Summary of Papers Presented at the 45th Annual McGuire Lecture Series* **

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It is the purpose of this presentation to quickly review some of the important points of the papers which were presented at the 45th Annual McGuire Lecture Series on the subject of immunology and rheumatic diseases. The first paper was presented by Dr. Mullinax who gave a background on the historical aspects of immunology, beginning with Jenner and cowpox immunology and immunity to attenuated smallpox demonstrated in milk maids, continuing through the contributions of Pasteur, von Pirquet (on serum sickness), Bence Jones, and Hargraves (with the LE cell in 1948), down to modern immunology with antibody structure by Dr. Porter in 1960. Dr. Mullinax also briefly alluded to light chains and heavy chains, suggesting that there were two domains in light chains and four domains in heavy chains. (This subject was later presented in more detail by Dr. Franklin.) He then turned to the B cells and T cells, indicating that B cells were producers of humoral or circulating antibodies whereas the T cells dealt more with cellular immunity and delayed hypersensitivity. He also introduced the five types of immunoglobulins known at this time.

Dr. Horwitz described the "three R's" of delayed hypersensitivity. The three R's included recognition, response, and reaction, all of which contributed to the afferent as well as the efferent limb of the inflammatory reaction. He demonstrated scanning electron microscopic pictures of B lymphocytes showing rough contour in contrast to the T lymphocytes which had a smooth contour. He then mentioned how these reactions were studied through skin windows and demonstrated the rosette technique with lymphocytes and sheep red cells. The disorders of recognition were due to absence of T lymphocytes. The diseases associated with serum inhibition of the lymphocyte function included various hematologic disorders and solid tumors, SLE, TB, multiple sclerosis, hepatitis, and leprosy. He also stated that as far as the immunosuppressant effects of drugs on delayed hypersensitivity are concerned, cyclophosphamide had the greatest effect on the B lymphocytes whereas 6-MP had the greatest effect on the T lymphocytes.

Dr. Moncure talked about laboratory studies in the diagnosis of rheumatic diseases, covering the third component of complement and ANA titers. He described the various immunofluorescent patterns which we see in SLE—peripheral, homogenous, and nucleolar. About one-half of the patients with nucleolar patterns are found to have systemic sclerosis. He stated that perhaps the ANA test was more sensitive and less specific than the LE test. Patients with juvenile rheumatoid arthritis were not likely to develop positive rheumatoid factor tests.

Dr. Davis discussed immune complex reactions of systemic lupus erythematosus. He demonstrated very well the work of Dixon in the original study with iodinated bovine serum albumin and anti-BSA antibody formation, with incorporation of complement and deposition of complexes in the skin, joints, and heart in complex disease. He also mentioned the fact that rheumatoid factor added to the system would further precipitate the DNA–anti-DNA in the system, possibly indicating the role of rheumatoid factor in rheumatoid arthritis.

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Dr. Rothfield's subject was the diagnosis and treatment of lupus nephritis. She mentioned the various types of kidney lesions—focal, diffuse, and membranous—in SLE nephritis and demonstrated beautifully the immunofluorescent pattern in the various types. She pointed out that in order to study the uptake in the immunofluorescent pattern in patients who have membranous glomerulonephritis, an H & E section present with the immunofluorescent sample is needed. She also stated that CNS lupus may have complexes deposited in the cord. Elaborating further, Dr. Rothfield indicated that focal glomerulonephritis patients do not die of renal insufficiency and that hematuria correlated closely with activity in SLE. Patients with the diffuse lesions are nearly all dead within three years even with prednisone and they have the worst prognosis. All membranous glomerulonephritis patients have nephrotic syndrome and in children, particularly, SLE presents a poor prognosis. Dr. Rothfield's general measures for treatment included rest, avoiding sun light and immunizations, proper handling of infections, and avoiding pregnancy. The treatment for focal nephritis is steroids. Patients with membranous nephritis do not do well on steroids or immunosuppressive drugs such as Cytoxan® since this is not an inflammatory lesion and, therefore, would not necessarily respond readily to them. Diffuse SLE nephritis, of course, is the indication for the use of combined steroid and immunosuppressive therapy. The question is still uncertain as to whether or not this really will prolong the life of patients with systemic lupus.

Next, Dr. Ziff delivered the first McGuire Lecture entitled, "The Rheumatoid Synovium." He pointed out that in the rheumatoid synovium there is a proliferation of the lining layer as well as an infiltration of the deep layer. The two types of cells which are present are phagocytic and synthetic cells, the synthetic cells being the fluid producers. He also mentioned the presence of the IgG rheumatoid factor complexes which are present in the deep layer. The formation of inclusion bodies with release of lysosomal enzymes is thought to be one of the methods of inflammatory reaction. The second half of the cycle is the activation of complement complexes which cause chemotaxis. The A and B cells are the cells in the lining layer, whereas the deep layer contains deposits of IgG and IgM and deposits of C3 and C4. This IgG site was indicated as the site at which rheumatoid factor is formed.

Dr. Owen spoke about synovial fluid. He demonstrated the value of examining a regular wet-prep and how one can use compensated polarized microscopy to differentiate between calcium pyrophosphate crystals and gouty crystals. He stated that rheumatoid arthritis (RA) cells are not diagnostic of rheumatoid disease but can be quite helpful in diagnosis if present in the synovial fluid. He also discussed the benefit of determining synovial fluid complement since when elevated, it is an aid in differentiating Reiter's syndrome from some of the other nonspecific cases of inflammatory synovitis.

Dr. O'Brien followed with a discussion of some of the newer nonsteroidal anti-inflammatory drugs used in the treatment of rheumatoid arthritis. He began by covering the use of aspirin, gold, and antimalarials. He pointed out that the problem in drug evaluation is that in early studies, particularly with indomethacin, investigators were not geared up for control studies. We now feel that indomethacin for treatment of rheumatoid arthritis is not as good as it was at first thought to be. It may be superior to placebo; perhaps, it is equal to small doses of phenylbutazone. Dr. O'Brien maintained that a patient should not be placed on a drug study unless he was not doing well. He mentioned newer preparations under investigation, some of which have been discontinued because of fatal hepatitis. Some promise was shown for the proprionic acid derivatives, one of which was fenoprofen calcium which is less toxic than aspirin. In a dose of 400 mg per day, it is about as effective as 15 aspirin tablets daily without the side effects of aspirin. We have been using this drug on an experimental basis here for over a year now and find that it is very effective in the management of some cases of rheumatoid arthritis. He mentioned some of the other indole derivatives, all of which have somewhat the same effect as Indocin®.

On the second day of the symposium, Dr. Buckley spoke on the immunodeficiency diseases. She discussed agammaglobulinemia associated with arthritis and reported four patients who had hypogammaglobulinemia. The B cells in these cases are not able to produce IgG. She also discussed selective IgA deficiency. Some of these patients have ataxia telangiectasia and chronic, recurring infections, atopic disease, autoimmune disease, and diarrhea. The lymph node biopsies from these patients may show two different types of findings. The B cell deficits will show absence of the cortical

follicles in the lymph node, whereas the T cell deficits may show some derangement in the medulla of the lymph node. She demonstrated some of the ways of marking B and T cells by using the rosette method which Dr. Ziff discussed later. The two types of agammaglobulinemia were contrasted—the Bruton type and the other type in which the plasma cells did not secrete IgA. Patients with B cell deficits can live to adulthood but severe T cell deficit patients die within two years. This is the "Swiss" type of agammaglobulinemia. Bone marrow transplantation from a histocompatible sibling may be a life-saver and about half of those done have been successful. For treatment of B cell deficiency, she indicated that the simple use of γ-globulin is not sufficient, that all five classes of immunoglobulin need to be replaced by plasma infusions in lieu of injection of γ-globulin. Dr. Buckley encouraged the use of the "buddy system," siblings or friends who live in the same home who are HAA negative.

Dr. Calabro talked about juvenile rheumatoid arthritis, early diagnosis, management, and prognosis. He indicated that juvenile rheumatoid arthritis usually came on before the 16th year of life and pointed out the differences in the features of juvenile rheumatoid arthritis and adult rheumatoid arthritis. The major difference is that adults have rheumatoid factor present and juveniles, as a rule, do not. Also, subcutaneous nodules are more common in adults than in children and the fever, rash, and iritis are usually not present in adult rheumatoid arthritis but are present in juveniles. Dr. Calabro described three modes of onset: the acute febrile or Still's type, the polyarticular, where four or more joints are involved, and the monarticular, where only one joint is involved. Patients of the third group are more likely to develop chronic iridocyclitis and they get into real difficulty as time goes on. The fever is a "double" type of fever whereby the temperature at sometime during the day may go down to below normal. The fever usually responds very promptly to aspirin in large doses. The Köbner phenomenon, similar to an urticarial type of reaction, is one in which the rash can be brought out with a simple stroke on the skin. Although quite helpful, this is not specific for the rash of juvenile rheumatoid arthritis in that other types of rashes may behave similarly. The laboratory aids here are the presence of anemia, elevated ESR and lymphocytosis. These children frequently have positive ANA titer, may have positive ASO titer, and the x-ray will frequently show periostitis. In Dr. Calabro's 15-year follow-up, many of the monarticular patients went on to develop polyarticular states and the same was true for patients with the oligoarticular type. Treatment consisted of aspirin, gold salts, and steroids, with steroids particularly advisable in the acute febrile Still's patient where there was pericardial or eye involvement.

Dr. Baum discussed ankylosing spondylitis which he said was not a variant of rheumatoid arthritis. He stated criteria for diagnosis of ankylosing spondylitis and demonstrated certain feaures in the examination of a patient with ankylosing spondylitis. A very interesting x-ray finding, the syndesmophyte, was discussed—vertical syndesmophytes in spondylitis versus horizontal osteophytes in osteoarthritis. The various associated complications—aortitis, iritis, heart block, amyloidosis, subluxation, and pulmonary fibrosis—were discussed. The variants of ankylosing spondylitis—psoriatic, chronic ulcerative colitis, Whipple's, and Reiter's spondylitis—were discussed. The work that has been done, particularly by Dr. Schlosstein and Dr. Terasaki at Los Angeles on the transplant antigen W-27 locus, was summarized. Eighty-eight percent of patients with ankylosing spondylitis demonstrated this antigen as opposed to an 8% incidence in a random population. This certainly points to some genetic aspect in ankylosing spondylitis. It may also have something to do with the prognostic significance, particularly in children, if a patient possesses a W-27 antigen locus.

Dr. Franklin, "Mr. Immunoglobulin," talked about the G, A, M, D, and E myelomas and described the structure of the immunoglobulin molecule with the Fab fraction or the antigen binding site and the constant fraction (Fc) of the immunoglobulin. He listed the various H-chains and L-chains of IgG, A, M, D, and E and talked about the J-chain. By the time a diagnosis of multiple myeloma is made, the chances are that the patient has had the disease some 15 years prior to the time that bone lesions appear. The bone pain is usually the factor which brings the patient to the doctor. The other disorders, macroglobulinemia, H-chain disease, and the benign monoclonal gammopathy were discussed. Benign monoclonal gammopathy is present in about 3% of patients over 60 years of age. There are about 35 cases of γH-chain, about 50 cases of αH-chain, and only 7 cases of μH-chain disease reported. These are very rare, but they have certain characteristics of γH-chain myeloma and may simulate lymphoma.

Palatal and uvula swelling are two things which sometimes aid in making the diagnosis. Rarely do these patients have bone lesions and recurrent infection is usually the reason for seeking medical attention. These patients have a characteristic electrophoretic pattern. Patients with αH-chain disease usually have malignant lymphoma of the intestine and malabsorption. The αH-chain is produced in the plasma cells lining the intestine and may or may not be malignant. Of seven elderly patients with μ-chain disease, all had chronic lymphocytic leukemia. Lymphadenopathy is usually absent and these patients have hepatosplenomegaly and a high incidence of Bence Jones protein and κ-light chains in the urine. The finding that is very helpful in diagnosis of μ-chain is the presence of a large vacuolated plasma cell which can be found in the bone marrow. The bad effects caused by these proteins are the hyperviscosity syndrome, cryoglobulinemia and Bence Jones protein, the latter of which damages the kidney. They have bleeding and clotting disorders, infections, hemolytic anemias, and amyloidosis. Dr. Glenner and his group at NIH now have indicated that light chain fragments are present in amyloidosis.

Dr. Waller discussed the serum agglutinators and indicated that rheumatoid factors were IgM, whereas the serum agglutinators were antiglobulin antibodies or IgG which are a normal constituent of serum. These are closely associated with suppurative infection, particularly gram-positive organisms. The hidden sites on the Fab fragment are responsible for the formation of the serum agglutinators after papain or pepsin digestion. There are about 14.9% positive serum agglutinators in a hospital population as opposed to 0.5% in our arthritis clinic. Large abscesses usually have positive tests; subacute bacterial endocarditis may have positive tests for serum agglutinators.

Dr. Ziff presented the second McGuire Lecture on "Viruses and the Connective Tissue Diseases." Again he stated that T cell lymphoblasts in the presence of antigen can convert B cells into plasma cells to produce serum antibody and that virus infections would diminish T cell formation. Dr. Ziff discussed further the concept of T cell helper and T cell suppressor substances in which he indicated that viruses might be an enhancing mechanism to stimulate the B cells to produce autoantibody.

Dr. Bisno spoke on the subject of acute rheumatic fever and glomerulonephritis with streptococcal antigen. He did mention the fact that ASO is frequently elevated in throat infections and not necessarily elevated in pyoderma. The sequelae of the throat infections are more likely to produce acute rheumatic fever than acute glomerulonephritis, whereas the sequelae of the skin infections are more likely to produce acute glomerulonephritis. Dr. Bisno briefly discussed the streptozon test, on which he and his associates are now working, which may be very helpful in the diagnosis of streptococcal infection and sequelae.

Dr. Blaylock's lecture included a discussion of urticaria, hives, eczematous dermatitis and rheumatoid lesions. IgE is the immunoglobulin which is present in patients with urticaria, hay fever, asthma, and penicillin allergy. He noted that pemphigus vulgaris has 7S γG which is usually laid down between the cells and around the keratinocytes. Gamma G globulins will vary in pemphigus vulgaris, whereas in bullous pemphigus the serum globulins usually stay the same. IgG is usually deposited on the basement membrane similar to that in SLE. Dermatitis herpetiformis produces IgA on the basement membrane.

Dr. Cooke discussed methods of early diagnosis of gonococcal arthritis and the absolute necessity of instituting prompt treatment.