T. Duckett Jones and rheumatic fever in 1986

T. Duckett Jones Memorial Lecture

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I AM HONORED to have been asked to give the 1986 T. Duckett Jones Memorial Lecture. Dr. Jones, shown in figure 1 in his younger days from a slide I obtained from Dr. Edward Bland, a colleague of his, died on November 22, 1954, almost exactly 32 years ago. Ironically, the cause of death was diffuse vasculitis, although not of rheumatic origin. I did not know Duckett Jones well but I believe it is fair, and accurate, to say that he is the father of modern-day acute rheumatic fever in that he did more than any other one person to advance knowledge about its nature and diagnosis, and about care and prognosis of patients with this dread disease. He is best known by far, however, for describing criteria for diagnosing acute rheumatic fever, which he published in the Journal of the American Medical Association in 1944 in an article entitled “Diagnosis of Rheumatic Fever.” Subsequently called Jones criteria, these were needed to prevent over- and underdiagnosis of the disease as well as to establish sound diagnostic criteria by which to recognize, manage, and study it. Jones described major manifestations as those that offered “the least likelihood of an improper diagnosis.” He then listed these as carditis, arthralgia, chorea, subcutaneous nodules, and recurrences of rheumatic fever. He wrote further, “In summary, a combination of these major manifestations makes a diagnosis of rheumatic fever reasonably certain. One must realize that even with the criterion a statistically small number of cases will prove to have been incorrectly diagnosed, after long clinical observations.” He then went on to describe the minor manifestations of fever, abdominal pain, precordial pain, rashes, epistaxis, pulmonary findings, and various laboratory findings, including electrocardiographic abnormalities, anemia, leukocytosis, and increased erythrocyte sedimentation rate. He suggested that no combination of these alone was sufficient to diagnose rheumatic fever but any two coupled with a major manifestation would “place the diagnosis on reasonably safe grounds.” It is of interest to note that the original criteria did not include supporting evidence of a preceding streptococcal infection. Indeed, there are only two mentions of streptococcal infections in Dr. Jones’ article, and those rather as passing remarks.

With this historic and classic article Dr. Jones paved the way for the modern study and management of patients with rheumatic fever. Over the years committees of the American Heart Association have made relatively minor but significant changes in the original criteria, the last published in 1984. These have clarified the major manifestations, simplified the minor manifestations, and emphasized the importance of a preceding streptococcus infection (table 1).

The most exciting happening in the rheumatic fever world in 1986 is that the disease seems to be disappearing in the industrialized world, as described by Leon Gordis in this Lecture two years ago. I hasten to add, however, that most of our world is not industrialized and rheumatic fever remains a problem worldwide. The recent Utah experience with 74 cases also suggests that it can return as a problem in this country. As a clinician/educator, I am impressed that we have raised an entire generation of young physicians who have never seen a case of acute rheumatic fever, and therefore don’t know what it looks like and have a very poor understanding of how to diagnose it. This is emphasized by the appearance in the pediatric rheumatology literature of a syndrome that is being called “poststreptococcal reactive arthritis.” There seems
to be great confusion about the relationship of this syndrome to rheumatic fever. This stems primarily from a lack of knowledge about the clinical diagnosis of rheumatic fever and confusion about what is entailed in diagnosing a preceding streptococcus infection. It is here that the Jones criteria assume great importance. Unfortunately, it is also here that we detect apparent weaknesses or problems in Jones criteria that need our attention.

It is natural that clinicians turn to the widely accepted Jones criteria when a patient with suggestive findings appears. At a time when rheumatic fever was common the criteria worked well. Now that classic rheumatic fever is so rarely seen the application of the criteria to questionable cases can be difficult. It should be made clear that Jones never inferred that his criteria were infallible. The biggest problem has always been to evaluate the role of arthritis. When rheumatic fever was the most common cause of acute arthritis in children and young adults we did not recognize this as a large problem. Now that other causes of arthritis outnumber rheumatic fever the problem becomes acute. Because I perceive these problems as substantially affecting our interpretation of what is happening to rheumatic fever in the United States, I decided to use them as the theme of this presentation.

I will first present briefly the natural history of rheumatic fever for those who have not had experience with the disease. This will be used to put into perspective the Jones criteria, which will be examined in some detail. In so doing I will point out the various criteria that are causing problems in 1986, primarily what is and is not the arthritis of rheumatic fever and how the clinician can diagnose a group A streptococcal infection in retrospect. The problems with these criteria will be put into perspective with regard to the other criteria, primarily carditis. I will then describe what I hope will be a reasonable approach to the diagnosis and management of the patient in whom the diagnosis of rheumatic fever is being considered. As you will see this may well require some alterations in Jones criteria — or at least some reinterpretations.

**Natural history of rheumatic fever.** Figure 2 depicts what I envision as the natural course or history of rheumatic fever.7,8 The sine qua non of rheumatic fever is a group A streptococcal infection — but not just any old group A infection. It must be of the upper respiratory tract — skin and deep infections, such as cellulitis and wound infections, do not precede rheumatic fever. Among the more than 60 presently recognized serologic types of group A organisms, a modest number have been recognized as rheumatogenic. This is to be contrasted with the rather limited number that precede glomerulonephritis. These cases of streptococcal pharyngitis typically occur in school-age children, with their peak in the 6 to 14 year age group. Rheumatic fever then follows, in some patients with untreated infections, an asymptomatic latent period that is rarely less than 10 days or more than 35 days, the average being about 3 weeks. The risk of developing rheumatic fever has been a controversial subject in recent years and now is clearly very low. In epidemics of streptococcal infections rates of 2% to 3% were accepted as the norm, but this figure was not applicable uniformly to all patients with untreated infections. Although the precise genetic occurrence of rheumatic fever has not been determined, it is clearly a genetically determined disease. Recent studies on cell

![Figure 2](image-url)
surface markers of B-lymphocytes of patients with rheumatic fever are beginning to clarify this issue. At the present time, however, the biggest recognized risk factor is the serologic response to the streptococcus — those patients who have an increased response are at increased risk.

The big factor at this stage of the natural history is the accurate recognition of the patient who has rheumatic fever: hence the importance of Jones criteria. As the diagram indicates, rheumatic heart disease follows in some, but not all, patients with acute rheumatic fever. Only those patients with carditis, and not all of those, develop this sequela. Figures vary; 30% to 60% of patients subsequently develop rheumatic heart disease, depending on the severity of the carditis. There then follows one of the more remarkable features of rheumatic fever, the vicious cycle of recurrences that may occur after subsequent streptococcal infections. Here again the sine qua non is the streptococcal infection. Without it, there are no recurrences. With it, however, the risk rises from its previous 2% to 3% to 25% to 75%. There are several factors that seem to determine the size of this risk. As with first attacks, those patients who have exaggerated serologic responses are at greatest risk. Also at greater risk are those patients who have their streptococcal infections soon after their initial attack, those who have carditis, and those who have had multiple recurrences. Rheumatic recurrences have a remarkable tendency to have clinical features similar to those found in the initial attack — that is, there is a mimetic tendency with each subsequent attack. The patient who has only arthritis is likely to have only arthritis subsequently, and so on.

**Jones criteria.** The unity and diversity of the syndrome we call rheumatic fever is truly remarkable and should be appreciated by those of you who are responsible for the health of our citizens. This leads quite naturally then to the diagnosis of rheumatic fever by Jones criteria (table 1). The principle features are major manifestations and minor manifestations, with the addition of supporting evidence of a streptococcal infection.

Among the major manifestations carditis is obviously the most important. It is the only part of rheumatic fever that leads to permanent disability, which is not a big problem in the United States today, but is a leading cause of heart disease in many parts of the world. In addition to stressing its importance, I want to make two points. Although it is the subsequent occurrence of valvular heart disease that stands out most clearly, acute rheumatic carditis can be and frequently is a pancarditis. Pericarditis can be quite severe, although large amounts of pericardial fluid are unusual. Myocarditis is responsible for many of the problems during the acute phases of disease. Endocarditis is at least in part responsible for the murmurs that are characteristic of some cases of rheumatic fever. These murmurs are augmented frequently by cardiac dilatation, due in large part to the myocarditis. The second point is to recognize the possible role to be played by modern diagnostic techniques in the detection of insufficiency of the cardiac valves during an acute attack. Two-dimensional Doppler echocardiograms, if properly interpreted, appear to be unusually sensitive for the detection of minimal degrees of insufficiency; this could clarify some of the puzzling issues concerning the risk of fixed heart disease and the relationship to happenings during the acute phase of rheumatic fever. Duckett Jones had a keen appreciation for the diagnosis and role of carditis in rheumatic fever and except to remind you of its continued importance and the possible role of new diagnostic techniques I see no reason to tamper with this part of the criteria.

The big problem is with polyarthritis. It is generally described as migrating and to involve primarily the large joints: it is never permanently disabling and

### TABLE 1

<table>
<thead>
<tr>
<th>Jones criteria (revised) for guidance in the diagnosis of rheumatic fever</th>
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<tr>
<td><strong>Major manifestations</strong></td>
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<tr>
<td>Carditis</td>
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<tr>
<td>Polyarthritis</td>
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<tr>
<td>Chorea</td>
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<tr>
<td>Erythema marginatum</td>
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<tr>
<td>Subcutaneous nodules</td>
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responds dramatically to aspirin therapy. Without other major manifestations polyarthritis has always been the toughest of the major manifestations to handle and this is true today.

Sydenham's chorea is a fascinating manifestation. When I entered clinical medicine I was taught there were two forms: rheumatic chorea and "pure" chorea not related to rheumatic fever. Evidence then accumulated that suggested that all chorea was rheumatic in origin. In very imaginative studies Taranta and Stollerman showed that chorea could be a late manifestation of rheumatic fever, often occurring several months after a streptococcal infection, in contrast to other major manifestations. We then considered chorea as only a manifestation of rheumatic fever. This concept has been shaken a bit by a recent publication by Berrios et al., who have reported their failure to associate all cases of chorea with a preceding streptococcal infection. Even so, until further data are obtained chorea should be considered as rheumatic in origin and managed as such. Chorea is never followed by permanent disability and is important because of its annoying clinical manifestations, and more importantly, its frequent association with carditis. Erythema marginatum and subcutaneous nodules are interesting manifestations, but are rarely found in the absence of other manifestations and never cause chronic disability. Because of their lack of diagnostic utility they will not be considered further.

The minor manifestations of importance, as determined by various committees over the years, are outlined in the table. This seems to be a reasonable group and I see no reason to consider alterations at this time.

In my opinion it is in the area of supporting evidence of streptococcal disease that most difficulty is encountered. I question that an increased titer of antistreptococcal antibodies is sufficient evidence in today's world. Streptococcal infections are very common and antibodies developed in response to them can persist for long periods, thus confusing attempts to use them diagnostically. The use of a positive throat culture for group A streptococcus can be equally confusing. The carrier state can persist for long periods after untreated infections. The isolation of streptococci in such cases does not necessarily indicate when the organism was acquired and might not help in identifying an infection responsible for the illness under study. In my experience, the use of a history of recent scarlet fever is rarely helpful. In today's world scarlet fever is unusually mild and can be confused with drug reactions and forme frustes of the scalded-skin syndrome. Unless the disease is classic, confirmed by a healthcare provider and by a throat culture, I would suggest this no longer be used as a criterion.

In summarizing this section I want to reemphasize the importance of the major manifestations of carditis and arthritis, carditis because it is the biggest reason that rheumatic fever is so important, and arthritis because it presents so many diagnostic and management problems. There are also many problems in the diagnosis of a preceding streptococcal infection. This is particularly important because rheumatic fever cannot occur in the absence of such infection. If a streptococcal infection has occurred the timing of the infection is critical in interpreting subsequent clinical events. This is not easy to decide and can be quite complicated. In the following sections I will consider these issues in the context of the natural history of rheumatic fever.

Supporting evidence of streptococcal infection. The group A streptococcus is a remarkable organism that can infect a wide array of organ systems, the tonsillar-pharynx being the only one of importance to rheumatic fever. Streptococcal pharyngitis varies widely in severity from asymptomatic to very disabling and occurs most commonly in school-age children, but can occur at any age. These infections occur most commonly under conditions of crowding and in the winter and spring but are certainly not restricted by these conditions. These facets emphasize the importance of laboratory tests in the diagnosis of streptococcal pharyngitis. For several decades the throat culture has been the gold standard for the diagnosis of streptococcal pharyngitis. It has proved to be exceptionally effective as a diagnostic tool. There can be minor problems in the use of bacitracin sensitivity to differentiate group A from nongroup A streptococci and a single culture fails to detect streptococci in about 5% to 10% of infected patients. Even so, the throat culture has reasonably good sensitivity and specificity. The newer methods of antigen detection appear promising but should be used to supplement, not replace, the throat culture. The biggest issue by far in interpreting the throat culture, or the results of antigen detection, is that of the chronic carrier.

The problem of the streptococcus carrier, as depicted by Kaplan, is presented in figure 3. During a bona fide group A streptococcal upper respiratory tract infection there is rapid multiplication of the organism and a host response; the patient can develop sequelae and there can be spread of the streptococcus to contacts. There then follows a period of transition as the host becomes a carrier. Following this the organisms do not appear...
to multiply very rapidly and there is no further immune response. There are no sequelae and the organism spreads poorly to contacts. Figure 4 quantitates the points made by Kaplan on the role of the pharyngeal carrier state in streptococcal infections and rheumatic fever. The data in this figure were all taken from studies done at the Streptococcus Laboratory in Wyoming.\textsuperscript{16, 17} I have taken the liberty of comparing data from different studies, which might not be scientifically very palatable, but which I believe is accurate enough to make my points. The duration of carriage after untreated infections was quite long; at the end of 11 weeks, we were still able to detect streptococci in about 90\% of young airmen. At 11 weeks, however, about one-half of the cultures contained 10 or fewer colonies of streptococci; that is, the degree of positivity decreased over time. The acquisition rate of streptococci in contacts according to the duration of the carrier state in the nearest carrier is also shown; the infectivity of a carrier decreases dramatically within a few weeks after acute infection. Finally, the occurrence of rheumatic fever is related to these events. It seems clear that positive cultures for streptococci are important to the infected host and to surrounding contacts for a limited time after the acute infection; after that they are of much less importance and seem to serve only as a nuisance, especially to the person attempting to assess their importance. In this situation, the clinician is advised to attempt to relate the positive culture to the time of the acute infection by epidemiologic and clinical findings, which can then be correlated with the quantitative throat culture.

The use of specific antibodies in making a retrospective diagnosis of a streptococcal infection is also a critical issue. The Jones criteria call only for an "increased titer" of an antistreptococcal antibody. This leads to an exploration of the meaning and possible interpretation of a single increased titer. Figure 5 demonstrates the efficiency of specific antibodies in indicating a previous streptococcal infection. In these studies taken from Stollerman's work, a single antibody titer, in this case antistreptolysin O, was found to be elevated in 78\% of patients with rheumatic fever. If, in addition, an antihyaluronidase titer was determined,

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FIGURE 3. Schematic representation of the transition from acute streptococcal pharyngitis to the streptococcal carrier state. (Reprinted from Kaplan\textsuperscript{15} with permission.)

FIGURE 4. The relationship between the streptococcal carrier state, the contagiousness of the carrier, and the occurrence of acute rheumatic fever. Note that the hatched part of the line showing the acquisition of streptococci means that the point at three weeks includes, in addition, all values after that time.

FIGURE 5. Detection of recent streptococcal infection in 88 patients studied within two months of onset of rheumatic fever. AH = antihyaluronidase; ASK = antistreptokinase. (Reprinted from Stollerman et al.\textsuperscript{18} with permission.)
the figure rose to 90%. If still another antibody was measured, then 95% of the patients demonstrated at least one elevated titer. These data confirm that elevated streptococcal antibody titers are found in most, but not all, patients with rheumatic fever, with 5% to 22% of patients, depending on the number of tests done, not being detected.

Table 2 shows the relationship of antistreptolysin O (ASO) titer rises to attack rates for rheumatic fever; these data address the issue of what can be considered an “increased” titer of antistreptolysin antibody. These data, taken from the Wyoming studies, show the clear relationship between ASO rises and the attack rates of rheumatic fever in young airmen with streptococcal infections. The data also show that rheumatic fever can occur in patients who have ASO titers that are not considered increased by usual criteria.

Figure 6 shows the ASO response temporally after untreated group A streptococcal infections and emphasizes the problem of interpreting a single antibody titer. This figure indicates that one can determine with accuracy the time of occurrence of a streptococcal infection only if paired serum samples are obtained during the first few weeks after onset of infection. Paired samples obtained after that time are next best, but are relatively poor in pinpointing the time of onset of infection. Elevated single antibody titers indicate only that a streptococcal infection has occurred some time in the past and are not helpful in determining when that occurred. Thus, as suggested in the Jones criteria, a single elevated antistreptococcal antibody titer has rather limited usefulness. In my experience, the absence of an elevated titer is more definitive information in a patient with questionable disease. If antibodies to three streptococcal antigens are not found, the clinician can be 95% certain that the patient has not had a streptococcal infection and is unlikely to have rheumatic fever — very useful information indeed.

To summarize, there can be problems with the criterion “supporting evidence of a streptococcal infection.” A positive throat culture for group A streptococci is helpful only if it can be related temporally to the time of the acute infection. The determination of streptococcal antibodies can be valuable in diagnosing previous infections but there are real problems in interpreting single elevated titers. In a small percent of cases a previous infection might not be detected. Rheumatic fever can occur after rather small antibody increases. The largest problem, however, is the inclusion of patients with elevated titers who have had a streptococcal infection that occurred at a time in the past when it could not be related to the illness under investigation.

Jones criteria in the clinical diagnosis of rheumatic fever. The paramount importance of carditis and the possible use of two-dimensional Doppler echocardiography in the diagnosis of valvular insufficiency have already been mentioned. I mention carditis again only to emphasize that rheumatic fever is important primarily because of carditis; this should be kept in mind in all cases in which the diagnosis of this disease is in question.

The greatest diagnostic dilemma usually occurs in patients with arthritis. This was recognized by Dr. Jones. I would like to quote from the first part of his section entitled “Arthralgia” as follows: “Migrating polyarthritis is generally considered the classic feature of rheumatic fever. While it is common, especially in the young adult patient, no one symptom offers greater diagnostic difficulty, whether the joint changes are objective or mere subjective complaints.” The very name of the disease under discussion indicates the association of arthritis with rheumatic fever. It is the most common manifestation, occurring in about three-quarters of patients; figures vary from about 60% to over 80% of patients, the figure rising with age. Severity can vary greatly from only arthralgia to joints so painful that the patient cannot tolerate any movement. Involvement is most common in the large joints; the

<p>| TABLE 2 |
| Relation of ASO rise to attack rate of rheumatic fever |</p>
<table>
<thead>
<tr>
<th>Rise in ASO titer (units/ml)</th>
<th>No. of patients</th>
<th>No. of patients with acute rheumatic fever</th>
<th>Attack rate for acute rheumatic fever (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>856</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>121-250</td>
<td>553</td>
<td>19</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt;250</td>
<td>545</td>
<td>30</td>
<td>5.5</td>
</tr>
<tr>
<td>Total</td>
<td>1954</td>
<td>56</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Data from Stetson. 18
spine and small joints are involved infrequently. Typically, there are several joints involved, at times in sequence — thus the origin of the term migratory polyarthritis. In untreated patients the arthritis usually lasts a few weeks and rarely persists longer than one month. Joint involvement is never permanent, a fact that seems poorly understood by some clinicians today.

It was noted by earlier clinicians that the severity of arthritis was related inversely to the severity of carditis. That is, the patient with very severe arthritis infrequently had severe carditis and vice versa. Again this was an age phenomenon — the young child might have severe carditis with little or no arthritis and the young adult might have severe arthritis with little or no carditis. This is not only a diagnostic nicety, but it also stresses that the two can and do occur in the same patient at the same time.

The response of patients with rheumatic arthritis to aspirin is one of the most dramatic and satisfying experiences I have had. It is so impressive that aspirin should not be administered to a patient with questionable rheumatic fever until the patient has been observed for a sufficient period of time for adequate evaluation. At that time aspirin can be administered diagnostically as well as therapeutically. The patient with arthritis who does not respond within one to three days probably does not have acute rheumatic fever.

Finally, the mimetic characteristics of the features of rheumatic fever should be mentioned. Feinstein and Spagnuolo documented that patients who had one feature during initial attacks almost invariably demonstrated the identical feature during recurrences. That is, patients with arthritis during the first attack would have arthritis in subsequent attacks, and so on. The negative aspect of this is also important. The patient without carditis during the initial attack is unlikely to have carditis subsequently. Unfortunately, up to now our ability to diagnose carditis with absolute certainty has been limited and patients thought to be free of carditis have ended up with rheumatic heart disease.

**Utility of Jones criteria in 1986.** Jones criteria probably are as useful as ever in parts of the world where rheumatic fever is still common. In this and in other industrialized countries I believe we have significant problems in the diagnosis of rheumatic fever. Because we no longer teach anything about rheumatic fever in medical schools and because most students and residents have never seen a florid case, we must be alert to the fact that they need to learn, and we possibly need to relearn, what rheumatic fever looks like. In my opinion, the Jones criteria have been and are extremely important in the diagnosis, study, and management of this important disease. I do believe, however, that under certain circumstances, we need to reevaluate their utility, especially with respect to the use of throat cultures and antistreptococcal antibody titers in the diagnosis of a previous infection. I suggest that the appropriate committee of the American Heart Association address this issue and give us their collective wisdom on how to handle these issues in the years ahead.

Let me end up on a practical note with a few words about the management of the patient with findings suggestive, but not diagnostic, of acute rheumatic fever — most commonly that would be the patient with arthritis, fever, and an elevated acute phase reactant. Most importantly, don’t rush into making a diagnosis of rheumatic fever. If the patient does not have carditis, danger to that patient’s health is not great. If there is serious concern the patient should be placed on antimicrobial prophylaxis and observed for future developments. With prophylaxis streptococcal infections will be prevented and there will be no recurrences. Without prophylaxis such patients should be observed closely with the knowledge that rheumatic fever will recur only after a subsequent streptococcal infection and this can be well documented by appropriate laboratory studies. With this information the patient can be managed correctly.

In closing, I think that Dukett Jones appreciated the fact that acute rheumatic fever was changing and I believe he would approve of our meddling with his criteria in 1986.

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