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PROPHYLAXIS AGAINST THE RECURRANCE OF RHEUMATIC FEVER

by

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INTRODUCTION

Prevention of the recurrance of rheumatic fever is of prime importance. As many investigators have noted, severe heart disease would in most cases be infrequent if the disease were monocyclic. However, it is polycyclic in children and young adults and with each febrile phase, severe inflammatory reactions are seen in the vascular tissues:

> "The initial attack seldom causes serious permanent medical damage. It is the recurrances that produce the more serious cardiac damage"(43)
>
> "Of extreme importance is the fact that the initial attack is seldom fatal and rarely damages the heart enough to permanently impair its normal function. Therefore, cardiac damage is involved in the recurrances. Therefore, the importance of preventing same."(15)

Because prophylaxis must be based on the etiological cause of rheumatic fever, there follows a brief resume of the etiological factors as they are thought to be today.

Rheumatic fever attacks predominantly the mesenchymal tissues. The principal substrate of this mesenchymal tissue is hyaluronic acid. Guerra (18) has pointed out the changes in per-

meability of mesenchymal tissues in the evolution of rheumatic fever. The structures which are composed almost entirely by hyaluronic acid--articulations, synovial fluid, etc.--are regions especially affected by rheumatism. Since changes in permeability of this substrate is characteristic of active rheumatic fever, it is of interest to note that over two humdred strains of hemolytic streptococci possess or produce the enzyme hyaluronidase. This enzyme is capable of decreasing the vicosity of hyaluronic acid, and thus favors the passage of fluids, exudates and pathogenic organisms. This now is thought to be the mechanism by which rheumatic fever causes its effects in the body. This work has just recently appeared in journals and more material is to be expected.

Admittedly not everything is known about the etiology of rheumatic fever, However, contrary to many, I believe we should look at the picture from a positive point of view. That is, that we do know alot about rheumatic fever and that on the known facts much can be done to prevent the recurrance.

Most investigators agree that the Beta hemolytic streptococcus is definitely in the picture as a etiologic factor; being of such importance that its curtailment results in diminished occurrance or recurrance of rheumatic fever.

The similarity between serum sickness, aller-

gic manifestations and rheumatic fever has been pointed out by several investigators. Coburn(11) speaks of the phases of a rheumatic attack. Phase I being an acute upper respiratory infection caused by the Beta Hemolytic streptococcus which may last from two to seven days. This is followed by Phase II which is quiescent and lasts from two to three weeks. Then, Phase III occurs with the presentation of a rheumatic attack in one or several of its protean forms--generally occurs the third week following the streptococcus infection. Therefore, in diagnosis a history of sore throat approximately three weeks before is of definite aid.

In normal individuals, Coburn(11) found a titre is built up during a streptococcus infection to antistreptolysin O and S. In the rheumatic individual the titre is not built up against the S form, there is some increase but not nearly as high as is seen in the non-rheumatic individual. Further, Coburn found that the titre is at a low ebb during recrudescense. However, other investigators don't agree with this finding of low titre. De Gara and Goldberg (13-14) in their studies concluded that there was no relationship between compliment and agglutimins and susceptibility to rheumatic fever.

A hereditary factor is implied above and both Coburn(11) and Wilson(49) are of a very definite

opinion that this is so. Their evidence presented independently seems very sound and is being given recognition today.

Further more, it is well known that rheumatic fever is a disease of the poorer class of people. Poor housing, improper clothing, unhygienic surrounding seem to be contributory factors but a faulty diet seems to be the main factor. This statement being made because the disease is seen in all classes and all classes may have faulty diet.

Coburn (11) has presented a formula or equation--the factors of which, when added, usually result in a rheumatic state. He points out that heredity is a primary factor, that only about five per-cent of the population are able under any circumstances to acquire rheumatic fever. It appears to be a Mendelian recessive. His second factor in the equation is the hemolytic streptococcus, beta group A. This organism through repeated attacks leads to the acquisition of a sensitivity. The third factor which seems to play such an important part in the production of the rheumatic infection is the diet, and coexistant with this, the environmental set-up. Also, reported by Jackson et al (23). These three factors; heredity, hemolytic strepococcus, and faulty diet add up to rheumatic fever. That is, if the

person has the Mendelian recessive and repeated streptococcus infection and a poor diet, he is a likely candidate for a rheumatic attack. Looking at these factors it is deducted that prevention must be carried out against the latter two factors, as only those can be controled. These two amendable factors then automatically divide the prophylaxis to be carried out into two natural divisions. The first being general--ie/diet, environment, climate etc.; the second, being chemotherapy carried out with the idea of reducing the incidence of beta hemolytic streptococcus infections.

A word as to the character of the recurrances is not out of order. Wilson (48), states that the incidence for recurrance is highest in the year immediately following an active attack and decreasing with each succeeding year. The form of the previous attack diesn't necessarily mean that a recurrance will manifest itself in the same manner; nor does one form of the disease predispose to a recurrance more than another. Severity of the disease doesn't appear to influence the rist of recurrance. And lastly, the risk of recurrance is not significantly different among children living under relatively favorable and unfavorable environmental conditions. It would seem that the only factor influencing recurrance was the time interval since the last attack.

DIETARY CONSIDERATIONS

It is becoming apparent that the diet plays more than just a passive role in rheumatic fever. Coburn and Moore(10) made a special study with respect to nutrition and the rheumatic state. They found that rheumatic susceptability occurs primarily in children with poor diets. The lack of a good diet being associated with the underprivileged. The diets which were faulty were found to be lacking primarily in protein, calcium, Vitamin A, and iron. They showed a definite relationship between nutrition and rheumatic susceptibility; they believed a diet deficient in protein and calcium was particularly inadvantageous. However, they attributed no one defeciency as a cause.

Jackson et al (23) carried the above study still further. They worked with the problem of preventing rheumatic fever recurrances through the use of diet alone. Using 266 children, all proven rheumatic fever patients a study was undertaken. First, the social aspect was studied. The home environment was improved as much as possible, proper clothing, own bed and room, isolation from intercurrent infection in family and if child had upper respiratory infection he was made bed fast. The diet was then stressed, each child had a certain amount of foodstuffs to be eaten each day to which other foods could be added. However, under no circumstances were the foods on the special

diet list to be omitted or replaced. The special diet list consisted of: 1 quart milk, 1-2 eggs, 1 serving of meat, fish, chicken or liver, 2 vegetables (½ cup is medium serving) 1 orange, apple, or tomatoe plus 1 other fruit, 1 teaspoon cod-liver oil; 6 teaspoons butter or margarine. Lastly, the child was allowed to play outside with other children but not to the point of fatigue.

With this closely regimented schedule it was found that the recurrance rate in the group 4-13 years was 7.9%; 14 years and above showed a recurrance of 4.3%. These figures were compared to a series of cases reviewed by Wilson and Lubschez (48) with respect to recurrance rates. These latter investigators found that the over all risk for a major recurrance in 4-13 year age group was 25%; 14-16 years was 8.6% and 17-25 was 5.7%. It must be emphasized that many of the patients utilized in Jackson's study had just recovered from a rheumatic attack--thus the group would be most likely to have rheumatic recurrance. Because the risk for major recurrance of rheumatic fever is 2-3 times greater in any one year following an attack. Thus, it is seen that diet alone did very much to decrease the number of rheumatic attacks. Wilson, states the fact that in their series, the risk of recurrance is not significantly different among children living under re-

latively favorable and unfavorable environmental conditions, thus diet is important. One other fact of interest brought out by Jackson was that there appeared to be a relationship between diet deficiency and incidence along with a degree of heart damage. Along this line of thought it is important to recall that carditis is most common during childhood and adolescence when nutritional requirements are high. Because of these findings every effort should be made to improve the home environment and the diet. This diet should have a high content of protein, calcium, Vitamin A and iron.

INFLUENCE OF CLIMATE

Coburn (11) reported how the navy handled the problem. As the navy men recouperated from the active stage of rheumatic fever, they were transferred to the climate of California, New Mexico, or Arizona, and interestingly enough, the incidence of recurrance did drop for them. However, these men were all 18 years or more and the likelihood of a recurrance in such an age group is not nearly as great as those under the age of puberty. They found the largest incidence of rheumatic fever in a camp located in the Rocky Mountain area (Idaho). Cannon (6) also reported that in the Rocky Mountain states, including Utah, Colorado, Nevada, Idaho, and Wyoming, 26.9% of the cardiac cases were attributable to rheumatic fever, this per-cent in other states was 5.8%. It would thus seem that there is a definite increase in the Rocky Mountain states and all through the northern states.

Brennemann (4) states that rheumatic fever seldom recurs if the patient is transferred to a warm, sunny climate--this must be permanent. Hanson (21) states in his paper that if it is possible the patient would be wise to move south to a more stable climate. Riecker (35) tells of factors which will cause one to anticipate recurrance, among these are northern locations. Thomas (42) states that transporting patients south for

the winter and spring months causes a decrease in rheumatic recurrances. Holbrook (22) also supports this general thought, stating that there is a striking distribution around the area of Denver, Salt Lake City, Sioux City, and Lincoln.

Studies on the incidence of rheumatic fever made by the New York Metropolitan Life Insurance Company (34) showed the distribution as follows: New England states and the Rocky Mountain states have the highest incidence; Southern and Middle-West states have the lowest incidence.

The reduction in recurrances upon removal to a warm climate could be explained by the decreased number of hemolytic streptococcal infections in such a climate.

INFLUENCE OF TONSILLECTOMY

Brennemann (4) states that removal of tonsils is called for only if they are chronically diseased or if frequent attacks of tonsillitis occur.

Thomas (42) states that a tonsillectomy doesn't cause any noticeable decrease in rheumatic recurrance.

Riecker (35) reports that Allan and Baylor over a 14 year period did 108 tonsillectomies in rheumatic subjects. In these a recurrance of 43.5% was seen. If there is definite disease of the tonsils, tonsillectomy is indicated; rheumatic fever in a child is not an indication. Should a tonsillectomy be done it should not be carried out during active phases of the disease.

Ash (1) reports no favorable influence on recurrances was noted following tonsillectomies. The presence or absence of tonsils at time of infection, as pointed out by Ash, had no influence on degree of heart involvement or death rate. However, if tonsillectomy was performed during active phases of the disease after it was thought to be quiescent, will precipitate another attack. Ash concludes that tonsillectomy is indicated only if the tonsils are diseased.

The above references make clear the position of tonsillectomy in the prevention of rheumatic

fever or its recurrance. As far as taking tonsils out, the indications are just the same as if the patient did not have rheumatic fever.

IMMUNOLOGIC ASPECT

Vaccination for prevention or protection against rheumatic fever is based on the hypothesis that the probable etiologic factor is the beta hemolytic streptococci. Wasson and Brown did some early work here using a filtrate made of the streptococcus. This was later modified and a toxoid made which was used intra-dermally. A series of four injections of increasing strength being used.(44,45 and 46). Using this technique 43 patients innoculated with three recurrances--7%; in a control group of 45 patients there were 19 recurrances or 40%. This was in the fall, winter and spring of 1939-40. The following season of 1940-1, they treated 35 similarly and had 4 recurrances--11%. The control group in this case consisted of 33 patients with 11 recurrances or 33%. The authors were of the opinion that if the serum could be made more specific against the etiolocial agent this method of handling recurrances could well be very advantageous. In 1941-42 they used the modified toxoid in 42 children and had no recurrances and the patients seemed generally in much better physical condition.

The reactions to the injections in all cases were very mild when they occurred. Most all reported local itching and heat. There was but slight tenderness and redness. There was no in-

stance of a generalized reaction, nor was there any abscess formation at the site of injection. Wasson and Brown (46) noted that those treated may gain immunity or increased resistance to rheumatic fever. These authors reported that as long as six years since injections were discontinued in patients with rheumatic fever, no recurrances have been sustained. Also, the health of these patients has remained materially better than that of the untreated patients. Much more work is still to be done here, the advent of the sulfonamides and penicillin rather eclipsing this phase of work.

SALICYLATE PROPHYLAXIS

It was natural that salicylates should be thought of in the prophylactic measures against rheumatic fever because of the success with the drug in the treatment of the active states. Not too much was done with it because of the success in prophylaxis with the sulfonamide drugs. However, with the recent report by Guerra (18) and Meyer and Ragan (32) interest has been rekindled.

Coburn and Moore (9) did some work with salicylate prophylaxis. They had the rheumatic patient report any upper respiratory infection and cultures were taken. If positive for the group A hemolytic streptococcus the patient was started on salicylate therapy. They gave 4-6 grams daily and continued therapy thru the rest of the season. Fourty-seven patients were so treated and there was one recrudescence, this one thought due to irregularity in taking the drug. A control group of 135 patients was run and of these 59 developed a rheumatic attack. Obviously the salicylate therapy was valuble in decreasing recurrances.

It should be noted in the above work that salicylate therapy was instituted when throat cultures was positive for hemolytic streptococcus. As will be seen this is a time when sulfonamide prophylaxis is ineffectual. Guerra (18) noted, as was mentioned in the opening remarks, that salicylates in the body are antagonistic to hyaluronidase and hyaluronidase is produced by the hemolytic streptococcus. Thus, it

is noted that the prophylaxis is carried out against this product produced by the hemolytic streptococcus. Meyer and Ragan (32) noted that this action of salicylates against hyaluronidase must be "in vivo", not occuring "in vitro". They also noted that eighty per-cent of the drug appears in the urine as salicyl compounds and twenty per-cent as breakdown products were responsible for the action of the salicylates. In experiments conducted by them it was found that this breakdown product was gentisic acid, and this substance was active "in vitro" as well as "in vivo". Furthermore, gentisic acid does indeed exert anti-rheumatic activity, its' anti-rheumatic activity being as great or greater than that of salicylates as such. They also noted that gentisic acid is relatively non-toxic never causing any effect with respect to toxicity in doses of 10 grams per day; not nearly this amount is needed for the anti-rheumatic effect. Thus, may be seen a possible solution to the great problem of salicylate toxicity which is often seen in prophylactic and active treatment of rheumatic fever.

The sodium salt and acetyl forms of salicylic acid are most often used in the prophylactic treatment. A blood level of 35 mgm % is needed for therapeutic effect, if this level goes above 60 mgm % toxic symptoms are apt to be seen. Generally 4-6 grams per day are needed.

SULFANAMIDE PROPHYLAXIS

A great amount of work has been done by a number of investigators as to the value of sulfa drugs in the prophylaxis against rheumatic fever. All divided the subjects into a control and treated group according to age, sex, degree of heart damage, last active attack and number of recurrances; thus the groups were matched as closely as possible.

It has been found that sulfanamides are of no value and may actually be detrimental in treatment of the active stage of rheumatic fever. Therefore, it is necessary to know that the rheumatic fever is inactive and this is most unanimously agreed to be when the sedimentation rate has returned to normal. Some believe that no recurrance of fever or other symptoms upon withdrawl of the salicylates used in treatment of the active state is indication enough of inactivity (41).

Thomas, France and Reichsman (40) and Coburn and Moore (7) did some of the early work using the sulfanamides in the winter season of 1939-40. All have followed patients through the years adding to the series of patients. Thus, by 1944, Thomas, France and Reichsmann had treated patients for a total of 114 patient-seasons with 4 recurrances while in a comparable control group of 150 patient-seasons, 21 recurrances were noted (40,41,42). Coburn and Moore by 1943 had treated patients through 184 patient-seasons with 1 recurrance and a like

group of controls composed of 263 patient-seasons saw a recurrance of 50. Both of the investigators reported toxic symptoms which occured in 10% and were mild in nature.

A number of investigators quickly entered this phase of activity including Hansen, Platou and Dwan with 131 patient-seasons and 7 recurrances in the treated group while 58 patient-seasons with 27 recurrances were noted in the control group.(19,20,21) Kuttner and Reyersbach in their series had 108 patient-seasons with 1 recurrance in the treated group, their 104 controls had a recurrance in 23 instances. (24,25,26) Dodge, Baldwin and Weber together and independently had 170 patient-seasons with 6 recurrances in the treated group and had 19 recurrances in a control group of 138.(2,3,15). Messelhoff and Robbins in their treated series of 50 patient-seasons had 3 recurrances and a similar number of recurrances among a control group of 60 patient-seasons.(31) Many others could be listed but all show just about the same results as the above and nothing is to be gained by further notation.

Rosenberg and Hench (36) did a masterful job in collecting and totaling the series of patients presented by the various investigators. Thus, in the total of 1,037 patients treated with sulfonamide compounds there were 22 recurrances or a recurrance of 2.2%; while of a total of 1,340 patient-seasons composing the control group 183 recurrances were noted

or 13.7%. There can be no doubt as to the effectiveness of the sulfonamides in the proplylaxis against the recurrances of rheumatic fever.

Toxicity has been a factor which has commanded interest. Stowell and Button (38) had one death due to the sulfa prophylaxis, this occured by the development of agranulocytosis. It should be stated that this patient did not present himself to the clinic as ordered with the appearance of toxic manifestations. This was of coarse an exception, the most common toxic manifestations being nausea, vomiting and/or rash and always mild, therefore, while disagreeable do no harm. Occasionally a mild leukopenia is noticed which seldom is severe enough to call for withdrawl of the drug. Because of this blood studies must be made frequently the first months of prophylaxis as toxic symptoms appear early, within the first several months generally. Thereafter, blood examination need be utilized only once a month. It is therefore recommended that the prophylaxis once started is continued through out the year, this obviates a lot of laboratory work (3, 41). Of the sulfa compounds used, sulfathiazole seems to be the cause of the least number of toxic reactions (50,21).

Sulfa prophylaxis to be effective must be carried out faithfully, and it is not of protective nature until it has been taken for at least a month (19, 28, 42). If a patient develops a strep throat the sulfa prophylaxis is ineffective, an indication that the streptococcus is the etiological agent. Thomas (42)

reported that in the navy where large numbers of men were involved, those receiving sulfa prophylactically showed an 85-90% reduction in number of hospitalizations for severe upper respiratory infections--along with a parallel reduction in rheumatic fever. Prophylaxis offers protection only as long as it is being taken faithfully and does not prevent recurrance in the following years (8).

Sulfonamides not only decrease recurrances but also several authors were impressed by the well-being of the patients (19). The drug did not act adversely on weight, those taking the drug gaining weight as would be expected (15, 19, 40).

Most authors are in agreement that the sulfa drug should be given in 0.5 gram doses twice a day, morning and evening. This should be given at the same time each day to establish the habit. The patient cannot be overimpressed with the necessity in taking the drug regularly.

A lot has been said regarding sulfa sensativity and sulfa resistent bacteria. Most of the investigators reported no such findings in their series of cases (15, 26, 28). This is by no means a closed subject and more work must be carried out before any statments can be made with finality.

Thus, if sulfa prophylaxis has been decided upon it is best to start prophylaxis immediately following cessation of the active state of rheumatic fever as determined by sedimentation rate return to normal and

well being of the patient. The sulfonamide, preferably sulfathiazole, should be administered twice a day, morning and evening, in 0.5 gram doses, the patient receiving a total of 1 gram daily. The necessity for faithfulness must be impressed at each visit of the patient to the physician. During the first few months the blood and urine must be checked weekly and later monthly--withdrawl of the drug if toxic symptoms severe. The patient is to report any toxic reaction to the doctor in person. The drug should be administered year-round because much laboratory work is obviated, habits are not broken, rheumatic fever can recur in summer, toxic reactions seen early after the start of the drug and because it takes fully a month before full protection is offered. The drug should be administered for at least five years or until adolescence is reached.

PENICILLIN PROPHYLAXIS

With the introduction of this antibiotic it was logical to think of the value of this drug in prophylaxis; as yet, few reports have appeared in the literature.

Maliner and Amsterdam (29) ran a series of 22 treated rheumatic's with a comparable number of controls; no recurrance was noted in the treated group, 4 were seen in the control group. Lapin (27) reported 248 cases treated with penicillin against upper respiratory infections and noted a definite decrease in the number of upper respiratory infections. As has been pointed out an attack of rheumatic fever is preceded by such an infection and therefore this information is pertinent. Burke (5) ran a short series of 20 patients, 10 of whom were treated and found the recurrances five times more frequent in the controls. All of these workers administered penicillin orally in doses of 5,000 Units three times a day. A check of saliva with this dosage schedule showed a bacteriocidal level of penicillin present for 3½ hours.

Massell et al (30) recently reported a small series of cases where oral penicillin was administered in dosages ranging from 300,000-1,000,000 Units per day, administered in fractionated doses three times a day. The patients were generally kept on 300,000 Units per day being advanced to 1,000,000 Units per day if patients did have hemolytic streptococcus infection of the throat. On this routine no rheumatic recrudescence was seen. This is of special importance be-

cause if a strep throat is seen with sulfonamide prophylaxis protection is not afforded.

The advantages to this type of proplylaxis is seen in the minimal amount of laboratory work necessary, the lack of toxic reactions, and therefore a decrease in number of office calls. The disadvantages are the expense of the drug and some believe there is a penicillin resistent strain of bacteria developed which would be most detrimental if such a patient should develop a sub-acute bacterial endocarditis.(33).

SUMMARY

A brief review of the etiological factors and the characteristics of the rheumatic recrudescences was presented.

The influence of the general factors; diet, tonsillectomy, climate and environment was presented and their influence on the rheumatic recurrance noted.

The specific proplylactic measures; salicylates, sulfonamides and penicillin were reviewed.

CONCLUSIONS

Any child who has had rheumatic fever should be protected from recurrance through the use of proplylactic treatment. This treatment must be followed routinely and carried out the year round. The drug of choice at the present time seems to be one of the sulfonamide preparations given morning and evening in 0.5 gram doses. Salicylate therapy is very effective and bears consideration as choice of prophylactic medication.

Every effort should be made to provide a diet with ample amount of protein, vitamin A, calcium and iron.

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