive in about 10-20 % of cases.
- **WBC AND SED RATE**. The WBC and sed rate may be elevated.
- **SPINAL FLUID**. Lumbar puncture is not usually indicated and may be contraindicated. The spinal fluid analysis usually is not helpful unless

there is a concomitant meningitis.

- **CT.** CT scans of the sinuses, ears, and mastoids should be obtained. Dental history and x-rays should be carried out. CT of the head will show changes from focal cerebritis to a mature capsule formation. This evolution usually takes about 2 weeks.
- **CEREBRITIS.** In the cerebritis stage the CT will show a non-enhancing focal low density lesion and the MRI will show a hypointense lesion.
- **RING ENHANCING LESIONS**. Ring enhancing usually doesn't occur until about 3 days and at this stage there may be no clinical symptoms. Most patients will present with a ring enhancing mass. Air may be seen in the mass, which helps in diagnosing the lesion as an abscess. The surrounding edema of abscesses tends to be less than that seen with brain tumors. The abscess may rupture into the ventricles and satellite lesions may be seen. Steroid administration can decrease the temperature and also reduce the size of the mass and surrounding edema.

DIFFERENTIAL DIAGNOSIS

- Brain abscess is usually diagnosed by CT or MRI. Ring enhancing masses are typically seen. However, ring enhancing masses may also be seen in tumors, cerebral infarction, radiation necrosis, acute demyelinating disease, granulomas and resolving cerebral hematomas.
- **BRAIN TUMORS**. Neoplasms are the most common cause of ring enhancing masses and are caused mainly by gliomas and metastasis. The average age for presentation for these two are 55-60 years of age. Brain tumor produces headache, seizures, mental changes, and focal weakness. The headache is usually relieved early by analgesics and is usually more severe in the morning hours. About 33% of brain tumors cause seizures.
- **POSTERIOR FOSSA TUMORS**. If the tumor is located in the posterior fossa or the patient develops hydrocephalus, gait ataxia may be present. Lesions that occur in the frontal, temporal or occipital lobes may be silent.
- **FRONTAL LOBE TUMORS**. Frontal lobe tumors may produce inattention, apathy and abulia.
- **TEMPORAL LOBE TUMORS**. Temporal lobes tumors can cause

olfactory hallucinations and personality alterations.

- The onset of brain tumors is usually subacute unless there is hemorrhage within the tumor which then can present as a stroke. Calcification in brain tumors is mainly seen with oligodendrogliomas. Gliomas characteristically spread through the corpus callosum to the opposite hemisphere.
- **BRAIN METASTASIS**. Brain metastasis usually originate from cancers of the lung, breast, or melanomas, but prostate, ovarian carcinomas and even sarcomas may metastasize to the brain occasionally. Lymphomas may metastasize to the brain, but account for only 1% of brain tumors. About 25% of lymphoma patients will have multiple lymphomatous brain lesions. Malignant gliomas are multifocal in only about 5% of cases. Clinically significant hemorrhage into the tumor occurs mainly in metastatic lesions from melanomas, choriocarcinomas, renal cell cancers and bronchogenic cancers.

BASICS OF ANTIBIOTIC THERAPY

- The organisms that are cultured from various sites of origin for cerebral abscess is well known, and therapy may be started empirically before stereotactic CT guided aspiration of the abscess is carried out.
- **PENICILLIN TREATMENT**. Those sites that have a high rate of isolation of streptococci are treated with penicillin G or cefotaxime of ceftriaxone. Penicillin G is also useful for Actinomyces and Fusobacterium anaerobic species. However, it is not active against Bacteroides fragilis which occurs in about 20-40% of brain abscesses.
- **METRONIDAZOLE TREATMENT**. For Bacteroides fragilis metronidazole should be used if possible, because it has several favorable attributes over alternative anaerobic antibiotics such as chloromycetin and clindamycin. Metronidazole achieves very high concentrations within the abscess, is bactericidal, and its influx into the abscess is not affected by concomitant steroid therapy.
- **NAFCILLIN AND VANCOMYCIN**. Staphylococcus aureus is common after cranial trauma and following neurosurgery. Nafcillin should be used in these cases unless the patient has a methicillin resistant

Staph aureus or is allergic to penicillin. If the latter is the case vancomycin should be used.

- **THIRD GENERATION ANTIBIOTICS**. For patients that have a high likley-hood of infection with the Enterobacteriaceae such as otitis patients, treatment is with a third generation cephalosporin or trimethoprim-sulfamethoxazole.
- **CEFTAZIDIME**. For Pseudomonas aeruginosa, ceftazidime is the drug of choice.
- **SULFONAMIDES**. If a Norcardial cerebral abscess is suspected sulfonamides either given alone or in combination with trimethoprim is a good initial choice.

EMPIRICAL THERAPY

- **SINUSITIS.** If the patient has CT findings consistent with sinusitis of the frontal, ethmoid or sphenoid sinuses the patient most likely is infected with Bacteroides species, Enterobacteriaceae, Streptococci, Haemophilus species or Staphylococcus aureus. The patient may be started on vancomycin 1 gram every 12 hours + metronidazole 30 mg/kg/day given every 6 hours + ceftriaxone 2 grams IV every 12 hours.
- **DENTAL INFECTION**. Dental infection is usually caused by streptococci, Bacteroides species and Fusobacterium. These will respond to Penicillin giving 4 million units IV every 4 hours + Metronidazole 30 mg/kg/day given every 6 hours.
- **OTITIS MEDIA AND MASTOIDITIS**. Bacterial isolates recovered usually consist of anaerobic or aerobic streptococci, Enterobacteriaceae and Bacteroides species. These will respond to penicillin 4 million units IV every 4 hours + metronidazole 30 mg/kg/day given every 6 hours + ceftriaxone 2 grams IV every 12 hours or Cefotaxime 2 grams IV every 4 hours.
- **LUNG ABSCESS, BRONCHIECTASIS OR EMPYEMA**. Organisms obtained from these sites include Bacteroides species, streptococci, Nocardia asteroides, Actinomyces and Fusobacterium. Treatment consists of penicillin 4 million units IV every 4 hours + metronidazole 30 mg/kg/day given as equal doses every 6 hours + Trimethoprim-sulfamethoxazole 10 mg/kg/day (trimethoprim) given every 12 hours.
- **BACTERIAL ENDOCARDITIS**. Common organisms isolated in

bacterial endocarditis include streptococci and Staphylococcus aureus. Empirical treatment would consist of vancomycin 1 gram IV every 12 hours + gentamicin 3-5 mg/kg/day given every 8 hours IV.

- **CONGENITAL HEART DISEASE**. Haemophilus species and streptococci are common bacterial organisms cultured out in congenital heart disease. If congenital heart disease is suspected as the cause of brain abscess begin therapy with penicillin 4 million units IV every 4 hours + ceftriaxone 2 grams IV every 12 hours or Cefotaxime 8-12 grams/day given every 4-6 hours.
- **POST NEUROSURGERY OR PENETRATING CRANIAL INJURIES**. Common infectious agents in this situation include Staphylococcus aureus, streptococci, Clostridium and enterobacteriaceae.
- **EMPIRIC TREATMENT**. Treatment before cultures have been obtained is with vancomycin 1 gram IV every 12 hours + ceftriaxone 2 grams IV every 12 hours or Cefotaxime 2 grams IV every 4 hours IV. Patients may be treated with surgery plus antibiotics or antibiotics only.

ANTIBIOTIC THERAPY WITHOUT SURGERY

- Patients that are treated with antibiotics alone include multiple abscesses, cerebral abscess plus meningitis or ependymitis, abscesses smaller than 3 cm, cerebritis that resolves with antibiotics, deep inaccessible locations of the abscess, and patients that are at high risk for brain surgery. If the patient has not had surgical excision of the abscess, but has been treated solely with antibiotics, the patient should be treated for about 4-6 weeks with IV therapy. Following the IV therapy, oral therapy with an appropriate agent may be continued for another 2-6 months.

ANTIBIOTIC THERAPY AND SURGERY

- If the patient has had surgical extirpation of the abscess, treatment with high dose IV antibiotics are given for about 3-4 weeks.

IMMUNOCOMPROMISE AND AIDS

- Of course, if the patient is immunocompromised, antibiotic treatment must be prolonged and in case of HIV infection must, in many cases,

be put on maintenance therapy. In AIDS, Toxoplasmosis is the most common cause of multiple enhancing brain lesions as seen on CT and MRI. Treatment of Toxoplasmosis is with pyrimethamine 25-100 mg/day orally given once a day + sulfadiazine 4-6 grams/day given every 6 hours orally.

D E M E N T I A

DEFINITION

- Dementia may be defined as an impairment of intellectual function, with gradual deterioration of cognitive function over a period of at least 6 months. There is impaired judgement and abstract thinking, personality change and altered cortical function such as apraxia, aphasia, and agnosia.
- The differential diagnosis is wide, but Alzheimer's dementia (DAT) and multi-infarct dementia (MID) account for about 85% of cases of dementia in those patients over the age of 65. There is no specific test for DAT and thus other causes must be ruled out. There is an increasing incidence of dementia as one ages.

ALZHEIMER'S DISEASE DEMENTIA

- **CLINICAL**. About 15% of DAT will have a family history of the disease. It is inherited as an autosomal dominant disease. Most cases, however are non-familial. DAT usually starts insidiously, but is always progressive with ultimate total disability. Death usually comes in about 15 years or sooner from infection or complications of the disease. In about 50% of patients there may be motor and extrapyramidal abnormalities. Depression is very common. Patients are unaware of their problems. There is inattention, difficulty with abstract reasoning and orientation. There is sparing of the visual system, the corticospinal and the corticosensory systems.
- **LABORATORY**.
- **CT**. CT of the head may show atrophy of the medial and anterior temporal lobes.
- **MRI**. The MRI also will show atrophy with a periventricular halo on the T2 weighted studies.
- **PET**. If positron emission tomographic scans are available they will show a decrease of cerebral oxygen and glucose metabolism, particularly in the parietal and temporal lobes.

MULTI-INFARCT DEMENTIA

- **CAUSES**. Multi-infarct dementia is less common than DAT, but can

easily be differentiated from DAT. MID is caused by multiple bilateral cerebrovascular occlusions as a result of either emboli or primary arterial occlusive disease. MID is usually caused by small lacunar infarcts with lipohyalinosis. Progression is usually predictable as each new infarct will worsen the clinical condition.

- **CLINICAL**. The patient may have a very slow thought process, irritability, apathy and inertia. MID is closely related to hypertension, diabetes mellitus, hyperlipidemia, smoking and cardiac disease. It becomes more common after the age of 60-70 and is more common in men. Depression is common and suicide may be entertained. The patient may develop pseudobulbar palsy, hemiplegia, extrapyramidal symptoms and abnormal inappropriate laughing and crying.
- **LABORATORY**
- **CT**. CT of the head typically demonstrates hypodensities in the periventricular white matter or the subcortical areas.
- **MRI**. MRI will also show these white matter lesions.

DRUG DEMENTIA

- **COMMON DRUGS**. Several drugs may cause a pseudodementia. The following medications in particular should send up a red flag in the elderly: Beta blockers, barbiturates, benzodiazepines, tricyclic antidepressants, anticholinergics, steroids, cimetidine, MAO inhibitors, reserpine, anticholinergics, and digitalis.
- **OCCASIONAL DRUGS**. Occasionally methyldopa, clonidine, phenytoin, baclofen, NSAIDs, and oral hypoglycemic agents will cause a dementia.

NORMAL PRESSURE HYDROCEPHALUS DEMENTIA

- **CAUSES.** Normal pressure hydrocephalus (NPH) is a communicating hydrocephalus. One should try to elicit a history of meningitis, encephalitis, subarachnoid hemorrhage or repeated head trauma as a cause for the dementia. A small minority of patients will have tumors of the midbrain causing the NPH.
- **CLINICAL**. The patient may present with a spastic ataxic gait, urinary incontinence and positive Babinski. The gait is usually described as slow, ataxic, shuffling and wide based.

- **LABORATORY**.
- **Isotope Cisternography**. Isotope cisternography may be useful in diagnosis.
- **CT**. The CT will show an enlargement of the ventricular system.
- **MRI.** MRI may show the CSF void sign which is a decreased image of the cerebral aqueduct due to increased CSF flow. Periventricular thinning may also be present.
- **TREATMENT**. Insertion of a ventriculoatrial shunt may alleviate some of the symptoms, but usually is not totally effective. Also, it is impossible to predict which patients will improve with the shunt.

AIDS DEMENTIA

- **CLINICAL.** Aids dementia usually is a late finding in HIV infection. The patient will have slowing of motor function and thinking, apathy, difficulty in concentrating, ataxia and extensor plantar responses.
- **TREATMENT**. Zidovudine may improve the dementia.

DEPRESSION DEMENTIA

- **CLINICAL**. A helpful clue in diagnosing dementia caused by depression is that the patient will often complain of memory loss, whereas in other dementias the patient will not complain of memory loss.
- Even though depressed patients respond to questions slowly, the answers are usually accurate.
- Current events are usually not lost in depressive dementia, and these patients also have their best behavior at night time.
- In addition, the appetite is poor, there is disturbance of sleep, and constipation.

METABOLIC DEMENTIA

- **HYPOTHYROIDISM AND HYPERTHYROIDISM**. Hypothyroidism and hyperthyroidism can sometimes be confused with dementias. However high sensitive TSH blood tests can be used to rule out these two causes.
- **HYPONATREMIA AND HYPERCALCEMIA**. Hyponatremia and hypercalcemia can also lead to a demented state.

SUBDURAL DEMENTIA

- **CAUSES**. In alcoholic and elderly patients a subdural hematoma should be suspected of causing a dementia. Most patients do not remember the trauma that caused the hematoma.

INFECTIOUS DEMENTIA

- **CAUSES**. Chronic meningitis from fungal and tuberculosis infections can cause dementias. Also neurosyphilis, HIV and viral infections as Creutzfeldt-Jakob disease may lead to dementias.
- **CREUTZFELDT-JAKOB DEMENTIA**. Creutzfeldt-Jakob is characterized by a rapidly progressing dementia, myoclonus, rigidity and behavioral changes. The EEG shows triphasic waves. There is no treatment for Creutzfeldt-Jakob disease and it usually is fatal in 1-2 years.

ALCOHOLIC DEMENTIA

- **CAUSES**. Wernicke's encephalopathy and Korsakoff's syndrome may cause dementia. Even chronic alcoholism itself may lead to cerebral atrophy and dementia.

B12 AND FOLATE DEFICIENCY DEMENTIA

- In particular, Vitamin B12 deficiency can cause a dementia. The dementia may occur early prior to the typical blood changes and peripheral neuropathy that accompany B12 deficiency.

LABORATORY

- The following lab tests should be done if deemed appropriate: B12 and Folate, FTA, CT or MRI of the head, heavy metal and toxicologic analysis, EEG, Lumbar puncture, thyroid tests, Cortisol, hepatic tests, electrolytes, HIV, isotope cisternography, VDRL, calcium, ceruloploasmin, magnesium and ANA.

ENTRAPMENT SYNDROMES

MEDIAN NERVE NEUROPATHIES

- Median nerve entrapment causes the carpal tunnel syndrome (CTS). CTS is the most common of the entrapment syndromes and is caused by compression of the median nerve beneath the flexor retinaculum at the wrist.
- **CAUSES.** The causes of this syndrome include pregnancy, rheumatoid arthritis, acromegaly, gout, myxedema, amyloidosis, trauma, idiopathic, calcium pyrophosphate dihydrate deposition, obesity, multiple myeloma, occupational trauma, and Waldenstrom's macroglobulinemia.
- **SYMPTOMS**. Symptoms of CTS include intermittent hand and finger numbness of the first three fingers including the thumb, index, and middle fingers. There may be pain and paresthesiae of the palm and fingers also. The pain may extend to the forearm and occasionally up to the shoulder. The pain is typically worse at night time, or can be precipitated by certain maneuvers as typing, driving, playing the piano and flexion at the wrist. Patients will typically try to eradicate the symptoms by shaking the hand, particularly at night time when the symptoms are worse.
- **NEUROLOGIC EXAM**. Neurologic exam of the hand reveals loss of sensation in the palm, first three fingers, atrophy of the thenar muscle, and weakness of the thumb pinching mechanism. Weakness and atrophy of the thenar muscles are late signs. There are three tests that help solidify the diagnosis.
- **Tinel's sign**. The first is Tinel's sign which consists of tapping the median nerve at an extended wrist in an attempt to reproduce the symptoms.
- **Phalen's sign**. Phalen's sign is reproduction of symptoms with the wrist in flexion for 1 min. This test is positive in about 80% of cases.
- **EMG and NERVE CONDUCTION STUDIES**. The third test includes EMG and nerve conduction velocity studies which will usually diagnose the condition.
- **TREATMENT**. Treatment consists of wrist splinting, nonsteroidal anti-inflammatory drugs, focal steroid injection around the median nerve and surgical release of the retinaculum.

PRONATOR TERES OR ANTERIOR INTEROSSEOUS SYNDROME

- **ANATOMY.** The median nerve as it passes below the elbow gives off a motor branch, the anterior interosseous nerve which then passes between the two heads of the pronator teres muscle.
- **CAUSES.** Compression of the median nerve or the anterior interosseous nerve in the forearm may be caused by osseous deformities, fractures, casts, trauma, fibrous bands or muscle hypertrophy in the forearm.
- **SYMPTOMS**. The symptoms of anterior interosseous nerve involvement are usually sensory loss and weakness of the pronator quadratus, flexor pollicis longus and the flexor digitorum profundus of the second and third digits. Painless weakness of flexion of the first three fingers can be confused with carpal tunnel syndrome.

ULNAR NEUROPATHY

- The ulnar nerve can become entrapped at two sites; either the cubital tunnel at the elbow or in Guyon's canal between the pisiform and the hook of the hamate at the wrist.
- **MOST COMMON SITE OF ENTRAPMENT**. The most common site of entrapment is at the elbow in the medial condylar groove or the cubital tunnel between the medial ligament of the elbow joint and the aponeurosis of the flexor carpi ulnaris. The ulnar nerve gives sensation to the ulnar side of the hand and the palmar and dorsal sides of the 4th and 5th fingers. Motor supply controls flexion of the 4th and 5th digits, flexion of the wrist, and flexion of the intrinsic muscles of the hand.
- **CAUSES.**
- **Elbow**. Causes of compression include displacement of the ulnar nerve from a shallow nerve groove, prolonged pressure trauma at the elbow, drug addiction and diabetes mellitus.
- **Wrist**. At the wrist, symptoms may be caused by hand drills, volleyball sports, prolonged bicycling, ganglions and, trauma.
- **SYMPTOMS.** Symptoms of ulnar compression at the elbow include pain over the ulnar side of the forearm, weakness of wrist flexion and weakness of finger adduction and abduction plus paresthesiae of the 4th and 5th digits. There may be atrophy of the first dorsal interosseous muscle and hypothenar wasting.

- **DIAGNOSIS**. Diagnosis is made by a positive Tinel's sign along with EMG and nerve conduction studies.
- **TREATMENT**. Conservative measures may be given a trial, but surgery often times is needed.

THORACIC OUTLET SYNDROME

- **SYMPTOMS**. Thoracic outlet syndrome (TOS) causes diffuse, poorly localized paresthesiae, weakness of the arm or hand and vascular changes. Patients will have sensory loss in the C8-T1 distribution with atrophy and weakness in muscles that are supplied by the lower trunk of the brachial plexus.
- There may be sensory loss along the ulnar border of the arm and
- clumsiness of the hand. The patient may complain of pain with exercise of the arm or coldness of the extremity.
- The symptoms may occur when the arms are extended above the head or when excessive weights pull the shoulder and arm downward as carrying heavy objects.
- **CAUSES**. Causes consist of compression of the neurovascular bundle by hypertrophied muscle, fibrous bands or cervical ribs as the neurovascular bundle exits the neck.
- **DIFFERENTIAL DIAGNOSIS**. The differential diagnosis would include median and ulnar neuropathies, cervical radiculopathies, sympathetic dystrophy and various vascular syndromes.
- **TESTING**. Tests include Adson's maneuver (loss of the radial pulse when the head is rotated to the opposite side and the involved arm is abducted, EMG and nerve conduction studies, MRI of the neck and angiography. All of these tests may be performed, but in most instances they seldom lead to a definite diagnosis.
- **TREATMENT**. Since the syndrome is somewhat nebulous, conservative therapy should be attempted before surgery. In about 2/3 of the cases exercises adapted to elevate the shoulders will afford relief of the syndrome. If the patient doesn't respond to conservative measures then surgical decompression with rib resection may help.

SCIATIC NEUROPATHIES

- **CAUSES**. Usually Sciatic radiculopathy is produced by nerve impingement in the lumbosacral spine area. However, entrapment

syndromes may be caused by Baker's cysts, tumors, retroperitoneal hemorrhage, intramuscular injections, emaciation and immobility, and sciatic notch obstruction by muscle.

- **SYMPTOMS**. The patient usually presents with foot drop, absent ankle reflexes, and sensory loss of the foot.
- **TESTING**. EMG is useful in localizing the defect in order to prevent back surgery due to erroneous diagnosis.

RADIAL NEUROPATHIES

- **SYMPTOMS**. Radial neuropathies usually present as a painless wrist drop and inability to extend the fingers. Most cases can be treated conservatively. The radial nerve supplies all of the extensor muscles of the fingers, wrist and forearm.
- **CAUSES**. The radial nerve is usually compressed in the axilla by crutches, or by hanging the arm over the back of a chair for prolonged periods, and humeral fractures. Inebriated individuals may injure the radial nerve in the spiral groove during sleep (Saturday night palsy), in which case there is sparing of the triceps muscle. The posterior interosseous nerve is a distal branch of the radial nerve and can be compressed at the elbow by trauma or synovitis which may produce pain in the forearm and loss of the ability to extend the fingers.
- **TESTING**. EMG will localized the lesion.
- **TREATMENT**. While conservative therapy will usually alleviate the axillary compression, surgical decompression is frequently required for entrapment of the posterior interosseous nerve.

MERALGIA PARESTHETICA

- **SYMPTOMS**. Any patient that complains of burning and paresthesias along the lateral thigh may have meralgia paresthetica. The symptoms are made worse by standing, hip extension, obesity, lumbar lordosis, pregnancy, diabetics, tight clothing or seat belts. Symptoms may be by relieved by sitting.
- **CAUSES**. The syndrome is caused by entrapment of the lateral femoral cutaneous nerve, a purely sensory branch arising from the L2 and L3 roots. The nerve runs under the lateral aspect of the inguinal ligament. There may be an anomalous split of the inguinal ligament which then pinches the nerve.

- **DIAGNOSIS**. A diagnostic injection of Xylocaine may be made just medial to the anterior iliac spine at the inguinal ligament. If this alleviates the symptoms then cortisone injections in this area may be of benefit. However, the underlying causes should be taken care of as correction of these will benefit many patients.
- **NEUROLOGICAL EXAM**. Examination of the lateral thigh area will reveal diminished sensation in this area.
- **TESTING**. Again EMG and nerve conduction studies will help differentiate the condition from lumbar radiculopathies.

COMMON PERONEAL NEUROPATHIES

- **CAUSES**. Entrapment of this nerve as it winds around the fibula may be caused by Baker's cysts, high boots, elastic stockings, post surgical procedures, casts, leg crossers, bedridden, emaciated and immobile patients.
- **SYMPTOMS.** The patient usually presents with a painless foot drop. If the patient has pain of the foot, sensory loss of the plantar aspect of the foot or weakness of plantar flexion then suspect a more proximal lesion.
- **TESTING**. If there is any doubt, EMG and nerve conduction studies should be done which will localize the lesion.
- **TREATMENT**. Most patients will recover within 2-12 months with such conservative measures as bracing of the foot.

TARSAL TUNNEL SYNDROME

- **ANATOMY AND NEUROLOGY**. Entrapment of the posterior tibial nerve is the cause of this syndrome. The tibial nerve, a branch of the sciatic nerve, gives off the sural nerve and then continues as the posterior tibial nerve passing through the tarsal tunnel behind and below the medial malleolus of the ankle. The posterior tibial nerve gives off branches to the plantar surface of the toes and the foot.
- **SYMPTOMS**. When the posterior tibial nerve and its branches are compressed there is numbness, paresthesias and pain over the plantar aspect of the foot. The heel is spared and the pain is usually worse at night just as in the carpal tunnel syndrome.
- **DIFFERENTIAL DIAGNOSIS**. The differential diagnosis would

include plantar fasciitis, synovitis, peripheral neuropathy and bursitis. There may be a positive Tinel's sign. Inverting and medially rotating the foot may also reproduce the symptoms.

- **TESTING**. EMG will confirm the diagnosis if there is any doubt.
- **TREATMENT.** Treatment includes non-steroidal inflammatory medications, arch supports, steroid injections around the nerve and surgical decompression of the posterior tibial nerve or its branches.

FEMORAL NEUROPATHIES

- **SYMPTOMS**. Femoral neuropathy typically presents as quadriceps muscle weakness, paralysis or atrophy. The knee jerk is diminished to absent and there is anteromedial thigh sensory loss. Occasionally there is pain in the groin.
- **CAUSES**. Causes include trauma, blunt or penetrating injury, diabetes mellitus, retroperitoneal hematomas, neoplasms or enlarging aortic aneurysms.

ESOPHAGEAL VARICEAL BLEEDING

- Bleeding esophageal varices can be a devastating disease with exsanguination occurring suddenly. There may be mortality rates of 50% at 6 weeks following the initial bleed and 75% at 2 years. Multiple therapeutic measures have been employed over the years to curb the bleeding, but the bottom line is that the underlying chronic liver disease, rather than the treatment, is the prognostic factor.

CHILD'S CLASSIFICATION AND MORTALITY

- Patients with Child's class A have a combined early and late mortality of 0-5% when treated surgically. Patients with Child's class C have mortality rates of 64-68%.

CAUSES OF PORTAL HYPERTENSION

- The most common cause of portal hypertension is cirrhosis, although any number of conditions can be associated with esophageal varices. These include prehepatic disorders such as portal vein thrombosis, intrahepatic disease (usually cirrhosis), and post hepatic obstruction as in vena caval thrombosis.

PHYSIOLOGY OF THE PORTAL SYSTEM

- Patients that have persistent elevation of the portal vein pressure greater than 12 mm Hg is commonly associated with the development of collaterals from the portal to the systemic circulation. In order to by-pass the liver, the blood travels through the short gastric and coronary veins, then coursing through the periesophageal plexus to the azygous system. This will in turn produce dilated veins in the esophagus and fundus of the stomach. Bleeding may occur from the esophageal varices, gastric varices, or other varices in the GI tract. The paraumbilical veins may dilate leading to abdominal wall veins and caput medusae. Dilation of the inferior mesenteric vein can result in hemorrhoids with bleeding. Portal pressure can be approximated by the hepatic vein gradient, which is the difference between the wedged hepatic vein pressure and the free hepatic vein

pressure.

CLINICAL

- About 30% of patients with esophageal varices will have bleeding. The typical presentation is with emesis of bright red blood. About 50% will stop bleeding temporarily, but rebleeds are common at 20-58%. About 60% will have rebleeding within the first week. Endoscopy is the procedure of choice for diagnosis and treatment. This may reveal active variceal bleeding or oozing, adherent clot to the varix, erosions over the varices, or overlying cherry red spots.

TYPICAL APPROACH TO TREATMENT

- **SCLEROTHERAPY OR BANDING**. In general, most patients that present with acute variceal bleeding should initially receive sclerotherapy or band ligation. If rebleeding occurs, there should be a second attempt to endoscopically control the bleeding. If successful, the patient should be placed in a program to obliterate their varices with banding or sclerotherapy. Following this, endoscopy should be undertaken every 6 months for repeat obliteration if there is found to be recurrence.
- **PHARMOCOLOGIC APPROACH**. If sclerotherapy and banding are unsuccessful, vasopressin and nitroglycerin, or somatostatin should be attempted.
- **TIPS**. If bleeding persists following pharmacologic methods, transjugular intrahepatic portosystemic shunting, or shunt surgery should be used.
- **BALLOON TAMPONADE**. Balloon tamponade is usually reserved as an emergency measure to curb the bleeding until a more definitive therapeutic maneuver can be employed.

THERAPY

- **GENERAL.** The patient should have nasogastric intubation to lavage the stomach prior to endoscopy using a large caliber Ewald tube. Two large bore IV lines should be established. Abnormal PTs should be corrected with vitamin K, fresh frozen plasma or fresh whole blood that is less than 5 days old.
- Patients should be continuously followed for hypoglycemia, alcoholic

withdrawal, renal failure, ascites, septicemia, malnutrition and hypoxemia. H2-receptor blockers are not beneficial in preventing recurrent variceal hemorrhage.

- **BLOOD TRANSFUSION**. Blood transfusion should be limited to a hematocrit goal of 30-35, because further expansion can increase portal vein pressure leading to more bleeding. Transfusion of 500 ml of whole blood can raise the portal vein pressure by 5 mm Hg.
- **HEPATIC ENCEPHALOPATHY**. Hepatic encephalopathy should be prevented or treated with lactulose 30-45 ml TID, or as a retention enema, 300 ml diluted to 1000 ml with water. To avert encephalopathy, neomycin can be added to provide synergistic support. Metronidazole 200 mg q6h may be just as effective as neomycin. Patients should not receive diuretics or sedation, as this will lead to encephalopathy and hepatic coma.
- **PHARMACOLOGIC THERAPY**.
- **Vasopressin**. The most commonly used agent is vasopressin which can be used to reduce portal pressure by causing vasoconstriction of the splanchnic vessels. To accomplish this, add 10-15 units of vasopressin to 100-200 ml D5W and administer over 10-15 minutes, followed by a continuous infusion of 0.1-0.5 units/min. (Add 600 units of vasopressin to 250 ml of D5W and deliver at 10 ml/hour, which will give a rate of 0.4 units/minute). It has been shown to temporarily stop variceal hemorrhage in 60-70% of patients.
- ***Side Effects of Vasopressin***. It does have several undesirable side effects, such as decreased coronary blood flow, angina, infarction, hyponatremia, bacterial peritonitis, hypertension, oliguria, bacteremia, local gangrene, activation of fibrinolysis, ischemic bowel disease, cardiac arrhythmias, and decreased cardiac contractility. Side effects occur in 17-35% of cases, and a 3% fatality rate. Vasopressin has no effect on survival.
- **Nitroglycerin or Nitroprusside**. It is recommended that nitroglycerin sublingually, or IV nitroprusside be given concurrently. Nitroprusside is given at 1-5 ug/kg/minute IV.
- **Somatostatin and Octreotide**. Somatostatin and its synthetic analogue octreotide will also decrease splanchnic blood flow. Somatostatin does not have the severe side effects associated with vasopressin, and nitroglycerin is not needed. However somatostatin is not commonly used because of its cost. Somatostatin

is given as a 250 ug loading dose then 250 ug/hour.

- **Beta Blockers**. Beta blockers have not shown consistently reduced rebleeding rates in patients who have bled from varices. However, beta blockers such as propranolol or nadolol has shown reduction of first bleeds in patients with esophageal varices.
- **TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS).** TIPS is a radiologic application of an expandable metal tent from a branch of the hepatic vein through the hepatic parenchyma into a branch of the portal vein.
- **Indications**. TIPS is probably most valuable in patients who have failed sclerotherapy, and are not candidates for decompressive surgery due to advanced liver disease, OR in those patients who bleed while waiting for a liver transplant. The success of this procedure is about 90% and active variceal bleeding can be controlled in greater than 90% of patients.
- **Complications of TIPS**. However, rebleeding rates of 10-20% have been seen at one year. Encephalopathy can develop in 25% of patients, particularly if the 10 mm stent is used, rather than the 8 mm shunt. Other complications of the procedure include shunt closure in 10% and shunt stenosis in up to 15%. However, this may be corrected by balloon dilation, or placement of another stent. Migration of the stent, portal vein thrombosis, hepatic infarction, abdominal hemorrhage are other complications.
- **SURGICAL THERAPY**.
- **Distal Splenorenal Shunt**. Blood flow to the liver is compromised with all shunting procedures and can lead to hepatic decompensation. The selective distal splenorenal shunt was devised in order to preserve blood flow and thus decrease the encephalopathy. However, this has not been the case, because of a high incidence of portal blood flow reversal with time. It also has a high perioperative mortality when done as an emergency, and is technically difficult to perform. It may be useful if the patient is a candidate for liver transplantation as it avoids the hilum of the liver.
- **Sugiura Procedure**. Another surgical procedure is transection of the esophageal varices with splenectomy and devascularization of the esophagus and stomach (Sugiura procedure). This procedure has met with some success.
- *Contraindications for Surgery*. Portosystemic shunts and esophageal transection should not be used in Child's class C cirrhotic

patients who have persistent encephalopathy and severe coagulopathies.

- **BALLOON TAMPONADE**. Balloon tamponade is only a temporizing measure. It can control bleeding in 90-95% of patients, but about 60% will rebleed following balloon deflation. The 3 lumen, 2 balloon Sengstaken-Blakemore tube or the Minnesota tube which is a four-lumen tube may be used to control active bleeding. The Linton-Nachlas tube, which is a 3 lumen tube with one gastric balloon is used more for gastric varices. The complication rate is high at about 25-30%, including esophageal perforation, ulceration and aspiration pneumonia.
- **SCLEROTHERAPY**. Sclerotherapy is the initial procedure of choice for variceal bleeding. It can control acute variceal bleeding in up to 95% of cases, with eradication of the varices in about 75%. Recurrent bleeding will occur in about 33% of patients that are treated with sclerotherapy alone.
- **Procedure**. Injection sclerotherapy is accomplished using a catheter with a retractable needle which is passed through the operating channel of the endoscope. Injections can be made directly into the varices, or in the paravariceal area. The sclerosing agents used most commonly in the USA are 5% ethanolamine oleate and 3% sodium tetradecyl sulphate, which have equivalent efficacy. Injection sclerotherapy not a benign procedure.
- **Side Effects of Sclerotherapy**. Side effects include esophageal ulceration, stricture, portal vein thrombosis, bacterial peritonitis, paralysis, pleural effusion, fever, chest pain, bacteremia, ARDS, brain abscess, sepsis, and pericarditis. Sclerotherapy should not be used as a preventative measure in those who have not bled from esophageal varices, as it is not consistently effective.
- **BANDING.** Because of the numerous side effects, endoscopic variceal ligation was developed. In this procedure elastic bands are placed directly onto the varix. This procedure is just as good or better than sclerotherapy in controlling bleeding. Furthermore, band therapy can eradicate the varices with a fewer number of sessions, and is associated with fewer complications than sclerotherapy.
- **Side effects of Banding**. The most common side effects of banding are dysphagia and chest pain.

G L O M E R U L O N E P H R I T I S - M I N I M A L

CLINICAL

- **OVERVIEW**. Minimal change glomerulonephritis (MCG) is a nephropathy that occurs mainly in children aged 2-6 years, but it may constitute up to 25% of adult cases of nephrotic syndrome. It has a male predominance of about 3:1, and is the most common cause of nephrotic syndrome in children. It also is known as nil disease, light negative glomerulonephritis or lipoid nephrosis.
- **CAUSES**.
- **Hodgkin's Disease and Lymphomas**. The cause is unknown but rarely may develop in Hodgkin's disease and other lymphomas.
- **Drugs.** Fenoprofen, ibuprofen, naproxen, tolmetin, sulindac, and indomethacin have also been known to cause a similar syndrome.
- **Immunologic**. Several factors as the following point to an immunologic cause. It is very responsive to steroids; it is associated with Hodgkin's disease; there is an increased prevalence of HLA-B12, and it is frequently seen in atopic individuals.
- **PRESENTATION.** Almost 75% of cases present with edema and about 33% develop after an upper respiratory infection. Hypertension, azotemia and hematuria are uncommon in minimal glomerulonephritis. Hypertension occurs in 10% of children and 35% of adults. Azotemia occurs in about 23% of children and in 34% of adults. Some patients have an atopic history with urticaria and asthma.
- **CLINICAL COURSE**. Most patient have a benign clinical course with spontaneous remission and relapses being common.
- **COMPLICATIONS**.
- **Infection**. There is an increased susceptibility to infection with Pneumococcus, Klebsiella and Hemophilus, if the proteinuria is profound.
- **Thrombosis**. There also may be thrombosis of renal and peripheral veins secondary to a hypercoagulable state.

LABORATORY

- **PROTEINURIA AND CHOLESTEROL**. Typically, there is proteinuria

over 50 mg/kg/day associated with a serum cholesterol greater than 300 mg/dl, and an albumin less than 2 gm/dl.

- In children, the proteinuria is highly selective, but is mostly albumin in adults.
- **OTHER FINDINGS**. There may be Maltese crosses, and lipiduria. Serum IgG may be decreased, and serum complement levels are normal.
- **LIGHT MICROSCOPY AND IMMUNOFLUORESCENCE**. The glomeruli are normal with light microscopy and immunofluorescence is negative.
- **ELECTRON MICROSCOPY**. Electron microscopy reveals fusion of the epithelial cell foot processes.
- **CIRCULATING IMMUNE COMPLEXES**. Even though there are no glomerular deposits, circulating immune complexes have been reported in children and adults.

TREATMENT

- **SPONTANEOUS RESOLUTION**. About 50% of patients with nil disease will have spontaneous remissions over a 2-3 year period. However, without treatment, thrombosis and spontaneous peritonitis may develop.
- **PREDNISONE**. Therefore, treatment is initially with prednisone, and the response is excellent. Greater than 90% will have a complete remission of the proteinuria within 2 months after starting prednisone at 60 mg/M2 or 1-2 mg/kg/day. This dosage is continued for about 4 weeks then tapered over 8-12 weeks and eventually discontinued after the patient has had no proteinuria for about 4 weeks.
- When adults are treated in the same manner, the response is only about 75-80% and adults may need a longer course of therapy up to 16 weeks of treatment.
- **Alternate Day Prednisone**. Alternate day therapy with prednisone gives a good initial response, but there is a relapse rate that is doubled over the daily regime. In spite of this, alternate day therapy may be used in certain subsets of patients such as those with diabetes mellitus, ulcer disease, chronic malnutrition and the elderly.
- **Relapse Rates**. The relapse rate in children at 1 year is 50% and at 5 years 80%. In adults, the relapse rate at 1 year is 30% and at 5 years 50%. After a child reaches puberty the relapse rate is about

10%.

- **CYCLOPHOSPHAMIDE**. For those that relapse, or are initially steroid resistant, cyclophosphamide should be started at 1.5-2.5 mg/kg given daily for 8-10 weeks. Some patients are steroid resistant because there is associated focal sclerosis.
- **Cumulative Dose and Duration of Treatment for Cyclophosphamide**. Because cyclophosphamide is capable of causing malignancy and gonadal toxicity, the cumulative dose of cyclophosphamide should be kept less than 250 mg/kg. The 8-10 week course may be repeated once. The goal is to keep the total neutrophil count above 1500/mm3. Fluids should be forced in order to prevent hematuria and bladder irritation.

PROGNOSIS

- About 75% of patients will be off therapy and will have no proteinuria at 10 years. There is no mortality related to renal insufficiency, but there can be less than 5% mortality secondary to infections and vascular complications.

H I R S U T I S M

DEFINITION

- Hirsutism is due to increased androgen production and can be defined as excessive coarse terminal hair accumulation on the face, abdomen, chest, lower back and thighs. Terminal hair on the lower abdomen, around the areolae and even on the face may be normal. This must be differentiated from hypertrichosis which is an excess of thin vellus hair, which depends on race and familial background.

ORGANS PRODUCING ANDROGENS

- Androgens include testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEAS). In women, the ovaries and adrenal glands produce androgens.
- **TESTOSTERONE AND ANDROSTENEDIONE BY THE OVARY**. Circulating testosterone is derived from direct ovarian secretion (60%) and by peripheral conversion from androstenedione (40%. Testosterone and androstenedione are secreted from the ovary, and androstenedione must be converted to testosterone in order to produce an androgenic effect. Testosterone is 98% bound. Only the free testosterone can exert an androgenic effect. Testosterone is converted to dihydrotestosterone (DHT) in the skin which can then stimulate the hair follicle.
- **ANDROSTENEDIONE SECRETION BY THE OVARY AND ADRENAL**. Androstenedione is secreted in equal amounts by the ovary and the adrenal.
- **DHEAS SECRETION ONLY BY THE ADRENALS**. DHEAS is only secreted by the adrenals. DHEA, DHEA-sulfate and androstenedione are produced by the adrenal gland.

DIFFERENTIAL DIAGNOSIS

- **CUSHING'S SYNDROME**. Cushing's syndrome is produced by excessive ACTH, either by the pituitary or ectopically, and usually is not a common cause of hirsutism. The dexamethasone screening test can be initially used, or the 24 hour urinary collection for free cortisol can be performed for diagnosis.

- **OVARIAN TUMORS**. Ovarian tumors such as Sertoli-Leydig cell tumors, dysgerminomas, hilar cell tumors and arrhenoblastomas may occasionally cause hirsutism. Most tumors of the ovary are palpable on the pelvic exam.
- **POLYCYSTIC OVARY**. Polycystic ovary syndrome may present with amenorrhea or oligomenorrhea, infertility, dysfunctional bleeding, obesity and anovulation. The obesity is only seen in about 50% of cases. Usually the polycystic ovaries are enlarged 2-5 times, with multiple follicular and atretic cysts, but not always. There may be a family history which is inherited as an autosomal dominant pattern. The testosterone is often elevated. The LH:FSH ration is > 2.0. By far, polycystic ovary syndrome and idiopathic hirsutism are the most common causes of hirsutism. The onset is at or near the time of puberty. If the DHEA-S is elevated, but below 700 ug/dl and the
- testosterone is elevated, but less than 200 ng/dl suspect PCO.
- **ADRENAL CARCINOMA**. Adrenal carcinoma can cause virilization which can be quite striking. DHEA-S values greater than 700 ug/dl are usually due to adrenal tumors. A CT should be done. If a tumor is not seen, adrenal hyperplasia can occasionally cause very high levels of DHEA-S. Some adrenal tumors are palpable.
- **CONGENITAL ADRENAL ENZYME DEFECTS**. Congenital adrenal enzyme defects such as a 21-hydroxylase deficiency can cause ambiguous genitalia and hirsutism in female patients. The 21-hydroxylase deficiency is the most common, but there may be 11-hydroxylase and 3 beta hydroxysteroid dehydrogenase deficiency. About 1.2 - 6% of adult patients have a partial defect in adrenal 21-hydroxylase that can cause hirsutism. In these patients you should measure the early morning 17-hydroxyprogesterone
- level as it is usually elevated.
- **IDIOPATHIC HIRSUTISM**. Idiopathic hirsutism has no detectable hyperandrogenism. Most of these patients have regular menses but can be irregular. In this subset, there is increased hair follicle sensitivity to androgens with normal androgen levels. If the DHEA-S is elevated, but below 700 ug/dl, and the testosterone is elevated, but less than 200 ng/dl, suspect idiopathic hirsutism.
- **PROLACTINOMA**. About 25% of women with prolactinoma and the amenorrhea/galactorrhea syndrome have idiopathic hirsutism or polycystic ovarian syndrome.
- **DRUGS CAUSING HIRSUTISM**. The following drugs can cause

hirsutism: Minoxidil, dilantin, diazoxide, androgens, steroids, cyclosporin, danazol, ACTH, metyrapone, anabolic steroids, and progestins.

- Prolactin elevation can cause hirsutism, and the following drugs can elevate the prolactin: Tranquilizers (thioxanthenes, butyrophenones), Narcotics (as morphine and heroin), Antidepressants (as MAO inhibitors), Antihypertensives (as aldomet, guanethidine and reserpine), Antiemetics (as metoclopramide), Antihistamines (as tagamet, meclizine and tripelennamine) and estrogens. Diseases capable of causing prolactin elevation are sarcoidosis, histiocytosis, hypothyroidism, renal failure and hepatic cirrhosis.

LABORATORY

- **FREE TESTOSTERONE**. Free Testosterone may be elevated due to adrenal or ovarian overproduction, or increased peripheral conversion of androstenedione to testosterone. In women with idiopathic hirsutism or Polycystic ovarian syndrome the serum testosterone is often elevated. (70-80% in polycystic ovarian syndrome). Levels of total testosterone greater than 200 ng/dl are frequently present in patients with ovarian and adrenal tumors, but rarely above 200 with idiopathic or polycystic ovarian syndrome. If patients with polycystic syndrome are put on the "pill" (estrogen-progesterone) the testosterone will normalize, but will not normalize with ovarian tumor.
- **PROLACTIN**. Prolactin may be elevated. If elevated, then MRI of the pituitary may be in order. If there is galactorrhea or menstrual disturbance then this test should be ordered. If the level is twice normal then evaluation for a pituitary tumor should be done. Values less than this are commonly elevated in idiopathic hirsutism and polycystic ovary syndrome.
- **DHEAS-S**. DHEAS-S may be elevated in adrenal overproduction. Extremely high levels of DHEA-S greater than 700 ug/dl may be found in adrenal tumors. Lesser elevations between 450 and 700 ug/dl may be seen in idiopathic hirsutism and polycystic ovarian syndrome, congenital adrenal hyperplasia and some virilizing adrenal tumors. The DHEAS-S is not a good test for congenital adrenal hyperplasia as the levels are usually normal.
- **LH:FSH RATIO**. LH:FSH RATIO is typically increased in polycystic

ovary syndrome.

- **17-OH PROGESTERONE**. 17-OH progesterone is typically elevated in congenital adrenal hyperplasia (21-OH deficiency).
- **ACTH STIMULATION TEST**. Basal levels of 17 OH progesterone may be normal, but elevated 17 OH progesterone levels in late onset 21 OH deficiency may be seen after ACTH stimulation. 0.25 mg of synthetic ACTH is given IV and then the 17 OH progesterone level is measured in 1 hour.
- **17-OH CORTICOSTEROIDS**. 17-OH corticosteroids and free cortisol in 24 hour urine samples is done for diagnosis of Cushing's syndrome. The 24 hour urinary free cortisol is the method of choice.
- **17-KETOSTEROIDS**. 17 Ketosteroids are usually markedly elevated in adrenal cancer.
- **CT OF THE ADRENALS**. CT scan of adrenals may reveal an adrenal mass.
- **PELVIC ULTRASOUND**. Pelvic Ultrasound may show polycystic ovaries or ovarian mass.
- **DEXAMETHASONE SUPPRESSION TEST**. If DHEA sulfate is increased to > 700 ug/dl, then do this test using .5 mg qid for 3 days, then repeat DHEA-S. If the DHEA-S is suppressed, this would indicate congenital adrenal hyperplasia. Tumors of the adrenal will not suppress.

TREATMENT

- **SPIRONOLACTONE.** Aldactone (Spironolactone) 100 to 200 mg daily in divided dosage may be beneficial.
- **BIRTH CONTROL PILLS**. Birth control pills are effective in only about 30%.
- **FLUTAMIDE**. Flutamide (Eulexin) is being investigated for hirsutism.
- **DEXAMETHASONE**. Dexamethasone .5 mg at h.s. is effective for congenital adrenal hyperplasia.
- **DISCONTINUE OFFENDING DRUGS**. Any drug that is causing the hirsutism should be discontinued.
- **TREATMENT OF SECONDARY DISEASES**. All secondary diseases that have caused the hirsutism should be treated.
- **OTHER**. Shaving, waxing, depilatories, electrolysis and bleaching all can be used.

HIV AND FEVER

- Fever may be assessed by using CD4 counts. Fever in the HIV patient may be infectious or non-infectious such as drug fever or non-Hodgkin's lymphoma. If there is protracted fever longer than 2 weeks, attention should be directed toward Pneumocystis carinii pneumonia, Mycobacterium avium complex infection, cryptococcosis, non-Hodgkin's lymphoma, sinusitis and tuberculosis.
- If a HIV patient has been on prophylactic trimethoprim-sulfamethoxazole (TMP-SMZ) you can probably exclude toxoplasma encephalitis, P. carinii pneumonia, and drug-susceptible salmonella bacteremia.
- It also is important to identify the TYPE of patient that you are dealing with as homosexual and bisexual men often do no practice safe sex. This can lead to fever secondary to proctitis from Chlamydia trachomatis, herpes simplex virus, or Treponema pallidum. Shigella or Campylobacter species, Entamoeba histolytica, C. Trachomatis, and Clostridium difficile may all cause a proctocolitis and fever. Patient that are known to use IV drugs are predisposed to soft tissue infections (necrotizing fasciitis, cellulitis and abscess), TB (pulmonary and extrapulmonary), infectious hepatitis (B, C, D), septic arthritis, osteomyelitis, bacterial pneumonia, endocarditis, mycotic aneurysm, meningitis, splenic and renal abscesses, septic thrombophlebitis, bacteremia, fungemia, and sexually transmitted diseases such as PID and syphilis.
- It is also valuable to review the patient's history for immunizations and base line lab values that were done initially when HIV was discovered.

DRUG INDUCED FEVER

- HIV patients may be taking multiple medications for prevention of infections, antivirals for controlling HIV, and medications to treat infections, neoplastic and autoimmune disease.
- **ANTIMICROBIALS**. TMP-SMZ, dapsone, amphotericin B and clindamycin may induce fever.
- **ANTIVIRALS**. Zodovudine, ganciclovir, and interferon alfa may induce fever.
- **HEMATOPOIETIC GROWTH FACTORS** such as granulocyte colony

simulating factor and erythropoietin may cause fever.

- **ANTIMYCOBACTERIAL AGENTS** such as isoniazid and rifampin may lead to fever.
- **ANTINEOPLASTIC** medications as methotrexate and bleomycin may cause fever.
- **ANTIEPILEPTIC** drugs as phenytoin may also cause drug induced fever.

PRIMARY HIV INFECTION

- Primary HIV infection presents as a mononucleosis-like syndrome with fever, malaise, weight loss, myalgia, anorexia, headache, nausea, vomiting, pharyngitis, diarrhea, and lymphadenopathy. This infection usually resolves spontaneously in 2-3 weeks.

CD4 >500/MM3

- These patients should be treated as if immunocompetent. Varicella zoster, TB and Streptococcus pneumoniae occur with a higher frequency in HIV positive patients than in HIV seronegative patients.

CD4 200-500/MM3

- Bacterial pneumonias are more common in this group with S. Pneumoniae the most common, but there is a higher incidence of Staphylococcus aureus and Haemophilus influenze pneumonia. Be aware if the patient is a drug injector, female, or an inner-city dweller.
- Sinusitis and viral upper respiratory infections are common in this group.
- TB will present as a classic case when the CD4 is above 200 with cavitation and pleuritis.
- **EVALUATION** in this group would include a PPD and anergy panel (HIV patients with CD4 >200 are usually not anergic and will test positive), sinus x-ray or CT, chest x-ray, cultures of sputum, blood and urine, and a CBC.

CD4 <200/MM3

- This is difficult group to diagnose as a host of diseases such as atypical, mycobacteria, CMV, disseminated histoplasmosis, M.

Tuberculosis and lymphoma may present with the same symptoms (weight loss, malaise and fever).

- The most common diseases in this group includes PCP, mycobacterial disease and lymphoma. The patient may be on prophylaxis when you evaluate them. Patients on aerosolized pentamidine for PCP lung disease may present atypically with extrapulmonary and pulmonary findings.
- Mycobacterial avium complex (MAC) infections may present with fever, weight loss, anorexia and night sweats. MAC infections may be disseminated affecting any organ.

SYSTEM INVOLVEMENT WITH CD4 < 200/MM3

- **GASTROINTESTINAL**. Patients may present with diarrhea secondary to Cryptosporidiosis, or microsporidiosis or diarrhea and fever due to Shigella flexneri, Salmonella, and Campylobacter jejuni. Salmonella species may only present with fever without diarrhea. HIV patients in advanced stages may present with CMV colitis and Clostridium difficile colitis is common.
- Evaluation should include bacterial stool cultures, iodine, trichrome and acid-fast preparations of the stool for ova and parasites. C. Difficile toxin stool assays should also be done along with colonoscopic exam and biopsy for those patients who have persistent diarrhea.
- **PULMONARY**. These patients may present with dyspnea, cough and fever.
- Evaluation includes a chest x-ray, induced sputum for Gram stain and culture, Pneumocystis direct fluorescent antibody or Gram-Weigert stain as well as acid-fast bacilli stains. Since chest x-rays may be negative, arterial blood gases should be done at rest and after exercise. A marked desaturation after exercise is suggestive of PCP. A lung gallium scan is also useful if the chest x-ray is negative. If one cannot arrive at a diagnosis after the above testing. Bronchoscopy should be done for cultures and biopsy for histopathology.
- **CENTRAL NERVOUS SYSTEM**. CNS lymphomas may present with fever. About 47% of patients with CNS toxoplasmosis will have fever while 80-90% of CNS Cryptococcal infections will present with fever and headache.
- Evaluation should include a CT or MRI of the head as the CT scan will

be abnormal in 19-50% in patients with Cryptococcus neoformans meningitis while 91%of patients with CNS Toxoplasmosis will have ring-enhancing lesions. In addition, if there are no contraindications, a lumbar puncture should be done to evaluate the spinal fluid for cell counts, protein, glucose, opening pressure, cryptococcal antigen, Gram, india ink and AFB stains, and culture for bacteria mycobacteria, and fungi. PCR of the spinal fluid and viral culture may show herpes simplex or CMV infection.

- **DISSEMINATED DISEASE**. MAC infections may present with weight loss, anorexia, fever, night sweats,diarrhea, and weakness. Rifabutin may prevent MAC is some patients but is unreliable. Diagnosis is established by isolation from blood using agar and radiometric methods, but takes weeks. Acid fast stains and culture of the stool and sputum along with Kinyoun or auramine rhodamine stains of blood smears or stain and culture of bone marrow biopsy, and liver biopsy may yield a diagnosis. Acid-fast stains do not differentiate M. Tuberculosis from M. Avium complex. Histoplasmosis may be suspected if the patient has inhabited the endemic areas of Ohio, Indianapolis, Mississippi River Valley or has immigrated from endemic areas such as Colombia, Dominican Republic or Puerto Rico. Disseminated Histoplasmosis may present with weight loss and persistent fever. Evaluation should include recovery from blood by lysis-centrifugation, bone marrow, bronchoalveolar lavage, CSF, isolation of organism from tissue, and serologic tests for antigen and antibody.

FEVERS OF UNDETERMINED ORIGIN

- Bone marrow and liver biopsies are useful in FUO. They may be used to diagnose mycobacterial disease and fungal infection.

NEOPLASMS

- Lymphoma is the most common neoplasm causing fever in HIV seropositive patients. Bone marrow biopsy is important in diagnosing these. Non-Hodgkin's lymphoma will present extranodally to bone marrow, CNS and GI tract in 61-87%. Systemic lymphomas typically involve the liver, meninges, GI tract and bone marrow. Furthermore, they are found at unusual sites in HIV patients such as the appendix, gingiva, testes, and parotid gland. Suspect lymphomas if there is

lymphadenopathy, hepato-splenomegaly, obstructive biliary disease, hilar adenopathy, elevated alkaline phosphatase, markedly elevated LDH, or sudden development of a pancytopenia.

LINE SEPSIS

- Indwelling catheters can produce fever with infection occurring in the catheter tunnel or exit site in patients with Broviac or Hickman catheters. Both gram positive and gram negative organisms may be involved, but gram positive are more common.

HYPERCOAGULABLE STATES

CAUSES

- Hypercoagulable states may be due to hereditary causes or acquired causes.
- **HEREDITARY CAUSES**. Hereditary causes include antithrombin III deficiency, Protein C deficiency, Protein S deficiency, dysfibrinogenemia, factor XII deficiency, plasminogen deficiency, plasminogen activator deficiency, and homocystinuria.
- **ACQUIRED CAUSES**. Acquired causes include antiphospholipid antibody, malignancy, pregnancy, nephrotic syndrome, hematologic diseases, sepsis, trauma and surgery.

ANTITHROMBIN III DEFICIENCY

- Antithrombin III deficiency is inherited through autosomal dominant genes and affects females and males equally. The incidence is 1:2000. Antithrombin III is a protein that is made by the liver, megakaryocytes and vessel endothelium. Its role is as an anticoagulant by binding and inactivating thrombin and factor Xa. The biologic half life of antithrombin III is about 2 days. There are 2 types of antithrombin III deficiency. The first is low levels of functionally normal antithrombin III, and the second is normal levels of dysfunctional antithrombin III. The first type is much more common than the second. The thrombotic and thromboembolic events usually start after puberty. Heterozygotes have antithrombin levels 25-60% of normal, and the homozygous state is not compatible with life.
- **PRESENTATIONS**. Most patients with antithrombin III deficiency will present with recurrent DVT and pulmonary embolism. However, the patient may present with mesenteric vein thrombosis, portal vein thrombosis, splenic vein thrombosis, disseminated intravascular coagulation, and axillary or subclavian vein thrombosis.
- About 40% will occur spontaneously, but about 60% will have an inciting factor, such as estrogen therapy, pregnancy, surgery, trauma or delivery.
- **TREATMENT**.
- **Heparin**. The patient is treated with heparin 100-150 units/kg IV

loading dose, followed by an infusion of 1500 units/hour IV. Antithrombin III activity is increased 100-1000 times when heparin or endothelial heparin sulfate is present.

- **Antithrombin III Concentrate**. If heparin is ineffective, antithrombin III concentrate purified from human plasma may be given at 50 units/kg. Giving this amount would raise the plasma antithrombin III levels to about 120% of normal in a patient that had a baseline level of 50%.
- **Warfarin**. The patient must be treated lifelong with warfarin in those patients that have had a thrombotic or thromboembolic episode.

PROTEIN C AND PROTEIN S DEFICIENCY

- Most patients will have a thromboembolic episode before the age of 35. Venous thrombosis is the most common, but arterial thrombosis can occur. Both protein C and S are vitamin K dependent plasma proteins that inhibit coagulation. They are both manufactured in the liver. Protein C deficiency is inherited as an autosomal dominant gene, and is seen in about 1:300, but clinically is not that common. Patients with the homozygous state may have neonatal purpura fulminans, which can be lethal if not treated with anticoagulation. The heterozygote states have protein C levels of 50-60%. Protein S deficiency is inherited as a co-dominant autosomal disorder.
- **PRESENTATIONS.** Patients with Protein C and S deficiency may present with DVT, pulmonary embolism, superficial thrombophlebitis, mesenteric vein thrombosis, splenic vein thrombosis, portal vein thrombosis, axillary or subclavian vein thrombosis, and disseminated intravascular coagulation.
- **TREATMENT.**
- **Heparin and Warfarin**. Treatment is with heparin initially. During heparin therapy, warfarin is started at 5-10 mg/day for 2-3 days. The PT ratio is then kept at between 1.5 and 2 times control. Dermal necrosis can occur, particularly with protein C which has a shorter half life than protein S. Warfarin causes a decreased level of protein C which can result in a temporary activation of factors V and VIII, leading to a hypercoagulable state and skin necrosis. This can be prevented by completely heparinizing the patient.

ANTIPHOSPHOLIPID ANTIBODY

- **LUPUS ANTICOAGULANT**. This is an acquired autoantibody

against phospholipids that may be seen in about a quarter of patients with SLE. It is also known as lupus anticoagulant. However, most of the patients that have the antibody will not have SLE. Furthermore, many of the patients with the antibody do not suffer any ill effects.

- **ANTICARDIOLIPIN ANTIBODY**. Anticardiolipin antibody is another antiphospholipid antibody. The causes of antiphospholipid antibody is thought to be genetic or drug induced.
- **Drug Causes**. Drugs that may be implicated include phenytoin, procainamide, quinidine, hydralazine and chlorpromazine. Patients that have drug induced antiphospholipid antibodies may have IgM antibodies, and usually do not develop thromboembolic events.
- **Laboratory**. Patients with antiphospholipid antibodies will have a prolonged PTT.
- **Recurrent Abortions**. There is an association between the antiphospholipid antibody and recurrent abortions. Some patients with the antibody may also have thrombocytopenia.
- **Presentations**. Patients usually present with venous and arterial thrombosis, such as DVT, pulmonary emboli, disseminated intravascular coagulation, mesenteric vein, splenic vein, portal vein, axillary or subclavian vein thrombosis.
- **Treatment**. Patients are treated with lifelong warfarin. Patients that are not candidates for warfarin may have some protection with ASA 80-325 mg daily + dipyridamole 50 mg QID.

PREGNANCY

- Pregnant patients have increased factors VII, IX, and X. There also are increased levels of fibrinogen, increased platelet adhesiveness and decreases in fibrinolysin.
- **RISK FACTORS IN PREGNANCY**. The greatest risk is in the later stages of pregnancy and the first 6 weeks after delivery, particularly in patients that are greater than 35 years of age, those with preeclampsia or eclampsia, those women postpartum from C-section, and those who are at bed rest.
- **PRESENTATION**. The most common presentation is with DVT.
- **LABORATORY**.
- **Duplex Ultrasound and Impedance Plethysmography**. DVT may be detected with duplex ultrasound. Impedance plethysmography may give false positive tests due to compression of

the iliac veins by the gravid uterus.

- **Ventilation/Perfusion Scan**. Diagnosis of pulmonary embolism is difficult in pregnancy due to the risk of radiation to the fetus. The best test is the ventilation/perfusion scan.
- **Pulmonary Artery Angiogram**. If pulmonary angiograms are needed, the abdomen should be shielded by a lead apron.
- **TREATMENT**.
- **Heparin.** Treatment is with heparin 100-150 units/kg IV as a loading dose followed by an infusion of 1500 units/hour IV. Warfarin is contraindicated in pregnancy. Therefore, heparin is used subcutaneously following the IV therapy, using 7,500-15,000 units SQ every 12 hours to maintain the PTT at 1.5 times the control.

MALIGNANCY

- **PRESENTATION.** Trousseau first described the Trousseau syndrome as a migratory venous thrombophlebitis in malignancy in 1865. The thrombophlebitis is peculiar in that it can occur anywhere, affects the deep and superficial veins and does not respond readily to usual anticoagulation therapy. The thrombosis is more common in patients with mucin producing tumors which are metastatic.
- **TREATMENT.**
- **Treatment of the Underlying Malignancy**. The best treatment is treatment of the underlying malignancy, since heparin and warfarin usually are ineffective and may be harmful by causing bleeding in necrotic tumors. Anticoagulants should not be used in those patients with CNS or pericardial tumors.
- **ASA plus Dipyridamole**. ASA may be used at doses of 80-325 mg daily plus dipyridamole 50 mg QID.

NEPHROTIC SYNDROME

- Patients with nephrotic syndrome are susceptible to renal vein thrombosis as well as other thromboembolic disease. The patients are hypercoagulable due to increased synthesis of procoagulants in the liver stimulated by hypoalbuminemia, and due to urinary losses of anticoagulants. Nephrotic syndrome patients have peripheral edema and this may make it difficult to diagnose DVT.

SURGERY AND TRAUMA

- These patients are at risk for thromboembolic disease due to immobilization and tissue damage.
- **COMMON ASSOCIATIONS**. Postoperative venous thrombosis occurs in about 70% of elderly patients with hip fractures, 50% of patients who have elective hip replacement, 30% of general surgical patients and about 15% of patients who have had a hysterectomy.
- **PROPHYLAXIS**. Prevention for patients being surgically treated for neurosurgical and urologic disease, is with pneumatic compression. Prevention in other types of surgery are benefited by elastic stockings, early ambulation and low dose heparin such as heparin 5000 units every 8-12 hours SQ. High risk orthopedic patients may be treated with low dose heparin keeping the PTT at the upper limits of normal, or by using warfarin keeping the PT 1.2-1.5 times the control.
- Low molecular weight heparin (Lovenox) is indicated in the prevention of deep vein thrombosis following hip replacement and has been very successful. In adults 30 mg is given subcutaneously BID within 24 hours of surgery for 7-10 days. It is not recommended in children. Side effects include thrombocytopenia, fever, nausea, hemorrhage and local irritation.

POLYCYTHEMIA VERA

- **PRESENTATION**. The most common event in polycythemia vera is a thrombotic CVA. It is caused by abnormal platelet function and hyperviscosity. About 30% of Polycythemia vera patients will have a thrombotic event.
- **TREATMENT.** The treatment is phlebotomy to decrease the red cell volume and the use of myelosuppressive agents to decrease RBC production.

SEPSIS

- Patients that are septic, particularly from gram negative organisms are prone to a hypercoagulable state due to endotoxin injury to the endothelium and activation of clotting factor XII which initiates the clotting cascade.

M E N O R R H A G I A

CLINICAL

- Menorrhagia is defined as excessive menstrual bleeding > 80-90 mL. Often, the patient will report flooding, heavy use of tampons and passage of clots. However, the total amount of blood loss may be less than 80 mL. Patients may develop iron deficiency anemia with hemoglobins less than 12 mg/dL which results in fatigue.

CAUSES

- The most common cause of menorrhagia is related to anovulatory menstrual cycles or idiopathic (dysfunctional uterine bleeding). Other causes may include cervicitis, endometriosis, leiomyomas, endometrial hyperplasia, endometrial cancer, hyperthyroidism, hypothyroidism, pregnancy, autoimmune thrombocytopenia, anticoagulants, spontaneous abortion, ectopic pregnancy, abruptio placentae, and placenta previa.

MEDICAL THERAPY

- **PROSTAGLANDIN INHIBITORS (NSAIDs)** may be initially tried. These consist of mefenamic acid (Ponstel) 500 mg TID, naproxen (Anaprox, Naprosyn), 375 mg BID, meclofenamate (Meclomen) 100 mg TID, indomethacin (Indocin) 25 mg TID, ibuprofen (Motrin, Nuprin) 400 mg QID. These may be used if the patient wishes to maintain fertility. They should only be used during the menstrual period. Side effects include GI distress and kidney dysfunction. NSAIDs act by improving platelet aggregation and degranuatlion, and increasing vasoconstriction. Mefenamic acid can potentially decrease menstrual blood loss by 30-50%.
- **HORMONAL THERAPY** is useful if pregnancy is not desired. Oral contraceptives are commonly used. Progesterones such as medroxyprogesterone (Provera) and norethindrone (Norlutin) may also be used in a cyclic fashion such as medroxyprogesterone 10-20 mg given daily from days 16-25 of each month. However, unlike oral contraceptives, the progesterone will need some form of barrier contraception since pregnancy can occur. Side effects of oral

contraceptives include acne, bloating, hair and weight changes. Patients are typically treated for 3 months.

- **DANAZOL (Danocrine)**, which has also been used in endometriosis, functions as an antiestrogen. It suppresses ovulation and prevents the synthesis and release of luteinizing hormone and follicle stimulating hormone. Danazol may be very effective, but about 75% of patients will have side effects such as acne, hirsutism, voice changes, decreased libido, spotting, hot flushes, GI distress, decreased libido, weight gain, atrophic vaginitis, muscle cramps, headaches and skin rashes. Furthermore danazol will prevent fertility, and must be taken daily and is expensive. Duration of therapy is problematic, as long term studies have not been performed.
- **GONADOTROPIN RELEASING HORMONE AGONISTS** may be used, but are not the initial drugs of choice as they have not been studied that well. They are expensive, will impair fertility, and may cause nausea, vomiting, hair loss, edema, amenorrhea, and can cause significant loss of bone density. GnRH agonists include goserelin (Zoladex), given at 3.6 mg monthly, nafarelin (Synarel), leuprolide (Lupron depot), and histrelin (Supprelin). Typically, these are given for three months at a time.

SURGICAL TREATMENT

- **ENDOMETRIAL ABLATION** may be accomplished by laser electrodiathermy, resection or excision, and by physical agents. They may be preferred over hysterectomy as they are effective, have less morbidity, quicker recovery times and can be done as an outpatient. In most cases, patients will not be able to become pregnant. On the other hand, repeat endometrial resections may need to be done, and eventually hysterectomy may be needed.
- **HYSTERECTOMY** is the most definitive treatment as it results in a 100% resolution of the menorrhagia. However, it is expensive, has potential morbidity, may cause psychologic changes in the woman's body image, and can result in prolonged recovery.
- **DILATATION AND CURETTAGE** may occasionally be used, but frequent D&Cs can produce Asherman's syndrome with intrauterine adhesions and prevent future pregnancy. It is usually only a temporizing measure, as it does not cure the menorrhagia.

MI-DRUG THERAPY

MORPHINE

- **INDICATIONS.** Morphine has important properties when used in MI. It is used for the pain of acute MI as well as to decrease preload and afterload by dilating peripheral venous and arterial beds.
- **DOSAGE**. Morphine is given IV at 2-5 mg IV q5-30 min for pain.
- **Precautions**. Morphine should not be used in severe chronic pulmonary disease, as it can cause respiratory depression. If it is used and side effects are prominent, it can be reversed by giving naloxone 0.4-2.0 mg IV.

OXYGEN

- Oxygen is usually given routinely, but there is no definite data to support its use. It can increase vascular resistance. It is given as 1-4 liters by nasal cannula.

ASA

- All patients with MI should be immediately started on ASA using 160-324 mg/day. The first dose should be chewed. The first dose has been shown to increase patency and reduce reocclusion after lysis. Long term therapy with ASA has also been shown to reduce reinfarction, and mortality, stroke and death.

BETA BLOCKERS

- **ACUTE USE OF BETA BLOCKERS**. Beta blockers are indicated in all patients with acute MI except those that have bronchospasm, severe heart failure, hypotension or bradycardia. By giving the beta blocker acutely, there has been a limitation of infarct size along with a reduction in mortality of 13%. Beta blockers also reduce ventricular fibrillation, reinfarction, intracranial hemorrhage after thrombolytic therapy, and cardiac rupture. Two drugs are used.
- **Metoprolol.** Metoprolol is given at 5 mg IV q2min x3, followed in 15 minutes by 50 mg PO bid x2, then 100 mg po bid as tolerated.
- **Atenolol**. Alternatively atenolol can be given as 5-10 mg IV followed

by 100 mg PO qd.

- **CHRONIC USE OF BETA BLOCKERS**. All patients with high risk should be maintained on beta blockers. Long term beta blockade in these cases reduces the rate of reinfarction and death (sudden death) up to 6 years post MI. Patients that have had revascularization such as PTCA or CABG, and are asymptomatic, without exercise induced ischemia, are usually not placed on long term beta blockers. Beta blockers are contraindicated in patients with heart block, asthma, hypotension and symptomatic bradycardia.
- **Propranolol.** Propranolol is given as 60 mg TID-QID.
- **Timolol.** Timolol is given as 20 mg daily. Beta blockers should be continued for at least 2 years.
- Patients that have good LV function without angina, ischemia, or arrhythmias during post MI treadmill testing, usually have an excellent survival, and may not benefit from beta blockers.

NITROGLYCERIN

- **ACUTE USE OF NITROGLYCERIN**. IV nitroglycerin can decrease infarct size and mortality if used within 4 hours of anterior MI, but should not be used in right ventricular MIs or in hypotensive patients. Tolerance may develop if used more than one day.
- **CHRONIC USE OF NITROGLYCERIN**. Oral and topical nitrates are usually not given. Oral nitrates started the day after an MI has not changed the mortality at 1 month.

LIDOCAINE

- Prophylactic lidocaine is no longer recommended as studies have shown a 38% increase in mortality, mostly due to asystole. Lidocaine is indicated for sustained, or recurrent hemodynamically significant nonsustained ventricular tachycardia.
- **DOSAGE OF LIDOCAINE**. Lidocaine is given IV as a loading dose of 1 mg/kg, followed by .5 mg/kg bolus in 10 minutes. An infusion is then started at 1-4 mg/min.
- **Precautions**. Patients that are in CHF or who are elderly should have the dose reduced. Side effects of lidocaine include perioral numbness, confusion, seizures, drowsiness, and respiratory depression.

HEPARIN

- **INDICATIONS**. Heparin is always indicated when tPA is given and in those patients with an acute anterior MI, left ventricular thrombi, low cardiac output and atrial fibrillation.
- **Anterior MI**. High dose IV heparin or subcutaneous heparin (12,500 units) will reduce the risk for left ventricular thrombus after an anterior MI.
- **tPA Thrombolytic Therapy and Heparin**. IV heparin is also needed to achieve a 1% mortality benefit of accelerated tPA over streptokinase. Following tPA IV heparin should be given for 5-7 days in order to diminish reocclusion rates.
- **Dosage of Heparin**. Heparin used for these indications is given as an IV bolus of 100 mg/kg, followed by an infusion of 1,000-1,300 units/hour adjusted to obtain a PTT 2-2.5 times normal.
- Routine heparin may not be necessary after Streptokinase or APSAC, because it has not been shown to reduce the rates of reinfarction or death, and there has been an increase in bleeding.
- **Immobilization**. Subcutaneous heparin is indicated during periods of immobilization to reduce deep venous thrombosis. It is given SQ as 5,000 units q12h.

WARFARIN

- **INDICATIONS**. Warfarin is indicated chronically in any patient that has had a LV thrombus, or in those patients who are at increased risk for thromboembolic events, such as low cardiac output, atrial fibrillation and prolonged immobilization.
- Longterm anticoagulation has been shown to decrease the rate of recurrent MI and death, but when compared to ASA, warfarin has not shown a decrease in reocclusion. Warfarin is given to achieve an INR of 2.5-4.5.

ACE INHIBITORS

- **INDICATIONS.** ACE inhibitors are indicated in patients that have symptomatic cardiac failure, and in those asymptomatic patients post-MI, with ejection fractions less than 40%.
- ACE inhibitors have been shown to reduce the rates of recurrent MI,

decrease short and long term mortality in asymptomatic patients post MI with LV ejection fractions less than 40%, reduce the progression to heart failure, and reduce the need for rehospitilization.

- ACE inhibitors should be started at low doses within a few days after the acute MI, titrated upwards, and continued indefinitly.
- **Captopril.** Captopril is given initially as 6.25 mg and then titrated to 50 mg BID or TID as tolerated.
- **Lisinopril.** Lisinopril is given as a maintenance of 10 mg daily.
- **Ramipril.** Ramipril is given as 2.5-5 mg orally BID.

MAGNESIUM

- Magnesium therapy has had conflicting reports as to its efficacy. It is usually not given, but may decrease ventricular arrhythmias.

CALCIUM CHANNEL BLOCKERS

- **INDICATIONS**. Calcium channel blockers are only indicated in non-Q-wave myocardial infarctions, if there are no contraindications such as severe LV dysfuntion.
- **CONTRAINDICATIONS.** Calcium channel blockers that do not slow the heart rate, such as nifedipine and nicardipine, should not be used. Nifedipine should not be given unless it is used concurrently with a beta blocker, as is is associated with an increased rate of recurrent infarction and death.
- **Diltiazem**. Diltiazem has been shown to prevent early reinfarction and angina in patients with non Q wave MI, but increased mortality in those patients with severe LV dysfunction and congestive heart failure. Diltiazem is given as 90 mg q6h.
- **Verapamil.** Verapamil has also been associated with a trend toward decreased reinfarction, and a marginal effect on mortality.
- Verapamil is given as 120 mg TID.
- Both diltiazem and verapamil should be started early in non Q wave MIs within 2-5 days and continued for one year.

M O N O C L O N A L G A M M O P A T H Y

- Monoclonal gammopathy (MG) is characterized by a monoclonal protein (M protein) in the serum or the urine. MG can be seen in several different diseases and consist of one or more of the immunoglobulins, a heavy chain and/or light chain.

TESTS TO ORDER

- If a MG is seen, the patient should have a CBC, serum protein electrophoresis, urinary protein electrophoresis, immunoelectrophoresis, quantitative immunoglobulins, chemistry profile, bone survey (x-rays), bone marrow biopsy/aspiration, and beta2-microglobulin.

SPIKE COMPOSITION

- The M protein may be IgG, IgA, IgD, or IgE. Patients with these elevations may have a solitary or extramedullary plasmacytoma, multiple myeloma, amyloidosis or a monoclinal gammopathy of unknown significance (MGUS).

IgM SPIKES

- Patients that have an elevated IgM can have Waldenstrom's macroglobulinemia, MGUS, or a lymphoproliferative disorder.

ODDS OF HAVING A PARTICULAR DISEASE

- Most patients with a monoclonal gammopathy will have MGUS (64%); Multiple myeloma (16%), amyloidosis (8%), non-Hodgkin's lymphoma (6%), chronic lymphocytic leukemia (2%) and Waldenstroms's macroglobulinemia (2%).

SOLITARY PLASMACYTOMA

- Solitary plasmacytoma usually presents with no M component in the serum or the urine. However, occasionally it does, and presents as a single area of bone destruction, and normal bone marrow. It comprises 5% of patients with plasma cell disorders.

- **DIAGNOSIS.** The diagnosis is made by examining the tumor histologically and finding plasma cells that are identical to those seen in multiple myeloma.
- **TREATMENT.** The treatment is local radiotherapy of 4000 rads and is curative in about 30%. Fifty percent will be alive at 10 years. However, the disease free interval is only about 20% because many patients will develop multiple myeloma. Therefore, all patients should be followed by serum and urine protein electrophoresis and immunoelectrophoresis.

EXTRAMEDULLARY PLASMACYTOMA

- Extramedullary plasmacytoma most frequently involves the upper respiratory tract (nasal cavity, sinuses, nasopharynx and larynx). These patients, as in solitary plasmacytoma, usually do not have a M component in the serum or urine. The bone marrow is not involved as in multiple myeloma, and no lytic lesions are seen on bone survey.
- **TREATMENT**. Treatment is radiation therapy which is curative in > 50% of patients.

MULTIPLE MYELOMA

- **MULTIPLE MYELOMA CRITERIA**. Multiple myeloma is characterized by > 10% bone marrow plasma cell infiltration, multiple osseous lesions, serum M component > 3 g/dl and usually light chains in the urine > 1 g/24hours.

MGUS

- MGUS is typical for the absence of multiple myeloma, solitary and extramedullary plasmacytoma, amyloidosis, macroglobulinemia or other lymphoprolierative disorders.
- **MGUS CRITERIA**. It is characterized by a M component < 3 g/dl, (IgG < 3 gm/dl and IgA < 2.5 gm/dl), no lytic lesions on bone survey, normal CBC, normal blood chemistries, normal levels of the uninvolved immunoglobulins, normal beta 2 microglobulin, and absence of hypercalcemia. The M component must remain stable with some time without the development of features indicative of the other disorders mentioned in the differential. MGUS has an incidence of 10% in patients greater than 80 years of age. Typical

findings may include the following: M component .3-3.2 g/dl, immunoelectrophoretic IgG (74%), IgA (10%), and IgM (16%), urinary monoclonal gammopathy (6%), and bone marrow plasmacytosis 1-10%.

- **EVOLUTION OF MGUS**. Over the years, multiple myeloma, amyloidosis, macroglobulinaemia and other lymphoproliferative disease will develop in about 22%. Of these, about 68% of patients will develop multiple myeloma in 2-21 years.
- **CLINICAL**. Most of the patients with MGUS will be asymptomatic, but there may be associated problems such as peripheral neuropathy, renal disease, and immune hemolysis. All patients should be followed for transition of the disease.

AMYLOIDOSIS

- **DIAGNOSIS**. Amyloidosis can be diagnosed with rectal, skin, tongue, and gingival biopsy, and/or needle fat aspiration of the abdomen.
- **CLINICAL**. Patients may present with weight loss, weakness, paresthesias, syncope, peripheral neuropathy, carpal tunnel syndrome, arthralgia, periorbital purpura, macroglossia, carpal tunnel syndrome, diarrhea and malabsorption syndrome, orthostatic hypotension, nephrotic syndrome, cardiac conduction defects, bleeding in the skin and GI tract, CHF and ankle edema.
- **TREATMENT.** There is no treatment for amyoidosis.

DIFFERENTIAL DIAGNOSIS

- **LYMPHOMA AND CLL**. Patients that present with a M component of < 3 g/dl associated with significant adenopathy should have a lymph node biopsy to rule out lymphoma, as these patients frequently have an underlying B-cell neoplasm. Lymph node biopsy can be used to exclude non-Hodgin's lymphoma and chronic lymphocytic leukemia. About 17% of patients with IgM MGUS will develop lymphoma with a median duration from presentation to the development of lymphoma of 4 years (range .4-22 years).
- **WALDENSTROM'S MACROGLOBULINEMIA**.
- **Diagnosis**. Patients with an elevated IgM > 3 g/dl, bone marrow > 10% lymphoplasmacytoid cells, hepatosplenomegaly and hyperviscosity will have Waldenstrom's macroglobulinemia. Rouleaux formation and positive Coombs's test are common,

as is a normocytic and normochromic anemia.

- **Clinical**. These patients also have bleeding, blurred vision, dyspnea, weight loss, paresthesisas, weakness, recurrent infections, epistaxis, fatigue, lymphadenopathy, and retinal lesions (sausage appearing lesions).
- **Treatment**. Hyperviscosity is treated with plasmapheresis. About 80% of patients will respond to chemotherapy with a median survival of > 3 years. Chlorambucil is the drug of choice.

MYASTHENIA GRAVIS

OVERVIEW

- Clinically, patients present with weakness with repeated activity and improvement with rest. The external ocular muscles, facial, pharyngeal and masticatory muscles are frequently involved with occasional involvement of the respiratory and limb muscles. It occurs at all ages and has a prevalence of 50-125 cases per million population or about 25,000 affected persons in the USA. It is most common in young women with HLA-DR3. However, if associated with thymoma, older men are more commonly involved.
- It is sometimes associated with thyrotoxicosis, rheumatoid arthritis and lupus erythematosus. Women have a peak incidence in the second and third decades and men are affected in the sixth and seventh decade. The onset is usually insidious, but may be brought on by an infection, just prior to menstruation and during or just after pregnancy.

CAUSES

- Myasthenia gravis is due to an antibody mediated autoimmune disease against the acetylcholine receptors at the neuromuscular junctions. These antibodies will reduce the quantity of functioning acetylcholine receptors. Moreover, cellular immune activity against the receptor is also found.

CLINICAL

- Many patients present with diplopia, ptosis, difficulty in chewing or swallowing, and weakness of limb and respiratory muscles. These difficulties may intermittently come and go. There also may be diurnal fluctuations in the intensity of the symptoms, but inexorably progresses to respiratory complications such as aspiration pneumonia.
- The ocular palsies and ptosis are commonly asymmetrical and the weakness may remain localized to the extraocular and eyelid muscles in about 15% of patients. The patient may have difficulty in swallowing and chewing and may have nasal speech.

Generalized weakness will develop in about 85% of patients. The neck extensors may be involved and the proximal muscles are usually involved if the limb muscles are affected. There are no reflex changes and sensation is intact.

DIFFERENTIAL DIAGNOSIS

- **BOTULISM**. Botulism produces a generalized weakness with ophthalmoplegia and dilated pupils. There is an incremental response on repetitive nerve stimulation.
- **EATON-LAMBERT SYNDROME**. The Lambert-Eaton syndrome produces areflexia, fatigue and weakness and about 60% are associated with oat cell cancer. There is an antibody to calcium channels present, and there is an incremental response on repetitive nerve stimulation.
- **DRUGS.** Aminoglycosides, quinine, procainamide and curare can cause weakness in the normal person and also exacerbate myasthenia, but recovery is usually seen when the drug is discontinued.
- Penicillamine can induce autoimmune myasthenia with recovery taking place weeks after the drug is discontinued.
- **HYPERTHYROIDISM.** Hyperthyroidism produces a generalized weakness and can make myasthenia worse. Grave's disease produces a diplopia and exophthalmos.
- **INTRACRANIAL MASSES**. Intracranial masses can compress the cranial nerves causing ophthalmoplegia and cranial nerve weakness. These can be detected with MRI and CT.
- **PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA**. Progressive external ophthalmoplegia produces ptosis, diplopia and generalized weakness, but mitochondrial abnormalities are usually present.

LABORATORY

- **ANA, RHEUMATOID FACTOR AND ANTITHYROID ANTIBODIES**. Patients should have testing for SLE (ANA), rheumatoid factor and antithyroid antibodies.
- **CHEST X-RAY OR MRI**. Chest MRI or CT should be done of the mediastinum along with chest x-ray for detection of thymoma.
- **SPIROMETRY, GLUCOSE, TB TEST, THYROID AND BONE**

DENSITOMETRY TESTS. Pulmonary function testing, glucose, TB test, thyroid function tests and bone densitometry in older patients, all should be done.

- **SERUM ACETYLCHOLINE RECEPTOR ANTIBODIES**. Serum acetylcholine receptor antibodies should be determined as they have a sensitivity of 80-90%. However, if the patient only has involvement of the ocular muscles, the sensitivity is reduced to 50%. The test is done by radioimmunoassay using detergent solubilized human acetylcholine receptor labeled with [125I] alpha-bungarotoxin.
- **EMG and NERVE CONDUCTION STUDIES**. Repetitive nerve stimulation is done at a rate of 3/sec and action potentials are recorded from surface electrodes over the muscle. A rapid reduction in the amplitude of the evoked muscle action potential (decremental response of 15%) is a positive response. Single fiber electromyography will detect delayed or failed neuromuscular transmission in pairs of muscle fibers that are supplied by branches of a single nerve fiber.
- **EDROPHONIUM TESTING**. The diagnosis can usually be confirmed by using edrophonium (Tensilon) IV in a dose of 10 mg (1 ml). Two mg is given IV initially, with the remaining 8 mg given in about 30 seconds if the test is tolerated. If the patient has myasthenia gravis there will be an improvement in muscle strength which will last for about 5 minutes.

ASSOCIATED DISORDERS

- **THYMIC TUMORS**. Thymic tumors occur in about 12% in patients with Myasthenia gravis. The thymus is usually normally seen until about mid-adult-hood or the age of 40.
- **HYPERTHYROIDISM**. Hyperthyroidism occurs in about 3-8%.
- **OTHER AUTOIMMUNE DISORDERS**. The patient may also have other autoimmune disorders as thyroiditis, rheumatoid arthritis, Grave's disease, and SLE.

CONDITIONS THAT EXACERBATE MYASTHENIA GRAVIS

- Conditions that can exacerbate myasthenia gravis include occult infection, hypothyroidism and hyperthyroidism, and various medications as antiarrhythmic agents, aminoglycosides and quinine.

Diabetes, tuberculosis, GI bleeding, renal disease, osteoporosis, asthma, hypertension and peptic ulcer can all interfere with therapy.

TREATMENT

- Anticholinesterase drugs as neostigmine and pyridostigmine can be used.
- **NEOSTIGMINE OR PYRIDOSTIGMINE**. Neostigmine is usually given as 7.5-30 mg QID (average 15 mg) OR pyridostigmine 30-180 mg (average 60 mg) QID.
- **THYMECTOMY**. Thymectomy should be considered in patients that are younger than 60 as it will lead to improvement. It is preferable to delay thymectomy until puberty because of the development of the immune system by the thymus. In patients with pure ocular symptoms, thymectomy has also been beneficial. Thymic tumors should be completely removed surgically as they are invasive and spread locally, but do not metastasize.
- The thymic tissue and related fat is removed via a sternal splitting approach with exploration into the neck. Mediastinoscopy with a cervical incision can be done, but the thymus gland may not be completely removed.
- If the thymus cannot be removed completely, or it becomes invasive, radiation should be given postoperatively.
- The mortality rate for thymectomy with experienced surgeons approaches that of general anesthesia.
- Immunosuppressive drugs should not be used preoperatively because they can increase the risk of infection.
- **PLASMAPHERESIS.** For vital capacities < 2 liters, plasmapheresis should be carried out prior to surgery to establish independent respiration in the post surgical period.
- Plasmapheresis can be used to stabilize patients who demonstrate myasthenic crisis, or in those patients planning to have a thymectomy. Usually 5 exchange treatments of 3-4 liters each are performed over a 2 week period. The results are immediate with improvement the same day as the plasmapheresis. The results, however, usually only last a few weeks. Complications include a risk of infection from the indwelling catheter, hypotension, and pulmonary embolism.

- **IV IMMUNE GLOBULIN**. Intravenous immune globulin may be used for the same situations as plasmapheresis is used. It is given as 400 mg/kg/day for 5 successive days. The improvement is slower, approaching 4-5 days when compared with plasmapheresis and may be as much as about 73%. The improvement may last for weeks to months.
- Side effects of immune globulin include fluid overload, headache, and renal failure which is rare. Immune globulin is also very expensive.
- **STEROIDS.** For patients that do not respond to anticholinesterase drugs, or thymectomy, steroids are indicated. Steroids should be started while the patient is in the hospital as initially there may be paradoxical muscle weakness which usually stabilizes after 2-3 weeks.
- **Prednisone Dosage**. This risk of exacerbation is decreased by starting with low doses of prednisone of 15-20 mg daily and increasing by about 5 mg every 2-3 days until the patient improves, or a total daily dose of 60 mg/day. Maximal benefit is usually seen after 6-12 months with some improvement seen as early as 2-4 weeks. After about 3 months of daily dosing, an alternate day treatment program can be instituted. There may need to be supplementation given on the off days. The dose is slowly reduced, but most patients will need some prednisone.
- **AZATHIOPRINE.** Treatment with azathioprine is also effective giving 2-3 mg/kg/day (total dose 100-250 mg/day). It is usually given in those patients in whom steroids are contraindicated, or in those patients who have responded incompletely to steroids, or given in conjunction with steroids to reduce the dose of steroids.
- About 10% will have an idiosyncratic reaction of fever, myalgias and malaise that will prevent its use. It also has a slow onset to time of therapeutic effect (3-12 months), with the maximal effect not until 1-2 years. The white cell counts must be monitored to achieve <3500/mm3.
- If allopurinol is used with azathioprine, the azathioprine must be reduced by as much as 75% and monitored frequently. Most patients will require life long therapy with azathioprine.
- **CYCLOSPORINE**. Cyclosporine is also being used more frequently in myasthenic patients. Cyclosporine has a faster onset of action (2-12 weeks) with maximal therapeutic effect at 3-6 months.

It is given at 5 mg/kg/day given in 2 divided doses (total dose is 125-200 mg BID). The blood pressure, serum creatinine, BUN and trough plasma cyclosporine levels should be monitored.

- **Side effects of Cyclosporine**. The side effects consist of hypertension, nephrotoxicity, and should not be used in uncontrolled hypertension or pre-existing renal disease. Cyclosporine is very expensive.
- **EPIDURAL MORPHINE**. Epidural morphine will decrease pain and not interfere with respiration.

COURSE OF DISEASE

- Postoperatively, the patient usually does not require as much anticholinesterase medication, using only about 75% of the preoperative dose. The benefits of thymectomy may not be realized until months or years following surgery. In general, acetylcholine receptor antibody levels will fall following thymectomy.

P I D

CLINICAL

- Pelvic inflammatory disease (PID) represents a bacterial ascending infection that starts with a colonization of the endocervix, and then results in endometritis, salpingitis, tubo-ovarian abscess or pelvic peritonitis. It is usually polymicrobial, including aerobic and anaerobic bacteria. The most common organisms are Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis and Ureaplasma urealyticum. Anaerobes include Peptococcus species, Bacteroides species and Peptostreptococcus species. Facultative aerobes include Gardnerella vaginalis, Haemophilus influenzae, Escherichia coli, and group B streptococcus.
- The diagnosis of PID may be difficult as there is no physical, laboratory, or historical aspect that will definitely make a diagnosis. All patients will have abdominal pain, 90% will have adnexal tenderness, 80% will have cervical motion tenderness, 73% will have a vaginal discharge, 61% will have abdominal rebound or guarding, while only 30% will have fever.

RISK FACTORS FOR PID

- Risk factors include multiple sex partners, frequent sexual intercourse and new sexual partners within the previous 30 days. IUDs usually also favor the development of PID. Women < 25 years of age comprise about 3/4 of the cases. Douching, smoking and socioeconomic status all impact on the development of PID. There is an increased risk of PID during or shortly after menses.
- Barrier methods such as diaphragms, vaginal spermicides, and condoms are associated with a DECREASE of STDs, PID and infertility.

LABORATORY

- Laboratory findings are all non-specific and cannot be relied upon to distinguish PID from other diseases in the differential. The sedimentation rate is only positive in 75% of cases. Leukocytosis is not found in all cases. Cervical gram staining that is positive for gram

negative intracellular diplococci with findings of more than 10 white cells/oil immersion field is suggestive of PID. Cervical cultures are not immediately helpful if positive for Chlamydia or gonorrhea, as growth may take 3-7 days. The sensitivity for tests such as Chlamydiazyme, Clearview Chlamydia, and Sure Cell Chlamydia is not 100%. Urine Ligase and Polymerase chain reaction technology may improve the diagnosis both for Chlamydia and gonorrhea. All patients suspected of PID should have a pregnancy test.

- Pelvic intravaginal ultrasound can detect abscesses and localize ectopic pregnancies. Culdocentesis that is positive for white cells and organisms may lend support for a diagnosis of PID. Endometrial biopsy is sometimes used for a histopathologic diagnosis.
- Laparoscopic exam is the best approach for a diagnosis of PID if a diagnosis is obscure. This may show tubes that are swollen, hyperemic, and positive for exudate. During the procedure, the pyosalpinx may be aspirated for cultures, adhesions may be lysed, and free purulent material may be removed.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis includes ectopic pregnancy, hemorrhagic ovarian cyst, torsion of the ovary, irritable bowel syndrome, appendicitis, endometriosis, gastroenteritis, and nephrolithiasis.

CRITERIA FOR DIAGNOSIS

- **MINIMUM CRITERIA** include cervical motion tenderness, adnexal tenderness and lower abdominal tenderness.
- **ADDITIONAL CRITERIA INCLUDE** a temperature >38.3 C (101.8 F), elevated sedimentation rate, abnormal cervical or vaginal discharge, and laboratory evidence of cervical infection with Neisseria gonorrhoeae or Chlamydia trachomatis.
- **OTHER CRITERIA** include a positive ultrasound for tubo-ovarian abscess, laparoscopic observations compatible with PID, and endometrial biopsy findings consistent with endometritis.

CRITERIA FOR HOSPITALIZATION

- The patient is pregnant.
- The patient is unable to follow or tolerate an outpatient regimen.

- The patient fails to respond to outpatient therapy.
- The diagnosis is questionable and surgical emergencies as appendicitis and ectopic pregnancy cannot be ruled out.
- A follow-up within 72 hours of starting antibiotics cannot be accomplished.
- The patient is noncompliant with outpatient therapy.
- The patient is an adolescent and compliance may be a problem.
- The patient has HIV.
- The patient is unable to tolerate an outpatient regime because of nausea and vomiting.
- Pelvic abscess may be present.

COMPLICATIONS OF PID

- Complications include an 8% incidence of infertility after the first episode, 20% after the second episode, and 40% after the third episode. There also is an increased risk for ectopic pregnancy that increases 2-10 fold. Recurrent PID has an incidence of 20-25%, tubo-ovarian abscess of 7-16% and chronic abdominal pain 17-18%.

OUTPATIENT TREATMENT

- **REGIMEN A** consists of cefoxitin (Mefoxin) 2 grams IM plus probenecid (Benemid, Probalan) 1 gram PO as a single dose given concurrently OR ceftriaxone (Rocephin) 250 mg IM [or other parenteral third generation cephalosporin such as ceftizoxime (Cefizox), or cefotaxime (Claforan)] PLUS doxycycline (Vibramycin) 100 mg PO BID for 14 days.
- **REGIMEN B** consists of ofloxacin (Floxin) 400 mg orally BID for 14 days PLUS clindamycin (Cleocin) 450 mg orally QID, or metronidzaole (Flagyl) 500 mg orally BID for 14 days.

INPATIENT TREATMENT

- **REGIMEN A** consists of cefoxitin (Mefoxin) 2 grams IV every 6 hours or cefotetan (Cefotan) 2 grams IV every 12 hours PLUS doxycycline (Vibramycin) 100 mg IV or orally every 12 hours.
- **REGIMEN B** consists of clindamycin (Cleocin) 900 mg IV every 8 hours PLUS gentamicin (Garamycin), giving a loading dose IV or IM of

2 mg/kg, followed by a maintenance dose of 1.5 mg/kg every 8 hours. These inpatient regimes are continued for at least 48 hours after the patient has shown clinical improvement, then followed with oral doxycycline at 100 mg BID for a total of 14 days.

S L E

OVERVIEW

- Systemic lupus erythematosus (SLE) is an autoimmune disease without an etiology that affects the joints, kidneys, skin, nervous system, digestive tract, heart and lungs.
- Women are affected 9 times more than men. Black women are affected twice as often as white women. The incidence of SLE is 1.8-7.6 cases/100,000.

DIAGNOSIS

- **ARTHRITIS** is a nonerosive arthritis that involves 2 or more peripheral joints.
- **KIDNEY** involvement is characterized by proteinuria > 0.5 grams/day or greater than 3+, or cellular casts.
- **MALAR RASH** is characterized by a flat or raised erythema over the malar areas.
- **DISCOID RASH** is an erythematous raised patch with adherent keratotic scaling and follicular plugging. Scarring is characteristic.
- **NEUROLOGIC** symptoms may consist of seizures or psychosis.
- **HEMATOLOGIC** disease may present as a leukopenia less than 4000/mm^3, lymphopenia less than 1500/mm^3, thrombocytopenia less than 100,000/mm^3, or hemolytic anemia in the absence of offending drugs.
- **PHOTOSENSITIVITY**
- **ORAL AND NASOPHARYNGEAL ULCERS**.
- **SEROSITIS** may present with pleuritis, pericarditis or peritonitis.
- **ANTINUCLEAR ANTIBODIES** are sensitive, but nonspecific for SLE. ANA negative SLE is very rare. Ninety-eight percent of patients with SLE have a positive ANA using the Hep-2 substrate. So, a positive ANA is useful in confirming a diagnosis of SLE. ANAs are present in 5-10% of healthy people, and also may be seen in chronic infections, drugs, chronic liver disease, neoplastic diseases, and other autoimmune connective diseases.
- **OTHER ANTIBODIES** include the anti-Sm antibody and the anti-DNA double stranded antibodies. The anti-DNA is very specific for SLE, but suffers from sensitivity. Patients may also have a false positive

serology for syphilis and positive LE cell preparation.

LABORATORY

- **HYPOCOMPLEMENTEMIA** (CH50, C3, C5) correlates well with active disease. The presence of hypocomplementemia with increased anti-nDNA antibodies points toward kidney and/or skin disease.
- **FALSE POSITIVE VDRL** can be present, and if present, 80% will have a circulating anticoagulant.
- **ANTI-nDNA ANTIBODIES**, when present, tend to fluctuate with disease activity. They are present in 50-60% of SLE patients.
- **The RIM FLUORESCENT ANA** is seen in SLE, while the homogeneous and speckled patterns can be seen in other diseases as well.
- **The ANTI-Sm (Smith) ANTIBODY** is seen in 30% of SLE cases.
- **The ANTI-ssDNA ANTIBODY** is seen in 100% of SLE, but is not diagnostic as it is seen in chronic infections, interstitial lung disease, chronic active hepatitis and other connective tissue diseases.
- **OTHER** findings in SLE include positive cryoglobulins, rheumatoid factor, LE prep, Coombs' test, false positive VDRL, and circulating anticoagulants.

RENAL DISEASE

- Patients may develop 6 different patterns of renal disease. These include mesangial, focal glomerulonephritis, diffuse proliferative glomerulonephritis, membranous glomerulonephritis, interstitial nephritis, and renal vein thrombosis with nephrotic syndrome. Patients may also have coexisting hypertension. Renal biopsy can help in classifying the type of involvement and treatment. Active inflammation, necrosis, proliferation and crescent formation will need aggressive therapy. Patients with scarring, tubular atrophy and glomerulosclerosis respond less to aggressive therapy. Renal disease is treated with steroids, pulse therapy, cytotoxic agents and plasmapheresis.

SKIN DISEASE

- Skin disease can involve the hair, nails and skin. Patients may develop the butterfly rash over the malar area which can be made worse by exposure to ultraviolet light. About 33% of SLE patients are

photosensitive and should avoid the sun, use sunscreens, and wear protective gear. Medications (tetracyclines, thiazides, and sulfonamides) can induce photosensitivity and therefore should be avoided.

- **TREATMENT OF SKIN DISEASE** includes topical steroids and antimalarial agents such as hydroxychloroquine, chloroquine, and atabrine. The most frequently used is hydroxychloroquine. It should not exceed 6 mg/kg/day as it can cause ocular problems. All patients should have a base line ophthalmologic exam followed by periodic exams every 6-12 months as corneal deposits and retinopathy can occur. Less than 5% of patients receiving 400 mg/day of hydroxychloroquine will develop corneal deposits which are usually asymptomatic. These may disappear with drug withdrawal. However, advanced retinal disease can end up with irreversible visual loss. Improvement ,characteristically, does not occur until 2-4 months of antimalarial treatment. Side effects of antimalarials include diarrhea, abdominal cramping and dyspepsia. Also, pigment changes can occur in the nails and skin along with skin dryness and rashes. Alopecia may need treatment with steroids.

GI DISEASE

- Abdominal serositis may present a difficult differential diagnosis involving infectious, noninfectious and vasculitic etiologies. Peritoneal fluid may be present. After all other causes have been ruled out, steroids may be used for the serositis. Mouth ulcers can be treated with steroids. NSAID induced gastropathy can be treated with H2-blockers.

NEUROLOGIC DISEASE

- Almost any neurologic symptom can develop in SLE, but the most common include seizures, headaches, aseptic meningitis, strokes, and motor and sensory neuropathies. Patients may also develop neuropsychiatric symptoms such as neurosis, psychosis, and adjustment reactions. Steroids are typically used for treatment. Complications of long term steroids include hypertension, diabetes mellitus, hypercortisolism, infection, osteonecrosis, cataracts, myopathy and osteoporosis. Therefore, tapering should be started as quickly as possible to the lowest dose needed to control the disease. If

unresponsive to steroids, cytotoxic drugs can be used.

MUSCULOSKELETAL DISEASE

- **ARTHRALGIAS** may be present. Erosive disease usually does not develop. Occasionally, there is joint swelling. Treatment is with NSAIDs and physical therapy. Failure to respond to these measures would require the use of hydroxychloroquine and steroids.
- **FIBROMYALGIA** is a common presentation, consisting of multiple trigger points and diffuse muscle aching. Treatment includes cyclobenzaprine and tricyclic antidepressants.
- **MYOPATHY** that develops may be due to steroids and antimalarial drugs. Therefore, drug myopathy should be ruled out before prescribing steroids.

CARDIOPULMONARY DISEASE

- **PLEURITIS** is the most common lung presentation. Symptoms include dyspnea, and chest pain. Chest films may reveal pleural effusions. Uncommon presentations include lupus pneumonitis, diffuse interstitial lung disease and pulmonary hemorrhage.
- **PERICARDITIS** can also present with dyspnea, chest pain and a pericardial rub. Pericardial effusion may be present, but rarely progresses to tamponade. Patients may also develop myocarditis, valve disease, conduction abnormalities, and premature atherosclerosis
- **TREATMENT** of mild pleuritis and pericarditis is with NSAIDs. Severe cases may need corticosteroids.

HEMATOLOGIC DISEASE

- **ANEMIA** is usually due to chronic disease, but may be NSAID-induced resulting in iron deficiency disease. Autoimmune hemolytic anemia can develop and is suggested by peripheral blood smear findings and a positive Coomb's test. Treatment of the autoimmune hemolytic anemia is with high dose steroids. Refractory cases may need cytotoxic drugs.
- **LYMPHOPENIA** usually does not need treatment.
- **THROMBOCYTOPENIA** is usually immune mediated, but other causes should be ruled out. It doesn't require treatment unless the

count falls below 50,000/mm^3 and bleeding. Treatment is with high dose steroids. Patients unresponsive, may need danazol and intravenous gamma globulin.

- **REFRACTORY CASES** may require splenectomy, but often it is not effective and may lead to infections.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

- About 40% of SLE patients will have antiphospholipid antibodies, while 25% of these will have the antiphospholipid antibody syndrome. These syndrome-positive patients may have a prolonged PTT, false positive test for syphilis (RPR and VDRL), positive ELISA for anticardiolipin antibodies, recurrent spontaneous abortions, thrombocytopenia, and may develop venous or arterial thrombosis (deep venous thrombosis, stroke and pulmonary embolism). Less common features include CNS disorders, livedo reticularis, and cardiac valvular disease.
- **TREATMENT** of the antiphospholipid syndrome will need continuous anticoagulation with heparin followed by warfarin, with a target INR of about 3. Patients without the syndrome, but positive antiphospholipid antibodies are treated with aspirin.

PREGNANCY AND SLE

- Pregnancy usually causes flares of the SLE, but doesn't affect fertility. Patients with SLE also have a higher incidence of pre-eclampsia, hypertension and fetal wastage.
- **TREATMENT** includes an appraisal of all medications. NSAIDs should be avoided, cyclophosphamide and methotrexate are teratogenic and need to be discontinued. Azathioprine, however, can be used during pregnancy with caution. Hydroxychloroquine should be discontinued during pregnancy. Prednisone is not contraindicated. During delivery, patients on steroids need supplements of hydrocortisone 100 mg IV every 8 hours to prevent adrenal collapse. Attention also needs to be directed toward the neonate, who can develop congenital heart block and neonatal lupus.

OVERLAP SYNDROMES

- Overlap syndrome is characterized by features of more than one

connective tissue disease as SLE, rheumatoid arthritis, systemic sclerosis and polymyositis. Patients may also have Hashimoto's thyroiditis, myasthenia gravis and Sjogren's syndrome (keratoconjunctivitis sicca and xerostomia).

DRUG INDUCED LUPUS

- Many drugs can induce SLE. Common drugs include procainamide and hydralazine. Less commonly, methyldopa, isoniazid, quinidine and chlorpromazine are implicated. There are several other drugs that may induce SLE, such as penicillamine, lithium, sulfasalazine, lovastatin, acebutolol, phenytoin, hormones, gold salts, NSAIDs, ethosuximide, carbamazepine, and propylthiouracil. Many of these drugs may just produce a positive ANA titer without the development of actual disease. Drug induced Lupus usually spares the kidneys and brain. However, fever, arthritis, rash and serositis are common.
- Often, antihistone antibodies are present (>95%), while anti-nDNA, and anti-Sm antibodies are absent. Treatment is terminating the offending drug and symptoms usually will disappear. Serum total hemolytic complement is usually absent in drug induced disease, whereas in SLE the test is positive.