THE USE OF COLEY'S MIXED TOXINS IN THE TREATMENT OF CHRONIC ARTHRITIS.

By THOMAS KLEIN, M.D.,

PHILADELPHIA, PA.

One need not look very far into the endless literature to realize fully the perfectly hopeless task of finding a suitable classification of the various forms of chronic arthritis. It is also not within the bounds of this short paper to enter into any lengthy discussion. Suffice it to say that the term chronic arthritis as here employed embodies those types which are variously classified as: Chronic non-suppurative arthritis; Rheumatoid arthritis; Chronic infectious arthritis; Chronic osteo arthritis or arthritis deformans. Gout or gouty arthropathies being a purely metabolic disease is not here considered. The same holds true to the arthropathies of nervous origin or those occurring in tabes dorsalis (Charcot joints) and in syringomyelia. The chronic hypertrophic osteo arthropathies occurring in the course of pulmonary tuberculosis, bronchiectasis, chronic bronchitis, malignant tumors of the lung, and various chronic cardiac conditions are again distinct and are not included in the above term chronic arthritis as here used. Syphilitic arthritis is again a more or less distant entity and is not here considered. Villous arthritis is probably a stage of chronic osteo arthritis and will be considered as such. Fibrositis and panniculitis will be described as a part of the chronic infectious process so frequently occurring in this type of case.

The vast majority of the remaining cases will fall into that group in which we are primarily interested. This group is characterized at the beginning by swelling of the smaller joints, both meta-carpo-phalangel and metatarso-phalangel. The process may be unilateral but is more often bilateral. In the early stages the joints gradually swell with little or no pain. This gives them the characteristic fusiform appearance. Upon examination they have a distinct doughy feeling. At times there is a questionable effusion into the joint. Pathologically this enlargement is due to swelling and hypertrophy

of the synovial membrane and capsular ligament. Pain is only present upon pressure and active or passive motion. The disease progresses with definite periods of acute exacerbations, characterized by fever and its accompanying symptoms; increased pain and stiffness in joints and surrounding structures — frequently by focal manifestations as increased swelling and redness in the joint structures themselves. These periods are also associated with a slight increase in leucocyte count as compared during the stage of quiescence. In all respects it follows clinically the course of an infection. During this time the disease progresses upward involving the larger joints, namely the wrist, elbow, shoulders, ankle, knee, hip and the joints of the spine.

Soon after the beginning of the process which in itself is essentially an hypertrophy of the periarticular structures, we have an atrophic process set up:—The atrophy involves the muscles, subcutaneous fat and skin. These atrophic changes are undoubtedly due in many instances to a reflex atrophy. Vulpains idea, namely that impulses carried from irritated articular nerves alter the trophic activity of the cells in the anterior horns without causing a lesion, but sufficient to cause atrophy and weakness, is an extremely good one and is the best explanation offered. It is the glossy atrophic condition of the skin, atrophy of the subcutaneous fat and muscles plus their subsequent contractures which gives the characteristic deformity. The extensor groups of muscles always suffer greater damage than the flexors. Hence flexor contractures always predominate. This is explained by the fact that the nerves which supply the extensors also supply the joints themselves, consequently they bear the blunt of the irritation and the greatest atrophy.

Associated with this degenerative process is a fibrositis involving both the aponeurosis and the muscles themselves. In fleshy individuals the subcutaneous fat is also caught in the process in the form of a panniculitis. These two conditions account for a good deal of the patient's suffering and as we will see later form a very important part of the treatment.

The feeling that this type of case is always due to a chronic infection is fast gaining ground. Even though the causative organism is not found, the clinical course with its frequent, regular, acute

exacerbation associated with fever, increased swelling, pain and redness of the joints, increased leucocytes as compared with the quiescent period, is sufficient to establish this fact. Consequently, when such a case presents itself for treatment we immediately look for a focal infection. Teeth and tonsils correctly occupy the foreground as the most frequent sites of focal infection. Following these are the sinuses, gall-bladder, prostrate, infected ingrown toe-nails, ulceration along the intestinal tract, mediastinal lymph nodes, etc. The femal pelvis has not been found an important factor in our groups of cases. In one case now under treatment the mucous membrane of the mouth afforded repeated rich groups of a hemolytic streptococcus; otherwise no source of infection could be found. The prostate and seminal vesicles are frequently overlooked and when found as a source are too often looked upon as gonorrheal. The streptococcus may long persist without any gonococci being found. Non-surgical biliary drainage, done in an aseptic way offers many opportunities for the study of the gall tract for infection. Too often we overlook the bacteriology of the feces, as here is not an infrequent source of streptococcus infection.

Again we must remember that in the vast majority of cases, we are dealing with not one focus of infection but many. The eradication of a dental abscess or a pair of tonsils does not mean that we have removed all the source of infection. When one considers a mediastinal lymph node or an intestinal ulceration as a focus he will readily realize the difficulties in their removal. It is because of this fact and the repeated failure in not getting good results, that lead us to the utilization of a streptococcus vaccine. The vaccine also has further assets. It probably stimulates antibody formation to overcome any focus not eradicated and at the same time seems to aid in a causation of a retrograde process in the periarticular structures themselves.

During the past seven years Dr. Robert G. Torrey and myself have been using Coley's Mixed Toxins (a mixture of the streptococcus of erysipelitus and bacillus prodigiosus) in the treatment of this type of case with surprisingly good results. This vaccine was selected solely because of the potency or virulency of the streptococcus used (.01 cc. of the cultures being sufficient to kill a white mouse in

twenty-four hours). It is again easily obtainable in the market which is a distinct advantage to many men. The action of this vaccine is undoubtedly that of a high powered foreign protein but on the contrary after observing quite a series of cases one cannot help but wonder if it is not in some way a specific. It suggests the thought that the strain of streptococcus causing this disease is in some way related to the streptococcus of erysipelas. Thus far I have treated a series of twenty-one cases. Of these twenty-one cases, twelve have been cured, seven are still under treatment with marked improvement (diminution of pain, swelling of joints, decrease of ankylosis, acute exacerbation being lessened in frequency and severity, and finally abolished, with general improvement in health and gain in weight). Two cases stopped treatment because of severe focal and local reactions. The type of cases treated have been in the vast majority of cases far advanced. The earliest case treated was that of three months duration. The oldest case of fifteen years standing. The average length of duration previous to treatment was 3¼ years. The length of treatment varied equally as well. The earlier the case was started, the shorter was the duration of treatment. In the earliest case the vaccine was given over a period of three months. In the longest case the vaccine was carried over a period of fifteen months.

Mode of Treatment.

When the case presents itself the patient is studied thoroughly from all standpoints, especial attention being paid to focal infection, teeth, tonsils, sinuses, gall-bladder, stools, etc. If the patient presents gastro-intestinal symptoms fractional gastric analysis, feces examination and x-ray studies are made. The colonic stasis which is rather frequent in this type of case is corrected by diet and frequent colonic irrigation, using large quantities of water. The patient is usually undernourished, especially so in young people and I always encourage forced feeding; diets of special food have not proven satisfactory in any other way. For the past few years I have been making complete blood studies including complement fixation tests and the examination of urea, nitrogen, blood sugar, uric acid, creatinin and the chlorides. It has proven very discouraging with the exception

of an occasional high uric acid content. This I believe is of extreme importance in helping to differentiate some of these cases. One of my cases has a combination of a rheumatoid and gouty arthritis. She runs a rather persistent high blood uric acid. When the gall-bladder is under question the bacteriology of the bile is studied after asceptic transduodenal lavage. Surgery is only employed after a proved focus has been found. Needless to say that other various x-ray studies are made as indicated, including the joints themsleves. These patients are usually placed in hospitals for a short time during the starting of the vaccine. Rest is a very essential element in these cases and a few weeks in bed usually affords benefit. At the same time it accustoms the patient to the reaction of the vaccine.

In starting the vaccine it is very essential to start with a small dose, usually $\frac{1}{4}$ minim in 1 cc. salt solution or sterile water. This is given subcutaneously. Three types of reaction are experienced, focal, local and general. It has been my practice to tell these people that after the vaccine injection they will have pain in joints heretofore unknown to be involved. The pain in the joints is invariably increased after the first four or five injections. This thereafter will gradually be diminished and the period of freedom from pain will gradually be increased. At the site of injection a marked erythematous area develops. The fluid is quite irritating and at times you will think of abscess formation. This I have not experienced but for a week or more the hard indurated nodules persist. These patients are very hypersensitive to the vaccine and the dose must be increased very slowly. This hypersensitivity persists surprisingly throughout the course of treatment and varies with each individual. The largest dose of vaccine given was 10 minims and that after eight months treatment. In the case of fifteen years duration in which we obtained a beautiful result, I could never give over four minims without causing a general reaction. It is to be remembered that in these cases of long standing the patient is usually anemic and markedly undernourished. The pain has been severe and their nerve has been broken. Consequently it is important to try and avoid a general reaction. While this does not do the patient any harm, it is bad from a psychological standpoint. In addition they have been through so many hands and tried so many forms of treatment that

they are always dubious of any new form of treatment and especially so if they are to have more pain in the beginning.

The time interval of the injections varies from three to four days at the beginning, gradually being lengthened to five or six days, as the symptoms improve. It has been my rule to gage the time of injection and the size of the dose entirely upon the local reaction. If it be severe the same dose is repeated. At times it is necessary to repeat the same dose as many as four or five times before increasing the vaccine. Especially is this true as the larger doses are used. The vaccine is continued until the patient is clinically well. Unfortunately the time of stopping the vaccine is entirely emperical as I know of no way of telling when the infection has been entirely killed out.

The benefits derived are a diminution of pain plus a loosening up of the joints. The acute exacerbations which are so characteristic of the disease gradually diminish and are finally obliterated. It is remarkable to see the rapidity of diminution in the size of the joint. The patient through his own efforts will begin to move the joint and loosen it up as soon as the pain subsides. In the febrile cases the temperature gradually returns to the normal course. The patient's general health improves and he soon loses his toxic appearance. The gain in weight is quite remarkable. One patient who has been under treatment for the past seven months has gained forty-two pounds.

At the beginning of the treatment in addition to clearing up foci of infection, rest and vaccine therapy, the patient is given daily electric bakes to the joints involved; this quite frequently being a general body bake. Care is taken not to massage the joints or the atrophic surrounding structures until after the acute tenderness and swelling have subsided to a great extent. When the massage is started it is of the most gentle character, care being exerted not to traumatize an already diseased tissue. Manipulation, extension, deep massage and other mechanical devices are only resorted to when the patient is well toward recovery. The fibrositis in some cases persists and occasionally it is necessary to stretch the muscles under an anesthetic. Casts are applied but are removed each day for the bake, massage and manipulation.

In conclusion it must be said that the treatment of these cases

is as complex as their source of infection. The more thoroughly they are studied the more frequently I believe we will find definite evidence of streptococcus infection. Unfortunately the streptococcus does not lend itself to the formation of agglutinins or precipitins; consequently serological tests, so far have failed to give us any definite information. Coley's mixed toxins when used cautiously and over a prolonged period of time have in our hands given us a very satisfactory and pleasing result.