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Dermatomyositis

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I. DERMATOMYOSITIS

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Dermatomyositis is a nonpurulent polymyositis with inflammation and degeneration in the skin and muscles. Due to its protean manifestations resulting from involvement of nearly all organs and tissues with varying intensities, the syndrome is ill-defined.

Case I

, an electrical assemblyman and a Navy veteran, was 20 years old in the fall of 1946 when he noted progressive stiffness, pain and weakness in the muscles of the shoulders and arms. Soon he was unable to tie his shoes and could not climb stairs. Because of recurrent throat infections the tonsils were removed. The disease progressed rapidly; three months after the onset he had to quit work and the following summer he was a complete invalid.

Associated with the onset of muscular symptoms, blotchy erythematous and violaceous rash appeared on the eyelids, forehead, elbows and hands. Soon small ulcerations appeared over the bony prominences, and the face, neck, and thighs showed atrophy, telangiectasia and pigmentary changes in the skin. He had difficulty swallowing fluids because of regurgitation through the nose. The jaw muscles became weak, and the mouth could be opened only partially. The heart was clinically enlarged, and systolic and diastolic murmurs could be heard over the apical area.

The patient was hospitalized repeatedly for prolonged periods from March, 1947, until his demise in October, 1950. His condition became progressively worse. All muscles of the extremities, shoulders and hips became atrophied, and the patient was completely incapacitated and unable even to feed himself. There were contractures of the elbows and knees, ulnar palsies and foot drop. The muscles of the chest wall were affected and soon there was little motion of the intercostals with full inspiration, resulting in dyspnea, difficulty raising secretions, and consequently, frequent attacks of bronchopneumonia.

Repeated laboratory studies revealed a persistent hypochromic normocytic anemia, borderline leukopenia (4000 to 6000 cells per cu. mm.) normal differential counts, and marked elevation of the erythrocyte sedimentation rate (100 to 120 mm. in one hour). Urinalyses were normal except for mild glycosuria during therapy with PABA. Urinary excretion of creatinine varied from 0.4 to 0.7 Gm. during a 24 hour period. Serum protein and albumin-globulin ratios were normal. Basal metabolic rate was minus 1%, and the blood cholesterol level was 137 mg%. The results of other chemical determinations on the blood were normal. Bacteriologic studies of the cutaneous ulcers revealed hemolytic staphylococcus aureus, coagulase positive, but blood cultures were always sterile. X-rays of the chest during afebrile periods revealed obliteration and thickening of the costophrenic sinuses, at other times the typical findings of bronchopneumonia. There was generalized demineralization of the bones and calcifications in the soft tissues of extremities and buttocks. Muscle biopsy showed a chronic degenerative myositis consistent with dermatomyositis.

Therapy consisted of antibiotics administered orally and parenterally for long periods, vitamin E, androgens in the form of testosterone and metandren, a high protein diet and other measures for general care and relief of symptoms. Administration of paraaminobenzoic acid secured a temporary feeling of well-being but resulted in sodium retention and beginning cardiac decompensation. The local ulcerations were treated with various ointments and attempts to relieve pressure, but they never healed to any extent.

During brief remissions, the patient was given physiotherapy, but relapses ensued with evidence of toxemia and recurrent abscesses in the muscles of the shoulders and thighs. The patient's condition progressively degenerated, and he became cachectic despite attempts to sus-

tain nutrition. Terminally he developed abdominal pain, distention and ileus, and expired after aspirating copius quantities of regurgitated fluid.

At post-mortem examination there was generalized peritonitis with numerous yellowish-green necrotic patches studding the abdominal peritoneum. Many of these areas were calcified as were several of the mesenteric lymph glands. Several centimeters above the cardia was an oval ulceration extending to the serosa but not perforating. In the prepyloric area of the stomach, in the pylorus and duodenum were similar irregular, ragged ulcers, acute and chronic, extending to and penetrating the serosa. Fibrous tags walled off pockets of greenish purulent material under the left lobe of the liver. There was evidence of bronchopneumonia bilaterally, and bands of adhesions bound the lungs to the thoracic walls. The heart did not appear dilated or hypertrophied, the valves were normal, and the coronary vessels patent.

Case II

, a 52 year old teacher, was a patient of Dr. Henry Michelson who authorized this report. At ten years of age she developed an acute protracted illness with swelling, stiffness and pain in the arms and associated cardiac involvement. She recovered after prolonged bed rest but had residual contractures and stiffness of the arms. Apparently there were no detectable cardiac sequelae. She remained well until 20 years later when she again became ill with symptoms of generalized weakness, stiffness and soreness of the muscles, fever, and erythematous eruption on the face and painful necrotizing lesions over the bony prominences of the knuckles, elbows and knees. Following symptomatic therapy, enforced rest and extraction of several devitalized teeth, her general condition improved. The eruption faded, the lesions over the knuckles healed with thin scars, but the muscle mass of the arms and shoulders was markedly diminished.

Mild symptoms recurred in March, 1951, and progressively increased in intensity. By June of that year she had marked stiffness and soreness of the muscles, aching and drawing pains in the arms and shoulders, stiffness of the jaws making mastication difficult, and diffuse edema and flushing of the face. There were thin violaceous scars overlying the knuckles, and marked atrophy of the muscles of the neck, shoulders, arms and hands, with limitation of motion of these parts.

Histologic examination of the skin showed thinning and atrophy of the epidermis and basophilic degeneration and edema of the collagen. Microscopic sections of the deltoid muscle showed focal areas of necrosis where the bundles were pale staining and homogeneous, with vacuolization and fragmentation. Surrounding these areas was a moderate lymphocytic infiltrate.

Laboratory studies revealed no abnormalities in the red and white blood cell counts or hemoglobin determinations. The erythrocyte sedimentation rate was moderately increased (34 to 50 mm. in one hour). Repeated urinalyses showed transient albuminuria and occasional pyuria and bacilluria. The 24 hour creatinine excretion was 1.35 Gm. on one determination, 0.8 Gm. on another. The serum albumin was 3.7, the globulin 2.5 Gm%. Three determinations of the basal metabolic rate showed an average elevation of 20%. The LE clot test (Gonyea method) was negative. Roentgenograms showed mild diffuse decalcification of the bones, particularly in the hands. The initial electrocardiogram was normal except for sinus tachycardia.

Following hospitalization therapy was instituted with adrenocorticotropin, 50 to 100 mg. daily, and aureomycin, 1 Gm. daily. Initially there was improvement in her condition; the muscle pains subsided and the facial erythema and edema diminished. Decreases in dosage of ACTH was followed by mild recrudescences of muscular symptoms and the erythematous rash. After one month, cortisone per os was substituted for the injections of ACTH. Steroid therapy was continued for three months, then discontinued without subsequent exacerbation of symptoms.

Initial examination of the heart was negative. The blood pressure was elevated, 150 mm. Hg systolic, 100 diastolic. Symptoms of coronary insufficiency occurred with increasing frequency however, with oppressing precordial pains radiating into the left arm and mild dyspnea and cyanosis following minimal physical exertion. Administration of nitroglycerine, vascular dilators, oxygen and analgesics afforded considerable relief of these symptoms. Serial electrocardiograms showed progressive changes, elevation of the ST segments and inversion and deepening of the T waves.

After prolonged hospitalization and therapy there were no apparent signs of activity of the dermatopathic process, and passive exercises were begun. At first mild exercises were followed by fever, elevated pulse rate, aching and swelling in the muscles of the extremities. Later she was able to tolerate a more active program of physical therapy without experiencing any relapse of symptoms.

The patient was then transferred to another institution for continuation of physical therapy. She regained considerable strength and was able to push herself up out of a chair and to climb a few stairs. She left the hospital and had resumed, to a limited degree, her previous teaching duties. In November, 1952, she entered a hospital to have several devitalized teeth extracted. Peripheral vascular collapse occurred during induction of Anesthesia (intravenous sodium pentothal), and she expired a few minutes later.

At post-mortem examination, performed by Dr. Ellery James of St. Paul, a fresh thrombus was found occluding the proximal portion of the anterior descending branch of the left coronary artery. Distally the lumen was occupied by an old pale thrombus, and the anterior portion of the interventricular septum showed a hemorrhagic area of infarction superimposed upon thin gray scar. Microscopically the heart showed recent infarction with old myocardial fibrosis, and severe atherselerosis of the coronary arteries. The muscles of the arms, legs, and shoulder girdle were completely atrophied and replaced by dense yellow-gray fibrotic strands. Muscles of the pectoral areas and abdominal wall were grossly normal. Microscopic sections of limb muscles showed complete replacement of muscle bundles with fat and fibrotic scars. The gastrointestinal tract was normal.

The first recognized report of this condition was made by Wagner[1] in 1863. Unverricht[2] 1887, termed acute progressive polymyositis a fulminating disease which resulted in degenerative changes in the muscles of deglutition and respiration. Independently Wagner[3] and Unverricht[4] 1887, observed and recorded similar cases, and Hepp[5] named "pseudotrichinosis" a fatal disease which showed muscle degeneration. Unverricht[6] considered the cutaneous changes and muscle lesions of prime importance and proposed the term "dermatomyositis" in 1891. Other designations are recorded in the literature, with a common denominator, myopathy. Senator[7] suggested the term "neuromyositis" for a similar condition with nervous as well as muscle symptoms; Oppenheim[8] called attention to involvement of the mucous membranes and Lorenz[9] pointed out the hemorrhagic tendency in many cases, designating a subgroup "hemorrhagic polymyositis". Subsequently other authors reported cases of dermatomyositis associated with other diseases, either co-existing, related etiologically, or varied by the presence of the latter. Klemperer[10] drew attention to the homogeneous ground substance and classified dermatomyositis along with lupus erythematosus and scleroderma in the "diffuse collagen system diseases". This terminology, though subsequently retracted and refuted by the author, was accepted and perpetuated by others.

Dermatomyositis occurs in both males and females, the former being more frequently affected[11]. Although usually occurring in young adults, it may be seen at any age. Lehmkuhl[12] found in the literature between 1895 and 1928, sixteen cases occurring in children, the youngest being three years old. Karelitz and Welt[13] outlined a description of the disease in children. Demel[14] reported a case of "sclerema of the newborn in the

form of polymyositis" commencing on the second day of life with fatal termination on the ninth day. Two fatal cases with similar involvement of muscles, skin and heart were recorded by Hazel and Hull[15]. Selander[16] considered the disease a rare occurrence in childhood, but Lamb[17] found fifteen percent of the cases reviewed were in children. Careful perusal of the past medical histories in the protocols recorded in the literature often reveals instances of rheumatic-type pains, cramps and other vague complaints which might well indicate the inception of an insidious process not recognized until years later.

Racial predilection is not inferred, since Irgang[18] described two cases of dermatomyositis in negroes, and Bradley[19] reported dermatomyositis with nephritis in a negro child.

The occurrence of the condition does not seem to be seasonal; although Friedman[20] believed that is is more frequent during cold weather, Caballero[21] reported cases occurring in the tropics, and O'Leary[22] believed the onset to show a predilection for the summer and autumn months. Epidemics of dermatomyositis have been reported by Lewy[23], Sick[24] and Curschmann[25].

The disease usually begins with the general symptoms of ill health --- chills, headache, vertigo, listlessness and gastrointestinal disorders. The muscle symptoms may be insidious, first presenting with a sense of heaviness in the limbs, then weakness and stiffness, progressing to drawing and tearing pains. Later the affected muscles become completely incapable of functioning as a result of progressive atrophy. The acute (Unverricht) form of the disease may be explosive, with sudden appearance of erythema and edema of the face, neck and extremities, fever of 104 degrees or higher, muscle pain and stiffness, and prostration. The course may be in one of several directions: fulminating, with death occurring in one or two months, subacute, lasting six to twelve months, or chronic, which may persist for several years. The acute form may pass through intermediate states in the transition to the chronic. The edema of the face becoming hard and infiltrative, producing a masklike expression. The cutaneous manifestations are variable and may assume characteristics of scleroderma, poikiloderma, lupus erythematosus and/or other conditions which will be discussed in detail later. The muscles become fibrotic and atrophic as the edema and inflammation subside, with marked weakness, violent pains and contractures. Death may occur from general asthenia, but generally results from pneumonia or complications resulting from involvement of other organs.

Any muscle or group of muscles may be involved by the inflammation, the proximal parts of the extremities are usually first affected and often immobile while the fingers are yet functional. In a few cases the disease has been limited to only one extremity, or even to a single muscle[26], but is usually bilaterally symmetrical. The involvement was generalized in one half of the cases[27], but most often affects the shoulder girdle, arms, neck and buttocks. Implication of the muscles of the jaw, tongue, soft palate and pharynx result in difficulty opening the mouth, disturbances in speech, yawning and mastication[28]. Difficult and painful swallowing resulting from affection of the musculature of deglutition may be the initial symptoms of the disease or may occur with progression of the process[29]. Regurgitation of food may occur through the nose in addition to inarticulate and nasal speech. Dyspnea, hypoxia, anxiety, asphyxia and aspiration bronchopneumonia result when the diaphragm and other respiratory muscles become fibrotic or atrophic, and the patient is thus unable to raise accumulated secretions or inhaled food particles.

The involved skeletal muscles are swollen, soft and doughy, or firm and fibrous; circumscribed nodules or pseudofluctuation may be present. Palpation of the muscles may be difficult when the overlying skin and subcutaneous tissue is edematous, hard, tensely infiltrated, or sclerotic and calcified.

The inflammation extends into the ten-

don sheaths, producing contractures and contributing to those pains first felt in the joints. Tendon reflexes are decreased or absent, and fibrillary twitchings are commonly observed.

Considerable histologic variation is found; degenerative changes such as vacuolization, loss of striation, hyalinization, fragmentation and atrophy, and variation in staining are often observed in varying degrees. The size of the muscle bundles and the number of the individual fibers varies markedly, and, in the advanced state, the fibers may have disappeared completely, leaving an empty sarcolemma. The most constant alteration is an increase in the number of muscle nuclei, often arranged in a row along the sarcolemma[30], indicating the course of a fiber from which the protoplasm has disappeared.

Edema is often found early and persistently in the perimysium. Loose cellular fibroblastic tissue proliferates between the muscle bundles and fibers; later it encompasses atrophic muscle or replaces it with a fibrous scar. Hypertrophy of the interstitial tissue is also apparent surrounding the blood vessels.

The infiltrate varies quantitatively, consists chiefly of lymphocytes, with monocytes, polymorphonuclear leucocytes, plasma cells and eosinophilic granulocytes, is diffused or arranged around the vessels or in foci.

In summary, in dermatomyositis the muscle undergoes degenerative changes varying in degree after an initial edematous stage. The perimysium proliferates and tends to replace the atrophic muscle fibers. The process is accompanied by some inflammatory reaction, and aggregates of lymphocytes may be found. Freudenthal concluded that the histologic changes in the muscles in dermatomyositis and generalized scleroderma showed no essential difference, and were similar to those found in pituitary hyperthyroidism. Madden and Karon[31] showed that the muscle changes in dermatomyositis are nonspecific, similar changes occuring in rheumatoid arthritis, lupus erythematosus, diffuse scleroderma, rheumatic fever and other disorders, and that muscle biopsies were of little or no value in differentiating these disorders in the presence of similar symptomatology. Pagel and associates[32] noted similarity of the fibrinoid degeneration of collagen fibers in dermatomyositis with those described by Klemperer in lupus erythematosus and suggested allergic mechanisms of the Arthus type in the pathogenesis.

Involvement of the heart is of common occurrence in dermatomyositis, although specific referrable symptoms are not pronounced. Abnormalities are often detected on physical examination and usually suggest a diffuse myocardial process, less frequently functional disturbances of the valves. The time, character, and points of maximum intensity of the murmurs are variable and may even change in the course of an individual case. Low pulse pressures are found in 25%, but signs of decreased cardiac output and congestive failure are less common. But such findings might indicate incidental disease antedating any symptoms referrable to dermatomyositis, particularly in the older patient, and thus present special problems in determining the extent of the myopathic process.

Electrocardiographic changes as a rule consist of rate and rhythm irregularities, low voltage QRS complexes and T waves, inversion of the T waves and prolongation of the PR intervals, suggesting generalized myocardial damage. The heart may appear grossly enlarged, flabby, fibrous, edematous and hemorrhagic, or shrunken and pale[33]. Histologic changes reported in the heart are generally identical with those found in the skeletal muscles but less severe. As a rule the valves and endocardium are not primarily affected, and Aschoff nodules are not observed in these cases.

Splenic enlargement is frequently reported in dermatomyositis, and may be slight or the spleen may even be doubled in size. Regression in degree of enlargement with remission of the systemic process has been noted. The superficial lymph glands are usually normal, but

painfully enlarged glands can occur. However, no specific histopathologic alterations attributable to dermatomyositis have been noted in these tissues. In Urbach's case of pseudoleukemia with dermatomyositis there was a severe involvement of the lymphatic system, and histologically the glands showed marked lymphocytic infiltration.

The bone marrow generally is normal, but inflammatory changes have been noted on several occasions.

Arthritis is occasionally present, the involvement limited to a few joints or generalized. Increase in the amount of synovial fluid and thickening of the synovia have been reported, but serofibrinous pleuritis, pericarditis and peritonitis occur more frequently, with hemorrhages, thickening and lymphocytic infiltrations.

Involvement of the respiratory system is generally a secondary complication which appears late in the course of the disease and accounts for the immediate cause of death in most of the cases. Bronchopneumonia and asphyxiation occur as the result of degeneration of the respiratory muscles or of passage of aspirated and regurgitated food and liquids into the bronchi via the trachea subsequent to impairment of the muscles of deglutition. But primary affection of the bronchi and parenchyma is possible, with catarrhal exudates, erosions, ulcerations and necrosis, and vascular lesions similar to those found in other tissues.

Symptoms referrable to the digestive canal occur commonly in dermatomyositis and are more often associated with muscle involvement in the pharynx, and hemorrhagic and necrotic mucous membrane lesions interfering with the intake of food. Gastrointestinal bleeding and peritonitis have been observed, due to ulcerations in the esophagus, stomach, duodenum, jejunum and colon as reported by several authors[34]. Punctate hemorrhages, ecchymoses, superficial erosions, necroses, ulcerations and perforations, single or multiple are described. Histologic findings consist of vascular lesions predominantly with necrotizing inflammation, hyalinization and thromboses of the arterioles and veins, most pronounced at the bases of the ulcers.

Specific changes in the liver and pancreas have not been described, and the parenchymatous degeneration and fatty infiltration have been regarded as secondary manifestations of a severe debilitating disease. Except for a single case report of primary carcinoma of the gallbladder, no other pathologic changes have been noted. In the liver near the gall bladder, Lugt found a focus of necrosis histologically showing tuberculoid structure but no organisms.

The histologic changes in the thyroid have been stressed by Dowling[35] who reported the characteristics of colloid goiter in the gland of a patient with fulminating dermatomyositis. He also cited other cases in the literature in which atrophy, fibrous increase in stroma and inflammatory infiltrations of the thyroid were prominent features.

The adrenals have been described as reduced in size with focal degeneration and cortical atrophy. Inflammatory and degenerative alterations in the gonads are not remarkable, but most of those cases of dermatomyositis associated with malignant disease had neoplasms of the ovaries.

Decalcification of bones has been repeatedly observed in dermatomyositis and may result from disuse atrophy secondary to muscle degeneration or to vasospastic phenomena. Disturbances in calcium and phosphorus metabolism have been detected in some instances and have been held responsible for generalized osteoporosis and calcium deposition.

Renal involvement is not frequently encountered in dermatomyositis, but when present effects alterations in the small arteries and arterioles not unlike those observed in lupus erythematosus and glomerulonephritis with hyaline fibrosis near the vascular root of the glomeruli and hylinization of the media and intima of the arterioles.

The central nervous system is not primarily affected in dermatomyositis, but late in the course of the disease, as a result of fever, exhaustion and debilitation, there may occur mental confusion, delerium and psychosis. Sensibility of the skin is usually preserved as are the superficial reflexes. However, the peripheral nerves may be involved, as in those cases of polymyositis with nervous symptoms reported by Senator in the earlier literature, with hyperesthesias, numbness, and formication. Lancinating and cramp-like pains, intense pains on pressure over the peripheral nerves, extreme tenderness of individual parts, and signs similar to those observed in syringomyelia may indicate a peripheral mono-or polyneuritis, but must be differentiated from those pains due to muscle inflammation and edema in the early acute stages. Sections of peripheral nerves may show demyelinization and perineural collections of inflammatory cells[36]. Such degenerative changes in the nerves may occur as a result of atrophy of the muscles, though, rather than as a primary neuropathologic process. The electrical reaction of degeneration does not occur. The tendon reflexes are decreased or wholly absent in the corresponding muscles involved in the disease. Such abnormalities may be due to the marked edema, to the inflammatory or degenerative processes in the muscles, or to the combination of neuritis with dermatomyositis. The myoneural junctions are normal.

Conjunctivitis, iritis, ptosis and paralysis of the external ocular muscles have been observed by Oppenheim, Wagner and others. Bruce[37] observed and reported retinal abnormalities which were identical in three cases of dermatomyositis. Around the discs and over the maculae were a number of irregular, indefinitely outlined patches of grayish-yellow exudate, largely superficial, but lying below the vessels in places. One case examined histologically showed albuminous deposits in the outer layers of the retina, and few small hemorrhages.

The cutaneous lesions of dermatomyositis are polymorphous and occasion considerable debate regarding etiologic considerations and taxonomy. The dermatologic component may be a mild erythema particularly of the photosensitive areas, localized, progressively extensive or generalized, or may be evanescent and disappear in a short time (dermatomyositis sine dermatite). Edema is a consistent finding in the acute and active stages of the disease and probably presents a better indicator than other phases. The degree of edematous infiltration of the skin is variable; it may be soft and slight, urticarial, pitting, or brawny and hard. When associated with thickening of the skin of the face, especially if the facial muscles are also involved, the countenance is immobile and mask-like, described by Oppenheim as "alabaster-like". On the thorax and trunk the edema may be so intense as to result in indurated, tense, shiny areas, not necessarily overlying affected muscles. Localized swellings may last a long time or disappear within hours.

Keil[38] classified the skin changes into those of diagnostic significance for dermatomyositis and those which are nonspecific, such as erythema multiforme, urticaria and purpura. He believes that the erythema of dermatomyositis may be distinguished from that of lupus erythematosus by the presence of numerous small telangiectases, the onset on the eyelids and the usual failure to involve the bridge of the nose. Albeit such features may be helpful, the extreme variability of these conditions prevents any reliance upon such criteria. Much is made of heliotrope eyelids since the upper lids are often first involved. Characteristically the lids are swollen and colored a rose-pink, and close inspection reveals that the heliotrope hue is caused by the presence of numerous closely-set telangiectases. But photosensitivity is present also in lupus erythematosus and such manifestations may well occur.

The facial eruption may remain visible for some time with fading and recurrence, and, when there is concomitant edema, may simulate erysipelas in appearance. Similar areas may occur on the neck, chest, abdomen and back. In later stages, as the redness and swelling subside,

mottled pigmentation and depigmentation, atrophy, telangiectasis, capillary hemorrhages and loss of subcutaneous fat ensue, the cutaneous picture resembling that following roentgen irradiation and termed poikiloderma.

The late changes in dermatomyositis also simulate closely those in scleroderma and cases are cited where patient with symptoms suggesting dermatomyositis in early stages later develop classic generalized scleroderma. Dowling concludes that progressive scleroderma and dermatomyositis are one and the same disease with clinical manifestations in the skin, skeletal muscles and blood vessels. Freudenthal pointed out that although the histologic changes in the skin and muscle in these two conditions showed no essential difference, such similarity alone could not be taken as conclusive evidence of the common cause of the two diseases, but must be considered with clinical and biochemical features.

Skin changes over the small articulations are frequent and are an outstanding feature of this disease. In the early stages these lesions are blotchy, illdefined, edematous, erythematous areas seen overlying the metacarpophalangeal and interphalangeal joints, bilaterally and symmetrically. Minute telangiectases can be seen at the periphery. Later the central area becomes thin and atrophic. Similar lesions are less commonly found overlying larger joints, wrists, elbows, shoulders and knees, or may occur on the back, not always on pressure points. These lesions are peculiarly sensitive and painful and present special problems in the care of the patient.

There may be present other lesions resembling those of other skin diseases. Urticarial, vesicular, eczematous, papulosquamous, lichenoid, bullous, nodose and multiform lesions may occur, either as manifestations of systemic noxae or as secondary exanthema.

Changes in the subcutaneous fat are grossly apparent, particularly the pronounced loss of substance which may be focal or diffuse and is more marked in places than can be accounted for by the general debilitated state. Pathologically, edema, mucoid degeneration, hyaline degeneration, round cell infiltration, fibrous tissue replacement and calcification have been described. Soft tissue calcification may occur in the subcutaneous fat or in the muscles themselves, giving the appearance of myositis ossificans. The extent of the calcification may be great enough to mimic universal calcinosis, although no consistent abnormality of calcium and phosphorus has been reported in this disease. Cornbleet and Struck[39] suggested that the calcium is taken up by the altered skin. Leriche[40] attributes the deposition of calcium in the skin and the existence of osteoporosis to chronic hyperparathyroidism, and that vasospasm results from hypercalcemia.

Raynaud's phenomenon occasionally occurs as an early symptom in dermatomyositis, particularly in those cases with scleroderma-like stiffening of the fingers. Jager and Grossman studied skin temperatures and responses to overcooling in their patients with dermatomyositis and found normal temperature responses but delayed recovery and incomplete return to initial temperature. They conclude that such observations indicate impaired blood flow to the fingers and increased vasomotor tone initiated by cold stimulus.

The microscopic appearance of the skin is not characteristic but merely suggestive, and must be considered as dynamic alterations in a progressive pathologic process. The epidermal changes are only secondary to the edema and sclerosis of the underlying tissues, and may be normal, thinned, or atrophic with only a few layers of epidermal cells. The horny layer may be thickened and lamellated, plugging follicular orifices. The rete pegs are usually flattened and diminished in number. The earliest demonstrable abnormality is edema of the collagen bundles which tends to swell or separate them. Later they lose their fibrillary structure and become hyalinized and sclerotic with decreased numbers of connective-tissue cells. The elastic tissue is usually diminished or

entirely absent. A fair amount of infiltration with lymphocytes and plasma cells, particularly about the vessels, is seen in the early stages, but later, when the cutis becomes sclerosed, little infiltration is seen. Dowling and Freudenthal reported loosely arranged collections of lymphocytes similar to the lymphorrhages previously described in the muscles. Thus, in dermatomyositis, the cutis becomes increasingly sclerotic and atrophic after an initial edematous stage, and the epidermis thinned and flattened out.

More recently other authors have reported further significant observations. Pagel, Wollf and Asher[41] noted edema as the earliest and most constant finding, with formation of a fibrinous and fibrinoid network which was later converted into a filmy collagenous mesh staining blue with Mallory's stain. In more severely affected areas there was "caking" of the collagenous fibers and fusion into homogeneous masses. These changes resemble the hematoxylin bodies described by Klemperer in lupus erythematosus. Striking alterations have been detected in the small arterioles in the skin as well as in other affected organs. These consist of subendothelial, homogeneous, eosinophilic fibrinoid thickenings, resembling fibrin in its affinity for eosin, but differing in its pale staining with aniline methyl violet and phosphotungstic acid-hematoxylin.

Laboratory studies are of little value in the diagnosis of dermatomyositis. Mild anemia of the normochromic, normocytic type is commonly found. The white blood count is usually normal, neither leukocytosis or leukopenia being characteristic. O'Leary found monocytosis of 8% or higher in 40% of his cases and Jager noted monocytosis of similar degree in three of his nine cases. Eosinophilia exceeding 5% occurred in one-third of O'Leary's series, and has been reported by others as high as 50% or more. The erythrocyte sedimentation rate is a useful aid in following the progress of a patient, the higher rates coinciding with greater degrees of activity of the disease process. Urinary abnormalities consist of mild albuminuria, red blood cells and casts depending upon the degree of toxemia and involvement of the kidneys. The serum proteins do not show a characteristic change but may be elevated or reduced with reversal or tendency toward reversal of the albumin-globulin ratio.

Creatinuria is a constant finding in dermatomyositis and may vary from 100 to 800 mg. per day, the higher amounts in the early stages of the disease and particularly in proportion to body weight and size. In the later stages of the disease when much of the musculature is grossly affected, the output of creatinine tends to be subnormal. The creatine tolerance test is normal, indicating there is no abnormality in the conversion of creatine to creatinine. Very little is known of the significance of creatinuria. Besides occurring in dermatomyositis, it is also a feature of thyroid disease, acromegaly, Cushing's syndrome, and muscular dystrophy, other conditions manifesting muscle weakness and degeneration. Griffiths relates creatinuria to abnormal carbohydrate metabolism in the muscles and peripheral insulin resistance, on the basis of findings of impaired glycogenesis in the muscles.

Dermatomyositis has occasionally been reported subsequent to an acute infectious disease. In recent literature, particularly from the Scandinavian countries, there have been reports of increased titres of antistreptolysin and antistaphylolysin in dermatomyositis, attempting to relate the disease to the onset of dermatomyositis. In two of Selander's cases the levels were normal; however, further investigations in this regard have been undertaken by Dr. Robert Good at this University, and results will be reported subsequently.

Silvestri[42] investigated concentrations of iron pigment in skin and muscles, urinary porphyrins, and mucopolysaccharides of skin in patients with dermatomyositis for the purpose of revealing possible abnormalities, but these studies produced negative results. Poli[43] concluded that quantitative and qualitative changes in the plasma proteins played an important part in the pathogenesis of

dermatomyositis, although the disease is not claimed to be a dysproteinemia.

The peculiar degenerated leukocyte and the phenomenon of clumping of leukocytes observed in lupus erythematosus have never been detected in cases of dermatomyositis. Those cases in which differentiation between dermatomyositis and lupus erythematosus has not been possible on clinical features alone are undoubtedly diagnosed lupus erythematosus when these cells are found.

Although there have been many interesting observations recorded associating dermatomyositis with other infectious and degenerative and neoplastic conditions, the cause of dermatomyositis is not known at the present time.

Most of the authors stress certain clinical features which favor an infectious agent. In some cases, though relatively few, bacteria have been isolated from the skin, muscles, blood stream and subcutaneous tissues[44]. Various organisms have been cited as the causative agents -- streptococci, staphylococci, meningococci, colon bacilli, gonococci, tubercle bacilli and many others. Selander and Jessen reported cases following measles. Onset of dermatomyositis or exacerbations of the disease have been noted following tonsillitis and pharyngitis of streptococcic origin. Rosenow reproduced the disease in animals with streptococci isolated from known cases of dermatomyositis. Sporozoa-like bodies[45], gregarines[46], trichina and other protozoans were thought to have produced the disease. A number of cases have been observed in the puerpeium, following exodontia, after influenza or other febrile illnesses. Madden[47] recorded the clinical course of a young male in whom the disease abated during administration of penicillin and flared when the drug was discontinued. More recently the beneficial effects of other antibiotics have been stressed as indicative of the infectious nature of the process. Greenaway and Lambie[48] carried out extensive virus studies with negative results, and Silvestri failed to isolate a filtrable virus on the chorio-allantoic membrane which would fulfill Koch's postulates. Weber's interpretation of the "toxic effects of an infection" seem plausible, but the pathogenesis is not clearly understood.

Griffiths, Petges and Dowling emphasized endocrine factors on the basis of similarities between dermatomyositis and thyrotoxicocis, Cushing's syndrome, acromegaly and hormonal disturbances associated with precocious sexual development. Altered carbohydrate metabolism, peripheral insulin resistance and other metabolic changes occurring in dermatomyositis are strikingly similar to those in pituitary basophilism and suggest a derangement of pituitary function in dermatomyositis. O'Leary has recorded two cases of dermatomyositis occurring simultaneously with Cushing's syndrome; since both diseases are extremely rare, the probability of mere coincidence is remote.

Various toxic influences may possibly cause dermatomyositis by acting through the endocrine-vegetative regulating mechanisms. Lugt suggests the theory that such dysfunctions of vegetative centers in the diencephalon result from an imbalance of endocrine and vegetative equilibrium associated with infection, degeneration or neoplasia, and that many of the changes noted in ductless glands have resulted not from direct involvement by the disease process, but by influence from higher regulatory centers. Although relatively little is known concerning central control of skin metabolism, certain altered physiologic states of the integument have been observed associated with diseases of the central nervous system. Seborrhea and seborrheic dermatitis have been noted in patients with Parkinson's condition, with epidemic encephalitis, even limited to affected areas of the skin in post-traumatic or post surgical (for brain tumor) hemiplegia[49]. Perutz[50] described alterations in hair growth of rabbits following lesions of the diencephalon induced by diathermy, and Kalz, Hoogstraten, and Hoff observed cases of dermatomyositis and scleroderma coexisting with and improving after therapy of meningovascular infectious processes[51]. This theory hardly covers the whole field of known

facts, but might possibly explain such disturbances as Raynaud's condition and other vasomotor disturbances, anidrosis or hyperidrosis, pulse aberrations and metabolic disturbances, commonly observed along with other symptoms of dermatomyositis.

Some writers have considered the disease to be due to a form of intoxication rather than to a specific micro-organism. Thus it has been observed in cases of food poisoning, after exposure to cold and sunlight, in gout, in alcoholic patients, and in patients with acute articular rheumatism. Greenbaum[52] felt that sun rays are definitely an exciting factor which produce a kind of trauma, provoking a cutaneous lesion as in lupus erythematosus, but there must be some endogenous factor, probably a toxin, which determines this reaction. Worthy of comment in this respect is the role which antecedent infection may exert on the disease. Many cases reported reveal such a sequence, onset of systemic symptoms following localized infections such as abscessed teeth, tonsillitis and furunculosis, and it is not unreasonable to consider such a possibility. Likewise in this respect the effect of malignant neoplasms, their toxic elaborations or catabolic products might act similarly in the pathogenicity of the disease.

The term allergy is used loosely in discussions of etiology of dermatomyositis, but, in the strict sense is hardly applicable. Many patients may present histories of "allergic reactions" or actually give evidence of altered reactions to ingestants and inhalants, but only certain histopathologic alterations, namely, fibrinoid degeneration in the intima of blood vessels, and edema are similar to those observed in known allergic conditions. Rich concluded that all maladies characterized by such pathologic alterations indicated hypersensitivity and thus had an allergic basis. True, collagen change may occur in allergy, but not all collagen alteration is due to allergy.

Pollack, Klemperer and Baer in 1941 proposed the term "collagen disease" stressed the intermediate cellular substances involving connective tissue, and attempted to group diseases on the basis of such anatomic alterations. They merely wanted to call attention to similarities in these diseases rather than attempt an explanation of common etiologic forces. They subsequently conceded hypersensitivity in some diseases, but not in lupus erythematosus, scleroderma or dermatomyositis. Fibrinoid substance is characterized only by its staining reaction and is not pathognomonic of any single pathologic process; it has been produced experimentally by such mechanisms as repeated injections of epinephrine. Further, tissue eosinophilia is not a feature of dermatomyositis, lupus erythematosus or scleroderma.

Hyaluronic acid and chondroitin sulfate are essential components of the interfibrillar ground substance and their alterations in certain pathologic conditions are being studied intensively. Deposition of these and other mucinous polysaccharides occurs in localized myxedema and in the retrobulbar spaces in Graves' disease, also in the cock's comb after administrations of testosterone. Selye and Loeb provoked mucinous edema and hyaline changes in the stroma of various organs by repeated injections of estrogenic substances. Cantor, cited by Klemperer, showed that fibrinoid from rheumatic skin nodules was not collagen chemically, and concluded that fibrinoid is variable, probably made up of several different substances.

Vitamin factors too must be discussed in the etiology of dermatomyositis, although obvious manifestations of deficiencies are lacking. Beckman[53] found a lowered level of tocopherol in the blood of two patients with dermatomyositis and attempted to show that abnormal phosphorylation and creatinuria resulted from decreased amounts of vitamin E in the enzymatic system of affected muscles. Goettsch and Pappenheimer[54] found they could produce degeneration in the voluntary muscles of experimental animals by giving them a diet deficient in vitamin E. These changes could not be reversed by addition of the vitamin to the diet, suggesting that such alterations resulted from metabolic upsets rather than quanti-

tative deficiencies. Milhorat's work on the effect of wheat germ on creatinuria in cases of dermatomyositis may be of further significance in this respect[55].

Stenger's[56] description of the pathogenesis of dermatomyositis is especially valuable, and indicates particularly the role of severe bodily-stressing situations such as infections and pregnancy as exciting factors in the production of observed pathologic alterations. In hyperemic skin areas are "blood lakes" formed by pronounced dilatation of capillary loops, with spastic thinning of the arterial loop and flabby dilatation of the venous vessel. With such functional disturbances of the capillaries the permeability for proteins of the blood plasma becomes increased, resulting in an exudation which surrounds the vessels. In the muscles there are edema and fine granular masses of coagulated edema-fluid pushing the muscle fibers apart. He theorizes subsequent dissociation of cell compounds by fermatative and mechanical factors; as the parenchyma is pushed away from the capillary wall the oxidation of the individual cell becomes diminished. The result is then the trauma to the muscle that is shown in increasing volume (swelling), formation of spaces with fine networks of detritus and granular masses, fatty and waxy degeneration. Edema and round cell infiltration is found in varying amounts, as well as fibrocytes and histiocytes, comprising a serous exudation. These stages in the genesis of the pathologic process are similar to those proposed by Eppinger in his theory of inflammation. The possibility that components of interstitial substance might be deposited by the circulating blood was suggested by Klemperer. Haserick demonstrated a fraction of serum gamma globulin in cases of acute disseminated lupus erythematosus capable of specific antibody formation. This fraction is believed to be capable of leukocyte clumping and, possibly, of forming LE cells. Alterations in concentration of serum proteins have been detected in edema of the extremities from various causes. In the normal, non-edematous leg, Wood found an increase in concentration of serum proteins and thus increased in intravascular osmotic pressure, whereas in edematous tissue there was no evidence of factors which might reduce filtration-pressure[57].

The chronic changes in the muscle and skin correspond with the late effects of serous inflammation observed in other pathologic conditions. Hypertrophy of the interstitial tissue leads to induration and remnants of the panenchyma can be seen. The end result depends upon the course of the disease, either mild and abortive, chronically progressive or acute and fulminating, in which case only the initial phase of the process is observed.

Although the early writers mentioned no coincidence of dermatomyositis with malignant tumors, recent authors have emphasized this association, speculating that a correlation may well exist between the two processes[58]. This further suggested by the observation that the inflammatory and degenerative process in the skin and muscles improved after removal of the neoplastic tumor and relapsed with the appearance of metastases[59]. In nearly all cases the symptoms of dermatomyositis preceded the appearance of the malignant process, and unexpected carcinomas have been found at postmortem examinations. There may be special significance to the higher incidence of malignant tumors of the ovaries, but neoplasms of the breast, stomach, esophagus, gallbladder and rectum have been found in association with the dermatomyopathic process, as well as reticuloendotheliosis and leukemia[60].

Considering the possible etiologic role of new growths, the mechanism involved in the production of dermatomyositis is unknown. The degenerative changes in the disease may be due to toxic effects of the tumors or its catabolic products, or such substances may act as allergens, again implicating allergy in the production of dermatomyositis[61].

Similar association with visceral cancer has been noted in other dermatologic conditions, eg., acanthosis nigricans, where the appearance and course of the cutaneous lesions follow and are associated with malignancy of the internal

organs. Such a comparison was made by Schuermann[62] who held that the association was more than coincidental and that an exhaustive search for such tumors must be made in all patients with dermatomyositis.

Even to attempt presenting criteria which may be of benefit in differentiating dermatomyositis from other conditions with similar clinical features would be an impossibility within the confines of this report. Therefore only those conditions most often considered will be listed herewith. In the acute edematous phase dermatomyositis is often confused with lupus erythematosus, scleroderma, trichinosis, polymyositis, polyneuritis, acute rheumatic fever and articular arthritis, erysipelas, polyarteritis nodosa, panniculitis and nephritis. The chronic progressive type, on the other hand, presents features not unlike those of myasthenia gravis, pituitary basophilism, and other endocrinopathies, myositis ossificans, universal calcinosis and poikiloderma of the Jacobi type.

The diagnosis of dermatomyositis may be a difficult one, particularly in the early phase when the presenting symptoms are general and non-localizing. Any one patient presenting such symptoms and signs of general ill-health may subsequently develop manifestations more typical of any one of these conditions. Michelson's statement is most apt, that the diagnosis of dermatomyositis is made by "observation and awareness",--prolonged observation of a suspected case by a physician aware of dermatomyositis and its diverse clinical manifestations.

The prognosis in dermatomyositis is grave with a mortality rate of 50%. Even an estimate is impossible in the early phases since the condition may pursue any one of several courses as described above. The nature and extent of concomitant disease, if present, whether coincidental or etiologically significant, would materially influence the outcome. The rarity of the disease, the variety of associated conditions, the age range, and the variability of the clinical picture-- all are proof that dispositional and constitutional factors play an exceedingly important role, and thus cannot be interpolated into terms of morbidity or mortality.

The large number of therapeutic agents recommended indicates that none is specific or particularly effective. In the past, drugs employed have been salicylates, calcium, arsenic, quinine, iodides, thyroid and parathyroid extracts, fibrinolysin and glycine. Diaphoresis, thermomassage, electrotherapy and wet packs have also been used, at times with some beneficial effect. Lane suggested the use of prostigmine, Lamb and Hazel androgenic substances to increase creatine content of muscles. Foreign protein injections have seemed to secure remissions, but not consistently.

Zarafonetis treated six cases with paraaminobenzoic acid and reported great improvement in two. The rationale of such therapy is not understood.

Since the advent of effective antibacterial chemotherapeutic agents there have been reports of satisfactory results and cures. Early cases have been benefited by the administration of sulfonamides, penicillin and aureomycin, adding credence to the infectious theory of the disease. Schmidt and Sturup administered ACTH and aureomycin to a case of dermatomyositis which had run an interrupted course over a period of 10 years. Although the myositis was improved, there was no definitive effect on the poikilodermatous cutaneous lesions[63]. Thorn[64] treated three cases with ACTH and cortisone with inconclusive results. Oppel and Milhorat[65] treated a patient with dermatomyositis in the acute phase with ACTH for a period of 53 days. Six hours after initiation of therapy the patient began to improve, and he was in good health within a few weeks. Williams and associates also reported complete remission after therapy with adrenocorticotropin[66].

The value of steroid substances is hardly one of specificity but, rather, as adjunctions to an over-stressed physiology. Many authors express discouragement

over failure of these substances to produce beneficial effects. Certainly one can hardly expect to replace scar tissue with regenerated parenchyma, but relief of agonizing symptoms and lessening of the degree of inflammation are to be desired, and are very likely possible with these agents.

Therapy of associated conditions, when present, certainly should be undertaken. Removal of infected tonsils and teeth, drainage of abscesses, surgical excision or radiation, as indicated, of malignant tumors is often followed by improvement in the myopathic process. Other general measures are of great importance and certainly render the patient more comfortable. Adequate diet with supplements is essential to maintain nutrition, and suitable substitutes must be administered when, because of involvement of the alimentary canal, the patient is unable to take nourishment. Bronchial secretions and aspirated food and fluid must be removed to prevent the occurrence of pneumonia. Topical applications to the skin are used only prophylactically and palliatively.

Rest is essential during the progressive phases of the disease, since exacerbations have followed early ambulation and other physical activities. However, once the inflammation has subsided, and all evidence of toxemia have abated, then a program of physiotherapy should be instituted to prevent atrophy and contractures and to effect rehabilitation. The program must surely be slowly progressive and interrupted at any time signs of disease recur.

SUMMARY

Two cases of dermatomyositis have been presented, both having similar clinical and pathologic changes in the skin and muscles, but differing greatly in involvement of other organs. In one case the gastrointestinal lesions were severe and extensive, accounting for distressing symptoms, inanition, and the immediate cause of death. The second case might not have been differentiated from any other case of coronary artery disease or articular arthritis were it not for the progressive muscular degeneration and cutaneous lesions which suggested the diagnosis of dermatomyositis.

Clinical, pathological, and therapeutic features of dermatomyositis have been reviewed.

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II. MEDICAL SCHOOL NEWS

Coming Events

May 21-23	Continuation Course in Radiology for General Physicians
May 27	Minnesota Medical Alumni Association Luncheon for Senior Students
June 8-13	Continuation Course in Electrocardiography for General Physicians
June 8	Special Lecture: "The Auricular Arrhythmias;" Dr. Myron O. Prinzmetal, Los Angeles; Owre Amphitheater; 8:00 p.m.

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Continuation Course

The University of Minnesota will present a continuation course in Radiology for General Physicians from May 21 to 23. The course, which will be presented under the direction of Dr. Leo G. Rigler, Professor and Head, Department of Radiology, will consist almost exclusively of practical work in film interpretation and fluoroscopic technique. Except for a brief introductory session, which will be held at 8:30 a.m. on Thursday, May 21, at the Center for Continuation Study, registrants will spend their time in the Hospital X-Ray Department under the supervision of Dr. Rigler and his associates.

* * *

Alumni Luncheon for Senior Students

The Minnesota Medical Alumni Association will hold a luncheon for the Senior Class of the Medical School on Wednesday, May 27, at 12:30 p.m. in the Junior Ballroom of Coffman Memorial Union. An alumnus or a member of the faculty of the Medical School will act as host to each Senior student. The program following the luncheon will include a brief outline of the objectives of the Medical Alumni Association and a short talk by Dr. E. T. Bell, Emeritus Professor of Pathology. Each member of the Senior Class will receive a personal invitation in the near future.

* * *

Student Activities

During the past year, several members of our Senior Class have been engaged in interesting research problems in association with members of the staff. Richard Aronson has been working with Dr. W. Lane Williams, Associate Professor of Anatomy in a study of the effects of a low protein diet upon the liver of rats. Thomas Kirschbaum is an associate of Dr. Henry S. Bloch, Research Associate in Surgery, in the investigation of the role of urease in gastric secretion. Edward Segal has been working with Dr. Samuel Schwartz, Associate Professor of Medicine, on a technique for performing the stercobilin tolerance tests in liver disease.

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Faculty News

Dr. William C. Bernstein, Clinical Assistant Professor of Proctology, is leaving to attend the meetings of the Section on Proctology of the American Medical Association in New York City and the meeting of the American Proctologic Society in Boston the following week. While in the east, he will be lecturing on proctology to the surgery residents at the Newington General Hospital, Newington, Connecticut.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

May 18 - 23, 1953

Monday, May 18

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U.H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

11:30 - 12:30 Physical Medicine Seminar; Therapeutic Exercise - Kabat Techniques; A. B. Quiggle; Heart Hospital Auditorium.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - Physiology and Physiological Chemistry Seminar; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Pediatric Seminar; Reports of Pediatric Meetings; Staff Members; Sixth Floor West, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

4:30 - Public Health Seminar; 15 Owre Hall.

4:30 - 6:00 Physiology 114A and Cancer Biology 140 -- Research Conference on Cancer, Nutrition, and Endocrinology; Drs. Visscher, Bittner, and King; Changes in the Skeletal Calcium; Leon Singer; 129 Millard Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Ancker Hospital

8:30 - 10:00 Tuberculosis and Chest Conference; Auditorium.

2:00 - 3:00 Surgery Journal Club; Classroom.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Erling Platou; Station K.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Monday, May 18 (Cont.)

Veterans Administration Hospital

1:30 - Cardiac Rounds; Drs. Ebert and Berman, and Richards.

4:00 - ECG Conference; Drs. Ebert, Berman, and Simonson.

Tuesday, May 19

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Physiology 114D -- Current Literature Seminar; 129 Millard Hall.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 X-ray Conference; Presentation of Cases from Mt. Sinai Hospital; Drs. Friedman and Zheutlin; Eustis Amphitheater, U. H.

Ancker Hospital

9:00 - 10:00 Medical X-ray Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

12:30 - Grand Rounds; Fractures; Willard White, et al; Sta. A.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Cal, and Lipschultz.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:30 - Infectious Disease Rounds; Drs. Hall and Zinneman.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery-Tumor Conference; L. J. Hay, J. Jorgens; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

Tuesday, May 19 (Cont.)

Veterans Administration Hospital (Cont.)

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

Wednesday, May 20

Medical School and University Hospitals

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:30 - 1:30 Physiology 114C -- Permeability and Metabolism Seminar; Nathan Lifson; 129 Millard Hall.

1:30 - 3:00 Physiology 114B -- Circulatory and Renal System Problems Seminar; Dr. M. B. Visscher, et al; 214 Millard Hall.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

12:30 - 1:30 Medical Journal Club; Library.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Platou; Station K.

12:00 - Surgery-Physiology Conference; Drs. Zierold and E. B. Brown; Classroom.

12:15 - Pediatric Staff Meeting; Classroom, Station I.

1:30 - Visiting Pediatric Staff Case Presentation; Station I, Classroom.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Nesbitt, Zieve, Hay and Goodnow.

12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

Wednesday, May 20 (Cont.)

Veterans Administration Hospital (Cont.)

4:00 - 5:00 Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics, Conference Room, Bldg. I.

Thursday, May 21

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

12:30 - Physiological Chemistry Seminar; Introduction to Scientific Research--Execution of Experiments; J. G. Hamilton; 214 Millard Hall.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - EOG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 Radiology Seminar; Further Studies on Effects of Pre-Irradiation on Sites of Tumor; Halvor Vermund & Donn G. Mosser; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

8:00 - 10:00 Medical Grand Rounds; Auditorium.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

2:00 - 4:00 Infectious Disease Rounds; Classroom.

4:00 - 5:00 Infectious Disease Conference; Wesley W. Spink; Classroom.

Veterans Administration Hospital

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

Thursday, May 21 (Cont.)

Veterans Administration Hospital (Cont.)

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

1:00 - Metabolic Disease Conference; Drs. Flink, Heller, and Jacobson, and Bolin.

Friday, May 22

Medical School and University Hospitals

8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 1:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Roentgen Studies of Effects on the Small Bowel from Emotional Disturbance; Jack Friedman; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Physiology 124 -- Seminar in Neurophysiology; Ernst Gelhorn; 113 Owre Hall.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Pediatric Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I, Classroom.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

Friday, May 22 (Cont.)

Veterans Administration Hospital (Cont.)

1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

2:00 - Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Saturday, May 23

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Eustis Amphitheater, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; The Adrenal Gland of the Fetus; Mona Luyten; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Goldish and Bolin, and Howard.
11:15 - 12:00 Morphology . . . . . Dr. Aufderheide, Conference Room.