5-1-1933

Chronic arthritis with special attention to vaccine therapy

Chauncey A. Hager
University of Nebraska Medical Center

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---Chronic Arthritis—With Special Attention To Vaccine Therapy.---

Senior Thesis

University of Nebraska
College of Medicine
1933

Chauncey A. Hager Jr. B.Sc., A.B.
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-----Preface-----

This thesis is an attempt to present the most recent work on vaccine therapeutic measures as used in cases of chronic arthritis. It has been observed that too many cases of chronic arthritis are considered hopeless and that cases of this type are not at all welcomed by the average general practitioner. It seems that a review and application of proper therapeutic measures to cases of chronic arthritis will give one the ability and confidence to care for cases not desired by many. It is with this in mind that this thesis is written.

Although dealing for the most part with therapeutic measures and especially with the vaccine phase of therapy, I am including, for the sake of completion, sections on history, classification, etiology and symptoms of chronic arthritis.

The most recent work and, in my opinion, the most conclusive along this line is that done by Clawson and Wetherby at the University of Minnesota College of Medicine, hence their work is considered here in detail and is presented as reported by them.

Chauncey A. Hager Jr.
Arthritis is a diseased state characterized by disability and, usually, by structural changes in one or more joints, the word being derived from the Greek "arthron", meaning joint, and the ending "itis", meaning "of the nature of", and now signifying inflammation.

Introduction-

Arthritis is one of the oldest diseased states of which there is any historical record, and evidence of its existence goes back to the Mesozoic period, long before the advent of man. The preservation of such evidence, after the lapse of some ten or fifteen million years, is due to the fact that the lesions of arthritis and the rheumatoid syndrome frequently involve or produce osseous structures which persist long enough to permit of being transformed into fossil form. The arthritic and rheumatoid syndrome is by no means confined in its expression to the bony system however, and it is certain, therefore, that the soft yielding structures must also have been involved. (1)

Disease processes at large apparently evolved more or less parallel with life itself, but there are only a few evidences of a pathological state older than that of arthritis.

These pathological manifestations perhaps hardly represent disease entities and consist in the following: dental carries, pyorrhea alveolaris, fracture, osteomyelitis, callus and parasitism. They appear in the age of amphibians during the later part of the paleozoic period, at which period bacteria and fungi were also abundant. (2)

In the next era, the Mesozoic, during the age of reptiles, various lesions appear in fossil remains, including hemangiomata, osteomata, the arthritides and others. From this time on the evidence of disease is more abundant.

Arthritis was a cause of suffering and disability to the reptiles of the cretaceous period as is clearly shown by the fossil bearing beds of Nebraska and Kansas. There are specimens showing involvement of the caudal vertebrae of Diplodocus, a giant dinosaur, and multiple arthritis in Platecarpus, a large swimming reptile.
Through the ages long subsequent to this, and after the arrival of mammals, other animals were victims of arthritis and the cave bear of Europe and the sabre-toothed tiger of California seem to have been especially subject to it. It is, therefore, not surprising to find that the early evidences of man show that he too suffered at remote periods from arthritis. The remains of men of the old stone age are by no means as numerous as those of many other varieties of animal life, preceding and contemporaneous with man, so that the probability of finding specimens showing arthritis is not great unless the disease were well-nigh universal. Notwithstanding this fact a considerable number of specimens has been found demonstrating that primitive man probably suffered from arthritis much as we do today. (3)

There is no question, therefore, that arthritis has been the cause of suffering to man from time immemorial, and, as one writer has put it, it was the disease par excellence of the ancient Egyptians. The emphasis which the Greeks, and especially the Romans, placed upon hydrotherapeutic measures of many kinds is evidence of their effort to seek relief from rheumatoid disabilities, and there are kurorts or spas in Europe, such as Aix les Bains, which have been frequented continuously for two thousand years. Arthritis is today one of the great scourges of society, and this fact is fairly well recognized by the laity, who, too frequently failing of relief at the hands of the profession, have resorted in large numbers to sanatoria and various springs of alleged value. The extent to which the general public has thus sought relief is well exemplified by the number of such institutions or "cures," which were for a long time, and are even now in some part, independent of medical oversight. The laity have ascertained that symptomatic and even permanent relief can frequently be obtained by measures which are not necessarily prescribed by the profession, and have, therefore, flocked in great numbers to resorts such as those mentioned.
Classification

Chronic arthritis is now usually divided into two main groups—atrophic and hypertrophic. This classification is open to objection in that it implies the existence of two different diseases. Much evidence has been presented in support of the view that both types are but different expressions of one and the same condition. Nichols (4) and Richardson concluded that both degenerative and proliferative changes could not be differentiated etiologically and that the same irritant acting upon different structures in the joint might be responsible for either type of arthritis. Billings (5) writes: "Various anatomical types of chronic infectious arthritis may occur, which doubtless depend upon the degree of virulence of the infectious organisms, the resistance of the tissues, the degree of bacteremia and the fact that the mode of infection is hematogeneous. Consequently we may have a periartitis, a synovitis, an osteoarthritis or a panarthritus. Any or all of these may exist in the same individual." Nathan (6) believes that the pathological variations depend upon the point of involvement, the intensity of the irritation, the duration of the infection and the stage during which the infected structures are examined. He thinks that the degenerative changes may be simply the terminal stage of a previous inflammatory process and that there are no joint diseases which are exclusively degenerative or proliferative; the one or the other may predominate in a particular joint, but there are evidences of both these conditions in practically all joint diseases. Stengel (7) and Fox write, "The lesions that go on in arthritis are now atrophic or degenerative, now relatively hyperplastic and productive of bone or cartilage, but with few exceptions it cannot be said that they present clinical or pathological entities."

McCrae (8) writes: "In many cases all forms of changes are found, which speaks against the view that there are two distinct diseases."
Cecil and Archer(9) studied a series of 612 cases of chronic arthritis in the Cornell Clinic. The classification which they propose is essentially clinical and the terminology of Nichols and Richardson was adopted in this classification. They placed the great majority of their cases in one or the other of their two groups. The entire series is grouped in table one, in which it will be seen that proliferative arthritis constitutes about two thirds of all the cases admitted to the arthritis clinic, while degenerative arthritis made up most of the remaining third.

Table 1.-Distribution of Cases

<p>| | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Proliferative arthritis</td>
<td>. . . . . . . . . . . . .</td>
<td>414 cases</td>
</tr>
<tr>
<td>Degenerative arthritis</td>
<td>. . . . . . . . . . . . .</td>
<td>162 cases</td>
</tr>
<tr>
<td>Gout</td>
<td>. . . . . . . . . . . . .</td>
<td>4 cases</td>
</tr>
<tr>
<td>Intermittent hydrops articularum</td>
<td>. . . . . . . . . . . . .</td>
<td>2 cases</td>
</tr>
<tr>
<td>Unclassified</td>
<td>. . . . . . . . . . . . .</td>
<td>10 cases</td>
</tr>
</tbody>
</table>

Proliferative arthritis includes all the frankly inflammatory arthropathies. It can be subdivided clinically according to Cecil and Archer(9) into-

1. Chronic infectious arthritis, referable to foci of infection.
2. Specific arthritis, caused by specific bacterial infection. The gonococcal, syphilitic and tuberculous cases come in this group, as well as the so-called surgical joints, staphlococcus arthritis, pneumococcus arthritis, etc.
3. True arthritis deformans, a chronic progressive polyarthritis of unknown origin.

The cases of degenerative were also divided into subgroups-

1. Arthritis of the menopause.
2. Degenerative monarticular arthritis (morbus coxae senilis)
3. Senile arthritis.
The complete classification of the 612 cases is given in Table 2, in which it will be seen that two types of arthritis make up the great bulk of the material in the Cornell Arthritis Clinic—chronic infectious arthritis and arthritis of the menopause.

Table 2.—Complete Classification of 612 Cases of Chronic Arthritis

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferative Arthritis</strong></td>
<td></td>
</tr>
<tr>
<td>1. Chronic infectious type</td>
<td>379</td>
</tr>
<tr>
<td>2. Specific arthritis</td>
<td>18</td>
</tr>
<tr>
<td>3. True arthritis deformans</td>
<td>17</td>
</tr>
<tr>
<td><strong>Degenerative Arthritis</strong></td>
<td></td>
</tr>
<tr>
<td>1. Arthritis of the menopause</td>
<td>145</td>
</tr>
<tr>
<td>2. Degenerative monoarticular arthritis</td>
<td>20</td>
</tr>
<tr>
<td>3. Senile arthritis</td>
<td>17</td>
</tr>
<tr>
<td><strong>Gout</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Intermittent hydrops articulorum</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Unclassified</strong></td>
<td>10</td>
</tr>
</tbody>
</table>

A more detailed discussion of the groups as outlined above follows—

Proliferative Arthritis

**Chronic Infectious Arthritis (Focal Infection Type)**

This was by far the most common type encountered in the clinic. This type of arthritis occurs much more commonly in females than in males. It is essentially a disease of young people, the average age being 35. Exposure plays a secondary role. The most common etiologic factor is some primary focus of infection. In this series, infected tonsils were the commonest focus, occurring either alone or in combination with other foci in 61 per cent of the cases. Next in frequency were infections about the teeth. The teeth alone or in combination with other foci were the seat of infection in 33 per cent of the cases. The sinuses, prostate, gall bladder, colon, and cervix harbored foci of infection in several cases. It is interesting to note that the age incidence was much earlier in the tonsil cases than in the dental cases, the average age
being 30 years in the former, and 42 years in the latter group.

The patient often dates the onset of symptoms from some disturbance of the physical equilibrium, such as an acute infection, exposure to cold, a surgical operation or a confinement. A majority of, but not all, of the tonsil cases give a history of a preceding attack of tonsillitis or sore throat.

Chronic infectious arthritis is a polyarticular disease which may involve any joint in the body. It may come on suddenly with fever and other acute symptoms or the onset may be very gradual. Locally, the lesions are characterized by inflammatory and proliferative change in the joints involved. It is almost always migratory in the early stages, but after several attacks the joints become permanently injured. The fingers, knees and shoulders are the joints most frequently involved. This is a painful form of arthritis, especially in the early stages, when there is considerable articular involvement.

Physical examination usually but not always reveals a patient somewhat underweight and anemic. The joints affected usually present a characteristic appearance. There is some swelling of the soft parts and the overlying skin is warm and sometimes reddened. The swelling is due for the most part to an outpouring of inflammatory exudate into the periarticular structures. Tenderness is usually present and motion, either active or passive, is painful. In the later stages the swelling may disappear, but usually there is enough new growth and fibrous tissue about the joint to cause a persistent periarticular thickening. This is shown most typically in the finger joints, in which the characteristic fusiform enlargement may be present for years. Ankylosis is very common in this type of arthritis, but usually does not occur until the second or third year of the infection. It is at first fibrous but later may become bony.

According to Cecil and Archer (9) the laboratory findings in this type are mostly negative. Cultures from foci of infection yield either Streptococcus hemolyticus or Streptococcus viridans. Streptococcus hemolyticus was more frequently obtained from the tonsil and Streptococcus viridans from root
abscesses. In fourteen cases the blood sugar showed an average of 125.3 mg. per hundred c.c. which is somewhat above the normal limit. In seven cases in which the basal metabolic rates were determined the results were negative.

Specific Infectious Arthritis.

Eighteen cases in the series fell into this group. Stiologically they may be divided as gonococcus arthritis, eleven cases; tuberculous arthritis, five cases and syphilitic arthritis, two cases.

Gonococcus Arthritis-Ten of these cases were in men and one in a woman. all gave a history of gonococcal urethritis. These patients were treated locally by the urologists, while the arthritic condition was being treated with physiotherapy and vaccine.

Tuberculous Arthritis-There were five cases of tuberculous arthritis distributed as follows: hip, two cases; wrist, one case; elbow, one case; ankle, one case. These cases presented the typical and roentgenological picture of tuberculous joint disease and were treated at the orthopedic clinic.

Syphilitic Arthritis-Two cases were classified as syphilitic arthritis, but neither of them was typical of the disease. One, a Charcot joint occurring in typical tabes, should more properly have been classified as a trophic arthropathy. The other case was that of a woman, aged 50, with tertiary syphilis and a chronic polyarthritis of the proliferative type. The typical syphilitic joint is usually monarticular and is caused by the extension of specific periostitis into the synovial membrane.

Arthritis Deformans-Eighteen of the series of cases were classified as arthritis deformans. This is the type spoken of by Barker as the "primary progressive polyarthritis" and, as he says, "is the most malignant of all arthropathies". English writers refer to this rather rare disease as "rheumatoid arthritis". This type is considered by many to be nothing more than an extremely severe grade of chronic infectious arthritis. Certainly in the early stages it presents very much the same clinical picture. Its chief characteristic is its steadily progressive course. It is sometimes referred to as atrophic arthritis. Usually there is considerable periarticular infiltration
and later on an actual thickening of the capsule. Ankylosis occurs early and there is marked destruction of the articulating surfaces, with telescoping of the joints and ulnar deviation of the hands and fingers. The process tends to be symmetrical. The temporomaxillary joints are frequently involved.

The average age of the eighteen patients in this series was 44 years. Fourteen were females and four males. It was very significant that the average duration of the disease on admission to the clinic was seven years. Most of these cases, if seen during the first years of the disease, would probably have been classified as infectious arthritis. However, in nine out of the eighteen cases no focus of infection could be located. In five cases the tonsils showed evidence of infection, and in two others root abscesses were found.

Three of these patients were subjected to tonsillectomy. One had the cervix cauterized. Streptococcus vaccine and physiotherapy, including high colon irrigations, were tried on most of the patients. The results of treatment were for the most part negative.

**Degenerative Arthritis**

Degenerative arthritis is usually a milder disease than proliferative arthritis. The lesions, for the most part originate in the bone and cartilage and in the majority of the cases the soft parts are never seriously involved. For this reason, degenerative arthritis is usually less painful than the inflammatory types already discussed.

Richardson has aptly described degenerative arthritis as occurring in those who are "physiologically old." It is usually associated with arteriosclerosis, obesity, gray and falling hair, and the other stigmas of somatic deterioration. For this reason this type of arthritis is usually looked upon as non-infectious. This, of course, is difficult to prove, but the character of the pathologic changes, its association with other sclerotic and degenerative processes in the body, the absence in most cases of foci of infection and the clinical course of the disease (absence of fever and inflammatory reaction about the joint), all speak rather strongly against the infectious origin of degenerative
arthritis.

Altogether, 182 of this series were in this group. These were subdivided clinically as: arthritis of the menopause, 145 cases; degenerative monarticular arthritis, 20 cases and senile arthritis, 17 cases.

Arthritis of the Menopause—Next to infectious arthritis, this was the most common type of arthritis seen in the clinic. More than 25 per cent of the entire series fall into this group. This is a chronic degenerative arthritis, involving multiple joints, and occurring in obese middle-aged women at, or just after the menopause. The average age was 53 years. In almost every case the patient was considerably overweight. Symptoms usually appear during the first two years after the menopause. Sometimes the arthritis occurs simultaneously with the menopause, and in a few cases the rheumatic symptoms have preceded the menopause by a short interval.

Foci of infection are rarely demonstrable, and for this reason the infectious origin of the disease has been questioned. The morbid changes are those of a degenerative osteoarthritis. The cartilage becomes thin, and there is lipping and spur formation of the bone at the margins of the joints involved. Occasionally there is a secondary thickening of the synovial membrane.

The onset of the disease is insidious. The first symptom is a slight stiffness in the knees, which gradually becomes more noticeable, especially in walking or bending. In this series of cases, both knees were usually involved. Sometimes, however, the symptoms were more marked in one knee than in the other. The lumbar vertebrae and the bones of the feet are often involved. In a large percentage of patients, there were well-developed Heberden's nodes on the distal phalangeal joints. At times a shoulder or hip joint was implicated.

The physical appearance of these patients is quite characteristic. They are almost always overweight, sometimes to a marked degree. The posture is faulty, and usually there is some degree of flat foot. Examination of the joints involved shows little, if any, swelling, but in cases of long duration, the heads of the bones adjacent to the joints may be enlarged. On flexion a
certain amount of crepitus is usually detected. Roentgenograms show distinct lipping and spur formation. True ankylosis does not occur.

The progress of this type of arthritis is very slow but with the passing years the patients discomfort becomes more marked. There is little tendency toward involvement of other joints. On the other hand, spontaneous recovery seldom, if ever, occurs.

Degenerative Monoarticular Arthritis—This is another form of degenerative arthritis which occurs most frequently in the hip, in which it is spoken of as "morbus coxae senilis". Occasionally it is seen in the shoulder or knee.

Twenty cases of this type occurred in this series. The distribution was as follows: hip, 16 cases; shoulder, 2 cases and knee, 2 cases. This type of arthritis occurs in late middle life. The average age was 58 years. Fourteen were men and six, women. Twelve of the fourteen men were outdoor workers. Eight of the twenty patients gave a definite history of trauma. Fourteen of the patients had had roentgenograms made. The pathologic changes in this group of cases are more marked than those occurring in menopausal arthritis. The lipping is more obvious and there is more destruction of the articular surfaces. In fourteen cases no focus of infection could be established. Six patients had dental treatment for pyorrhea, and in one case the tonsils showed some evidence of infection.

In a middle aged patient with chronic monoarticular arthritis of the hip, the presumption is that the lesion is of the degenerative type. It must be remembered, however, that infectious arthritis is occasionally monoarticular and that it may involve the hip joint. The possibility of tuberculous arthritis must also be considered.

This type of arthritis is not usually correlated with focal infection. Furthermore, the removal of possible foci, such as pyorrhea, has never resulted in benefit to the patients condition.

Senile Arthritis—Seventeen cases were classified under this heading.
This form of arthritis is also of a degenerative type, but has a somewhat different distribution from the two forms already discussed. The average age of the patients was 67 years. Three were men and thirteen were women.

Definite foci of infection were noticeably absent. One patient had an infected prostate, and two showed severe pyorrhea. The rest were without and demonstrable foci.

This form of arthritis may attack almost any joint in the body. It is always polyarticular. It is almost physiologic in the spine and also in the distal phalangeal joints, in which it shows itself in the form of Heberden's nodes. The knees, knuckles, feet and shoulder joints are frequent sites of involvement.

The lesion here, as in the other two types, is essentially an osteoarthritis, manifesting itself as a new growth of bone and cartilage around the edges of the joint. As in the other forms of degenerative arthritis, true ankylosis does not occur.

Gout

There were four cases of gout included in the series, three men and one woman. The average age was 35 years. When seen in the clinic only one showed an involvement of the great toe, but the others gave histories of previous attacks in the big toe. Three cases showed involvement of the knees and other large joints. The fingers were affected in two cases. Only one patient showed tophi in the ear. The average uric acid content in the blood was 6 mg. per hundred c.c.

Intermittant Hydrops Articulorum

Two of these cases were encountered in this series. Both patients were men, one aged 40 and the other aged 49. In both the attacks came regularly every ten days. The duration was two or three days in one case and one day in the other. In the first patient the right ankle became swollen, and in the second patient both knees and occasionally the right hip were swollen and painful at regular intervals of ten days.
Both patients showed infected tonsils. One had a tonsillectomy without any improvement. Later on, however, he was found to have a chronic infection of the prostate.

**Spondylitis**

Spondylitis perhaps deserves especial mention. The vertebral joints, like other joints in the body, are susceptible to the various types of arthritis. Infectious arthritis may occur in a single vertebral joint, but more frequently it involves a group of several vertebrae. It usually occurs more frequently in the cervical and dorsal vertebrae. In severe cases, however, it involves frequently the entire vertebral column, producing considerable periarticular reaction and spasm of the dorsal muscles. Fibrous ankylosis may occur early, with production of the so-called "poker spine." Like other forms of infectious arthritis, it is amenable to successful therapy if the foci of infection, usually in the tonsils, are removed early.

True arthritis deformans frequently attacks the spine and progresses rapidly to complete ankylosis.

Degenerative arthritis usually occurs in the lumbar spine and is frequently seen in association with arthritis of the menopause and senile arthritis. Indeed, lipping of the lumbar vertebrae is almost a physiologic process in late middle life.

**Heberden's Nodes**

Heberden's nodes are present in nearly every case of menopause arthritis. They may develop independently, however, of any joint involvement, when they fall in the category of senile arthritis. They are usually more apt to develop in people who work hard with their hands and are exposed to the rigors of cold weather.

**Pathology of Chronic Arthritis**

Space does not permit an extensive review of the literature on this subject. One of the most thorough studies of the pathology of arthritis is that
of Nichols and Richardson(10) published in 1909. They divide the joint lesions of chronic arthritis into two very definite pathological groups:

1. Those which arise from primary proliferative changes in the joints, chiefly in the synovial membrane and in the perichondrium. This is the type known as "proliferative" arthritis.

2. Those which arise primarily as a degeneration of the joint cartilage. This is the group referred to as the "degenerative" type.

These two pathologic types are characterized by distinct gross and histologic differences, and each type manifests itself clinically by a characteristic group of symptoms. (9)

In proliferative arthritis, proliferation of the synovial membrane produces a layer of granulation tissue which sooner or later may extend over the joint cartilage with more or less destruction of the cartilaginous tissue. Furthermore, proliferation of the perichondrium may lead to the formation of new cartilage or bone. The capsule and other periarticular structures are also involved in this process. These truly inflammatory changes, if not checked, lead eventually to partial or complete destruction of the joint cavity with subsequent fibrous or bony ankylosis. In the opinion of Nichols and Richardson, these changes represent a reaction to injury that may be either bacterial or toxic in their nature.

In degenerative arthritis, the primary change in the joint is a degeneration of the cartilage of the articular surfaces, which gradually becomes softened and eroded. The underlying bone thus becomes exposed, so that eventually two bony surfaces may be in contact. As a result the exposed bone becomes extremely dense and acquires a high degree of polish. The head of the bone is enlarged and leads to an actual increase in size of the articular surface. Secondary changes consist of an increase in the activity of the perichondrium at the periphery of the joint where the cartilage and the capsule come together. As a result of this perichondrial activity, there is a new formation of cartilage which may become transformed into bone. The newly formed bony tissue takes the form of lipping and irregular exostoses, so readily demonstrable in
This important work of Nichols and Richardson corroborated the earlier work of German and English pathologists and has more recently been verified by the studies of Ely. According to these authors, these two types of chronic arthritis could not be distinguished etiologically. They thought that the same cause might produce the primary change either in the synovial membrane or in the cartilage, and that different causes might produce the same type of pathologic lesion.

Etiology of Chronic Arthritis-

Inasmuch as the main substance of this thesis deals with the specific vaccine therapy in the treatment of chronic arthritis, some detail will be gone into in the establishing of a more or less definite etiological factor in the majority of cases of chronic arthritis.

Since the association of focal infection with arthritis has already been mentioned, it seems pertinent to bring forth the statement of Columella in Liber de Re Rustici, "that there are minute organisms which the eye cannot see and which enter the body and cause disease". This is the first and last reference to bacteria until Arthanasius Kircher advanced the theory of a "contagium animatum" in 1658.

Lucian of Saramosta wrote a tragic comedy on podagra. Diocletian exempted from public burdens and taxes those severely crippled with arthritis (morbus articularis). Caius Aurelianus in the fourth century A.D., described sciatica as an arthritic manifestation. Alexander of Tralles in the sixth century, A.D., used colchicum for relief of pain. Paulus Aegineta regarded podagra and rheumatism as the same disease, and like Hippocrates advised the use of emollients to the joints and adequate care of the gastro-intestinal tract. Bartholomeus Anglicus in the thirteenth century described arthritis as of the blood therefore systemic rather than articular only. Ballonius in the sixteenth century described arthritic manifestations as involving not only the joints but the subcutaneous nodules, muscles, tendons and aponeuroses, and
noted as did Hippocrates before him, the viscous serosity of the affected joints and tendon sheaths. He also first differentiated and vividly described rheumatic fever.

Malpighii wrote on arthritis and somewhat antedated Baer in noting lymphatic gland involvement.

Leeuwenhoek noted chain bacteria growing around the teeth. Musgrave in 1703 wrote a sizable book on arthritis in which he cited the connection of the disease with almost every focus known today, thus antedating the work of Billings and Rosenow by some two hundred years. The highlights, only, have been most briefly touched on, but the thought has been to lead up to the crux of this very short historical resume—namely, the prophecy of Robert Boyle that the problem of infectious disease would be solved when the nature of fermentation was discovered.

This prediction was fulfilled by the investigations begun by Redi, Cagniard, Latour and Schwann and carried to a brilliant culmination by Pasteur who demonstrated the living nature of ferments and the specific nature of micro-organisms which cause fermentation and putrefaction, thus paving the way for rational investigation of the infectious diseases and showing the etiological relationship between bacteria and disease, fulfilling the prediction of von Plenciz of Vienna, who, in 1762, expressed the belief that bacteria were the causative factor in disease, and that cure would be possible when the distinct causal agent in each malady was discovered.

As this astounding statement predicted, Pasteur, 120 years later, was able to isolate pathogenic bacteria and gave treatment by vaccine, in such cases as chicken cholera and anthrax.

In 1878, Pasteur found the streptoccus in septicemia. In 1885 Wilson isolated a bacterium in a case of rheumatism with pleurisy. In 1886 Mantle found a coccus in a rheumatic case. In 1887 Popoff experimentally produced arthritic lesions with streptococci. From 1887 to 1889, more than a dozen research workers were actively engaged on the bacterial causative theory of rheumatism. In 1889
Wasserman obtained streptococci from the blood, brain and heart of a young woman with cerebral symptoms followed by chorea, which had been preceded by a rheumatic attack. These organisms grew outside and when injected into rabbits caused an infective arthritis.

Such straws began to show which way the wind blew and pointed to arthritis as an infective disease.

In more recent times, the most important contribution to the etiology of chronic arthritis was that made by Billings (12) and his co-workers over twenty years ago, when they pointed out the relationship which existed between focal infection and chronic infectious arthritis. Other students of arthritis were quick to recognize this important work, and now the role of focal infection in the etiology of this disease is widely recognized. Billings believed that the joint manifestations were nothing other than metastatic infections, and he preferred the term chronic infectious arthritis to arthritis deformans or rheumatoid arthritis.

In spite of the popularity of the theory of focal infection, modern authorities are not entirely in agreement as to the importance of such foci in the etiology of chronic infectious arthritis. Furthermore, even among those who accept the theory of focal infection, there is considerable disagreement as to what bacteria are actually responsible for the disease. The almost constant presence of streptococci, of some form, in the original foci of infection has naturally led to the presumption that some type of streptococcus was responsible for the arthritic condition as well as for the focal infection. Unfortunately, the bacterial flora in the tonsils and about the teeth is so varied and contains such a multiplicity of streptococcal forms or types that it has been impossible to determine whether Streptococcus viridans, Streptococcus hemolyticus or the indifferent streptococcus plays the etiological role. This confusion is enhanced still further by the presence of just as many varieties of streptococci about the teeth and tonsils of healthy persons as in those patients suffering with chronic infectious arthritis.
McRae (13) took the view that the condition is always secondary to a focal infection somewhere in the body, but doubted whether this means actual infection of the joint with organisms. He thought that the joint changes in many cases might be due to toxins. He ventured no opinion concerning the actual bacteria responsible for the disease.

Pemberton (14) expressed the belief that focal infection in the teeth and tonsils is responsible in many cases, but that a large variety of diseases of an infectious or inflammatory nature may act in an analogous way. He believed that the most important causative organisms are Streptococcus hemolyticus and Streptococcus viridans, "although probably any other organism is capable of producing the same results".

Osgood (15) stated that rheumatoid arthritis is a disease in which no specific organism has been found which can be held constantly responsible for its causation. He concluded that there are probably many different types of organisms and many other factors that play etiological parts in its onset and course.

Nichols and Richardson (16) after careful investigation of the pathologic changes in sixty five cases of chronic arthritis, came to the conclusion that the lesions in the rheumatoid type might result from a great variety of origins, such as infection, disease and trauma.

Hench (17) of the Mayo Clinic expressed the belief that arthritis deformans is primarily of infectious origin. He emphasized the systemic nature of the condition.

A considerable amount of research has been carried out on the bacteriology of chronic infectious arthritis, but none of this can be said to have furnished conclusive evidence as to the exciting cause of the disease. The constant presence of various types of streptococci in the tonsils and about the teeth has naturally focused the interest of investigators on these organisms. Davis (18), in 1911 took cultures from the various foci of infection which he found associated with chronic arthritis. In the great majority of cases the hemolytic streptococcus was the predominating organism. With these streptococci, Davis
was able to produce arthritis experimentally in rabbits. Blood cultures and cultures from the joint fluids of patients with chronic arthritis never gave positive results. However, Davis felt that, from his own investigation, the hemolytic streptococcus was probably the etiologic agent.

Working on the assumption that chronic deforming arthritis was a streptococcal disease, Hastings (19), in 1913, resorted to the complement fixation test as a method of determining which type of streptococcus was instrumental in causing the disease. By employing the old Wasserman technic, Hastings obtained positive complement fixation with the serum of arthritic patients and strains of streptococci isolated from foci of infection. In this way he believed that he could determine the exact biologic type of streptococcus with which the patient was infected.

More recently Burbank and Hadjopoulis (20) have repeated Hastings' complement fixation work with a slightly modified technic. They found that patients with periarticular or deforming arthritis reacted positively to some form of hemolytic streptococcus, whereas patients with osteo-arthritis reacted positive to streptococci of the viridans group.

E.C. Rosenow (21) was disposed to look on Streptococcus viridans as the exciting agent in chronic infectious arthritis. This investigator took cultures from the enlarged lymph nodes of patients with chronic arthritis and was able to isolate Streptococcus viridans in a large number of cases.

Small (22) believed that a certain number of cases of chronic infectious arthritis are nothing more than a chronic form of rheumatic fever, and as such are referable to infections with the indifferent streptococcus (Streptococcus cardio-arthritis)

From this review of the literature, it is evident that while bacteriologists have suspected the streptococcus as the exciting cause of chronic infectious arthritis, there is considerable disagreement among them as to which type or types of streptococci are responsible for the disease.

The natural and obvious place to look for the causal agent of chronic infectious arthritis is in the joints involved. Unfortunately, efforts to
cultivate bacteria from the joints themselves has not been successful consistently.

Rosenow (22) in 1914, made cultures of the joint fluid in cases of chronic infectious arthritis and of the lymph nodes that drained the involved joints. He stated that in several instances he recovered Streptococcus viridans from both the glands and the joint fluid.

Moon and Edwards (23) in 1917, took cultures from the joints in ten cases of chronic infectious arthritis, and recovered a non-hemolytic streptococcus in six cases. They did not give any further description of the organism found.

Richards (24) in 1920, took cultures from the joints in fifty-four cases of chronic infectious arthritis, and isolated Streptococcus viridans in four cases.

Billings, Coleman and Hibbs (25) in 1926, took cultures from the joints in fourteen cases of chronic infectious arthritis. One yielded a hemolytic streptococcus; five gave either a non-hemolytic or a green producing streptococcus, and one gave a mixed streptococcus culture with the non-hemolytic predominating. In six cases the results were negative, and in one the observations were not recorded.

H. Warren Crowe (26) took cultures from the joint tissue of five patients suffering from rheumatoid arthritis, and isolated a staphylococcus, the so-called Micrococcus deformans, in four of five instances. Control cultures from tissue removed from nonarthritic patients did not show this organism.

Forkner, Shands and Poston (27) recently took cultures from the joints in sixty-three cases of chronic infectious arthritis, recovering organisms in fourteen or 22 per cent. Eleven of the joint cultures contained Streptococcus viridans, two yielded gonococcus and one Staphylococcus aureus. Cultures of the lymph nodes draining the involved joints were made in twenty-one cases. Ten of these cultures were positive, nine showing Streptococcus viridans and one, gonococcus.

During recent years, several investigators have studied the bacteriology
of the blood in rheumatoid arthritis.

Moon and Edwards (23) in 1917, using Rosenow's technic, made blood cultures in eighty-three cases of rheumatoid arthritis, and recovered a non-hemolytic streptococcus in eighteen. They felt, however, that a diphtheroid bacillus, or B. mucosus-capsulatus, as well as the streptococcus, could act as the exciting agent in this disease. Moon and Edwards made no attempt to classify the streptococci which they isolated by sugars or by immunologic tests. Furthermore they did not report on non-rheumatoid conditions.

Richards (24) in 1920 made blood cultures in cases of chronic arthritis, making use of North's medium. Blood cultures were taken in 104 cases of chronic arthritis, and fourteen yielded positive results. Richards referred to this organism as Streptococcus viridans, although he remarked that the growth was not always typical, only three of his strains showing green in the original culture.

Hadjopoulos and Burbank (28) took cultures from the blood in 145 cases of chronic arthritis and obtained a streptococcus in fifteen (10 per cent). Nine of these strains produced hemolysis, while six were of the viridans type. In eight cases a diphtheroid bacillus was obtained, while five others showed Staphylococcus aureus. These workers do not give the technic employed other than to state that their success was due to "neutralization of alexin in the freshly drawn blood." No control cultures were reported. These investigators were able to produce an experimental arthritis in rabbits with their streptococci.

Syranyi and Forro (29) recently took cultures from the blood of twenty-five cases of polyarthritis and obtained a streptococcus in 68 per cent. In nineteen of the cases described as "polyarthritis with fever," fourteen or 73.6 per cent were positive. In the remaining six cases of the group, referred to as "polyarthritis without fever," three or 50 per cent were positive. This organism isolated by these two workers was classified as Streptococcus viridans. The various strains differed slightly in their reactions on sugars, but they all fermented saccharose, salicin and lactose. These investigators did
not report any experimental work on animals.

H. Warren Crowe (26) took cultures from the urine of patients suffering from rheumatoid arthritis and isolated a staphlococcus, Micrococcus deformans in a high percentage of cases. This organism was not found in control cultures. He was unable to produce an experimental arthritis in animals with this strain.

From this brief review of the literature, several conclusions seem to be justified:

1. While the relation of focal infections to chronic infectious arthritis is rather generally recognized, there is doubt in the minds of many as to whether the joint manifestations are actually metastatic infections or whether they are merely an expression of some toxic influence on the joint.

2. In respect to the bacterial agent responsible for the disease, a majority of the investigators look on the streptococcus as the exciting cause, but some believe that the staphlococcus, the gonococcus, the diphtheroid bacillus or some other micro-organism, as well as the streptococcus, can produce a deforming arthritis.

3. Even among those investigators who accept the streptococcus as the cause of rheumatoid arthritis, there is considerable disagreement as to which type of streptococcus is responsible, some considering it a hemolytic streptococcus infection, while others look upon the indifferent or the green streptococcus as the causative agent. Another group of writers believes that the condition may be caused by any of the various types of streptococci.

4. A number of workers have found streptococci in the joints and even in the bloodstream in cases of chronic infectious arthritis, but the results have been inconsistent and uncontrolled.
Recently Cecil, Nicholls and Stainsby (30) report their work carried out at the Cornell Clinic. They studied a series of seventy eight patients with chronic infectious arthritis and concluded that:

1. A streptococcus can frequently be isolated from the circulating blood of patients with chronic infectious arthritis (61 per cent in this series of seventy eight patients).

2. Of these streptococci, 83.3 per cent are culturally and biologically identical, and appear to be attenuated hemolytic streptococci. The remaining strains fall into either the viridans or the indifferent group of streptococci.

3. A streptococcus, culturally and biologically identical with the strain isolated from the blood, can sometimes be cultivated from the infected joints in the same patient.

4. A streptococcus, culturally and biologically identical with the strain isolated from the blood and joints, can sometimes be isolated from a focus of infection in the same patient.

5. When the typical strain of streptococcus is injected intravenously into rabbits, a majority of the rabbits develop a chronic non-suppurative polyarthritis. Microscopically, the histologic changes in the rabbit's joints are practically identical with those observed in the joints of patients with chronic infectious arthritis.

6. Cultures from the blood and from the joints of animals infected with experimental arthritis frequently yield a streptococcus identical with the strain originally injected.

7. These observations tend strongly to confirm the theory that chronic infectious arthritis is a streptococcal infection, caused in a large proportion of cases by a biologically specific strain of this organism. The presence of this specific strain of streptococcus in the blood stream of several patients with advanced
Arthritis deformans goes far to corroborate the view already widely held that arthritis deformans and chronic infectious arthritis are one and the same disease.

Margolis and Dorsey (31) in their work on cases of chronic arthritis conclude that the non-hemolytic green producing and indifferent streptococci seem to be of first etiologic significance as they isolated non-hemolytic streptococci from the epiphyseal marrow and bone, from the synovial membrane and from the cartilage obtained from joints affected with chronic non-specific arthritis. The synovial fluid from these cases did not yield organisms other than those from occasional contamination. As it was found that the epiphyseal marrow and bone yielded bacteria more frequently than other tissue they called attention to the fact that this may indicate a significant site of infection in the pathogenesis of arthritis which had not been given due consideration in the past. In their experiments with laboratory animals they found that several of the streptococci isolated from arthritic tissues showed marked elective affinity for joints when injected intravenously into rabbits. Thus this work tends to bear out the fact that the Streptococcus viridans is for the most part the etiological organism.

Not only is there a difference of opinion as to the etiological organism in chronic infectious arthritis but there is also some question as to the mechanism of the action of the causative organism. Whether the action be due to direct invasion of an organism circulating in the bloodstream, whether a toxin is formed at a focus of infection which is carried to the joint or whether the joint change is of the nature of an allergic action is a much discussed question. The fact that some investigators have isolated their organisms from the joint fluid and from the tissues in the region of the joint would support the direct invasion point of attack, but we see many clinically typical cases in which no organisms can be isolated and it becomes of convenience to consider the reaction as being due to a circulating toxin or an allergic reaction.
Since the work of Herry (32) in 1914 and particularly that of Farber (33) in 1915, there has been a growing tendency to explain the manifestations of rheumatic fever on an allergic basis. This conception differs essentially from those which attribute the disease to a bacteremia or a toxemia, in that, while it associates the etiology of rheumatic conditions with streptococci, it declares in favor of no particular species or type strain of this organism since the allergic manifestations may be excited by streptococci which differ widely both in biologic characters and in serologic relationships. That is to say that animals sensitized to one variety of streptococci, react not only to the homologous antigen, but to antigens derived from heterologous strains.

Small (34) in his work on the role of streptococci in rheumatic disease, offers an hypothesis embracing a dual nature of its pathogenesis. A specific toxin of a streptococcus is suggested as operative in the production of the "destructive" and "proliferative" types of lesions in rheumatic conditions, while the patients hypersensitization to an allergen associated with the protein of streptococci is presented as concerned in producing the exudative lesions. He concluded that this sensitizing substance, or allergin is not dependent upon the type of streptococcus supplying it. Small emphasizes the fact that chronic arthritis is an allergic disease, the hypersensitive state of the patient being due to this allergin contained in the streptococcus, without regard to a particular type. He therefore concludes that the treatment of chronic arthritis should largely be concerned with the elimination of foci harboring streptococci, and with adequate desensitization.

Freiberg (35) has noted the development of a characteristic joint lesion in rabbits following the repeated injection of a bacterial filtrate. The joint changes which followed the repeated injections of this bacterial filtrate were localized, altered tissue responses, otherwise identified as a hypersensitivity reaction to the products of bacterial growth, this disease process being termed allergy. Following the repeated intra-articular injection of a bacterial filtrate, in the rabbit, a monarticular arthritis
This arthritis did not become evident until two or more injections of the filtrate were made. With each successive injection the localized reaction in the joint became more pronounced. Coincidentally, in the rabbits which had received these bacterial filtrate injections, there developed not only specific agglutinins in the blood as shown by a high titer serum agglutination reaction against the bacteria used in making the filtrate, but also a skin hypersensitiveness to the filtrate when injected intradermally. Other factors possibly concerned in these reactions such as nonspecific foreign proteins and variations in hydrogen ion concentrations were controlled by numerous experiments and excluded thereby.

Freiberg concluded that this may be the case in cases of chronic arthritis in which joint fluid and tissue cultures are negative. It is his opinion that such lesions are not due to active and maintained infections in the joints themselves, but are rather the expression of a sensitized tissue to an antigen which remains in a persisting focus elsewhere in the body. Such a sensitization may be brought about in two different ways; either from repeated exposure to soluble toxins from a distant focus, or from transient bacteremias, during which the joint cavities have been "seeded" with organisms which have failed to grow, due perhaps to decreased oxygen tension. A joint so sensitized may be expected to "flare up" whenever it is reexposed to the sensitizing antigen, and in many instances a focus far removed from the involved joint may be a constant source of supply for the antigen which keeps the allergic action active.

Small (34) has a like view of the situation. His theory is that the patient with chronic arthritis is extremely hypersensitive to the protein of streptococci. He considers the various types of streptococci as having a common protein which is entirely unrelated to their toxins, which, as is well known, is species specific. The closed focus recognized as being concerned in the production of chronic arthritis usually harbors germs of low virulence, so that it is regarded not as a focus distributing bacterial toxins, but as a
focus supplying the bacterial protein in amounts sufficient to hypersensitize the patient.

As regards the establishing of the etiology in chronic arthritis, more will be said later when the work of Clawson and Weatherby, who have done considerable work recently on the production of a specific vaccine, is taken up.

The Treatment of Chronic Arthritis

There is practically no end to the literature on therapy in chronic arthritis and a complete review of the literature is impossible here. It is the purpose of this thesis to cover, in detail, the methods of vaccine therapy, hence only a rather brief resume will be made of the other more accepted lines of therapy.

Wyatt (36) in a recent publication on the treatment of chronic arthritis sets forth those considerations upon which sound management must rest. They are:

1. Throughout the treatment of the patient, constant vigilance must be exercised to prevent the assumption of positions which may lead to deformity.

2. The physician should also bear in mind that rest and exercise of the joint are essential to its well being.

3. Motion should be encouraged in all stages of the disease, but must never be forced; the activity should consist wholly of the patient's attempt to do what he can in the normal use of the joint.

4. Rest in a position least likely to cause strain or contracture should be secured when the joint is not in use, particularly at night, as position during sleep is most important.

While different joints require special positions and care the principles involved are of greater practical significance than the details of method.

Joints that are connected with weight bearing present additional problems of a special character. The number of patients who overuse their
legs is vastly greater than the number that over exercise their arms. The strain on all the joints of the lower extremities, from the hips to the metatarsal arches is enormously increased by weight bearing and, in chronic infectious arthritis, the arches are prone to yield to the pressure upon them. Moreover, in obese patients with chronic degenerative arthritis a similar condition of the arches is encountered.

In the majority of the cases the proper elevation of the inner side of the sole and heel will give the ankles a correct position and transfer the weight to the outer side of the foot; while properly fitting shoes are always necessary.

The nonsurgical correction of the deformities embraces the application of heat, massage, traction, manipulation, exercises, applications, etc., which must be used in every instance according to the special and individual needs of the patient.

Exercises-

Joint exercises, joint movements and massage, while of importance in preventing deformity, will be considered here primarily from the viewpoint of their value in improving joint function and muscle tone.

The effects of various exercises have been ably described and summarized by Wyatt (36) as follows:

Neck exercises act upon blood vessels and nerves, as well as upon the muscles, and have a quiting influence through circulatory response.

Shoulder circling strengthens the chest and shoulder muscles, expands the lungs and relieves the work of the heart. It increases the flow of blood to the heart, especially from the brain.

Arm circling expands and elevates the chest and lungs, strengthens the nerves and muscles of the shoulders, limbers the shoulder joints and straightens the back.

Elbow and wrist exercises produce similar effects upon the muscles, nerves and other structures coming under their influence.

Trunk exercises produce a beneficial effect upon the spine, the nerves and circulation; trunk torsion has a special action on the respiratory mechanism,
and on the digestive processes.

Leg elevation, sideways, brings into strong action the gluteal muscles, the tensor vaginae femoris, and the sartorius, and, like all balancing exercises, has a strengthening effect on the nervous system. In leg elevation, forward, the abdominal muscles and flexors of the thigh and extensors of the leg are strongly contracted, and at the same time the hamstrings and sciatic nerve are passively stretched. Leg elevation, backward, produces passive stretching of the abdominal muscles and flexor muscles of the thigh.

Knee, ankle and toe joint exercises improve nervous, circulatory and muscle tone.

It must be pointed out that the movement of the inflamed joints, muscles etc., and even the massage of these structures, is often harmful and that as long as any manifestations of an acute character are present, it is usual that rest is indicated and not exercises or manipulations.

Massage—

The vast number of massage manipulations that may be used with benefit in chronic arthritis precludes any detailed description of them; but among their outstanding effects may be noted the prevention of muscle atrophy and the restoration of tissue structures and function after muscle atrophy has occurred. Massage is not followed by an increased alkalinity of the blood as is the case with the application of heat, nor by the increase of acidity which regularly accompanies exercise. Massage manipulations may be utilized to influence those bodily processes by means of which the tissues are constantly undergoing chemical change, in addition to being beneficial through effects that are of an essentially mechanical nature. It has been observed that most patients with chronic arthritis present evidence of a sluggish capillary circulation. Anything that speeds up the flow of blood to and from the affected tissues is of value and the results of massage are most gratifying.

While the skillful employment for the relief of pain in muscular rheumatism is an important exception to the general rule previously cited
relative to abstaining from exercises and manipulations when manifestations of an acute character are present, it should be emphasized that only on the rarest occasions is massage of an actually inflamed joint either indicated or justified. Moreover, while massage is usually specially beneficial when combined with some other form of treatment, such as radiant heat, for example, it should never be practiced in conjunction with joint movements or manipulation unless specifically ordered.

Electric Currents—

The more common forms of electric currents that have been employed in the treatment of chronic arthritis are the faradic, galvanic, sinusoidal and high frequency currents, static modalities, diathermy, ultraviolet light and radiant heat. Wyatt (36) states that in his experience the first five mentioned have had a very limited scope of usefulness and this also has been true of the chemical substances that have been introduced through ionization. On the other hand, diathermy currents, which heat the tissues as well as the skin and produce dilatation of the deeper vessels, was considered to be exceedingly beneficial in relieving pain, swelling etc.

Ultraviolet Radiations—

Ultraviolet radiations have been found to be of great value in stimulating the processes of metabolism. Furthermore, they exert a sedative action upon certain painful forms of chronic arthritis and fibrositis. Much has been written upon the different subdivisions of the ultraviolet region of the spectrum and it is highly important that one or two basic facts be emphasized. Very short ultraviolet rays have a lethal or destructive effect upon tissues, while longer ultraviolet radiations possess a stimulative reaction. The shortest rays that reach the earth from the sun are approximately 2960 Angstrom units in length, and, consequently, man has had no opportunity to habituate himself to those of shorter wavelength. In chronic arthritis it is the stimulative effects of ultraviolet light that are desired and, whatever the type of the artificial source of energy, a minimum of radiations below 2800 Angstrom units will give the best results. Even in regions which are favored with an
abundance of sunlight, rich in ultraviolet rays, it is usually necessary to employ some type of lamp in order to maintain continuity of treatment—a matter of the greatest practical importance. An artificial source of energy which increases the amperage after the current has been taken off the main has many advantages over one that does not.

The individual response of patients to ultraviolet light will vary not only with the technic and dosage, but also with other factors. Wyatt (36) has called attention to the difference in the sensitiveness of different parts of the body, based upon the time required to give a certain degree of reaction. His figures are as follows: chest 1, abdomen 1, back 1 plus, groin 1 plus, anterior surface of the arms 1/2, posterior surface of the arms 1 and three fourths, anterior surfaces of legs 2, back of hands 5, palms of hands 15 and soles of feet 25. The relatively small areas of the hands and feet, when considered in conjunction with the slight differences in the reaction time of the larger surface areas, constitute the basis for employing properly timed exposures of the entire body, beginning with the first treatment, as the procedure of choice.

Radiant Heat—

Radiant heat probably enjoys a much more general use than any other single therapeutic measure. This is doubtless accounted for by the fact that it is easily applied; a relatively simple equipment fulfills all requirements and great temporary relief of symptoms follows its application. In regions where there is an abundance of sunlight, a most satisfactory source of radiant heat is derived from this source. Appliances that are based on the principle of heating "black bodies" by means of an ordinary electric current and reflecting the heat rays upon the patient are very popular in this country, while abroad the Greville and Dowsing system of electric baths are much in vogue. Of course there are many methods of applying dry heat, but radiant heat possesses a number of distinct advantages.

The degree to which radiant heat may penetrate into the tissues of the body is still a matter of controversy and depends, to a certain extent at least, upon the source of energy and the method of application. That the
degree of penetration is sufficient, however, to produce important local and
general reactions is beyond all question. When general exposures of the body
to radiant heat are employed there is a rise in the temperature of the body,
a considerable increase in water vapor given off by the lungs, loss of fluid
from the body through the sweat and urine, and usually a slight fall in blood
pressure. The elimination of carbon dioxide is accelerated and, as a result,
a relative excess of alkali in the blood is found.

In view of the fact that the general application of radiant heat is often
followed by a temporary loss in body weight and certain manifestations
arising from heightened circulation and increased metabolism, great care
must be used in the selection of patients. Moreover, it should rarely be employ-
ed after surgical procedures and never in combination with a weight reduc-
tion diet. The greatest benefits are derived in well nourished patients with
either the degenerative or metabolic types of chronic arthritis.

Sunlight, which in southern latitudes is particularly rich in infrared or
heat rays has been used a great deal by Wyatt (36). As a result of comparativ-
eely recent developments, whereby perfect "black bodies" are marketed at a very
nominal cost, there is, in what is known as "infrared lamps" a highly effective
means of treatment. By using equipment of different sizes, both local and general
effects may be produced and, as a rule, the larger the surface irritated the
more satisfactory the outcome. The fact that radiations of known wavelength
may be employed enables great precision in dosage to be obtained.

Hydrotherapy-

In the larger clinics it is usually found that the number of patients who
respond to hydrotherapy is relatively small when compared to the response
to sun bathing. However, there are some cases in which balneotherapy seems best
to provide the necessary stimulation and those elements which promote recovery.
The use of hot water to promote the elimination through the skin and kidneys
is well established. When evidences of acute inflammatory changes are present,
hydrotherapy is rarely beneficial. The brief stimulating action of hot baths
is rapidly followed by a depressing effect which lasts much longer and is
most marked when the temperature of the water is as much above the skin temperature as can be tolerated. Patients with lowered vitality or weak heart action react badly to hot baths and those with the infectious type of chronic arthritis rarely receive much permanent from complete immersion, except when it is employed as an adjunct to the correction of deformities and the restoration of joint functions. Needle sprays, which enable the operator to use hot and cold water alternately are preferred. It is also desirable to follow hydrotherapeutic measures with massage.

Colonic Therapy-

This special form of hydrologic treatment is most useful and should occupy a more important place in the treatment of chronic arthritis than is the case at the present time. The frequency with which secondary foci of infection in the intestinal tract is encountered is noteworthy. Every physician with experience in the field of chronic arthritis has seen patients who did not improve following primary foci of infection in the teeth and tonsils. The manner in which the intestines may become infected in such cases is clearly apparent and by no means rare. Colonic therapy, when employed according to the technic of Plombiere as reported by Wyatt (36) and in combination with diet and various forms of physical therapy is exceedingly valuable. Improvement of the patient often occurs with great rapidity and the introduction into the colon of either acidophilus or bulgaricus bacilli following the Plombiere douche, rarely increases the effectiveness of the procedure.

Drug Therapy-

With the possible exception of colchicum for the metabolic type of arthritis, there are no drugs which may be employed for their selective curative action, such as quinine is believed to possess with relation to malaria. There are, nevertheless, a considerable number of medicinal preparations that are of therapeutic value when administered for the relief of symptoms. Glandular extracts and products, iodine and iodine compounds, arsenic, and the congeners of the salicylates, may be mentioned among those that are useful when prescribed in accordance with well defined indications. Laxatives are an occa-
sional "nécessary evil" and the best results will be obtained from preparations of the petrolatum group. The internal administration of mineral waters has long been much in vogue abroad and is growing in popularity in the United States. Water will shortly be considered as an essential to diet, but aside from the dietary importance, which is in no wise related to its mineral content its role in treatment is inconsequential.

The value of cod liver oil in some patients with chronic infectious arthritis has long been appreciated. Its value lies in both its vitamins and its calories. The more recently developed irradiated oils may be used as substitutes from the viewpoint of their vitamin content, but cannot replace cod liver oil from the point of view of their food value.

Diet-

Diet is of the greatest importance in the treatment of chronic arthritis and presents quantitative as well as qualitative aspects. The undernourished patient with chronic infectious arthritis not only needs more fuel, but also foods that will provide vitamins and an alkaline ash. Patients who are overweight present a problem in mechanics as well as dietetics. The significance of obesity as a secondary cause of chronic degenerative arthritis is generally recognized. This form of the disease is more commonly found in patients beyond middle life in whom the rapid reduction in weight may be accompanied by serious loss of muscle tone. In chronic metabolic arthritides, gout, we are dealing with a disturbed purin metabolism, and, assuming that the total food intake is neither immoderate or beyond the nutritive needs of the patient, the restriction of special food elements is the guiding principle.

One of the most common dietary restrictions in all types of chronic arthritis is meat, especially the red meats. Since anemia is one of the common manifestations of chronic infectious arthritis and since meats such as liver, kidneys, sweetbreads etc., assist in the regeneration of the blood elements, meat should not be excluded from the diets of these persons. Meat and other protéins, however, should be added to the diet in a manner so that their effect on the patients acid-base equilibrium will be counteracted. For this purpose the use
of fresh pineapple juice is recommended. If for any reason meats are not well tolerated, then, either "liver fraction" or concentrated gastric tissue may be substituted.

When patients are underweight one of the best ways of increasing the dietary standard is by the addition of olive oil, cod liver oil, mayonnaise, cream, butter and milk.

Besides meat, fruits, especially the acid fruits, are regarded with suspicion by many patients. While certain fruits contain organic acids, they produce no practical effect upon the acid-base equilibrium; others, such as fresh pineapples, give rise to an increasing alkalinity; plums and prunes, although giving an alkaline ash, increase the acidity of the urine through the production of hippuric acid. To ban fruits is a very serious matter because the great value of their vitamins is lost to the individual.

Fluids, in adequate amounts, are essential to any diet and this is particularly true for the diseases under consideration. Water is required in quantities varying from not less than six or eight glasses a day to double that amount.

Attempts should always be made to regulate the bowel function by food and those items which contain a large percentage of "roughage" are useful in certain cases.

Were it possible to epitomize the subject of diet in chronic arthritis it should be emphasized that a reduction of both the "mechanical" and the "metabolic" loads is frequently necessary; that adequate quantities of the vitamins F and G should always be prescribed; that for chronic atrophic arthritis, alkaline ash foods should predominate; while for the hypertrophic type an acid residue is commonly indicated.

Climate-

That climate is of great importance in the treatment of chronic arthritis is well established. Physical and physiological, as well as those that are psychic and mental, are influenced by humidity, temperature and atmospheric electricity operating either as separate factors or in combination. Moreover,
in any chronic disease—and even in health—the cheering effects of warm, dry sunshine are too well known to require special emphasis. However, climate like many other factors that aid in the recovery of the patient, must always be regarded as an adjunct to and never as a substitute for other established therapeutic measures.

Heliotherapy

A discussion of the results to be derived from climate naturally leads to a consideration of heliotherapy. The employment of sun baths for the treatment of chronic arthritis is by no means new, for we find that as long as 1840 they were recommended by Bonnet as the method of choice. Among the effects of solar radiations upon the body that have a bearing upon the value of heliotherapy in chronic arthritis may be mentioned:

1. The stimulation of elimination by the lungs, kidneys and skin.
2. The increased production of white blood cells and blood platelets.
3. The augmentation of the iron content of the red blood cells.
4. The acceleration of gaseous exchange in and the removal of toxic products from the tissues.
5. The activation of reflex muscular contractions.

That sun baths should be of great benefit in the treatment of patients with chronic infectious arthritis is apparent from a study of their physiological effects. The individual response of the patients will vary with their age, complexion, temperament, skin texture, state of nutrition, etc., and the results are dependent upon a general rather than a local reaction.

Regardless of the clinical or the pathological type of the chronic arthritis, it appears that the return of the joint structures to normal is materially aided by heliotherapy. Moreover, whatever may be the effects produced by the ultraviolet rays, there are many indications that one of the reasons for the notable benefits of solar therapy is the improvement of joint circulation through the action of the infra-red rays. Certain it is that the best results from heliotherapy in chronic arthritis are obtained with unusual rapidity.
during the summer months in Southern Arizona.

Before beginning sun treatments a period of aerotherapy is usually important. Moreover, when general exposures to the direct rays of the sun are initiated, they should not be commenced until one hour after meals and should be terminated one half hour before meals. The head and eyes should always be protected. Two short exposures are preferable to a single exposure of longer duration, since a more prompt adjustment of vasomotor reactions will thereby be obtained.

The angle of exposure is of the greatest significance and the bed or cot should always be placed with its long axis at right angles to the rays of the sun so that when the patient is lying on either side the beam of sunlight will fall on him as perpendicularly as possible. Fractional exposures of the body—otherwise known as zoning—possess no advantages, as a rule, and general radiations are employed from the beginning.

Individualisation in heliotherapy is as necessary as in vaccine or any other form of therapy, and the indiscriminate use of solar therapy is fraught with great danger. Sun bathing is both an agreeable and an effective way of stimulating the natural curative forces of the body and should play a role of rapidly and constantly increasing importance in the treatment of chronic arthritis.

Surgical Measures-

Any discussion of reconstruction operations is clearly outside the scope of this thesis but, unfortunately, it is necessary to state that at the present time, surgery is altogether too frequently required. Today, the orthopedic surgeon is called upon, primarily, to treat deformities that have resulted either through neglect of early diagnosis and proper treatment, or, in rarer instances, to correct joint positions that have developed despite the various measures herein considered. The principal aims of surgical measures are to relieve pain, restore function and to correct deformity. In addition to these more or less "orthodox" indications, the work that is being done at the Mayo Clinic in connection with the resection of sympathetic ganglia and trunks appears to justify the belief that an important contribution to established
Non-specific Protein Therapy-

The treatment of arthritis by the non-specific proteins is still in the experimental stage, and the clinical reports are relatively few. There exist in the body non-specific splitting enzymes, protein in character, that attack invading protein toxins, whether they are bacterial, chemical or vegetable. These non-specific enzymes may be activated by the injection subcutaneously, intramuscularly or intravenously of various foreign proteins in proper dosage.

Betz (37) in 1921 treated arthritis with typhoid vaccines and obtained appreciable results, when other methods had failed.

Schmidt (38) used milk by intramuscular injection. In 1910, and during 1916 many articles were written in German and Austrian publications on the use of milk for parental injection in the treatment of various affections, especially arthritis. Shahon (39) has used milk exclusively as the injection substance and has obtained gratifying results in most cases and good results in gonorrheal arthritis. His method is given here in detail.

Cow's milk is used. It is sterilized by boiling for ten minutes and subsequently cooled to a comfortable temperature. The intramuscular route is the best. The intravenous route of milk administration is not recommended.

The sites of injection are the muscles of the arm and the gluteal region. All the precaution as to asepsis and the avoidance of entry into the vein are taken. The initial dose for an average adult is $\frac{1}{2}$ c.c. The injection is generally repeated every other day, and the dose is increased by $\frac{1}{2}$ c.c. at every injection. The total number of injections required varies with the individual case and may be anywhere between ten and twentyfive. Some have used 4 c.c. as the initial dose and increased by 1 c.c. at each injection. It is well to remember that the second injection should never be given unless it can be given after an interval of less than ten days, on account of the danger of a severe constitutional reaction. When the patient has a severe constitutional reaction, the dose injected following such a reaction should not be increased at all
over the previous one; it rarely has to be reduced. The local disturbance at
the site of injection is never severe enough to incapacitate the patient.

The reaction following an intramuscular milk injection rarely comes at
once. The patient is instructed to wait for a period of ten minutes before
leaving the office or clinic. He is often told to go home and stay in bed
for four or five hours. This treatment is applicable to all forms of arthritis
but particularly to the infectious or gonorrheal cases.

The milk injections should not be used in patients who are subject to
asthma, organic heart disease, hypertension or who are pregnant. It is well to
remember of course that none of these are absolutely contraindicated, if they
are used with caution by beginning with smaller doses and keeping the patient
in bed.

Within one to four hours following an injection of milk the patient will
have a chill or chillness of varying degree of severity and duration. The
temperature may rise to 102° or higher, and a profuse sweat may follow. In
most cases the patient experiences mild headaches. The local process in the
joints is temporarily aggravated. Following the disappearance of the chill
the blood picture is that of a leucocytosis. This has been found as high as
50,000, but usually is a good deal lower. The increase is largely in polymuclear
neutrophils. There is no eosinophilia. At the end of 24 hours the leucocytes
are back to normal. The kidneys show no constant disturbance.

Vaccine therapy—

Within the last number of years, a great deal of bacteriological research
has been done by various workers in the field of chronic arthritis.
They have concerned themselves with the endeavor to isolate some specific
organism, if possible, which acts as the etiological factor in the causation of
arthritis. Outstanding amongst these workers may be mentioned Burbank, Hadji-
apoulis, Cecil, Pemberton, Small, Clawson and a host of others. Of course in their
efforts they have also kept in mind the application of this knowledge in a
practical way; that is, how best they might utilize information thus obtained.
in the treatment of affected patients. For it nets but very little to do work of this kind if the same cannot in the end point toward a more rational and logical attack upon the diseased condition.

Goldsain (40) reviews the work of the various investigators and shows how their studies may be applied in the treatment of arthritis, possibly, to compare these in an impartial manner, and come to some opinion as to whether or not the different methods of approach of these workers do not at bottom appear to be more or less similar; that they are really utilizing one and the same idea in their therapeutic attack upon this diseased state, with the exception that their technic is somewhat different.

First we will set forth the complement fixation test of Burbank (41). In this test Burbank uses the principles that are used in the Wasserman test in identifying organisms that may be causing a chronic infectious state in the patient. This test is as follows: The blood of the patient is drawn as for the Wasserman test. The serum is separated from the clot in the tube, which has been standing at room temperature overnight. Test tubes are set up, one for each antigen that is to be tested. Control tubes are set up in order to determine whether or not the patients serum may happen to be anti-complement-ary. To the four control tubes is added .01, .02, .04 and .06 cc. of serum. Saline solution .5 cc. is added to each of the control tubes. To the tubes that are for the fixation tests on the patients serum, there is added .04 cc. of the patients serum and .5 cc. of the antigen. The tubes are put in a water bath for thirty to forty minutes at 37° C. They are then removed and to both control tubes and special tubes is added .5 cc. of 3 per cent sheep cell suspension containing antisheep hemolysin. These tubes are then incubated and watched until the control tubes are hemolyzed. When such has occurred the tubes are removed and readings are taken as to whether they are one, two, three or four plus to the antigen. This gives us information as to the type of antigen or organism which is causing the disturbance in the patient. We can then make a vaccine of such organisms and administer same to the patient in proper dosage.
Cecil (42) has isolated an attenuated hemolytic streptococcus which he thinks is the causative organism in chronic infectious arthritis. He, therefore, tests the patients by the agglutination method. Ten tubes are set up. To the first tube 0.9 cc. of saline or clear broth is added. To the other nine tubes ½ cc. saline is added. To the first tube is added 0.1 cc. of the patient's serum. This is well mixed with a pipette and 0.5 cc. from the first tube transferred to the second, well mixed. 0.5 cc. is thus carried from the preceding tube to the succeeding tube, except the last one which does not receive any of the patient's serum. It is the control tube. 0.5 cc. of antigen is then added to each tube. The antigen is a twenty-four hour broth culture of this specific attenuated hemolytic streptococcus. This, therefore, gives dilutions of the patient's serum, varying from 1 to 20 in the first tube to 1 to 5120 in the ninth tube, the tenth being control and not containing any serum. The tubes are shaken and put in a water bath at 56°C for two hours. From the water bath they are put into the ice box overnight. They are read the next morning.

Small (43) has isolated what is known as an indifferent streptococcus, which he has found to be present in rheumatic fever and in various cases of infectious arthritis. He has found that these organisms produce both antitoxins and by extraction antigenic substances. He feels that the reason for a patient reacting the way he does in chronic infectious arthritis may be due to extreme sensitzation to these organisms developed over a long period of time. He, therefore, makes an antigen, which is a saline extract of these organisms, and this antigen is diluted in some cases to ten to -16 power. For instance, if the antigen is a saline extract of a dilution of his organisms of one to one million, that is considered to be as ten to the -6 power. Then as this is increased to ten million, it is ten to the -7 power, and so on until sixteen cipher dilution is reached. Of this last dilution, he will start with 0.05 cc., giving as is evident from the above discussion an almost ridiculously small injection. Yet if this dosage is increased too quickly or in the extremely hypersensitive case, a reaction from such dosage may be secured, showing that whatever is there is extremely potent.
Touart (40) of the French Hospital tests his patients with organisms from the various parts of the body, isolated from the teeth, throat, tonsils but most especially the stools. The autogenous organism is centrifuged and one part of that is added to ninety-nine parts of one quarter per cent of tricresol saline solution. Of this, one per cent dilution, 0.01 cc. is injected intradermally. A saline control of the same amount is injected at a small distance away. Other control strains of organisms similar to the organism that has been isolated are also injected in the same amount in order that the reactions obtained from the autogenous organisms may be controlled. For example, if a hemolytic streptococcus has been obtained from the patient, a control strain streptococcus is also used. The formation of a wheal is noted in fifteen minutes. The patient is then requested to return in forty-eight hours for a final check up, at which time, these tests are observed and records made as to whether an areola, wheal, tenderness or ecchymosis is present. If the reaction is positive, the patient is then treated with that particular organism in the form of a vaccine.

If we glance back at the above resume of the methods for diagnosis bacteriologically of these various investigators, we are immediately struck by the fact that they, all leaders in their work, are apparently of one and the same opinion: that infectious arthritis is, as the name applies, caused by an organism, most likely of the streptococcus family.

Burbank (41), based upon his compliment fixation and autogenous cultures, places his main reliance upon vaccine therapy. He gives his vaccine in very small doses, apparently feeling that the effect of the vaccine is due to other causes than the bacterial body instigating antibodies against itself when injected subcutaneously.

Cecil (42) also gives vaccines in small doses, sometimes ranging as low as fifty thousand, intravenously, made from his specific attenuated hemolytic streptococcus.

Touart (40), in his skin testing work, also seems to follow the same principle, in that he uses vaccines in small amounts for treatment of his arthritis.
patients. The vaccine is made up of the same organism that the patient has reacted to in the skin testing.

Small (43) apparently carries this idea even farther and instead of giving any bacterial bodies to the patient, simply uses in his treatment a saline extract of his streptococcus cardio-arthritis which does not contain any of the bacterial cells but does contain highly powerful substances apparently attached to the bacterial cells and to which the patient has become sensitized. By using this antigen in very minute doses, he desensitizes the patient. By so doing, he seems to secure a remission of the active process.

In vaccine therapy, the vaccine used may be either an autogeneous or a stock vaccine. In the event that organisms may be isolated from the involved joints or if a positive blood culture may be obtained, then it may be more desirable to use an autogeneous vaccine. If, however, there can be no organisms isolated from the joint tissues or fluid, and if the blood cultures are negative, then the only method of approach is to use a stock vaccine. There are several workers in both fields and some of their work will be reported on in this thesis.

Vipond (44) calls attention to a number of cases of chronic arthritis treated with a vaccine prepared from a hemolytic streptococcus which were isolated from the enlarged external lymph nodes present in this disease.

In 1915, Vipond (45) published a paper entitled "Recent Work on the Bacteriology of Rheumatoid Arthritis and its Treatment," embodying certain observations made at that time. Examination of rheumatoid patients revealed a definite enlargement of the external lymph nodes, and from these a streptococcus was obtained. Twelve cases were treated with a vaccine made from this organism. The following conclusions were drawn at this time:

1. In ten of twelve cases of rheumatoid arthritis the same streptococcus was recovered from the enlarged nodes. A vaccine made from this organism produced a cure, or a marked improvement in the symptoms and in the local and general lesions.

2. In the early stage of the disease, that is, up to the third and fourth
year, before grave articular changes have taken place, we can hope for relief of pain, disappearance of swelling and a return of the function of the joints.

3. In chronic or advanced cases, from fifteen to twenty-five years standing, we may expect to get relief of pain, lessening of the swelling, and increased power of motion, though we cannot hope to restore articular cartilage or produce new joints.

4. Culturing of nodes in severe cases, after four or five months treatment, and in much less time in early cases, proved to be negative, notwithstanding the fact that the streptococcus in question had been present in the nodes before treatment was instituted.

As to the technic used by Vipond, it will be taken up in some detail as an example of treatment by the use of an autogeneous vaccine. As mentioned before, the external lymph nodes in the case of patients with chronic arthritis are enlarged and can be palpated, at least in thin subjects. A needle attached to a glass syringe is inserted into one of the nodes and a small amount of lymph extracted. From this, on culture, a streptococcus can be obtained in most cases. This organism grows best on dextrose blood agar or on blood serum. It hemolyses blood agar slightly, producing a greenish halo. There is slight acid production in dextrose broth, but no gas formation. In all manipulations the usual care is taken to prevent extraneous contamination. In stout people it may be impossible to isolate a lymph node for the purpose, and in such cases, if it is desired, a node may be excised under novacain.

A vaccine is prepared from the organism in question, containing 500 millions to the cc. This amount is given two or three times a week, and the dose is increased to 1.5 cc. and, finally, to 2 cc., at which point it is maintained. He gives the inoculations deeply into the leg or arm muscles.

After receiving the first treatment, or at times the second, the recipient may complain of pain in every joint of the body. This state, however, does not persist, and after a week the patient will begin to improve and improvement will be steady. On the other hand there may be no reaction. Children stand the vaccine better than adults and may be given the same dose.
In some few cases a dose of sixty-five to seventy-five minims, or even less, will produce an intense reaction. There will be severe chill, headache, anorexia, the swelling of the joints and the pain will be aggravated. Under these circumstances the patient may object to continuation of the treatment. It is well, therefore, to warn him beforehand that such results may follow, but with perseverance improvement eventually becomes quite noticeable. Usually four or five days will suffice to show the benefit.

Case reports on patients treated by this method follow (44)

Case 1. A woman of about middle age had suffered from chronic arthritis for more than a year. Practically all the joints in the body were involved, but especially the knee, ankles, wrist, elbows and shoulders. At the time of the first examination she was having an acute exacerbation. After ten months' treatment cure was complete.

Case 2. T.C., male, aged 53 years, a baggage man at the C.P.R. station. He developed an obstinate arthritis in the right foot, which was painful, red and swollen. In about six months practically all the joints in his body were affected. He could not feed or dress himself and was confined to bed. His spine was rigid and he could not move his head. His hands were useless as all his finger joints were painful, red and swollen. The elbows and ankles were in the same condition and flexed. In fact, he resembled an advanced case of myositis ossificans, as he could move only his eyes. This man was inoculated twice weekly for about fifteen months. He is now well and has returned to his former occupation.

Case 3. J.J., female, aged 19 years, had suffered from chronic arthritis for five years. She had been under the treatment commonly employed in these cases and was unimproved, rather worse. She could neither walk nor feed herself. On examination, the fingers, hands and shoulder joints were all implicated; the elbow joints were flexed at a right angle; the knees were also swollen and painful; the feet were swollen and the ankle joints were painful, swollen and fixed.

After one year's treatment improvement has been marked and still continues.
The pain has disappeared; her ankle and knee joints are normal to all appearances; and she has put on weight. There is still, however, considerable atrophy of the muscles. When the joints are moved grating is still very perceptible. The forearms and legs can be almost completely extended. The hands are much improved. The patient can write a good hand, can feed herself without difficulty and can knit and do fancy work. She can bring both her hands behind her head and lock her fingers.

Case 4. Mrs. P., married, aged 35 years, began to suffer from arthritis in 1924. First the right knee became swollen and painful and soon the left. Then the feet and ankles began to swell, and the left wrist, left elbow, and the shoulder joints quickly became involved, followed by the right wrist and elbow. The middle finger of the left hand became flexed into the palm.

The wrists became badly deformed; the elbows were fixed nearly to a right angle; partial dislocation of both radii and ulnae took place. The toes and ankles were painful, swollen and rigid. The cervical spine was anklyosed and the head could not be moved more than half an inch in any direction. The jaw was anklyosed and she could not open her jaw more than a quarter of an inch. She was practically helpless, suffered agony and had lost much weight. She was ten weeks in a hospital, leaving unimproved.

After four months' treatment, she could open her mouth one and a quarter inches. The right arm and elbow, and both shoulder joints showed marked improvement; she can use her fingers with considerable freedom. Strange to say, the dislocations have disappeared and she is also putting on weight.

Shuster (46) makes a comparison between the results obtained in cases treated with a stock streptococcus vaccine, with a vaccine made up of the complement fixation strains alone, with a complement fixation strain plus autogeneous strains and a selective streptococcus vaccine.

In series 1, a stock streptococcus vaccine containing many antigenically different hemolytic, non-hemolytic and viridans strains was employed. No other treatment was administered; even infected foci were left untouched. Subcutaneous
injections were given bi-weekly; the initial dose in all but the very acute cases was twenty five million, the subsequent dosage depending entirely upon the reaction, exhaustion, loss of weight, increase in pulse rate and marked focal or general reactions were the indices of overdosage. The result of the 456 cases so treated is given in table 3.

Series I

Table 3.- 456 Cases: Stock Streptococcus Vaccine

<table>
<thead>
<tr>
<th></th>
<th>Total Number of Cases</th>
<th>Cases Showing Marked Improvement</th>
<th>Percentage Showing Marked Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Males-143</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophic arthritis</td>
<td>86</td>
<td>54</td>
<td>63</td>
</tr>
<tr>
<td>Hypertrophic arthritis</td>
<td>36</td>
<td>22</td>
<td>58</td>
</tr>
<tr>
<td>Mixed arthritis</td>
<td>19</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>B. Females-postmenopause-200</td>
<td>111</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>Atrophic arthritis</td>
<td>62</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>Hypertrophic arthritis</td>
<td>26</td>
<td>16</td>
<td>61</td>
</tr>
<tr>
<td>Mixed arthritis</td>
<td>26</td>
<td>16</td>
<td>61</td>
</tr>
<tr>
<td>C. Females-premenopause-113</td>
<td>91</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>Atrophic arthritis</td>
<td>16</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Hypertrophic arthritis</td>
<td>6</td>
<td>4</td>
<td>66</td>
</tr>
</tbody>
</table>

Summary: 286 or sixty three per cent of the cases were markedly improved. Recoveries were almost as frequent in the hypertrophic cases as in the atrophic. Menopause arthritis also responds as well as the other types. On the average marked recovery required at least six months of uninterrupted treatment, the slowness of response being due to the marked dilution of the stock antigens.

As has previously been mentioned, Burbank and Hadjopoulis (41), after much experience in the treatment of chronic arthritis, found that their best results were obtained with streptococcus vaccines prepared after complement fixation. Although they made no claims for the diagnostic value of this test, they felt that it pointed out the probable infecting streptococci in each case. By adding all the focal streptococci to the fixation strains, Burbank feels that he has reduced to a minimum the possibility of the noninclusion of the
specific strains. The high percentage of recoveries of thousands of cases of arthritis treated by Burbank, to be discussed later, is sufficient proof of the efficacy of this method.

Some critics argue that the results reported by Burbank are due principally to the added autogeneous strains. That this is not so was shown by Shuster (46) by the results of two series of cases treated by him: in the first only complement fixation strains were administered; in the second both complement fixation and focal strains. These results are recorded in tables four and five:

**Series 2**

Table 4. - 500 Cases: Complement Fixation Strains Alone

<table>
<thead>
<tr>
<th>Total Number of Cases</th>
<th>Cases Showing Marked Improvement</th>
<th>Percentage Showing Marked Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic arthritis</td>
<td>303</td>
<td>212</td>
</tr>
<tr>
<td>Hypertrophic arthritis</td>
<td>197</td>
<td>130</td>
</tr>
</tbody>
</table>

**Series 3**

Table 5. - 450 Cases: Complement Fixation Plus Autogenous Strains

<table>
<thead>
<tr>
<th>Total Number of Cases</th>
<th>Cases Showing Marked Improvement</th>
<th>Percentage Showing Marked Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic arthritis</td>
<td>298</td>
<td>230</td>
</tr>
<tr>
<td>Hypertrophic arthritis</td>
<td>162</td>
<td>107</td>
</tr>
</tbody>
</table>

Summary: In series 2, 342 or 68 per cent of the 500 cases were markedly improved; in series 3, 337 or 75 per cent of the 450 cases were markedly improved. These results show that the addition of the autogeneous strains increased the number of the recoveries by only seven per cent, proving the value of complement fixation in preparing the vaccines used in chronic arthritis.

Since the 25 per cent failures in series three were clinically identical with those that had improved, their unresponsiveness was thought to be due
either to the absence of their specific antigens in the vaccine or to their presence in insufficient therapeutic concentration owing to dilution. To confirm these possibilities, 112 of the unimproved cases were divided into two equal groups. The patients of the first group were subjected to defocalization. Autogenous vaccines were prepared from the streptococcus strains isolated and bi-weekly immunizing doses administered for six weeks. The results at the end of this time were marked improvement in eighteen or thirty-two per cent, showing that swab cultures from the surfaces of foci did not always isolate the specific arthritic strains.

Since in series 3 the administered vaccines always consisted of a large number of strains, it was a possibility that even though the specific strains were included, their dilutions by the other antigens might impair their antigenic activities. Thus in the second group of fifty-six cases, the original strains were again administered, but a few at a time. If there was no apparent improvement after six weeks, other strains were substituted until all had been tried. This procedure resulted in a decided improvement in twelve or twenty-one per cent of the cases that had previously failed to respond. This proved that over-dilution of the specific antigens decreases their immunizing powers, often making them therapeutically ineffective.

Although complement fixation is perhaps one of the most sensitive of all immune reactions, its value in determining the infection in chronic arthritis is denied by many immunologists. The criticism of streptococcus complement fixation is based principally on the fact that it is impossible to accurately differentiate specific from nonspecific reactions. It has been pointed out that normal or non-arthritic sera often gives fixations identical with those obtained with arthritic sera. Since this is true, how can one be certain that the reactions indicate the presence of such infections?

Streptococcus antibodies may be produced by:
1. A relatively recent streptococcus infection.
2. A nonsymptomatic streptococcus invasion.
3. An existing streptococcus infection
Thus positive fixations may be due to the presence of any of the above antibodies and since the intensity of the reaction is not always of value in differentiating between these three types of antibodies, interpretation of the results must be carefully made to eliminate from the vaccine the non-specific antigens.

It has always been the aim of bacteriologists to prepare a vaccine containing only the etiological organisms causing the infection. Experience has taught that the presence of other antigens in the vaccine nearly always decreases the antigenic value of the specific strain. The presence of many antigens, providing the essential one is among them, necessitates the giving of large doses before a favorable therapeutic response is possible. The inoculations of massive dosages, however, is against all modern teaching. It has been thoroughly established that the best results in chronic arthritis are obtained with small amounts of vaccine. Employing, in arthritis, a vaccine containing all the strains determined by complement fixation often defeats its own purpose, for by stimulating immunity to all these antigens, for the majority of which immunization is unnecessary since they are not causing infection, the specific response to the essential strain is retarded. Thus it is important to attempt to determine which of the fixations are evidences of infection and which the results of non-specific properties of the serum.

That a single complement fixation cannot be accepted as a true index of the infection in arthritis is shown by the fact that repetition of this test nearly always gives a different result. For accurate interpretation of the results it has been found necessary to repeat it three times at weekly intervals. Only those antigens that give fixation every time are selected as the probable infecting ones.

If the streptococcus antibodies are the result of an established immunity or the response to invasion not causing infection, then the patient's blood should be capable of inhibiting the growth of the organisms to which such fixations are obtained. The inability of an organism to grow in the patient's whole blood establishes its nonpathogenicity, and since it is not causing
infection there is no need to stimulate immunity against it.

Solis-Cohen (47) and his associates, in 1926, demonstrated that pathogen culturing—culturing focal strains in the patient's whole blood—could be used as a means of determining the pathogenicity of such organisms. They found that nonpathogenic focal strains were unable to grow in their host's blood. As a result of their findings they write "When an organism present in the respiratory passages, sputum or feces grows in the whole blood of an individual there is a probability that it may be etiological or a complicating organism".

Shuster (46) states that this bactericidal test is of definite value in helping to choose the strains needed for immunization in chronic arthritis.

He states that pathogenic culturing of the strains that are fixed each time makes it possible to eliminate from the vaccine the nonpathogenic organisms formally administered. This weeding out increases the concentration of the infecting strains making them antigenically more active.

That reliance on complement fixation alone will often lead to failure because of the absence of the specific strains among the test antigens was pointed out by the results in series two and three. The importance of adding the autogenous streptococcus strains has also been suggested.

The mere presence of an infected focus does not, however, signify its relationship to the arthritic involvement. Thus the removal of a focus not responsible for the joint changes can hardly be expected to bring about recovery. An infected focus most often contains a number of different streptococci, pathogenic and nonpathogenic. A vaccine prepared from all the suspicious foci is thus certain to consist of a number of different antigens. Since the potency of an antigen is dependent upon its concentration the necessity of eliminating the nonpathogenic, noninfecting strains is clearly evident. Here again Solis-Cohen's bactericidal test is an aid in distinguishing pathogenic from nonpathogenic organisms, making it possible to discard the latter. A vaccine prepared in this manner contains only those strains able to resist the bactericidal power of the patient's blood, indicating the necessity of
establishing an immunity against them.

The fact that an organism is able to grow in a patient's blood does not necessarily mean that it is causing infection. A pathogenic strain as determined by pathogen culturing should be considered as only potentially infective. The administration of all the pathogenic strains in a given case without regard to their actual infectiousness is little better than nonspecific immunization, since not only may the arthritic strain be absent but if it is present it is only one of many. By means of complement fixation, using the pathogenic focal strains as test antigens, Shuster (46) believes that it is possible to determine which of these is infecting the host; thus the non-infecting pathogenic strains are eliminated, again increasing the antigenic value of those that remain.

The therapeutic value of such vaccines is shown by the results in a series of 386 cases treated by Shuster (46) in table 6.

Series 4

Table 6.-386 Cases: Selective Streptococcus Vaccine

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Marked Improvement</th>
<th>Percentage of Marked Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic arthritis</td>
<td>212</td>
<td>174</td>
<td>84</td>
</tr>
<tr>
<td>Hypertrophic arthritis</td>
<td>174</td>
<td>142</td>
<td>81</td>
</tr>
</tbody>
</table>

Summary: 332 or 86 per cent of the 386 cases were markedly improved by selective streptococcus therapy. Not only was the percentage of recovery greater than in series 1, 2 and 3 but the response was much more rapid, in fifty per cent the improvement was apparent within the first few weeks of treatment.

Burbank and Christensen (48) report on the treatment of 1,016 cases of chronic arthritis, 726 being of two or more years duration. Tubercular, luetic and gonorrheal joints were not considered in this report. A brief review of the method of treatment used by Burbank and Christensen must be considered here.

In the report of Burbank (49) on vaccine therapy and serological diagnosis
in the arthritides, his method is taken up. Complement fixations were done with a number of strains of streptococci. Fixations done with these antigens would give fixation with only certain strains, sometimes with one, sometimes with several and Burbank started using the strains which fixed with the patients' blood and found that the results were more satisfactory than had been obtained with any previous method of treatment. In preparing these antigens for vaccine, heat is not employed to kill the bacteria as the effect of 56° C promotes a quick autolysis of the bacterial cell envelope; but when attenuated with phenol, bacteria remain intact for a much longer period of time and injections prepared in this way are actual bacterin emulsion instead of a disintegrated mass of bacterial protein. With this method of procedure, it is necessary to use a much smaller dose and frequently a patient who has taken without reaction five or more billion of a supposedly autogenous vaccine, will have a severe focal or even general reaction, lasting twenty four to forty eight hours with a dosage of five million streptococci prepared from complement fixing strains which have been phenol attenuated. According to the technic of Burbank, thirty five strains of streptococci of various types and from various foci were employed. A patient may give a four plus fixation to the blood culture diagnostic strains, and yet may fix only one or two of the focal strains. By this method, Burbank feels that he has approached a high degree of specificity in vaccine therapy.

Each case that is reported here was first searched most carefully for possible foci of infection. In many of the cases in which no primary foci of infection were found above the vocal cords, as is the usual case, a secondary focus was found in the intestinal tract.

Any foci found were carefully cultured, the pathogenic organisms isolated, and such organisms as correspond to the patients' fixing strains were employed in making up the vaccine to be used in that case.

The first step in the examination of the patients' blood was the determination of its complementary power, for it is considered by Burbank that one of the
reasons for frequent failure in vaccine therapy is that no one has taken into consideration the complimentary value of the patient's blood before beginning treatment of a case. For complement determinations the anti-sheep cell hemolytic value of human serum is employed, as broadly this value is an index to the bacteriocidal complementary values. A certain percentage of the cases seen were utterly deficient in complementary value and the use of vaccine is not only inadvisable but is almost certain to do such patients definite harm.

After having determined the complementary value, the case is then considered under its seriological classification, the three major groups of which are as follows:

(a) arthritis reacting to hemolytic streptococcus and iso-atrophic or exudative in character; this type in pure form is periarticular without actual bony involvement.

(b) arthritis reacting similarly to hemolytic streptococcus but of different fixing properties; this type shows a non-bony deformity with ulnar deviation, marked atrophy, muscle weakness as an initial symptom, and is aniso-atrophic or deforming in character.

(c) arthritis reacting to the viridans streptococcus and belonging to the osteoarthritic or productive form; bony change as demonstrated by x-ray is often a very early manifestation in this group. The majority of arthritis cases that are not arrested or cured early in the disease have a tendency to undergo further changes leading to mixed types, with a consequent mixed serological picture.

A five million initial dose in autogenous and complement fixation vaccines was found ample. The heart, weight and the patient's general condition were all watched and reactions were avoided which would give weight loss and general lassitude even if in such cases it was necessary to hold the dosage throughout the entire course of treatment at not over five to ten million bacteria per injection.

Every patient, as already stated, went through a routine search for foci.
careful urine analysis and culture was made, the stool was examined and bacteriology determined; all possible sources of absorption are cultured and autogenous vaccines made when pathogenic organisms are found, these autogenous strains being combined with the complement fixation strains if they correspond in character and type. When such determinations have been made the patients diet is regulated, the usual recommendations for general hygiene and elimination are made, the vaccine is given once or twice a week according to the response or reaction, and if progress is not satisfactory the examinations are made still more detailed by a specialist on any doubtful point.

The results of the 1,016 cases of chronic arthritis so treated by Burbank, are given in table 7.

Table 7.—Results of 1,016 Cases of Chronic Arthritis Treated With Vaccine Therapy.

<table>
<thead>
<tr>
<th>Case Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cases made worse or unimproved</td>
<td>7.5%</td>
</tr>
<tr>
<td>2. Cases showing slight improvement</td>
<td>10.7%</td>
</tr>
<tr>
<td>3. Cases showing moderate improvement</td>
<td>8.5%</td>
</tr>
<tr>
<td>4. Cases showing very marked improvement</td>
<td>56.6%</td>
</tr>
<tr>
<td>5. Cases becoming symptom free</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

Another outstanding worker in this field is Crowe of England. He gives a report of his method and in summary gives the procedure used in an hypothetical case which will be reviewed here in order to give an idea of his method. (50).

At the preliminary interview, after entering up the history and results of examination, arrangements must be made for dental radiograms and the collection of specimens of urine and feces and also cultures from the posterior nares if catarrh is present. A tooth must be extracted for culture purposes if dental sepsis is present. Pathogen selective blood tests are also made. It is advisable to start the treatment by some doses of stock vaccine to test the tolerance of the patient. In this way also no time is wasted. The treatment should begin with an injection of 100,000 polyvalent streptococcus vaccine; five days to a week later 100,000 M. deformans is given. There must follow
from one or other or both of these doses, (a) a focal reaction, (b) a general reaction, (c) definite improvement, or (d) no change whatsoever. There are now two distinct lines of advance, (1) To carry on alternating the streptococcus and M. deformans vaccine until we find the reaction point of each and then to combine the two together in just that proportion, or (2) to combine them at once in equal quantities. The amount of the dose is then regulated entirely by the dose of the organism to which that patient is most sensitive. The second method is to be preferred in all cases at the beginning of treatment. Later if difficulty arises the two kinds of vaccine can be tested out separately, but in no case must either be entirely omitted, according to Crowe.

After the third dose the autogenous vaccine should be ready and must then be combined with stock vaccine and given in doses of from ten to one hundred thousand organisms, depending on the degree of reaction.

The length of treatment depends upon the progress of the cure and is very variable. There is no fixed term or definite number of doses that constitute a course. One should keep in mind that so long as the injections are found necessary to prevent relapse, they should be continued.

The work of Clawson and Wetherby at the University of Minnesota during the last three years has been outstanding in that they use a stock vaccine and have reported a large number of improvements in their work on vaccine treatment of chronic arthritis. Because of the results obtained and because of the methods used in establishing this vaccine, the remainder of this thesis will be given over to a review of their work along this line.

The factors considered as a basis for streptococcus vaccination, by Clawson and Wetherby (51) are (1) etiology and (2) a method of vaccination which will not produce hypersensitiveness but will desensitize patients already sensitive and will produce a high degree of protective immunity.

The etiology of chronic arthritis has been previously taken up in this thesis. Clawson and Wetherby studied the etiology from the bacteriological, the immunological and the pathological standpoints (51).

Bacteriology——Clawson and Wetherby concluded from their large series
of cultures made from the blood, the joint fluid and tissues, the lymph nodes and the subcutaneous nodules in cases of chronic arthritis that the main etiological organism is the Streptococcus viridans, although beta hemolytic streptococci were found in a few cases. This, in general, is in accordance with the findings of other investigators whose work has been previously mentioned.

The strains studied by Clawson and Wetherby have in most cases cross agglutinated with one another and equally well with strains of acute rheumatic origin. The strains of streptococci from both rheumatic fever and chronic arthritis have in their experience tended to fall within a fairly well defined group which generally grew poorly when first isolated and produced a faint green discoloration on the blood agar plate when incubated at 37° C. for 24 hours. These organisms did not seem to represent a specific strain.

Immunological Reactions—The two immunological reactions studied in patients with chronic arthritis were (1) hypersensitiveness as indicated by the skin test and (2) streptococcic agglutination.

Birkhang (52) showed by skin tests that patients having chronic arthritis were hypersensitive to streptococcic protein in a higher percentage than normal persons. Clawson and Wetherby obtained similar results in a study of 127 cases of chronic arthritis and 107 normal persons (51). For these results see table 8.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. Cases</th>
<th>No. Positive</th>
<th>Per-cent Pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic arthritis</td>
<td>127</td>
<td>112</td>
<td>88.1</td>
</tr>
<tr>
<td>Normal persons</td>
<td>107</td>
<td>53</td>
<td>49.5</td>
</tr>
</tbody>
</table>

Nicholls and Stainsby (53) found that the serums of patients with chronic arthritis agglutinated streptococcus in higher dilutions than the serums from normal persons. Clawson and Wetherby tested the serums from 81 normal persons and from 60 patients with chronic arthritis. See table 9.
Table 9

Percentage of Streptococcic Agglutination in Normal People and in Patients With Chronic Arthritis.

<table>
<thead>
<tr>
<th>Dilutions</th>
<th>1:0</th>
<th>1:50</th>
<th>1:100</th>
<th>1:200</th>
<th>1:400</th>
<th>1:800</th>
<th>1:1600</th>
<th>1:3200</th>
<th>1:6400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, 61 cases</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>18.5</td>
<td>44</td>
<td>26</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis, 60 cases</td>
<td>0</td>
<td>0</td>
<td>1.6</td>
<td>6.6</td>
<td>31.6</td>
<td>38.3</td>
<td>10</td>
<td>10</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The strain of streptococcus used had been isolated from a case of chronic arthritis. The greatest number of the serums from the normal persons showed agglutination in the dilution of 1:400 and the greatest number of the chronic arthritics in the dilutions of 1:800. Only 28 per cent of the normal persons showed agglutination above 1:400. The per cent above 1:400 in the group of chronic arthritics was 60.

The higher percentage of positive skin tests and streptococcic agglutinating titers, Clawson and Wetherby considered as suggesting a possible etiological relationship of the streptococci to chronic arthritis.

Pathological Findings——The cellular reactions in the joint capsules and membranes as described by Nichols and Richardson, Margolis and Dorsey and others were polyblastic in character and decidedly resembled those described by Swift in joint lesions in acute rheumatic fever.

Clawson and Wetherby observed subcutaneous nodules in 30 per cent of a series of 300 cases of chronic arthritis. They found the cellular reaction in these nodules, as did Coates and Coombs, to be similar to the reactions in subcutaneous nodules and heart valves in acute rheumatic fever and in heart valves in subacute bacterial endocarditis. The reaction was also similar to that in subcutaneous nodules produced experimentally in rabbits by injecting streptococci.

The bacteriological, immunological and pathological findings described above were suggested by Clawson and Wetherby as evidence of a causal relationship between streptococci and chronic arthritis.
Method of Vaccination—An effort was made to see what could be done by vaccination toward protecting patients having chronic arthritis. Animal experiments were carried on toward developing an efficient method of vaccination which would give the highest degree of immunity against the streptococcus.

The things considered necessary in a vaccine for chronic arthritis were (1) not to make the patient hypersensitive by giving the vaccine, (2) to desensitize the patients who are already hypersensitive and (3) to bring about a high degree of protective immunity.

The following experiments in rabbits showed that the intravenous injections of streptococci by Clawson and Wetherby (51) met the three above requirements while subcutaneous injections did not.

Hypersensitivity—The degree of tissue response as an indicator of hypersensitivity is shown in table 10.

<table>
<thead>
<tr>
<th>Number</th>
<th>Normal</th>
<th>Hypersensitive</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3 %</td>
<td>10.0%</td>
<td>0.1 %</td>
</tr>
<tr>
<td>2</td>
<td>0.1 %</td>
<td>6.0%</td>
<td>0.2 %</td>
</tr>
<tr>
<td>3</td>
<td>0.2 %</td>
<td>3.0%</td>
<td>0.0 %</td>
</tr>
<tr>
<td>4</td>
<td>0.1 %</td>
<td>3.0%</td>
<td>0.0 %</td>
</tr>
<tr>
<td>5</td>
<td>0.2 %</td>
<td>10.0%</td>
<td>0.2 %</td>
</tr>
<tr>
<td>6</td>
<td>0.3 %</td>
<td>3.0%</td>
<td>0.2 %</td>
</tr>
<tr>
<td>7</td>
<td>2.0 %</td>
<td>10.0%</td>
<td>0.2 %</td>
</tr>
<tr>
<td>8</td>
<td>0.0 %</td>
<td>10.0%</td>
<td>0.0 %</td>
</tr>
<tr>
<td>9</td>
<td>0.0 %</td>
<td>3.0%</td>
<td>0.2 %</td>
</tr>
<tr>
<td>10</td>
<td>0.0 %</td>
<td>9.0%</td>
<td>0.0 %</td>
</tr>
</tbody>
</table>

Average Agglutination Titers

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hypersensitive</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1:25</td>
<td>1:3200</td>
<td>1:200,000</td>
</tr>
</tbody>
</table>

The tissue response in terms of percentage was compared in normal, hypersensitive and immune animals. The hypersensitivity was produced by injecting animals subcutaneously in one area with a mixture of agar and streptococci. The immune state was brought about by repeated intravenous injections of
streptococci. Each of the animals in the three groups was then injected subcutaneously in each of ten places on the back with a known number of streptococci. All animals were killed ten days later and the number and size of the nodules at the site of the small subcutaneous injections were determined. The tissue response in these nodules was similar to the type of reaction found in lesions in chronic arthritis. The tissue response in the normal animals was 3.2 per cent, in the hypersensitive animals, 58 per cent and in the immune animals 1.1 per cent. The average streptococcal agglutination titer in the hypersensitive animals was 1:3200; and in the immune animals 1:200,000. These experiments confirmed the work of Swift (58) in that animals injected subcutaneously were made hypersensitive while the animals injected intravenously were not. This phenomenon is explained by Swift (58) as follows; when streptococci of low virulence are introduced into the bloodstream of normal animals they disappear rapidly, and, in doses here used, do not, as a rule, set up gross focal lesions in the tissues of the body. Their influence is probably exerted over a relatively wide area as represented by the ramifications of the circulatory system. Doubtless certain organs bear the brunt of the attack more than others, but all are usually able to dispose of these streptococci without undergoing severe damage. When, on the other hand, these organisms are introduced directly into the tissues there is a local reaction with a certain amount of tissue destruction, and before the body has been able to dispose of them effectively the inflammatory material has been produced either in sufficient quantity or quality to alter the bodily response in the direction of over-reaction to a second inoculation at a distant site. The subcutaneous method of giving a vaccine will not desensitize the hypersensitive animals, for hypersensitivity is produced and maintained by subcutaneous injections.

Desensitization——Ten animals were made hypersensitive as described above and later vaccinated intravenously with Streptococcus viridans. The degree of tissue response, indicative of hypersensitiveness in these ten vaccinated animals, was compared with that in hypersensitive animals which had not been
vaccinated. See Table 11.

Table 11
Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococci in Hypersensitive Animals Following Intravenous Vaccination.

<table>
<thead>
<tr>
<th>Number</th>
<th>Not Vaccinated</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2</td>
<td>6.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>3</td>
<td>9.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>4</td>
<td>8.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>5</td>
<td>10.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>6</td>
<td>8.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>7</td>
<td>10.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>8</td>
<td>10.0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>9</td>
<td>8.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>10</td>
<td>9.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average Agglutination Titers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non vaccinated-----------------1:3200</td>
</tr>
<tr>
<td>Vaccinated----------------------1:50,000</td>
</tr>
</tbody>
</table>

The non-vaccinated hypersensitive animals showed 88 per cent of tissue response. The hypersensitive animals which had been vaccinated intravenously gave a tissue response of 5.2 per cent. The average agglutination titer in the non-vaccinated hypersensitive animals was 1:3200, and in the vaccinated hypersensitive animals, 1:50,000. The hypersensitive animals were desensitized by the intravenous method of vaccination. Thus the intravenous method met the two necessary requirements in not producing hypersensitiveness and also in desensitizing animals already hypersensitive. As far as the hypersensitiveness is concerned the intravenous method of vaccination rather than the subcutaneous method should be used.

Protective Immunity-----It was seen in the preceding experiments that the streptococcal agglutinating titers were decidedly higher in animals injected intravenously than in animals injected subcutaneously. To test the protective merits of the subcutaneous and intravenous methods of injecting streptococcus vaccine two groups of animals were selected. Group 1 was vaccinated subcutan-
eously at five weekly intervals with one billion killed streptococci. Group 2 was vaccinated intravenously at the same periods with the same doses. The streptococcal agglutination titers of the two groups were then determined. See table 12.

Table 12

<table>
<thead>
<tr>
<th>Number</th>
<th>Normal</th>
<th>Subcutaneous</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:50</td>
<td>1:3200</td>
<td>1:400,000</td>
</tr>
<tr>
<td>2</td>
<td>1:100</td>
<td>1:6400</td>
<td>1:200,000</td>
</tr>
<tr>
<td>3</td>
<td>1:0</td>
<td>1:3200</td>
<td>1:400,000</td>
</tr>
<tr>
<td>4</td>
<td>1:0</td>
<td>1:1600</td>
<td>1:400,000</td>
</tr>
<tr>
<td>5</td>
<td>1:0</td>
<td>1:1600</td>
<td>1:400,000</td>
</tr>
<tr>
<td></td>
<td>1:30</td>
<td>1:3200</td>
<td>1:360,000</td>
</tr>
</tbody>
</table>

The animals vaccinated subcutaneously had titers ranging from 1:1600 to 1:6400. The animals vaccinated intravenously had titers of from 1:200,000 to 1:400,000. If the height of the agglutination titer can be relied upon as an indicator of the degree of immunity, then it is obvious that a much higher degree of protection can be produced against streptococcus by intravenous injections than by subcutaneous injections of a vaccine.

The evidence of a correlation between the height of an agglutinating titer and protection was shown by comparing the rate at which streptococci were killed in normal animals and in animals which had a higher agglutination titer and by comparing the bactericidal power of the blood of vaccinated and non-vaccinated chronic arthritic patients.

Normal rabbits and rabbits highly immune to streptococci were injected intravenously with 50,000,000 live streptococci. In 15 minutes 1 cc. of the blood was taken from the heart of each animal and plated on agar. In two hours the animals were killed and a gram of liver from each animal was ground in a mortar and plated in dilutions on agar. It was found in the series of ten rabbits of each group that the rate of disappearance of the streptococci from the blood in 15 minutes was three times greater in the immune than in
the normal rabbits. The rate at which the streptococci were killed in the livers of the animals in two hours was three and three tenths times greater in the immune animals. The streptococcal agglutination titers averaged 1:45 in the normal animals and 1:170,000 in the immune animals. See tables 13 and 14.

Table 13

Organisms per Cubic Centimeter Alive 15 Minutes after Injecting 50,000,000 Streptococci Intravenously into Normal Animals and Animals Made Immune to Streptococci.

<table>
<thead>
<tr>
<th>Agglutination</th>
<th>Normal</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titer</td>
<td>Number per cc.</td>
<td>Agglutination</td>
</tr>
<tr>
<td>1:50</td>
<td>55</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:50</td>
<td>40</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:100</td>
<td>41</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:100</td>
<td>44</td>
<td>1:50,000</td>
</tr>
<tr>
<td>1:50</td>
<td>40</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:100</td>
<td>47</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:0</td>
<td>50</td>
<td>1:50,000</td>
</tr>
<tr>
<td>1:0</td>
<td>70</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:0</td>
<td>23</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:0</td>
<td>25</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:45</td>
<td>435</td>
<td>1:170,000</td>
</tr>
</tbody>
</table>

Table 14

Number of Streptococci Alive in a Gram of Liver Two Hours after Injecting 50,000,000 Organisms into Normal and Immune Animals

<table>
<thead>
<tr>
<th>Agglutination</th>
<th>Normal</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titer</td>
<td>No. per Gram</td>
<td>Titer</td>
</tr>
<tr>
<td>1:0</td>
<td>3,500</td>
<td>1:400,000</td>
</tr>
<tr>
<td>1:50</td>
<td>4,200</td>
<td>1:400,000</td>
</tr>
<tr>
<td>1:0</td>
<td>7,000</td>
<td>1:400,000</td>
</tr>
<tr>
<td>1:0</td>
<td>2,500</td>
<td>1:100,000</td>
</tr>
<tr>
<td>1:0</td>
<td>4,500</td>
<td>1:100,000</td>
</tr>
<tr>
<td>1:50</td>
<td>2,250</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:50</td>
<td>10,200</td>
<td>1:400,000</td>
</tr>
<tr>
<td>1:100</td>
<td>10,000</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:0</td>
<td>5,600</td>
<td>1:400,000</td>
</tr>
<tr>
<td>1:0</td>
<td>6,000</td>
<td>1:200,000</td>
</tr>
<tr>
<td>1:25</td>
<td>55,750</td>
<td>1:280,000</td>
</tr>
</tbody>
</table>
It was found by using the method of Sutliff and Rhoades (59) for determining the bactericidal power of whole blood that the whole blood of vaccinated chronic arthritic patients with an agglutination power of 1:6400 or more had a much greater bactericidal power for streptococci than the blood of non-vaccinated patients with an average agglutination titer of 1:200.

Since the agglutination titer rises decidedly higher by the intravenous method of vaccination than by the subcutaneous method and since the above experiments in animals and patients showed a correlation between an elevated agglutination titer and desensitization and protective immunity, the intravenous method of administration was concluded to be the most desirable by Clawson and Wetherby.

Type or Species Specificity in Desensitization and Protective Immunity——

If desensitization and immunity should be strain specific, then it would seem that autogenous vaccines should probably be used in most cases. If, on the other hand, these two phenomena should be only species specific, then a stock streptococci vaccine would in most cases likely be sufficient. This is an important consideration, for it would be impracticable to use autogenous vaccine in treating chronic arthritis in most cases. Experiments were carried on with animals to determine the relation of acquired desensitization and immunity to type and species specificity.

Animals made hypersensitive to Streptococcus viridans of acute rheumatic origin were vaccinated intravenously with Streptococcus hemolyticus from a case of puerperal sepsis. The degree of tissue response to Streptococcus viridans indicative of hypersensitiveness was determined and compared with non-vaccinated animals which had been made hypersensitive to Streptococcus viridans. See table 15.

The response in the non-vaccinated animals was 68 per cent and in the animals vaccinated with Streptococcus hemolyticus, 0.4 per cent. The desensitization did not therefore appear to be strain or type specific.
Table 15

Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococci (S. viridans) into Hypersensitive Animals (S. viridans) following Intravenous Vaccination (S. hemolyticus)

<table>
<thead>
<tr>
<th>Number</th>
<th>Non Vaccinated</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>2</td>
<td>6 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>3</td>
<td>9 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>4</td>
<td>8 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>5</td>
<td>10 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>6</td>
<td>8 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>7</td>
<td>10 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>8</td>
<td>10 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>9</td>
<td>8 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>10</td>
<td>9 %</td>
<td>0.4 %</td>
</tr>
</tbody>
</table>

In a series of ten animals each animal was immunized with a different strain of streptococcus of chronic arthritis origin and later each of the animals was injected with 50,000,000 organisms of another strain of streptococcus. The rapidity with which this organism disappeared from the blood (tested in 15 minutes) and from the liver (tested in two hours) was much greater than in normal animals. These experiments also suggested that protective immunity was not type specific.

Non-specific Protein Therapy (B. typhosus) in Streptococcal Infections——

Intravenous injections of B. typhosus are commonly used in treating chronic arthritis. Experiments were performed in animals to see what relation intravenous injections of B. typhosus bore to the desensitization of animals hypersensitive to Streptococcus viridans and to the protection of animals against Streptococcus viridans.

Animals were made hypersensitive to Streptococcus viridans and vaccinated intravenously with B. typhosus, see Table 15.

Table 16

Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococcus in Hypersensitive Animals following Intravenous Vaccination With B. typhosus.

See page 65
Table 16
Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococci in Hypersensitive Animals following Intravenous Vaccination (B. typhosus)

<table>
<thead>
<tr>
<th>Number</th>
<th>Non Vaccinated</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 %</td>
<td>10 %</td>
</tr>
<tr>
<td>2</td>
<td>6 %</td>
<td>8 %</td>
</tr>
<tr>
<td>3</td>
<td>9 %</td>
<td>10 %</td>
</tr>
<tr>
<td>4</td>
<td>8 %</td>
<td>5 %</td>
</tr>
<tr>
<td>5</td>
<td>10 %</td>
<td>8 %</td>
</tr>
<tr>
<td>6</td>
<td>8 %</td>
<td>5 %</td>
</tr>
<tr>
<td>7</td>
<td>10 %</td>
<td>10 %</td>
</tr>
<tr>
<td>8</td>
<td>10 %</td>
<td>10 %</td>
</tr>
<tr>
<td>9</td>
<td>8 %</td>
<td>6 %</td>
</tr>
<tr>
<td>10</td>
<td>9 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>

88 % 82 %

Average Agglutination Titer
Not vaccinated------1:3200
Vaccinated--------Streptococcus--1:4000
B. typhosus------1:6400

The tissue response to Streptococcus viridans in these animals was compared to the response in non-vaccinated animals, which were hypersensitive. The response in the non-vaccinated animals was 88 per cent and in the animals vaccinated with B. typhosus, 82 per cent, as compared with 0.7 per cent in the hypersensitive animals vaccinated with streptococci. It was concluded by Clawson and Wetherby that desensitization to streptococci was not brought about by a non-specific protein reaction.

Animals vaccinated intravenously with B. typhosus developed a high agglutinating titer to B. typhosus but the titer to Streptococcus viridans was raised but slightly. When these animals were injected intravenously with 50,000,000 streptococci it was found that the rate at which the streptococci disappeared from the blood was even less than in normal animals. Protection against streptococci was not, therefore, brought about by intravenous injection of B. typhosus.

Thus Clawson and Wetherby concluded on fairly good experimental grounds that streptococcal desensitization and protection are species specific but not type specific and that they are not brought about by a non-specific protein reaction.
Their summary of this work was (51):

1. Non-specific chronic arthritis in most cases appears to be due to a streptococcic infection.

2. Subcutaneous injections of a streptococcic vaccine do not desensitize the hypersensitive individual but tend to increase the hypersensitive state.

3. The subcutaneous method develops only a slight degree of protection.

4. The intravenous method of giving a streptococcic vaccine desensitizes the hypersensitive patient, does not produce hypersensitivation and does cause a high degree of protective immunity to be developed.

5. Neither the desensitizing nor the protective phenomena are type specific but they appear to be species specific. They are not of the nature of a non-specific protein reaction.

Clawson and Wetherby report the results of a clinical application of this method on three hundred and sixty five cases of chronic arthritis treated at the outpatient department of the University of Minnesota Hospital (60).

The cases reported had been treated during the fifteen months previous to the publication of the report (60). The cases were not grouped into such distinct classes as "rheumatoid arthritis" (atrophic, proliferative) and "osteoarthritis" (hypertrophic, degenerative). Most patients had multiple joint involvement and all had the common complaint of joint pain. Rigler, roentgenologist of the University of Minnesota Hospital, in a series of sixty two consecutive cases, roentgenographed every joint in which there had ever been pain. In this group there was a high percentage of mixed cases from the point of view of accepted roentgen diagnosis. The age of the patient may possibly modify the type of tissue reaction to streptococcus infection. Table 17 shows by decades the age range of the patients in this series.

Some people have the opinion that in many cases arthritis in older people is non-infectious in origin. There are a number of older patients without symptoms in whom hypertrophic changes are noticed by roentgenographic examination. Such cases may not be of an infectious nature. In this group of older patients complaining of joint pains the joint lesion was probably infectious.
in most instances. Evidence for this is that the incidence of subcutaneous nodules was greater in the older than in the younger patients in a series of two hundred cases. See Table 18.

Table 17
Age Distribution by Decades of 365 Chronic Arthritics

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>1</td>
</tr>
<tr>
<td>10-19</td>
<td>9</td>
</tr>
<tr>
<td>20-29</td>
<td>32</td>
</tr>
<tr>
<td>30-39</td>
<td>61</td>
</tr>
<tr>
<td>40-49</td>
<td>103</td>
</tr>
<tr>
<td>50-59</td>
<td>92</td>
</tr>
<tr>
<td>60-69</td>
<td>58</td>
</tr>
<tr>
<td>70 and over</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 18
Age Distribution by Decades of Patients with Subcutaneous Nodules

<table>
<thead>
<tr>
<th>Decade</th>
<th>Number of Cases</th>
<th>Number of Nodules</th>
<th>Percentage of Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>20</td>
<td>5</td>
<td>25.2</td>
</tr>
<tr>
<td>30-39</td>
<td>27</td>
<td>6</td>
<td>22.2</td>
</tr>
<tr>
<td>40-49</td>
<td>50</td>
<td>13</td>
<td>26.5</td>
</tr>
<tr>
<td>50-59</td>
<td>55</td>
<td>24</td>
<td>43.6</td>
</tr>
<tr>
<td>60-69</td>
<td>32</td>
<td>8</td>
<td>25.0</td>
</tr>
<tr>
<td>70-79</td>
<td>6</td>
<td>3</td>
<td>50.0</td>
</tr>
</tbody>
</table>

It is probable that some of these cases were not true examples of non-specific chronic arthritis. Other forms of arthritis may simulate streptococcic arthritis. Gonorrheal and tuberculous arthritis are known to present a similar picture in some instances. Probably the staphlococcus may be responsible for occasional cases, although there is little definite evidence that this is so.

Method of Treatment——Intravenous injections of streptococcic vaccine were given. The organism used was isolated from the blood of a patient with rheumatic fever and pericarditis. This strain had been under cultivation for nine years and had been repeatedly used in previous animal experiments. It has been shown
to cross agglutinate in high dilutions (1:50,000) with a large percentage of strains of streptococci of rheumatic and chronic arthritic origin. This cross agglutination extends to strains of beta hemolytic streptococci as well as to viridans strains. This organism does not agglutinate spontaneously, is of low virulence and is safe for intravenous injection.

The injections were given at weekly intervals for at least eight weeks in the average case, though there were some variations in this routine. After eight injections the interval was usually extended to two weeks for several more injections, and later extended to three or four week intervals, or treatment suspended for months. The extension of treatment was guided largely by the clinical improvement and the height of the agglutination titer. The agglutinating titer appears to be a valuable indicator of the immunizing effect of vaccine therapy. An attempt was made to raise the titer to at least 1:6400.

The initial dose was 100,000,000 killed organisms. This was increased by 100,000,000 at each weekly injection, if no marked reaction had been experienced. If a disagreeable reaction followed the previous injection, the dose was usually kept at the same level in the following injection. The maximum did not usually exceed 800,000,000, though this was exceeded in some cases in which reactions were minimal and the agglutination titer difficult to bring up to 1:6400 or more. In some of the earlier cases treated a maximum dose of five billion was given. The reactions were apt to be more severe with such a dosage, and there seemed to be no better clinical results, though possibly more prompt response. The workers were careful to avoid other therapy in connection with vaccine treatment in order to determine the results more fairly. The only medication advised was 10 grains of acetylsalicylic acid following the injection to lessen or to avoid a reaction.

Reactions of some sort were experienced following about 50 per cent of the injections. There seemed to be a considerable amount of variation in different individuals. A person might have reactions at one time and not at another. In more than 3,000 injections, only one case was seen with immediate symptoms suggestive of anaphylaxis. In that case the patient experienced a transient
dyspnea and chest pain that quickly passed over and has not been present following other injections. In most cases when a reaction was present the onset was from two to ten hours following the injection. The reactions usually consisted of chills of varying degree and duration, followed by fever. The chills lasted usually from one to two hours, and the fever had about the same duration. The fever when present was most often 100 to 101, though occasionally higher. In a few instances there was some severe aching at the time of reaction especially in the back, though this was present in only an occasional case. Nausea, vomiting and diarrhea were sometimes present. Patients quite frequently felt tired and ached the day following the injection, but more often there were no ill after-effects. There did not appear to be any correlation between the improvement and the reaction experienced, in fact reactions were avoided as much as possible in order not to incapacitate the patient or discourage proceeding with the therapy.

Results of the Treatment——Three hundred and sixty-five patients received treatment. Three hundred and one of these patients received adequate treatment to determine the results of the therapy. To be considered adequate for results, patients must have reported following at least five injections. The sixty-four patients without adequate treatment consisted of those who discontinued treatment and those who were treated at the time of the report who had not yet received five injections.

Clinical improvement was based on three general criteria: (1) decrease in pain, (2) decrease in joint swelling and (3) increase in joint movement. An attempt was made to discount the psychologic factor as much as possible. The fact that most of these individuals were outpatients and not on any other therapy did away with the objectionable factor of increased rest and change in surroundings, such as is encountered with hospital patients under any type of therapy.

Results of the different criteria for improvement are given in table 19, excluding the small number of questionable cases. In considering joint motion improvement implied such factors as the ability to close the fingers more
completely, to raise the hand to the head when unable to do so previously, to be able to extend the leg at the knee more completely, to be able to step upstairs when unable to do so previously, and other similar experiences. The most impressive factor in improvement was the high incidence in the decrease in joint swelling, as this could not be explained on a psychologic basis.

Table 19

Criteria of Improvement

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of cases</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain (282 cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased pain</td>
<td>233</td>
<td>82.6</td>
</tr>
<tr>
<td>Unchanged</td>
<td>49</td>
<td>17.4</td>
</tr>
<tr>
<td>Joint swelling (197 cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased swelling</td>
<td>160</td>
<td>81.2</td>
</tr>
<tr>
<td>Unchanged</td>
<td>37</td>
<td>18.8</td>
</tr>
<tr>
<td>Joint motion (243 cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased motion</td>
<td>206</td>
<td>84.7</td>
</tr>
<tr>
<td>Unchanged</td>
<td>37</td>
<td>15.3</td>
</tr>
</tbody>
</table>

A study was made of the number of injections required before definite clinical improvement was manifested. In many cases, questionable improvement might precede definite improvement by several weeks and in some instances the designation of the time of improvement was somewhat arbitrary. It is again to be noted that the treatments were given at weekly intervals. Table 20 shows the time of beginning of definite improvement during the treatment.

Table 20

Time of Beginning Definite Improvement

<table>
<thead>
<tr>
<th>Number of treatments</th>
<th>Number Improved</th>
<th>Percentage Improved</th>
<th>Total Percentage Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>16.7</td>
<td>22.3</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>19.7</td>
<td>42.0</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>20.2</td>
<td>62.2</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>14.5</td>
<td>76.7</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>7.7</td>
<td>84.5</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>5.7</td>
<td>90.2</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>3.4</td>
<td>93.6</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>4.7</td>
<td>97.4</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1.3</td>
<td>98.7</td>
</tr>
<tr>
<td>Over 10</td>
<td>2</td>
<td>1.3</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Nearly two thirds of the patients experiencing clinical improvement did so after five injections; nine tenths did so after seven injections. Very few patients reported clinical improvement if it was not present after ten treatments. Some of the unimproved patients received as many as twenty-five treatments without any change in the clinical course. In some instances the clinical improvement was very striking, while in others it was more gradual and less pronounced.

Improvement once manifested, was usually fairly well sustained and increased while the patient was under therapy. There were some exceptions to this however as will be discussed in the correlation of clinical improvement and agglutinating power. It is impossible to predict improvement in any individual. In general the results were better in earlier and less severe cases, although there was some report of striking examples of improvement in cases of many year's standing. Some of the patients observed over a period of months have made a marked gain in weight and have shown definite hypertrophy in previously atrophied muscle groups. Contrary to the experience with subcutaneous injections of vaccines, there has not been a definite aggravation of the arthritic process in any case.

Agglutinating Titer and Vaccine Therapy——In correlation with the vaccine therapy, agglutinating titers were with the organisms with which the chronic arthritic patients were treated. Agglutinating titers were obtained before therapy was instituted in 300 cases of chronic arthritis, table 21.

**Table 21**

<table>
<thead>
<tr>
<th>Initial Agglutination Titer in Chronic Arthritis—-300 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilution</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>1:10</td>
</tr>
<tr>
<td>1:50</td>
</tr>
<tr>
<td>1:100</td>
</tr>
<tr>
<td>1:200</td>
</tr>
<tr>
<td>1:400</td>
</tr>
<tr>
<td>1:800</td>
</tr>
<tr>
<td>1:1600</td>
</tr>
<tr>
<td>1:3200</td>
</tr>
<tr>
<td>1:6400</td>
</tr>
</tbody>
</table>
The greatest percentage showed the highest agglutinating power to be 1:200. There was no marked difference in the agglutinating titer of normal persons and chronic arthritics except for the tendency of a small number of titers to be at a higher level in chronic arthritics. For the most part, the slightly higher titers in the cases of chronic arthritis were obtained in those with a more active involvement. It must be borne in mind that streptococcic infections are common. Few individuals can be considered "normal" in relation to streptococcic infection. No more favorable response to treatment was observed in cases with high initial titers than in those with lower initial titers, such as 1:0 or 1:50. Tables 22 and 23 show the relation of the heights of the agglutination titers to the clinical improvement.

Table 22

Distribution of Maximum Agglutination Titer in One Hundred and Eighty-eight Improved Treated Arthritic Patients.

<table>
<thead>
<tr>
<th>Titer</th>
<th>Number</th>
<th>Percentage</th>
<th>Total Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:800</td>
<td>4</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>1:1600</td>
<td>9</td>
<td>4.7</td>
<td>6.8</td>
</tr>
<tr>
<td>1:3200</td>
<td>27</td>
<td>14.3</td>
<td>21.1</td>
</tr>
<tr>
<td>1:6400</td>
<td>54</td>
<td>28.8</td>
<td>49.9</td>
</tr>
<tr>
<td>1:12800</td>
<td>71</td>
<td>37.8</td>
<td>87.7</td>
</tr>
<tr>
<td>1:25600</td>
<td>20</td>
<td>10.6</td>
<td>98.3</td>
</tr>
<tr>
<td>1:512000</td>
<td>3</td>
<td>1.7</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 23

Distribution of Maximum Agglutination Titer in Thirty-seven Unimproved Treated Arthritic Patients.

<table>
<thead>
<tr>
<th>Titer</th>
<th>Number</th>
<th>Percentage</th>
<th>Total Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:100</td>
<td>1</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>1:200</td>
<td>0</td>
<td>0.0</td>
<td>2.7</td>
</tr>
<tr>
<td>1:400</td>
<td>2</td>
<td>5.4</td>
<td>8.1</td>
</tr>
<tr>
<td>1:800</td>
<td>3</td>
<td>8.1</td>
<td>16.2</td>
</tr>
<tr>
<td>1:1600</td>
<td>1</td>
<td>2.7</td>
<td>18.9</td>
</tr>
<tr>
<td>1:3200</td>
<td>8</td>
<td>21.6</td>
<td>40.5</td>
</tr>
<tr>
<td>1:6400</td>
<td>12</td>
<td>34.2</td>
<td>72.9</td>
</tr>
<tr>
<td>1:12800</td>
<td>5</td>
<td>13.5</td>
<td>86.4</td>
</tr>
<tr>
<td>1:256000</td>
<td>5</td>
<td>13.5</td>
<td>100</td>
</tr>
</tbody>
</table>

Intravenous vaccine therapy elicited a definite rise in the agglutinating titer of the serum of most treated patients. The maximum dilution in which
agglutination occurred was 1:100,000. Such a titer was obtained in one patient. Several hed titers of 1:50,000 and many of 1:25,000. A definite correlation was observed between the height of the agglutination titer and the clinical improvement of the patient. Those who showed marked improvement after one or two injections have in most instances shown a corresponding elevation in the agglutinating titer. It is difficult to place any definite level of titer as that at which improvement should be manifested, though in general most patients felt definitely better when the titer was raised to 1:6400 or more. Clinical improvement was found in some cases with an agglutinating titer as low as 1:3200. In a few cases individuals improved with a lower titer.

Once raised, the agglutinating titer tends to remain at a high level, but occasionally it may drop back unexpectedly. Acute respiratory infections and too high doses and too frequent treatments may be factors in reducing the agglutination titer. If eight or ten injections were given and and the titer went to 1:6400 or higher, and the patient clinically improved, treatment was suspended for several months or until there was a recurrence of joint pain or of other symptoms. Agglutinating titers should be checked at monthly intervals if possible after suspending treatment. Titers will often remain at a high level for months. With recurrence or aggravation of symptoms, only a few small injections are usually sufficient to restore the titer to a high level with a corresponding clinical improvement. A number of patients in this series of Clawson and Wetherby were followed for from two to eight months without therapy and with observation of the agglutinating titer and clinical improvement. See table 24.

The agglutination titer was considered in unimproved treated cases. It is apparent that two types of cases are seen in the unimproved treated group. The first type are those in whom it is difficult to bring up the agglutination titer even though large doses of vaccine are given. It is of interest that the maximum titer in the improved group was less than 1:6400 in 21.1 per cent of the cases (tables 22 and 23), while in the unimproved group the titer was less than 1:6400 in 40.5 per cent of the cases. Some of the unimproved patients
however had a high titer sustained over a period of several months.

Table 24

Duration of Elevated Agglutination Titer and Clinical Improvement Following a Course of Therapy and Without Further Injections.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time since treatment</th>
<th>Titer after course of treatment</th>
<th>Titer after interval</th>
<th>Improvement sustained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 months</td>
<td>1:100,000</td>
<td>1:6400</td>
<td>Never improved</td>
</tr>
<tr>
<td>2</td>
<td>3 months</td>
<td>1:6400</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>7½ months</td>
<td>1:6400</td>
<td>1:3200</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>7 months</td>
<td>1:25,000</td>
<td>1:25,000</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>7 months</td>
<td>1:12,800</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>6 months</td>
<td>1:1600</td>
<td>1:3200</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>6 months</td>
<td>1:25,000</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>6 months</td>
<td>1:6400</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>9</td>
<td>6 months</td>
<td>1:12,800</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>10</td>
<td>5 months</td>
<td>1:25,000</td>
<td>1:25,000</td>
<td>yes</td>
</tr>
<tr>
<td>11</td>
<td>4 months</td>
<td>1:6400</td>
<td>1:12,800</td>
<td>yes</td>
</tr>
<tr>
<td>12</td>
<td>3 months</td>
<td>1:3200</td>
<td>1:12,800</td>
<td>yes</td>
</tr>
<tr>
<td>13</td>
<td>3 months</td>
<td>1:3,200</td>
<td>1:3,200</td>
<td>yes</td>
</tr>
<tr>
<td>14</td>
<td>3 months</td>
<td>1:12,800</td>
<td>1:12,800</td>
<td>no</td>
</tr>
<tr>
<td>15</td>
<td>2½ months</td>
<td>1:6400</td>
<td>1:12,800</td>
<td>yes</td>
</tr>
<tr>
<td>16</td>
<td>2 months</td>
<td>1:25,000</td>
<td>1:800</td>
<td>no</td>
</tr>
<tr>
<td>17</td>
<td>2 months</td>
<td>1:6400</td>
<td>1:1600</td>
<td>yes</td>
</tr>
<tr>
<td>18</td>
<td>2 months</td>
<td>1:12,800</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>19</td>
<td>2 months</td>
<td>1:6400</td>
<td>1:6400</td>
<td>yes</td>
</tr>
<tr>
<td>20</td>
<td>2 months</td>
<td>1:6400</td>
<td>1:6400</td>
<td>yes</td>
</tr>
</tbody>
</table>

As a further check on the significance of the agglutinating titer, the bactericidal power of the blood was determined. Blood of normal persons and of untreated and treated arthritics was used. The blood from treated patients, with an agglutinating titer of 1:6400 or more, was found to have a much higher bactericidal power against the streptococci used in the vaccine than did the blood of normal persons, untreated arthritic patients, or treated patients with low agglutinating titers.

Contraindications to Vaccine Therapy——Pregnant women were not treated because of the frequency with which abortion was produced in pregnant hypersensitive rabbits receiving intravenous injections of streptococci. It was also considered inadvisable to administer intravenous vaccine to patients with chronic arthritis who also had glomerulonephritis. In acute phases of arthritis with persistent fever the dosage was either reduced or therapy postponed until the acute febrile period was ended.
A series of case reports of patients so treated by Clawson and Wetherby at the outpatient department of the University of Minnesota Hospital follows:(61)

Case I.-History.-Mrs. E. P., aged 39, had had acute tonsillitis when 21 years of age (1913) and pains soon developed in most of the joints of her body. Transitory swelling and redness were present in the involved joints and she had a fever. She was confined to bed for three weeks. Her physician made a diagnosis of inflammatory rheumatism. Shortly afterward he told her that a heart murmur was present. Since then she had had joint pains off and on most of the time. Seven months before this report (June 1930), her joints became much worse and remained painful. She had involvement especially in her knees and fingers, and had some swelling in these joints most of the time. She had been up and about for the most part, but had marked pain at times.

Examination.-There was a definite pre-systolic murmur over the apex of the heart, and the heart was enlarged with a mitral contour. There was swelling of many of the metacarpalphalangeal joints and phalangeal joints. Both knees were swollen, and the left knee was tender to pressure, as was the right wrist. Roentgen examination of the right wrist was reported as follows, "There is a slight atrophy of the bones and some slight cartilaginous absorption, especially in the radiocarpal joint. The appearance suggests an atrophic arthritis of the periarticular type with very little improvement of the joints as yet. Conclusions; atrophic arthritis, periarticular type." A blood culture showed Streptococcus viridans.

Vaccine Therapy.-The patient received nine injections of vaccine, in doses of from 100,000,000 to 500,000,000 organisms at weekly intervals. Reactions, consisting of moderate fever and chills of a few hours' duration came on about three hours after each injection. No improvement followed the first three injections. Since then the pain has been much reduced, and she is able to do much more physical work than prior to treatment. The agglutination titer was raised from 1:0 to 1:12,800 after six injections.
Case 2.—History.—Mr. H. M., aged 22, first noticed pains in the hips and spines four years before this report. Eighteen months before, soreness developed in the right shoulder. During the past six weeks the knees had been definitely painful. He now had marked difficulty in walking and took short steps. During the past six weeks he has been sleeping very poorly because of pains; he had been unable to work during the past month.

Examination.—The patient was unable to extend the thighs at the hips because of pain. Tenderness was present over the hips and knees. Limitation of motion of the spine was present. Roentgen observations on the right hip and left knee were: "Some suggestion of arthritis in the right sacro-iliac region; otherwise negative." A blood culture gave negative results.

Vaccine therapy.—The patient received five injections over a period of one month. The doses were from 100,000,000 to 2,000,000,000 organisms. The reactions were chiefly slight chills and fever of from one to two hours duration. The joints were slightly improved after the second injection and much improved after the third. At that time the patient was able to return to work after being out for a month because of joint pains. The pain was practically all gone after the fourth injection.

Case 3.—Miss M. A., aged 18, noticed pain in the toes of the left foot, first, two years before this report. Since that time the feet, ankles, knees, hips, fingers, wrists, hands, elbows and shoulders had been involved. The joints had frequently been warm, swollen and tender. She had had no fever. The joints had tended to be acutely involved in succession and partially cleared up after a few days to a few weeks.

Examination.—Limitation of motion was present in the left arm at the shoulder. The wrists were definitely swollen and tender to touch. There was definite limitation of motion at the wrists. The left knee and feet were moderately swollen. Roentgen observations on the left knee and right wrist were, "There is some atrophic arthritis involving the right wrist and the left knee. Slight cartilaginous destruction and some bone destruction are present."
Conclusions: Atrophic arthritis, fairly marked degree, right wrist and left knee. A blood culture gave negative results.

Vaccine therapy. — The patient received twelve injections over a period of two and a half months of doses of from 100,000,000 to 3,000,000,000 organisms. The reactions varied from none to moderate chills and fever for a few hours. There was perhaps less joint pains after two, and much less pain was noted after four injections. Five days after the sixth injection, the patient had pain and was unable to walk for five days because of swollen, painful ankles. The agglutination titer was depressed to 1:0 at that time. Seven hours after the seventh injection, the swelling in the feet had subsided and the patient could walk about freely. She was practically free from joint pains while under treatment during the following six weeks. Skin tests, positive before treatment, were very faint after five injections. The agglutination titer was raised from 1:200 to 1:6400 after five injections.

Case 4. — History. — Mrs. C. B., aged 39, had noticed multiple joint pains in the left shoulder, left hip, left foot, lower part of the spine and right temporo-mandibular joint for about three months (since October, 1930). No redness or swelling was seen in any of the joints. She had been working as a scrubwoman. This work had been very difficult recently because of the joint pains.

Examination. — No definite swelling or deformity was present. The roentgen report was: "Left ankle negative; lumbo-sacral spine negative." A blood culture yielded Streptococcus viridans.

Vaccine therapy. — Six injections ranging from 100,000,000 to 600,000,000 organisms were given at from four to seven day intervals. On two occasions there were no reactions; at other times she had chills of from two to four hours duration. She had a temperature of 102°F on one occasion. The pain in the left hip, present constantly, disappeared after the third injection; there was much less pain in all joints after four injections, and the patient was able to perform her duties as a scrubwoman much more easily. The condition was still improved after two and one half months. The agglutination titer was raised.
from 1:50 to 1:6400 after five injections.

Case 5.—History.—Mrs. E. M., aged 51, had had joint pain for the past forty years. This had been present in nearly all her joints, although there had never been any redness or swelling. Recently she had had marked pain in the knees and some swelling at times.

Examination.—Moderate swelling of the knees was observed. There were no gross deformities of any joints. Roentgen examination of the left knee was reported as follows, "Slight evidences of static arthritis are present, but no other evidence of pathology. Conclusion, slight static arthritis." A blood culture gave negative results.

Vaccine therapy.—The patient received thirteen injections of from 1,000,000 to 3,000,000,000 organisms over a period of nearly four months. Most of the reactions consisted of slight chills and fever for two or three hours. There was some relief of pain after the first injection and definite relief after three injections. The patient is doing housework and has recently been able to do a complete washing for the first time in two years. Increased motion in the arms is now present. The agglutination titer was raised from 1:6 to 1:6400 after three injections, and remained at that level after eight injections.

Case 6.—History.—In Mrs. A. R., aged 63, pain was present in the right knee for about fifteen years. Stiffness was also present. These symptoms were aggravated by the patient being on her feet a great deal; the knee was more painful in the evening than in the morning; there was no other joint involvement and no history of any injury. The patient was always of less than average weight. She had a tendency toward constipation and functional gastro-intestinal symptoms.

Examination.—General findings were essentially negative. Roentgen examination of the right knee was as follows, "There is a definite narrowing of the medial portion of the joint space, such as is commonly associated with a
static arthritis. There is a small amount of bone production around the patella and the tibia, characteristic of a chronic hypertrophic arthritis. Opinion: Static arthritis with hypertrophic bone production. A blood culture gave negative results.

Vaccine therapy. - The patient received eight injections of from 100,000,000 to 1,000,000,000 organisms over a period of more than two months. Reactions consisted of slight chills a few hours after injections. On one occasion some diarrhea was present. The knee began to be slightly less painful after the third injection and has continued to improve since that time, so that there is much less pain at the present time and walking is definitely easier. The agglutination titer was raised from 1:200 to 1:12,800 after five injections.

Case 7. - History. - Mrs. A. J., aged 29, had had pain in the left hip for the past two months so that walking was painful and difficult. There was some pain in other joints, especially the left knee.

Examination. - The patient walked with a definite limp. Pain was present over the hip on abduction of the thigh. Roentgen examination of the left hip and left knee was reported as follows, "There is a very slight hypertrophic change around the left hip, suggesting an old, rather low grade arthritis. A small amount of effusion is present in the left knee. Conclusion: effusion of left knee; slight hypertrophic arthritis of the left hip." A blood culture gave negative results.

Vaccine therapy. - The patient was given ten treatments over a period of three months at intervals of from four to twenty days with doses of from 100,000,000 to 4,000,000,000 organisms. Most of the last doses were from 1,000,000,000 to 2,000,000,000. Slight or no chills and fever occurred after most injections; this reaction was quite marked after the dose of 4,000,000,000 organisms, lasting about seven hours. The pains were definitely less painful after four injections and after that time the patient walked without a limp. She stated recently that there is now only occasional joint pain and that she is much improved. Skin tests have remained positive. The agglutination titer was
raised from 1:0 to 1:3200 after seven injections.

Case 8.-Mrs. C. M., aged 61, had had persistent pain in the region of the thoracic spine for six years (since 1925). Pain often would waken her at night and was present at all times while she was working. She had also had slight pains in the ankles and knees during the past four years. These pains were inconstant and not severe and were noticed chiefly on damp or rainy days.

Examination.-Limitation of motion of the thoracic spine was observed. Other joints showed no changes. The roentgen report was, "Thoracic spine: There is a marked scoliosis of the thoracic spine. There is some evidence of atrophy of the bodies. There is only a slight amount of hypertrophic arthritis present." A blood culture showed Streptococcus viridans.

Vaccine therapy.-Fourteen injections were given over a period of three months at one week intervals. The dosage was from 100,000,000 to a maximum of 2,000,000,000 organisms, the last injections being 2,000,000,000. The patient had no reaction from the first two injections. With the larger dosage she had no reactions at times, but at other times had chills and fever for three or four hours. Herpes labialis was noted on one occasion and increased aching for a few hours on another occasion. She had no relief until after five injections.

Since that time, the previous moderate pain in the extremities has subsided, and the severe backache had entirely disappeared for the first time in six years. While previously unable to walk more than two blocks because of severe back pain, she can now walk several miles. Some residual stiffness persists through the thoracic spine, but there is no severe pain. The agglutination titer was raised from 1:0 to 1:200 after two injections.

Case 9.-History.-Mrs. T. D., aged 64, had had marked pain and swelling in the knees for the past six months. The pain was worse on motion after a rest period.

Examination.-The patient walked with a limp. The knees were definitely tender and swollen. Roentgen observations on the left knee were, "There is a slight
degree of chronic hypertrophic arthritis, involving the left knee joint and
patella. There is no evidence of destruction of cartilage or of bone. Conclusion:
Slight chronic hypertrophic arthritis. A blood culture was negative.

Vaccine therapy.—The patient received thirteen treatments over a period
of three and one half months. The dosage varied from 100,000,000 to 2,000,000,000 organisms. The last four doses were reduced to 5,000,000,000. Reactions were variable; none was present until a dose of 1,000,000,000 was used. With a larger dosage she had no reaction at times, and at other times chills and fever of from two to four hours duration. After the second injection the pains were much lessened and swelling subsided in the knees. Improvement has continued. Skin tests, strongly positive before treatments, became negative after three injections and remained negative when rechecked after five injections. The agglutination titer was raised from 1:100 to 1:800 after two injections.

Case 10.—History.—Mrs. B. S., aged 57, had had pain and, at times, swelling in
many joints for ten or twelve years. The hands had frequently been involved, and there had also been some pain in the knees, ankles and shoulders. During the past two weeks, the soreness had been more marked, especially in the left knee.

Examination.—The patient walked with a limp. Some swelling and tenderness were present over the left knee. Roentgen observations on the left knee were:

"There is a fairly marked hypertrophic arthritis, involving the left knee joint with a number of spurs projecting from the tibia and patella. Conclusions: chronic hypertrophic arthritis." A blood culture yielded Streptococcus viridans.

Vaccine therapy.—The patient received nine injections of from 100,000,000 to 2,000,000,000 organisms, over a period of two and one half months. The reactions varied, the patient usually having chills and fever of about four or five hours' duration; on one occasion she had some fever for a day. The joints were less painful after the second injection, and the swelling in the knees definitely subsided. The patient has markedly improved; she walks easily and with very little pain. Skin tests, previously positive, became negative after
five injections. The agglutination titer was raised from 1:100 to 1:12,800 after five injections.
(1) Pemberton, R., Arthritis and Rheumatoid Conditions, Lea and Febiger, Philadelphia, 1929

(2) Moodie, R.L., Palaeopathology, University of Illinois Press, 1923

(3) Osborn, Men of the Old Stone Age, Scribners, New York, 1923


(6) Nathan, P.W., Arthritis Deformans as an Infectious Disease, Journal of Medical Research, 36; No. 2, 187-223, May 1917

(7) Stengel, A., and Fox, N., Text Book of Pathology, Edition 6, 1927

(8) Osler, W., and McCrae, T., Principles and Practice of Medicine, D. Appleton and Company, 1126, New York, 1920


(11) Ely, L.W., Inflammation in Bones and Joints, J.B. Lippencott and Co., Philadelphia, 1923

(12) Billings, F., Chronic Focal Infections and Their Relation to Arthritis and Nephritis, Archives of Internal Medicine, 9: 484, April 1912

(13) McCrae, T., Arthritis Deformans, Modern Medicine, Leo and Febiger, Philadelphia, 1915, Vol. 5

(14) Pemberton, R., Arthritis in Nelson's Loose Leaf Living Medicine, Vol. 5, pp. 605


(16) Nichols, F.H., and Richardson, F.L., Arthritis Deformans, Journal of Medical Research, 16: 149, 1903

(18) Davis, D.J., Bacteriological and Experimental Observations in Focal Infections. J.A.M.A. 61: 724 September 6, 1913

(19) Hastings, T.W., Compliment Fixation Tests for Streptococci, Conococcus and Other Bacteria in Infective Deforming Arthritis and Arthritis Deformans. J.A.M.A. 60: 1208 April 15, 1913

(20) Burbank, R., and Hadjopoulas, L.G., Serologic Significance of Streptococcus in Arthritis and Allied Conditions. J.A.M.A. 84: 637 Feb. 28, 1925


(22) Small, J.C., Rheumatic Fever. American Journal of Medical Science. 175: 638 May 1928


(29) Syranyi, L., and Forro, E., Streptokkin in Blute mit bisonderer

(31) Margolis, H.M., and Dorsey, A.H.E., Chronic Arthritis, Archives of Internal Medicine. 46; 121, 1930

(32) Henry, Bulletin of the Royal Academy of Medicine of Belgium. 28 Series 4, 76, 1914


(34) Small, J.C., The Role of Streptococcus in the Rheumatic Diseases, Journal of Laboratory and Clinical Medicine. 15: 1144, 1929

(35) Freiberg, J.A., Allergy as a Factor in the Production of Proliferative Arthritis, Archives of Surgery. 18: 645, 1929

(36) Wyatt, B.L., The Treatment of Chronic Arthritis, J.A.M.A. 133: 369, 1931

(37) Betz, L., Treatment of Arthritis by Non-specific Therapy, Medical Records. 94: 920, 1921

(38) This was mentioned in (39) but no reference was given.

(39) Shahan, H.I., The Treatment of Arthritis with Special Reference to Non-specific Protein Therapy, New York State Journal of Medicine. 30: 1214, 1930

(40) Goldfain, E., Rationale of Vaccine Therapy in Chronic Infectious Arthritis, Journal of the Oklahoma State Medical Association. 24: 332, 1931

(41) Burbank, R., and Hadjopoulis, L.G., Seriological Significance of Streptococci in Arthritis and Allied Conditions, J.A.M.A. 84: 637, 1925

(42) Cecil, R.L., The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, Archives of Internal Medicine. 43: 571 1929
(43) Small, J.C., The Biologic Products of Streptococcus Cardiogardarthritis and the Latest Developments in the Technic of their Therapeutic Application, Journal of Laboratory and Clinical Medicine. 15: 1093

(44) Vipond, A.E., Vaccine Treatment of Chronic Arthritis, Canadian Medical Association Journal. 25: 452, October, 1931

(45) Vipond, A.E., Recent Work on the Bacteriology of Rheumatoid Arthritis and its Treatment, American Medicine. 10 New series, 894 1915

(46) Shuster, M., Selective Streptococcus Vaccine Therapy in Chronic Arthritis Medical Journal and Records. 134: 347, October 7, 1930


(48) Burbank, R., and Christensen, B., Specific Vaccine Treatment in 1,000 Cases of Chronic Arthritis With Results and Clinical Observations, Journal of Bone and Joint Surgery. 13: 246 April 1931

(49) Burbank, R., Vaccine Therapy and Serological Diagnosis in the Arthritis, Journal of Bone and Joint Surgery. 8: 657, 1926

(50) Crowe, H.W., Specific Vaccine Treatment of Chronic Arthritis and Rheumatism, Journal of Laboratory and Clinical Medicine. 15: 1072

(51) Clawson, E.J., and Wetherby, M., An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients, Annals of Internal Medicine. 5: Pt. 2 1447, 1932

(52) Birkhaug, K.E., Skin Hypersensitivity of Patients with Rheumatic Fever and Chronic Arthritis to Filtrate, Autolysates and Bacterial Suspension of Streptococci, Journal of Infectious Diseases. 44: 363, 1929

323, 1931


(55) Margolis, H.M., and Dorsey, C.H.E., Chronic Arthritis; Bacteriology of Affected Tissues, Archives of Internal Medicine. 46: 121, 1930


(60) Clawson, B.J., and Wetherby, M., Intravenous Streptococcus Vaccine in Chronic Arthritis, J.A.M.A. 98: June 4, 1922

(61) Clawson, B.J., and Wetherby, M., Chronic Arthritis, Archives of Internal Medicine. 49: 303, 1932