Post-Graduate Short Course In Medicine

MARCH 26th-29th, 1956

The fifth annual short course in Medicine for the general practitioners of the Atlantic Provinces was held March 26th-29th by the Post-Graduate Committee of the Faculty of Medicine in co-operation with the Department of Medicine of Dalhousie University.

On this occasion, in keeping with the policy of covering all phases of medicine, the program featured Rheumatism and Arthritis and Neurology. Two guest speakers took part in the discussions on Rheumatism and Arthritis; they were Dr. D. C. Graham of Toronto, Medical Director of the Canadian Arthritis and Rheumatism Society and Dr. H. O. Tonning, Director of the New Brunswick Society.

In Neurology, the Guest Speaker was Dr. John S. Prichard, Neurologist and Assistant Physician at the Hospital for Sick Children, Toronto.

Three general medical clinics were held, another clinic featured Injection of Joints and in two others, neurological cases were presented. One afternoon was devoted to various aspects of Poliomyelitis ranging from Diagnosis to the Economic Aspects of the Present System of Handling Poliomyelitis. Other Symposia dealt with Management of Rheumatoid Arthritis, Marie Strumpell Spondylitis, Cerebral Vascular Disease and Cerebral Palsy and Allied Disorders. An evening lecture was given by Dr. D. C. Graham on "Joint Manifestations of Systemic Diseases"—other lectures by guest speakers were Introduction to Rheumatoid Arthritis, Surgical Procedures for Patients receiving Steroid Therapy, Gout, Low Back Pain, Epilepsy and Its Management in Children and Neuro-Muscular Diseases. Members of Faculty covered the other major aspects in the handling of these two phases of medicine. On Monday evening the following medical motion pictures were shown: "Foxgloves in Medicine", "The Management of Coronary Artery Disease", and "Mind and Medicine" with members of Faculty providing appropriate commentary.

Three of the Atlantic Provinces were represented among the candidates of this course and registration was as follows:

Dr. E. H. Freeman	Chatham, N. B.
Dr. J. C. Wickwire	Liverpool, N. S.
Dr. P. A. Cole	Hubbards, N. S.
Dr. A. M. Creighton	Tatamagouche, N. S.
Dr. Henry Moyse	Summerside, P. E. I.
Dr. F. F. P. Malcolm	Dartmouth, N. S.
Dr. C. E. Dumont	Campbellton, N. B.
Dr. J. A. MacCormick	Antigonish, N. S.
Dr. J. A. McDonald	Glace Bay, N. S.
Dr. G. McL. Moffatt	Springhill, N. S.
Dr. C. H. Young	Dartmouth, N. S.
Dr. H. I. MacGregor	Halifax, N. S.
Dr. H. C. Still	Halifax, N. S.
Dr. E. Hofstaedter	Springhill, N. S.

Articular Manifestations of Systemic Diseases*

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JOINT pain, swelling, tenderness, local heat, stiffness, limitation of movement, deformity and ankylosis are all familiar manifestations common to a large number of so called "rheumatic" disorders which primarily and predominantly affect articular tissues. These conditions are usually considered to be forms of primary arthritis or "rheumatism". Any or all of these articular manifestations may, however, represent only one facet of a more widespread systemic disease process. This fact demands constant vigilance and diagnostic acumen on the part of the clinician if oversights or errors which may endanger the well being or even the life of the patient are to be avoided. In this presentation I will omit discussion of the various types of "primary arthritis" and will confine my remarks to the various articular manifestations which are secondary to systemic disorders although they may well be prominent or presenting features of the underlying disease. Strictly speaking, several conditions which we customarily look upon as forms of primary arthritis, such as rheumatoid arthritis, ankylosing spondylitis and gout, are in the true sense systemic diseases in which the arthritis is only a part of the total illness. However, to keep the scope of this discussion within reasonable bounds, I will not belabor this point further.

Diseases of Collagen-Containing Tissue

Systemic Lupus Erythematosus

Pain in the joints is one of the most commonly encountered manifestations of systemic lupus erythematosus and is frequently the earliest symptoms being apparent long before cutaneous or visceral alterations are observed. The joint manifestations may remain the only symptoms and signs of the disease for some time or may be so prominent that other lesions are overlooked or obscured. As there is nothing specific about the joint changes of lupus, the arthritis may be a very misleading clinical feature, suggesting other disease states. The joint involvement may present in a variety of forms, the most common being arthralgia or mild, vague, aching discomfort passing from one joint to another, with no objective evidences of joint inflammation, the subjective symptoms being out of proportion to the observable joint abnormalities. This discomfort waxes and wanes from time to time and may be considerably relieved by salicylates. In other instances there may be acute joint involvement with marked local heat, redness, swelling, tenderness and limited movement. These findings may remain confined to a single joint or may affect multiple joints in a migratory manner. Any joint may be involved but those of the extremities are most commonly affected and the spine is usually spared. The joint manifestations may undergo exacerbations and remissions paralleling the course of the underlying systemic disease. Infrequently they may gradually take on the appearance of advanced rheumatoid arthritis with characteristic rheumatoid deformities, muscle atrophy, contracture and anklosis. In this state a mistaken diagnosis of rheumatoid arthritis is often made. The X-ray

*Presented at the Post-Graduate Course in Medicine March 26-29.

changes in the joints are entirely non-specific. There may be no radiolodical abnormalities or any or all of the X-ray changes seen in rheumatoid arthritis may be evident.. Occasionally, the skeletal muscles may be the site of soreness, tenderness, weakness and atrophy without accompanying joint involvement. These findings may be so prominent as to suggest a primary muscle disease.

Polyarteritis Nodosa

In polyarteritis nodosa the joints themselves usually exhibit little or no objective evidence of intra-articular disease or arthritis in the strict sense of this term. However, joint and muscle pains, tenderness and stiffness are among the most common symptoms of this disease; they may be the sole presenting manifestation; or they may dominate the clinical picture and overshadow the other lesions for some time. In such cases the clinician's attention may be concenrtrated on the investigation of one of the primary muscle or joint disorders until subsequent events clarify the diagnostic picture. Chronic, destructive joint changes and a deforming or disabling arthritis are not common manifestations of polyarteritis nodosa but have been observed.

Dermatomyositis

Dermatomyositis is an uncommon, obscure and poorly defined disorder which may develop acutely and run a fulminating course but usually the onset is insidious with vague constitutional symptoms of fever, malaise, anorexia, weakness, joint and muscle aching and later involvement of the skin, muscles and various viscera. The muscular lesions are characterized by progressive weakness, pain on movement, and eventually extensive atrophy which may account for a major degree of weight loss. Sometimes pain is absent. The involved muscles may be tender on pressure and as the disease progresses they may feel doughy and eventually firm and boardlike. Utimately muscle contractures may result in extensive symmetrical joint deformity and fixation, rendering the patient helpless. The muscles of the shoulder and pelvic girdles, the neck and shoulders tend to be involved early and may give rise to a characteristic posture with the shoulders falling forward and the head drooping. In some instances, weakness is the main manifestation of muscle involvement, in others stiffness and contractures predominate.

In its later stages dermatomyositis is not uncommonly mistaken for rheumatoid arthritis because of the joint deformities, contractures and fixation. These are not due to intra-articular disease of course, but to the muscle contractures and fibrosis of the skin and subcutaneous tissues. Arthritis, per se, is not a feature of dermatomyositis.

Calcinosis is not uncommonly associated with dermatomyositis and is manifested by diffuse calcium deposits through the skin, subcutaneous tissues, muscles and tendons. In rare instances, calcifications in the lungs or kidneys may be present.

Progressive Systemic Sclerosis (Scleroderma)

In 1945 Goetz recommended the term "progressive systemic sclerosis" in preference to "scleroderma' to indicate that this is not merely a disorder of the skin but frequently involves visceral tissues as well.

Early complaints of paresthesias, arthralgia and clinically characteristic Raynaud's phenomenon are common. Later there is stiffness and tightness of the skin in the affected areas and inability to fully flex or extend the fingers. These symptoms gradually merge into the late stage of multiple contractures and deformities.

The skin of the head, neck and upper extremities is commonly affected with less emphasis on the torso and lower limbs though there are exceptions to this distribution and every area of the body may eventually be involved. A form involving the fingers in association with Raynaud's phenomenon, leading eventually to varying degrees of absorption of the digits, is frequently referred to as sclerodactylia or acrosclerosis and is regarded by some as a separate entity.

The affected skin at first presents the appearance of thickening due to non-pitting edema, though sometimes this initial phase of thickening is absent. It is followed by a stage of induration in which the involved skin can not be pinched or picked up. Later skin and subcutaneous tissues become bound down firmly to the underlying structures and movement is limited by fibrosis. The affected areas become hard and inelastic with varying combinations of increased or decreased pigmentation, loss of hair and sometimes erythema about the lesions. Some patients show a diffuse yellowish-brown pigmentation. As atrophy progresses, the skin and subcutaneous tissues form a thin parchment stretched over the underlying bones and atrophic muscles. In this stage the face appears narrowed, "bird-like" and expressionless with pinched nose, thin gaping mouth and sometimes ectropion, the whole producing a mummified appearance. Similar changes in the extremities give rise to various types of contractures, limitation of joint movement and sometimes the disease may first be noticed because of joint pain, swelling and stiffness. However, these joint changes are readily distinguishable from the characteristic fusiform joint swellings, muscle atrophy, ulnar deviation-hyperextension deformities and tenderness typical of rheumatoid arthritis in which the widespread cutaneous and visceral lesions of systemic sclerosis are not a feature.

One of the most common radiological abnormalities is the presence of calcinosis which varies in appearance from that of minute spicules in or under the skin to that of huge globular or irregular calcifications deep in the region of the larger joints. Diffuse laminated or lace-like calcifications may occur subcutaneously or along muscle sheaths and fascial planes though this appearance is more common in dermatomyositis.

Hypersensitivity and Drug Reactions

Serum sickness is a disease created by the medical profession with the introduction of diphtheria antitoxin in 1890. It is well established that the clinical manifestations of this condition occur as a result of allergy or hypersensitivity to foreign protein. Though in general the incidence of serum sickness depends on the amount of serum given, the symptoms parallel the titer of precipitins which develop during the so-called "incubation period." In other words, the amount of immunity, rather than the amount of antigen regulates the manifestations of this disease, though it is also true that large amounts of antigen produce correspondingly large amounts of antibody.

The symptoms of serum sickness begin from one to three weeks after the administration of serum and as a rule the illness runs a course of similar duration. Generalized enlargement and variable tenderness of lymph nodes is an early and consistent finding. Itching is a prominent symptom and may precede or accompany an urticarial skin eruption which may become widespread and confluent. Diffuse or macular erythema and occasionally purpura may be noted in severe cases. Edema of the face and extremities accompanied by albumin and casts in the urine may be distinctly suggestive of acute glomerulonephritis. Variable fever may be present.

Joint pain and stiffness occur frequently in severe cases and may be the outstanding feature of the illness. Any or all of the joints may be involved, most commonly the large and medium sized ones which may exhibit gross swelling, heat, tenderness and effusions.

Rheumatic fever, rheumatoid arthritis, the so called "collagen diseases" and glomerulonephritis often enter into the differential diagnosis but the history of onset following a one or two week interval after serum injection, the accompanying severe itching and urticaria and the ultimate complete recovery with no residua, assist in establishing the diagnosis.

Hypersensitivity reactions identical in all respects with serum sickness may occur following the administration of penicillin.

Less frequently, sulphonamides have been associated with arthralgia, urticaria and at times other manifestations of the serum sickness reaction.

Painful osteoporosis has been reported in about two per cent of patients receiving potassium thiocyanate therapy for hypertension. Pain, usually in the lower extremities develops insidiously three to six months after the drug has been started gradually becomes more severe and may be accompanied or followed by mild swelling of the joints without acute inflammation.

One of the most interesting and striking "rheumatic" manifestations of drug reaction is seen in about seven per cent of patients receiving moderate to large doses of hydralazine (apresoline) for ten months or more. This hydralazine reaction may be characterized by fever, malaise and clinical symptoms and signs which may closely resemble rheumatoid arthritis or systemic lupus erythematosus, the latter at times being accompanied by the presence of typical L. E. cells in the peripheral blood. The point of particular interest is that here we appear to have a pharmaceutical agent which is capable of reproducing the clinical symptoms and signs of rheumatoid arthritis and of lupus erythematosus which will entirely disappear after withdrawal of the causative agent. This observation may well hold promise for further fruitful investigation along this line.

Allergic sensitivity to specific foods such as eggs, fish, nuts, etc., has been reported in several patients with pain, swelling, inflammation and stiffness of any or all of the joints of the extremities. These articular signs and symptoms would clear completely on elimination of the offending foods from the diet. These are examples of what could be legitimately termed "allergic arthritis" which must be a rather rare condition.

Erythema nodosum and erythema multiforme are disorders of undetermined etiology usually considered to represent a manifestation of hypersensitivity which may occur following administration of drugs such as the halogens

or sulphonamides, or in association with a wide variety of systemic diseases including rheumatic fever and tuberculosis. Both of these erythemas may be accompanied by a mild generalized arthritis with arthralgia, swelling, local heat and stiffness of joint movement which may persist as long as several weeks but leaves no permanent joint damage.

Endocrine Disorders

With the possible exception of acromegaly, no specific endocrine disorder has been identified with a particular type of joint disease, and there is little or no justification for the term "endocrine arthritis."

In many cases of acromegaly, degrees of degenerative joint disease (or osteoarthritis) in excess of that expected at the patient's age are commonly encountered in the spine and peripheral joints. In most of these the process conforms clinically, radiologically and histologically to the familiar pattern of osteoarthritis. In certain sites however factors other than primary degeneration of cartilage appear to be involved and excessive new growth of cartilage and bone suggests reactivation of cartilage growth and ossification which is not physiological at the age of these patients and may result from a hormonal stimulus, possibly by growth hormone. This suggestion is further strengthened by the observation of similar bone and joint changes in adult rats after prolonged administration of purified growth hormone. The acromegalic spine is characterized by additional growth of vertebral bodies with newly formed bone more evident on the anterior and lateral margins of the vertebrae clearly shown by X-ray studies. In addition to the spine the fingers, hips, wrists and elbows may be the sites of symptoms. These peripheral joints may be enlarged and painful and show some limitation of movement though they may be surprisingly hypermobile with a striking absence of stiffness. Radiologically they may show an *increase* in joint space due to increased growth and thickening of the articular cartilage and other intra-articular soft-tissue structures.

These excessive degenerative and proliferative osteochondral changes in the joints and spine of the acromegalic frequently result in considerable pain to add to the other miseries of these unfortunate individuals.

Disorders of Metabolism (Other than Gout)

Ochronosis

Ochronosis is a clinical syndrome resulting from a long continued metabolic disorder known as alkaptonuria and alkaptonemia in which the urine contains a chemical compound, homogentisic acid, a strong reducing substance readily oxidized on exposure to air imparting a black color to the urine. This metabolic disorder is believed to result from the hereditary absence of an enzyme which normally breaks down tyrosine and phenylalanine, and is inherited as a mendelian recessive characteristic. When this unusual disorder of metabolism has been present for a prolonged period of time, the clinical syndrome of ochronosis results in some cases. Ochronosis is characterized by pigmentation of certain body tissues, particularly the cartilage of the ears, nose and joints, the cornea of the eye, sometimes the intervertebral discs and rarely the skin.

There may be no associated symptoms but in time the pigment deposits in joint cartilage and intervertebral discs produce extreme degeneration and a special type of arthritis termed "ochronotic arthritis". This condition is more common in males in whom the pigmentation tends to become more marked with advancing years. The pigment is usually depositied intracellularly and in the late stages is so dense that the involved cartilage may appear black. The symptoms are those of low grade rheumatoid or osteoarthritis which runs a chronic course with occasional exacerbations. At times there may be effusions into the joints. Severe arthritic manifestations may be present even though there may be no pigmentation in the eyes, ears, nose or skin. Homogentisic acid has been demonstrated in the joint fluid in some cases. The X-ray findings are unusual and striking and once seen and recognized, are of considerable help in making the diagnosis. The intervertebral discs show marked thinning, calcification, and marginal osteophytic fringing, at times accompanied by calcification in the paravertebral ligaments. The peripheral joints show excessive narrowing of joint space and osteophyte formation. Most of these patients show homogentisic acid in the urine. This can be demonstrated by the simple procedure of placing a drop of alkalinized urine on a piece of ordinary sensitized photographic paper which turns black if homogentisic acid is present. Some patients with this disorder also show melanin in their urine.

Gaucher's Disease

Gaucher's disease is a rare familial disorder of lipoid metabolism occurring in children and characterized by deposition of the lipoid, kerasin, in reticulum cells throughout the reticulo-endothelial system. The onset of this disease is often associated with low grade fever, intermittent pain in various bones and joints, enlarged spleen and liver, secondary anemia and frequently leukopenia, thrombocytopenia, browish skin pigmentation and purpuric spots. While actual joint lesions are not common, there are increasing reports of hip involvement in patients with Gaucher's disease. In children the several varieties of hip involvement include (1) lesions of the femoral head often suggesting tuberculosis or Legg-Perthes disease, (2) lesions of the femoral neck with simple bone infiltration as seen in the X-ray, (3) pathological fracture of the femoral neck, or (4) coxa vara deformity with broadening and irregularity of the epiphyseal line. In adults the hip lesions may present the symptoms and signs of osteoarthritis. In one reported case, the disease began as a migratory polyarthritis with spindle shaped swelling of the finger joints and ecchymoses. X-rays revealed narrowed joint spaces and multiple cystic changes in the femoral heads and biopsy from an involved area of bone marrow revealed typical Gaucher cells.

The findings of large, foam-like Gaucher cells in material aspirated from the sternal marrow can be demonstrated in most cases and is a useful diagnostic procedure.

Blood Dyscrasias

Haemophilia

Joint cavities are a characteristic site of bleeding in haemophiliacs, frequently associated with the most trivial type of trauma. The onset of haemar-

throsis is often sudden with severe pain, warmth, swelling and fixation in flexion. Bleeding may occur directly into the joint cavity or into either the epiphysis or the diaphysis. Usually one joint is involved at a time though other joints may be the site of subsequent haemarthrosis. Recurrences are common. The large joints of the limbs are the most common site, the spine and small joints of hands and feet being affected less frequently. Shoulder involvement is rare. The acute phase may last a few days to several weeks. Absorption of blood is often incomplete, the retained blood resulting in a chronic synovial irritation with persistent pain, swelling and tenderness. As acute haemarthroses are repeated, the capsule becomes greatly thickened and punched out areas due to haemorrhages in subchondral bone may be evident on X-rays. Villous hypertrophy of the synovial membrane is accompanied by erosion of cartilage at the joint margins with subsequent irregular cartilage destruction extending over the joint surfaces. Fibrous ankylosis may occur early. Osteophyte formation is rare. Bizarre distortion and joint deformity is a frequent end result with subluxation, fibrous or bony ankylosis. Extensive destruction of subchondral bone especially in the smaller joints is common. Bleeding into a single joint may simulate the clinical and X-ray picture of sarcoma. Chronic haemarthroses may at times resemble tuberculosis, rheumatoid arthritis, Legg-Perthes' disease, syphilis or tumors of bone, cartilage or soft tissues.

Purpura

Idiopathic or anaphylactoid purpura, one of the non-thrombocytopenic purpuras may occur as one or a combination of several variants. The type characterized by uncomplicated skin haemorrhages is known as purpura simplex. If bowel or kidney lesions are present, it is often referred to as Henoch's purpura, and if articular lesions predominate, the terms Schonlein's purpura, or purpura rheumatica are commonly used. While the aetiology is obscure, preceding acute infections or food allergies have been incriminated in some cases. There is no demonstrable abnormality in the platelets, bleeding or coagulation time. The basic lesion is an increased permeability of small vessels. This disorder occurs most commonly in children and young adults and is generally characterized by recurrent episodes which last for days or weeks and tend to become gradually less severe and less frequent, finally disappearing as the patient gets older. The clinical manifestations may be extremely variable and exhibit various combinations of skin, gastro-intestinal renal and joint manifestations. The joint involvment takes the form of an acute, self-limited polyarthritis which is transient and leaves no permanent joint damage.

Sickle-cell Anemia

Some patients with sickle-cell anemia, during exacerbations of their disease, may complain of weakness, fatigue and aching pain in the peripheral joints and non-articular areas of the limbs. Transient joint swelling has been observed in some during relapses. Bone deformities such as kyphosis, scoliosis and saber shins may be a feature of this disease.

Neuropathic Disorders

It has not been established whether the so called neuropathic joint disorders which accompany lesions of the nervous system are secondary to trophic impulses as Charcot postulated or are the result of repeated microtrauma to an insensitive joint as proposed by Volkmann and Virchow. Lesions of the nervous system which may give rise to such neurogenic arthropathies include tabes dorsalis, taboparesis, syringomyelia, lesions of the spinal cord due to trauma, tumor, infection or developmental anomalies such as spina bifida, lesions of the posterior roots, peripheral nerve injuries, diabetes mellitus, poliomyelitis and leprosy. This type of joint disease has been reported in the hip, knee, shoulder, elbow, hand, foot, ankle, spine and rarely in the sacroiliac joints. The earliest changes usually begin in the cartilage and in the zone of calcification between the cartilage and underlying cancellous bone and include erosion of the cartilage, chip and compression fractures and proliferation of the marginal bone. Later, ossification in muscles and spontaneous fractures may occur. There is a gradual decalcification of adjacent bone and destruction of joint surfaces followed by excessive marginal bony overgrowth which is not uncommonly mistaken for degenerative joint disease (osteroarthritis). The articular cartilage is invaded by fibrous tissue from the pannus which extends onto its surface. At times there may be joint effusions and edema and infiltration of periarticular tissues. As cartilage becomes fragmented, loose bodies may form within the joint and may later become ossified with eventual grinding down and destruction of the articulating bone ends resulting in gross distortion. In the hips there is early erosion of the acetabulum with irregularity of the joint line. Later the acetabulum becomes enlarged and eventually destroyed with absorption of the head and neck of the femur. In the kneee, X-rays reveal early breaking down, flattening and condensation of the subchondral bone in the condyles, and later genu varus or valgus and subluxation of the knee may occur. Loose bodies in the knee, exostoses and ligamentous and intramuscular ossifications are noted in late cases. Neuropathic joint lesions may develop gradually or with striking suddenness. One or several areas may be involved and the process is not uncommonly bilateral. It may remain stationary for years or may gradually progress to complete disintegration of the involved joints. Although these joints are usually painless, pain may be present at some time during the course of the disease. They are characterized clinically by the loss of normal joint contours, the projecting knobs, the "bag of bones" feel and the extraordinary hypermobility which may permit the most remarkable distortions with no evident discomfort. The occurrence of joint disease without heart, pain or tenderness should always make one consider the possibility of a neuropathic arthropathy.

In syringomyelia the joint changes are basically similar to those seen in tabes but they occur more often in the upper extremity, they tend to develop more slowly and do not usually progress to the extreme degree of destruction seen in lower limb neuroarthropathies, possibly because the extra trauma of weight bearing does not enter the picture.

In recent years there have been interesting reports of comparable neuroarthropathy occurring in patients with long standing diabetes mellitus (ten

years or more), who have shown definite evidence of neuritis, usually severe in degree. In these patients the earliest gross change is unilateral or bilateral thickening in the tarsal region. This swelling is painless, without effusion or redness, heat or tenderness. These changes progress gradually, usually resulting in a thickened flattened foot with eversion and external rotation. X-ray changes are similar to those described in connection with other forms of neuroarthropathy.

Secondary Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy, first described as an ossifying periostitis by Bamberger in 1889, and in further detail by Marie, the following year, is a phenomenon secondary to a variety of widely differing primary lesions which include (1) chronic, long standing suppurative diseases within the thorax such as empyema, bronchiectasis and lung abscess, (2) any neoplastic process in the lung, mediastinum or pleura, the most common of which are carcinoma and the lumphoblastomas, (3) congenital heart disease, subacute bacterial endocarditis and rarely, valvular heart disease, (4) chronic liver disease, (5) disorders of the gastro-intestinal tract characterized by chronic diarrhea and, more rarely, (6) polycythemia vera, (7) leukemia and (8) hypothyroidism.

Because this unusual bone and joint disorder may occur with extra-pulmonary and extra-thoracic diseases, the term "secondary hypertrophic osteoarthropathy" is considered more appropriate than "pulmonary hypertrophic osteoarthropathy." The pathogenesis is obscure. It has been attributed by some to an increased rapidity of blood flow to the bone and soft tissues of the terminal portions of the extremities with consequent inadequate oxygenation of these tissues. Others have postulated that the osteoarthropathy results from overstimulation of the anterior pituitary by the primary disease but such an explanation is difficult to apply in all cases. The simplest clinical manifestation is clubbing of the digits but this process is not necessarily confined to the terminal phalanges of the fingers and toes and may extend to involve the shafts of the phalanges, the metacarpal, carpal, metatarsal and tarsal bones, the tibia and fibula, radius and ulna and any or all of the intervening joints. The humerus and femur are less commonly involved and then usually in the distal portions of their shafts. The clavicle, ribs and pelvis are rare sites of this disorder. Involvement of the ankle and lower leg, the wrist and forearm, or the knee region, in some cases may precede clubbing of the digits or may be the sole manifestation of secondary hypertrophic osteoarthropathy in the complete absence of digital clubbing. Clinically, the earliest sign of clubbing is an increased fluctuation of the nail bed, followed by thickening and proliferation of fibroelastic tissue at the base of the nail resulting in a filling out of the angle between the nail and the basal tissues and later by increase in nail curvatures, both longitudinally and transversely. Clubbing, per se, is usually asymptomatic. However as the pathological process extends to areas proximal to the distal phalanges, joint pain may be experienced and the involved areas of the foot, hand, ankle, wrist and lower portion of the leg or forearm may exhibit a painful, tender, firm, non-pitting edema. The lower forearm or leg may show a uniform, cylindrical, "tree trunk" like enlargement. The underlying pathological process is a periostitis with deposition of an extra layer of new

periosteal bone about the involved portion of the shaft. This new layer of cortical bone is a characteristix X-ray finding. The overlying soft tissues become thickened, tender and edematous. The joints in the involved areas may show synovial and peri-articular soft tissue swellings, intra-articular effusions and occasionally erosion of the articular surfaces and ultimate ankylosis. The importance of recognizing this condition is obvious. Arthralgia due to hypertrophic osteoarthropathy may be the earliest symptom of serious intrathoracic disease. It is not at all uncommon for a bronchogenic carcinoma to masquerade as some form of arthritis, usually resembling rheumatoid arthritis, for several months before the underlying primary disease is recognized. It is often amazing how rapidly the manifestations of hypertrophic osteoarthropathy may disappear if the primary disease process can be eradicated.

Sarcoidosis

Joint manifestations of sarcoidosis consist of vague arthralgias during the active phase of the disease and tightness and stiffness due to involvement of the skin of the digits. The latter may show some fusiform swelling which is located mainly between rather than at the joints and there is rarely any deformity or significant restriction of motion. Skin nodules may be present over the interphalangeal joints. Active inflammation of joints has been observed when the disease process has extended into the synovium from adjacent tissues. X-rays of the hands may reveal characteristic circumscribed osteolytic lesions in the phalanges, metacarpals and carpal bones without any periosteal change.

Ulcerative Colitis

Arthritis is an uncommon complication of idiopathic ulcerative colitis. Its incidence has been estimated as about four per cent of cases of this disease. It is more apt to accompany later exacerbations of ulcerative colitis, rather than the initial attack. Joint involvement may be monarticular or polyarticular and it varies considerably in severity. The joint lesions resemble those of rheumatoid arthritis with early periarticular involvement and intra-articular changes at a later date. Many of these patients experience complete and sometimes permanent remission of their arthritis but some do progress to a chronic, symmetrical, destructive type of joint disease with subluxations, deformities and ankylosis indistinguishable from typical rheumatoid arthritis.

Systemic Infections

Infective arthritis, that is the actual invasion of joint tissues by infecting organisms with resultant inflammatory changes in those tissues, is a well recognized complication of systemic infections due to a wide variety of pathogenic organisms, the most common of which are the staphylococcus, pneumococcus, streptococcus, gonococcus, meningococcus and tubercle bacillus. Practically any of the pathogenic micro-organisms are capable of causing a septic arthritis if they gain a foothold within the articular tissues which they may enter via the blood stream, by extension from infected tissues adjacent to the joints or directly through perforating wounds. Septic or infective arthritis

is usually an acute process with marked joint pain, swelling, tenderness, local heat, redness, effusion and limitation of movement. In some instances however and particularly in the case of tuberculous arthritis, the process may be much less acute, may develop insidiously and progress in a more indolent manner. Permanent and extensive destruction of cartilage, subchondral bone, ligaments, capsule, synovium and surrounding muscles, tendons and other connective tissue structures, with residual subluxation, contracture, deformity, ankylosis and muscle wasting can develop rapidly, sometimes in the space of a few days. This underlines the urgency of establishing an early diagnosis in such cases, followed by the immediate institution of treatment with suitable antibiotic or chemotherapeutic agents. If such treatment is begun early, if the proper drug or combination of drugs is given, and if they are continued in adequate dosage over a long enough period of time, such permament destructive joint changes can be minimized or avoided entirely in the great majority of cases. The only positive proof of the presence of septic arthritis lies in the isolation of the specific causative organism from material aspirated from the joint. Unfortunately much valuable time can be lost in attempting to culture organisms, time during which much destructive change can occur in the joint structures. Therefore if the general clinical picture is strongly suggestive of this condition, it seems justifiable to begin vigorous treatment with one of the broad spectrum antibiotics, *after* material for culture has been obtained. When a specific organism has been isolated and its sensitivity to the various antibiotics ascertained, the chemotherapy can be altered in accordance with the results of these bacteriological studies. In most instances early and vigorous treatment with appropriate antibiotics will obviate the necessity for surgical drainage of infected joints. Nevertheless if aspiration reveals the persistent presence of pus, adequate drainage is indicated just as it is for any collection of pus elsewhere in the body.

In many diseases due to specific infecting micro-organisms, the articular manifestations may be the presenting or most prominent feature of the illness. Aside from the matter of septic arthritis due to direct infection of the joints by the causative organism of the disease, certain rather unusual joint manifestations of some infective illnesses are worthy of separate comment.

Tuberculous Rheumatism (Poncet's Disease)

In rare instances, patients with tuberculosis of the lungs or sites other than bones or joints, may exhibit an interesting and puzzling form of non-destructive synovitis known as "tuberculous rheumatism" or Poncet's disease. In these cases there is no evidence of actual infection of the involved joints by tubercle bacilli, either by culture of joint fluid or by microscopic section. It has been suggested by some that this type of synovitis results from an abnormal immune response of the host to tubercle bacilli on the same basis that an immune response to streptococci results in the synovitis of rheumatic fever.

Syphilitic Arthritis, Synovitis and Bursitis

Systemic infection by the treponema pallidum of syphilis may result in a variety of "rheumatic" conditions aside from the neuropathic arthropathy of

neurosyphilis. These are rare complications which occur in less than one per cent of cases of systemic syphilis.

Parrot's Syphilitic Osteochondritis is the commonest of these rare luetic joint lesions and is seen in the early months of congenital syphilis, usually in the first three weeks of life and rarely after three months of age. This is an osteochondritis occurring close to the epiphyses, involving the upper limbs more often than the lower, and characterized by a gelatinous change in the bone and cartilage which breaks down to form a greenish-yellow fluid. Considerable periarticular swelling is usually present and complete separation or fracture of the epiphysis may occur. If adequate treatment is given in time, complete recovery may ensue but if the growing line has been damaged, shortening or deformity of the limb will result.

Clutton's Joints

Clutton's joints, another of the manifestations of congenital syphilis occurring in children between eight and fifteen years of age, are characterized by symmetrical swelling, stiffness and effusion involving the knees in 85 per cent of cases but also occurring in the elbows, wrists, ankles and fingers. Joint effusions usually accumulate rapidly and re-form promptly after aspiration. Pain is usually slight or absent, there are no significant X-ray changes and while the response to penicillin therapy is unsatisfactory, complete cure with no residual disability is the usual end result.

Syphlitic Dactylitis is a rare complication of congenital syphilis characterized by typical spindle-shaped swellings of the fingers or toes of children from one to three years of age. Marked shortening and deformity of the digits and absorption of the involved bone may eventually occur.

Bone and Joint Lesions of Acquired Syphilis

Syphilitic arthritis is a very rare disorder which has been described in the secondary stage, tends to involve multiple joints particularly the large joints such as the knees and is frequently bilateral and symmetrical. The joints appear swollen and fusiform with thickening of the synovium and peri-articular tissues and spasm and atrophy of adjacent muscles though the amount of pain and limitation of movement is variable. Some deformity may result though bony ankylosis does not occur.

Transient hydrathrosis may involve several joints, usually the knees, with associated pain, swelling and limited movement. Mild, relatively painless swelling of tendon sheaths and bursae may occur during the course of secondary syphilis.

Syphilitic periostitis adjacent to a joint may cause articular pain.

Syphilitic spondylitis may occur in the early or late stages of congenital or acquired lues, has a marked predilection for the cervical vertebrae and is manifested by cervical pain, often more marked at night, stiffness, tenderness on palpitation and tendency to avoid any movement of the head.

In the tertiary stage, gummatous involvement of synovium or adjacent bone or soft tissue may result in considerably joint destruction, deformity, instability, variable limitation of movement or ankylosis.

It is probably superfluous to stress that the mere presence of a positive serological test for syphilis in a patient with arthritis does not establish a diagnosis of bone or joint syphilis, which are very rare complications of this disease. Arthritis in a luetic patient is more likely to be one of the more common types of joint disease unrelated to syphilis.

Typhoid

Arthritis is a rare complication of typhoid fever, occurring in about one per cent of cases. Spinal involvement is usually confined to the vertebral periosteum and should be suspected in patients with backache, localized tenderness and limited movement during or following an attack of typhoid fever. Septic arthritis of the peripheral joints due to Styphosa and other salmonella does occur but is quite rare.

Brucellosis

Arthralgia occurs in almost all cases of infection by any of the brucella but actual arthritis is much less common. When actual joint inflammation, or arthritis, does occur it is most common in infections due to brucella melitensis, less commonly associated with brucella suis and rarely with brucella abortus. Joint phenomena may occur during the height of the disease or in the period of convalescence. The commonest of these is a migratory arthralgia, often of burning character, flitting from joint to joint, associated with no objective signs of joint inflammation and frequently mistaken for rheumatic fever. In about 10 per cent of cases of brucellosis, a true arthritis may dominate the clinical picture, most commonly involving the shoulders, knees, hips, ankles, small joints of hands and feet and sacroliliacs but any joint in the body may be affected. When arthritis does occur, it is usually a self-limited, non-suppurative type of joint inflammation, frequently confused with rheumatoid arthritis but rarely if ever characterized by the chronic, progressive, symmetrical and persistent arthritis so typical of the rheumatoid type. The usual result of brucella arthritis is ultimate complete resolution with no residua. Only in rare instances is brucellosis associated with a purulent arthritis leading to destructive changes, deformity or ankylosis.

Acute or subacute bursitis may complicate brucellosis with or without associated arthritis. The popliteal bursa is a common site of this lesion.

Brucella spondylitis is not uncommon, occurring most frequently several months after the onset of the febrile period but localization in the spinal column has occurred as early as three weeks and as late as a year after the initial infection. Destructive lesions, usually limited to a few vertebrae in the lumbar region, with wedging of vertebral bodies, narrowing of intervertebral spaces and destructive changes in the sacro-iliac joints usually confined to one sacro-iliac, constitute the lesions of brucella spondylitis.

Infectious Hepatitis

Several Scandinavian physicians have drawn attention to the observation that some cases of infectious hepatitis are introduced by arthritic symptoms lasting from days to months and accompanied by joint swelling which may simulate rheumatoid arthritis. These rheumatic symptoms and signs usually

disappear after the onset of jaundice and are considered to represent manifestation of the virus infection.

Subacute Bacterial Endocarditis

A non-suppurative arthritis due to the lodging of emboli in or about joints may occur in subacute bacterial endocarditis. This usually subsides in a few days. Purulent arthritis due to the strepococcus viridans has been reported but it is rare.

The Contagious Diseases

Slight joint swelling, effusion, pain and tenderness occasionally appear during the course of *mumps* and usually subside within a week or so leaving no residual joint disease.

Articular complications including septic arthritis and spondylitis have been reported in association with *measles* but their relationship to the virus of measles is not generally accepted and they are usually found to be due to secondarily infecting bacteria.

Arthritis is a rare complication of *variola* (small pox) or vaccinia, usually occurring in children. The joint symptoms as a rule begin three or four weeks after the onset of the disease, frequently after the skin eruption clears and scales begin to fall off. Swelling, pain on motion and limitation of motion involving the elbows, often bilaterally, may persist for several weeks. X-rays may reveal destruction of the epiphysis and subperiosteal new bone formation without loss of cartilage or joint space, most often involving the head of the radius. Suppurative arthritis may result from secondary infection of the pustules of variola or vaccinia with blood stream dissemination of the infecting organisms.

Polyarthritis is a well recognized complication of *scarlet fever* and is generally considered to represent a manifestation of hypersensitivity to hemolytic streptococci or their products, akin in all respect to rheumatic fever.

Systemic Infections Which Are Rare in Canada

(a) Arthralgia or (b) non-suppurative arthritis or (c) suppurative arthritis due to joint infection by the causative organism of the underlying disease, have also been observed in a large variety of systemic infections which are rare in Canada. These include yaws, rat-bite fever (Soduku), Haverhill fever, bacillary dysentery, granuloma inguinale, lymphogranuloma venereum, coccidiomycosis, histoplasmosis, trichiniasis and tularemia.

The Effects of Hormones and Drugs on Connective Tissue

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IN spite of the great advances made in the treatment of the diseases of connective tissue, we know very little about the way therapeutic agents affect its function. The use of salicylates still rests on purely empirical grounds and much is unknown about the action of hormones on supporting tissue. In the following review I will restrict myself mostly to the chemical aspects of the problem, since the morphological changes occuring during rheumatic diseases have been known for a long time.

As most other tissues the alveolar or loose connective tissue is composed of an intracellular and extracellular part. However the extracellular portion in connective tissue is of major importance, because it performs the supportive function of the connective tissue, the collagen, elastin being extracellular. The amorphous part, which is neither cellular nor fiber, is called the ground substance. Dorfman summarized our knowledge of the composition of the extracellular space in connective tissue:

(1) Substances derived from the blood stream, having remote origin.
  - (a) H_2O
  - (b) Inorganic ions
  - (c) Glucose, etc.
  - (d) Blood proteins
  - (e) Other unknown components

(2) Metabolic products of parenchymal cells

(3.) Metabolic products of connective tissue
  - (a) Fibrous structure (Imbedded in ground substance)
    - (1.) Collagen
    - (2.) Elastin
    - (3.) Reticulin (?)
  - (b) Mucopolysaccharides
    - (1.) Chondroitin sulfuric acid
    - (2.) Hyaluronic acid
    - (3.) Mucopolysaccharide protein complexes
    - (4.) Others (?)
  - (c) Soluble proteins
    - (1.) Procollagen
    - (2.) Others (?)

There is little doubt that the precursors of collagen and elastin are formed by fibroblasts and are precipitated into fibers in the ground substance. The compounds listed under mucopolysaccharides are of special interest. They are found in connective tissue (alveolar and cartilage) and in the aqueous humor. They are secreted either by the fibroblasts or the mastcells, it is not yet clear by which. Their chemical nature gives a clue as to their function:

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Hyaluronic acid is a straight chain polymer of d-glucuronic acid and N-acetyl-d-glucoseamine, while chondroitin sulfuric acid is a polymer with units of one glucuronic acid and one sulfated N-acetyl-d-glucoseamine. Both are acidic in character and act similarly to ionic exchange resins. As the resins, they are large molecules with free acidic radicals and can bind different ions. The configuration of these giant molecules is changed by the ions attached to them. We picture them forming a mesh in the tissue, the pores of which determine the ease of spreading of fluid in the tissue. Another function of the mucopolysaccharides is the coating of the surface of collagen fibers and thus they regulate the exchange of ions between the fibrils and the ground substance. Probably aging of the connective tissue has to do something with this hyaluronic acid coat: the amount of hyaluronic acid relative to the amount of collagen present decreases with age. (See the high mucopolysaccharide content of embryonal tissue and the umbilical cord.) Ascorbic acid probably is built into this polysaccharide chain and in this manner takes part in the function of the ground substance.

There is an enzyme associated with hyaluronic acid in the tissues, the hyaluronidase, which breaks it down into smaller components, it depolimerizes the hyaluronic acid. This is also called the spreading factor, because by breaking down the regulating mesh in the tissues, it promotes the spreading of dyes and water. This enzyme occurs in the skin, but there are large quantities in the testis and is also produced by certain bacteria.

Pathological processes like rheumatic fever and rheumatoid arthritis have profound effects on the polysaccharide mesh in the connective tissue. So have different hormones and drugs.

There is still a controversy, as to whether or not an increased spreading of a dye injected intradermally can be found in rheumatic diseases. However, there is much evidence that there is a change in the mucopolysaccharide structure. It has been found that the reconstitution of the hyaluronic acid barrier, after breaking it down with hyaluronidase, is much delayed in these diseases. This delay disappears when the symptoms of rheumatic fever subside, but is still maintained in latent rheumatoid arthritis and Still's disease. The viscosity of the synovial fluid, which is due to its polymerized hyaluronic acid content, decreases in rheumatoid arthritis. This would perhaps show that the synthesis of the polysaccharide is faulty in this disease, because there is no hyaluronidase in the synovial fluid, which could break it down. There is also evidence for the accumulation of polysaccharides different from the one occuring normally in rheumatic nodules, together with a large concentration of a new protein, called fibrinoid, but which has nothing to do with fibrin.

The effect of hormones on connective tissue can best be divided into localized and non-localized effects. Sex hormones act on a certain kind of connective tissue, like the chick's comb, or the sex skin of certain monkeys. Testosterone will cause a selective growth in these parts, accompanied by an increase in mucopolysaccharide content. Other hormones which have a generalized effect, do not act on these tissues. Another selective reaction is that of the retroorbital loose connective tissue to pituitary thyrotropic hormone.

However, we are concerned here mostly with the response to hormones of alveolar connective tissue throughout the body. Hormones, which affect

connective tissue can be classified into two groups: those which promote the reaction of connective tissue to external stimuli and those which suppress it. Their effect is antagonistic, they prevent the action of one another when given together. The reaction promoting hormones are the growth hormone or somatotrophic hormone, desoxycorticosterone acetate and the new natural mineralocorticoid, aldosterone. The reaction suppressing hormones are cortisone, hydrocortisone,and the new semisynthetic hormones like fluorohydrocortisone and l-dehydrocortisone (metacortandracin). ACTH belongs to this group too, because it stimulates selectively the production of hydrocortisone in the adrenals, without affecting the production of aldosterone.

The action of adrenal glucocorticoids (the suppressing hormones) on the connective tissue is complex. The hyaluronic acid-hyaluronidase system is certainly affected: although cortisone or hydrocortisone have no direct effect on hyaluronidase in vitro, in animals or patients treated with these hormones the spreading of dyes is reduced. The plasma mucoprotein level decreases and less mucopolysaccharide is excreted in the urine under glucocorticoid treatment, making the substances which are suspended in urine precipitate. The reduced viscosity of synovial fluid in rheumatoid arthritis returns to normal under treatment. The permeability of the synovial membrane is reduced by cortisone and the appearance in urine of the dye injected intraarticularly is delayed. It seems that glucocorticoids correct the faulty synthesis of the polysaccharides and make them more resistant to the action of hyaluronidase.

The action of adrenal hormones on formed elements is important too. The vascular bed is constricted under cortisone treatment making it less fragile. The diapedesis of leukocytes is inhibited. There is the well-known inhibition of fibroblast formation, which delays or entirely inhibits wound healing. The cohesion of collagen is decreased, but the amount of collagen is not decreased in normal tissue. However, where pathological proliferation occurred, the excess amounts of fibroblasts are broken down and the collagen disappears with them. It could be shown that hydrocortisone, in which radioactive C^{14} was incorporated, is accumulated in the fibroblasts. Other formed elements are also inhibited. When a cholesterol pellet is implanted, foreign body reaction appears, consisting of the accumulation of a large number of fibroblasts, lymphocytes and giant cells. None of these can be seen around a cortisone pellet. The phagocytosis by the leukocytes and the macrophages is also inhibited. The number of mast cells is decreased in the skin after local application.

Another important application of cortisone and like hormones, namely their beneficial action in allergic diseases, has a sound biochemical background. It has been shown, that they inhibit the incorporation of the amino acid histidine as histamine into the tissues. In this manner the antibody-antigen reaction is not followed, as usual, by the release of histamine. The effect of these hormones on antibody formation is controverisal, probably they depress it slightly.

Whether the effect of the reaction-suppressing hormones will be beneficial to the organism as a whole, depends on the stimulus which provoked the reaction. If the stimulus is a pathogenic organism, the tissue reaction serves as barrier to the infection and by this the body tries to restrict the penetration

of the organisms. Inhibiting this defense mechanism would be clearly to the disadvantage of the host. Indeed, infections present at the beginning of cortisone treatment or occurring during therapy, have a tendency to become generalized, for example the dissemination of tuberculosis bacilli from lung foci. If however the reaction did not serve a useful purpose, like an allergic reaction, where the organism overshoots its aim, an inhibition of tissue reaction would be beneficial. In most cases cortisone and ACTH do not affect the underlying hypersensitivity and when the hormones are withdrawn, the reaction appears.

The tissue reaction promoting hormones like growth hormone and DOCA, have in general an opposite effect. They increase the spreading of dyes in the skin and increase the permeability of the synovial membrane. Animals treated with large doses of DOCA will show lesions of the kidneys and the heart and also develop arthritis. The inflammation promoting effect of aldosterone is of special interest, because it raises the old question again, whether an excessive production of the inflammation promoting hormone over its antagonist is a causative factor in rheumatic diseases. Somatotrophic hormone has effects similar to DOCA, promotes the formation of granulation tissue and can produce, in large doses, nephritis and heart lesions.

It is probable that the beneficial effect of cortisone, ACTH and other similar substances is derived from the combination of the effects described above. There etiological role is a challenging problem.

The situation is entirely different with the drugs which have been used for a long time in the treatment of rheumatism: the salicylates and related drugs. Their value has doubtlessly been established both clinically and experimentally. They decrease the incidence of rheumatic involvements in experimental serum sickness and at least symptomatically are of great value in the treatment of rheumatic fever and rheumatoid arthritis.

In the last ten years two fashionable theories were developed in order to explain their beneficial effect, both theories reflecting a certain orientation in the thinking at that time. It seems that research workers are waiting for a new experimental finding which has some bearing on an unexplained phenomenon and then they try hard to clear up everything by this new lead. Later difficulties arise and the enthusiasm peters out. Perhaps the story of the salicylates is the best example of this

The first lead involving the hyaluronic acid-hyaluronidase system, was the observation that the cutaneous spreading of dyes is diminished in patients under salicylate therapy. The explanation naturally given was that salicylate inhibits the enzyme, hyaluronidase. However it was soon found that only concentrations much larger than occur in vivo have such an effect in vitro. Therefore the attention turned to gentisic acid, which is a metabolite of salicylate, 4.8 per cent of the administered salicylate being transformed into this compound in the body. This sounded attractive, because gentistic acid has also an antirheumatic action equivalent to that of salicylate. First investigators found that gentisic acid does inhibit hyaluronidase in vitro in small concentrations, but other workers repeating this experiment, showed that pure gentisic acid is inactive, and an impurity due to the oxidation of gentisic acid was responsible for the inhibition. This impurity, related to humic acid, has not been shown to occur in the body.

The second wave of enthusiasm was created when the beneficial effects of cortisone and ACTH became known. The logical hypothesis was that the effect of salicylates is mediated through the adrenal cortical hormones. This suspicion was strengthened by the fact that animals given large doses of salicylates showed increased adrenal secretion and few reports appeared on the increased excretion of 17-ketosteroids in patients treated with salicylates. Difficulties soon arose however, when it was shown that compounds devoid of antirheumatic activity stimulate the adrenals to the same extent. The increased excretion of 17-ketosteroids in patients was due rather to the underlying illness, than to the salicylate treatment. There are also differences in the metabolic effects of glucocorticoids and salicylates: cortisone and ACTH decrease glucose tolerance, while salicylates increase it. In general salicylates antagonize the effect of glycocorticoids on carbohydrate metabolism.

The conclusion is clear that we have no explanation for the potent antirheumatic action of salicylates as yet. It also shows very well, that parts of medicine are still largely in an empirical state, and progress is still made by the combination of empirical observations and scientific research.

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LEUKEMIA SOCIETY, INC.

The Leukemia Society, Inc., formerly the Robert Roesler de Villiers Foundation, established specifically for the purpose of encouraging research directed at finding a means for a preventive measure, control or cure of Leukemia, will award grants-in-aid to support research projects on Leukemia for the year 1956-57. Various amounts will be awarded depending upon the requirements of the investigators. Grants offered in 1956 will take into consideration requests covering more than one year. Renewal of grants at the termination of the initial period will also be considered. Applications may be made throughout the year. In order to be reviewed at the meetings of the Selection Committee on June 1 and September 1, 1956 and March 1, 1957, they should be received not later than May 15 and August 15, 1956 and February 15, 1957.

The Leukemia Society, Inc. will also accept applications for fellowships for studies in the field of Leukemia and allied diseases to be given during the year 1956-57, to be awarded by the Selection Committee on the dates of the meetings mentioned above.

Qualified investigators are encouraged to apply to:

LEUKEMIA SOCIETY, INC.
67 WALL STREET,
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THE ANNUAL MEETING

The 103rd Annual Meeting of The Medical Society of Nova Scotia will be held in Halifax at the Nova Scotian Hotel.

The Executive Meetings will be held on Tuesday, September 4th, and the General Meetings will be held on Wednesday, Thursday and Friday, September 5th, 6th and 7th, 1956.

The Chairman of the Housing Committee is Doctor A. W. Titus, 32 Connaught Avenue, Halifax, who will look after all requests for hotel accommodation for the meeting.

Please use Application Form for hotel accommodation on other side of this page.

HOUSING APPLICATION FORM

103rd Annual Meeting — Halifax, N. S., September 4 - 7, 1956
The Medical Society of Nova Scotia

Dr. A. W. Titus,
Chairman, Committee on Housing,
32 Connaught Avenue,
Halifax, N. S.

I am planning to attend the Annual Meeting of The Medical Society of Nova Scotia at Halifax, N. S., September 4 to 7, 1956.

Will you please reserve the following:

..... Double room with bath or shower (double bed).

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..... Room for..... persons (bath or shower).

In view of a large expected attendance no single rooms will be available at the Nova Scotian Hotel unless cancellations permit. If coming alone please check here.....(v) if you are willing to share a room. If you have a preference for some party to share with please insert name here.....

Name of persons who will occupy above reservations:

NAMES (Dr. and Mrs.).....

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There are in addition very lovely motels situated on Bedford Highway. If you prefer this type of accommodation please check here.....(v) and we will endeavor to arrange reservations for you.