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PREVENTION OF RHEUMATIC FEVER RECURRENCES

BY

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Sulphonamides were first used in the prevention of rheumatic fever recurrences nearly 20 years ago (Coburn and Moore, 1939; Thomas and France, 1939). In 1941, Thomas, France, and Reichsman published their results in a controlled series that had been followed for four years. They found that the frequency of throat cultures positive for Group A haemolytic streptococci was less in a group of 55 patients protected by daily sulphanilamide and that none in this group had had acute streptococcal throat infections or further attacks of rheumatic fever. In the control group (67 patients) there were 15 major attacks of rheumatic fever and four deaths. Rosenberg and Hench (1946) summarized the results of 10 controlled series published between 1939 and 1946, involving over 1,000 person-seasons in each of the two groups: the recurrence rate in the protected series was 2.2% per patient-season and in the unprotected 13.7%.

In 1947 Burke published the first results with penicillin. One group of 10 patients had been given 1,500 Oxford units by mouth daily, and another group of 10 were studied as controls: both had been followed for one year after discharge from hospital. There was a higher incidence of infection of the upper respiratory tract in the unprotected group, and one relapse occurred in this group but none in the protected. There have been many American studies in the past 10 years (summarized by Stollerman, 1954), but only few from this country. Pitt Evans (1950) gave 100,000 units of penicillin daily by mouth to one group of 155 children in a convalescent home; another 145 children were studied as controls. Both groups were followed as in-patients for an average period of 22 weeks. The incidence and duration of the Group A haemolytic streptococcal carrier state was approximately four times greater in the unprotected than in the protected group, and clinical pharyngitis and tonsillitis was over seven times more frequent. There were no relapses of rheumatic fever in the 155 protected patients and four in

the 145 unprotected. Gale *et al.* (1952) observed 73 patients for eight months after discharge from hospital: 41 were given 200,000 units of penicillin daily: the remaining 32 received lactose and glucose. Throat swabs were taken every two weeks. There was a lower incidence of positive throat cultures in the treated group, and, whereas two rheumatic relapses occurred in the 32 controls, there were none in the 41 treated.

Prophylaxis was not used on any large scale in this unit until 1951. We relied instead on isolation (and, if necessary, treatment) of all new admissions until their throat cultures were known to be negative for haemolytic streptococci, and on weekly throat-and-nose swabbing of all patients and staff; anyone with a positive throat swab was isolated and given intramuscular penicillin. In this way the number of streptococcal infections was kept at a very low level and the recurrences in hospital were few. Experience in this country indicated that recurrences of rheumatic fever after discharge from hospital were much less frequent than had been reported in the U.S.A., where estimates ranging from 40% per year (Wilson and Lubschez, 1944) down had been reported. Up to 1951, therefore, in view of possible toxic effects from long-continued administration and of the low recurrence risk, our patients had not been put on to prophylaxis on discharge from hospital.

Present Investigation

In the years 1949 and 1950 there were 96 patients in this unit who were diagnosed as having rheumatic fever; none were put on to prophylaxis in hospital. All fulfilled the criteria for diagnosis of rheumatic fever as defined by Duckett Jones and modified by the American Heart Association (1955). They had, therefore, either two major and one minor, or one major and two minor, criteria (major criteria: polyarthritides, chorea, nodules, erythema marginatum, and carditis; minor criteria: fever, arthralgia, prolonged P-R interval, raised sedimentation rate, evidence of preceding haemolytic streptococcal infection or previous history of rheumatic fever or rheumatic heart disease). Four patients died in hospital. The remaining 92 were not put on to prophylaxis at the time of discharge from hospital. They were seen for follow-up examination at three-monthly intervals for the first year, and thereafter once each year. At each examination a careful history was taken, with special reference to sore throats and limb or joint pains; a complete physical examination was carried out; and blood was taken for sedimentation rate. All 92 were seen at one year, 91 at two years (1 defaulter), 89 at three years (3 defaulters), 87 at four years (4 defaulters and 1 patient who had died in a recurrence at three years), and 85 at five years (2 more defaulters). Thus there were six defaulters by the fifth year and one had died at three years.

In view of the mounting evidence of the efficacy of prophylaxis and the low incidence of toxic reactions, we started to use prophylaxis as a routine measure for both in-patients and out-patients in 1951 as stipulated in the U.S.-U.K. treatment trial in which we were participants (Co-operative

TABLE I.—Comparison Between Protected and Unprotected Groups on First Admission into Hospital

Group	Total No.	Sex		Age in Years on Admission		Degree of Carditis on Admission			Duration of Disease Activity on Admission in Days		
		M	F	0-10	11-16	None	Pres. 1st Attack	Pres. 2nd or Later	0-14	15-43	43 +
1949-50 (un-protected)	96	53	43	46	50	28	42	26	50	22	24
1951-52 (protected)	88	44	44	38	50	13	49	26	30	32	26

Clinical Trial, 1955). In the years 1951 and 1952, 88 patients were admitted with rheumatic fever, all of whom fulfilled the same diagnostic criteria as the previous group. The two groups were also similar as regards age and sex incidence, degree of heart involvement, and duration of disease before admission (Table I).

All 88 patients admitted in 1951 and 1952 were given prophylaxis in hospital (tablets containing sulphathiazole, sulphadiazine, and sulphamerazine ("sulphatriad"), 1 g. daily). Two patients died in hospital. In the remaining 86 prophylaxis was continued after discharge. These 86 patients were seen for follow-up examination at six-monthly intervals for the first two years and thereafter once each year. They were interrogated and examined in the same way as the previous group, and blood samples were taken for packed cell volume, sedimentation rates, and anti-streptolysin O titres. Urines were also tested for sulphonamide (La Rosa, 1945). 85 were seen at one and two years (1 defaulter), 81 at three years (5 defaulters), 79 at four years (6 defaulters), and 71 at five years (6 defaulters and 9 not yet due for follow-up).

Results

Recurrences were defined as further episodes of rheumatic activity after discharge from hospital in which the criteria for diagnosis were again fulfilled—that is, there were two major or one major and two minor criteria. None had more than one recurrence in any 12-months period.

In the unprotected group of 92 patients admitted between 1949 and 1950, 18 patients had recurrences during the first five years of follow-up. 17 of them had further attacks of rheumatic fever: 14 had one such attack, 2 had two, and 1 had three. Thus the 17 patients had a total of 21 recurrences. The remaining patient had three attacks of chorea. There were therefore 24 episodes of fresh rheumatic activity. Of the 86 in the protected group, 5 had further attacks of rheumatic fever.

Table II shows the number of recurrences in the two groups at or before each annual follow-up. In the unprotected group, 9 of the 17 with recurrences of rheumatic

TABLE II.—*Number of Recurrences Per Year at Annual Intervals in Cases that Survived*

Years from Admission:	0	1	2	3	4	5
Unprotected group:						
No. at risk ..	92	92	90	86	81	77
% of recurrences ..	—	5	6	5	4	4
% ..	—	5.4	6.7	5.8	4.9	5.2
Protected group:						
No. at risk ..	86	85	85	81	79	71
% of recurrences ..	—	1	1	0	2	1
% ..	—	1.2	1.2	0	2.5	1.4

fever were put on to prophylaxis during their readmission to hospital; none of them had further attacks. These cases have therefore been excluded from the "number at risk" after their discharge from hospital, as they were then receiving prophylaxis. At one year there were 92 unprotected "at risk"; at two years 90 (1 defaulter and 1 on prophylaxis); at three years 86 (3 defaulters and 3 on prophylaxis); at four years 81 (4 defaulters, 1 dead at three years in a recurrence, and 6 on prophylaxis); and at five years, 77 (6 defaulters, 1 dead, and 8 on prophylaxis). In the protected group, 85 were seen at one and two years (1 defaulter at each); 82 at three years (5 defaulters); 79 at four years (6 defaulters); and 71 at five years (6 defaulters and 9 not due for follow-up).

The mean incidence of recurrences per patient-year was 5.6% in the unprotected and 1.2 in the protected.

Discussion

Whilst the number of recurrences during the 12-months period after discharge from hospital was consistently and considerably less in the protected group, the reduction is less than reported in American series. This is because the recurrence rate in the unprotected was much lower than seems to be the usual experience in the United States. The

total mean incidence of recurrences per patient-year in our unprotected group was only 5.6%. Wilson and Lubschez (1944), in New York, found an overall recurrence rate of 25% in children aged between 4 and 13, and Fischel's unpublished figures from another hospital in New York (quoted by Stollerman, 1954) showed that of 239 unprotected patients 43 (18%) had recurrences during the first year.

Such large differences in recurrence rate in unprotected populations may depend on different criteria for recurrences or on other factors. Thus, out-patient prophylaxis is less stringent and effective than in-patient prophylaxis. In our protected group, of the five that had recurrences, one was known to have stopped taking sulphonamide two months previously and in another it was probable that the drug had been discontinued. Under barrack conditions (and some of the American figures come from Service camps) the risk of contracting streptococcal infection is greater than in the home, and the attendance of patients for illness may be different in different countries. However, most of the American series seem to agree on a high incidence of recurrences in unprotected series of whatever age, while in the few series reported in this country the incidence has been low (Pitt Evans, 1950; Gale *et al.*, 1952; present series). This difference may account in part for prophylaxis being taken up less enthusiastically in this country than in America.

Although the two groups of cases in this series were not run concurrently, the five-year period of study overlapped by two to four years in the two groups. In both groups the recurrence rate was similar during each of the five years of follow-up. This is of considerable interest, for Wilson and Lubschez reported that the risk of recurrences in the year following an attack was 38.7%, whereas the risk after one year's freedom from attacks was only 11.7%. In our series the recurrence rate has remained at a similar level throughout the five-year period despite the fact that the children were getting older and were further from their initial attack. Furthermore, Wilson and Lubschez found an overall recurrence rate of 25% in children aged 4 to 13, and only 9% in those aged 14 to 16. In our unprotected cases the age distribution on admission to hospital was 46 patients up to and including the age of 10, and 50 between 11 and 16. Of the 46 up to and including the age of 10, 7 had recurrences; of the 50 aged between 11 and 16, 10 had recurrences. There is manifestly no great falling off of recurrence rates after puberty.

Objections that have been raised to prophylaxis have been discussed in a previous publication (Bywaters *et al.*, 1957). Among these have been the fear of toxic reactions (agranulocytosis, drug rashes, and renal damage) and of streptococcal resistance to sulphonamide. In this series, though patients were given sulphonamide over periods of four and five years, such reactions were few. Two in the protected group complained of lassitude during the first year after discharge. One, a girl of 12, was found to have a white blood cell count of 3,850 per c.mm. with 25% polymorphs. She was admitted to hospital and sulphonamide prophylaxis was changed to penicillin. One week later she had recovered: the white-cell count was 7,450 per c.mm. with 70% polymorphs. The other, a boy of 5, had a white-cell count of 2,000 per c.mm. with 20% polymorphs at the sixth month follow-up. Penicillin prophylaxis was substituted, and, although the white-cell count remained low for some months before returning to normal, prophylaxis continued uneventfully.

No patient in this series developed agranulocytosis, although another of our patients (not included in this series because she was over the age of 16 on first admission) developed agranulocytosis at the eighth week; she responded satisfactorily to intramuscular penicillin. One patient in the series developed urticaria after 10 weeks on sulphonamide. The drug was stopped after four days and penicillin prophylaxis substituted. The rash persisted for another four days and then subsided. No instance of streptococcal resistance to sulphonamide was encountered.

though in another patient (not included in this series because he had chorea only) haemolytic streptococci resistant to sulphonamide were found in routine weekly throat swabs after eight weeks of treatment. The patient was treated with bactericidal doses of intramuscular penicillin, a tonsillectomy was performed, and prophylaxis was then continued with oral penicillin.

Since that time, all patients with rheumatic fever or chorea have been given sulphonamide or penicillin prophylaxis in hospital, and this has been continued after discharge (sulphatriad, 1 g. daily, or penicillin G, 200,000 units twice daily). Our original impression of the efficacy of this prophylaxis has been confirmed, and toxic reactions have been few in number and harmless. Most have occurred within a few weeks of starting treatment—that is, whilst the patients were still in hospital. Prophylaxis has then been changed from one drug to the other and there has been no further trouble.

We have no data available on differences in the recurrence rate between cases treated with sulphonamide and penicillin. Assuming both drugs to be equally effective, penicillin would be the one of choice, for there is the possible though small danger of agranulocytosis with sulphonamide. The slight extra cost of penicillin (3.6d. a day as compared with 1.6d. a day for sulphonamide) does not seem important, and storage of penicillin presents no problems, for the tablets retain their potency for three months if kept in an airtight tin in the cool. Injections of benzathine penicillin have been advocated by some as preferable to penicillin by mouth. Though this method ensures that prophylaxis is carried out, it is difficult to impose a regime of weekly injections on children in the knowledge that this must be continued for years. The Rheumatic Fever Committee of the Royal College of Physicians (1957) recommends 200,000 units of penicillin G twice daily, or 120 mg. of penicillin V twice daily, and that benzathine penicillin should be used if for any reason oral prophylaxis cannot be given. With this we concur.

Finally, for how long should prophylaxis be continued? This is a matter for individual judgment, taking into account parental attitudes and circumstances. It is our belief, based on these figures for recurrence rates, that prophylaxis should continue for at least five years after the last attack or until the child has left school, whichever period is the longer (Rheumatic Fever Committee of the Royal College of Physicians, 1957). If, after leaving school, patients are exposed to an increased risk of streptococcal infection—that is, should they enter a university or one of the Services—then prophylaxis should be continued for a further period. If liability to reinfection is based on M antibody level, it may be that even more prolonged prophylaxis will be necessary.

Summary

Two comparable groups of patients with rheumatic fever were followed for a period of five years. One group of 96, admitted in 1949–50, were given no prophylaxis either in hospital or after discharge. The other, comprising 88 patients admitted in 1951–2, were given 1 g. of sulphonamide daily in hospital and after discharge. The period of follow-up in the two groups overlapped by two to four years.

The mean incidence of recurrences per patient-year was 5.6% in the unprotected and 1.2% in the protected. There was only small variation from year to year in each group, and no tendency for the recurrence rate to decrease with time. The reasons for the relatively low incidence of recurrences in the unprotected group and other differences between this and American series are discussed. Toxic reactions were few: none were serious. The duration, dosage, and merits of various forms of prophylaxis (sulphonamide, oral penicillin, and long-acting penicillin by intramuscular injection) are discussed.

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DESENSITIZATION TO BEE STINGS BY INTRACUTANEOUS INJECTIONS OF WHOLE-BEE EXTRACT

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Reports of more or less severe reactions to bee stings are not infrequent in South Africa, and deaths therefrom are occasionally reported in the lay press. Our own information about bee-sting sensitivity and the effects of bee stings derives largely from many physicians in various parts of the country who, describing more or less severe reactions in their patients, inquire about the possibility of prophylactic desensitization.

Persons sensitive to bee stings commonly manifest local reactions in redness and swelling at the site of the sting and general reactions in rash, urticaria, oedema of face and glottis, and often anaphylactic shock, with collapse, unconsciousness, and even death. There may also be malaise, vomiting, dyspnoea, or bronchospasm. These effects appear within minutes after the sting or reach their climax some hours later.

The majority of patients who show a high degree of sensitivity to bee stings have suffered symptoms of progressively increasing severity after each sting, following a longer or shorter period of freedom from significant reactions after the initial sensitizing sting, which may have been many years ago. The following examples are given in illustration:

A farmer 44 years old had frequently been stung, as a boy and young man, with more or less severe local reactions after each sting. When he was stung again in 1952 there was little local reaction, but within three minutes he became unconscious and remained so for two hours. On recovery he had a "choking" sensation, with headache and malaise continuing for a day or two.

A medical man with no family history of allergy was stung at the age of 3½ years by about a hundred bees. The stings were removed and he suffered no ill effects. When he was 12 years old he was stung on the hand and developed a swollen face. Two years later he was stung between the toes. This resulted in swollen eyes, oedema of the glottis, and extreme dyspnoea requiring urgent medical attention. At the age of 29 he was stung once on the forearm, and, although he was injected with adrenaline within 20 minutes and with three further injections at hourly intervals, he had to have treatment at hospital, where he was detained for some time. He was stung again 10 years later, and, although adrenaline was administered within 10 minutes, he developed alarming swelling of the face.

A physician wrote from the Transvaal: "A patient of mine was stung by a bee in the soft tissue around his eye and had a severe systemic reaction. He became semiconscious and vomited profusely; rapid heart, with fall of blood pressure. He had never been affected by a bee sting previously although stung many times."

As a result of our advice and recommendations concerning the possibility of desensitization, bee-venom extracts are