A History Of Rheumatic Fever

Gordon Manson
A HISTORY OF RHEUMATIC FEVER*

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“There is perhaps no serious disease more familiar to us than acute articular rheumatism; it is one of the disorders most commonly seen in the wards of a general hospital; it is constantly encountered in private practice; and I must confess that when I chose rheumatism as the subject of the lectures you have done me the honour to ask me to deliver, I was almost afraid that it might be deemed too trite and commonplace, destitute of sufficient novelty and interest. But there is a certain advantage in treating of a matter with which the audience are familiar, and I trust I shall be able to present it to you in some new aspects, and to attract attention to certain points of great interest hitherto, I think, insufficiently considered, and thus I hope that my choice may be justified, and any unfavourable criticism in this aspect eventually disarmed”.

I regret to say that this introduction is not original with your speaker but rather is the introduction of Dr. W. B. Cheadle to his Harveian lectures for the year 18891. These lectures by Dr. Cheadle are of particular significance in the history of the development of our thinking regarding rheumatic fever and we shall speak more of them later. Suffice it to say, however, Dr. Cheadle’s introduction is a fitting prologue to our consideration this evening of the evolution of our concept of the rheumatic state.

The word rheumatism, of course, derives from the Greek 'pew and refers to the flowing of humors into the joints of affected persons. Rheumatism is a disease well known to medical antiquity and one of the earliest historical accounts we have of the condition is attributed by Guillaume Baillou2 in 1616 to Hippocrates whom he quotes as follows: “In those in whom pains and swellings come and go around the joints, and these not after the manner of gout in the foot, one will find large viscera and in the urine, a white sediment . . . Now this disease occurs in those in childhood and youth who were wont to have nose-bleeding but have since lost it”. In the second century after Christ that astute clinical observer Aretaeus3 noted — “In many cases the gout has passed into dropsy and sometimes into asthma, and from this succession there is no escape”. Here he refers to those unfortunate rheumatics with chronic heart disease and congestive failure before the days of the fox-glove. We should remember that early physicians did not differentiate clearly between what today we know as rheumatism and gout. Aretaeus’ clinical acumen is not confined to rheumatism for we had the opportunity last year of hearing from Fred Whitehouse4 of his contributions to our knowledge of diabetes. We should also remember that he was the first to describe the flaring of the ala nasi and expiratory grunt seen in the lobar pneumonia patient. Finally to Aretaeus belongs the credit of being the first to note the great importance of a positive family history in the diagnosis of the acute rheumatic state. Some 1700 years have elapsed since his contributions and we are

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Manson

still faced with the problem of trying to prevail on house officers and staff physicians to take an adequate family history from the acute rheumatic fever patient. About the same time Celsus noted that, "... children in whom there has been nose-bleeding, which has ceased are sure to be troubled by pains in the head, or they have some severe joint ulcerations, or they also become debilitated by disease".

Not much is found in the medical literature from the second or third century until the observations of Guillaume Baillou in 1616. Baillou is remembered chiefly for his original description of pertussis in 1578 but in 1616 made the following significant observations about the two principal clinical types of rheumatic fever: "Two kinds of persons experience teaches are attacked especially by this affection — one of them healthy seen in the fullness of health but soon attacked by the disease; when now this disease attacks, a spontaneous lassitude precedes it and the blood is diseased, and indeed this is found to be the case, as was noted by Hippocrates — they are obviously sick as soon as they are attacked. The other kind of persons usually attacked by this affection are those who at the time are really sick, indeed especially with a chronic disease, which has now desisted or seems dissolved by a false and hasty crisis, but however it survives and is not destroyed — the case of Pres. Greyotte demonstrates this, whom this type of disease attacked most severely". Thus we see that in the early 17th century it was appreciated that rheumatic fever might present not only as a severe acute illness but also be seen as a subtle, insidious, low grade inflammatory process eventuating in the type of patient whom we occasionally see in the height of young adulthood with a tight mitral stenosis in the absence of a history of acute rheumatic fever.

Thomas Sydenham was apparently the first to note that acute rheumatic fever usually follows an acute respiratory infection. He wrote: "The sad list of symptoms begins with chills and shivers; these are followed immediately by heat, disquietude, thirst, and the other concomitants of fever. One or two days after this (sometimes sooner) the patient is attacked by severe pains in the joints, sometimes in one and sometimes in another, sometimes in his wrists, sometimes in his shoulder, sometimes in the knee — in this last joint oftenest. The pain changes its place from time to time, takes the joints in turn, and affects the one that it attacks last with redness and swelling. Sometimes during the first days, the fever and the above named symptoms go hand in hand; the fever, however, gradually goes off whilst the pain only remains; sometimes, however, it grows worse. The febrile matter has, in that case, been transferred to the joints".

In 1686 Sydenham described the chorea minor which bears his name but did not associate it with the rheumatic state. The popular eponym, St. Vitus' dance, applied to this manifestation, interestingly, derives its name from a fancied resemblance of patients so afflicted to a dancing mania seen amongst young people smitten with religious fervor in the early 15th century in the Strasbourg area of Alsace. History records that the chief magistrate of that community ordered those persons so affected to St. Vitus' chapel in Zabern in Alsace. Today we note with interest that our patients may know what St. Vitus' Dance is and yet have no knowledge of the word "chorea" when we take our clinical histories.
Rheumatic Fever

Scarlet fever, which later came to be associated etiologically with the onset of acute rheumatic fever, was described by Daniel Sennert (1572-1637) of Breslau, Germany. Major states that the existence of the disease as a clinical entity was probably suggested to Sennert by his brother-in-law Döring. Sennert was a conscientious and devoted physician. Six times epidemics of plague invaded his city and because of fear of the disease, most of the physicians in the city fled. Sennert was one of the few who invariably remained to care for his people and as a consequence died of plague when the 7th epidemic raged through his community. It remained however for Sydenham to clearly differentiate the clinical courses of scarlet fever and measles which had hitherto been confused. According to Lettsom, Sydenham died a "martyr to the gout". In the way of therapy Sydenham is remembered for his emphasis on the clinical uses of quinine though he did not make particular reference to the use of this drug in the rheumatic state. 200 years were to elapse before the clinical usefulness of antipyretics in the rheumatic state would be appreciated.

With the rise of pathologic anatomy in the early 18th century, inevitably descriptions of rheumatic lesions began to appear. Valvular vegetations were first noted by Lancisi, a papal physician in the year 1709 who published autopsy findings. Similar findings were later published in 1761 by Morgagni. A year previously Anton Störck of Vienna, a pharmacologist and student of the famous pathologist Boerhaave, described the autopsy findings of pleural and pulmonary lesions in acute rheumatic fever. In 1761 Richard Pulteney an English pharmacist, provided an excellent description of rheumatic heart disease at autopsy without recognizing the nature of the disease. In the latter part of the 18th century, various clinical and pathological observations began to be correlated which served to relate the acute rheumatic state as seen clinically with organic heart disease seen at autopsy. In 1776 William Cullen, Professor of Pharmacology in Edinburgh, pointed out that rheumatic joints never suppurated. Lettsom, a biographer of Sydenham, reported what appears to have been the thrill of mitral stenosis in the following graphic terms: "Upon laying the hand on the sternum, it gave a sensation to the touch — somewhat like a fluid passing through a cylinder, in the central substance of which a ball had been infixed, against which the impulse of the circulating fluid had been directed, and by it repelled with a vibratory motion along the cylinder".

Edward Jenner in July 29, 1789 addressed the Fleece Medical Society on a disease of the heart following acute rheumatism, illustrated with dissections. This paper was never published and has apparently been lost. One finds no reference to its content in the literature. Our only knowledge of its existence comes from the fact that in 1805 Jenner wrote to a Dr. Parry regarding a friend’s death and in this letter referred to the paper and requested its return. So far as is known the paper was never returned. Matthew Baillie, whose text on Morbid Anatomy contained some of the finest pathological plates printed up until that time, in 1797 stated in his text, “the causes which produce a morbid growth of the heart are probably not all of them ascertained. The chief causes are ossification or thickening of some of its valves. On some occasions the heart will become enlarged from rheumatism attacking it”. Baillie appended a footnote to this observation as follows, “Dr. Pitcairn observed this
Manson

in several cases and is to be considered as the first person who made this important observation". (The observation was made in 1788 by Pitcairn). The career of Matthew Baillie as a physician and pathologist deserves further comment. He was the last of a quartet of famous English physicians immortalized in "The Gold Headed Cane". These men — Mead, Askew, Pitcairn and Baillie were successive owners of the Gold Headed Cane signifying professional leadership in 18th century and early 19th century London. When Baillie died, his widow presented the Gold Headed Cane to the Royal College of Physicians in whose museum it still resides as a tribute to the medical acumen of these great clinicians.

John Haygarth in 1805 made the significant observation that acute rheumatic fever is not always accompanied by fever and stated: "The term rheumatism, both in common and medical languages includes a great variety of disorders, which ought to be distinguished from each other by different names. After separating it from the nodosity of the joints, tic douloureux, sciatica, lumbago, and other diseases which the nosologists have placed under this classification, there still remain 470 cases of rheumatism. This disease is generally classed with fevers, and yet only 170 (about one-third of them) had any fever". With this introduction, Haygarth then discusses the clinical description and course of the disease. He was among the first to find Peruvian Bark excellent in the management of rheumatic fever though Sydenham had earlier appreciated its symptomatic effects in a variety of disease states.

The early 19th century was punctuated by a variety of climatological and epidemiological observations, largely speculative in character. In this period we also see contributions regarding various manifestations of the rheumatic state. In 1810 William Wells described rheumatic nodules. Wells' background was interesting from an historical point of view. He was born in Charleston, South Carolina of staunchly Loyalist parents and as a child his father dressed him in a blue coat lest he be mistaken for an American. His education was largely English and in his younger days he made a number of contributions as a physicist and his "Essay on Dew" was read before the Royal Society in 1814. A year earlier he had proposed a theory of natural selection which antedated by some 40 years the publication of the "Origin of Species" by Charles Darwin. This priority of Wells was acknowledged by Darwin in his classic volume. In describing rheumatic nodules in regard to a 15 year old girl he states: "many of the tendons of the superficial muscles of this patient were studded with numerous small hard tumors, an appearance which I have observed only in one other person, a thin and feeble man forty-one years old, who also labored under rheumatism".

The association of rheumatism and chorea is attributed to Thomas Addison of Guy's Hospital, by Babington to whom we are indebted for the development of laryngoscopy. The importance of myocarditis and its preponderance in the pediatric age group was noted by Robert Adams of the Jervis Street Hospital, Dublin, in 1827. It was later re-emphasized by Sturges in 1876 whose name is perpetuated in the Kalischer-Sturges-Weber-Dmitri Syndrome, to give it its full and historical appellation. Another Guy's Hospital physician, Richard Bright in 1831 described what he termed
Rheumatic Fever

roseola annulata as a manifestation of the rheumatic state, and in 1835 Thomas Watson stated: “I confidently believe the to and fro sound to be always indicative of inflammation of the external membrane . . . the blowing sound to be always indicative of inflammation of the internal membrane of the heart”. We might today take issue with Watson regarding the interpretation of abnormal heart sounds but we must acknowledge his important observation regarding the age distribution of the cardiac and arthritic manifestations of the rheumatic state which he expressed as follows: “One law respecting the connection between the cardiac and the arthritic symptoms may be stated with confidence, namely, that the younger the patient who suffers acute rheumatism (and I have seen it as early as the third or fourth year) the more likely will he be to have rheumatic carditis. The chance of this combination appears to diminish after puberty as life advances”. Interestingly enough, we probably owe the term “Waterhammer Pulse” to Watson rather than to Corrigan since Corrigan, in his description of the collapsing pulse of aortic insufficiency, does not use the term Waterhammer Pulse.

During the 18th century various theories were proposed regarding the pathogenesis of the rheumatic state. One of the earliest was suggested by Baron Corvisart who was Napoleon’s physician. It was the Baron’s suggestion that rheumatic valvular vegetations were internal manifestations of venereal warts. Whether this is a serious hypothesis or is a consequence of the inclinations and habits of the French army is open to conjecture. In 1827 William Prout, an English chemist, found elevation of blood lactic acid and suggested that a disturbance in this metabolite was responsible for the rheumatic state. His methods are not available to us and it is interesting to consider what accounted for the increase in blood lactic acid he observed. It is entirely possible that it may have been due to congestive failure which has been observed to produce an increase in blood lactic acid level in terminal patients following unsuccessful cardiotomy. It may also have been due to unrecognized cases of Pompe’s disease. During the middle 18th century the idea that the rheumatic state was a consequence of an increased blood uric acid level was popular until A. E. Garrod demonstrated that the uric acid level was normal in acute rheumatic fever patients. Garrod later distinguished himself by giving us the concept of inborn errors of metabolism. In 1861 Armand Trousseau, who is known for the sign of tetany which bears his name, pointed out the temporal relationships of rheumatic angina (i.e. tonsillitis) to subsequent acute rheumatism.

The major contribution, and indeed our modern concept of the rheumatic state, was proposed by W. B. Cheadle in the Harveian lectures for the year 1889. Dr. Cheadle himself was a remarkable individual. He was the co-author of a book on explorations in the Canadian Rocky Mountains which he undertook before embarking upon his medical career. His explorations took place in the 1860’s at a time when travelers in the area stood a good chance of having their scalps lifted by any of the several techniques described to us a couple of years ago so capably by our late colleague, Dr. Robert Clifford. Cheadle’s interests and original work lay in the area of measles, infant feeding, heart disease, cirrhosis, Grave’s Disease and he was one of the first to separate infantile rickets and scurvy. He had a deep personal interest
Manson

in the rheumatic state for his appreciation of the importance of family history was heightened by the fact that his wife and son suffered from rheumatic fever. Oddly enough he made no original contributions to our knowledge of the rheumatic state but in the matter of a very few years became known throughout the world as an expert on rheumatism as a consequence of his Harveian lectures. This was further insured by his authorship of the section on rheumatic fever in Keating’s “Cyclopedia of Diseases of Children,” published in Philadelphia in 1890 which was the standard American pediatric text of the day. Cheadle took the various divergent manifestations of the rheumatic state and put them together for us in a neat pathogenetic package which has remained unchanged to the present time. He appreciated the fact that the manifestations in childhood differ from those in adulthood and that childhood manifestations are followed by adult manifestations as the individual grows older. American and British pediatricians in the early part of the present century all learned what was termed “Cheadle's Cycle” consisting of: endocarditis, pericarditis, pleurisy, exudative erythema, chorea, nodules and tonsillitis. He recognized the predilection of the disease for connective tissue and pointed out that usually two or three phases occurred together. The major and minor criteria proposed by the late T. Duckett Jones do not differ from this concept. He found that the disease had a familial tendency as strong as gout and remarked that our appreciation of this, “varies according to the minuteness of the inquiry made”. His discussion of chorea is illuminating to the pediatrician today. He shrewdly noted that the transient nature of other rheumatic manifestations in the chorea patient are often evanescent enough to be easily missed and hence chorea is thought to be of non-rheumatic origin. He reminds us that Roger, whose name is not unknown to us, pointed out that chorea usually preceded the later development of arthritis and he states in conclusion that, “I do not think the evidence warrants the assumption that chorea is inevitably of rheumatic origin ... but I am convinced that rheumatism is the most common and potent factor”. I do not believe that the question of the etiology and pathogenesis of chorea has progressed much since. Cheadle clearly differentiated clinically between innocent and organic murmurs and laments the impossibility of obtaining adequate data on rheumatic patients for statistical analysis. Here he finds himself in company with Thomas Barlow to whom we owe our knowledge of the pathogenesis of infantile scurvy. That cardiac hypertrophy and dilatation without valvular disease can occur in the acute rheumatic fever, Cheadle pointed out, was recognized in 1881. He noted that Henoch’s “Diseases of Children” in 1883 stated that post scarletinal endocarditis and pericarditis may be of either rheumatic or uremic origin and hence we see two important manifestations of streptococcosis may both lead to carditis but by entirely different means.

Cheadle lived in a remarkable period in pediatric history. He was contemporary with Barlow known for his work in scurvy, Garrod who gave us the concept of inborn errors of metabolism, Thomson whose contribution to the care of the brain damaged child represented a new concept in the understanding of these children and with Still whose disease bears his name today. Cheadle's differential diagnosis of the child who presents with acute arthritis is interesting when compared with a similar differential diagnosis published in 1958 by a rheumatism center in England:
Rheumatic Fever

Cheadle's Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>The Rheumatism Research Unit</th>
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<tbody>
<tr>
<td>a. Leptic epiphysitis</td>
<td>Taplow, 1958, 196 patients</td>
</tr>
<tr>
<td>b. Scurvy</td>
<td>1</td>
</tr>
<tr>
<td>c. Rickets</td>
<td>0</td>
</tr>
<tr>
<td>d. Tetany</td>
<td>0</td>
</tr>
<tr>
<td>e. Hemophilia</td>
<td>2 (blood dyscrasias)</td>
</tr>
<tr>
<td>f. Tuberculosis</td>
<td>2 (pulmonary only)</td>
</tr>
<tr>
<td>g. Pyarthrosis</td>
<td>10</td>
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</tbody>
</table>

The differences in the above disease distribution represent some 70 years of Pediatric progress. The virtual disappearance of Lues is a tribute to prenatal blood testing and the efficacy of Fleming's penicillin. The complete disappearance of the nutritional diseases, scurvy, rickets and tetany are a clear reflection of improved infant feeding. In the field of two of these nutritional disorders Cheadle himself made original contributions together with Barlow. Blood dyscrasias remains with us as always. Tuberculosis is still seen in a small but significant number of cases, more frequently today in England than in the United States. It might be remembered in passing that in the United States we have never as a nation embraced BCG vaccination. Finally, pyarthroses remain with us and the causative organisms remain much as they were in Cheadle's time, despite current concern over the ubiquitous staphylococcus.

Some six years after Cheadle's remarkable Harveian lectures, the first epidemiological study of the disease was summarized in the Milroy Lectures by Sir Arthur Newsholme in the year 1895. These are published in Lancet for the same year. His data was the result of a cooperative study and a number of important conclusions were reached regarding the epidemiology of rheumatic fever. Essentially the same tendencies were found by Coburn in the 20th century. Newsholme showed that the disease was one affecting individuals in temperate climates. It was shown that the affected individuals had an inherited predisposition to their disease thereby confirming the observations of Aretaeus in the second century. Frequently stress, in the form of fatigue, chill or injury precipitated acute rheumatic activity, foreshadowing by some 40 years, the observations of Selye. Certain years were observed in which there appeared to be epidemics of acute rheumatic fever usually following a sore throat. These observations were later confirmed, of course, during World War II in the armed forces. Then tendency of acute rheumatic fever to recur was well established by Newsholme. He concluded that the disease was probably caused by an organism of low infectivity which tended to be concentrated about the joints and was probably a saprophytic organism which could on occasion become parasitic. This latter conclusion represents the one false note in these Milroy lectures on rheumatic fever in the light of our knowledge of the disease today. It was not until the second decade of the 20th century that the concept of hypersensitivity was suggested as a mechanism of pathogenesis. Nine years after Newsholme gave the Milroy lectures, Ludwig Aschoff in 1904 reported the histologic characteristics of the lesion we have come to associate as the essential criterion of acute rheumatic activity, the Aschoff Body. His description of this important lesion is quoted at length since it is found that our current textbooks of pathology suffer by comparison:
Manson

"We find peculiar nodules, which appear to be specific to rheumatic myocarditis. These regularly occur in the neighborhood of small or medium sized vessels and most frequently in the vicinity of the adventitia, or there existed simultaneously a disease of all of the vascular layers, such as is described in arteritis nodosa. The nodules are unusually small, mostly submiliary, and originate by the conglomeration of large elements, with one or more abnormally large indented polymorphic nuclei. Arrangement of the cells frequently occur in the form of a fan or rosette. The periphery is formed by the large nucleus, the center by the paler, necrotic mass of confluent cell protoplasm . . . small and large lymphocytes and polymorphonuclear leukocytes force themselves a short distance between the large cells of the periphery or form a peripheral zone, and irregular projections from these may extend far into the connective tissue partitions. In these projections . . . are found giant cell-like large nucleated elements appearing singly or collected in nodules . . ."

With the coming of the 20th century, many different etiologic theories began to appear in rapid succession. Various organisms were reported as etiologic organisms because they had been isolated from a fair number of rheumatic fever patients. In no instance, however, were Koch's postulates fulfilled with any of the various organisms reported in the literature. Poynton and Paine isolated a strain of streptococcus viridans which met an unhappy fate when it was blown up by German bombing in World War I. Birkhaug recovered a hemolytic streptococcus. Small reported an organism he termed streptococcus cardioarthritidis in 1928. Swift suggested the role of hypersensitivity in the production of the rheumatic state and this was soon supported by Faber and Zinsser. Schlesinger, Sabin and others in the early 1930's demonstrated that certain particles could be agglutinated by the sera of rheumatic fever patients and felt that was supporting evidence for a viral etiology of the disease. In 1935 Rinehart suggested the role of Vitamin C in the production of acute rheumatic fever. Certainly an important contribution to our knowledge of the rheumatic state was made by Coburn who published his study on the factor of infection in the rheumatic state in 1931. Like others before him, he emphasized the variability of the disease. It is interesting to those of us who are Pediatricians to note his description of the pulmonary hyaline membrane at autopsy which we have come to think of as an exclusively primary neonatal phenomenon, which it clearly is not. Coburn's major contribution to our knowledge of the rheumatic state consisted of transporting a group of known rheumatic fever patients from New York City, where the streptococcus was frequent, to Puerto Rico, where the streptococcus was infrequent, for a period of 6 months. In the relatively streptococcus-free atmosphere of Puerto Rico, these children experienced a gratifying regression of their rheumatic activity and a large proportion returned to a state of physical health. However, when these children were returned to New York City, a significant proportion experienced a recrudescence of rheumatic activity. Coburn also carried out some interesting skin tests with bacterial nucleo-proteins from various organisms, not all of which were streptococci. In some individuals these skin tests produced interesting and rather startling results. Unfortunately the results were not consistent regarding the streptococcus in these rheumatic susceptible individuals. Certain rather disturbing reactions were seen—among them; the development of generalized erythema marginatum, the development of rather extensive purpuric
Rheumatic Fever

reactions, the appearance of rather deep sloughs and the appearance of nodular erythema. Coburn felt four factors were involved in the production of rheumatic fever symptomatology which he stated as follows; inherited susceptibility, age, environment and infection. It was concluded that rheumatic fever represented a special tissue response to upper respiratory disease and that the streptococcus was an important contributory factor.

No historical consideration of the rheumatic state would be complete without an account of the curious and interesting history of the use of salicylates in this disease. We recall that in 1805 John Haygarth found Peruvian Bark excellent for the symptomatic treatment of the condition. In 1827 Leroux isolated the glycoside salicin from Willow Bark. In 1838 Leroux obtained his salicin from the ordinary white willow (Salix alba) found in Europe. Piria isolated salicylic acid in 1838. He hydrolyzed salicin which yielded glucose plus salicylic acid. Not much was done in an investigative way until Thomas MacLagen in 1874 observed that rheumatic fever was “apt to occur in low-lying, damp localities . . . and was of miasmic origin”, MacLagen felt that the disease was allied to, but distinct from malaria. He reasoned that since Cinchona bark was of value in malaria and was an extract of a bark indigenous to the area in which malaria occurred, it was therefore only logical to seek a bark from the native areas where rheumatic fever occurred to find a drug suitable for the treatment of rheumatic fever. Hence, the bark of the willow, and its extract salicin, should logically be used in the management of acute rheumatic fever. These observations were published in Lancet in 1876 and the suggestion was immediately accepted by the medical profession and so salicylates have continued to be used to the present day for the treatment of rheumatic symptomatology.

Interestingly enough, however, the train of thought noted above is not the only one which led to the development of the very useful drug we know today as aspirin. In 1865, Joseph Lister conceived his idea of antisepsis through the use of a carbolic acid spray and this work was published in Lancet in 1867. It was followed by the attempt in 1874 of Herman Kolbe, a professor of chemistry in Leipzig, to produce salicylic acid for use as an antibacterial agent with the idea in mind that it was a phenol derivative which could be given by mouth. A little clinical experience soon showed that salicylic acid produced only symptomatic relief and its antipyretic and analgesic properties became well defined. Franz Stricker in Berlin found salicylates were effective in the treatment of rheumatic fever, rheumatoid arthritis, neuritis, neuralgia and headache, thereby antedating our current television advertisements by some 85 years. Clinicians of the time found the gastro-intestinal side effects of salicylic acid and sodium salicylates were quite troublesome. This undesirable side effect of the drugs stimulated a Bayer chemist, Felix Hoffman, whose father had rheumatoid arthritis, to search out acetyl salicylic acid which he found about 1880. Actually this compound had been synthesized in 1853 by Charles Von Gerhardt and nothing further had been done with the material. It remained for almost thirty years a laboratory curiosity. At Hoffman’s suggestion, clinical trails of acetyl salicylic acid were conducted by Heinrich Dresser, Bayer’s pharmaceutical research chief, who found it useful clinically. It was he who termed the material aspirin since natural salicylic acid came
from plants of the spiria family and because it was also known as spiric acid, the acetyl derivative might logically be called aspirin and so we have the name which persists today. In reviewing the literature of the time, one can infer, I think, that clinicians of the period not infrequently encountered salicylism in patients under treatment. Some of us may recall such patients in our own practices. Cheadle, in his memorable monograph, suggests the advantages of the administration of alkalis to patients who are receiving salicin. Today we are biochemically aware of the ability of alkali to enhance the renal excretion of salicylates.

The commercial aspects of acetyl salicylic acid are not without interest. Quite naturally, the Bayer Company took full patent advantage of the work of Hoffman, Von Gerhardt and Heinrich in producing aspirin as a clinically useful drug. The firm held exclusive rights for the commercial production of the material until the expiration of the American patents in 1917. Anticipating this, the Monsanto Chemical Company sent Dr. Gaston Dubois to Switzerland where he purchased rights to a process for the cheap and efficient commercial production of the compound and with the expiration of Bayer’s American patents, Monsanto immediately went into production. Extensive litigation followed which ended in the year 1919 with the Bayer Chemical Company losing the judgment. In that year, the Monsanto Chemical Company produced 480,874 pounds of acetyl salicylic acid. By 1956 the Monsanto Chemical Company had produced its 100th million pound of acetyl salicylic acid and an excellent history of the drug was given by Dr. Carroll Hochwalt of the Monsanto Company in the fall of 1956 at a Symposium on Aspirin Research. This address is printed in the Journal of Pediatrics of the year 1957 and is well worth reading in its entirety.

With a review of the fascinating history of that most useful drug, aspirin, we shall conclude consideration of the history of the development of our concept of the rheumatic state. Many of those present this evening are more intimately familiar with the details of the development of the potent steroid hormones than is the speaker. In a sense, steroids are still in the process of making medical history. While we know they are effective in ablating rheumatic symptomatology, we do not have sufficient experience with them nor have we observed patients so treated for a sufficient period of time to determine their ultimate long term effect on the rheumatic individual. Moreover, after eleven years we are still not fully acquainted with their widespread and subtle metabolic effects. Then too, the drug houses continue to add confusion by producing synthetic steroids at an alarmingly rapid rate, the actions of which have never been previously inflicted on the human organism. Possibly in twenty years another T. Duckett Jones will appear to assay adequately that which we do today.

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Rheumatic Fever


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