THE USE OF THE SULPHONAMIDE GROUP OF DRUGS IN THE TREATMENT OF TONSILLITIS DUE TO THE BETA-HÆMOLYTIC STREPTOCOCCUS AND IN ACUTE RHEUMATIC FEVER*

By W. A. HOPKINS

INTRODUCTION

OVER forty years have elapsed since Poynton and Paine (1900) first indicted streptococcal infection as the cause of rheumatic fever, and since then numerous investigations have been carried out which go far to support their views. Owing to the difficulty which exists in reproducing the disease experimentally, conclusive evidence that this organism is directly responsible is still lacking, but sufficient data have been accumulated to show that a definite relationship exists between the two. The literature on the subject is voluminous, but recent significant work in support of the streptococcal theory has been carried out by Green (1939), who isolated hæmolytic streptococci from the heart valves in eight out of nine cases of fatal acute rheumatic fever. In five of these cases hæmolytic streptococci were isolated from throat cultures during life, and these were serologically identical with those isolated from the cardiac lesions. Collis (1939) and Thompson and Innes (1940) have reported similar findings. Additional support from the serological aspect has been given by Todd (1932), who found a rise in the anti-streptolysin titre in a high proportion of cases of acute rheumatism; since then, Coburn and Pauli (1932, 1935) and Green (1941, A) have carried out work confirming Todd's findings. If the view that the hæmolytic streptococcus is of ætiological significance in acute rheumatic fever is accepted, it is reasonable to suppose that this organism gains access to the body through the most obvious route, the naso-pharynx, and numerous observers have noted the relationship which exists between streptococcal sore throat and acute rheumatism. Glover and Griffith (1931) found that in a number of schools where naso-pharyngeal infection with the hæmolytic streptococcus had been

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epidemic there followed outbreaks of acute rheumatism; and so long ago as 1884 Haig Brown (Coburn and Pauli, 1932) described an epidemic of tonsillitis among a group of public-school boys which, after a time lag, was followed by an outbreak of acute rheumatism. Green (1941, B) has shown that in a community where hæmolytic streptococcal infection was epidemic the distribution of acute rheumatism resembled that of tonsillitis, but was unlike that of any other disease, and, furthermore, that the peak incidence of the former occurred some six weeks later than that of the latter. The same observer (1938) found that in a series of two hundred cases of acute or subacute rheumatism 58 per cent. had hæmolytic streptococci in the naso-pharynx at the onset of their illness—a figure much above that to be expected in a series of healthy controls.

With such strong evidence, circumstantial though it may be, in support of the view that the hæmolytic streptococcus is of ætiological significance in acute rheumatic fever, and that the disease is commonly preceded by an attack of streptococcal tonsillitis, it was obvious from the first that the introduction of new chemotherapeutic agents in the form of the sulphonamide group of drugs might prove of the greatest importance in the treatment of a condition which hitherto it had only been possible to treat empirically and, it must be admitted, unsuccessfully. Two approaches to the therapeutic problem seemed feasible: if this new drug proved successful in the treatment of streptococcal tonsillitis, there was reason to hope that the matter would be solved prophylactically; and there was also reason to hope that the drug might prove to be efficacious in the treatment of acute rheumatism itself.

Domagk's (1935) publication on the use of prontosil in the treatment of experimental streptococcal infections of mice was closely followed by numerous papers dealing with the use of the drug in various infectious processes affecting the human body, and some six months after Domagk's original article Roth (1935) reported favourably on the use of prontosil in hæmolytic streptococcal infections. Since then a large volume of experimental and clinical data has been built up concerning the use of this drug and similar compounds which have been synthesised more recently. In a voluminous literature there are numerous references concerning their value or otherwise in the treatment of both streptococcal sore throat and acute rheumatism.

Encouraging and, in some cases, enthusiastic reports of the value of these drugs in the treatment of tonsillitis due to the hæmolytic streptococcus appeared at first, and continued to do so for some time. In a series of thirty-nine cases of streptococcal tonsillitis, Smith (1937) used prontosil album (*p*-amino-phenyl sulphonamide) in twenty-two cases and proseptasine (*p*-benzyl-amino benzene sulphonamide) in the remaining seventeen. Hæmolytic streptococci were isolated from throat cultures in thirty-one of these cases. Using an initial daily dosage of 7.2 gms. of the former drug and, in some instances, as much as 12.5 gms. of the latter, he found that in twenty-six of these cases the response was satisfactory, nineteen having normal temperatures within twenty-four hours and the remainder within thirty-six hours. He also noted that "pain in the throat and general discomfort soon disappeared" and that in "no case were there any new complications." Perkins (1937) was also enthusiastic, and, using prontosil rubrum in a series of ten cases with ten controls, he found that both the period of hospitalisation and the period of convalescence were reduced. It is to be noted, however, that hæmolytic streptococci were only isolated from two of the treated cases and not at all from the controls. Successful results were also published by Basman and Perley (1937), by Peters and Havard (1937), by Kramer (1936), and by Long and Bliss (1937). Other observers noted that the use of the drug materially reduced the time for which throat cultures remained positive, and Gallagher (1937), in a series of thirty-three cases, published a report to this effect. The carrier problem was also dealt with by Brennenman (1937), who found that in almost every case carriers of hæmolytic streptococci became negative shortly after treatment with sulphanilamide was instituted. He also noted that one to six days after the drug was discontinued the throat swabs became positive again. By no means all of the early observations were equally enthusiastic, and several less convincing reports appeared. Watson Williams (1937) was of the opinion that the results were no better than when sodium salicylate was used; McIntosh *et al.* (1937) reported unconvincing results; and Whitby (1937) had seven successes and two failures. That patients already receiving treatment with sulphonamides were still liable to contract tonsillitis was shown by Kenny *et al.* (1937), who reported two such cases. So far no properly controlled series of cases had appeared in the literature, but in

1940 Rhoads and Afremow published details of a group of thirty-one sulphanilamide-treated patients with thirty-six controls. These observers found that the use of the drug did not reduce "the severity of the symptoms, shorten the period of incapacity, reduce the incidence of complications, or reduce the duration of the carrier state." In addition they noted that, using an average daily dose of 3.6 gms. and attaining an average blood level of 6.38 mgms. per 100 c.c., toxic manifestations of the drug other than the usual cyanosis occurred in one-half the cases in which sulphanilamide had been administered.

A search of the literature shows that reports of the value of the sulphonamides in the treatment of acute rheumatism are few and far between. However, when the drug was first introduced a few favourable reports appeared; using "streptozon," Veil (Recknagel, 1935) found that cases of acute rheumatism improved and that the blood sedimentation rate was lowered, and Klee and Romer (1935) were favourably impressed with the use of prontosil in similar cases. Most observers, however, were of the opinion that no beneficial results could be expected from the use of these drugs; Massell and Jones (1938), in a series of fifty-eight patients, found that sulphanilamide did not produce any symptomatic relief or shorten the course of rheumatic fever; Hench (1938) and his co-workers came to the conclusion that not only was sulphanilamide of no value, but that it seemed to be particularly toxic in this condition; and Swift *et al.* (1938) drew similar conclusions from a careful study of eight cases. They noted also that, of the eight patients, the antistreptolysin curve for six was indicative of recent infection with hæmolytic streptococci, the other two being equivocal, and that there was no evidence that the formation of antistreptolysin was in any way influenced by the exhibition of the drug. In this connection it is interesting to note that Green (1941, C), in a study of the effect of prontosil on the production of antistreptolysin O in rabbits, found "no evidence of inhibition or stimulation of antibody response" following the use of the drug.

Although the matter is outside the scope of this paper, mention must be made of the use of the sulphonamide group of drugs in preventing recurrence of rheumatic fever. Thomas and France (1939) carried out studies on this aspect of the problem during the years 1937 and 1938 with encouraging results, and Coburn and Moore (1939, 1940, 1941), in a very carefully followed

series of cases, found that a level of sulphanilamide in the blood of about 40 micrograms, maintained throughout the school year, protected against streptococcal pharyngitis and rheumatic recurrences. Furthermore, they found that withdrawal of the drug from one hundred of these patients resulted in 39 per cent. developing streptococcal pharyngitis, and of this 39 per cent. 40 per cent. developed rheumatic recrudescences. The importance of this work can hardly be overestimated.

My interest in the use of the sulphonamide group of drugs in the treatment of tonsillitis and acute rheumatic fever was aroused in 1939, at a time when a number of patients suffering from one or other of these conditions came under my care. They were drawn from a community of young male adults whose physical fitness was above the average of that of the general population, who lived under the same environmental conditions, and who were under constant medical supervision. This last meant that the minimum of delay ensued between a man reporting sick and his admission to hospital. The results of this investigation will be reported in two parts, the first dealing with the treatment of tonsillitis due to the hæmolytic streptococcus, and the second with that of acute rheumatic fever.

(A) TONSILLITIS.—Alternate patients were placed on sulphonamide therapy. As experience during the few months previous to the study had shown that over 80 per cent. of the patients admitted to the hospital suffering from tonsillitis harboured beta-hæmolytic streptococci in their throats, it was decided to institute therapy immediately on their arrival in the ward and to exclude from the series those whose throat swabs proved negative for this organism. Others excluded from the series were patients who had suffered from symptoms for over forty-eight hours and those who were afebrile on admission to hospital. Throat swabs were taken immediately on admission to the ward and before any form of therapy, either local or general, was instituted. These swabs were applied to a blood-agar plate containing 10 per cent. horse blood, spread in the usual manner, and incubated under aerobic conditions at 37° C. for twenty-four hours. The cultures were then examined for colonies showing a clear ring of hæmolysis, and such colonies were picked off into broth which was incubated at 37° C. for sixteen hours, when the presence of hæmolysin was tested for. Only those patients whose cultures yielded typical colonies which

on subculture into broth gave a positive "tube test" are included in the series. Throat swabs were taken again after the local symptoms and pyrexia had subsided, and at intervals thereafter, until the cultures yielded negative results. The series comprises forty-nine treated patients with fifty controls, and the initial symptomatology of all patients was very similar. In almost every case the attack started with headache, severe sore throat and general prostration. A proportion of patients complained of attacks of shivering, and a minority of general body aches and pains. Examination on admission to hospital revealed pyrexia ranging between 100° and 103.5° F., acute pharyngeal inflammation and exudation, and, in almost all cases, cervical adenopathy. As has been said, alternate patients were treated with sulphonamides, the control group receiving aspirin in 10-grain doses three times a day. Apart from this, both groups received exactly similar treatment—*i.e.*, rest in bed until the temperature had been normal for three days, a light diet, and glyco-thymoline gargles. Two drugs—colsulanyde (para-amino benzene sulphonamide) and May and Baker "693" (sulphapyridine)—were used in the treated group, twenty-five patients receiving the former and twenty-four the latter. The dosage employed was uniform, 2 gms. being given four-hourly for four doses and thereafter 1 gm. four-hourly until the temperature was normal, when the amount was reduced to 1 gm. three times a day. Treatment was discontinued when the patient had been afebrile for forty-eight hours. In order that the blood concentration of the drug might be maintained adequately, patients were awakened during the night for their earlier doses. In assessing the results of treatment the following factors were taken into consideration: (1) duration of fever; (2) the number of days spent in hospital; (3) the duration of local manifestations (pharyngeal inflammation, exudate, and cervical adenopathy); (4) the length of time for which throat swabs remained positive; and (5) the occurrence of complications. The results obtained are shown in the following table; complicated cases are excluded, as the inclusion of such figures as eighty-six days' hospitalisation due to acute rheumatism supervening would grossly distort the general picture.

From the table on page 239 it will be seen that the average number of days' fever in the treated groups of cases was 2.4, as against 2.0 in the control group; that the average number of days spent in hospital was 9.0 as against 7.6; that the duration of local

	<i>Colsulanyde- treated Group</i> (21 uncomplicated, 4 complicated cases).	<i>M. and B. 693 treated Group</i> (19 uncomplicated, 5 complicated cases).	<i>Control- Group</i> (43 uncomplicated, 7 complicated cases).
Average duration of fever (in days) . .	2.2	2.7	2.0
Average number of days spent in hospital	8.5	9.6	7.6
Average duration of local manifestations (in days) . .	3.3	3.3	3.1
Average duration of positive throat swabs (in days)	6.1	6.3	5.1
Percentage of complicated cases . .	16	20.8	14

manifestation was similar in both groups of cases; and that hæmolytic streptococci remained in the throat for a day longer in the treated group. The incidence of complications was some 4.4 per cent. greater in the treated group. A total of nine complications occurred in the treated group of forty-nine patients the percentage being slightly higher in those treated with sulphapyridine. These complications were as follows: Five cases of peritonsillar abscess, two cases of persistent tachycardia, and two cases of rheumatic fever which supervened during the patients' stay in hospital. In neither case was there a previous history of acute rheumatism. In the control group of fifty patients there were only seven complications—four cases of peritonsillar abscess, two cases of persistent tachycardia (tachycardia was considered to be a complication when the pulse rate remained above 90 for over a week in the absence of pyrexia), and one case of otitis media. The general impression gained was that on the whole those complications encountered were less severe in the untreated group of cases.

In spite of the relatively high dosage employed, toxic reactions in the sulphonamide-treated group were conspicuous by their absence. Cyanosis was of common occurrence, and, in addition, some 40 per cent. of those patients who received sulphapyridine suffered from vomiting. It is felt, however, that these reactions are not contra-indications to the continued use of the drug. Apart from these, the only other complication noted was the occurrence of a toxic rash four days after therapy had been instituted. There were two cases of persistent tachycardia,

which may or may not have been due to the drug; it is to be noted that two such cases occurred in the control group as well. Leucopænia did not occur in any of the cases.

(B) ACUTE RHEUMATIC FEVER.—Twelve cases of acute rheumatic fever were treated chemotherapeutically, half with M. and B. 693 and half with colsulanyde. Of these, nine were patients admitted suffering from their first attack and in whom no previous form of therapy had been employed; the remaining three were patients who were already in the ward and who developed rheumatic recrudescences. In view of the unfavourable results obtained in all the cases in the series, no attempt will be made to make any comparison with a control group. The dosage of the drug employed was similar to that used in tonsillitis—*i.e.*, 2 gms. four-hourly until 8 gms. had been given, then 1 gm. four-hourly until a total of some 20 to 25 gms. had been attained. In addition, patients were treated with absolute rest in bed and simple palliative local measures. The extent of the lack of success obtained can be seen from the following précis of the case notes.

CASE 1.—B. D., aged sixteen, admitted with a three days' history of pain in his left leg and left knee joint. He reported sick the day before admission, and his previous treatment had consisted of rest in bed only. There was no history of any previous attack of rheumatism. On admission the patient presented the typical picture of acute rheumatism, with sweating, pyrexia of 101° F., and polyarthritides, the left knee and right ankle joints being affected. He was ordered sulphapyridine 2 gms. four-hourly. During the next four days his condition became steadily worse; the left wrist, left ankle, right wrist and right shoulder joints became affected in turn, being painful, swollen, hot and acutely tender. No fall in temperature was noted. On the sixth day of hospitalisation, when the patient had had 20 gms. of the drug, its use was discontinued and salicylate therapy was instituted. Following this, his condition improved rapidly; his temperature fell to normal, and within three days all joint pains and swellings had cleared up. On the eleventh day of his illness early signs of carditis were noted, and six weeks later systolic murmurs were still present at apex and base, and the blood sedimentation rate was still grossly abnormal. Hæmolytic streptococci were isolated from his throat on admission.

Comment.—Full doses of sulphapyridine, with a total amount of 20 gms., failed to influence the course of a typical case of acute rheumatism in any way, nor was the onset of carditis prevented. The only toxic reaction to the drug was occasional vomiting.

CASE 2.—F. J., aged nineteen. Two days before admission he suffered from vague pains in his legs from the knees downwards, and the day before admission he found difficulty in standing, owing to the pain in his feet. There was no previous history of rheumatism. On admission both ankle

joints were swollen, hot and tender; temperature was 102.4°F. , and pulse rate 100. Sulphapyridine 2 gms. four-hourly was prescribed, and this drug was continued until a total of 20 gms. had been given. During the next five days no improvement in his condition was noted; his temperature remained high, polyarthritis continued, and on the third day of his illness signs of carditis presented themselves. On the fifth day of his illness he developed acute nephritis, with albuminuria, hæmaturia, a low urinary specific gravity, slight œdema, a moderate degree of hypertension, and a blood urea of 84 mgms. per 100 c.c. This complication cleared up slowly and was followed by a moderate degree of hypochromic anæmia. Two months after the patient's admission to hospital well marked signs of carditis were still present and the corrected blood sedimentation rate (Wintrobe's method) was 23 mm. at one hour.

Comment.—Twenty gms. of sulphapyridine was not followed by any improvement, nor did it prevent the onset of carditis. Cyanosis was marked and vomiting was troublesome during the period in which the drug was used, and the case was complicated further by the occurrence of acute nephritis.

CASE 3.—G. I., aged twenty-one. Two days before admission he suffered from pain and swelling in his right wrist joint. The following day the pain and swelling spread to his left wrist and finger joints, and he reported sick. There was no previous history of rheumatic fever. On admission, both wrist joints and the interphalangeal joints of his left hand were swollen and tender, and the patient's temperature was elevated to 99.6°F. Colsulanyde 2 gms. four-hourly was prescribed, and this drug was continued until a total of 18 gms. had been given. No improvement followed; new joints became involved and low-grade pyrexia continued. Carditis did not ensue. Apart from cyanosis, no toxic manifestations followed the use of the drug. At the end of a month, when it became necessary to transfer the patient to another hospital, there was still evidence of rheumatic activity in the shape of a raised blood sedimentation rate.

Comment.—As compared with several similar patients in the ward, it was not felt that this patient derived any benefit from his treatment. Carditis did not occur, but neither was this complication found in a number of similar cases which had been treated with salicylates.

CASE 4.—E. G., aged twenty. Admitted to hospital with a history of having suffered from a sore throat for one day. No previous history of note was elicited. On admission to hospital, temperature was 103.2°F. and pulse rate 120. Fauces were grossly inflamed, and the left tonsil was covered with a yellowish exudate. A throat swab yielded hæmolytic streptococci. There was little change in the patient's condition during the next two days; both pyrexia and tachycardia persisted, and his throat remained sore, inflamed and septic. On the third day of his illness he complained of pain in his left wrist joint, which on examination was found to be swollen, inflamed and tender. At this time there was pyrexia of 103.5°F. and a pulse rate of 120. Colsulanyde therapy was instituted, 2 gms. being given four-hourly. On the following day the patient's temperature had dropped to 99.4°F. , with a pulse rate of 100, and his throat was much easier. No improvement, however, was noted in his wrist joint. Following this, the typical rheumatic picture with low-grade

pyrexia and fleeting polyarthritis presented itself, and on the eighth day of the patient's illness signs of carditis were noted for the first time. At the end of a month, when he was transferred to another hospital, signs of carditis were still present.

Comment.—This patient developed acute rheumatism during an attack of streptococcal tonsillitis. A full course of 20 gms. of sulphanilamide failed to ameliorate the symptoms or to prevent the onset of carditis.

CASE 5.—S. S., aged nineteen. Admitted to hospital with a history of having suffered from fleeting joint pains for several days. There was a history of an attack of rheumatic fever five years previously, with a recrudescence of activity three years later. On the second occasion the patient was ill for five months, and his heart was mentioned during the course of his illness. Following this bout, he was advised to avoid strenuous exercise, but he stated that he was able to cycle eighty to a hundred miles in a day without any fatigue or distress. On admission to hospital, temperature was 100° F., pulse rate 100, and there was polyarthritis affecting both elbow joints, the left ankle joint and the interphalangeal joints of the left hand. In addition there was evidence of cardiac involvement with left ventricular enlargement (apex beat in the fifth space, 15 centimetres from the middle line), a forcible cardiac impulse, and the characteristic bruits of aortic incompetence. In the hope of limiting the attack, colsulanyde was prescribed in doses of 2 gms. four-hourly. The patient's condition remained unaltered for forty-eight hours, but at the end of that time he complained of præcordial pain. The following day signs of pericarditis were present, and twenty-four hours later a diagnosis of pericardial effusion was made. This was confirmed radiologically. There followed a stormy illness, with numerous recurrences of pyrexia and polyarthritis in addition to the cardiac complications. Sulphanilamide therapy was discontinued when a total of 18 gms. had been given.

Comment.—Sulphanilamide failed to alter the course of a rheumatic recurrence, failed to prevent the onset of pericarditis, and was without any beneficial effect in this complication.

CASE 6.—M. A., aged eighteen. Admitted with a two days' history of stiffness in his legs and gradually increasing pain in both knee joints, left foot and right wrist. He gave a history of having had a severe attack of tonsillitis a month previously. On admission, there was pyrexia of 101.6° F., with a pulse rate of 104, marked sweating, and polyarthritis affecting both knee joints and the left ankle joint. Sulphapyridine 2 gms. four-hourly was prescribed. Pyrexia, tachycardia and polyarthritis continued, and on the third day of the patient's illness signs of carditis were noted. The drug was withdrawn when a total of 20 gms. had been given, and sodium salicylate in maximal doses was substituted in its place. Following this the patient's temperature fell to normal and his arthritis subsided. During the next six weeks there were several minor recrudescences, with short bouts of a low-grade pyrexia coupled with polyarthritis. Evidence of carditis was still present when the patient was sent to another hospital at the end of seven weeks.

Comment.—Sulphapyridine failed to benefit a case of acute rheumatism which responded promptly to salicylate therapy. Nor did the drug prevent the onset of carditis.

CASE 7.—C. S., aged sixteen. Admitted with a two days' history of pain and swelling in his right foot and ankle. He gave a history of an attack of sore throat two months previously. On admission, there was pyrexia of 99.2° F., with a pulse rate of 116, and arthritis of the right ankle joint was found to be present. Colsulanyde in 2-gm. doses four-hourly was prescribed, and was continued until a total of 32 gms. had been given. The patient continued to suffer from fleeting polyarthrititis, an irregular low-grade pyrexia persisted, and the pulse rate remained unduly high. On the tenth day of his illness his temperature was still 100° F., with a pulse rate of 112, and joint pains and swellings were still present. Two months later there was evidence of continued rheumatic activity in the shape of a raised B.S.R. (corrected B.S.R. 26 mm. at one hour), and tachycardia still persisted.

Comment.—Thirty-two gms. of sulphanilamide had no effect on the course of a case of acute rheumatism, nor did it prevent the onset of carditis as shown by persistent tachycardia.

CASE 8.—T. F., aged seventeen. Admitted with twenty-four hours' history of a sore throat and pains in his elbow joints. There was no history of any previous attack of rheumatism. On admission there was pyrexia of 100° F., with a pulse rate of 88, slight faucial inflammation (a throat swab yielded no hæmolytic streptococci), and arthritis of both elbow joints. Colsulanyde was prescribed and was continued until a total of 34 gms. had been given. Pyrexia continued for four days and fleeting arthritis for six days, at the end of which time the patient was afebrile and symptom-free. A week later there was a recurrence of activity with pyrexia and arthritis, and this bout continued for a further eight days. Signs of carditis were noticed during this bout, and two months later examination of the heart showed left ventricular enlargement with systolic murmurs at the apex and base.

Comment.—A full course of sulphanilamide failed to influence the course of a typical case of acute rheumatism, or to prevent the onset of carditis.

CASE 9.—J. J., aged eighteen. Admitted with forty-eight hours' history of generalised body stiffness and pains in both knee joints. On admission there was pyrexia of 101° , with a pulse rate of 120, sweating, and polyarthrititis affecting both knee joints and the left ankle joint. Sodium salicylate in 20-grain doses four-hourly was prescribed. Fever and polyarthrititis continued for three days, but then responded to salicylate therapy. A week later there was a recurrence of pyrexia and polyarthrititis; this bout in its turn responded to salicylates, and when it had ended colsulanyde in 1-gm. doses four-hourly was prescribed, in the hope that a further recrudescence might be prevented. Four days later a further recurrence, with pyrexia of 101° F. and polyarthrititis, manifested itself. The dose of colsulanyde was increased to 2 gms. four-hourly, but no improvement followed. On the contrary, there was continued pyrexia, all joints of the upper and lower limbs became affected in turn, and signs of acute carditis were noted. Sulphanilamide therapy was continued for another three days, at the end of which time it was stopped, as it was obvious that the patient, instead of improving, was getting worse. There followed a protracted illness with numerous recurrences of pyrexia and arthritis, together with severe pancarditis. At the end of three months,

when the patient was transferred to another hospital, he was still being nursed as a strict bed case; evidence of severe pancarditis was still present, and the corrected B.S.R. was 26 mm. at one hour.

Comment.—Sulphanilamide failed to prevent a rheumatic recurrence, and had no beneficial effect on the recurrence that took place.

CASE 10.—T. P., aged seventeen. Admitted with three days' history of vague pains in his ankle joints. On admission there was pyrexia of 101° F., with a pulse rate of 92, sweating, and arthritis affecting both ankle joints. Sulphapyridine 2 gms. four-hourly was prescribed. Pyrexia, tachycardia and fleeting polyarthritis persisted, and sulphapyridine was discontinued when a total of 18 gms. had been given. Salicylate therapy was substituted in its place, and the use of this drug was followed by rapid improvement. Signs of carditis were noticed at the end of ten days' illness, and at the end of three months' illness, when the patient was transferred to another hospital, examination of the heart revealed left-sided enlargement with systolic murmurs at the apex and base.

Comment.—This case is comparable to Case No. 1. No improvement followed the use of sulphapyridine in a case of acute rheumatism, nor was the onset of carditis prevented.

CASE No. 11.—H. F., aged twenty. Admitted with acute bronchitis. During the course of his illness typical acute rheumatism with pyrexia, sweating, and polyarthritis developed, and was treated with sodium salicylate. Carditis appeared a week after acute rheumatism was first diagnosed. Three weeks later sulphapyridine 1 gm. T.D.S. was prescribed, in the hope that a recurrence might be prevented. Four days afterwards there was a recrudescence of activity with pyrexia and arthritis; the dose of sulphapyridine was increased to 2 gms. four-hourly, but the symptoms persisted. The drug was withdrawn when a total of 22 gms. had been given; salicylates were reinstituted, and, following this, pyrexia and arthritis subsided.

Comment.—Sulphapyridine failed to prevent a rheumatic recrudescence or to influence the course of the recrudescence that did appear.

CASE 12.—H. J., aged eighteen. Admitted with a history of pain in both feet and both knees of forty-eight hours' duration. On admission he was afebrile, with a pulse rate of 84, and there was arthritis affecting both ankle joints and the right knee joint. Sulphapyridine 2 gms. four-hourly was prescribed. Following this, his temperature rose to 101° F., with a pulse rate of 104, and fleeting polyarthritis persisted. The pyrexia and local symptoms continued unabated during the next few days, during which time sulphapyridine was persevered with. When a total of 22 gms. had been given, the drug was discontinued and salicylate therapy was substituted in its place. This was followed by rapid improvement; the patient's temperature fell to normal within three days, and his arthritis cleared up. At the end of a month, when it became necessary to transfer him to another hospital, his pulse was still unduly rapid, but no other signs of carditis were noted.

Comment.—Twenty-two gms. of sulphapyridine was given without beneficial effect in a case of acute rheumatism, which responded rapidly to salicylate therapy.

DISCUSSION

Perusal of these case notes will show that in no instance did sulphanilamide or sulphapyridine have any beneficial effect on the rheumatic process. The use of these drugs was not followed by any fall of temperature, polyarthritis was not relieved, and the onset of carditis was not prevented. Although full doses of the drugs in question were given, toxic reactions to their use were not troublesome. A degree of cyanosis was apparent in most patients; vomiting was troublesome in two of the sulphapyridine-treated cases, but apart from this no anxiety was caused. Leucopænia did not develop in any case; on the other hand, the leucocyte count tended to rise rather than to fall.

CONCLUSIONS

(A) STREPTOCOCCAL TONSILLITIS.—1. A series of forty-nine sulphanilamide- or sulphapyridine-treated cases is compared with fifty controls.

2. No beneficial effect followed the use of these drugs in the treated series of cases. As compared with the control group there was no shortening of the period of pyrexia, of the duration or severity of the local manifestations, or of the period of hospitalisation.

3. The incidence of complications was found to be greater in the treated group than in the control group.

4. That streptococcal tonsillitis can develop in patients already undergoing intensive sulphapyridine treatment is shown by the occurrence of two such patients in this series.

5. The carrier state was not influenced by the use of these drugs.

6. Toxic reactions to the use of these drugs were not found to be troublesome.

(B) ACUTE RHEUMATISM.—1. A series of twelve cases of acute rheumatism was treated with sulphanilamide or sulphapyridine. Of these, nine were patients suffering from their first attack and three were patients suffering from recrudescences.

2. In no case was the use of these drugs followed by any fall in temperature or amelioration of arthritis.

3. The withdrawal of these drugs and the substitution of salicylates in their place was followed by immediate improvement.

4. Carditis was not prevented.

5. Toxic reactions to the use of the drug, other than cyanosis, were not found to be troublesome.

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