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THE TREATMENT OF RHEUMATIC CARDITIS: SALICYLATES vs. STEROIDS

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THE TREATMENT OF RHEUMATIC CARDITIS: SALICYLATES vs. STEROIDS

For the past twenty years, the treatment of rheumatic fever has evolved around two drugs, salicylates and steroids. During this time, a great deal of literature and controversy has accumulated concerning the relative merits of these two therapeutic approaches. It has been generally appreciated that both drugs are effective in controlling joint symptomatology, fever and other toxic manifestations of the disease. However for the most part rheumatic fever is a self-limited disease, and carditis is the only rheumatic manifestation which results in sequelae. Thus, it is the treatment of rheumatic carditis and the prevention of residual heart disease that has primarily concerned investigators in the field.

Salicylates were first popularized for the treatment of rheumatic fever in 1876 by Maclagan.[13] His remedy was extracted from the bark of a willow belonging to the Salicaceae family. Following his discovery, salicylates in varying dosages became immensely popular in the treatment of rheumatic fever. It was not until 1949 when Hench[10] introduced steroids to rheumatic therapy that the superiority of salicylates was challenged. Subsequently numerous contradictory reports concerning the advantages and limitations of these two therapeutic regimens were published and the need for a carefully controlled study became essential.

Clinical trials of therapeutic agents for a disease as unpredictable and variable as rheumatic fever are beset with many pitfalls, which may invalidate the findings. Stollerman[23] in his review of the subject remarked, "It should be obvious that the variables involved in matching

groups of patients to therapeutic trials are so numerous that few studies can satisfy all criticism of their design." Many factors must be taken into consideration. In order to exclude the possibility of previous injury to the heart, a complete history is essential to confirm that the rheumatic episode represents a first attack. Furthermore, the symptoms must be of relatively short duration, otherwise irreversible changes may have occurred before treatment is initiated. Secondly, the drugs must be administered concurrently to prove the superiority of one over the other. Results obtained in studies undertaken in previous years cannot be used for comparison as it appears that the severity of rheumatic fever is declining and its pattern changing.[19] Thirdly, cardiac status at the time therapy is instituted must be strictly defined and treatment groups must be comparable as to severity of carditis. Patients with mild carditis should be excluded, because irrespective of therapy they tend to recover without residual heart disease.[26] Finally, to insure complete objectivity, patients must be allocated to their respective treatment groups on a blind and random basis.

It is the purpose of this paper to review and criticize the various controlled studies concerning the treatment of rheumatic carditis. Emphasis will be placed on the U.K. and U.S. Cooperative Report as it is very comprehensive and represents a model clinical trial. Therapeutic concepts will be summarized and a program of rheumatic therapy proposed.

In 1950, when steroids became available the need for a controlled study was apparent in order to obtain definitive information on the value of these drugs in the treatment of rheumatic fever. Twelve research centers in Great Britain, Canada and the United States embarked on a cooperative study under the sponsorship of the American Heart Association, and the

Medical Research Council of Great Britain.[25] The study was designed to compare the therapeutic effects of the hormones, ACTH and cortisone, with the usual treatment of rheumatic fever at the time. Answers were to be sought to two questions: (1) What is the relative effectiveness of each of these hormones and of aspirin in altering the course of the acute disease in suppressing its clinical manifestations? (2) What is the relative effectiveness of these three agents in preventing rheumatic heart disease?

Only children under 16 years of age who met the modified Jones criteria (1955) for the diagnosis of rheumatic fever were included in the study. In all, 497 patients were accepted and allocated at random to treatment with one of the three drugs - ACTH, Cortisone or Aspirin. Each regimen was given for six weeks according to a defined schedule and detailed observations were continued for an additional three weeks. Follow-up examinations were made at specific times after these nine weeks, and the first report extended one year from the initial nine weeks.

DOSAGE SCHEDULES OF U.K. AND U.S. REPORT

DRUG	DAILY DOSE		DAY OF TREATMENT
Acetylsalicylic Acid	60 mg/lb		1-2
	40 mg/lb		3-7
	30 mg/lb		8-42
Cortisone	300 mg		1
	200 mg		2-5
	100 mg		6-21
	75 mg		22-35
	50 mg		36-42
ACTH	U.K CASES	U.S. CASES	
	80 USP units	120 USP units	1-4
	60 USP units	100 USP units	5-7
	40 USP units		8-21
		80 USP units	8-14
		60 USP units	14-21
	30 USP units	40 USP units	22-35
	20 USP units	20 USP units	36-42

As will be noted, many critics of this study considered the hormone dosages too small and the treatment period too short. On the other hand, nearly all cases receiving hormones developed Cushingoid cosmetic effects.

All patients received penicillin to maintain therapeutic levels for 14 days to eradicate streptococci foci, followed by oral sulfadiazine to prevent intercurrent streptococcal infections during the hospital stay and throughout the follow-up period. All patients were kept at bed rest for the nine weeks of therapy and observation.

The three treatment groups were further subdivided into three groups according to the length of time of each case between the date of onset of the attack and the date at which therapy began. The three duration - from - onset groups were (1) 14 days or less; (2) 15-42 days; (3) 43 days and over. Of the 497 cases, just over half (255) began therapy within 14 days within onset of the attack and 60 per cent of these (149) were treated within one week of onset. In nearly two-thirds (327) there was neither history of a previous attack of rheumatic fever, or evidence of pre-existing rheumatic heart disease. Approximately one-fourth (128) of the 497 cases were definitely diagnosed as having pre-existing rheumatic heart disease at the start of therapy.

Random construction of the three treatment groups caused them to be remarkably similar in many aspects such as; the treatment - from - onset period, age, sex, weight, temperature, pulse during sleep, erythrocyte sedimentation rate (ESR), frequency of polyarthritis, incidence of subcutaneous nodules, incidence of erythema marginatum, and incidence of basal diastolic murmurs. However, two differences exist: (1) The aspirin group included more patients with chorea as a presenting symptom (15.5%) than ACTH (5.6%) and cortisone (11.4%) (2) The ACTH group had a larger proportion

of severe carditis represented by congestive heart failure and/or pericarditis. Such cases numbered 27 for ACTH, 24 for cortisone and 17 for aspirin. The fact that fewer cases of severe carditis were present in the aspirin group has also been criticized by those who maintain that differences in drug effectiveness are most evident in very severe carditis.[4] It is also noted that four cases in the aspirin group were eventually administered hormone treatment because of the severity of their illness. Statistically, these four cases remain in the aspirin group but are none the less indicative of some investigator bias concerning the treatment of severe cases.

During the acute illness and the first year follow-up, six deaths occurred, one in the ACTH, two in the cortisone and three in the aspirin group. Two of the three aspirin deaths were switched to hormone therapy prior to death. Apart from the six deaths, there were some in each group who, during the one year period, were retreated for persisting or recurring manifestations. Retreatment was given to 10 of the 161 ACTH cases surviving to one year, 8 of the 165 cortisone cases surviving to one year, and 19 of 165 aspirin cases surviving to one year. However further analysis of these cases shows that the greater proportion of retreatment in the aspirin group occurred primarily among the chronic cases (43 days or more between onset and treatment) and was influenced by the larger number of cases initially admitted with chorea to the aspirin group.

It is important to note that practically all the ACTH and cortisone cases showed one, or a combination of the following side effects of therapy: moonface, hirsutism, acne or stria. There were only 10.5% of the ACTH and 4.8% of the cortisone without any of these side effects

by the end of the ninth week. In addition to these side effects many others were reported, but not tabulated. These included cases of hypertension, mental symptoms, convulsions, renal hemorrhage, water and salt retention, glycosuria, infections, hepatomegaly, febrile reactions, pigmentation, increased fat deposition and unusual increase in appetite. Furthermore relatively few aspirin cases developed side effects. There were 26.7% of the aspirin group that developed side effects such as tinnitus or deafness, nausea or hyperventilation. These side effects all appeared in the first week of therapy while the aspirin dosage was relatively high and promptly disappeared when the dosage was reduced.

The report concluded that: (1) The temperature and pulse rate during sleep returned to normal during treatment in the great majority of cases in all treatment groups, but there was a greater tendency in the groups treated with the hormones for them to become elevated in the 6-9 week observation period. (2) The erythrocyte sedimentation rate decreased more rapidly during treatment in the hormone treated group but was elevated more frequently in the 6-9 week observation period. There were no differences between treatment groups at the thirteenth week. The temperature, pulse and ESR re-elevation during the observation period was later termed "rebound phenomena." (3) The behavior of joint involvement, chorea and erythema marginatum was essentially the same in the three treatment groups. Nodules, however, disappeared more rapidly in the patients treated with hormones although new nodules appeared in some patients during treatment in all three groups.

In the evaluation of the cardiac status of their cases, the study used the parameters of heart size, PR interval, murmurs and congestive heart failure, and/or pericarditis. Cases were further subdivided into

three cardiac groups: (A) those without pre-existing heart disease or current carditis; (B) those currently with carditis but without pre-existing heart disease; (C) those with pre-existing heart disease.

The study reported that when heart size was measured by the proportion of patients with a cardiothoracic ratio of .55 or more, the cardiac subgroups and the total cases revealed no differences between treatment up to and including the one year follow-up period. The PR intervals decreased more frequently and rapidly in the hormone groups than in the aspirin group. This difference lessened during the observation period and was absent at nine weeks and one year. It may be questioned whether the early decrease in PR intervals in an effect of the hormones on the disease or merely a direct effect on the atrioventribular conduction time. Also, it was reported that there appeared to be no relationship between treatment groups and the appearance or disappearance of congestive heart failure and pericarditis.

Concerning murmurs, findings indicated: (1) The development of an apical systolic murmur, or basal diastolic murmur among those without such murmurs at the start of therapy, regardless of the presence or absence of carditis, was infrequent and not related to therapy. (2) The disappearance of soft apical systolic murmurs was more rapid among the hormone groups than among those receiving aspirin, but at the end of one year the treatment groups did not differ significantly. (3) The disappearance or diminution of loud apical systolic murmurs rarely occurred regardless of therapy. (4) At the end of one year there was no evidence that the treatment groups differed in the frequency with which murmurs had appeared or disappeared.

In summary, the report concluded that there was no evidence that

any of the three agents resulted in uniform termination of the disease. Treatment with either of the hormones resulted in more prompt control of certain acute manifestations, but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment (rebound phenomena). Treatment with the hormones also leads to the more rapid disappearance of nodules and of soft apical systolic murmurs. However at the end of one year, there was no significant difference between the treatment groups in the status of the heart.

In October 1960, the five year report of the U.K and U.S. Cooperative Clinical Trial was published.[26] At this time, 445 of the original 497 cases were known to be alive (89.5%) and 16 were known to have died (3.2%). Thus 92.7% of the 497 cases were traced at 5 years. The findings of the report confirmed those reported at one year, in that there was no appreciable difference in the cardiac status of the three treatment groups, and thus the prognosis had not been influenced by one treatment more than another. The Report was however, able to definitely correlate cardiac prognosis with the status of the heart at the time treatment was initiated. For cases without carditis initially the prognosis was excellent since in 96% there was no residual heart disease. In cases with carditis initially but without pre-existing heart disease the proportion without residual heart disease decreased progressively from 82% for those with only a grade I apical systolic murmur to 30% for those with failure and/or pericarditis. In cases with pre-existing heart disease the prognosis was poor. Only 30% of those without pericarditis or failure and none of those with pericarditis or failure were without heart disease at 5 years. Most of the deaths from rheumatic fever

(10 of 14) occurred among cases with pre-existing heart disease and there were no deaths among the cases without heart involvement at the beginning of treatment. All in all, the report concluded that the treatment of rheumatic fever cannot be properly evaluated unless the cardiac status at the start of therapy is taken closely into account as this is probably the most important factor in the prognosis.

In September 1965, the ten year report was released.[27] Three hundred and ninety-seven cases (79.9%) were known to be alive at ten years and 19 (3.8%) were known to have died from rheumatic fever or rheumatic heart disease. Again, it was confirmed that prognosis had not been influenced by treatment and that the initial cardiac status was the most important prognostic factor. It was also noted that the fatality rate was very low in each of the groups, indicating that the patients had done well regardless of treatment.

Following the Cooperative Study, numerous reports were published advocating the superiority of steroids in the treatment of rheumatic carditis. For the most part, these studies were uncontrolled and based on the premise that the steroid dosage of the Cooperative Study had been too low and administered for too short a time. Greenman and his co-workers (1952)[9] were among the first to report good results with 300 mg. of cortisone given daily for 6 to 8 weeks to patients in their initial attacks of rheumatic carditis. With this regimen the author observed a very low residual of heart disease. Other investigators reporting a low incidence of residual heart disease in patients treated with large amounts of steroids for 10-12 weeks include Markowitz and Kuttner, 1955,[14] Roy and Massell, 1956,[22] Ferencz et al., 1959;[7] Massell et al., 1961.[18]

In 1957 Illingworth[11] published the results of a comparison of six treatment groups: (1) no specific treatment; (2) salicylates in low dosage; (3) salicylates in high dosage; (4) steroids alone; (5) steroids with salicylates in low dosage; (6) steroids with salicylates in high dosages. The study concluded that cortisone was superior to salicylates and that cortisone combined with salicylates, especially in high dosage was superior to cortisone alone in the treatment of rheumatic fever. However, this study is a retrospective study encompassing 200 children treated over a period of 9 years. The patients were not allotted to the respective treatment groups in a blind random basis and were not treated concurrently. Over one-fourth (55) of the children were not part of any controlled study, but were blended in with the controlled. The groups were grossly dissimilar numerically ranging from 61 in the high dosage salicylate group to 16 in the low dosage salicylate group. Moreover, the proportion of patients in each of these groups with carditis is even more distorted. Evidence of carditis was almost exclusively limited to the presence or absence of a murmur and there is a notable lack of patients with severe carditis. In summary, this study is very interesting but cannot be classified as a valid study.

Uncontrolled studies reporting that prolonged intensive steroid therapy would reduce the incidence of residual rheumatic heart disease continued to be published and it became essential to have a concurrent group of patients treated with salicylates. In 1956 the pediatric services of 8 hospitals situated in Baltimore, Boston, Cleveland and New York combined in a study to compare large doses of prednisone given 12 weeks with acetylsalicylic acid given for a similar length of time. What the study lacked in quantity it compensated in quality. Fifty-seven

patients were allotted on a blind, random basis to the two treatment groups. Only patients with their first rheumatic episode, the onset of which was within 28 days and who showed clinical evidence of moderate to severe carditis, were admitted to the study. Criteria for the diagnosis of carditis were the presence of one or more of the following: pericardial rub or effusion, unequivical cardiac enlargement, congestive heart failure, significant aortic or apical diastolic murmurs or Grade 3 apical systolic murmurs. Twenty patients were allotted to the prednisone group and twenty-eight assigned to the aspirin group. Both groups were comparable as to average age, onset to therapy interval and cardiac status. Prednisone dosage was 60 mg. daily for three weeks with gradual reduction during the following nine weeks. Aspirin was given at 50 mg/lb daily in divided doses for nine weeks, and then tapered over the next three weeks.

Results obtained by the Combined Study were published in 1960.[2] At the end of one year follow-up, no significant difference was observed in the incidence of residual heart disease in the two treatment groups. Furthermore, the study reported that regardless of treatment, the institution of therapy as late as 20-28 days after onset did not result in a higher incidence of residual heart disease. By the same token even the prompt control of the acute symptoms did not prevent cardiac damage in either treatment groups. However, as was noted in the Cooperative Study, a few patients (4) were changed from aspirin to prednisone because of the severity of their manifestations and their lack of response to salicylates. Of these four patients, one died and after 1 year two had residual heart disease and one had a normal heart. In this study the patients were allotted to the two treatment groups on a random

single blind basis. The decision to transfer these four patients represents clinician bias. The study admitted "the majority of investigators conducting this study are of the opinion that prednisone suppresses the inflammatory reaction of the acute rheumatic attack more rapidly than acetylsalicylic acid and in patients with congestive heart failure may be life saving." Even though the group felt the steroid dosage represented a definite risk, there were no incidents of serious untoward reactions to the therapy.

In contrast to the Combined Study, Dorfman and his associates[5] in 1961, reported that large doses of steroids continued for 12 weeks were more effective than salicylates in the prevention of residual heart disease. His study encompassed 131 patients without a history of a previous attack and treated within 18 days from the onset of their attack, that met the modified Jones criteria. Patients were randomly and comparatively distributed into four treatment groups: (1) hydrocortisone (2) aspirin (3) hydrocortisone and aspirin (4) no specific antirheumatic therapy. As customary, all four groups received penicillin prophylaxis and were kept at bed rest as a basic regimen. Patients weighing more than 80 lb received 250 mg. of hydrocortisone each day for the first four days; then 100 mg. per day through the eighth week after which the dosage was reduced gradually through the twelfth week. Those weighing less than 80 lbs were started on 200 mg., reduced 80 mg. and then tapered. Aspirin dosage was determined by blood level as 20 to 30 mg/100/ml was maintained through nine weeks and then tapered.

In reviewing Dorfman's study, it becomes apparent that he was generally dealing with mild carditis. Although his criteria for carditis is noble, the incidence of pericarditis, congestive failure,

cardiac enlargement and diastolic murmurs is too small for any critical evaluation. In essence, Dorfman has based his findings on the incidence of apical systolic murmurs. Of the 85 patients admitted to the study with "carditis" 67 (79%) had minimal carditis manifested only as apical systolic murmurs of grade 1 or 2 intensity. It should be recalled that the Combined Study required that an apical systolic murmur be of grade 3 intensity before accepted as sole criteria for carditis. Both studies use 1-4 as a basis for gradation. As previously noted and emphasized by the U.K. and U.S. Joint Report, patients with mild carditis, irrespective of therapy, rarely develop residual heart disease. However, it must be conceded that Dorfman's statistics were impressively favorable toward steroids in the abolishment of apical systolic murmur during the one year follow-up. These murmurs disappeared nearly three times as frequently in the groups receiving hormones as opposed to the other regimens. Dorfman's data also showed that patients admitted to the study who did not have organic murmurs have a low risk of developing them regardless of treatment. Another important fact about this study is that it is one of the few controlled studies to actually report serious therapeutic side effects. Two patients in the aspirin plus steroid group developed bleeding ulcers.

In an attempt to evaluate the relative merits of the two drugs in severe carditis, Czoniczer published a retrospective study in 1964.[4] As many investigators, Czoniczer felt that the effect of aspirin and steroids in preventing residual heart damage could best be judged on those patients most likely to develop residual damage. For this reason, he selected 145 patients with severe rheumatic carditis as indicated by congestive heart failure or pericarditis. Patients were selected from

admissions to the House of the Good Samaritan between the years of 1939 and 1963. Needless to say, treatment groups were far from comparable. Dosage schedules were variable, selection was not random and the groups were not treated concurrently. Many of the aspirin group did not receive penicillin therapy or prophylaxis and a larger proportion of the steroid group were observed in their initial attack. Czoniczer attempted to minimize the dissimularities of his treatment groups through subdivision analysis however, the groups remained grossly incompatible. His data the validity of which is questionable, indicated a lower death rate and higher recovery rate with steroids. Czoniczer concluded that steroids in high dosage were the treatment of choice in severe rheumatic carditis.

Short-term high dosage steriod therapy was introduced by Wilson and her co-workers in a series of papers beginning in 1953.[28-32] She reported that 100 - 160 mg. of prednisone given daily for an average of 7 days and instituted early in the course of the disease would terminate the rheumatic process and prevent residual heart disease. In 1960, she stated, "Our observations clearly demonstrate that in patients with progressive clinical symptoms of active carditis, adequate short-term hormone therapy will terminate the inflammatory process, significantly shorten the duration, and prevent or minimize residual cardiac damage."[28] However, none of Wilson's studies included concurrent observations on patients treated with salicylates and her criteria for carditis was subject to much criticism. Nevertheless, short-term intensive therapy was very appealing in that serious untoward reactions to steroids rarely occur within one or two weeks, and the length of hospital stay could be shortened.

In an attempt to confirm Wilson's result the Combined Rheumatic Fever Study Group (1965) undertook a second study in which short term intensive steroid therapy was compared with aspirin.[3] Seventy-three children whose first rheumatic episode had occurred within 21 days of the onset therapy and who exhibited moderate to severe carditis were admitted to the study. Criteria for the carditis was rigid and identical to that used in the first Combined Study. Patients were randomly assigned to two treatment groups. One group received 3 mg. of prednisone per pound of body weight daily up to a maximum of 200 mg/lb/day for seven days. The drug was then discontinued without tapering. Patients in whom definite signs of active carditis persisted after the seven days received a second seven day course with the same dosage. The second group received aspirin, 50 mg/lb of body weight daily for six weeks and then 25 mg. per pound per day for an additional two weeks. The two groups were comparable in most aspects except that more patients with congestive heart failure and cardiac enlargement were randomly allotted to the aspirin group. Patients were followed for one year after the completion of therapy.

The study was conducted over a four and a half year period. During the first two years of the study, three children receiving aspirin were transferred to the prednisone group because of the severity of their carditis. The investigators realized that this represented a clinical bias and accordingly conducted the last two and a half years of the study on a double-blind basis. During this period there were no deviations from the prescribed medication. In 1965, the study reported that there was no significant difference in the incidence of residual rheumatic heart disease in either the single-blind or the double-blind series.

Of the 34 patients who received prednisone, 15 still showed signs of active carditis after their seven day treatment course. These 15 patients were given a second seven day course after which 8 of the 15 again showed active carditis. After one year, more than half of the prednisone patients (19 of 34, or 55.8%) had residual rheumatic heart disease. Similarly after one year 25 of 39, or 64.1%, of the aspirin group had heart disease. The differences between treatment groups were small and not statistically significant.

Obviously, the Combined Study could not confirm Wilson's remarkable results. We can assume then, that Wilson's loosely constructed studies were probably based on patients with mild carditis, the majority of whom would not have residual heart damage regardless of therapy. However, the Combined Study also reported that the high dosage of prednisone was well tolerated, rebound phenomena were minimal and no untoward reactions were encountered. They further added that it was their clinical impression that "steroids were useful in controlling the exudative phase of acute severe myocarditis in critically ill patients." Their recommendation was that steroids be given to severely ill patients with myocarditis for one or two weeks to be followed by aspirin therapy for six to eight weeks.

Perhaps the most recent comparative study is that by Stolzer et al[24] in which 135 airmen admitted to Warren Air Force Base Hospital with rheumatic fever were evaluated. Patients were randomly assigned to aspirin, cortisone and ACTH groups. A 14 month follow-up showed that cortisone prevented the appearance of significant murmurs and caused the disappearance of existing significant murmurs to a greater degree than the other two. However, Stolzer is very careful to deal in

impressive percentages. Simple computation reveals that at the onset of therapy, only 17 of the 135 patients had a carditis and the majority of these had a mild carditis. Therefore, little importance can be given to the results of this study.

SUMMARY

In summarizing the findings of the various reports on rheumatic therapy, a statement of Bywaters seems applicable. "Broadly speaking, the observers may be grouped as those with enthusiasm but no controls and those with controls and no enthusiasm."[1] However, certain aspects have obtained general agreement. First of all, the incidence of carditis in initial attacks of rheumatic fever would seem to be somewhere between 40-50%. That is, at least 50% of rheumatic patients do not require intensive suppressive therapy to prevent residual heart disease. With these patients, salicylates remain the treatment of choice. Secondly, in those patients with carditis, the most important prognostic factor concerning residual damage is the initial cardiac status at the time therapy is instituted. Those patients with severe carditis - congestive failure, pericarditis or unequivical cardiac enlargement - have a poor prognosis as approximately 70% will develop residual heart disease, irrespective of therapy. Patients with mild or minimal carditis, usually manifest as a grade I or II apical systolic murmur, will commonly (75-80%) recover without residual damage regardless of therapy. Thirdly, it is generally accepted that neither steroids or salicylates alter the duration of a rheumatic attack. Feinstein and Spagnuolo[6] have conducted extensive studies and concluded that the average duration of acute inflammatory activity is 109 ± 57 days with or without treatment. Finally and most importantly, there has been

no definite or consistent demonstration that cardiac damage is prevented or minimized by either salicylates or steroids given early or late in the course of the illness, in high or low dosages, or for long or short periods of time.

From the review presented it should become evident that the selection of a suppressive agent can hardly be regarded as critical to the outcome of most attacks of rheumatic fever. Steroids and salicylates are palliative but not curative. Both drugs are effective anti-inflammatory agents in controlling the toxic manifestations of the disease such as fever and arthritis. Steroids are a more potent anti-inflammatory agent than aspirin and accordingly clinical observations have shown that the toxic effects of rheumatic fever are often more rapidly controlled with steroids. Not only are steroids more promptly effective, but they are also tolerated better than aspirin in the acutely ill patient and often produce a feeling of well being. Also instances in which the acute illness failed to respond to salicylates but was subsequently controlled by steroid therapy have been well documented. Now keeping in mind that there is no "proof" that steroids reduce ultimate cardiac scarring, let us propose two practical questions. (1) Why would steroids not be likely to have a similar prompt suppressive effect on acute edematous myocarditis? It stands to reason that the longer an acute infectious process persists the more likely residual scarring will result. (2) In a severe carditis when the heart is laboring to remian compensated would it not be advantageous to reduce the added stressful burden of the toxic manifestations as rapidly as possible? Thus, it is the time factor that favors steroids.

What then are the disadvantages of steroid therapy: Namely three; (1) side effects, (2) rebound phenomena and paradoxically (3) too prompt of a suppression. As has been previously noted, the occurrence of Cushingoid cosmetic effects is a common observation with prolonged steroid therapy. Varying degree of weight gain, moon-face, central obesity, "buffalo hump," stria, acne and hirsutism are likely to occur if therapy is continued for more than a week or two. However, these effects are dosage related and usually disappear within several months after cessation of therapy. The major concern is with the "serious untoward reactions"[8] to steroid therapy. These include adrenal insufficiency, sodium and fluid retention, excess potassium excretion, hyperglycemia and glycosuria, hypertension, psychosis, convulsions, myopathy, osteoporosis with compression fractures of the spine, peptic ulcers and the development and spread of bacterial and viral infections. A review of the controlled study reveals very few untoward reactions. Massell et al[18] treated more than 200 rheumatic patients for several weeks with significant doses of steroids and reported that serious side effects were infrequent. Furthermore, it appears the risk is even further reduced if steroid therapy is short-term and limited to a 7-10 day period.[3] Aspirin too, is not without side effects such as hyperpnea, tinnitus and gastric irritation. However, these effects are promptly controlled by dosage reduction, and are of less serious nature than steroid reactions. We must conclude then that the risk of steroid therapy is small but is a significant factor in the selection of a therapeutic regimen.

The U.K and U.S. Cooperative Study reported that the more prompt control of acute manifestations by steroids was balanced by a greater

tendency for a reappearance of these manifestations following cessation of treatment. This reactivation has been termed the rebound phenomenon. The severity of rheumatic fever during a rebound may be as great or greater than at the start of treatment and residual heart disease may result. The mechanisms of the rebound phenomenon are poorly understood, but it seems likely that an incomplete suppression of the rheumatic process is a plausable explanation. This would be consistent with the higher incidence of this phenomenon in long-term low dosage therapy such as employed in the U. K. and U. S. study. Rebounds were non-existent with the short-term intensive therapy used in the Combined Study (1965). Salicylates should be used in the treatment of rebounds as subsequent rebound is less likely after salicylates than after steroids.

A third therapeutic disadvantage is the premature vigorous administration of suppressive agents before the signs and symptoms of rheumatic fever are unmistakable. Both aspirin and steroids have been indicted, but steroids appear to be the greater offender. Stollerman[23] points out that "after a well documented streptococcal infection the conscientious physician may seek evidence suggestive of rheumatic fever, such as persistence of an increased ESR, a prolonged PR interval in the electrocardiogram, vague pains in the extremities, borderline temperature elevations, increased intensity of a functional murmur, and tachycardia during the physical examination of an anxious or hyperactive patient." The early use of steroids results in an ill defined syndrome, only presumptively rheumatic fever, and the subsequent management of the patient particularly the indications for long-term prophylaxis is in doubt. The emotional burdens that accompany the diagnosis and

management of rheumatic fever need not be enumerated. Massell and co-workers[17] have pointed out that patients with an acute onset of rheumatic fever rarely show a long delay in the appearance of carditis if this manifestation is going to occur. In their large series of patients, 76 per cent of the patients with evidence of heart damage had cardiac involvement during the first week of illness. The five year U.K. and U.S. Cooperative Report confirmed Massell's findings and added that prognosis is excellent in those patients with initial unequivocal evidence of carditis. The diagnosis of acute rheumatic fever should therefore be made conservatively and with insistence upon clearly expressed major manifestations.

RECOMMENDATIONS

Having considered the various aspects of anti-rheumatic therapy it now becomes possible to formulate a practical regimen. Bed rest and penicillin prophylaxis are very important elements in this regimen, but their discussion is beyond the scope of this paper. Aspirin is the drug of choice for patients without rheumatic carditis. Aspirin should also be the initial treatment for minimal carditis. Markowitz and Kuttner[16] define minimal carditis as questionable cardiac enlargement, apical systolic murmurs of grade 1 or 2, AV dissociation of prolonged PR interval. A dosage of 50 mg. of aspirin per pound of body weight administered in six divided doses over 24 hours will usually result in an adequate blood level (25-35 mg%). This dosage should be maintained until a satisfactory clinical response is obtained, i.e. until the patient has complete relief of symptoms and signs of arthritis and the temperature has returned to normal range. Such response should occur within one to two weeks at which

time aspirin may be discontinued and the patient observed for about ten days. If there is no recurrence of symptoms, no further therapy is needed. In those patients in which fever or arthritis persists or recurs, aspirin is continued until all clinical symptoms have subsided. However if aspirin does not appear to control the acute manifestations, or if carditis becomes more definite, steroid therapy should be considered. Children usually tolerate aspirin well and small amounts of milk may be taken with each dose to reduce gastric irritation. The patient should be carefully watched for toxic manifestations such as vomiting, tinnitus, and hyperpnea at which time the dosage should be reduced appropriately.

Patients with moderate carditis should receive the benefits of short-term steroid therapy. Moderate carditis is arbitrarily defined as the presence of grade 3 or louder apical systolic murmur, or an aortic diastolic or mitral mid-diastolic murmur of any intensity. The dosage of steroid is debatable. The Combined Study (1965) has recommended 1 mg. of predisone per pound of body weight. Rothman[21] has more recently pointed out that it is safer to err or the side of high dosage. Perhaps then 2 mg/lb of body weight daily would also be acceptable. It is purely a matter of clinician preference. The total dosage is divided into four equal doses over a 24 hour period and continued until the acute stage has subsided, the cardiac signs have stabilized, and the patient's general condition has improved. Such a response usually occurs within 7-10 days at which time the steroid can be discontinued abruptly and salicylates begun. Aspirin (50 mg/lb/day) is continued until all clinical and laboratory signs of rheumatic activity have subsided. Prednisone is preferred as it tends to cause fewer electrolyte disturbances

than other steroids. Further minimization of electrolyte imbalance is accomplished by using low salt diet. In general, short-term steroid therapy is well tolerated and Cushingoid side effects are minimal. Similarly, serious untoward effects and rebound phenomena are rarely encountered when therapy is limited to a 7-10 day period.

Cardiac enlargement, pericarditis and congestive failure constitute severe carditis and a direct indication for steroid therapy. However, no matter how promptly and completely the acute manifestations are suppressed, residual rheumatic heart disease will not be prevented in the majority of these patients. Steroids are given primarily in hope that they may be life saving. Again this is a clinical impression and has not been scientifically documented. Severe carditis usually requires a somewhat longer course of therapy. Prednisone (1-2 mg/lb/day) should be continued for 2-4 weeks. When steroids are administered for more than ten days the dose must be tapered before discontinuing therapy in order to prevent adrenal insufficiency due to endogenous suppression. In these patients, it is advisable to overlap the steroid therapy with aspirin for one week before the steroid therapy is stopped so that rebound phenomena are minimized. Aspirin therapy should then be continued until all signs of rheumatic activity have disappeared.

In view of the declining severity of rheumatic fever it is unlikely that a well controlled prospective study of the value of steroid therapy in critically ill patients with rheumatic carditis will be possible in the near future. Even at that, clinician bias is such that the random selection of drugs in severely ill patients is generally thought to be contra-indicated. Perhaps the following comments

by Nadas[20] summarize the current trend of thought. "While all this (Cooperative Clinical Trial) was going on, members of the study group made their own observations without the aid of IBM machines. Other investigators throughout the United States, Canada and England drew their own conclusions without statisticians, as physicians have done since time immemorial. The almost unanimous conclusion was that from the clinical view point the hormones were immensely useful indeed."

A review of the treatment of rheumatic carditis has been presented. Controlled studies matching the effectiveness of salicylates and steroids have been summarized and objectively criticized. Advantages and limitations of both regimens have been discussed and therapeutic recommendations proposed.

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