T. PAUL-RAMSEY HOSPITAL
and
MEDICAL CENTER
ST. PAUL, MINNESOTA 55101

Department of Pathology

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CUMULATIVE DIAGNOSES - CASE OF THE MONTH
1974 - 1976

1974 NO SLIDES

1. Benign glandular inclusions, para-aortic lymph nodes.
2. Hemochromatosis with cirrhosis and hepatoma.
3. Alcoholic hepatitis.
4. Pseudomonas endocarditis.
5. Embryonal teratoma with choriocarcinoma-ovary
6. Cytomegalic inclusion disease-kidney and lung-stillborn infant.
7. Congenital hepatic fibrosis.
8. Eccrine acrospiroma.
9. Farmer's lung.
10. Polycystic kidney disease-Type II.

1975

1. Listeriosis-placenta. no slide
2. Floppy valve with myxoid degeneration. 2
3. Regional enteritis-small bowel. 3
4. Rheumatoid lung. 4(a,b)
5. Multiple phlebectasia-small bowel. 5
6. Tuberculosis-prostate. 6
7. Necrotizing enterocolitis. 7
8. Islet cell hyperplasia with hypoglycemia-newborn. 8
9. Jakob-Creutzfeldt disease. 9
10. Basophilic degeneration of myocardium associated with myxedema. 10 (a,b)
11. Coronary artery aneurysm. 11
12. Portal vein thrombosis. 12

1976

1. Western Equine Encephalitis. 13
2. Marantic endocarditis associated with carcinoma of the pancreas. 14
3. Vaginal adenosis associated with DES. 15
4. Ethylene glycol toxicity-kidney. 16
5. Mesothelioma of the A-V node associated with sudden death. 17
6. Complicated congenital heart disease. no slide 18 - NO SLIDE
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8. Immunoblastic lymphadenopathy. 20
9. Amyloid tumor-lung. 21
10. Peripartum cardiomyopathy. 22
11. Berylliosis-axillary lymph nodes. 23
12. Pulmonary alveolar proteinosis. 24

ST. PAUL-RAMSEY HOSPITAL
ST. PAUL, MINNESOTA 55101

CASE 2

DEPARTMENT OF PATHOLOGY

1975 - Case #2
St. Paul-Ramsey Hospital
A75-15

CASE OF THE MONTH

CLINICAL HISTORY: This 74 year old white female was admitted to St. Paul-Ramsey Hospital because of ketoacidosis and respiratory distress. The patient had a history of a hospitalization from August to October, 1975, in Bismarck, North Dakota for subacute bacterial endocarditis (streptococcus viridans, by culture) and from October to November, 1974, at Midway Hospital in St. Paul for a workup of increasing confusion with a tentative diagnosis of "cerebral vasculitis". During thse two hospitalizations the patient showed evidence of congestive heart failure and was on Diazide, one tablet q day, and Lanoxin, 25 mgm q every third day.

On arrival at St. Paul-Ramsey Hospital the patient was felt to be in septic shock with a blood pressure of 70/40 and was unresponsive except to deep pain. She had a holo-systolic grade III/VI murmur which radiated to the axilla and a grade I/VI systolic ejection murmur heard best at the left sternal border. The chest x-ray showed a pneumonic infiltrate and the blood sugar was 1098 mm%. She was given supportive care, but had a sudden respiratory arrest and was not resuscitated at the request of the family.

GROSS SPECIMENS OF INTEREST: A photomicrograph and a glass slide of the mitral valve are included with this report.

The heart weighed 440 grams and showed only mild atherosclerotic change within the large coronary arteries. The myocardium revealed no areas of fibrosis. There was partial fusion of the leaflets of the aortic valve near the annulus, which was probably not hemodynamically significant. The posterior leaflet of the mitral valve was thickened and ballooned into the left atrium. On the anterior leaflet there were raised yellow fibrin nodules approximately 5 mm. from the free margin. The chordea tendineae were thin but intact and the mitral annulus was grossly not thickened or calcified. The left atrium appeared dilated. The tricuspid valve was thin and delicate and the pulmonary valve appeared normal.

MICROSCOPIC DESCRIPTION: Microscopic sections show a cross section of the ballooned posterior mitral leaflet with areas of replacement of the fibrosa by a loose myxomatous tissue which stained positively with Alcian Blue. There is a fibroelastic thickening of the surrounding endocardium. No vascularization or valvulitis is present. On some sections there is a small focal calcification at the basal portion of the valve. There is, however, no extensive calcification of the annulus and no extension of this calcification into the atrium. Sections of the myocardium show no ischemic or rheumatic change. There is no small vessel atherosclerotic disease and only minimal large vessel disease. Sections of the tricuspid valve show no involvement by this degenerative process.

DIAGNOSIS: MUCOID DEGENERATION OF THE POSTERIOR LEAFLET OF THE MITRAL VALVE

DISCUSSION: This case is an example of a degenerative valvular disease. With the introduction of antibiotics the pathology and the course of infective endocarditis has been radically changed and there is a marked decrease in the incide of chronic rheumatic and syphilitic valve disease. Because of these factors and the increasing longevity of our population degenerative valvular heart disease is becoming more important. Apart from the rarieties such as valvular amyloidosi degenerative valvular disease can mainly be thought of as two forms: calcificati involving the valve ring, and mucoid (myxomatous) degeneration involving the cusp fibrosa. The case presented here is an example of the latter.

Calcification of the annulus fibrosis of the mitral valve is commonly present i older people at autopsy (8% of patients over 50) (1). Although this process may be the sequela of rheumatic, rheumatoid and other types of endocarditis (9,10) evidence for previous inflammation or pathology is often absent. Therefore this disease probably represents the end stage of a degenerative process (5). The posterior leaflet is more commonly involved and this massive calcification may e into the adjacent myocardium and septum with disruption of the bundle of His. Th change is associated with complete heart block, and rarely with mitral stenosis. Korn et. al (5) described a series of 14 cases of women between the ages of 56 and 88 years with massive calcification of the valve ring, with elevation of the valve leaflet, stretching of the cordea tendineae and resultant valvular incompet and stenosis. The leaflets usually show only moderate thickening and microscopic there are calcium deposits within the ring which are embedded in a matrix of almo acellular eosinophilic material that resembles hyalinized collagen. Within this matrix there may be scattered lipid filled clefts and spaces containing dust-like and sometimes more solid clumps of calcified material. Coursing through this les are fibrous trebeculae, some of which may be calcified. Extension of this calci process into the mitral leaflets occurs more often in the anterior than the poste leaflet and is usually limited to the fibrous layer at the base of the leaflet. There are also varying degrees of involvement of the aortic valve but no involve of the right side of the heart.

The etiology of this lesion is thought to be an exaggeration of aging changes (5) and the main importance of this lesion is the differentiation from healed rheumat valvular disease and the differentiating features are listed in Table I.

TABLE I

Feature	Rheumatic Disease	Calcific Disease
Leaflet involved	Both, more often posterior	Anterior
Gross	Distal tip, margins of closure	Basal portion
Microscopical	Primarily spongiosa	Primarily fibrosa
Interadherence of leaflets at commissures	Prominent	Variable, exclusively basal
Verrucae	Common	Absent
Chordae tendineae	Thickened, shortened, fused	Normal or slightly thickened
Annulus calcification	Variable, focal	Severe
Other findings	Involvement of other valves MacCallum's patch Microscopical rheumatic signs	Variable calcific aortic sclerosis

Another form of degenerative heart disease involving the mitral valve is mucoid degeneration which in the series of Pomerance et. al.(6) is present in almost 1% of autopsies on adult patients over 10 years of age and the incidence rises with the age of the patient. Patients usually have a long history of a murmur and the process occasionally involves both mitral cusps, the aortic, and the tricuspid valve. The lesion is known under a wide variety of names such as "floppy valve syndrome", "ballooning", "billowing", "aneurysmal protrusion", "prolapse", "mucin degeneration" and "myxomatous degeneration". (1) The increased cusp area, the parachute-like appearance, the lack of cusp edge adhesions, and fibrous contraction of the chordae contrast with the usual findings in rheumatic disease. Although the incidence of this anomaly is more common in failing hearts, it is also present in the patient who has no history of heart failure and is thought to be a contributing cause, rather than the primary cause, of failure. Endocardial thrombosis and ulceration, which appear to be present in about one-third of the cases, predispose to the increased incidence of infective endocarditis. Another complication is "spontaneous" rupture of the chordea tendineae. Caulfield et. al (3) described similar areas of mucoid degeneration within the chordea tendineae in patients with spontaneous rupture but with no evidence of ischemia or endocarditis. Surgical correction of the valve abnormalities presents difficulty because of the abnormal consistency of the tissues.

The pathogenesis of mucoid degeneration is unknown and, although common in the aged, it has also been found in congenital valvular disease and probably represents the end stage lesion of several processes. A similar condition is present in dogs and is related to aging and breed (11). Several authors have noted a similarity to inheritable connective tissue abnormalities of the Marfan type and many familial cases have been reported without all the stigmata of the Marfan's syndrome. In most cases, however, there is no evidence for either a generalized connective tissue disease or a familial incidence.

Microscopically the valves appear as described in our case and the basic abnormality appears to be a fibrosal degeneration with loss of the normal dense collagenous supporting structures with resultant stretching of the cusp and formation of the characteristic ballooning leaflet. This findings may represent enzymatic dissolution of a portion of the fibrosa followed by healing by fibroblastic proliferation.

IN SUMMARY: We have an elderly female with ballooning thickened posterior leaflet of the mitral valve who was in congestive heart failure. At autopsy the mitral valve showed areas of mucoid degeneration which stained positively with Alcian blue. This form of degenerative valvular disease is to be differentiated from massive calcification of the annulus. The etiology for both of these conditions is unknown, but probably represents the endstage of various processes including aging. In the differential of chronic valvular disease the degenerative valvular diseases should be considered along with the rheumatic, congenital, syphilitic, and infective diseases.

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ST. PAUL-RAMSEY HOSPITAL
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Department of Pathology

CASE #3

1975 - Case #3
St. Paul-Ramsey Hospital

CASE OF THE MONTH

A 27 year old bricklayer was admitted to the hospital with mid-epigastric pain and fever which had been present for five days. Two days before admission the pain extended to the periumbilical area and radiated to the back. It was not associated with nausea, vomiting or any change in bowel habits.

Examination on admission showed a temperature of 101°. There was rigidity of the abdominal muscles with rebound tenderness in the periumbilical area and right lower quadrant. The Hgb was 13.5 gms., the white count 9,600 with 84% PMN's. A stool examination for occult blood was weakly positive. X-rays of the gallbladder, upper G.I. tract, and small bowel were "normal". A barium enema showed contraction and spasticity of the cecum. A laparotomy and right hemicolectomy were performed on the 5th hospital day.

The specimen submitted included 60 cm. of terminal ileum, cecum, appendix, and 30 cm. of ascending colon and associated mesenteries. The length of bowel and mesentery were thickened and fibrotic, dusky red in color and the serosa shaggy and dull. There were several pockets of pus present around the appendix. In the cecum there was a 6 cm. serpiginous ulceration of the mucosa which extended proximally into the ileum. At the cecal end of the ulcer there was a small dimple opening into a fistula tract which extended for a length of 4 cm. through a markedly fibrotic and thickened ileal wall into the adjacent mesentery and associated inflammatory reaction. The mucosa adjacent to the ulcer showed edematous broad flat folds which ended abruptly at the margins of the ulcer.

MICROSCOPIC: The slide submitted shows a section of terminal ileum with patchy ulceration of the mucosa with intervening broad swollen mucosal folds. The submucosa is thickened, edematous, and packed with a dense inflammatory infiltrate composed chiefly of plasma cells, and lymphocytes with scattered eosinophils and red blood cells. Well circumscribed aggregates of lymphocytes are present within the submucosa, the muscular and subserosal layers. The muscularis is thickened, the subserosa fibrotic and edematous. At one edge of the section there is a broad band of acute inflammatory cells extending through the muscularis which is suggestive of a margin of inflammation adjacent to a sinus tract. Granulomas were present in some but not all sections examined.

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DIAGNOSIS: Regional enteritis, small bowel and colon.

DISCUSSION: First described by Crohn in 1932 as a granulomatous disease of the terminal ileum, the spectrum of regional ileitis has since been enlarged to include involvement anywhere within the alimentary tract. Characterized as a chronic, remitting, granulomatous disease of the gastrointestinal tract with peak incidence in young adulthood, the disease affects men and women equally. Within the last 10 years much attention has been devoted to Crohn's disease due to an apparent increased incidence of chronic inflammatory diseases of unknown etiology of both the small and large bowels and to the application of recent immunologic technique to solving the etiology of such conditions. The recent literature is replete with articles on Crohn's disease, its relationship to ulcerative colitis and the possible etiology of each. Although usually histologically distinguishable, they have much in common. Each is a chronic inflamma disease, both may affect the large bowel, and both are of unknown etiology.

Involvement of the small bowel alone is the most common presentation of regional enteritis. It is three times more common than involvement of both the small and large bowel, or the large bowel alone. Acute and chronic ileitis are the most common forms of the disease followed by localized disease elsewhere in the small bowel, ileocolitis, colitis, anorectal involvement, and finally, stomach and duodenum. The mouth and esophagus are rarely involved.

Characteristically, Crohn's disease involves the entire thickness of the bowel wall with transmural inflammation. The most consistent feature is the presence of discrete lymphoid aggregates at the mucosal-submucosal junction, the submucos the muscularis and serosal surfaces. Non-caseating sarcoid-like granulomas are found in 60% of the cases and are thought by some to be diagnostic, but they are not necessary for the diagnosis. The mucosa may be ulcerated, thus confusing it with ulcerative colitis. The ulcers are frequently located over lymphoid follicles. Fissures are present in 30% of the cases, usually extending from the base of the ulcers through the muscularis propria. Regional lymph nodes contain granulomas in 30 - 40 % of cases. Unlike ulcerative colitis which is a disease affecting primarily the mucosa, Crohn's disease involves the full thickness of the bowel wall and the mucosa, if not ulcerated, has a well maintained goblet c population and normal glandular architecture.

The etiology of Crohn's disease is unknown. As in ulcerative colitis, much evidence suggests that patients with Crohn's disease have a state of altered immunological activity. Some studies show an increased incidence of positive Kveim tests and both phytohemagglutinin and DNCB skin tests suggest a degree of anergy. There is evidence of a transmissible factor: Crohn's disease has been produced in an animal model by injection of the ileum with a homogenate of diseased bowel. However, identification of the transmissible agent and product of a remitting disease remains to be accomplished.

Since 1956 twenty-six cases of adenocarcinoma of the small bowel associated wit regional enteritis have been reported. More than 70% of these were diagnosed postoperatively. Although the sex distribution is the same as that of primary carcinoma of the small bowel, carcinoma associated with regional enteritis is found in younger patients (mid-forties) and the prognosis is much worse with an average survival of six months after diagnosis.

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CASE 4

CASE OF THE MONTH

HISTORY: In October, 1974, this 64 year old white male was admitted with a three week history of progressive dyspnea, nonproductive cough, fever, chills and chest pain. He had severe, chronic, active rheumatoid arthritis for 25 years, complicated by keratoconjunctivitis sicca. This condition most recently was treated with mild physical activity and PRN ASA. Past chest x-rays demonstrated prominent, bilateral interstitial markings, most prominent at the bases.

There were dry rales heard over both lung fields. The wrist, MP, PIP, and knee joints demonstrated chronic rheumatoid changes. Subcutaneous nodules were noted on the left elbow. The chest x-ray demonstrated a right pleural effusion and infiltrates in all three right lung lobes and the left lower lobe. Despite appropriate therapy his course was marked by progressive respiratory insufficiency and he expired on the 8th hospital day.

AUTOPSY FINDINGS: Both the right and left pleural spaces were obliterated by confluent sheets of firm fibrous connective tissue. The pericardial space was obliterated by fine sheets of fibrinous adhesions. The right lung weighed 980 grams and all three lobes were consolidated. On sectioning, the cut surface was congested, edematous, and demonstrated a markedly increased consistency. A honeycomb pattern was evident with numerous small trabeculated cysts lying within firm fibrous tissue. In addition there were numerous, widely scattered small pockets of yellow purulent material. The left lung weighed 800 grams. On sectioning, both lobes demonstrated changes similar to, but less striking than, those described for the right lung.

MICROSCOPIC EXAMINATION: Multiple sections of both lungs demonstrated extreme distortion of the normal architecture by several processes. These included: marked fibromyxomatous pleural thickening; moderate to severe fibrotic thickening of the alveolar septae; a diffuse lymphocytic and plasma cell interstitial infiltrate; scattered areas of collapse and fibrosis of the alveolar spaces and bronchioles forming large patches of fibrous connective tissue studded with cystic spaces lined by hyperplastic and desquamating epithelial cells; scattered microscopic perivascular nodules, characterized by a necrotic center, an intermediate, palisaded layer of fibroblasts surrounded by a dense infiltrate of lymphocytes and plasma cells; large confluent areas of bronchopneumonia; fibrosis and hyaline thickening of the intimal and medial layers of the small pulmonary arteries and arterioles; and scattered organizing thrombi.

DIAGNOSIS:
1. Chronic interstitial pneumonitis and fibrosis, compatible with rheumatoid lung.
2. Subpleural perivascular rheumatoid nodules diagnostic of rheumatoid lung.

DISCUSSION: There are five pulmonary lesions which have a valid association with rheumatoid arthritis. These include:
1. Pleural disease, with or without effusion.
2. Rheumatoid pneumoconiosis (Caplan's syndrome).
3. Nonpneumoconionic intrapulmonary rheumatoid nodules.
4. Diffuse interstitial pulmonary fibrosis and pneumonitis.
5. Pulmonary hypertension.

PLEURISY: Pleural disease is the most frequent form of rheumatoid involvement of t respiratory system. There is a significantly increased frequency of a history of pleurisy or x-ray documentation of pleural thickening or effusion in rheumatoid groups as compared to normals or groups with degenerative joint disease. There is a correlation between pleural effusion and subcutaneous nodules but none between th clinical or radiographic severity of the disease. There may be an association with pericarditis in men. The pleural effusion may be unilateral or bilateral. The pleural fluid has a variable cytology and may be prdominately lymphocytic, polymorp nuclear, or mixed. Protein levels are variable and have no diagnostic value excep to indicate the presence of an exudate. A low glucose is strongly suggestive, but normal levels can be found. High levels of LDH have been found. A punch biopsy of the parietal pleura in patients with effusion or pleural thickening will demonstrat diagnostic pathological changes, i.e. rheumatoid nodules, in 40% of cases. In the remaining 60% nonspecific changes are noted. Approximately 70% of effusions demon strate an elevated SCAT (sheep cell agg test) titer. In 10 to 20% of cases, the effusion SCAT titer will be positive while the blood titer will be negative.

The duration and behavior of the effusion is variable. It may persist for years. Pleural thickening is occasionally extensive and may require decortication. The effect of oral corticosteroid treatment for effusion is variable, but in some case their administration is accompanied by a rapid resolution.

Infrequently, large necrobiotic lesions, similar in structure to those commonly found in the subcutaneous tissue, may be found in the visceral pleura and subjacen intra-lobular septae.

NONPNEUMOCONIOTIC INTRAPULMONARY RHEUMATOID NODULES: Nonpneumoconiotic intrapulm nodules are a rare but diagnostic feature of rheumatoid involvement. They are mo frequent in men, occur at any stage of rheumatoid disease, and may occur before th onset of clinical arthritis. They are often accompanied by pleural effusion, sub- cutaneous nodules, and interstitial pulmonary fibrosis. Other systemic manifestat especially cardiac lesions, are frequently present. They vary from minute up to se cm. in diameter. Cavitation of these lesions may occur. They may be single but, more frequently, are multiple. Their histological structure is that of a classic rheumatoid nodule and there may be a polymorphonuclear infiltrate in the necrotic center.

They have a necrotizing nature and a tendency for regional involvement of bronchi and pleura. Unless they attain large size respiratory symptoms are absent. Necro tizing lesions at the lung surface may rupture and cause spontaneous pneumothorax. These lesions may increase in size and number, may resolve, or improve, spontaneou or with Chloroquin or corticosteroid therapy.

RHEUMATOID PNEUMOCONIOSIS, CAPLAN'S SYNDROME: The most exentisvely studied of th rheumatoid lung diseases is Caplan's syndrome, the association of pneumoconiosis and rheumatoid arthritis. In 1953 Caplan drew attention to the occasional presenc of rounded, discrete densities on the chest x-rays of coal miners with rheumatoid arthritis. The lesions were found to develop in crops, evolve rapidly, and occasionally undergo cavitation. The nodules were found three times as often in miners with rheumatoid arthritis than in those without. The characteristic x-ray appearance consists of multiple, well defined, nodular opacities from 0.3 to 5.0 c in diameter, distributed throughout both lung fields but predominately in the peri with little or no other evidence of pneumoconiosis. The vast majority of the case

reports have come from Europe. The combination of nodules and pneumoconiosis in persons with rheumatoid arthritis may develop in workers exposed to any source of inhalable silica, i.e. from dusts of sand blasting, brass, iron, pottery, boiler scaling and asbestos.

The pneumoconiotic rheumatoid nodules consist of concentric layers of partially necrotic collagen, dust, an occasional foci of tuberculosis, and nonspecific inflammation. The center may be partially cavitated and is surrounded by a layer of palisaded fibroblasts. Pigment forms the black rings seen microscopically. Peripheraly there is a dense lymphocyte and plasma cell infiltrate and then further concentric layers of collagen fibers. Arteries, lying adjacent to the lesion, usually demonstrate endarteritis with an intramural lymphocytic and plasma cell infiltrate. The most attractive hypothesis concerning the pathogenesis is that rheumatoid pneumoconiosis is a consequence of the interaction of a component of rheumatoid arthritis with a residue of silica in the lungs which, of itself, is insufficient to produce gross pneumoconiosis. The schema proposed requires years of exposure to silica dust. Then, if rheumatoid arthritis should develop, either concurrent with this exposure or years after, the rheumatoid factor may increase the granulomatous reaction to silica in the lungs leading to a very rapid onset and progression of the pulmonary nodulation. Experimental investigations have indicated that both tuberuloprotein and rheumatoid factor increase the granulomatous reaction to silica in lungs. In some cases, however, the characteristic x-ray appearances preceed the arthritis by several years.

INTERSTITIAL PULMONARY FIBROSIS: In a prospective series of 516 patients with rheumatoid arthritis 1.6% had diffuse interstitial fibrosis. No cases were found in 309 patients with degenerative joint disease serving as control group. The earliest change is a nonspecific, interstitial pneumonia consisting of lymphocytes, plasma cells, and macrophages surrounding small arteries, arterioles, and bronchioles with subsequent spread into the adjacent interalveolar septae. This stage is probably reversible and resolution likely occurs in many cases. If resolution does not occur there is fibrosis and cystic dilatation of bronchioles and alveoli, which in its extreme form becomes honeycombing. These changes are also seen in idiopathic interstitial lung disease and are nonspecific, but when seen in association with rheumatoid granuloma are considered part of the rheumatoid lung process.

Despite the fact that both rheumatoid arthritis and idiopathic interstitial pulmonary fibrosis are more common in women, the fibrosis accompanying rheumatoid lung is more common in men. There is at least some suggestion that environmental factors play a role in the etiology of this condition in rheumatoid arthritis. The clinical and radiological features are similar to those of idiopathic pulmonary fibrosis.

PULMONARY HYPERTENSION: Apart from the effect of interstitial pulmonary fibrosis on the pulmonary circulation, pulmonary hypertension may occur as the sole intra-thoracic manifestation of rheumatoid arthritis. This association, although of great rarity, has been well documented. In several reported cases of unexplained pulmonary hypertension, rheumatoid arthritis, Raynaud's phenomenon, and a positive SCAT were noted. It is thought that endarteritis involving the pulmonary and digital vessels accounts for the pulmonary hypertension and Raynaud's phenomenon. Autopsy study of these cases demonstrated fibrous proliferation of the digital and pulmonary arteries and arterioles.

PATHOGENESIS: The pathogenesis of rheumatoid lung lesions is uncertain at this time. Recent immunofluorescent studies of rheumatoid lung specimens have demonstra dense deposition of gamma M and 19 S rheumatoid factor in the alveolar walls and pulmonary capillaries. Moderate deposits of gamma G and gamma A antibodies were noted, but did not approach the massive deposits of gamma M. No complement deposit was noted. It was postulated that the 19 S rheumatoid factor is fixed in pulmonary tissues after having reacted with circulating antigen-antibody complexes. This entrapment or deposition within the pulmonary capillaries may reflect local intrins inflammation native to the rheumatoid process. This might explain their local pulm ary concentration and the absence of renal lesions in these same patients.

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CASE 5

DEPARTMENT OF PATHOLOGY

1975 - Case #5
St. Paul-Ramsey Hospital

CASE OF THE MONTH

HISTORY: This 74 year old man who suffered from chronic alcoholism, arteriosclerotic heart disease, and sequellae of two major cerebrovascular accidents was admitted to St. Paul-Ramsey Hospital for the tenth and final time on 2-4-75 after being transferred from a local nursing home because of fever and weakness. The pertinent past history was negative for episodes of gastrointestinal bleeding and no family members had suffered from gastrointestinal hemorrhage.

On physical examination the patient's skin was without vascular lesions as were the nasal cavities, nasal pharynx, oral pharynx, and oral cavity.

Further hospital workup disclosed left lower lobe pneumonia. The patient was treated with appropriate antibiotics; however, his condition continued to deteriorate and on the sixth hospital day he succumbed with massive bronchopneumonia and sepsis.

AUTOPSY FINDINGS: The topic of this discussion is the incidental autopsy finding of multiple vascular lesions within the small intestine. The mucosal surface of the duodenum and jejunum was interrupted by a myriad of grossly visible submucosal reddish blue nodules ranging in size from minute to 8 mm in greatest diameter. These did not blanche after digital pressure. The mucosa overlying all lesions appeared to be intact and no active bleeding sites could be identified. The lesions were most numerous in the proximal jejunum, few in number in the terminal jejunum and absent in the ileum. The remainder of the gastrointestinal tract was unremarkable.

MICROSCOPIC: The lesion consists of dilated, thin walled vascular channels lined by normal appearing endothelium and often traversed by thin strands of fibrous connective tissue. In some areas thrombosis and organization are seen. The lesions are confined to the submucosa while the overlying mucosa remains intact.

DIAGNOSIS: Multiple phlebectasia, small bowel.

DISCUSSION: A useful anatomic classification of intestinal angiomata is that of Obendorfer-Kaijser which follows:

I. Multiple phlebectasia: Multiple phlebectasia are the most frequently encountered type of vascular dysplasia in the small intestine. Grossly, they are small, red to blue-black nodules which occur mainly in the small intestine, the jejunum usually being most heavily involved. They are usually submucosal but occasionally are noted subserosally. Microscopically, they are composed of a multiplicity of large, communicating endothelial lined spaces. Moeller demonstrated with the aid of wax models that the lesions are caused by a diverticulosis of the walls of small intestinal venules with which they always remained in continuity.

II. Cavernous hemangiomas - These may be of two types.

A. The diffuse infiltrating cavernous hemangioma may replace the intestinal wall from serosa to mucosa. It often encroaches upon and narrows the intestinal lumen. It is most frequently found in the rectum. Microscopically, the lesions are composed of multiple, dilated, tortuous

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vessels within a stroma containing an abundance of smooth muscle and fibrous connective tissue. Clinically, the great majority of these lesions cause hemorrhage or obstruction.

B. The polypoid cavernous hemangioma also exhibits a typical cavernous vascular structure. The polypoid type protrudes into the intestinal lumen and approximately 80% of these lesions produce either obstruct or gastrointestinal bleeding.

III. Hemangioma simplex: These lesions most often appear as a single lesion the submucosa. They project into the intestinal lumen and may become pe culated. Microscopically, they are formed from numerous dilated capilla and endothelial cells which may proliferate to the point of a cellular hemangioendothelioma. They also may cause obstruction and intestinal bl

IV. Angiomatosis: The lesions of this category are histologically similar t those of multiple phlebectasia, however, they have a more widespread distribution. When they are part of a heterofamilial syndrome and appear o the skin, in the oral and nasal cavities and within the intestinal tract, they are dignified by the term Osler-Weber-Rendu syndrome.

In the case under discussion, with the multiplicity of the lesions, thei confinement to the submucosa of the small intestine, and the absence of positive family history, the most favorable categorization is that of multiple phlebectasia. In our case the lesions were an incidental autops finding; however, they may present a problem in the diagnosis of occult gastrointestinal hemorrhage. Significant hemorrhage may occur from isol phlebectasias and has been reported in patients ranging in age from 6 to years. The great majority of these cases have onset of hemorrhage after age of 40 and males predominate in a ratio of 3 to 1. Surgical excision is the only means of cure, and is obviously most successful when the les are confined to a small segment of bowel. In diffuse disease, attemps should be made to determine the site of bleeding since an isolated lesio may be the source. The fact that our patient lived to the age of 74 with significant gastrointestinal hemorrhage implies that the prognosis in su cases is quite good.

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CASE 6

DEPARTMENT OF PATHOLOGY

1975 - Case #6
Submitted by Yat-sun Leung, M.D.
Bismarck, North Dakota

CASE OF THE MONTH

HISTORY: There is a very short clinical history available on this case. The patient is a 70 year old male American Indian with lung infiltrates by x-ray. Sputum cultures were negative. The patient now presented with urinary complaints and a urinary culture was positive for Mycobacterium tuberculosis. A trans-urethral prostatic resection was performed.

MICROSCOPIC: Sections show numerous fragments of fibromuscular tissue and glands which are generally lined by double layers of mucous secreting epithelium. In most fragments the normal prostatic architecture is replaced by an interstitial granulomatous process composed of variable sized granulomas with central necrosis, multinucleated giant cells surrounded by epitheloid cells and lymphocytes. In addition, in focal areas, a few lymphoid aggregates are present and great numbers of plasma cells infiltrate the stroma. Acid fast stains are positive.

IMPRESSION: Granulomatous inflammation, tuberculosis, prostate.

DISCUSSION: Primary isolated tuberculosis of the prostate gland is a rare entity. In most cases prostatic tuberculosis is secondary to direct spread from other genitourinary organs. It can also follow pulmonary, bone and gastrointestinal foci via the blood stream and lymphatics. Genitourinary tuberculosis is also more prevalent in older individuals and in lower socio-economic groups. Its incidence has not declined at the same rate as its pulmonary counterpart. One of the reasons being its slow clinical course, remaining silent for long periods of time. In most cases it starts in the kidney, the lesion varying from small miliary tubercles to a frank caseating process extending down into ureters and bladder.

Involvement of the prostate gland alone is noted in about 1% of patients with positive urine cultures for M. tuberculosis, and about 80% of the cases with prostate involvement show infection of the epididymis and testes with enlargement and tenderness of these organs.

The diagnosis of genitourinary tuberculosis depends on positive urine culture or biopsy with positive stains. Cultures of three morning specimens are considered as good as a 24 hour urine collection. In cases of chronic urinary infection genitourinary tuberculosis should be suspected and a needle biopsy of the prostate may lead to the diagnosis. If surgery is considered a suprapubic prostatic resection should be performed because of the chances of spreading the disease by trans urethral resection. (Note that a TUR was performed in this case.)

On gross inspection the lateral lobes of the prostate are involved. The lesion is primarily interstitial, rapidly progressing to the glands with formation of large caseating cavities surrounded by fibrous walls. If healing occurs areas of calcification can be seen on x-ray examination. With superimposed infections fistula tracts can be formed into the perineum, rectum, and peritoneum. Microscopically the granulomas are extensively necrotic and confluent. Typical tubercles are not the usual feature. The remaining glands are not usually cystically dilated and do not contain inflammatory cells in the lumina. The bacilli may or may not be demonstrable by acid fast staining.

The differential diagnosis includes all types of granulomatous inflammation: fungus infections (histoplasmosis, blastomycosis, coccidioidomycosis, and cryptococcosis), granulomatous prostatitis, and syphilis. In granulomatous prostatitis there is severe disruption of the glands which are replaced by an inflammatory exudate containing plasma cells, lymphocytes and polymorphonuclear neutrophils. In other areas large groups of clear cells with slightly eosinophilic or vacuolated cytoplasm are present which are, in most instances, fat positive with fat stains. This pattern may be confused with carcinoma. Polymorphonuclear leukocytes and cellular debris are present within ducts and tubercle-like areas with foreign body giant cells can be present. The tuberculosis bacillus cannot be demonstrated and caseation necrosis is not present.

The fungal infections show a similar histologic picture to that of tuberculosis but the fungi can be demonstrated with fungus staining (PAS, silver). Syphilitic prostatitis shows massive plasma cell infiltrate and vasculitis. Large macrophages may be present resembling tuberculosis. Spirochetes are demonstrable on tissue sections in secondary syphilis. Gummas may also occur with caseous necrosis but they are usually surrounded by large numbers of plasma cells and lymphocytes and marked capillary proliferation with inflammation of the vessel walls.

In this present case acid fast bacilli were present. Tuberculosis of the kidney was suspected but could not be proved. There was no involvement of any other genitourinary organ.

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DEPARTMENT OF PATHOLOGY

CASE 7

1975 - Case #7
St. Paul-Ramsey Hospital

CASE OF THE MONTH

HISTORY: The patient was a 1400 gram infant caucasian female of 32 weeks gestational age who was delivered with midforceps extraction after approximately 12 hours of labor. Premature rupture of membranes had taken place 15 days previously, requiring treatment with intravenous ethanol. The mother was 17 years of age, serology negative, and PARA 1001, and the pregnancy had been previously uneventful.

The infant's one minute and five minute apgar scores were 6 and 8 respectively, and she required oxygen support first by head box and subsequently by endotracheal tube. Within 48 hours, she became icteric with abnormal clotting parameters. A 260 cc. exchange transfusion was performed 3 days after birth, and heparin therapy was begun for possible low grade DIC. At four days, her abdomen became distended and hard. Pneumatosis intestinalis was seen on an abdominal x-ray. Laparotomy performed at that time showed extensive segmental necrosis of the entire small and large bowel, which was judged unresectable, and a transverse loop colostomy was performed. The clinical course continued downhill, with the onset of peripheral cyanosis, truncal ecchymosis, and bright red nasogastric return. The infant expired on the fifth day after delivery.

AUTOPSY FINDINGS: Both lungs were fleshy and completely solidified. The entire gastrointestinal tract, from mid-duodenum to anus, was dusky and hemorrhagic and much of the intestinal mesentery was covered by a thin yellow sheet of pus. Many areas, particularly within the large bowel, were extensively thinned and showed occasional subserosal hematomas, and the descending colon contained one perforation. The small and large bowel mucosa was extensively necrotic. The stomach was normal.

MICROSCOPIC DESCRIPTION: In both the small and large bowel, there is total necrosis of the mucosa with extensive sloughing, submucosal and subserosal hemorrhage, submucosal edema, and pockets of pneumatosis. A moderate to severe inflammatory infiltrate is present, and many sections of large bowel wall have been attenuated almost to paper thinness.

DIAGNOSIS: 1. MASSIVE NECROTIZING ENTEROCOLITIS, SMALL AND LARGE BOWEL
2. HYALINE MEMBRANE DISEASE

DISCUSSION: Necrotizing enterocolitis (NEC) of infancy first began to appear in the literature as a separately defined disease in 1965 when Mizrahi *et al* reported finding autolytic and necrotic changes in segments of surgically resected infant bowel which had not been devitalized long enough for these changes to represent post-surgical artifact. Their observations were corroborated by reports from other centers with active pediatric surgery services. Although NEC has features in common with bowel necrosis of other etiologies, it is set apart by the clinical setting in which it occurs

NEC is very predominantly a disease of premature infants, particularly those that are small for dates. Virtually all afflicted infants have suffered some form of intrauterine stress, and there is a high incidence of associated respiratory distress syndrome. There is also a strong positive correlation with intrauterine infection and premature rupture of membranes.

The disease typically develops within the first 7 days post-delivery, beginning w nonspecific gastrointestinal signs and symptoms (vomiting, often bile stained, poo feeding, or diarrhea, sometimes bloody) and progressing to ileus and abdominal dis tention with or without signs of peritonitis. Abdominal x-rays show distended loo of bowel, commonly with air-fluid levels. The crucial finding, which virtually establishes the diagnosis, is the presence of penumatosis intestinalis on the abdo film. If the disease is advanced, free intraperitoneal air and/or portal venous g may also be radiologically visible. Stool cultures are typically negative, but blood cultures may be positive for gram-negative organisms in up to 25% of cases.

The pathology of the early lesion consists of coagulation necrosis of the mucosa without underlying inflammation. Later, mucosal sloughing, submucosal hemorrhage, inflammation, and submucosal and subserosal pneumatosis set in. Intestinal vascul thrombosis is not seen during the early stages, but is a common finding in advance disease. Any segment (or all) of the gut from the duodenum distalward may be invo and NEC differs from other forms of bowel necrosis in that it typically involves l and continuous segments of intestine rather than multiple or skip areas.

The pathogenesis of NEC is now understood as a sequence of events beginning with i breakdown of the gut mucosa. Enteric bacteria, including gas-forming organisms, e the gut wall at points of mucosal disruption and proliferate rapidly, leading firs local tissue necrosis and pneumatosis and later to frank perforation, generalized sepsis, and pneumoperitoneum with intravascular gas formation.

The etiology of the disease and its predilection for immature infants are thought be intimately related to the incomplete development of both native enteric immunit and fine autonomic vascular control. The initiating hypoxic insult to the intesti may be any of a wide variety of stress stimuli which cause (in this case too marke a reactive shunting of blood away from the gut. Even then, the development of NEC seldom supervenes in breast-fed infants but regularly does so in those fed formula The immature infant lacks the ability to secrete adequate levels of intestinal muc coproantibodies, and it is believed that immunoglobulins present in mother's milk confer passive protection against tissue invasion by gut flora.

The prognosis for an infant with NEC is bleak, and the disease is almost uniformly fatal in preemies who are small for dates. Treatment must be vigorous, and usuall includes laparotomy with resection if possible. Survival has been less than 25% in the past, but this may be expected to improve with more ready recognition of th disease and earlier institution of appropriate therapy.

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DEPARTMENT OF PATHOLOGY

CASE 8

1975 - Case #8
St. Paul-Ramsey Hospital

HISTORY: The patient was a 2150 gram infant Negro male of 36 weeks gestational age who was delivered by emergency cesarean section when the mother developed acute fulminant eclampsia. The mother was 19 years of age, serology negative, non-diabetic, and PARA 0000, and the pregnancy had been uneventful until 2 weeks prior to section, at which time toxemic symptoms first appeared.

At section, the infant was apneic and without heartbeat but was successfully resuscitated. The 1-minute and 5-minute Apgar scores were 1 and 1.

The infant survived for approximately 48 hours, and during that time required vigorous treatment for numerous major problems. These included severe hypoxemia requiring continuous respiratory support and high levels of supplemental oxygen; DIC requiring infusions of fresh frozen plasma and ultimately a partial exchange transfusion; congestive heart failure and pulmonary edema requiring digoxin, diuretics, and phlebotomy; a period of hypotension shortly after delivery, and possible septicemia.

In addition to the above, the post-delivery blood sugar was unrecordable, and despite corticosteroid therapy, serum glucose values remained abnormally low throughout the hospital course, never approaching normal except immediately following intravenous glucose infusions. A serum insulin value of 100 μ units/ml (nl 0-25) was recorded. The clinical course was relentlessly downhill.

AUTOPSY FINDINGS: Both lungs were fleshy and solidified, and grossly hemorrhagic. Hemorrhages were also found in the cerebral ventricles, in the subdural space, in the hepatic parenchyma, and within the stomach. The pancreas was grossly normal.

MICROSCOPIC DESCRIPTION: The lungs are extensively atelectatic and hemorrhagic, and nearly all of the dilated terminal bronchioles are lined by thick hyaline membranes.

The pancreatic islets are markedly increased in number and variable in size. Although no individual islet is abnormally large, there are numerous fields in which clusters of islets abut one another with little or no intervening acinar tissue.

Special stains indicate normal granulation of the beta cells of the islets.

DIAGNOSES:

1. Severe pulmonary atelectasis and hemorrhage, with hyaline membranes.

2. Intractable hypoglycemia, secondary to pancreatic islet hyperplasia.

DISCUSSION: The causes of infantile hypoglycemia are numerous, and the table below categorizes the types of conditions in which this may occur.

Classification of Hypoglycemia

I. Neonatal hypoglycemia
  A. Hypoglycemia associated with small-for-gestational-age infant
  B. Transient hyperinsulinemia of newborn infant
    1. Infant of diabetic mother
    2. Infant with erythroblastosis
II. Hypoglycemia of infancy and childhood
  A. Hyperinsulinemia
    1. β-cell hyperplasia
    2. β-cell tumors
    3. Nesidioblastosis
    4. Functional β-cell secretory defects
  B. Substrate limited
    1. Ketotic hypoglycemia
    2. Hypoglycemia associated with endocrine disorders
      a. Panhypopituitarism
      b. Isolated growth hormone deficiencies
      c. Corticotropin deficiency
      d. Addison disease
      e. Hypothyroidism
  C. Hepatic enzyme deficiencies
    1. Glycogen storage diseases
      a. Glucose-6-phosphatase
      b. Amylo-1,6-glucosidase
      c. Defects of the phosphorylase enzyme system
    2. Disorders of glyconeogenesis
      a. Fructose-1,6-diphosphatase
      b. Pyruvate carboxylase
    3. Other enzyme defects
      a. Glycogen synthetase
      b. Galactose-1-phosphate uridyl transferase
      c. Fructose-1-phosphate aldolase

Only those conditions listed under heading II.A. (hypoglycemia with hyperinsulinemia) are known to be caused by or associated with anatomic abnormalities of the pancreas.

In 1941, Potter et al. published their benchmark study of beta cell hyperplasia in the infant pancreas and noted the strong correlation, confirmed many times since, with maternal diabetes and erythroblastosis fetalis. They pointed out, however, that the condition could also be found not only in the absence of these diseases but in the absence of other specific etiologic factors as well. Potter and subsequent authors have found that beta cell hyperplasia may take the form of increased numbers of whole islets of Langerhans, abnormally large islets, increased numbers of beta cells per islet, increased numbers of secretory granules per beta cell, or any combination of these. The accepted normal diameter for an infant islet is 20 to 300 micra, and in the normal infant pancreas most islets should be separated by acinar tissue, much as in the adult. Special histochemical techniques can identify the beta cells, or the concentration of secretory granules within the beta cells.

Beta cell adenomas are very rare pediatric tumors (fewer than 50 cases have been reported in the world literature), and usually present no diagnostic difficulties microscopically, but may be quite small and may require extensive sectioning of the pancreas.

Nesidioblastosis represents a disordered differentiation of islet cells from embryonic pancreatic duct buds. Islet cells are scattered in nests throughout the pancreatic parenchyma, instead of organizing into discrete islets, and show a particular tendency to clump around pancreatic ducts, on occasion forming papillae which protrude into the ductal lumina. The condition is therefore essentially one of intrapancreatic islet cell ectopy.

Functional beta-cell secretory defects are difficult to establish histologically, but functional hypersecretion of insulin may be suggested by the findings of increased concentrations of secretory granules in the beta cells.

Finally, cases of hyperinsulinemic hypoglycemia have been reported in which no underlying etiology could be discovered and in which detailed examination of the pancreas was non-contributory. In Welch's study (see below), ten of twenty-one infants with this problem were found to have no recognizable pancreatic abnormalities.

Hypoglycemia of infancy is established on the basis of blood glucose values (less than 30 mgm/100 ml in the first 72 hours of life and less than 40 mgm/100 ml thereafter for a full term infant, or a fasting value of less than 20 mgm/100 ml for preemies), and if uncorrected often results in serious and irreversible central nervous system damage. The association of this condition with hyperinsulinemia and an anatomic abnormality of the pancreas (group II.A. in the preceding table) is of considerably more than academic interest, since the required treatment is 90% pancreatectomy as soon as possible after the diagnosis has been established. Welch collected 90 such cases and found that 56 normalized their blood glucose values post-operatively without further treatment, and 23 others achieved normal values with the additional help of short-term steroid therapy. The remainder failed to improve after surgery, but, significantly, had had 50% or less of the pancreas removed. In 14 cases, neurologic dysfunction was evident before surgery, and these patients remained mentally retarded, even after correction of serum glucose regulation.

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CASE 9

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

1975 - Case #9
St. Paul-Ramsey Hospital

HISTORY: The patient is a 48 year old white female, former registered nurse, admitted to St. Paul-Ramsey Hospital on 6/5/75 because of a progressive inability to continue to care for herself.

The patient had been previously well until March, 1974 when she was hit on the head with a baseball and subsequently noted to have stuttering speech, increasing forgetfulness making minor errors at first with fine motor articulations such as driving but progressed to the point where she had to give up her job as a nurse. Speech was described as slow, halting and stuttering.

Multiple evaluations at several institutions up to October, 1974 disclosed severe deterioration in intellectual functioning with deficits in listening, reading, speaking, writing, memory, calculations and general information. EEG's demonstrated widespread nonspecific generalized slowing. Spinal proteins were 26 mgm% with a gamma globulin of 11 and normal 12-channel blood determinations, endocrine function, folate and B12 levels, and urine testing.

Examination in February, 1975 revealed progressive worsening in mental functioning, plus signs of pyramidal and extra-pyramidal dysfunction with marked postural instability. The patient was noted to be completely mute, could not cooperate, and did not appear to understand verbalizations. She appeared to grimace and smile inappropriately. The patient was placed on a regiment including Mellaril 100 mg. qhs, Symmetreland Dilantin.

Examination at St. Paul-Ramsey in June, 1975 revealed an alert but poorly cooperative white female with marked facial grimacing, no spontaneous speech, no comprehension, diffuse truncal rigidity, marked bilateral hyperactive deep tendon reflexes and primitive sucking reflexes, and urinary incontinence. The family consented to a brain biopsy and an approximately 2 x 2 x 2.5 cm. segment of right temporal lobe was submitted. The major portion of the specimen was sent to NIH. From the remaining tissue light and electron microscopic examinations were performed.

Light microscopic examination revealed severe vacuolization of the entire gray matter (status spongiosus) obliterating the principal layers. The vacuoles, different in size are prominent around neurons and within neuropil. Some large vacuoles form clusters causing distortion of cytoplasm and nuclei of nerve cells. The different degree of neuronal degeneration with marked gliosis is obvious in many areas of the specimen. There are many intracellular, PAS positive granules. Closely spaced astrocytic nuclei are numerous indicating proliferation of this cell. The white matter shows intense gliosis with a few vacuoles. In spite of the widespread degeneration there is a striking absence of acute inflammatory cells in the specimen.

Electron microscopic study shows that the status spongiosus corresponds to both swelling and vacuolization of neurons. Membrane bound vacuoles of different size found in the perikaryal cytoplasm of nerve cells, in dendrites, pre and post synaptic nerve endings and occasionally in small non-myelinated axons. Rupture of plasma membrane and fusion of adjacent swollen cells or cell processes can be found. These multi lobulated spaces correspond to the large vacuoles seen in the neuropil by light microscopy. The vacuoles are either empty or filled by finely granular material, disrupted organelles or fragments of membranes. These membrane profiles reveal curled, whorled vesicular configuration and can occasionally be traced to the surface of cell or cell processes. Some neurons show early vacuolization and large electron dense bodies (probably lipofuchsin) in the cytoplasm. The myelin sheaths show focal disintegration, probably secondary to axonal changes. The extracellular spaces are generally normal except around the markedly distended processes, where focal dilatation can be seen. Astrocytes

reveal only reactive changes in this specimen. At higher magnification two types of "Virus particles" are observed. The larger ones are round, electron dense and surrounded by membrane approximately 160 - 180 nm. in diameter. The smaller particles are approximately 70 - 85 nm. in diameter. Both particles are seen frequently in the cell processes and post synaptic endings.

DIAGNOSIS: SPONGIOFORM ENCEPHALOPATHY, CONSISTENT WITH CREUTZFELDT-JAKOB DISEASE.

DISCUSSION: The clinical, light and electron microscopic studies of this patient are highly compatible with one of the slow virus diseases. The term "slow infection" was introduced by the late Bjorn Sigurdsson in 1954 (1). He applied this term to three chronic diseases of sheep which he studied in Iceland. The concept of slow infection was introduced to the medical literature in 1959, when the remarkable similarities between epidemiologic, clinical and pathologic manifestations of scrapie in sheep and kuru in the Fore peoples of New Guinea were pointed out by William Hadlow (2). This analogy stimulated the search for a transmissible agent in kuru - a search which led to the first documentation of a human slow infection with the successful transmission of kuru from man to chimpanzees in 1966 (3). This success led in turn to the transmission of Creutzfeldt-Jakob disease to chimpanzees in 1968 (3) and the search for viruses in other chronic neurologic diseases with the recovery of measles-like viruses from subacute sclerosing panencephalitis is 1969 (4,5) and isolations of papova viruses from progressive multifocal leukoencephalopathy in recent years (6,7).

In view of this recent progress the term "slow virus infection" can be better defined. It is obvious that the adjective "slow" should not be limited to the virus infection only, neither does it describe a property inherent in infectious agents (virion). A slow viral infection is a virus-host interaction in which the virus fails to cause acute disease, in which the host fails to clear the virus and in which ultimately either viral effect on cells or host response to virus results in the evolution of pathologic changes and clinical signs. This process should be clearly differentiated from latent infections in which virus persists in some occult form but can be reactivated, causing acute disease. It should also be differentiated from acute infections followed by chronic sequelae, sequelae that are not dictated by persistence of intracellular parasitism.

The causative agents in slow viral infections appear to belong to two groups of infectious agents.

One group of agents causing slow infections is classic viruses, which are antigenic and are also capable of causing acute infections (e.g.: measles-like virus in subacute sclerosing panencephalitis; papovaviruses in progessive multifocal leukoencephalopathy). This group will not be discussed here further.

The second group is the poorly characterized unconventional agents ("atypical viruses") of transmissible mink encephalopathy (TME), scrapie, kuru and Creutzfeldt-Jakob disease (CJD), which fail to evoke immune responses. These diseases have the following in common: "a) transmissibility by injection of infected organs; b) incubation time of several months to years; c) regular proctracted fatal clinical course and d) pathologic changes restricted to the brain and consisting of vacuolar neuronal degeneration and gliosis" (3). This group of diseases concerns us in connection with our patient.

The TME and scrapie are animal diseases. The TME is a relatively rare disease of commercially reared mink which was first observed in the U.S. in 1947. The responsible agent most likely represents yet another strain of scrapie virus. Pathologic changes are also very similar to scrapie. The scrapie is a disease of sheep that was well known for centuries in England and other European countries. In the U.S. it was recognized only in 1947. The name is derived from the characteristic tendency of the sheep to rub or scratch their flanks against fixed objects. Although the transmissibility of this disease by inoculation of brain

tissue to other sheep has been established more than 40 years ago (8) it is still not clear how natural transmission occurs. Contact spread among sheep is well documented and a role of insect bite with an intermediate host has also been suggested. Significant pathologic changes are always found in the brain in a form of spongioform alteration of gray matter with intense gliosis but without leukocytic infiltration and no proof of any humoral or cellular immune response. Virus-like particles (35-40 nm.) have been found in neuronal processes. The size of the agent is between 27 and 47 nm. It is resistant to heat, formalin, digestive enzymes, ultraviolet radiation, but sensitive to 95% phenol, ether, periodate.

The kuru and CJD are fatal human diseases. The kuru means in Fore language to shake or shiver from cold or fear. Natural transmission is believed to be related to the mourning rituals of the Fore people which consisted of cannibalistic consumption of their dead relatives. The striking predominance of afflicted women and children of both sexes could be related to the customs that they were engaged in the preparation of food (self inoculation) and they consumed the less well cooked offal (including brain). These mourning rituals have now been abandoned and if these transmission theories (3) are correct, kuru should die out in New Guinea. The current trend indicates that this is occuring because the kuru is now mainly a disease of adults. Significant pathological changes are found only in the central nervous system and are essentially similar to those described in scrapie and in our patient. The size of infective agents is between 220 and 450 nm. These agents are also very resistant to freezing, lyophilization, storage at -70°C. and heat at 80°C. for 30 minutes. It is important to note that experimental kuru has been transferred to chimpanzees by inoculation tissues other than brain (3).

The concept of Creutzfeldt-Jakob disease was introduced by Creutzfeldt in 1920 (9) and by Jakob in 1921 (10). Since that time over 200 cases were reported including those recent cases whose inoculated brain tissue transmitted the same disease to primates. Most patients of both sexes are 40 to 60 years of age when they die after an illness that lasts approximately 1 year. The frequency of clinical characteristics of patients with this disease is the following: Dementia 100%, Myoclonus 95%, Pyramidal tract signs 95%, Characteristic EEG 80%, Behavior disturbances 60%, Basal ganglia signs 60%, Cerebellar signs 60%, Visual abnormalities 55%, Early higher cortical dysfunction 50%, Lower motor neuron signs 35%, and Family history 15%. The symptomatology and the clinical findings can be confusing and a brain biopsy of cerebral cortex can confirm the diagnosis. It is very important to preserve the tissue properly for electron microscopy, because early lesion of status spongiosus can not be recognized in light microscopic level. The tissue should be sent to NIH to establish the presence of a transmissible agent. The brain is usually grossly unremarkable, except for slight atrophy. The widespread status spongiosus of the gray matter and intense gliosis (as described in scrapie, kuru and in our patient) are the characteristic light and electron microscopic findings with the striking lack of inflammatory and immunologic response. After primary passage (man to chimpanzees) experimental CJD develops after an incubation period of from 11 to 14 months and the animals are moribund after an illness lasting 1 to 2½ months. (These times are considerably shorter than in experimental kuru.) The size of the infectious agent is approximately 220 nm. and it is also resistant and sensitive to those agents which are listed under scrapie and kuru.

The epidemiology of CJD is by no means well understood. Most cases are sporadic, but there are well documented families in the literature in which several cases of the disease have occurred in relatives. This familial, apparently genetically determined form of the disease is also transmissible as is the sporadic form (11).

The problem of origin of kuru and CJD has long been cause for conjecture. In the case of kuru - which is present only for approximately 80 years among the natives - it is possible to establish a few reasonable hypotheses. One is that some ubiquitous virus has been made defective and modified by long serial brain passage in this cannibal society (losing its surface antigens, increasing its neurotropism) and has become the "new" agent of kuru. On the other hand a spontaneous case of CJD in a Melanesian native could, in association with the practice of ritual cannibalism, have produced the kuru epidemic, and in serial passage in man the histologic properties of disease are somewhat modified. The third attractive explanation originates from transmission experiments of TME, scrapie and kuru. Since many workers now assume that the agent of TME is a virus originating from a scrapie agent by passage through mink, and the scrapie agent has a similar very long incubation as kuru agent in transmission experiment, it is very tempting to speculate that the scrapie virus, with its world wide distribution in domestic sheep may not be innocuous for man. It could be therefore the source for the kuru epidemic.

For the mode of transmission of CJD we are without a good hypothesis. There are reported cases which indicate the possibility of contact infection (12,13), but generally it is unlikely that such a virulant agent has survived by passage from one rare patient to another. A transmission from animal (especially from sheep) to man has been postulated (13) but a definite history of eating infected sheep brain was almost never obtained and the size of infective agents of scrapie is different from CJD. It is more likely that the agent is far more ubiquitous than the evidence would indicate. The agent may, like the Epstein-Barr virus, usually exist in silent, fully masked infections causing no symptoms. The factors which could serve to determine in whom and under what conditions it would be activated to produce fatal neurologic disease remain unknown.

The nature of the atypical infective agents causing the CJD and other spongioform encephalopathies is also the subject of wide speculation and heated argument. The resistance to U.V. radiation, high temperature and to other chemical agents as well as the failure of many electron microscopist to demonstrate recognizable virions in high titer suspension or in pathologic tissues led to the speculation that the agents do not contain nucleic acid, and that they might be replicating basic proteins (14) polysaccharides (15) or plasma membrane fragments (16). Recent results in virus research, however, strongly suggest that genetically active nucleic acid moities ("viroids") strongly bound to plasma membrane fragments might be protected from inactivating agents including U.V. radiation (17). On this basis it is now believed by some workers that the TME, scrapie, kuru and CJD infective agents are probably small fragments of plasma membrane to which fragments of genetically acitive nucleic acids may be tightly bound (3). Electron microscopic findings of our patient seem to support this hypothesis. Fragmented plasma membranes are clearly visible in the vacuoles of nerve cells and dendritic process. (See enclosed electron micrograph.) The virus-like particles are found in our specimen in cell processes, synaptic endings. They have a central (sometimes granular, sometimes electron dense) core and a membrane envelope some of which on higher magnification seems to have small granules on the surface. The size - 160 - 180 nm. - is in the range of the proved infective agent and they are very similar to those described by Vernon et al (18). Although the morphology of these particles resembles certain of the myxoviruses and the murine and avian tumor viruses, it has to be emphasized that there is no proof that they are real viruses or they have any etiologic significance in this disease.

Because of all this controversy about the viral nature of the agents of TME, scrapie, kuru and CJD it appears prudent to refer to them as agents rather than as viruses as long as their structure as virus is not clearly defined.

PRECAUTIONS IN AUTOPSIES ON CREUTZFELDT-JAKOB DISEASE: The NIH Group (19) recommends the following procedures when performing post mortem examinations on patients with known CJD or patients with a course suggestive of presenile dementia. All persons in the autopsy room should wear surgical gown, gloves and mask. The skull is opened with a Stryker saw, taking care not to cut the brain with the saw. The Stryker saw is also used for removal of the spinal cord. All of the patients' tissues should be regarded as being potentially infectious not just the central nervous system. After the procedure, instruments, gowns, masks, gloves and other objects potentially in contact with the patients' tissues are autoclaved for at least 45 minutes, at temperatures of at least 121°C. and pressures of at least 20 pounds/square inch. Surgical instruments should be immersed in distilled water prior to and during autoclaving in order to protect them from corrosion. Disposable items should be incinerated. Contaminated surfaces and other objects not suitable for autoclaving or incineration (such as the Stryker saw) are sponged down with 5% sodium hypochlorite and further flushed with 0.5% sodium hypochlorite solution (commercial bleaches are usually 5% sodium hypochlorite).

Using these procedures, no case of laboratory infection has occurred in more than 15 years of research in the NIH, during which hundreds of experimentally infected animals have been autopsies.

LEGEND OF ELECTRON MICROGRAPH: Multiple swollen, vacuolated dendrites (Den) can be seen. Note the disrupted mitochondria (m) and the accumulation of curled fragments of membranes at the margin of the vacuolated cytoplasmic processes. Small myelinated nerves show vacuolization of axon and focal demyelinization. Most of the axon terminals (At) are severely impaired around the swollen dendrites. Virus-like particle (arrow) is located in an outpouching area of a dendrite. The electron dense core and a membrane coat are clearly visible. Astrocyte reveals reactive change with an indented nucleus (N). The cytoplasm of this cell is filled with mitochondria, dilated rough and smooth endoplasmic reticulum, free ribosomes, Golgi apparatus and fibriles. Several bundles of astrocytic fibriles (f) can also be noted.

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CASE 10

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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PATHOLOGY DEPARTMENT

CASE OF THE MONTH

1975-Case #10
Hibbing General Hospital

HISTORY: This 65 year old female who had not seen a physician in years had a history of chronic fatigue, facial puffiness and peripheral edema. She died suddenly without a physician in attendance.

At autopsy, the body was moderately obese, with facial puffiness and 1+ edema of the extremities. The heart weighed 525 grams, was dilated and flabby. The right coronary artery was 90% occluded at one point. The thyroid was slightly enlarged, firm, and not adherent to adjacent structures. The cut surface was white and had a whorled appearance.

MICROSCOPIC: The myocardial fibers are hypertrophied with nuclear enlargement and hyperchromatism. There is slight interstitial fibrosis, especially surrounding the intramyocardial arteries and veins. Large amounts of intracytoplasmic lipochrome pigment are present, particularly at the nuclear poles. Numerous myocytes have pale blue longitudinally oriented, fusiform accumulations of crystalloid finely granular intracytoplasmic material in the center of the myocardial fibers, tending to surround nuclei.

There is extensive obliteration of the thyroid follicles by fibrosis. There are a few foci of lymphocytes and plasma cells, some of which surround distorted and collapsed thyroid follicles devoid of colloid. Some follicles are lined by Hurthle cells.

DIAGNOSIS: Basophilic degeneration of myocardium associated with hypothyroidism (end-stage Hashimoto's thyroiditis).

DISCUSSION: The microscopic changes in the myxedematous heart consist of myocardial fiber enlargement or swelling, nuclear hyperchromatism, interstitial edema, focal fibrosis, relatively inapparent cross-striations, and basophilic or mucoid degeneration of the myocardial fibers. These basophilic myocardial deposits tend to stain blue-gray with H and E and consist of fusiform aggregates of granules with flat edges and sharp corners. They are generally perinuclear and are often associated with increased lipochrome pigment. There is a positive staining reaction with PAS, Langhan's iodide, Best's carmine and Gomori's lithium silver. They are negative with muci-carmine, toluidine blue, alcian blue, feulgen, PTAH and Congo red (2).

The changes of basophilic or mucoid degeneration of the myocardium (BD) were first described by Geipel in 1905 (1). Subsequent authors have found it present in small amounts in 30 to 89% of autopsy specimens (2,3), most frequently in hypertrophied and aging hearts. In three diseases, however, myocardial BD is present in much larger amounts than usual: hypothyroidism, idiopathic myocardiopathy and Lafora's disease, a type of familial myoclonic epilepsy in which similar inclusions are also found in neurons. In glycogenosis IV similar deposits are present in striated muscle. The basophilic material, which was previously thought to be a glycoprotein or mycoprotein, has recently been characterized as a branched polymer of D-glucose similar to normal glycogen, but having slightly different EM, histochemical and biochemical characteristics (2,4,5). It is felt to be an insoluble residue of abnormal glycogen metabolism.

Basophilic degeneration has also been described in the hypothyroid aorta and has been associated with spontaneous aortic rupture and dissecting aneurysm (7). Skin biopsy of hypothyroid patients reveals PAS+ granular material in cells of the secretory coils of the eccrine glands (8). BD has also been described in skeletal muscle (4). The accumulation of these abnormal metabolities of glycogen in the myocardium and other organs of hypothyroid patients is possibly related to a disturbance in the normal glycogenolytic processes mediated by thyroxine (2).

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DEPARTMENT OF PATHOLOGY

CASE 11

1975 - Case #11
St. Paul-Ramsey Hospital

CASE OF THE MONTH

HISTORY: The patient was a 72 year old caucasian female who suddenly collapsed at home one evening without premonitory symptoms. She was rushed to the hospital, and upon arrival was found to be comatose with flaccid paraplegia, fixed and dilated pupils, bilateral upgoing toes, a cyclic respiratory pattern, and an irregularly irregular pulse which was shown by EKG to consist of atrial fibrillation with coupled PVC's. A series of cardio-respiratory arrests followed almost immediately upon her arrival, and despite transient success of resuscitative efforts, her course was downhill and she expired within four hours of admission.

Past medical history indicated two old right-sided, cerebral vascular accidents of indeterminate age.

AUTOPSY FINDINGS: The cause of death was a ruptured fusiform aneurysm of the anterior communicating artery. The ensuing hemorrhage had filled the basilar subarachnoid space, and had dissected through the orbital surface of the right frontal lobe, filling the intracerebral ventricles with blood. A second aneurysm, an intact berry, was present at the trifurcation of the right middle cerebral artery.

A purple globoid protrusion was present on the anterior surface of the heart, within 2 cm. of the aortic root. This was found to be a saccular aneurysm of the left anterior descending coronary artery, 1.5 cm. in diameter and beginning 2 cm. distal to the left coronary ostium. The aneurysm was filled with coagulated blood in various stages of organization, but a 4 mm. diameter patent flow channel was present along one margin of the sac. All three coronary arteries were diffusely calcified and concentrically atheromatous, but none was narrowed by more than 25%. The atheromatous and calcific changes were also present throughout the wall of the aneurysmal dilatation. The left ventricle was hypertrophic.

MICROSCOPIC DESCRIPTION: The wall of the coronary aneurysm is intact, with no evidence of rupture or creation of false channels. Atherosclerosis and focal calcification are present within both the sac and the parent artery. The aneurysm is filled with partially organized clotted blood.

DIAGNOSES:
1. Saccular aneurysm, left anterior descending coronary artery.
2. Ruptured aneurysm, anterior communicating artery, with massive dissecting subarachnoid hemorrhage.
3. Intact aneurysm, right middle cerebral artery.

DISCUSSION: Aneurysms are uncommon lesions of the coronary arteries (1.4% of autopsies in one large study), but may be encountered at any age from infancy to the ninth decade of life. The right and left coronary arteries are involved with comparable frequency, and the sexes are about equally affected.

The low incidence of these aneurysms may be in part attributable to the fact that they are nearly always clinically silent. Despite their apparent potential for disaster, they seldom thrombose completely or rupture, and because of their location are usually not distinguishable on routine chest films. They are therefore most likely to be incidentally discovered at autopsy or during cardiac angiographic procedures.

Coronary artery aneurysms may be grouped etiologically into five broad categories: congenital, atherosclerotic, inflammatory, mycotic-embolic, and traumatic. Atherosclerosis is the commonest predisposing condition in the older age group (and also the commonest cause overall), with a peak incidence in the sixth decade, and septic emboli are most common in young adults. Hypertension may aggrevate the development of an aneurysm, but has not been found to be a primary etiologic factor.

Complications of coronary artery aneurysms are infrequent but almost always catastrophic. Dissection results typically in acute myocardial infarction secondary to a sudden sharp decrease in myocardial blood flow. Some authors report that coronary artery aneurysms in pregnant women are particularly likely to dissect but this phenomenon is not extensively documented and the reasons for it remain obscure. Rupture of an aneurysm is nearly certain to produce sudden death from a combination of cardiac tamponade and acutely compromised myocardial perfusion. Totally occlusive thrombosis has similar consequences. Although the great majority of coronary aneurysms are atherosclerotic or septic-embolic in origin, the disease entities with the greatest likelihood of resulting in the development of such aneurysms are the vascular inflammatory diseases, and in particular polyarteritis nodosa.

The associated finding in this particular patient of multiple aneurysms of the cerebral circulation appears entirely incidental, and there is no well established correlation between aneurysms of coronary arteries and aneurysms elsewhere, although aneurysms of the aortic root may extend contiguously through the coronary ostia.

Treatment of an aneurysm discovered during life (11 cases reported in the literature is problematic, but saphenous vein bypass grafting has been successful in several instances.

Case Submitted and Prepared b
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DEPARTMENT OF PATHOLOGY

CASE 12

1975 - Case #12
St. Paul-Ramsey Hospital
A75-227

CASE OF THE MONTH

HISTORY: The patient was a 46 year old housewife with biopsy-proven portal cirrhosis, chronic alcoholism, and three prior hospitalizations for acute upper GI hemorrhage secondary to esophageal varices documented by endoscopy. She was found unresponsive on the floor of her kitchen and she had no spontaneous respirations, no blood pressure, no heart sounds, and bright red blood was issuing from her mouth and nares. Resuscitative measures failed to retrieve spontaneous respirations or vital signs and she was pronounced dead in the emergency room of St. Paul-Ramsey Hospital the same evening.

AUTOPSY FINDINGS:

STOMACH AND ESOPHAGUS: There were 1.2 kgms. of fresh blood in the stomach. Dilated ruptured venules with exuding blood was noted at the esophago-gastric junction.

ABDOMEN: 2 liters of clear straw-colored fluid was found in the abdominal cavity. The serosal surfaces of the jejunum and ileum are wet, glistening, and boggy.

LIVER AND PORTA HEPATIS: A dark purple, firm, lumen-occluding thrombus was found adherent to the wall of the portal vein running from a point near the confluens of the portal and superior mesenteric veins, through the entire length of the portal vein and involving the major right and left branches of the portal vein within the hepatic parenchyma. The liver texture was diffusely pale yellow-tan, firm, and nodular. The liver weighed 2100 grams.

SPLEEN: The spleen weighed 350 grams and was a pale rose-gray color and firm.

MICROSCOPIC DESCRIPTION: Sections of the liver show fibrous bands traversing pseudolobules of fat-filled hepatocytes. No alcoholic hyaline is seen. Intrahepatic branches of the portal vein show thickening of the subendothelium by fibrous tissue and collagen accompanied by thrombus formation. Sections of the extrahepatic portal vein show similar changes as well as a lumen-occluding thrombus with beginning organization at the thrombus-endothelial interface.

DIAGNOSES:

1. Portal vein thrombosis.
2. Laennec's cirrhosis, with congestive splenomegaly and esophageal varices with acute hemorrhage.
3. Phlebosclerosis, portal vein.

DISCUSSION:

REVIEW OF ANATOMY AND PHYSIOLOGY OF THE HEPATIC BLOOD SUPPLY: The liver is perfused by the portal vein and hepatic artery and so has a dual afferent blood supply. The portal vein is a venous segment containing no valves, with an average diameter of 1.2 cm., formed by the confluens of the mesenteric and splenic veins. It runs a distance of 6-8 cm. to the hilum of the liver where it terminates into major right and left branches which eventuate into portal vein radicals within the hepatic parenchyma. The hepatic artery arises from the celiac trunk of the abdominal aorta.

Both vessels provide nutritional blood supply to the liver with the portal vein delivering 75% and the hepatic artery delivering 25% of the total. This dual blood supply of the liver affords some protection if one flow is impaired. Normal liver cells can extract up to 3.25 volumes % of oxygen but if the portal vein is occluded in an otherwise normal liver the volume of oxygen extracted can be doubled to 6.5 volumes %. In addition, hepatic artery blood flow can preferentially increase if the portal vein is impeded in an otherwise normally oxygenated, normally functioning liver. This mechanism has been proven to be ineffective in the cirrhotic liver.

Portal vein thrombosis can occur coincident with terminal disease, and therefore has no clinical significance, or it can actually be found as the cause of death. When it occurs in the clinical setting of Laennec's cirrhosis, death due to hemorrhagic shock from bleeding esophageal or gastric varices has been recognized and reported (case records NEJM, Vol. 290 No. 17). In the cirrhotic patient, the incidence of portal vein thrombosis has been reported from 2% to 10% of cases. Albacete, et al, found the occurrence of portal vein thrombosis consequent to cirrhosis in 5% of their cases studied. In their series of 100 cirrhotic patients who were autopsied, 89% had Laennec's cirrhosis, 6% post necrotic, and 5% had mixed patterns of cirrhosis. They also studied patients coming to autopsy with malignant disorders and found that if hepatoma was present, then 32% of those patients had portal vein thrombosis as compared with 5% occurrence if the tumor in the liver was metastatic. If both hepatoma and cirrhosis were present then the incidence of portal vein thrombosis was six times that observed with cirrhosis alone. Patek considers thrombosis of the portal vein in cirrhosis to be a relatively rare event encountered in only approximately 2% of cases.

In the setting of cirrhosis alone, it is not clear why thrombosis of the portal venous system occurs, especially in view of its relatively rare occurrence. It is possible, (and it is postulated here), that the combination of phlebosclerosis of the portal vein plus the setting of portal vein hypertension may precipitate spontaneous thrombosis, which, if subtotal, may propagate to a total occlusion.

The antemortem diagnosis of portal vein thrombosis can be made by splenoportography. The condition can be suspected in the presence of a rapid onset of abdominal ascites accompanied by shock and hematemesis from gastric or esophageal varices.

Nonhepatic causes of portal vein thrombosis include abdominal septic states such as peritonitis, especially pyelophlebitis, dehydration, trauma, pancreatitis, carcinoma of the pancreas, polycythemia, thrombocythemia, and Banti's syndrome. Probably the most common cause of the condition in neonates is sepsis, particularly in those cases where umbilical vein catheters have been present.

Case submitted and prepared b
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ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

CASE 13

1976 - Case #1
St. Luke's Hospital
Fargo, North Dakota

CASE OF THE MONTH

CLINICAL SUMMARY: This 78 year old caucasian male was admitted to St. Luke's Hospital, Fargo, North Dakota, on 8/3/73 complaining of intermittent chills and fever for approximately one to two weeks.

Past medical history indicates failing health in recent years, characterized by increasing slowness of both mental and general functions. He had experienced poor balance and had fallen several times. He was fearful of physicians and his only hospitalizations in the past had been related to trauma from his numerous falls.

Physical examination on admission revealed an elderly white uncooperative male lying motionless in bed. The vital signs were as follows: temperature 103°F., blood pressure 190/100, pulse 100 and regular, and respirations 23 per minute. Neurological examination revealed coarse tremors of all extremities and hyperactive deep tendon reflexes with bilateral equivocal Babinski signs. No localizing signs were noted.

The laboratory values on admission were as follows: hemogram WBC 7,300 with 31% lymphocytes, 4% monocytes, 64% neutrophils, and 1% eosinophils. The hemoglobin was 12.0 grams, and the indices were within normal limits. Abnormal values from a 12-channel analysis revealed a BUN of 36 and a creatinine of 3.8. Urinalysis showed a 1+ protein. Spinal tap showed colorless, clear fluid with 20 erythrocytes, 32 leukocytes (differential cell count: 90% lymphocytes and 10% neutrophils/ml), spinal fluid protein 48 mgm%, and glucose 80 mgm%. Chest and abdominal x-rays were unremarkable. Electrocardiogram was normal.

Shortly after admission the patient developed increasing weakness, severe headaches, and deteriorated to a semicomatose state. He continued febrile and his temperature was recorded as high as 105.5°F. He remained semicomatose and was unable to take food for three days after admission. He became comatose and died six days after admission. Serologic tests showed a rise in antibody titer for Western Equine Encephalitis from 1:10 to 1:40 for sera drawn daily during his hospital stay.

SIGNIFICANT GROSS AUTOPSY FINDINGS: Massive cerebral congestion and edema plus bronchopneumonia.

MICROSCOPIC FINDINGS: Sections taken from the basal ganglia show diffusely scattered perivascular lymphocytic infiltrates and nodular proliferation of the microglial cells consistent with viral encephalitis. In addition, the arteriolar vessels show moderate medial thickening and sclerosis with perivascular hemosiderin, and an area of old cystic encephalomalacia consistent with hypertensive vascular disease.

DIAGNOSIS: Western Equine Encephalitis

DISCUSSION: In the period of July through September, 1975, 85 cases of febrile central nervous system disease were reported from North Dakota and adjacent Northwestern Minnesota. Nine of these cases were confirmed as Western Equine Encephalitis by a fourfold or greater rise in hemaglutin inhibition antibody titer. Five other cases were considered "probable" based on hemaglutin inhibition antibody titers to Western Equine Encephalitis of 1:80 or greater on a single specimen determination. Six deaths occurred. Three of these deaths were confirmed as Western Equine Encephalitis based on the above serological studies.[1]

The arthropod born viruses (arboviruses) comprise a large group of some 200 serologically distinct types which are transmitted to susceptible vertebrates by blood sucking arthropods. The arboviruses are classified into three distinct groups. The group A arboviruses include Eastern Equine Encephalitis (EEE), Western Equine Encephalitis (WEE), and Venezuelan Encephalitis (VEE), Group B includes St. Louis Encephalitis (SLE) and Group C includes California Encephalitis Virus (CE) which is also known as the LaCrosse virus. Only SLE, WEE, and CE seem to occur in Minnesota, North Dakota, and adjacent Canadian Provinces and over 3,000 cases of WEE occurred in this area in 1941. In recent years, cases of CE have been increasingly found in Minnesota and North Dakota,[2] and now outnumbers WEE.

The epidemiology for WEE has been well established. The primary reservoir is wild birds with the intermediate primary vector being the mosquito, Culex tarsalis. Man, equine animals, and some reptiles are merely incidental hosts. The clinical infections in man occur during summer or fall months and are related to the prevelance and types of mosquitos. WEE and SLE infections frequently occur in rural areas and affect both adults and children whereas EEE and CE generally are diseases of children.

The incubation period for WEE is somewhere between four and twenty-one days. Onset of disease is generally a sudden onset of severe symptoms such as headache, chills, fever, nausea, vomiting, malaise, lethargy, tremors, and confusion. Convulsions and coma develop in severe cases with death generally occurring in three to five days. Most clinical infections last from four to ten days with sudden recovery. Mortality rates range from 3 to 4% for WEE, 6 to 8% for CE and SLE.[2,3] During epidemics the mortality rates have been known to triple.

Gross pathological findings for these encephalitides generally consist of marked CNS swelling and congestion. Microscopically the inflammatory changes are greatest in the brain stem and basal ganglia, but widespread cerebral cortex involvement can be found. In WEE a diffuse lymphocytic perivascular infiltrate and nodular proliferation of microglial cells are most often found in contrast to EEE where necrosis and neutrophils predominate. Perivascular necrosis may be found and extensive cystic degeneration has been seen in the younger individuals.[5,6]

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DEPARTMENT OF PATHOLOGY

CASE 14

1976 - Case #2
A75-274

CASE OF THE MONTH

CASE PRESENTATION: This 42 year old lady presented to the St. Paul-Ramsey Emergency Room on several occasions during a three week period because of upper and lower extremity venous thromboses. The patient was then admitted and heparinized but continued to evidence venous thrombosis and then had a pulmonary embolus while apparently adequately heparinized. During the following three months, her course was stormy and downhill. An inferior vena caval plication was performed but continued venous thrombosis was observed and arterial thrombosis was strongly suspected because of unilateral lower extremity dry gangrene, which eventually required B-K amputation. The clinical picture was further complicated by rapid development of massive ascites which was refractory to medical therapy. Exhaustive radiographic procedures were performed along with abdominal ultrasound and radionucleotide scans; all were nondiagnostic. Progressive hepatic insufficiency was evidenced by rising enzymes, bilirubin, and serum ammonia. The patient became comatose, was mechanically ventilated for two weeks, and finally expired without a definite diagnosis having been made.

AUTOPSY: Numerous ecchymoses and petechial hemorrhages were observed over the entire body along with subungual splinter hemorrhages and digital dry gangrene on the remaining lower extremity. Approximately 15 liters of chylous ascites was observed, and a 7 cm. tumor was found in the body of the pancreas, invading and causing occlusion of both the splenic artery and vein. A myriad of peritoneal implants were found along with prominent abdominal lymphatics plugged with tumor. Widespread systemic metastases involved all major organs. Golden brown, polypoid, friable vegetations were observed on all leaflets of the tricuspid, mitral, and aortic valves. The largest vegetations measures 2.5 cm. and were located on the tricuspid valve. There was no evidence of leaflet destruction or involvement of the chordae tendinae. Stains for organisms were negative. Hematoxylin and Eosin sections revealed no evidence of tumor within these vegetations. Numerous arterial and venous thromboses were histologically observed in many organs, along with thrombo-emboli, histologically identical to the valvular vegetations. The enclosed slide and photo are of the tricuspid valve.

DIAGNOSES:

1. Pancreatic adenocarcinoma with widespread metastases
2. *NONBACTERIAL THROMBOTIC ENDOCARDITIS with pulmonary and systemic arterial embolization (*NBTE: MARANTIC ENDOCARDITIS)
3. Disseminated intravascular coagulation

DISCUSSION: Recurrent thrombophlebitis and hypercoagulable states may be associated with pancreatic adenocarcinoma and other disseminated malignancies, especially adenocarcinomas. Explanations ranging from generalized thromboplastin release from tumor necrosis to a specific, and as yet unidentified, tumor product have been offered.

Thrombotic nonbacterial endocarditis is also associated with neoplastic diseases, especially adenocarcinomas. Marantic lesions have been described in up to 25%[1] of patients autopsied with metastatic adenocarcinoma. These lesions have been less frequently described in certain other inflammatory, infectious and neoplastic diseases. Left sided valvular lesions predominate, and of these the mitral valve is involved slightly more frequently than the aortic, but the percentages are variable. Involvement of both aortic and mitral valves occurs in approximately 15% of cases of NBTE. Right sided valvular lesions represent approximately 15% of those described, and of these, the vast majority involve the tricuspid valve; pulmonic valvular lesions are rare.

Previously it was thought that marantic valvular lesions were mere incidental anatomic findings observed in a multitude of wasting and neoplastic diseases. Recently it has been appreciated that these lesions may cause arterial embolization resulting in systemic infarctions and multi-system symptomatology. Right sided lesions may result in recurrent pulmonary embolization without evidence of peripheral venous thromboemboli. With the widespread use of antibiotics the relative incidence of nonbacterial thrombotic endocarditis is increasing and its pathogenesis and association with DIC have been recently studied.[2] In this study of 14 cases of NBTE, 5 patients were proven to have disseminated malignancy, 2 congestive cardiac failure, 2 bronchopneumonia, and 2 with no associated anatomic findings. In all cases, systemic macro and micro embolic phenomena were widespread, and infarcts were observed in all major organs. From the available data, it is suggested that nonbacterial thrombotic endocarditis may both initiate and occur as a result of disseminated intravascular coagulation.

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ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

CASE 15

1976 - Case #3
S75-2435

CASE OF THE MONTH

CLINICAL HISTORY: This 22 year old female (para 0) was admitted for multiple vaginal biopsies because of a maternal history of diethystilbesterol medication during pregnancy. The patient related a past history of vaginal bleeding and pain. Different physicians had previously noted an "abnormal appearing" cervix and vagina. The patient had two prior Class II pap smears.

Pelvic examination demonstrated an anterior vaginal hood overlying a hypertrophic cervix with slight eversion. Colposcopic examination demonstrated abnormal vascularity. The remainder of the physical examination and laboratory tests were unremarkable.

PATHOLOGY: Four biopsy specimens, two from the cervix and one each from the posterior and anterior vagina were submitted.

Microscopic sections of the vaginal biopsies demonstrate irregularly shaped fragments of fibrous stroma bordered by nonkeratinized stratified squamous epithelium. Several glandular structures lined by tall columnar to metaplastic squamous epithelium are noted. Some glands are contiguous with the basal portion of the overlying squamous epithelium while others are apparently lying free within the stroma. A scattered lymphocytic infiltrate is noted within the stroma. No cellular atypicalities are noted. The cervical biopsies demonstrated chronic cervicitis with squamous metaplasia.

DIAGNOSIS: Vaginal adenosis associated with maternal DES.

DISCUSSION: Vaginal adenosis has been defined as the presence of columnar epithelium within the vagina, most often in the form of glandular structures beneath the surface epithelium. The surface epithelium may either be replaced or partially replaced by columnar epithelium. The columnar epithelium may be tall, mucin filled cells with basal nuclei which closely resemble endocervical lining cells, or it may consist of pseudostratified, cuboidal to columnar cells with subnuclear vacuoles and cilia, which resemble endometrial or tubal cells. Some lesions incorporate a mixture of both types. Fibrous stroma may surround the glandular elements and distinguish it from endometriosis. Often a round cell infiltrate will lie adjacent to the glandular structures. The surface lesion is frequently papillary with a marked chronic inflammatory infiltrate in the stroma. The epithelium at the base of the fronds may be in direct continuity with subjacent glands. Glands may also communicate with the surface in areas where papillae are absent. In most cases the epithelial cells are typical and exhibit very little nuclear pleomorphism.

Vaginal adenosis was first described in 1877 by von Prauschen[1], who reported endocervical-like glandular structures in the vaginas of four adult females at autopsy. (In 1964 Sandberg[2] reviewed the literature and recorded 64 cases of benign vaginal adenosis.) The clinical diagnosis of this lesion has remained rare until recently. With the discovery of the association of clear cell vaginal carcinoma in young women and intrauterine exposure to DES, subsequent studies of exposed young women revealed that many harbored vaginal adenosis.

Both retrospective and prospective studies of young females demonstrated that vaginal or cervical transverse fibrous ridges, abnormal vaginal mucosa which fails to stain with iodine solution, and adenosis are all strongly associated with intrauterine exposure to stilbesterol and other related non-steroidal synthetic estrogens. The incidence of adenosis is highest in daughters of mothers who starte treatment before the eighth week of pregnancy. It is felt that DES related cases of adenosis will not occur in those whose mothers began their therapy after the eighteenth week. The incidence of vaginal adenosis in DES exposed females varies from series to series. Studies using colposcopy have reported that up to 95% of susceptible individuals demonstrate adenosis. Other studies, however, utilizing clinical examination and biopsy of abnormally staining mucosa relate incidences of between 30% and 60%. Differences between series may relate to variations in the time of maternal therapy in addition to method of clinical diagnosis. Another source of variation is the different definitions of the boundary between the vagina and the cervix with the inclusion of glandular epithelium on the portio vaginalis of the cervix in some statistics for vaginal adenosis.

The incidence of vaginal adenosis in unexposed females is unknown. Several autopsy studies of neonates and fetuses demonstrated a 3 to 5% incidence. Sandberg[3] serially sectioned vaginas obtained at autopsy from thirty-five consecutive females and demonstrated the presence of occult adenosis in nine of twenty-two vaginas from post pubertal patients. None of these had been exposed to DES. Sandberg failed to discover adenosis in prepubertal females.

The mechanism of the histogenesis of DES related vaginal adenosis is uncertain. During the embryological development of the human female genital tract, at approximately 12 weeks, a solid core of squamous epithelium extends upward from the urogenital fossa into the primordial müllerian epithelium.[9] It becomes canalized to form the permanent lumen and lining of the vagina and replaces the pre-existing müllerian lining. Several authors have speculated that DES either inhibits the upgrowth of the squamous epithelium or results in the persistence of some original müllerian epithelium elements in the vagina. Scully[4] suggested that there is persistence of müllerian cells in the basal layer of the vaginal epithelium. On the basis of his studies he feels that foci of these cells proliferate, bud into the underlying stroma, and eventually canalize forming gland-like structures. Perhaps a more cogent and convincing view is espoused by Hart[5] and Stafl[6,7] who feel that the DES inhibits the growth of the squamous epithelial core causing the fusion between the squamous epithelium and müllerian epithelium to take place much lower in the vaginal canal. Thus, the squamocolumnar junction is displaced from the cervical os downward, to some variable location within the vagina. It is suggestes that the acidic environment of the vagina stimulated an extensive squamou metaplasia of the superficial müllerian columnar epithelium with relative sparing of the deeper glands. Therefore, contrary to the view of Skully, the occult form is thought to be a secondary rather than a primary phase of adenosis. Furthermore, Hart[5] has recently proposed that adenosis include those cases of extensive vaginal squamous metaplasia identifiable by the immaturity and poor glycogenation of the squamous cells, and the associated squamous pegs in which residual gland openings may be seen.

Vaginal adenosis is usually asymptomatic. The most common complaints are abnormal vaginal bleeding, dyspareunia, and discharge. The frequency of diagnosis appears to correlate with the methods of detection employed. Visual examination may reveal a red granular mucosa if columnar epithelium is on the surface. These areas are patchy and friable. Also, small cysts or papillary lesions may be seen. However, gross examination of the vagina is unreliable and in one large series[6] was complete normal in 71% of girls with histologically proven vaginal adenosis. Pelvic examination with palpation is also inconclusive. Colposcopy with directed biopsy is the

method of choice for identifying vaginal adenosis. Colposcopic examination in large series of exposed patients may detect adenosis in 70 to 95%. Based on present knowledge routine surgical excision of areas of adenosis is not warranted. It is multicentric and may recur, thus requiring multiple excisions. Excision, cautery, or cryosurgery may be utilized if atypical changes occur. With time the adenosis may heal by squamous metaplasia. Therefore, follow-up is the proper recommended approach to DES exposed subjects without carcinoma.

The prognosis for adenosis is uncertain at this time. Vaginal adenosis has been found near vaginal clear cell adenocarcinomas of young women in over 95% of the cases. It is usually at the periphery of the lesion but may occasionally be admixed with the tumor. Adenosis may be a non-neoplastic precursor of clear cell adenocarcinoma but transitions have not yet been recognized. There have been approximately 250 reported cases of vaginal clear cell carcinoma within the hundreds of thousands of DES exposed females in the United States. It's risk of development therefore, appears small.

Of more crucial concern is the possibility that patients with adenosis may, in the near future, show an increased incidence of squamous cell carcinoma of the vagina.[7,8,5] Squamous carcinoma and dysplasia of the cervix arise near the zone of transition between squamous and columnar epithelium. The metaplastic squamous epithelium in these areas appears to be uniquely susceptible to oncogenic stimuli. Thus, in cases of adenosis with large and displaced transformation zones, malignant degeneration into squamous cell carcinoma is possible. This hypothesis, however, cannot be evaluated presently. Carcinoma in situ of the cervix reaches a peak incidence of occurrence at about age 30 and invasive squamous carcinoma peaks at age 40. The average age of DES exposed patients with adenosis is about 20 years and the oldest is about 26 years. If the vaginal metaplastic areas behave as those of the cervix these exposed females are only now beginning to approach the age of highest potential for the development of squamous metaplasia.

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CASE 16

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

1976 - Case #4
St. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient was a 60 year old woman with a long history of alcoholism and a psychiatric disorder which included multiple attempts at suicide. She was brought to the hospital emergency room after being found in her home lethargic and uncommunicative. Ethanol intoxication was strongly suspected but there was no evidence of alcohol on the patient's breath. Three hours later she was found responsive only to deep pain and deep tendon reflexes were absent. A toxicology screen showed the presence of barbiturates as well as ethylene glycol. No ethanol or methanol was detected. The urine specific gravity was 1.011. There were occasional red cells, hyaline casts, and bacteria present in the urine as well as numerous calcium oxalate crystals. The patient was given supportive care and intravenous ethanol. Hemodialysis was begun four hours after her admission, but shortly after the dialysis run began, the patient suddenly became hypotensive and expired.

AUTOPSY FINDINGS: There were ecchymotic areas present over the sternum between the fourth and fifth interspaces, both anticubital fossae, and the right femoral triangle (the site of the catheter placement), and Cullen's sign was present. The soft tissues of the anterior and posterior abdominal wall, the retroperitoneal spaces, pelvic basin and the entire supporting mesenteries of the small bowel, colon, and pelvic organs were distended and swollen due to soft tissue hemorrhage. There was an estimated 500 cc. of unclotted blood present within the pelvis. Painstaking examination of the right femoral vessels as well as the retroperitoneal vessels up to the level of the diaphragm failed to reveal a perforation site.

MICROSCOPIC EXAMINATION: Sheaves of calcium oxalate crystals were present within the kidney tubules. Post mortem toxicology determined a phenobarbital level of 7.5 micrograms/ml and the presence of ethylene glycol greater than 300 mgm%.

DIAGNOSIS:

1. Ethylene glycol toxicity
2. Retroperitoneal hemorrhage, presumably due to vessel rupture with dialysis catheter placement.

DISCUSSION: Ethylene glycol is a common component of many antifreeze solutions and a humectant in aerosol sprays. It has been used as a substitute for glycerin in many commercial preparations which include detergents, paints and lacquers, polishes, and cosmetics. Ethylene glycol has a high boiling point and low heat of vaporization and, as far as is known, is toxic only when ingested. Its pleasant sweet taste and its ready availability may be responsible for its popular use as an agent for suicide. Ethylene glycol is metabolized in both the liver and kidneys. The first step in its metabolism is its oxidation to glycoaldehyde by alcohol dehydrogenase which is dependent on NAD. The next step in its metabolism is oxidation of glycoaldehyde to glycolic acid by mitochondrial aldehyde oxidase and then subsequently to glyoxylate. Glyoxylate may in turn be metabolized in several ways: to glycine, a pyridoxine dependent reaction which necessitates amino acid donors; to oxalate, an irreversible reaction; or to various conjugation pathways. There are many cofactors necessary for the metabolic breakdown of ethylene glycol some of which include NAD, pyridoxal phosphate, thiamine pyrophosphate, and various amino acids.

Ethylene glycol itself is apparently nontoxic but its various metabolic products are highly toxic. Aldehydes and oxalates are apparently the two most important toxic metabolites in humans and their formation is associated with the consumption of cofactors needed for other cellular activity. The accumulation of aldehyde inhibits protein synthesis as well as DNA replication and ribosomal RNA synthesis. In addition, aldehydes react with enzymes which require -SH groups for activity, collagen, and amino groups on proteins. The accumulation of oxalates has long been considered responsible for most of the clinical symptoms seen with ethylene glycol toxicity. Oxalates are in themselves highly toxic and may produce all of the symptoms seen in ethylene glycol poisoning but may do so in much smaller quantities. Oxalates are not significantly metabolized further and their eliminati depends entirely upon renal excretion. Although accumulation of both aldehydes and oxalates is important in the pathology seen with ethylene glycol, it is also thoug that the consumption of cofactors as well as the accumulation of lactic acid may disrupt the normal cellular metabolism, and in some poorly understood way, further increase the toxic effects.

The clinical syndrome and resultant pathology of ethylene glycol poisoning can be divided into three stages, the severity of each dependent on the amount of the chemical ingested. These stages are characterized by central nervous system depres cardiopulmonary failure, and renal failure. The central nervous system findings usually occur within the first twelve hours after ingestion and are characterized b nausea and vomiting which may be followed by coma, convulsions and even death. (The patient often appears intoxicated but there is a notable absence of alcoholic odor on his breath.) Occular abnormalities may be present and the reflexes may be depressed or absent. There is usually a metabolic acidosis, probably related to th accumulation of lactic acids. Hypocalcemia may be present during this early perio due to chelation of the calcium ion by oxalates. The urine may show a low specific gravity with proteinuria, microscopic hematuria, cylinduria and profuse crystaluria The crystals are usually calcium oxalate but hippuric acid crystals have also been reported.

The second state, that of cardiopulmonary failure, is seen between twelve and seven two hours after ingestion of the compound. Tachypnea, mild hypertension, and cyano are often found. In extreme cases, pulmonary edema and congestive failure ensue. the patient survives the initial central nervous system depression and the cardio-pulmonary effects of the poison, renal failure of varying severity may become the predominant clinical problem. This may vary from a mild increase in the BUN and creatinine with spontaneous recovery to a picture of acute tubular necrosis. Oligu often is seen within the first twelve hours after ingestion of ethylene glycol and may persist for as long as fifty days.

The pathology in the central nervous system is variable. If death occurs within th first seventy-two hours the brain may only appear grossly edematous and hyperemic. If the patient lives longer there may be evidence of meningoencephalitis and characteristic calcium oxalate crystals may be found in the leptomeninges, vessel walls, and perivascular spaces. The significance of the oxalate crystals in relati ship to the central nervous system symptoms is poorly understood. It is felt by some authors that the central nervous system depression is more closely related to the presence of aldehyde metabolites rather than the presence of calcium oxalate crystals.

The toxic action of ethylene glycol on the cardiopulmonary system is obscure. Petechial hemorrhages may be seen in the pleura, lungs, heart, and pericardium. Occasionally degenerative myocardial changes are present. The relationship of these findings to the presence of either ethylene glycol or any of its metabolites has not been defined. The pathogenesis of the renal lesions is apparently related to the toxicity of glycoaldehyde, glycolic acid and glyoxylic acid, all of which are far more toxic to the renal tubules than either ethylene glycol or oxalates. It is speculated that these toxins result in edema with subsequent compromise of the intrarenal blood flow and renal failure. The kidney often shows dilated proximal tubules with degenerating tubular epithelium and intratubular crystals which are yellow in color and arranged in sheaves or prisms.

The diagnosis of ethylene glycol intoxication should be suspected when, in the absence of a diabetic ketoacidosis, there is an ethanol-like intoxication with the absence of the odor of ethanol, when the clinical course is that of coma with metabolic acidosis, or a urinalysis demonstrates massive calcium oxalate crystaluria. Serum levels of ethylene glycol and oxalic acid are difficult to determine and may be time consuming. The estimated lethal dose of ethylene glycol is 100 ml. and spontaneous recovery without supportive care is rare. Therapy includes correction of metabolic acidosis and hypocalcemia with replacement of thiamine and pyridoxine. Intravenous ethanol has been used since both ethanol and ethylene glycol are metabolised via alcohol dehydrogenase and ethanol has a much greater affinity for the enzyme than ethylene glycol. In the presence of good renal function, mannitol has been used to promote an osmotic diuresis to both eliminate the ethylene glycol and its metabolites and to reduce renal edema. In the face of renal failure, dialysis has been used effectively for both the renal failure as well as for the removal of the ethylene glycol and its metabolites.

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CASE 17

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

1976 - Case #5
St. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient was a 9 year old girl who collapsed suddenly and unexpectedly while playing. Witnesses at the scene described a grande mal-like seizure episode, followed by urinary incontinence and vomiting. A paramedic rescue team found her in a lifeless cyanotic state and were not able to re-establish cardiac rhythm after appropriate resuscitative measures including endotracheal intubation, intracardiac epinephrine, Levophed, and manual cardiopulmonary assistance.

PAST MEDICAL HISTORY: The patient had been hospitalized at age 2 following aspiration of a metal polish which resulted in a serious but reversible chemical pneumonitis. One month prior to death the patient experienced a week long period of upper respiratory symptoms, fever, and a peculiar complaint of an inability to breathe due to vague, bizarre discomfort occurring at the base of the throat. This complaint had persisted following the upper respiratory infection and was noted to be increasing in frequency during the weekend prior to death (as observed by the child's parents). In addition to this unusual complaint of throat discomfort, which was always brief and transitory, the mother would observe concomitant episodes of profuse sweating. No premortem electrocardiograms had ever been obtained.

AUTOPSY FINDINGS: There were 150 cc. of clear yellow effusion fluid in both pleural cavities. The heart weighed 140 grams and showed a moderate amount of biventricular hypertrophy, with the left ventricle having a maximum thickness of 1 cm. while the right ventricle was as thick as 6 mm. Other than biventricular hypertrophy there were no gross cardiac abnormalities appreciated. Structures of the upper airway, central nervous system, and the abdomen were normal.

MICROSCOPIC EXAMINATION: Sections of the S-A node, HIS bundle, and general ventricular myocardium were normal other than changes of hypoxia. However, sections of the junction of the inner atrial and ventricular septum near the os of the coronary sinus (which locates the region of the A-V node) demonstrated the presence of "gland-like" spaces and compressed crypts embedded within a loose fibrous connective tissue stroma occupying the general area between the endocardium and the central fibrous body. The matrix of loose fibrous connective tissue contains a few tissue mast cells and lymphocytes scattered diffusely. A few of the spaces contain amorphous amphophilic fluid as well as desquamated cells. The epithelium of the gland-like spaces and crypts varies from a single layer of cuboidal cells to a more complex lining of inner eosinophilic flattened endothelial-like cells followed by more polygonal, urothelium-like cells in the outer peripheral layers. A longitudinal groove is seen in the nuclei of some of these deeper lining cells, the so-called "coffee bean" cell. Multiple serial sections of the A-V junction showed the maximum extent of this glandular area to be 0.8 cm. The tumor was not found in sections of the rest of the conduction system including the superior inner atrial areas adjacent to the crista terminalis.

DIAGNOSIS:
1. Mesothelioma of the A-V node associated with sudden unexpected dea
2. Biventricular cardiac hypertrophy.
3. Bilateral pleural effusion.

DISCUSSION: Although once quite rare, mesothelioma of the A-V node is now being reported in increasing frequency as the conduction system, specifically the A-V node, is being dissected with greater frequency in cases of sudden unexpected death or in those cases where there was known partial or complete heart block. Since the first report of this entity by Armstrong in 1911 to the present time (where this case would represent approximately the fortieth report), the entity has been labeled epithelial inclusion cyst, lymphangioendothelioma, A-V node hamartoma, mesocardial cysts, and mesothelioma. The diverse names reflect the diverse theorie of origin of this remarkable, histologically unusual, and clinically significant tumor. The general prevalence of this entity is not known at the present time nor is there conclusive evidence for the origin of this tumor if it indeed is a neoplasm. Armstrong[2] regarded the cryptic spaces to be lymphatic in origin while Rezek regarded them as endodermal inclusion rests and Mahaim[6] regards the entity as being derived from entrapped mesothelial cells. In an exhaustive review of the literature, one can find arguments for and against all the various theories of origin for this entity. However, particularly good monographs dealing with the subject can be found in papers by Sopher, Manion, James, and Wanless.

Patients with this lesion reported in the literature have ranged in age from newbor to age 84. The entity is more predominant in the female sex, particularly in the younger age ranges, and the tumor is usually manifested clinically by either partia or complete heart block, chronic or intermittent. The tumor is frequently associat with sudden unexpected death although a handful of patients died in congestive hear failure. Most of the diagnoses have been made postmortem, but two cases survived due to placement of permanent cardiac pacemakers. Many of the patients experience Stokes-Adams attacks and other less severe forms of cardiac syncope. Although complete heart block is the most frequent arrhythmia noted in these patients all forms of tachyarrhythmia, superventricular tachycardia, and junctional rhythms have been described. It is not known what circumstances predispose patients with meso-thelioma of the A-V node to experience sudden unexpected death, since the tumor doe not seem to grow and proliferate in the usual neoplastic fashion. Furthermore, encroachment on the A-V node seems to be maximally present even in the newborn. Since the tumor is confined to the A-V node itself or the superior portion of the crista terminalis in the inneratrial septum and never encroaches on the His bundle, physiologically the His bundle should provide a focus for escape pacemaker activity This has been reported in one case and by His bundle electrocardiograms this escape rhthym is predictable. This may explain why patients have this entity for years in a chronic heart block state and not experience sudden death.

At autopsy the common finding is biventricular cardiac hypertrophy which reflects a premortem state of chronic heart block. The tumor may or may not be appreciated grossly depending on the size of encroachment. Maximum size seems to be 2 x 2.5 cm and some cases have been described where the tumor could be seen as a small bulge. Many cases, however, (this one included) are not appreciated grossly unless the conduction system is serially blocked and sectioned. When present grossly, a tan background with enmeshed small variably sized cysts can be seen. Usually no other anomalies have been described although Edwards reported a case of ventricular septa defects in association with mesothelioma of the A-V node and Leighton[17] described a case in which he felt there were associated cystic changes in the ovaries and

breasts as well as the A-V node. Microscopically the tumor is composed of variably sized cysts, gland-like spaces and crypts which may have columnar, cuboidal, squamoid, or polyhedral epithelial cells, either monolayer or multilayer. Several workers have called attention to the fact that some areas resemble urothelium. These glandular spaces are usually embedded in a loose fibrous connective tissue stroma and there usually is eosinophilic amorphous PAS positive Alcian blue negative fluid. The tumor has not been found in any other part of the heart although Mahaim compared the histologic appearance of the tumor to pericardial "milk spots" found in neonatal hearts.

Although the specific origin of this lesion remains a question, there is an undisputed high propensity for sudden unexpected death, and indeed Wolf[15] has referred to this entity as "the smallest tumor which causes sudden death". This entity should be sought for in any young patient, especially female, who has documented recurrent or persistent arrhythmias, particularly a heart block. Deaths due to this entity can possibly be prevented by the implementation of a permanent cardiac pacemaker in appropriate instances.

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CASE 18

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

1976 - Case #6 NO SLIDE
St. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient was a 33 year old white female who had known congenital heart disease. Cyanosis was noted shortly after birth. She had a cardiac catheterization in 1967 at the University of Minnesota Hospitals which revealed (1) a persistent left superior vena cava draining into the left atrium; (2) an endocardial cushion defect, ostium primum or common atrium, with mitral insufficiency and probably tricuspid insufficiency; no ventricular septal defect was demonstrated; (3) severe pulmonary hypertension with the pulmonary arterial systolic pressure only 10 mm. Hg. less than the aortic systolic blood pressure; (4) a sizable left to right shunt at the atrial level; (5) a moderate right to left shunt, superior vena cava to left atrium; and (6) probably a small right to left shunt exclusive of left ventricle. "The overall left to right shunt was calculated at 49% and the right to left shunt at 30%." The patient was not considered a candidate for surgery because of the marked pulmonary hypertension but was functioning fairly well in her daily life although she was hospitalized in 1974 with congestive heart failure (probably secondary to birth control pills). She demonstrated no stigmata of Down's syndrome and had a negative family history for congenital heart disease.

On the day of admission to our hospital the patient had collapsed suddenly at church, and although successfully resuscitated was markedly hypoxic. Over the next several days she had persistent hypoxia (in spite of being on the respirator) and finally progressed to an intranodal rhythm and death.

AUTOPSY: At necropsy the major findings of significance included: cyanosis and clubbing of the fingernails, multiple spleens, and cardiac, venous and pulmonary anomalies. The pulmonary anomalies included bilateral bilobed lungs with hyparterial bronchi. The cardiovascular anomalies included a common atrium, a persistent A-V canal with cleft anterior leaflet of the mitral valve and only a rudiment of the septal leaflet of the tricuspid valve. The coronary arteries showed only minimal atherosclerosis and arose from a common ostium, which was behind the posterior (non-coronary) leaflet. There was a persistence of the "left superior vena cava" and this anomalous vessel entered the common atrium on the left side with absence of the coronary sinus. The right innominate vein descended in the normal path of the vena cava (forming a "right superior vena cava") and entered the common atrium on the right side. The right pulmonary veins entered anomalously to the right of the common atrium just superior and posterior to the ostium of the "right superior vena cava". The left pulmonary veins entered in the normal location and were superior and posterior to the "left superior vena cava". The inferior vena cava bifurcated just below the liver and both branches proceeded through the liver to enter the common atrium. (See enclosed kodachrome slide.) One branch of the inferior vena cava was in the normal location while the other penetrated the right lobe of the liver and had a separate path to the common atrium.

Other findings at autopsy included: pulmonary hypertension (macroscopically and microscopically), nine spleens (illustrated on one of the enclosed kodachrome slides), dextrocardia and hypertrophy of the right ventricle. Negative findings of importance included: a normal symmetry of the lobes of the liver, the presence of a gallbladder, and nomral organ situs with no ventricular inversion or inversion of abdominal structures.

DISCUSSION: The association of extracardiac with intracardiac anomalies is said to have an overall incidence of as much as 37.1%[1] and is of importance from a clinical, pathological and embryological viewpoint. The complex presented in this patient is thought to represent a disturbance in body symmetry with "bilateral left-sidedness" or levoisomerism[2] in contrast to the asplenia complex which is thought to represent "bilateral right-sidedness". Features stated to prove the "left-sidedness" include: two lobes per lung and hyparterial bronchi (as seen in normal left lung), nearly equal-sized lobes of the liver, and occasionally the lack of a gallbladder. The polysplenia complex consists of: (1) multiple spleens (two or more nearly equal-siz splenic masses; (2) total or partial situs inversus; (3) anomalies of the inferior a or superior vena cava; (4) anomalies of the interatrial septum (usually septum secundum); and (5) anomalous pulmonary venous return. Although polysplenia is not a common as the asplenia complex, the congenital defects involved seem more constant a our case illustrates many of these features. A list of the anomalies in both syndro is given in Table 1 and the pulmonary picture is seen in Figure 3.

Normally the right superior vena cava results from a confluence of the right innomin and the left brachiocephalic veins and enters the right atrium (Figure 4). Embryo- logically the superior vena cava develops from paired common cardinal veins which a joined by the inferior vena cava to form the sinus venosus. At five weeks, the sinu venosus forms a "lopsided U"[3] or "horns of the sinus" (Figure 2a). With the formati of the left brachiocephalic vein between the anterior cardinals, the blood is shunte to the right cardinal vein and this becomes the superior vena cava whereas the left anterior and left common cardinal veins become much smaller, acquire tributaries fro the heart and become the coronary sinus (Figure 2b). If the polysplenic syndrome truely represents bilateral left-sidedness, then persistence of the "left" superior vena cava is understandable. This vein may empty into an "enlarged coronary sinus" or directly into the right atrium with congenital absence of the coronary sinus. If the left brachiocephalic vein fails to develop or the flow is from the right to the left then there may be bilateral venae cavae, as in our case, or a single left-sided vena cava (Figure 5). All these patterns are common and are thought to develop duri the 33 to 36 day period.

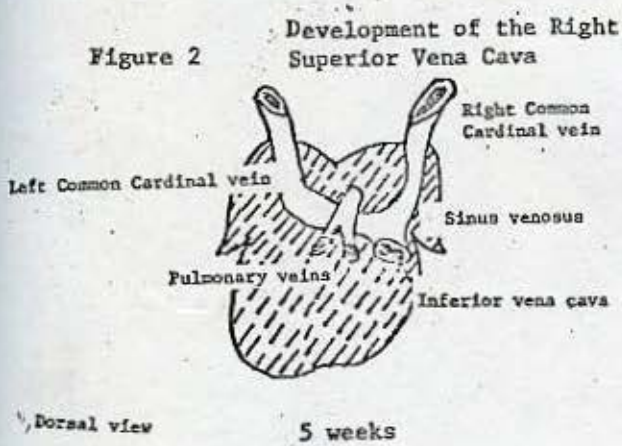
The inferior vena cava develops from several systems (posterior cardinal, lateral sympathetic, subcardinal veins and hepato-cardiac channel. The latter developes fro the vitelline vein.) These originally are paired structures but develop normally in a unilateral "right-sided structure which may be left-sided in complete situs invers and if there is a failure of one side to dominate, then some components may fail to "link up" and will eventually disappear.[9] The most common is called "absent IVC" an refers to the failure of the prerenal portion of the inferior vena cava to develop, probably because of failure of the subcardinal veins and the hepatocardiac channel t join. This anomaly occurs at the 33 - 36 day period and is a common anomaly in both the asplenia and polysplenia complexes. In association with either the asplenia com or the polysplenia complex there may be anomalous drainage in which the inferior ven cava remains dorsal and joins either the asygous or hemiazygous veins, which are con sequently greatly enlarged. These may join either the "right" superior vena cava or "left" superior vena cava. In this case the hepatic veins (developed from hepatocar channel) form a common branch which joins the right atrium in the normal manner (Fig 6). The case presented does not fit into the classic pattern since both branches penetrate the liver and enter the common atrium as two separate vessels (Figure 7).

The spleen develops from mesodermal cells on the left side of the dorsal mesogastri and the size of the spleen and the relative sizes of the lobes of the liver depend on their vascular development. Both the spleen and the asymmetrical liver develop after the 33rd day.[9] The determination of "situs" occurs at an earlier stage and is intimately if not causally related to all of the above anomalies.

Figure 1 Comparison of Features of Asplenia and Polysplenia

Organ system	Features associated with asplenia	Features associated with polysplenia
Cardiac	Corrected transposition of great vessels with ventricular septal defect or single ventricle Pulmonary atresia or stenosis Common atrium Bilateral superior venae cavae Total anomalous pulmonary venous connection Malposition	Continuity of inferior vena cava with azygos or hemiazygos vein Anomalous pulmonary venous connection to venous atrium Atrial septal defect or common atrium Ventricular septal defect Bilateral superior venae cavae Malposition
Pulmonary	Three lobes-each lung Bilateral epiarterial bronchi	Two lobes-each lung Bilateral hyparterial bronchi
Abdominal	Heterotaxy Complete Situs inversus Partial Horizontal liver Malrotation of bowel Duodenum-common mesentery Midline gallbladder	Heterotaxy Complete Situs inversus Partial Horizontal liver Malrotation of bowel Absent gallbladder

Figure 2 Development of the Right Superior Vena Cava



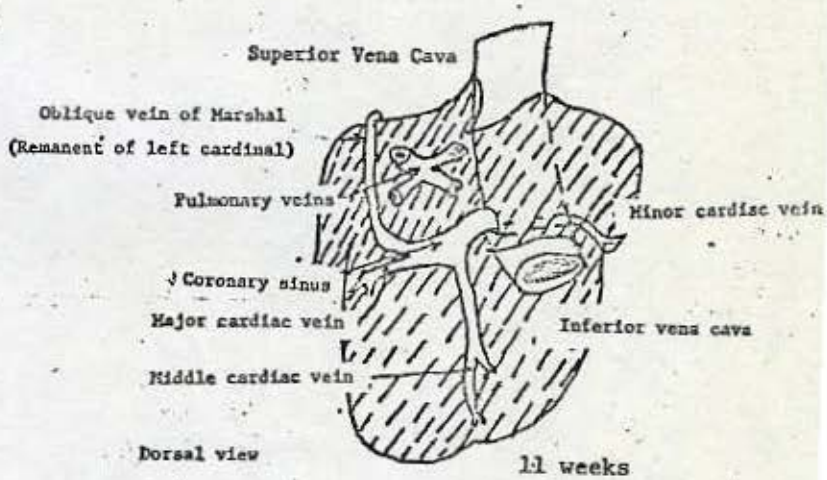
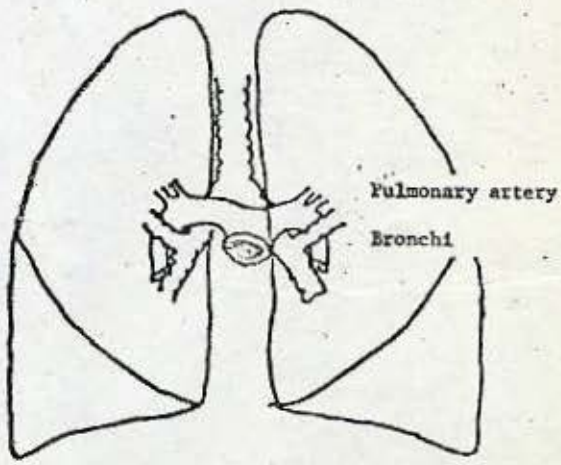


Figure 3
Diagramatic representation of characteristic relationship between the major bronchi and pulmonary arteries in polysplenia



Bilateral hyperarterial bronchi

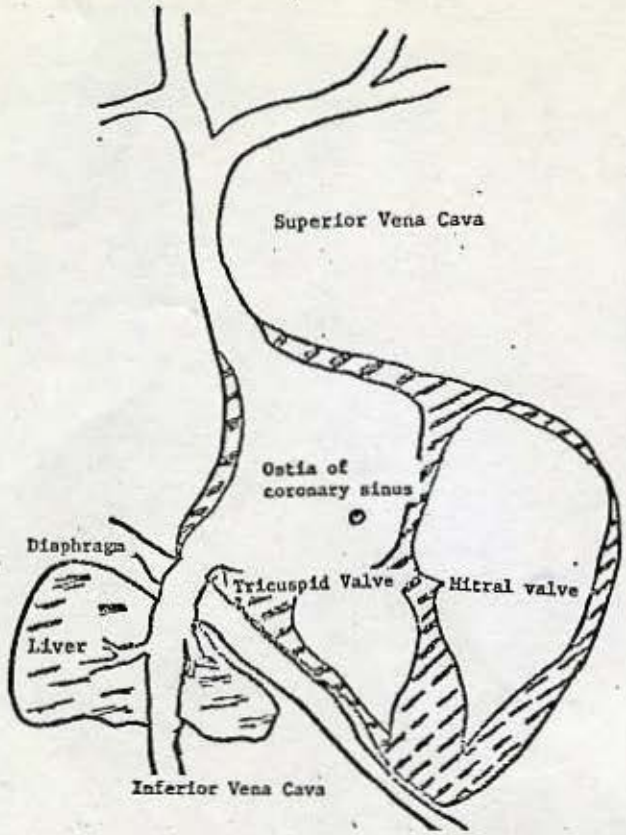


Figure 4 Normal Arrangement

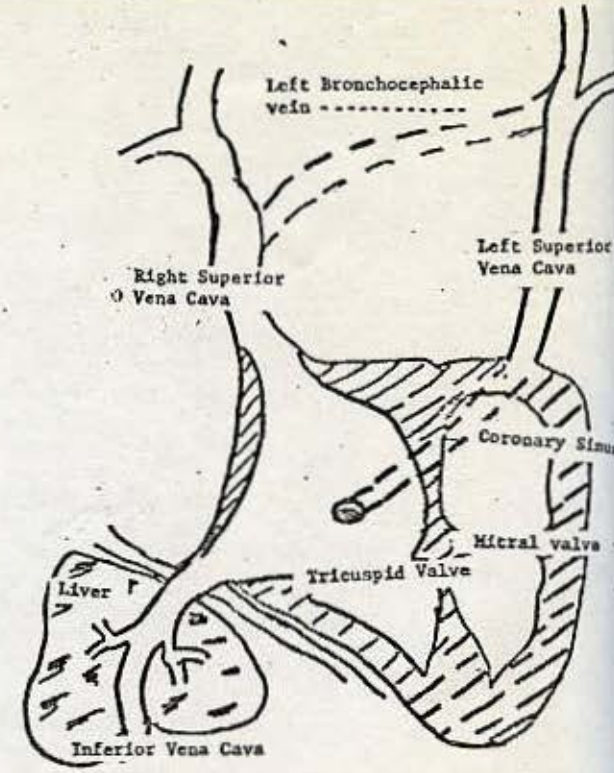


Figure 5 Persistant Left Superior Vena Cava

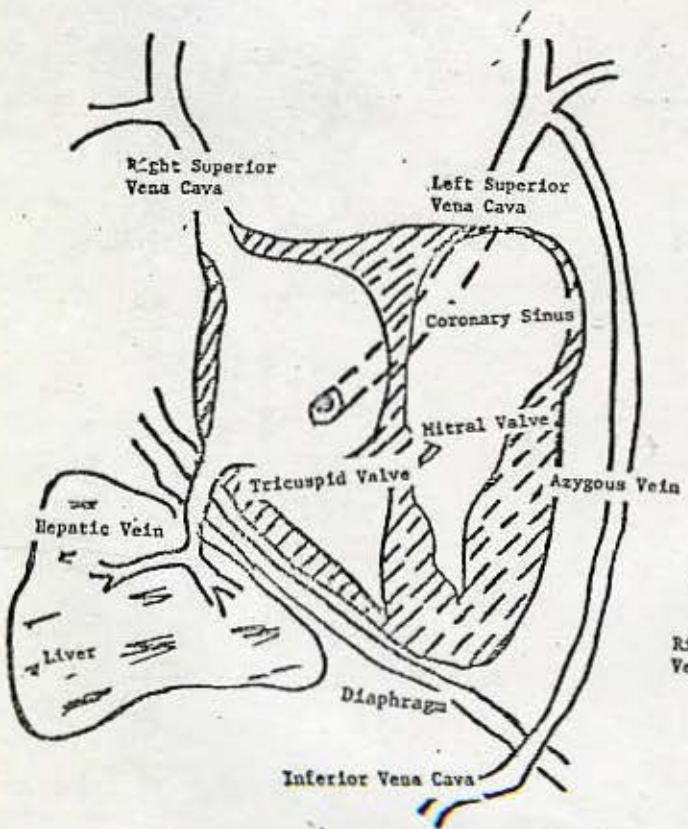


Figure 6 Anomalous Veins

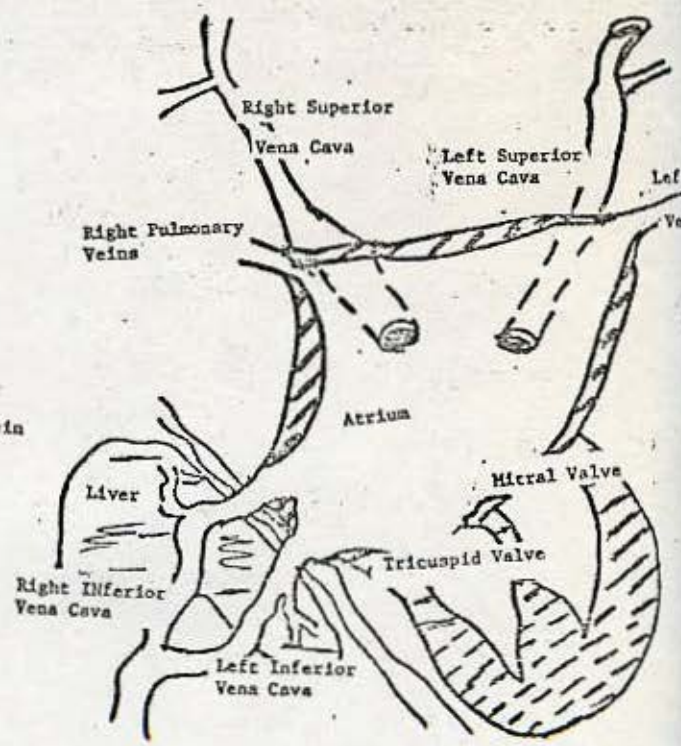


Figure 7 Patient Presented

In conclusion, we have a relatively old (most patients with this syndrome die as children) white female who has the polysplenia complex with: (1) bilateral superior vena cava, (2) common atrium, (3) persistent A-V canal with cleft anterior leaflet of mitral valve and only rudiments of septal leaflet of the tricuspid valve, (4) dextrocardia, (5) right ventricular hypertrophy with pulmonary hypertension, (6) anomalous bifurcation of inferior vena cava with both branches penetrating the liver and entering the common atrium, and (7) multiple spleens with a total mass of 120 grams. Our patient had a sudden arrest which was probably on the basis of hypoxia and a cardiac arrhythmia. She demonstrated the pulmonary findings consistent with "bilateral left-sidedness" but the abdominal organs were in their normal location.

I want to express my thanks and to acknowledge the help of Dr. Jesse Edwards with whom this case was discussed.

Case Submitted and Prepared by James W. Wahe, M.D.
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CASE 19

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
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DEPARTMENT OF PATHOLOGY

1976 - Case #7
ST. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient was a 65 year old white male who was admitted for treatment of osteomyelitis of the left foot. He was a known alcoholic and had a 14 year history of insulin dependent diabetes mellitus with retinopathy and peripheral vascular disease. He also had a right below-the-knee amputation performed in March, 1975. He was also known to have prostatism, aortic stenosis (since adolescence) and hypertension. In September, 1975, the patient developed a decubitus ulcer on the lateral aspect of the left foot while being prepared for a TUR. His ulcer was treated on an outpatient basis with soaks and dicloxicillin for two months and then soaks only for two more months. X-rays at the end of this period revealed erosion of the cartilage of the 5th metatarsal-phalangeal joint and he was admitted to our hospital in the hope the medical treatment would avoid a second amputation. Staph aureus and pseudomonas were cultured from the wound base and the patient was treated as shown in the table. Bone aspirates grew out staph aureus resistant to Penicillin and Ampicillin. The wound did not heal and the patient was scheduled for a B/K amputation, but he first developed a rash (2-14) then eosinophilia (2-17) and urinalysis revealed hyaline casts, protein, RBC, WBC, and eosinophils. The methicillin (suspected as the cause clinically) was discontinued and surgery was delayed. The creatinine was stable at 1.4 but a few days later (2-21) began to rise. On the 19th the patient had developed chest pain and was transferred to the CCU to rule out MI. The patient was thought to have had an anterior myocardial infarction. Over the next several days the patient went into congestive heart failure with increasing BUN and creatinine. On the 25th pulmonary edema developed and he had a cardiac arrest and died.

TREATMENT OR LAB DATA	SEPT 1975	NOV 75	JAN 22	JAN 29	JAN 30	FEB 5	FEB 6	FEB 17	FEB 18	FEB 19	FEB 20	FEB 21	FEB 21	FEB 23	FEB 24	FEB 25
	Outpatient		Admission													
DICLOXACILLIN 250 mgm QID + soaks	x x →		1													PATIENT DIED
METHICILLIN 2 mg IVPB q 8 hrs.				x						DC						
GENTAMYCIN 60 mgm IVPB q 8 hrs.					x	DC										
120 mgm IVPB q 4 hrs.							x			DC						
100 mgm IVPB q 4 hrs.			▸							x	DC					
CARBENACILLIN 5 gm IVPB q 4 hrs.								x		DC						
BUN mgm/dl			28						25		22	33	55	57	69	
CREATININE CLEAR. mgm/dl/24 hrs.											62			34		
CREATININE mg/dl						1.4			1.7	1.8	1.6	2.1	2.8	2.5	3.0	
EOSINOPHILIA % of total Abs. cells/mm^3 Normal - 150-300/mm^3			4% 350	6% 720		4% 480		8% 930	19% 2109	7% 790	6% 970	17% 790	2% 260			
WBC x $10^3/mm^3$			8.8	12.0		12.0		11.6	11.1	11.3	16.2	11.3	10.3			

AUTOPSY: At necropsy the significant findings included an acute anteroseptal myocardial infarction of approximately three weeks age, pulmonary edema, two ulcers on the lateral aspect of the left foot at the base of the fifth toe, a multinodular thyroid goiter and renal disease. The renal disease was a composite of three different pathological processes (enclosed microscopic slide). The first consisted of diffuse and nodular glomerulosclerosis, the result of his diabetes. The second process showed the changes of hypoperfusion (heart failure): loss of nuclei and vacuolization and fragmentation of the cytoplasm of the tubular cells. The final lesion was in the interstitium and consisted of edema and a patchy infiltration of lymphocytes, plasma cells, neutrophils, and numerous eosinophils. The infiltrate abutted against the tubules and "tubulitis" was focally present. Papillary necrosis was not observed.

An immunoflourescent study was performed on the autopsy kidney. In the glomeruli some deposits of IgG, IgA and C4 were found along the capillary basement membrane. There were a few mesangial deposits. IgG albumin and C4 were found along the tubular basement membrane. Interstitial plasma cells contained IgM and beta 1C.

Electronmicroscopic examination was also performed on the autopsy kidney. Although the marked post mortem changes restricted the ultrastructural evaluation, some general observations still could be made regarding the structural changes of the renal tubules. These changes were focal and involved both the epithelium and basement membranes (see attached electronmicrograph). The most striking finding was the basement membrane thickening which was due mainly to an increase basement membrane material. In the thickened basement membrane there were vesicular structures containing electron dense bodies, probably representing degenerative changes of the membrane. The observed glomeruli showed only focal sclerotic changes.

DIAGNOSIS:

1. Acute myocardial infarction
2. Acute interstitial nephritis
3. Diabetic glomerulosclerosis

DISCUSSION: The case presented here is an example of an acute, drug induced interstitial nephritis in a patient with pre-existing glomerular disease.

The term interstitial nephritis was used for a long time to describe the findings in the kidney tissue of patients who died in infectious disease. In recent years it has also been applied to a clinical pathological entity characterized by the development of varying degrees of renal failure in patients exposed to different drugs. The clinical presentation of interstitial nephritis is diverse and varies from a minor and transient depression of renal function to frank renal failure with oliguria. Most of the patients fully recover following discontinuation of the drug which presumably precipitates the interstitial nephritis. In a few cases, however, the renal function deteriorated to such an extent that death was reported. The patients may have other symptoms such as fever, skin rash, eosinophilia, hematuria, elevated BUN and IgE levels. Recently certain drugs received attention as etiologic agents: particularly penicillin and its analogs, sulfonamides, anticoagulants, diuretics, diphenylhydantoin, allopurinol and azathioprine. In some cases immunofluorescent studies with anti-penicillin-related antigen serum showed a proof for an immunologic injury caused by penicillin (1,2,3). Histologic hallmark of the disease is a moderate to severe interstitial infiltration with a relative sparing of the glomerular structures. Eosinophilic infiltration with more or less severe tubulitis seems to be characteristic. The pathogenesis of this disease is still

obscure but the presently available findings offer some explanation. The presence of IgG, beta 1C, fibrinogen, lymphocytes, eosinophils in the renal interstitium, the elevated serum IgE levels and eosinophilia would suggest that in the interstitial nephritis several components of the immune process, e.g. immune complex-particularly allergen-IgE complexes-and sensitized lymphocytes may be involved in the genesis of this lesion.

In our patient, the acute interstitial nephritis was almost certainly due to methicillin treatment. Indeed, its histologic, electronmicroscopic and some of the immunofluorescent findings were quite similar to those in previously reported cases (1,2,4). Absolute proof of this mechanism, however, could not be afforded in the absence of immunofluorescent studies for the presence of methicillin antigen. Because the patient had pre-existing glomerular disease and hypoperfusion caused by cardiac failure, the contribution of interstitial nephritis to his progressive renal failure cannot be evaluated.

LEGEND OF THE ELECTRONMICROGRAPH: Electronmicrograph shows a portion of a degenerated tubule.

1a) The thickened basement membrane (BM) contains numerous vesicular structures (arrow). The partially disintegrated cell shows numerous phagolysosomes with electron dense myelin structures. Magnification x 13500

1b) High magnification of the basement membrane area. Vesicular structures with electron dense granules and membrane fragments probably represent basement membrane degeneration. Magnification x 16800.

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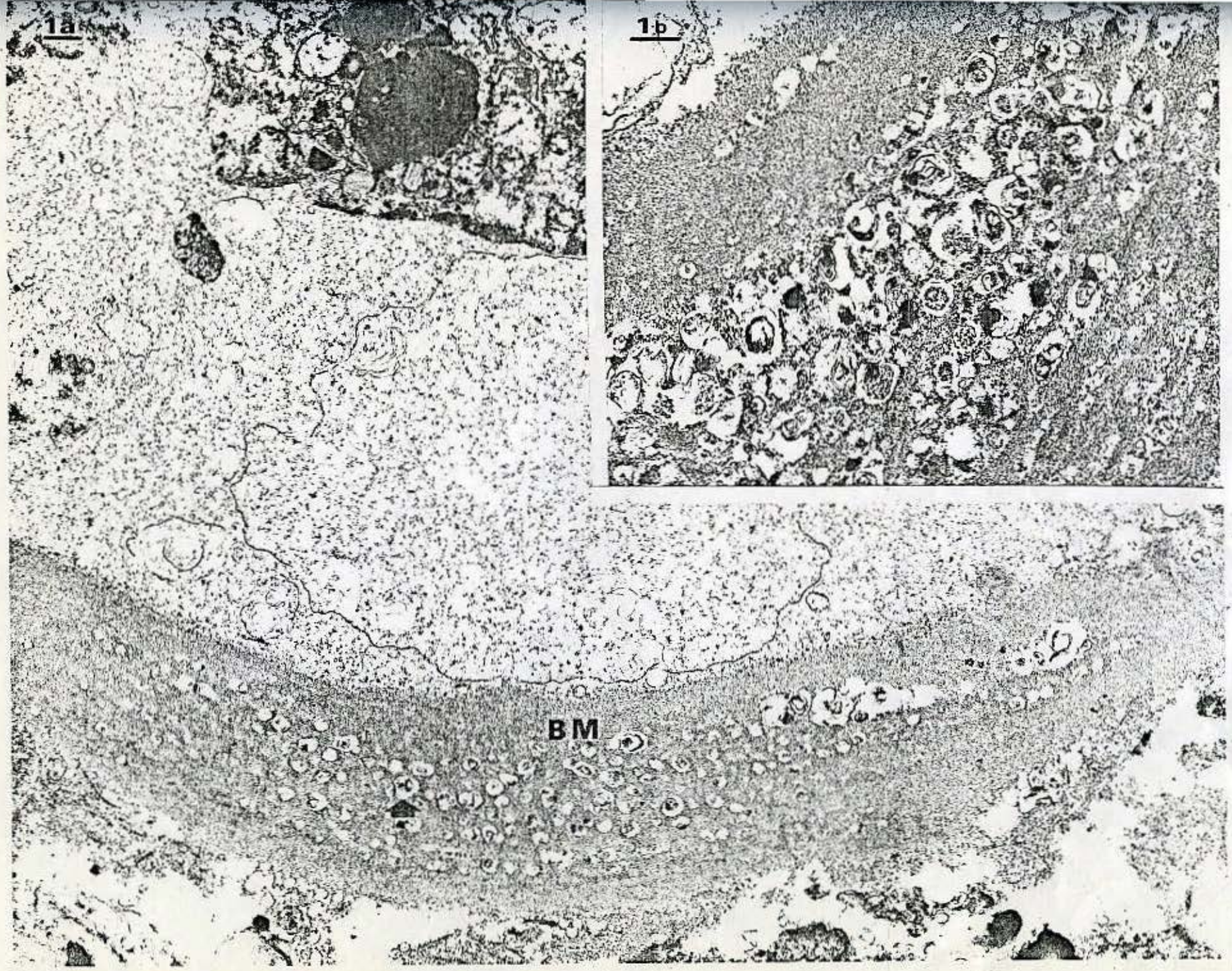
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1b
BM

CASE 20

ST. PAUL-RAMSEY HOSPITAL and MEDICAL CENTER
ST. PAUL, MINNESOTA 55101
DEPARTMENT OF PATHOLOGY

1976 - Case #8
St. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient was a 73 year old white male found at home in bed on 6-15-76, in a demented state, and admitted for treatment of dehydration and a left lower lobe infiltrate. No past history was available. Initial examination disclosed an extensively distributed maculopapular rash, generalized lymphadenopathy and hepatosplenomegaly. A normochromic, normocytic anemia, and a monocytosis (23%) were diagnosed on peripheral smear. Therapy was initiated with IV penicillin. Twenty-four hours following admission, the patient became hypotensive and had a respiratory arrest, necessitating intubation, steroids and dopamine drip therapy. He developed disseminated intravascular coagulation, with elevated protimes (19 to 21), partial thromboplastin times (77 to 99), and fibrin split products (greater than 40). Platelet count was 50,000. The patient's status improved following transfusion with two units of whole blood. Additional laboratory studies included bone marrow sampling, revealing foci of plasma cell proliferation, protein electrophoresis with a broad polychromal elevation of the gamma globulin fraction, and hypoalbuminemia. The patient continued to vacillate between disorientation and relative clarity, but was weaned from the MA-1 respirator on 6-21-76. Left axillary lymph nodes were biopsied on 6-28-76. Following the procedure, the patient became restless, and on 6-29-76 arrested and expired.

SURGICAL BIOPSY: The architecture of the lymph node was diffusely disrupted, with absence of the marginal sinus, and obliteration of the germinal centers. Occasionally, remnants of germinal centers were detected. The disruption was caused by a pleomorphic cellular infiltrate, composed of plasma cells, plasmacytoid lymphocytes and immunoblasts, all of which were brightly pyrinophilic on methyl green pyronine staining. Mitoses were occasional. A marked proliferation of branching vessels was apparent on a reticulum stain. Focally distributed throughout the interstitium were amorphous, eosinophilic, PAS positive deposits. When electron microscopic studies were performed on the surgical lymph node, the entire range of transitional forms from immunoblast through plasmacyte were apparent.

AUTOPSY: At autopsy, significant findings included: splenomegaly (580 grams), splenic fibrosis with lymphocyte depletion, pulmonary edema with focal hemorrhage, multiple foci of acute and chronic hepatic necrosis, and micronodular cirrhosis with a small, circumscribed hepatocarcinoma. The identical changes found in the surgical lymph node, i.e. disruption of the architecture by pleomorphic cellular infiltrate, proliferation of arborizing vasculature, and interstitial deposits, were repeated in the remaining axillary and in periaortic lymph nodes (slide enclosed). Clusters or "nests" of plasma cells and plasmacytoid lymphocytes were found in gastric submucosa and smooth muscle bundles, and scattered perivascularly in the liver.

DIAGNOSIS:

1. Immunoblastic lymphadenopathy.
2. Micronodular cirrhosis with focal hepatocarcinoma.

DISCUSSION: As recently as 1973, a new syndrome with a characteristic lymphoma-like clinical presentation and a unique histological picture was proposed. Clinically, the entity presents in older patients, generally over the age of 60, as a rapidly developing generalized lymphadenopathy accompanied by hepatosplenomegaly, and frequently a macropapular rash. Other lymphoma-like symptoms include: fever, sweats, pruritis, and weight loss. Laboratory studies consistently reveal a hypergammaglobulinemia, most often in the form of a polyclonal elevation. Normochromic, normocytic anemias are another frequent finding. A small percentage of these are of a coombs positive, hemolytic variety.

The histologic picture is distinctly different from Hodgkin's disease. A proposed diagnostic triad for lymphoid tissue consists of: 1) a prominent immunoblastic proliferation with plasmacytoid immunoblasts and plasma cells; 2) a proliferation of arborizing vasculature; and 3) interstitial deposition of an amorphous, PAS positive material. A variable feature is the concomitant occurrence of histiocytes and eosinophils. Similar infiltrates have been found in the liver, spleen, bone marrow, and occasionally the lungs, kidneys, GI tract, bladder and gallbladder.

At least two theories are available to explain the mechanism of this immunologic response. The first draws an analogy between a graft vs. host reaction and immunoblastic lymphadenopathy. Recently, Schultz and Yunis documented the course of a patient who developed this syndrome after chronic antigen stimulation. Whether due to chronic antigen stimulation, graft vs. host reaction, or some other cause the clinical outcome is identical. The majority of these patients succumb to a variety of infectious diseases. Death has been attributed to other processes as well, including massive hepatic necrosis, acute pancreatitis, and renal failure. Remissions have been achieved with an assortment of chemotherapeutic agents, but are generally short lived.

An interesting sidelight presented in two cases, in which the course progressed to a fulminant neoplasia with features characteristic of immunoblastic sarcoma.

LEGEND OF THE ELECTRONMICROGRAPH: Pictured is a large immunoblast (x 19,200) with a bi-lobed nucleus (N) containing two nucleoli, abundant and dilated rough endoplasmic reticulum (arrow), and well developed Golgi apparatus (G).

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CASE 21

1976 - Case #9
St. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient is a 69 year old caucasian female who had always been in good health. Early in 1976 a "small density" in the right upper lateral lung appeared on a routine chest x-ray. A prior chest film taken in 1972 was normal. Physical exam and tumor workup revealed no abnormalities. The patient was subjected to a thoracotomy in February 1976 at which time a subpleural wedge resection of the right upper lobe was performed with removal of a 3 x 2 x 2 cm. piece of pulmonary tissue. Within the central portion of this tissue there was an ovoid firm red-tan "putty-like" mass 2 x 1 cm. in diameter.

LABORATORY DATA: The hemoglobin was 14 gm.%; the white count was 4,800. Urinalysis was within normal limits. Specifically there was no proteinuria. The serum proteins were 7 gm.%. Serum protein electrophoresis was unremarkable. Urine protein electrophoresis quantitative immunoglobulins and immunoelectrophoresis were not performed. No bony abnormalities were demonstrated by x-ray.

MICROSCOPIC DESCRIPTION: The mass consists of a well-circumscribed subpleural nodule. There are interconnecting bands of brightly eosinophilic acellular homogeneous material surrounded by fibrous tissue containing numerous fibroblasts, lymphocytes and a large number of plasma cells. Numerous foreign-body type giant cells are present at the interface between the fibrous tissue and the acellular masses. There are also occasional Touton giant cells. Significant negative findings are the absence of bone or cartilage within the lesion, the lack of hamartomatous bronchi, no calcification and no evidence of fungi or rheumatoid nodules. Staining with Congo red reveals lime-green birefringence of the eosinophilic material and the pulmonary arteries near the lesion.

DIAGNOSIS: Solitary amyloid nodule of lung (amyloidoma)
Single or multiple amyloid tumors localized to the lung parenchyma are rare, but important because they are generally first perceived as coin lesions on x-ray and would therefore probably be submitted for frozen section at thoracotomy.

Diffuse involvement of the lungs by amyloidosis, especially in vessel walls is estimated to occur in about 30% or primary amyloidosis and 10% of secondary forms (1). Tumoral amyloidosis, characterized by solitary or multiple nodules has been reported in breast, bladder, nasal cavity, skin, cornea, vaginal mucosa, stomach, esophagus and urogenital systems but the most common area for tumoral amyloidosis is the larynx, trachea and bronchi. (2).

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Pulmonary amyloidosis has been classified by Prowes (3,4) into the following groups:

Group I Symptomless solitary or multiple nodules of amyloid confined to the peripheral lung parenchyma.
Group II Solitary amyloid tumor of major bronchus with symptoms of stenosis.
Group III Diffuse tracheobronchial amyloidosis of mucous membranes causing cough hemoptysis, stridor dyspnea and hoarseness.

About 30 cases of nodular parenchymal pulmonary amyloidosis has been reported. Approximately 10 of these have been single nodules of amyloid which have varied 2 to 15 cm. in diameter (5). The peripheral tumors occur in elderly patients, are usually asymptomatic and have a benign course. There are several case reports of pulmonary tumors associated with amyloidomas, including lymphoma and angioma (6). Asbestos bodies have also been found in association with amyloid tumors (7).

Only a few cases have had long-term followup (8). Systemic amyloidosis multiple myeloma and benign monoclonal gamopathy does not appear to occur. In one case however a second pulmonary amyloid tumor developed 9 years after resection of a single nodule.

Since the original description of amyloid by Rokintansky in 1842 (9 & 10) the origin and composition of the amyloid deposits have been controversial. Although the immune system has been implicated in pathogenesis of amyloidosis and an immunoglobulin origin has been suspected for decades, the chemical composition of the proteins have remained a mystery, largely because of the extreme insolubility of the deposits. However, in the past few years amyloid proteins have been solubilized purified and subjected to physical, chemical and immunochemical characterization. The details of these investigations are found in reference #9. In short, amyloid may be of either immunoglobulin or nonimmunoglobulin origin. Amyloid of immunoglobulin origin, as one might expect, is more frequently associated with plasma cell dyscrasia and primary systemic amyloidosis. The amyloid fibrils actually consist of amino acid chains with molecular weights varying from 5,000 to 18,000. Amino acid sequence analysis revealed them to be fragments of light chains, specifically from the variable or antigen binding regions. Amyloid of nonimmunoglobulin origin, generally associated with secondary amyloidosis, is a poorly characterized protein. Almost all amyloid fibers of unknown origin appear to have an identic amino acid sequence in contrast to amyloid of immunoglobulin origin which varies from patient to patient. The composition of nonimmunoglobulin amyloid may be derived from proteins associated with the immune system i.e. complement secretory piece material, etc.. The amyloid associated with medullary carcinoma of the thyroid is a third form of amyloid material, unrelated to the other two.

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CASE OF MONTH #9
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ST. PAUL-RAMSEY HOSPITAL
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Department of Pathology

CASE 22

1976 - Case #10

CASE OF THE MONTH

CLINICAL HISTORY: The patient is a 57 year old woman who intially manifested symptoms of cardiac disease two weeks following a normal delivery in 1951. At this time she had symptoms of congestive heart failure, and she was also noted to have atrial tachyarrhythmias. A diagnosis of post partum cardiomyopathy was suggested at this time. Over the next 20+ years, the patient had no more pregnancies and was essentially symptom free. In 1974, she experienced atrial tachyarrhythmias and a pacemaker was placed at that time. Severe cardiac arrhythmias continued, refractory to medical management, and in late 1975, a combined atrial and ventricular pacemaker was installed. In March of 1976, she was again admitted for control of similar cardiac arrhythmias. During this hospitalization, the patient developed bilateral pneumonia and had evidence of multiple pulmonary emboli. She expired suddenly.

AUTOPSY: At autopsy the heart weighed 500 grams and exhibited normal valves with normal valve circumferences. Transverse sectioning of the coronary arteries along their traceable lengths disclosed only minimal evidence of atherosclerotic plaque formation which never occluded more than 10% of the lumen. The atrial and ventricular chambers were markedly dilated and there was right and left ventricular hypertrophy. The myocardium was pale pink in color and contained many irregularly shaped areas of yellow to tan coloration. There was no evidence of atrial or ventricular mural thrombi. The lungs revealed severe bilateral necrotizing bronchial pneumonia. There were multiple thrombo-emboli found in the pulmonary vasculature some of which were associated with pulmonary infarcts. The liver showed severe chronic passive congestion.

MICROSCOPIC: Sections of the left ventricular myocardium reveal marked fibrosis which is most prominent in the subendocardial areas. There is disorganization of the normal myocardial architecture. There is also a diffuse inflammatory infiltrate present within the myocardium, composed of lymphocytes, plasma cells, histiocytes and occasional polymorphonuclear leukocytes. There is diffuse enlargement of the myocardial cell nuclei. Occasional myocardial cells exhibit pyknotic nuclei, cytoplasmic tinctorial change and cytoplasmic hydropic degeneration.

SS 2203

DIAGNOSES: Peripartum cardiomyopathy.

DISCUSSION: Peripartum cardiomyopathy is a syndrome of cardiac failure which is usually defined as occurring in the last trimester of pregnancy or the first month of the puerperium without any obvious underlying cause and without evidence of heart disease before the second half of pregnancy. The incidence of this condition is difficult to determine but estimates varying from 1 to 1,3000 to 1 in 4,000 pregnancies are generally accepted figures. Pathological the heart is soft and grossly enlarged with dilation of all four chambers. Mural thrombi are present in many cases, but there is no evidence of significant coronary artery, valvular, or pericardial disease. Light microscopic examination reveals degeneration or hypertrophy of muscle fibers, focal or diffuse myocardial fibrosis, scattered mononuclear cell infiltration, interstitial edema, and fatty infiltration. Electron microscopy of the myocardium generally shows an increase in the number and size of mitochondria, fragmentation of the mitochondrial cristae, presence of dense intramitochondri inclusion, varying degrees of mild fibrillar destruction, fragmentation of the sarcoplasmic reticulum, increased numbers of lipofuscin granules, and increase glycogen deposition. Histochemical studies have shown an increased deposition of neutral lipid in the myofibrils as well as a decrease in the myocardial oxidative enzymes, especially succinate dehydrogenase activity. In general, these findings are not significantly different than the findings in other forms of idiopathic congestive cardiomyopathy.

The etiology remains obscure. It has been suggested that the occurrence in pregnancy may be no more than fortuitous, but the absence of evidence of heart disease before pregnancy and the tendency for recurrence with subsequent pregnancies suggests that peripartum cardiomyopathy is a specific entity. The disease appears more commonly in blacks, in multiparous older women, in the presence of twin pregnancies, and in association with toxemia of pregnancy. Brockington has suggested that peripartum cardiomyopathy may be secondary to hypertension. He states that transient hypertension, developing rapidly in th postpartum period, might be responsible for heart failure that could recur in subsequent pregnancies. Others have suggested that peripartum cardiomyopathy is really a viral myocarditis. Farber and Glasgow in 1970 demonstrated in MLM 1 mice that viral reproduction in cardiac muscle is enhanced during pregnancy and that a severe viral myocarditis may result. Another possibility is that hormonal factors are involved in the etiology of peripartum cardiomyopathy. Seftel and Susser noted that peripartum cardiomyopathy is more common in lactating women. This theory however is not widely accepted. Still another possiblity is that the immune response to fetal tissue is a cause of peripartum cardiomyopathy in some instances. Becker and Taube postulated this after finding circulating trophoblastic tissue in maternal circulation. Also the recognized association of peripartum cardiomyopathy with stillbirths, abortions, twin births and multiparity seems compatible with an immunologic response of maternal tissue to fetal tissue. Still another possibility is tha the fetus might produce an antimyocardial antibody which can damage the matern myocardium. However, objective evidence to support these later two concepts is lacking at the present time. It is also possible that antibodies to rapidl involuting smooth muscle of the uterus might cross react with the myocardium.

The clinical picture of peripartum cardiomyopathy is that of congestive heart failure. Pulmonary emboli occur in approximately 50% of patients in whom cardiomegaly persists after six months. Atrial fibrillation occurs in approximately 25% of patients. Demakis et al divides peripartum cardiomyopathy patients into two groups on the basis of cardiac size at the end of six months following diagnosis. Group A included patients whose heart size had returned to normal, and group B included patients with persistent cardiomegaly. Over a ten and one-half year average follow-up period group A patients had a mortality rate of 14%, and over a 5.4 year average follow-up period group B patients had a mortality rate of 85%. During their time of follow-up, approximately 80% of the surviving group A patients showed some evidence of cardiovascular pathology or limitations. The great majority of these patients with persistent cardiovascular changes had EKG abnormalities, while others had recurrent cardiac failure with subsequent pregnancies, or had focal myocardial fibrosis on myocardial biopsy. Demakis et al in the same study stated that the influence of a subsequent pregnancy on aggrevation of the peripartum cardiomyopathy was seemingly related to whether the patient's cardiac size returned to normal. It was his conclusion that a patient with a past history of peripartum cardiomyopathy whose heart size had not returned to normal should avoid becoming pregnant. Despite the apparent clinical differences of group A and B patients Demakis states that pathological findings in the myocardium were indistinguishable between the two groups.

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CASE OF THE MONTH # 10

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ST. PAUL-RAMSEY HOSPITAL
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Department of Pathology

CASE 23

1976 - Case #11
Midway Hospital - 076-5442

Case of the Month

CLINICAL HISTORY: This 25 year old man was first seen in St. Paul in November of 1976 complaining of a "problem in his armpits". At that time he had bilateral axillary lymphadenopathy and in the left axilla there was a draining sinus tract productive of thick gray fluid which had no odor. The lymph nodes were tender but the overlying skin had no redness. The pertinent past history revealed that this man had been "temporarily detained" by law enforcement officers in the state of California in 1972. During his stay he volunteered for medical experimentation. In late 1972 or early 1973 he received intradermal injections of beryllium oxide in solution. These injections were carried out over the upper back in the general region between the scapulas. They were given by a University of California dermatoligst and the patient stated that he received approximately eleven such injections over a period of two years. Sometime during the course of this injection series he received transfer factor from a control group who were found to be allergic to beryllium oxide. This was injected deep into the triceps muscle and soon after that he developed nodularity in the regions of the intradermal injections of the upper back. Shortly after that he received injections of transfer factor together with beryllium oxide. About one year later he began having asthma-like attacks but it was never ascertained whether or not these attacks were related in any way to any of the previous procedures. There has been no trouble with these respiratory attacks for several years.

At Midway Hospital in early December of 1976 several right axillary lymph nodes were removed.

GROSS DESCRIPTION: The specimen consisted of an elliptical mass of fibrofatty tissue within which there were several tan nodules, measuring up to 2 cm. in greatest dimension. Several of the larger tan nodules had areas of central cheesy necrosis.

MICROSCOPIC DESCRIPTION: Sections show obliteration of the normal lymphoid architecture by collections of granulomas of varying size and shape. The small granulomas consist of an admixture of epithelioid cells and multinucleated giant cells. Both Schaumann bodies and asteroids are readily found. There is no necrosis within these smaller granulomas. However, the larger granulomas demonstrate central necrosis with the necrotic areas surrounded by a mantle of epithelioid cells again admixed with multinucleate giant cells. Stains for organisms are negative and cultures are negative.

DIAGNOSIS: Granulomatous inflammation, mixed pattern, compatible with berylliosis, axillary lymph nodes.

DISCUSSION: Berylliosis is generally considered to be an occupational disease. In 1713 Ramazzini, the father of occupational medicine, published De Morbus Artifactum Diatriba in which he listed the hazards of fifty-two occupations including wrestling, nursing, and grave digging. (It seems that there might be some common denominator within those three occupations. Perhaps it is the order in which they are listed.) I do not know if he listed the incarcerated medical volunteer as one of the hazardous occupations. If it was unlisted at that time let us now add this noble vocation to the list of high risk (and low pay) jobs. We readily admit that we have not proven that the reaction in this patient's axillary lymph nodes is due specifically to the injections of beryllium oxide since we have not submitted this tissue to spectroscopic analysis or chemical analysis. However, on the basis of the history of exposure plus the types of changes present in the lymph nodes, we know that this is beryllium disease of the axillary lymph nodes. Ex cathedra.

Beryllium disease is generally a pulmonary condition. Acute pulmonary berylliosis is a type of chemical pneumonitis with the lungs showing congestion and edema. Hyaline membranes are often found. The chronic form of pulmonary beryllium disease is a type of diffuse interstitial pneumonitis with the additional feature of granuloma formation. It is often stated that there are no histologic features specific for beryllium disease and the diagnosis must be supported by a history of exposure. However, this exposure may be very subtle or indirect since people living in the neighborhood of industries associated with beryllium products will occasionally develop pulmonary beryllium disease. It has also been reported in people who handle or wash the clothes of workers in beryllium industries and contaminated work clothes are probably more important than contaminated air in "neighborhood" cases. The history may also be difficult to obtain since many affected workers leave the industry years before the onset of their respiratory symptoms. Hypersensitivity is believed to play a definite role since only a small percentage of people exposed to beryllium develop beryllium disease.

Although beryllium disease is almost always a condition which involves primarily the lungs there are also cases involving primarily the skin. These were almost always secondary to a skin laceration involving a fluorescent light bulb. Prior to 1949 these light bulbs contained beryllium phosphors and introduction of this material into the skin caused granulomas which very closely resembled sarcoidosis. However, the larger granulomas in those instances often demonstrated central necrosis as well. Williams reported the first case of beryllium skin granuloma due to beryllium oxide (which was the compound injected into our patient). His patient eventually had to have the inoculation site amputated and this was then followed by lymphatic spread of beryllium causing granulomas in the forearm. He noted that in addition to the more common subcutaneous sarcoid-like granuloma there is a second type of skin disease with berylliosis, this being an acute type which is essentially contact dermatitis and an acute ulceration which shows nonspecific histology. These are due to the soluble acid salts of beryllium rather than due to beryllium oxide.

There is very little specific information in the American medical literature relative to the histopathology of lymphoid tissue in beryllium disease. Most major references make fleeting reference to the changes within lymphoid tissue. For example, Spencer says "in chronic berylliosis the lesions are generally not confined to the lungs but will also occur in the skin, liver, kidney, spleen, and lymph nodes". Anderson states that in beryllium disease "granulomas will be found within the lungs as well as within the adjoining hilar nodes. The basic

lesion is a noncaseating 'sarcoidal' granuloma." Other references treat the nodal pathology in beryllium disease in a similar cavalier fashion. Furthermore, there is a definite inconsistency in the American literature concerning the specific types of granulomas found in beryllium disease. Some authors state that the granulomas are generally small, discrete, and noncaseating. Other authors state that there are variable degrees of necrosis found within the granulomas. On the basis of our case, I would say that a compromise is indicated, with both necrotic and non-necrotic or noncaseating granulomas present. All authors agree that asteroids and Schaumann (conchoidal) bodies are very frequent in this condition, even more so than in sarcoidosis, which is the condition most commonly confused with beryllium disease.

Beryllium is a metal with a high degree of elasticity which gives it the ability to resist all types of stress and also has the property of imparting hardness, lightness, and heat resistence to materials. As a result, it is used in space capsules as well as in the manufacture of fishing rods, furnace bricks, brake linings of jet airplanes, bed springs (stress?), guidance systems, and other aspects of military defense and space exploration. It has also been investigated as a component of solid fuel propellants and is used in the manufacture of plastics. With this degree of utilization it is not unlikely that a pathologist might come across a case of berylliosis although this would most likely be pulmonary disease rather than skin or lymphoid involvement. With the exception of the mining of beryl ore, all beryllium operations have caused illness and cases of each type are documented in the United States Beryllium Case Registry which was organized in 1952 at the Massachusetts General Hospital.

The treatment of berylliosis generally hinges around the role of steroids. Steroids will modify the clinical course of the patients and are felt to have some value at least in terms of life expectancy. Almost all patients will definitely show clinical improvement on steroids. It is also recommended that skin innoculation sites be removed if present. This was subsequently accomplished in our patient.

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CASE 24

DEPARTMENT OF PATHOLOGY

1976 - Case #12 076-5579A
Midway Hospital

CASE OF THE MONTH

CLINICAL HISTORY: This 22 year old woman first complained of shortness of breath 4½ months prior to admission. A chest film was taken and the patient was told she had "pneumonia" and was given a course of treatment with antibiotics without improvement. She tolerated her symptoms of continuing shortness of breath for the next 2 months and was seen in November, 1976 because the dyspnea was limiting her physical activities as well as the development of a productive cough. She was hospitalized for evaluation which revealed scattered rales at the lung bases, nodular fluffy infiltrates at the lung bases and left apex on chest x-ray which suggested Hamman-Rich syndrome or subacute pneumonia to the radiologist.

The only medication that the patient chronically took were birth control pills. She denied an allergy history although she had been employed in a plastics factory but without direct exposure to aerosolyzed noxious materials. She admitted to smoking 1-2 packs of cigarettes a day but denied history of exposure to Tuberculosis. The working diagnosis became sarcoidosis and workup included standard skin tests, bronchial washings, and scalene node biopsy, all of which were noncontributory or negative. Arterial blood gases showed diminished arterial oxygen saturation and pulmonary function tests showed marked diminution of forced expiratory volume.

An open lung biopsy was performed with frozen section diagnosis of this condition.

A 2½ cm. wedge of lung from the apex of the left upper lobe grossly demonstrated dull pink rubbery to moderately firm tissue having a meaty consistency which would exude dull gray fluid on slight digital pressure.

Microscopic examination of the lung shows marked dilatation of the alveolar spaces which are filled with amorphous, acellular, slightly granular, eosinophilic material which proves to be strongly PAS positive. The intervening alveolar septa show minimal epithelial proliferation and no atypical cells. The septa are intact. This material is present in a "skip" arrangement with intervening areas of pulmonary parenchyma showing moderate to marked atelectasis and a smaller amount of similar eosinophilic material. Terminal bronchioles also contain eosinophilic material. Stains for fungi, parasites and specifically Nocardia are negative.

DIAGNOSIS: Pulmonary alveolar proteinosis.

DISCUSSION: Pulmonary alveolar proteinosis (PAP) has only recently been recognized as a clinical entity having been first described in 1958 by Rosen, Castleman and Liebow in a New England Journal of Medicine. In their original series most of the patients with this disorder were adults between 20 and 50 years of age. There was a male preponderance of 2.5 to 1 in their series. By occupation, the patients were carpenters, electrical workers, munition workers, electricians, fluorescent tube workers, and others who were chronically exposed to organic solvents which had been aerosolyzed by hot metal. Almost half the patients had antecedent febrile illnesses which were usually classified

clinically as pneumonia. In most patients studied the onset is insidious but accompanied by creeping progressive dyspnea with cough and sputum production. Chest x-ray usually demonstrate a classic pattern consisting of a fine diffuse radiating somewhat nodular soft density infiltrate not unlike that of pulmonary edema. Absence of significant enlargement of hilar lymph nodes on chest x-ray is characteristic of PAP.

Since Rosen's description of PAP a predictable histologic pattern has been consistent demonstrated in patients with the disorder. Basically the lesion consists of the dep tion of a PAS positive granular and floccular proteinaceous acidophilic material whic is rich in lipids within the distal air spaces where little if any cellular inflammat response is ellicited. Occasionally crystals and intensely staining laminated bodies have been seen to occur which are believed to be cellular fragments. The intra-alveo septae and their capillaries by light microscopy usually are normal in appearance.

A review of the world literature by Sunderland in 1972 demonstrated that superimposed fungal infections may complicate the course of PAP. At that time Sunderland and Camp had noted 26 cases of aspergillosis, mucormycosis, cryptococcosis or Nocardia out of case reports of PAP. Other papers dealing with the question of association with unde lying infection have shown a similar pattern of about a 10% association with funcal i tation complications. As regards the alveolar lipid itself many authors have noted t similarity in chemical composition of the material to that of alveolar lining surfact Ramirez and Harlan found the predominent lipid to be phospholipid in the form of palm goyl lecithin. This same pair of investigators noted that the removal or degradation alveolar phospholipid was found to be impaired in their patients. They and others ha since advanced the concept that PAP results from prolonged retention of the metabolic products and by-products of the alveolar lining cells.

Many investigators have experimented with forms of therapy ranging from chemotherapy consisting of steroids to enzymatic therapy with Trypsin to mechanical measures such as transtracheal lavage with or without heparin. Results of the different modalities of therapy, just as the clinical course itself, are quite variable. Arora et al were able to induce complete clinical remissions in 2/3 of their patients with the use of crystalline Trypsin as the sole method of therapy.

While the peak incidence of the disorder occurs in patients between the ages of 30 an several accounts have now been cited in the literature dealing with infants less than year of age. And of their series at the Mayo Clinic Colón et.al. noted that their pediatric patients had a survival time which averaged less than 1 year after the onse of symptoms. Interestingly enough, 7 of their 23 patients had thymic alymphoplasia, observation which led them to speculate that there was an associated immuno incompete Others, Mork et. al, have demonstrated elevations in immunoglobulins in patients with the disorder.

As in many other countless chronic states of pathophysiologic derangement, no direct cause and effect relationship has been varified as regards the initial inciting event or stimulus. While many patients had a heavy cigarette smoking exposure, with others having an industrial inhalant exposure, others, infants included, had no known exposu And since McClanahan and Mussenden's biochemical work, most workers are in agreement the intra-alveolar material in PAP represents an accumulation of modified normal surf tant and serum rather than an accumulation of abnormal lipids or proteins and that furthermore there is an an impaired removal of such accumulation.

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ST. PAUL-RAMSEY HOSPITAL
and
MEDICAL CENTER
ST. PAUL, MINNESOTA 55101

CASE 25

DEPARTMENT OF PATHOLOGY

1977 - Case #1
St. Paul-Ramsey Hospital

CASE OF THE MONTH

HISTORY: The patient is a 53 year old American Indian male who developed sudden onset of severe abdominal pain and tenderness. Free air was present on abdominal x-rays. Emergency surgery disclosed a perforated cecum and a dilated, thin-walled proximal colon. A right hemicolectomy was performed. Grossly, multiple, confluent mucosal ulcerations, measuring up to 5 cm. were evident.

MICROSCOPIC: The sections are of colon involved with extensive mucosal ulceration. Ulcers extend through the submucosa and into the muscularis externa. Necrotic and fibrinous material, admixed with neutrophils and mononuclear cells, fills the ulcer craters and there is undermining of the remaining mucosa. Peritoneal exudate is also visible. Organisms, resembling large histiocytes with faint or absent nuclei, are present within the superficial exudate.

DIAGNOSIS: Amebic colitis with perforation.

FOLLOW-UP: One week later the patient's 47 year old sister developed identical symptoms and also underwent a right hemicolectomy. Both the patient and sister received chemotherapy postoperatively and recovered uneventfully. Two acquaintances from the same North Dakota reservation developed diarrhea and had demonstrable amebic trophozoites on stool examination. None of the four individuals had recently traveled from the state.

USUAL SYMPTOMATOLOGY: This series of cases illustrates a common misconception regarding amebiasis, i.e. that it is a tropical disease. By conservative estimates, five percent of individuals in this country harbor the parasite. An amebic infection can take many forms and is a notorious immitator of ulcerative colitis, granulomatous colitis, acute appendicitis, bacillary dysentery, colonic carcinoma and hepatic tumors. Much of the initial misdiagnosis relates to the physicians' low index of suspicion.

The host-parasite relationship can be divided into three groups: 1. Asymptomatic intestinal infection, 2. Symptomatic colitis, and 3. Extraintestinal infection. Ninety-five percent of cases fall into the asymptomatic category and are the most infective hosts, since they excrete the greatest number of cysts. These individuals may or may not develop colitis, extracolonic abscesses or both.

The reason for this varying host response is not known but may be related to underlying nutritional status or the associated bacterial flora. Westphal successfully converted his own asymptomatic carrier state into near fatal amebic dysentery by ingesting the intestinal bacteria of a symptomatic patient.

Cases of colitis are typically manifested by the gradual onset of diarrhea and abdomi cramping. The term "amebic dysentery" should be reserved only for those cases of profuse diarrhea accompanied by the passage of mucus and blood. Occasionally an infected focus of bowel may evolve into a mass of edematous granulation tissue, the "ameboma". Amebomas are most common in the cecum and closely mimic annular carcinoma radiographically. Perforation, intussuseption and toxic megacolon are additional complications of colonic infection. Surgical treatment, without appropriate chemotherapy, will frequently lead to a fatal outcome.

Extracolonic amebiasis takes the form of single or multiple abscess, with the liver being, by far, the most common site. Abdominal mass, tenderness, fever or cough may be symptoms of hepatic abscess, however many remain occult until spontaneous rupture into the peritoneal or pleural space. Only one-half of patients with extraintestinal abscess will have demonstrable parasites in the stool and one-half will have no history suggesting colitis. Amebic hepatic abscess should not be confused with "amebic hepatitis". The later is a syndrome of enlarged, tender liver associated with amebic colitis and is theorized to be the result of toxin release by the organism. Liver biopsies are of little use in such cases. Miliary and cerebral abscesses are rare medical curiosities.

LABORATORY DIAGNOSIS: The laboratory investigation should be directed toward three areas: 1. Stool examination, 2. Biopsy, and 3. Serology. Wet-prep examination of three very fresh stool specimens, taken over 7-10 days will detect 90% of colitis cases, when performed by an experienced laboratory. Both cysts and trophozoites deteriorate rapidly from specimens. The CDC provides mailing kits containing 10% formalin and polyvinyl alcohol fixatives, which will preserve both morphologic forms of organism. These should be utilized by the smaller laboratory for initial diagnosis or even by experienced facilities for verification. Difficulty arises not only in identifying the parasite, but in differentiating E. histolytica from the nonpathogenic amebae, e.g. E. coli and E. hartmanni. Detailed morphologic differences are discussed by Markell and Voge.

Biopsy of colonic lesions may show a spectrum of changes, from nonspecific interstitial colitis to the typical flask-shaped ulcers. Organisms are usually found within the surface exudate or at the advancing ulcer margin. There is evidence that E. histolytica invades only passively after its lysing enzymes have disrupted the mucosal surface. Parasites will not be found deep within crypts nor within the wall of nonulcerated bowel. A PAS stain is extremely helpful. Smears performed at the time of colonoscopy are also helpful. Material should be transferred to a glass slide by curetting or aspirating the base of an ulcer.

Amebae are tenaceous characters and will adhere to the fibers if a cotton swab is used. Trophozoites are usually demonstrable in biopsies from hepatic abscess wall or in the abscess contents. If needle drainage is perfromed, the last bit of aspirated material should be examined, immediately and again after trypsin digestion.

Serology is very useful in establishing a diagnosis. Various methods have been developed, and a recently described counterelectrophoresis (CEP) technique appears to be accurate and quite simple. A negative serology rules out a hepatic abscess, however cases of mild or asymptomatic colitis occasionally will be negative. False positive serologies are rare.

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Prepared by: Thomas Vorpahl, M.D.
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ST. PAUL-RAMSEY HOSPITAL
ST. PAUL, MINNESOTA 55101

CASE 26

CASE OF THE MONTH

1977 #2
St. Paul Ramsey Hospital
A77-25

HISTORY

A five year old male entered a local hospital on December 15, 1976 with a ruptured appendix and peritonitis. E. coli was cultured from the peritoneal fluid. He received Clindamycin for 4 days, Gentamicin and ampicillin for another several days. After discharge he did well until January 26, 1977, when he presented with a 3 day history of vomiting, diarrhea, and abdominal tenderness. There was moderate dehydration and a temperature of 103°. Because of deterioration in spite of rehydration he was transferred to SPRH. On admission he was alert but hypotensive and oliguric with a BUN of 39 and K of 5.3. X-rays revealed dilated loops of small bowel with air-fluid levels. Peritoneal aspiration revealed foul turbid fluid containing gram positive and negative rods. Clostridium perfringens and E. coli were cultured.

Exploratory laparotomy failed to disclose perforation, necrosis or significant bowel adhesions, although the parietal peritoneal surface of the right lower quadrant was covered by a fibrino-purulent exudate and the bowel appeared congested and edematous. Postoperatively the patient was in DIC and refractory shock with GI bleeding, oliguria, hypoglycemia, acidosis, hyperkalemia and hypothermia. He was pronounced dead at 3 AM on Jan. 28, 1977.

FINDINGS

At autopsy, nine hours after death, no areas of bowel perforation could be identified. Almost the entire small bowel and portions of the colon had a congested red-purple serosa. The bowel was dilated with foul-smelling gas and pasty pale fecal material. The muscularis was edematous. The mucosa was covered by a thick yellow-gray "diphtheric" type of membrane involving both small and large bowel. The mesenteric nodes were prominent and the spleen was extremely soft.

The lungs, blood, spleen, peritoneum and mesenteric nodes were cultured aerobically. None of the cultures produced growth. Cultures of bowel mucosa were not obtained.

Histologically the bowel mucosa was partially necrotic and was covered by a fibrinomucous pseudomembrane. The lamina propria contained a chronic inflammatory infiltrate. The submucosa was edematous. The serosa was congested, edematous and contained a chronic inflammatory infiltrate. Peyers patches, mesenteric nodes and spleen had necrotic foci in the centers of lymphoid nodules. Stains of lymphoid tissue for etiologic agents were negative.

DIAGNOSIS

Pseudomembranous enterocolitis with mesenteric adenitis.

Pseudomembranous enterocolitis was first described by Billroth in 1867 as a postoperative complication (1). In the late 1950's there appeared numerous case reports associated with antibiotics.

Clindamycin, tetracyclines, penicillin, ampicillin, Lincomycin, Amoxycillin and cephalosporins were implicated, among others (1,2,3,9,10,11, 14). Antibiotics were postulated as toxic to the mucosa or it was thought that they might allow overgrowth of Staphylococcus or other organisms (1,11, 12,13). Numerous other conditions have also been implicated, including lymphoma, aplastic anemia, leukemia, shock, ischemia, uremia, cachexia, carcinomatosis, pneumonia, chronic hepatic disease, heart failure, heavy metal poisoning and bacteria, especially Salmonella and Yersinia (1,11,12,13,15).

Grossly the "pseudomembrane" is a gray-yellow plaque overlying a reddened mucosa. Foci of ulceration may give a cobblestone appearance. Microscopically there is partial mucosal necrosis, chronic inflammation, goblet cell hyperplasia and fibrinomucous membrane. The submucosa is edematous and the muscularis usually is not severely involved.

In this case the lymphoid hyperplasia and distinctive pattern of necrosis suggests a bacterial component. Clostridium, cultured from antemortem peritoneal fluid, has been implicated in "enteritis necroticans" in sporadic cases described in the German literature, as well as endemic cases in the New Guinea highlands related to ingestion of rotten pork (15). Necrotizing mesenteric adenitis has not been described however.

In a number of cases with similar pathology, Yersinia enterocolitica has been demonstrated serologically or by culture (13). Yersinia is usually associated with the "benign" mesenteric adenitis of childhood often clinically indistinguishable from acute appendicitis. In addition to adenitis it may cause a severe terminal ileitis and, in fact, appendicitis. In one fatal case an acutely inflammed appendix was removed, the patient was treated with antibiotics and expired three weeks later with pseudomembranous enterocolitis and mesenteric adenitis. Yersinia infection was demonstrated serologically. The antibiotics may have had a permissive role in altering bacterial flora.

In almost all cases of pseudomembranous enterocolitis there is a "preparatory" history of one of the conditions listed above, followed by an acute phase of partial to complete mucosal necrosis. A localized bacterially mediated Shwartzman reaction has been postulated as the underlying pathological process, rather than an infective, ischemic, "toxic" or immunological (Arthus) reaction. Although the etiology remains unknown, future investigation aimed at induction of a localized Shwartzman reaction may be fruitful (17). There are numerous useful animal models. In fact, necrotizing enteritis in domestic animals, especially pigs, is well known (18).

SUMMARY

This case of fatal pseudomembranous enterocolitis and mesenteric adenitis occurred in a child recovering from an acutely perforated appendix six weeks previously. He had a brief course of several antibiotics, recovered and had not been on medication for over a month. Although lacking cultural or serological confirmation, the presentation, clinical course and histopathology of the bowel and lymph nodes is similar to cases described of fatal post-appendectomy pseudomembranous enterocolitis and mesenteric adenitis caused by Yersinia enterocolitica (13).

Submitted & Prepared by: Stephen M. Larkin,
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MEDICAL CENTER
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CASE 27

DEPARTMENT OF PATHOLOGY

1977 - Case #3
076-3540
Midway Hospital

CASE OF THE MONTH

HISTORY: The patient is a 28 year old gravida 1 para 0 who had an EDC of 8/25. On 8-1 she complained of progressive right lower back and chest pain. A chest x-ray was reported as suspicious for pulmonary embolism in the left lower lobe and there was some pleural fluid. She was admitted for treatment. Following this she developed right upper quadrant abdominal pain along with nausea and vomiting. Her blood pressure at this time was 140/106 and 3 days later she developed jaundice. Her bilirubin rose to 14.8 mg/dl total with 8.1 mg/dl direct. The SGOT was 900 units, and alkaline phosphatase was 390 units. The seventh day after admission she underwent a Cesarean section at 37½ weeks gestation along with an exploratory laporotomy for apparent obstructive jaundice. She was delivered of a live male, 5 lbs. 12 oz. with APGAR scores of 7 and 8 at 1 and 5 minutes. The exploration was negative except for a "mottled" liver with a smooth capsule. A needle biopsy was performed.

MICROSCOPIC DESCRIPTION: Sections of liver are characterized by dense areas of necrosis and hemorrhage sharply separated from preserved tissue. Small islands of degenerating parenchymal cells are present in the necrotic areas. Loose aggregates of polymorphonuclear leukocytes and lymphocytes are present along the edges of the necrosis. The distribution of the necrotic parenchyma is mainly periportal but extends into the centrilobular region. Vessels are dilated with amorphous, eosinophilic debris which is positive for fibrin by special stain. The hepatocytes in the preserved areas demonstrate changes ranging from nuclear enlargement to ballooning degeneration. A slight increase in periportal fibrous tissue is also present in the viable areas along with a mild increase in lymphocytes in these areas.

DIAGNOSIS: Liver biopsy demonstrating extensive ischemic necrosis, consistent with eclamptic liver disease.

FOLLOW UP: Following surgery, the patient became obtunded with an inaudible blood pressure and a pulse of 160 per minute. She was transferred to the University of Minnesota Hospital and underwent an exchange transfusion. Diffuse intravascular coagulation (DIC) was considered part of the presenting problems. Renal failure developed on 8-10 and she was successfully treated with conservative measures. Pneumonitis and a urinary tract infection also occurred but the patient was discharged home on 8-26. There was gradual improvement of her liver function studies at that time.

DISCUSSION: This rare liver disease associated with eclampsia is usually diagnosed retrospectively after rupture of the liver occurs. Almost all of the patients reported were multiparous and of advanced maternal age. Onset of the disease is usually late in the third trimester. Jaundice is "rare" and considered to be a bad prognostic sign along with evidence of DIC. The mortality is high and is related to subcapsular and intraparenchymal hemorrhage with hematoma formation, leading to disruption of the capsule. The clinical presentation is usually right upper quadrant abdominal or right lower chest pain followed by signs of cholestasis and, rarely, jaundice. The alkaline phosphatase and SGOT rise to high levels. On

AN EQUAL OPPORTUNITY EMPLOYER

physical examination, a palpable liver in the third trimester is reported in Schiff as "probably pathological". Shock secondary to hemorrhage and hypovolemia occurs if the hepatic capsule ruptures. The prognosis is related to severity of the disease along with the presence of eclampsia and/or DIC.

The microscopic picture ranges from "normal" to "characteristic necrosis", especi severe in the periportal areas. Centrilobular hemorrhage is reported to be associated with cases of hepatic rupture. Hemorrhage from sinusoidal engorgement and fibrin deposition is present. Kupffer cell prominence and cholestasis may also be identified. Absence of an inflammatory infiltrate was reported as a stable histologic negative. Periportal fibrosis is variable. Other causes of hepatic rupture in pregnancy are malaria, aneurysm, angiomatous tumor mass, tertiary syphilis, and typhoid fever.

The mechanism of eclampsia is proposed to be DIC or a similar local phenomenon involving the kidneys. The histologic picture of eclamptic liver disease parallels that of DIC and may represent extension of this process into another organ system.

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and
MEDICAL CENTER
ST. PAUL, MINNESOTA 55101

CASE 28

DEPARTMENT OF PATHOLOGY

077 - Case #4
077-384
St. Paul-Ramsey Hospital

CASE OF THE MONTH

CLINICAL HISTORY: The patient is a 26 year old white male with an 18 month history of Stage IV-B mixed cellularity Hodgkin's disease diagnosed by laparotomy. The patient was undergoing an apparently successful therapeutic treatement with MOPP when he developed an erythematous papular squamous plaque on his glands penis and an enlarged 2-3 cm. right inguinal lymph node. A VDRL test was done and found to be negative. A biopsy of the penile lesion showed a nonspecific cutaneous ulceration and inflammation. The patient's penile lesion was treated topically, but the rash continued to get worse until he developed a generalized rash approximately one month later. At that time the patient's VDRL was positive at 1:128. His F.T.A. test was found to be 4+. He was treated with 2.4 million units of of Benzothine penicillin and the VDRL Titers were followed. Approximately two weeks later the inguinal node measured approximately 4 cm. in greatest dimension. This node was excised and submitted for evaluation of a possible recurrence of Hodgkin's disease.

MICROSCOPIC: Multiple sections of lymph node show the normal nodal architecture to be maintained. The capsule of the node, however, is thickened and fibrotic. A large number of plasma cells and a few eosinophils are seen within the capsule. The reaction centers are enlarged and present within the medullary portion of the node as well as the cortical. The reaction centers show a proliferation of histiocytes and reactive immunoblasts. There is extensive cytolosis with nuclear fragmentation. The internodal areas show a proliferation of enlarged and slightly atypical histiocytes admixed with eosinophils and moderate numbers of plasma cells. Large numbers of mitotic figures are seen within the tissue but no atypical mitoses are found. No typical Reed-Sternberg cells are seen, although a fair number of binucleated histiocytes are found. A few vessels show inflammatory cells including plasma cells within their walls.

MICROSCOPIC DIAGNOSIS: Right inguinal lymph node showing changes compatible with luetic lymphadenitis.

DISCUSSION: The clinical and histological changes seen in secondary syphilis and other non-specific disease with generalized lymphadenopathy can be difficult to distinguish from a malignant lymphoma, as seen in this case. The distinction between a reactive process and a lymphoma is generally made on several criteria. In the reactive processes, the follicles generally vary in size and shape. The margins are generally well delineated. There is an admixture of small and large lymphoid elements and the reaction centers generally contain numerous tingible bodies and mitoses. In the lymphomas, (nodular) the follicles are generally round to oval and not sharply outlined. There is generally a paucity of phagocytes and mitoses. The nodules are generally monomorphic.

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The changes typically seen in luetic lymphadenitis include capsular and pericapsular thickening with extensive fibrosis and infiltration by numerous chronic inflammatory cells including many plasma cells. There is a diffuse plasma cell proliferation and a proliferation of blood vessels with endothelial swelling. The blood vessel walls are infiltrated by chronic inflammatory cells including numerous plasma cells. The follicles are reactive with enlarged active reaction centers.

The changes seen in this lymph node are not diagnostic of luetic lymphadenitis, but on the basis of the clinical history and the specific changes within this lymph node the diagnosis of luetic lymphadenitis seems to be a valid conclusion. There was no other evidence of recurrent Hodgkin's disease.

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CASE OF THE MONTH

CASE 29

1977 - Case #5
SPRH A76-316

HISTORY: This stillborn male infant was the product of a 23 year old multigravida (32 weeks gestation) who had no complications of pregnancy and no history of trauma or drug abuse. Her previous two pregnancies were uneventful and gave rise to two, normal, term male infants. Her VDRL was unreactive.

Postmortem examination revealed a 1,090 gram macerated male infant measuring 38 cm. from heel to crown and 28 cm. from crown to rump. The ears were devoid of cartilage. There was absent nipple tissue and the testes were descended into the scrotum bilaterally. There were no missing members or congenital defects. Amniotic bands were absent. The placenta weighed 220 grams and was grossly normal. The umbilical cord was 41 cm. and laterally inserted on an otherwise unremarkable placenta. The umbilical cord had a normal caliber and had a cross sectional diameter of 1.8 cm. except at the region of the fetal insertion where it was markedly firm and had a cross sectional diameter of 0.8 cm. This area of narrowing involved 2 cm. of the cord. The remainder of the postmortem examination was within normal limits and revealed a patent ductus arteriosus and foramen ovale.

Microscopic: Sections from the grossly narrow portion of the umbilical cord reveal thickened vessels with a diffusely hyalinized media. The arterial and venous lumens are markedly narrowed. The interstitial mesenchymal tissue is replaced by slightly edematous fibrous tissue.

DIAGNOSIS: Stricture of the umbilical cord.

DISCUSSION: Constriction of the umbilical cord has been reported in 15 cases in the last century with few authors presenting more than 1 case. Dohrn (1) reviewed the literature in 1861 and reported on 85 cases of umbilical cord torsion. Constriction was present in some of these cases. The first case reported of constriction is uncertain, but according to Dohrn, it was described by Burdack (2) in 1758 in conjunction with torsion.

Constriction of the umbilical cord is frequently associated with excessive torsion. However, in this case, localized constriction alone was present with accompanying vascular stenosis. As presented in the literature, the constriction usually involves the first two or three cm. of the umbilical cord at the fetal end as a solitary defect. Two cases involving the placental end (3,4) and two cases involving multiple sites have been reported (3,4). The presence or absence of amniotic bands has not been mentioned. In two cases of umbilical cord constriction, living full term infants were delivered(5). Constriction of the umbilical cord involving a solitary twin has been reported (3).

PS 7263

Theories regarding the etiology of constriction have been postulated. Edmonds (6) proposed that the phenomonem was a postmortem event secondary to hypoxia. The fetal end, being the furthest from the placental oxygen supply, degenerated. This theory is erroneous for several reasons: it does not explain the occurance of constriction at other locations, albeit rare: living births; or the low incidence of constriction vs. the high incidence of maceration. The consistent finding of only a few cm. involvement is likewise incompatible with this theory since progressive changes would be expected with longer segments of cord involvement being reported.

Torsion of the cord is also unlikely as the cause of this condition. When a pliable cord is anchored at 2 separate planes, and one plane representing the fetus, is rotated, the result is a twist or coil midway between the two planes. The greatest tension, however, is exerted at the points of attachment, but this does not explain the relative infrequency of placental end involvement as compared to fetal end involvement. Constriction unassociated with torsion has frequently been observed as in this case. Some authors claim that its absence is merely the result of postmortem reversal of the area of torsion. An area of stricture is predisposed to torsion, and, torsion is probably a result and not a cause.

The possibility of arteritis secondary to an infectious agent as a causative factor, as proposed by Browne, (7) is unlikely. No microscopic signs of inflammation are present.

Umbilical cord stricture in this case, as in others, remains a mystery. That it can affect one infant in a set of identical twins and not the other, considerably lessen the probability of a genetic factor. Loss of Wharton's jelly in a strictured area may represent mucoid degeneration as described by Bergman, but, as Perrin has demonstrated, it is usually accompanied by calcification and is a diffuse phenomena unlike a solitary stricture.

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1977 - Case #7
Mpls. CHC
77S-109

CASE 30

CASE OF THE MONTH

CLINICAL HISTORY: This 7 year old white male was referred for staging and treatment of Hodgkin's Disease. Several weeks prior to admission he had developed a transient rash, sore throat, and persistent left cervical adenopathy. A cervical node biopsy was interpreted as malignant lymphoma, probably Hodgkin's disease. He was in otherwise good health with no significant past medical history and an unremarkable physical exam. During his hospitalization, before laporatomy, asymptomatic bilateral inguinal and right cervical adenopathy developed. Inguinal node biopsy demonstrated benign hyperplasia. Laporatomy was deferred and the left cervical node was excised.

Laboratory data included: wbc 16,000 with 36% lymphs, 52% PMN's, 10% bands, 10% eos, 1% basos; hgb 11, MCV 79, MCHC 33, platelets 318,000, sed rate 70, retic count 1.5% and serum copper 183 (normal 75 to 145). The chest x-ray, IVP and skeletal survey were normal.

PATHOLOGY: The left cervical lymph node measured 4.2 x 2.2 x 2.4 cm. The cut surfaces were pale red with yellow mottling of the central areas. Microscopic sections demonstrate a heterogeneous pattern. There are large, confluent areas with effacement of sinuses and follicles by a diffuse infiltrate of lymphocytes, plasma cells, and scattered eosinophils. In some areas plasma cells are abundant. A few, large lymphocytes with single, vesicular nuclei and prominent basophilic nucleoli are seen but Reed-Sternberg cells are absent. The follicles are variable in structure. Many are enlarged and show typical reactive changes. A few are small and demonstrate central, sclerotic capillaries and concentric lamination of follicular center cells. Small vessels with thickened fibrotic walls are prominent in many sections.

DIAGNOSIS: Giant lymph node hyperplasia, benign, plasma cell variant.

DISCUSSION:[1] In 1956 Casselman et al reported a small group of asymptomatic patients with large, benign, mediastinal lymph nodes which were thought to resemble thymomas. These lesions have since been described under several designations including lymphnodal hamartoma, follicular lymphoreticuloma, angio-follicular mediastinal lymph node hyperplasia, angiomatous lymphoid hamartoma, and benign giant lymphoma. Although approximately 70% of lesions are situated in the mediastinum they have been described in the neck, axilla, retroperitoneal space, mesentery, and rarely in the lung parenchyma and gastric wall. All cases contain lymph follicles and usually one of two histological patterns, hyaline vascular or plasma cell, predominates.

The hyaline vascular pattern comprises 80-90% of all cases. It is characterized by a variable number of lymphoid follicles with small centers that are radially penetrated by capillaries. Some of the penetrating capillaries are ensheathed by hyalinized collagenous tissue. The follicular center cells may be flattened and concentrically layered, thus assuming a squamoid appearance. The interfollicular

areas demonstrate capillary proliferation with variable, perivascular hyaline fibrosis, effacement of sinuses, and a heterogenous cell population of lymphocytes, immunoblasts, plasma cells and eosinophils. Remnants of normal architecture, peripheral sinuses and normal follicles, are seen in more than 60% of cases. On gross exam they present as a single, rounded mass measuring from 1 to 16 cm. in diameter. Adjacent lymph nodes are often enlarged and occasionally exhibit the hyaline vascular histology. Sinusoidal dilatation, plasmacytosis and an occasional hyaline follicle may also be seen in adjacent nodes.

The plasma cell pattern is found in 10 to 20% of cases. The defining feature is the presence of sheets of mature plasma cells in the interfollicular areas. An occasional reticular lymphoblast or immunoblast may be seen. The lymphoid follicles are normal sized or slightly enlarged and demonstrate hyperplastic, reactive centers with mitotic figures, nuclear fragments, histiocytes, and lymphoblasts. Hyalinization or prominent vascularization is absent. Remnants of normal lymph node architecture are present. The gross specimen measures from 3 to 11 cm. in diameter and is comprised of a mass of discrete lymph nodes.

Hybrid forms do occur. In some plasma cell cases a variable portion of the follicles are of the small hyaline vascular type. A few hyaline vascular lesions may harbor many plasma cells or large follicular centers.

Clinically the two variants are quite similar. The patient age range for both includes the first to the eigth decade. There is no sex predilection. They usually present as a rounded mediastinal or hilar mass on x-ray. About 1/3 of the intrathoracic lesions produce symptoms due to compression of the tracheal-bronchial tree. If followed radiographically for extended periods of time they show very minimal or no enlargement.

The plasma cell variant differs in that up to 50% of patients demonstrate a mild normochromic normocytic anemia, an elevated sed rate, hypergammaglobulinemia, and hypoalbuminemia. Other, less frequently encountered, clinical and laboratory abnormalities include: fever, diphoresis, fatigue, hypotransferrinemia, leukocytosis, splenomegaly, thrombocytosis, hyperfibrinogenemia, elevated alkaline phosphatase, elevated serum copper, and elevated ceruloplasmin.

The etiology of giant lymph node hyperplasia is unknown but the character of the histology suggests a chronic inflammatory response to an antigenic or an infectious agent. The associated laboratory abnormalities are also seen in chronic inflammatory conditions. It has been postulated that the two histological varience reflect differences in host response to identical etiological agents.

Other entities in which enlarged nodes with follicles may be found include Hodgkin's disease, nodular lymphoma and rheumatoid arthritis. In Hodgkin's disease Reed-Sternberg cells are present, and vascular, hyalinized follicles are absent. Hyaline follicles or plasma cell sheets are not present in nodular lymphoma. Rheumatoid lymph nodes contain PMN's and are seen in patients with generalized adenopathy, rheumatoid factor, and arthritis. Additional, differential consid-

erations include thymoma and immunoblastic lymphadenopathy. Thymomas rarely contain Hassal's corpuscles, which may be confused with hyaline vascular follicles, and lack inflammatory cells and capillary proliferation. Cases of immunoblastic lymphadenopathy demonstrate generalized lymphadenopathy, hepatosplenomegaly, and hemolytic anemia. Histologic features include: an abundance of immunoblasts with a relative paucity of lymphocytes; prominent, aborizing small vessels that are thin walled and lack hyaline sclerotic changes; and intercellular deposition of amorphous, eosinophilic material.

The giant lymph node hyperplasia exhibits benign behavior and has not been linked with mortality. Surgical excision is curative. Associated clinical, laboratory, or hematological abnormalities return to normal shortly after complete excision.

Case submitted & prepared by:

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PAUL-RAMSEY HOSPITAL
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CASE 31

1977- Case #8
SPRH

CASE OF THE MONTH

CLINICAL HISTORY: The patient was a term female infant, who shortly after delivery was noted to have a mass lesion protruding from her oral cavity. This mass was pedunculated and lobulated and was attached to the anterior portion of the superior maxillary alveolar ridge. Several days after delivery, this mass was excised. On gross examination, this mass was pinkish-tan in color, measured up to 2.7 cm. in greatest dimension, and was rubbery to palpation.

MICROSCOPIC DESCRIPTION: The lesion was well circumscribed and was collared by histologically unremarkable stratified squamous keratinizing epithelium. The central portions displayed numerous solid and irregularly shaped nests which were composed of large polygomal cells. These cells displayed eosinophilic cytoplasm which was granular in character. Numerous small vascular channels were identified separating occasional nests of the eosinophilic, polygomal cells.

DIAGNOSIS: Granular cell myoblastoma (congenital epulis).

DISCUSSION: Granular cell tumors are usually solitary lesions (however, approximately 8% of cases are multiple) which occur most commonly on the tongue. Approximately 40% of these lesions are located in that area, however numerous other anatomic regions may be involved including skin, breast, subcutaneous tissue, skeletal muscle, larynx, bronchus, pituitary gland, and gastrointestinal tract.

In the neonatal period, the most common locations for granular cell tumors are the alveolar ridges, especially the anterior portion of the maxillary alveolar ridge. These lesions are usually solid in nature, and have been noted to be up to 4 cm. in greatest dimension. Female infants are for unknown reasons almost exclusively affected. This tumor, like other granular cell tumors, is thought to be derived from Schwann cells. Electron microscopic studies have sited three main similarities between Schwann cells and granular cells, these being: 1. both cell types are surrounded by basal lamina, 2. occasional tumor cell contain axon cytoplasm, and 3. the tumor cells contain granules which are morphologically similar in appearance to those identified in subcutaneous neurilemmomas. However, several authors continue to doubt the Schwann cell origin. These investigators have consistantly failed to identify axons within the granular cell cytoplasm. Also, in contrast to Schwann cells, investigators have failed to identify normal or degenerating myelin.

Occasionally congenital epilus tumors are covered by epithelium which is hyperplastic with irregular proliferation of the rete ridges, and occasionally displays horn-pearl formation. However, these epithelial changes are less frequently observed in infants as compared to granular cell tumors in adults (especially tongue lesions).

Malignant change in granular cell tumors is relatively infrequent. Various authors have estimated the incidence to be between 1 and 2 per cent.

The standard therapy for congenital epilus involves local surgical excision. No figures in literature could be found in regard to recurrence, however, most authors state that it is infrequent.

Case Submitted & Prepared by:

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Pathology Resident

AN EQUAL OPPORTUNITY EMPLOYER

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1977- case #9

CASE 32

CASE OF THE MONTH

HISTORY: The patient is a 35 year old para 3 gravida 3 with a year's history of irregular menses, breast tenderness and right lower quadrant fullness. On physical examination a firm, large right ovarian mass was palpated. The remainder of the examination was unremarkable. Specifically there was no evidence of virilization.

At surgery a 12 x 10 x 8 cm. gray-white smooth right ovary was removed. There was no evidence of torsion. The surface was smooth and firm. Upon cutting, a copious amount of fluid exuded from the surface. An 8 cm. cyst filled with clear fluid, and numerous 3-6 mm. subcortical cysts were present. Diagnosis was made on frozen section.

DIAGNOSIS: Massive edema of the ovary.

PATHOLOGY: Sections of ovary reveal a thin, distinct but unremarkable ovarian capsule. There are occasional follicle cysts, developing follicles and involuting corpora lutea. Beneath the thin rim of cortex the stroma is markedly edematous. Luteinization is not generally present. There are numerous dilated lymphatics and a few scattered foci of lymphocytes throughout the stroma. There is minimal congestion.

DISCUSSION: Although this lesion is probably not rare, only 8 cases had been reported as of 1976, (2). The original report in 1969 described four patients with massive ovarian edema which had been mistaken for a benign stromal tumor on gross examination (1). Massive edema of the ovary assumes importance because of its association with various hormonal syndromes including infertility, menstrual irregularity and virilization, (1,2).

Massive ovarian edema may occasionally present as an acute abdomen or as vague abdominal fullness. In some instances the ovary may be tremendously enlarged weighing up to 2400 grams. As in this instance, nearly every reported case involves only the right ovary. The contralateral ovary is generally normal. No explanation for this unilaterality has been offered.

The typical microscopic appearance consists of a compact cortical stroma with edema of the inner cortex and medulla. Stromal luteinization is common. Congestion, thrombosis and necrosis are rare. Tissue mast cells are often increased.

The edema is generally thought to result from partial torsion of the ovarian pedicle. However, torsion is not usually described at surgery and there is rarely evidence of extensive vascular congestion or necrosis. The role of torsion in the pathogenesis of this lesion is therefore somewhat in question. Regardless of the etiology of the edema there does appear to be a correlation between the stromal edema and increased hormonal activity and luteinization.

In summary, this ovarian pseudotumor may clinically mimic a malignancy because of its cryptic hormonal activity and unusual size. Although probably not rare, it has not received much attention in the literature. At frozen section, diagnosis is possible if the pathologist is aware of the condition.

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MEDICAL CENTER
PAUL, MINNESOTA 55101

CASE 33

CASE OF THE MONTH

A 54 year old Caucasian male complained of two skin lesions on the left lateral neck, present "for years". The first of these, both clinically and histologically, proved to be a seborrheic keratosis. The second, which had been increasing in size, measured 1.8 cm. in diameter and was elevated and rubbery. The surface was smooth and dull gray.

Histologically, this nodular lesion is located in the dermis, encroaching upon the epidermis, but separated by variable amounts of collagen. At no point is there epidermal invasion. A pilosebaceous collarette and a mixed lymphocytic-plasmacytic infiltrate are found adjacent to the blunt borders. Variable solar elastosis is apparent in the uninvolved dermis. The tumor itself is composed of three pleomorphic components, elongate fibrocytic cells, histiocytes and multinucleate giant cells in a haphazard, whorling, dense, pattern. Mitoses are frequent, and often bizarre. The fibrocytic cells are streaming, and occasionally suggestive of herring-bone pattern. Their nuclei are vesicular to hyperchromatic, and fragmented, eosinophilic cytoplasm streams from the polar ends. The histiocytes are plump with lacy cytoplasm and vesicular nuclei with prominent nucleoli. Bizarre tumor giant cells with multiple nuclei, often fused together, are common. Small capillary vessels are strewn at intervals throughout the lesions.

Atypical fibroxanthomas have been described in the literature since 1949, under a variety of names, including fibrosarcoma, paradoxical fibrosarcoma, pseudosarcomatous reticulohistiocytoma, and others. Clinically, atypical fibroxanthomas present as solitary, well-circumscribed, firm, ulceronodular lesions. Frequently, the clinical differential diagnosis includes basal cell epithelioma, squamous cell carcinoma and pyogenic granuloma. The lesion need not be ulcerated; Fretzin and Helwig reported an incidence of ulceration in 36%.

Presentation occurs in two subpopulations, depending upon age and anatomic distribution of the tumor. Lesions of the head and neck occur in an age group with a median of 69 years. This distinctly represents the majority of cases, 109 of 140 in Fretzin and Helwigs' study of 1973. The remaining cases occur on the trunk and limbs in a group with a median age of 39. The actual age range of this second group is broad, 6-88, but it is significant to note that atypical fibroxanthomas of the subpopulation generally occur on unexposed body areas. The male to female ratio is 3:2, but appears to be significant only in the older age groups.

Characteristically these lesions are asymptomatic. The patient is not likely to notice pain or pruritis, and only infrequently, bleeding (26%). Most of the tumors are small, less than 2 cm. in diameter, however massive cases have been reported, measuring greater than 2 cm. in diameter, however massive cases have been reported, measuring greater than 6 cm. The average duration of the lesion prior to surgery is 4-6 months, but may be several years.

Microscopically, the lesion is limited to the dermis, and has blunted, pushing borders, frequently surrounded by a pilosebaceous collarette and adjacent solar elastosis of variable severity. Occasionally, there is a peripheral lymphocytic infiltrate. In non-ulcerated lesions, the tumor may be separated from a hyperkeratotic or parakeratotic epidermis by a collagen band. There is rare penetration to the subcutaneous tissue but never into the deeper soft tissues.

AN EQUAL OPPORTUNITY EMPLOYER

Within the tumor itself, adnexal structures occasionally remain intact, but are surrounded. There are no reported cases of invasion of cells along nerve sheets or into vascular channels.

The tumor cells, as we have seen in this case, are markedly pleomorphic and consist of three distinct types, elongate fibrocytes, atypical histiocytes, and multinucleate giant cells. All three elements should be present within thelesion for diagnosis. The fibroblastic spindle cells generally have vesicular or hyperchromatic nuclei. Their cytoplasm may stream from the polar ends of the cells. The histiocytes are polyhedral with vesicular nuclei, prominent nucleoli, and frequently vacuolated cytoplasm. The most variable component is the multinucleate giant cell, which may present as Touton-type or bizarre tumor types with fused nuclear masses. Mitotic figures are a prominent feature of these lesions and bizarre mitoses are not at all unusual. Mixed inflammatory responses and granulation-type tissue with neo-vascularity are seen within ulcerated lesions.

Electronmicroscopy has been performed on many of these lesions, but has generally failed to find pathognomonic features. Langerhans giant cells have been found by some researchers (Alguacil-Garcia et al).

Radiation, when attempted in the early cases, was unsuccessful in producing regression, and the current recommended therapy is surgical excision.

In a survey of 351 reported cases, Starink et al reported a recurrence rate of 25, or 7%. Twenty-two of these had one recurrence. Two recurrences occured in two patients and one case had three recurrences.

The overall prognosis is excellent. No deaths have been reported, however two cases of metastases are in the literature (Fretzin and Helwig, 1973, and Jacobs, et al, 1975). Several other authors feel these cases do not represent true atypical fibroxanthomas, but may be malignant fibrous histiocytomas.

The differential diagnosis is broad, including fibrosarcoma, dermatofibrosarcoma protruberans, amelanotic melanoma, malignant fibrous histiocytomas, and pleomorphic squamous cell carcinoma. These can generally be eliminated because of a monomorphic pattern, presence of invasion, or sequestration in the deeper soft tissues.

Case submitted by Jack Uecker, M.D.

Case prepared by Laurel Krause, M.D.

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ST. PAUL-RAMSEY HOSPITAL
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CASE 34

1977 Case #11
Midway Hospital
077-3776

CASE OF THE MONTH

This 25 year old woman first developed swelling of her left knee two years prior to admission. Several aspirations of the knee joint had been performed during that two year period but the patient had not noted any significant improvement. On physical examination there was atrophy of the quadraceps muscle and thickening of the entire synovium. There was marked limitation of flexion of the left leg. An arthrogram was reported as "inconclusive" by the radiologist but the orthopedic surgeon felt that the findings were suggestive of "villous synovitis". A synovectomy was performed.

Gross tissue - the specimen consisted of approximately 80 grams of reddish-brown to golden yellow tissue fragments which varied in texture from soft to rubbery. In several areas a distinctive villous configuration was evident. (See gross photograph).

Microscopic - multiple sections of synovial tissue show a markedly variable appearance from area to area. In many areas the synovium is replaced by granulation tissue admixed with large numbers of histiocytes. However, in other areas the synovium is thrown into villous folds and within these villous projections there are massive numbers of histiocytes, many with clear cytoplasm, together with multinucleate giant cells and moderate numbers of plasma cells and lymphocytes. Throughout all fragments of the tissue there is a generous amount of golden brown pigment which stains positive for iron. (See enclosed photograph).

Diagnosis: Pigmented villonodular synovitis.

Discussion: Pigmented villonodular synovitis (PVS) is a benign proliferative disease of synovial tissue. It is of cryptogenic nature and may be either diffuse or localized and nodular. This lesion is noted for its locally invasive capabilities and it shows a propensity for recurrence after surgical excision. Although the first case was probably reported by Chassignac in 1852 as a case of "cancer of the tendon sheath" the term pigmented villonodular synovitis was suggested by Jaffe and colleagues in 1941.

The finger and the hand are the most commonly affected sites and in those locations the lesion is most frequently called "giant cell tumor of tendon". In these locations the lesion is usually of the nodular type rather than diffuse or villous. The most common site for the villous variant is the knee joint. Other locations include the ankle joint, hip joint, tarsal and carpal joints, elbow joint and shoulder joint. This lesion is monoarticular. Occasional cases have been reported in nonarticular locations. The etiology of this condition is controversial. Trauma is the most frequently mentioned predisposing factor but others have suggested the possibility of this entity being a low-grade malignancy. Infectious agents have also been considered as the cause of this condition. Viral-like inclusion bodies within synovial endothelial cells have been reported in PVS.

AN EQUAL OPPORTUNITY EMPLOYER

The differential diagnosis of this condition includes synovial sarcoma and granulomatous inflammation of the synovium. In particular, this lesion must be differentiated from synovial sarcoma since PVS, although it may be locally aggressive and recurrent, is a benign lesion.

Jack Uecker, M.D.

CASE 35

1978 - Case #1

ST. PAUL-RAMSEY MEDICAL CENTER
ST. PAUL, MINNESOTA 55101

CASE OF THE MONTH SPRMC-078-2376

HISTORY: This 60 year old white male has been followed 9 years for a macerated, scaling, papillomatous eruption of the scalp, neck, axillae, and groins. Family history is unavailable. Various therapies including soaks, topical steroids, systemic steroids, antibiotics, and Dapsone have resulted in only temporary improvement. Left and right axillary skin excisions and split grafts were performed in 1971 and 1972 respectively. At this time he is admitted for excision and split-thickness grafting of the groin skin.

GROSS: The specimen consists of 13, irregularly shaped fragments of skin and underlying tissue which range from 3 cm x 2 cm x 1 cm to 12 cm x 7 cm x 1.5 cm. in greatest dimensions. The epithelial surface of all fragments is covered by numerous, small, closely arranged, papulo-nodular structures which measure 2 mm. in diameter and 2 mm. in height.

MICROSCOPIC: The epidermis demonstrates numerous, confluent, suprabasal bullae. Dermal papillae, lined by a single layer of basal cells, protrude into the bullous cavities. Many, detached, individual cells and cell groups from the stratum malpighii lie within the cavity spaces. Much of the detached stratum malpighii shows a decrease or loss of intercellular bridges resulting in narrow slits between cell or acantholysis, respectively. These detached portions thus exhibit a "delapidated brick wall appearance". Some epithelial cells have an eosinophilic, homogeneous cytoplasm suggesting premature keratinization and resemble the grains of Darier's disease. Corps ronds are not seen. The dermis contains a sparse, patchily distributed plasma cell and lymphocyte infiltrate.

DIAGNOSES: Familial benign pemphigus (Hailey and Hailey).

COMMENT: Familial benign pemphigus is a rare, dominantly inherited disease characterized by recurrent, localized eruptions of vesicles and bullae on areas exposed to friction, ie. groin, neck, and axilla. Clusters of small vesicles erupt on normal or reddened skin. Initially clear, the vesicles soon become turbid and eventually rupture forming erosions and crusts. The lesions extend peripherally, may assume a circinate configuration, and may exhibit central healing or soft, flat vegetations.

Onset is in adolescence or in the early adult years. Long remissions are common and the severity of the disease usually lessens after 50. Antibiotics are usually successful in controlling exacerbations. Topical steroids and Grenz radiation may be useful adjuncts. Skin grafting should be considered for severe, localized lesions.

The condition is irregularly dominant and generations bearing the gene may be asymptomatic. A positive family history is obtained in only 60-70% of cases. The responsible gene results in poor cellular adhesions with a tendency to acantholysis exacerbated by friction, heat, ultraviolet radiation, and of primary importance, infections, both bacterial and fungal. The basic defect is thought to be an abnormal synthesis or maturation of the tonofilament-desmosome complex or the intercellular substance.

Early lesions show small suprabasal lacunae which eventually coalesce to form vesicles and bullae. Familial benign pemphigus, Darier's disease and pemphigus vulgaris all demonstrate epidermal acantholysis, suprabasal

clefts, and protruding dermal papillae. In Darier's disease, however, the suprabasal separations are smaller and rarely attain the size of bullae. Acantholysis is less prominent and usually limited to the suprabasal area. Dyskeratosis, characterized by corps ronds and grains is pronounced. Pemphigus vulgaris exhibits acantholysis restricted to the suprabasal area. The detached epidermis therefore lacks the "delapitated brick wall appearance" seen in benign familial pemphigus. Dyskeratosis is absent and eosinophils are often present in the bullous cavity. The acantholytic process of familial benign pemphigus halts abruptly at the adnexal structures, while acantholysis in pemphigus vulgaris will usually involve the adnexal. Acantholytic suprabasal clefts may also be seen in transient acantholytic dermatosis and occasionally in solar keratosis. Transient acantholytic dermatosis may closely mimmic familial benign pemphigus or pemphigus vulgaris. Clinical presentation and history are required to make the diagnosis.

Prepared by Dale Odell, M.D.

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ST. PAUL-RAMSEY MEDICAL CENTER
ST. PAUL, MINNESOTA 55101

COIF 36

CASE OF THE MONTH

CLINICAL HISTORY

C.T. is a 63 year old Cambodian male who presented to the Emergency Room complaining of a rash on his abdomen, arms, and legs for the past three months. Further questioning revealed a 20 year history of intermittent generalized rash, the last episode occurring in Vietnam several years ago.

Physical exam showed a diffuse macular rash with both focal nodular and ulcerated areas, along with facial edema. Neurologic exam demonstrated decreased sensation in the fourth and fifth fingers of the right hand and decreased vibratory sensation in both lower extremities.

Chest x-ray, CBC, platelets, U/A, thrombin time, protime, and G-6-PD were all within normal limits. Sedimentation rate was 20 mm/hour (Wintrobe). The total LDH was 300 I.U. times two on SMA-12/60 (normal = less than 225 I.U.).

A skin biopsy was performed.

PATHOLOGY

The tissue consisted of a 3mm. punch biopsy of grossly atrophic appearing skin. The subcutaneous tissues were pale tan on cut section. Microscopic sections reveal an atrophic but normally maturing stratified squamous epithelium overlying a thin zone of normal dermis. The deeper dermis contains a dense infiltrate of foamy histiocytic-like cells which extend into the subcutaneous tissue. Cystic structures are present which are filled with fibrillary material on H & E. All of the normal skin adnexal structures are effaced. AFB (Z-N) stain shows the presence of multiple acid-fast bacilli within the histiocytes (Lepra-cells) and the cystic structures and fibrillary material are seen to be dense aggregates of mycobacteria (globi).

DIAGNOSIS (078-4036 SPRH)

Skin, back (punch biopsy) - Lepromatous leprosy.

DISCUSSION

Five discrete forms of leprosy are recognized histologically: tuberculoid (TT), borderline-tuberculoid (BT), true borderline (BB), borderline-Lepromatous (BL), and lepromatous (LL). These probably represent the spectrum of a single disease process, the histologic picture reflecting the degree of cellular immunity present. This is borne out by the fact that the histology can progress from TT to LL with time and if no treatment is given. Experimental evidence (in mice) has demonstrated an initial immunologic response which weakens and eventually disappears with time. The loss of immunity can be accelerated by injection of antigen, implying an "overwhelming" of the system with breakdown as the ultimate outcome.

EQUAL OPPORTUNITY EMPLOYER

Case of the Month
1978 - Case #2

The histopathology ranges from a nonspecific granulomatous inflammatory reaction with rare stainable organisms seen in the dermis and involving peripheral nerves (TT), to total effacement of skin structures and nerves by diagnostic cells (lepra cells and globi) which contain massive numbers of mycobacteria (LL). The borderline lesions represent the intermediate forms between the two histologic (and immunologic) extremes.

Clinically, leprosy presents as a nonspecific skin rash which may spontaneously heal in its "indeterminate" form but then progresses over a long period of time to erythematous macules, nodules, and ulcers. The initial lesions are usually single, becoming confluent and symmetrical as the disease progresses. Reactive lesions (erythema multiforme, Lucio phenomenon) may also occur spontaneously or during treatment with acute leukocytoclastic vasculitis as the histologic picture.

Treatment currently revolves around the use of Dapsone but recent articles are stressing multiple drug therapy with some initially encouraging results from the use of Rifampicin.

Leprosy, previously thought to be extremely rare in the U.S., should be added to the differential diagnosis of any "fungal" skin lesion that has repeated negative KOH preps and cultures along with non-healing after appropriate fungal therapy. Endemic areas of the U.S. include: Louisiana, Florida, Texas, and Hawaii; outside the U.S. endemic areas include Mexico, Central and South America, Far East, India, Africa, and European and Middle East countries that border on the Mediterranean Sea. Birth or long term residence in any of those areas should increase the index of suspicion of leprosy in patients with chronic dermatoses.

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Gross Photography: Department of Dermatology, St. Paul-Ramsey Hospital

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