THESIS FOR DEGREE OF M.D.

A STUDY

of the

AETIOLOGY AND SYMPTOMATOLOGY

of

"SCARLATINAL RHEUMATISM"

By

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The articular manifestations of a rheumatic character which appear in the course of Scarlet Fever shew considerable differences from those found in the acute specific disease of bacterial origin which we know as "Acute Rheumatism" or "Rheumatic Fever". They do not declare themselves with the same frequency as affections of the larger joints with much effusion and profuse sweating, nor does the natural course of an attack of Scarlatinal Rheumatism tend to be so long as that of Rheumatic Fever, while, in most instances, it does not seem to be cut short, nor do the pains associated with it seem to be relieved by the exhibition of the Salicylates. Endocarditis, moreover, does not occur in Scarlatinal Rheumatism as a complication or as a sequela, with the same frequency as in Acute Rheumatism.

Arthritis in the course of Scarlet Fever is of two kinds - the "rheumatic" form which is the subject of this paper, and an acute infective form which is accompanied by swelling and oedema round the affected joint, and which

usually results in a purulent effusion into the joint, leading to destruction of tissue and necessitating surgical interference. It is to be noted that the destruction of tissue in an acute infective arthritis in Scarlet Fever is not so great as that observed in similar infective joint processes apart from the incidence of the Scarlatina, and the prognosis, as far as the local condition is concerned, with regard to complete recovery of function, is distinctly favourable. From the peri-articular tissues and from the purulent effusion into the joint in this infective form of arthritis, a streptococcus is always recoverable. But by far the greater number of attacks of arthritis in Scarlet Fever are of the "rheumatic" type, not associated with any oedema of the peri-articular tissues, while if an effusion into the joint be present at all, it is serous in character and not purulent, and is, in the cases which I have examined, sterile on cultivation. Many cases of Scarlatinal Rheumatism proceed with no effusion into the joints which present no other abnormal feature than a little peri-articular fibrous thickening which may persist for some time after the acuter manifestations have passed off, and which in some cases may lead to permanent slight enlargement of the joints. Pain is a notable feature of the rheumatic affection, and is pres-

ent, as a rule, in excess of the visible affection of the joints. This is in striking contrast to the comparatively painless character of the acute suppurative lesions in Scarlet Fever, affecting both joints and bone, which are curiously free from either pain or tenderness.

The time in the course of Scarlet Fever at which the rheumatism appears is variable, and, according to the early or late appearance of the articular manifestations, the character of the arthritis is somewhat different. In the majority of cases the rheumatism appears during the first fortnight of the attack, but it also appears with considerable frequency during the third, fourth, fifth and sixth weeks of the disease, and occasionally as late as the seventh, eighth or ninth week.

I have analysed for the purposes of this paper the cases of Scarlatinal Rheumatism which occurred during the seven years 1901-1908 in the Glasgow Fever Hospital at Belvidere. The cases amounted to 137 in all, and of these 101 or about 73.7% began in the first fortnight of the attack of Scarlatina. The following table shews readily the incidence of the rheumatism in the various weeks of the disease:-

TABLE I

OCCURRENCE of Rheumatic Arthritis in weeks of attack of Scarlet Fever

In 1st week	48 Cases
" 2nd "	53 "
" 3rd "	8 "
" 4th "	7 "
" 5th "	9 "
" 6th "	7 "
" 7th "	3 "
" 8th "	1 "
" 9th "	1 "
	137 cases

According as the rheumatism appears early or late in the course of the disease, there is considerable difference in the groups of joints involved. In the "early" cases a greater proportion of the smaller joints are involved than in the "late" cases, while in the "late" cases the larger joints are involved in a greater degree than the smaller. Taking wrists and fingers as an example of the smaller joints, and elbows and knees as examples of the larger joints, the following table shews in what pro-

portion the larger and smaller joints are affected in the various week-periods during which the rheumatism has its onset.

As in the arthritis of Acute Rheumatic Fever, it is usual to find more than one joint or set of joints involved, and the figures given in the table are the percentages of one set of joints or another out of all joints affected in the particular week-period under consideration.

TABLE II

PROPORTIONATE INVOLVEMENT of fingers, wrists, elbows and knees in various week-periods expressed in percentages of all joints attacked

	Fingers	Wrists	Fingers & Wrists	Elbows	Knees
In 1st week	13.67%	31.63%	45.3%	19.65%	11.1%
In 2nd week	10.8%	25.2%	36.0%	17.0%	17.%
In 3rd week	10.57%	18.83%	29.4%	17.65%	23.53%
In 4th week	6.6%	13.4%	20.0%	20.0%	33.33%
In 5th week	0.0%	23.0%	23.0%	14.28%	28.56%
In 6th week	7.92%	7.46%	15.38%	15.38%	30.77%

From this table it is seen that as the incidence of the rheumatism falls later in the attack of Scarlatina there is a gradual increase in the percentage of the larger joints involved, while there is a corresponding decrease in the frequency with which the smaller joints are attacked.

The severity of the attack, also, varies a good deal with the time of onset of the rheumatic symptoms. The "early" cases tend on the whole to be more severe than the "late" cases, not only in respect of duration but in acuteness. They tend more frequently to shew fluid effusion into the joints, the accompanying fever is higher, and the pain is more severe. The cases occurring in the first fortnight of the attack of Scarlet Fever appear, as a rule, after a severe initial fever and other scarlatinal manifestations of a severe kind. The condition of the throat is usually of the graver type, and there is frequently an early adenitis present in the cervical region. In many cases there is no defervescence of the temperature at the time when this might normally be expected to occur, while in others the usual lysis towards the end of the first week is not completed, but the curve is caught up again by an exacerbation more or less severe, which is the accompaniment of the rheumatic attack. In 41 cases out of the

101 which appeared in the first fortnight, there was, besides the rheumatic attack, some one or another of the usual complications of Scarlatina, viz., otitis media, cervical adenitis occurring about the usual period of normal defervescence, or an anginous condition of the throat, with much sloughing and ulceration of the tonsils. Such complications occur immediately before, during, or shortly after the attack of rheumatism without any definite rule, save that cervical adenitis and sloughing of the throat tend rather to precede or run together with the arthritis, while otitis media tends to occur towards the time of subsidence of the joint symptoms. In one case, the arthritis, which was mild, was followed at the beginning of the third week of the disease by a well-marked acute nephritis with much blood in the urine. The "early" cases frequently have a severe myalgia as an accompaniment of the arthritis.

In the majority of the "late" cases the initial attack has been mild, terminating in a normal way without any great inflammation of throat and without any early adenitis. As a general rule, too, the arthritis is the only complication. The attack is mild, the joint affections being slight, and the temperature elevated but little above the normal. This remark holds even when the arthritis lasts over a considerable number of days or even

weeks. The longest duration of a "late" case observed was 24 days. In this case the knees and elbows were affected in a very mild degree. There was but little pain or tenderness in the joints, no effusion was apparent, and the temperature never rose above 100° F. In three of the "late" cases observed, however, the arthritis was severe and acute, accompanied by high fever. One of these cases occurred in the 4th week of the disease after a very mild initial attack of Scarlet Fever, and was followed by a severe otitis media which gave rise to an acute mastoiditis, for which a radical operation had to be performed. In another, occurring in the 5th week, the arthritis was prolonged over a period of 17 days, and was accompanied by a secondary tonsillitis of considerable severity. The case terminated fatally in the 79th day from cardiac failure, a well-marked lesion of incompetence having developed at the mitral valve on the 39th day. In the third case, where the rheumatism began in the 8th week, it was accompanied by a moderately severe secondary tonsillitis.

In one "late" case, where the arthritis began in the 9th week of the disease and lasted for only three days, the initial fever had been severe and prolonged, but the case was complicated by an acute dry pleurisy, which was present from the 3rd to the 20th day of illness.

As exceptions to the general rule that in the "early" cases of rheumatism the initial attack is severe, may be quoted 18 cases occurring in the first fortnight of the fever when the initial manifestations of the Scarlatina were very slight, with short fever and mild throat affection. In three of these, cervical adenitis developed as a complication shortly after the beginning of the arthritis, and in one a mammary abscess developed as a late complication. In this last case the woman had been suckling a child until the onset of the Scarlatina. In the other 14 cases no complication other than the arthritis was present. None of the 18 cases had prolonged or severe arthritic manifestations.

Only two out of the whole 137 cases terminated fatally. One died on the 20th day, having developed a cervical adenitis on the 6th day and a double otitis media on the 14th day. The rheumatism began on the 8th day. The other fatal case is the one previously mentioned who died on the 79th day of illness, having developed a mitral lesion on the 39th day. The rheumatism developed in the 5th week. This child took a secondary tonsillitis on the 63rd day of illness, which was ushered in by severe vomiting. The tendency to vomiting persisted, and the child died from cardiac failure. The urine was albuminous for a week be-

fore death, but this was evidently the result of the cardiac failure and not of any toxaemia directly due to the attack of Scarlatina. There was no evidence of the mitral lesion being of an ulcerative character.

Besides this case, two others developed systolic murmurs heard best at the mitral area. In one of these cases where the murmur was heard first on the 20th day, there was no doubt that the lesion was organic, but in the other, where the murmur developed on the 8th day, it was so faint and so limited in distribution even on dismissal that there is reasonable ground for doubting its having been of organic origin, the more so as there was at no time any enlargement of the heart to be made out, and no accentuation of the pulmonic second sound, while the child was, on the defervescence of the initial attack, notably anaemic, and remained so during the whole of his convalescence which, however, was not unduly prolonged.

Treatment by the salicylates was resorted to in a certain proportion of the cases, but the treatment was not followed by such results as to recommend it, particularly in the "early" cases. The number of cases observed is perhaps too small to enable one to draw any absolute conclusion from the results obtained by treatment, but the following table shews the duration of the rheumatic

attack in cases which were treated by the Salicylates, and in cases which were either treated only by means calculated to insure increased elimination by the ordinary channels or by such means combined with local sedative applications. In the table, those to whom Salicylates were given are called "Treated Cases".

TABLE III

Week	No. of cases in all	Aver. duration	Shortest	Longest	No. of cases "Treated"	Aver. duration	Shortest	Longest
		Days				Days		
1st	48	8.27	1	55	15	13.66	2	55
2nd	53	7.41	2	25	29	10.34	2	25
3rd	8	9.125	4	24	4	6	4	8
4th	7	6.28	3	11	4	6.28	3	10
5th	9	6.66	2	17	3	5.63	2	8
6th	7	7.57	3	24	2	13.5	3	24
7th	3	4.66	3	8	2	5.5	3	8
8th	1	4	-	-	-	-	-	-
9th	1	3	-	-	1	3	-	-

A bacteriological examination was made in all cases when it was possible for me to do so, but unfortunately

it was not within my power to make such an examination in all the cases. A careful examination was, however, made in 27 of the 137 cases observed, the method adopted being the puncture of affected joints and the withdrawal of what fluid was possible, while at the same time two cultures were made from the blood which was withdrawn from a vein in the arm, after laying it bare by an incision, by means of a sterilised syringe. In no instance was blood withdrawn by piercing the skin with the needle of the syringe; 2 c.cm. of blood were used for each culture. The blood was incubated in bouillon at 37° C. in the first instance for 24 hours, and sub-cultures were made on glycerin agar and blood-serum. The same methods of cultivation were employed in the case of the fluid withdrawn from the affected joints. The only antiseptic means used in the preparation of the skin were the scrubbing of the surface with turpentine and methylated spirit after careful washing with soap and water. The syringe, needle and scalpel employed were boiled, and taken out of the sterile water just before using.

Two-thirds of the cases examined were "early" cases, occurring between the first and second weeks of the disease, and the onset of the Scarlatina was in all cases severe, with marked throat affection.

The examination was made on the second day of the rheumatic in all the cases "early" and "late", and the joints punctured in the "early" cases were the metacarpo-phalangeal joints which happened to be affected.

The other third of the cases examined were "late" cases, which occurred at the end of the fourth and beginning of the fifth week, and in each instance the knee-joint contained fluid and was punctured.

The result of the bacteriological examination was similar in all cases. The blood cultures were sterile, and the only organisms which grew after cultivation from the joints were, in one of the "early" cases, a few colonies of staphylococcus albus, and, in two of the "late" cases, a few colonies of a large coccus which was evidently due to a contamination of the needle by the skin.

Any attempt to draw final and definite conclusions from a limited number of bacteriological examinations which have yielded negative results is, of course, rightly subject to adverse criticism, and the number of cases examined bacteriologically in this series are admittedly too small to warrant any definite statement being made from their results alone. But the results are of sufficient value to be used as confirmatory evidence in favour of the idea which I wish to maintain, namely, that the

arthritis of a rheumatic type which occurs in Scarlet Fever is not due to a direct invasion of the blood or joints by micro-organisms, but is due to the action of toxins elaborated at a distance from the part affected by micro-organisms which are not in direct communication with the general circulation.

That inflammatory processes may be set up during the course of Scarlet Fever without a direct invasion of the organ implicated by micro-organisms has already been shewn by my former colleague in Belvidere, Dr. Andrew Love, who has not yet, unfortunately, been persuaded to publish his results. His investigations were in the direction of endeavouring to discover if the presence of streptococci in the urine of persons suffering from Scarlatinal Nephritis, which has been frequently stated as a fact, could not be due to contamination of the urine in its passage through the meatus to the vessel held for its reception. He accordingly made cultivations from some 30 patients who were the subject of Scarlatinal Nephritis, the urine being withdrawn by catheter after careful sterilisation of the meatus. The urine so withdrawn was cultivated on agar and incubated at 37° C. for 24 hours. All the cultures made from the urine in this way were absolutely sterile.

If, then, the rheumatism of Scarlet Fever is to be regarded as not due to the presence of micro-organisms in the blood and in the joints, it is necessary to seek for proof of this idea in some rheumatic condition which is known and recognised to be produced by the action of toxins on the organism without the presence of bacteria in the general circulation. Such an analogy can, I think, be found in the rheumatic arthritis which is sometimes the result of the injection of any of the anti-toxic sera presently in use which are derived from the horse.

In the course of the first small epidemic of Plague in Glasgow in 1900, I and the other members of the staff at Belvidere were injected with Yersin's plague serum as a protective measure. We were unable to take any particular care of ourselves at the time either in the way of rest or diet, and, besides the ordinary effects resulting from the injection of horse-serum, viz., urticaria, local and general, with some slight headache and nausea, four of us suffered, at the end of an incubation period which varied in individuals between eight days and a fortnight, from moderately severe articular pain and swelling and even, in one instance, from effusion into a joint with slight rise in temperature. Professor Zabototny of St. Petersburg, too, who had been repeatedly injected with

Yersin's serum as a protection against plague, presented all the features of chronic rheumatism in the way of pain in various joints, with peri-articular thickening and deformity of certain of his joints, notably the fingers and knees, in which distinct crepitation of a fine kind was to be found.

Although rheumatic attacks are uncommon after the injection of serum for the cure of Diphtheria, when the patients are strictly confined to bed and are on a limited dietary, while special attention is being paid to their eliminative functions, I have had four such cases under my observation at different times, and, while two of the cases suffered only from slight pain and very moderate fever, in the other two cases the attacks resembled in severity Rheumatic Fever. The onset was sudden and sharp, the joint pains were severe, the affected joints were swelled and, although much of the swelling was peri-articular, there was quite definite effusion into the knees. In one case the attack ran a moderately severe course for ten days and then rapidly subsided, but in the other, two relapses occurred after the first attack had passed off, and the patient did not recover from the effects of the serum until many weeks had elapsed. In none of these cases was the exhibition of the salicylates of

any service in the alleviation of pain. Further, it is quite common to have articular manifestations after the injection of anti-diphtheritic serum for purposes of prophylaxis, where the patients are not at rest but are living an ordinary life. In such cases the smaller joints are particularly liable to be affected, and the patients complain also of myalgia which is, at times, very severe.

It seems to be a reasonable hypothesis that when a toxin is introduced into the organism, as occurs when horse serum is injected into the human body, anti-bodies are produced which are allied to, but not identical with, those substances which induce precipitin formation, and that these bodies are responsible for the so-called "serum reaction" which is found in such varying degrees of severity in those who have been treated by the diphtheria or plague antitoxin. It may be that the anti-bodies are elaborated in some instances in excess of requirement and may themselves act as toxins towards certain tissues, or it may be, as seems more likely, that the toxin which produces the reaction is the resultant of the interaction of the injected toxin and its anti-body. Why it should produce symptoms in one man and not in another is difficult of explanation save on the supposition that in most

instances the anti-body is brought gradually into existence and, uniting with its exciting toxin, gradually frees a toxic product which is the result of the combination, in such quantities that it is eliminated easily, without disturbance of the organism. On this hypothesis it is easy to understand how in the case of an unusually quick response to the irritation of the toxin, anti-body may be produced in such quantity that the union of toxin and anti-body sets free such an amount of toxic product as is beyond the eliminative power of the individual, with the result that the tissues for which the toxic product have an affinity are attacked in proportion as they are most readily susceptible and an urticaria or an arthritis is the result.

As in the case of "serum disease" so it may be in Scarlet Fever. It is a notable fact that in the majority of the "early" cases of Scarlatinal Rheumatism the initial attack is severe, but at the same time it is equally evident, from the mortality rate in the cases quoted, that the patients have all been capable of good reaction to the invading toxins. It is thus credible that the "early" cases of Scarlatinal Rheumatism may be due to the elaboration of a toxic product, which is the result of an inter-

action between a toxin and its anti-body, in such quantity that it is incapable of rapid elimination by the organism and which, remaining in the body, acts as an irritant towards those tissues for which it has an affinity, namely, the serous membranes of the joints and the fibrous tissue which surrounds them. On this hypothesis, also, it is possible to account for the "early" cases which are not preceded by a severe onset of the Scarlatina. In these cases it may be reasonably supposed that, although there is no excessive freeing of toxic product, yet the eliminative power of the individual may be of such low value that it cannot readily dispose of even the moderate amount of toxic product which it is called upon to deal with, and thus a certain quantity remains in the circulation and, fixing upon the susceptible tissues, causes the arthritis. Again, these "late" cases which are not accompanied by any other complication or evidence of re-infection may be accounted for in precisely the same way as those "early" cases which follow on a mild initial attack of Scarlatina. We have evidence in the relapsing cases of serum rheumatism that toxin and anti-body may go on producing toxic substance for long periods. Similarly this may occur in Scarlet Fever, and it only needs some influence to be brought to bear on the organism which will

limit its eliminative capacity to provide all the materials necessary for the production of a rheumatic attack. Those "late" cases which are accompanied by a secondary tonsillitis or a late adenitis or some other infective complication of Scarlet Fever fall naturally into the same group as the "early" cases which follow an acute scarlatinal onset.

This, then, is the position which I seek to maintain - that Scarlatinal Rheumatism is an arthritic manifestation due, not to a bacterial infection of joints as in the case of Rheumatic Fever or Gonorrheal Rheumatism, but due rather to a toxic product which results from the interaction of a toxin elaborated by the infecting microorganism, whatever it may be, and its corresponding antibody; that the occurrence of the arthritis depends on the body's incapacity for eliminating this toxic product, whether the eliminative deficiency be due to great excess and rapidity of toxic-product-formation, or to an eliminative capacity on the part of the organism which is less than normal. And in support of this idea I adduce the facts that the arthritis differs in all respects from the arthritis in Scarlet Fever which is known to be of bacterial origin; that it differs in important details from the manifestations of acute Rheumatic Fever; that bacter-

iological examination of the blood and of affected joints has yielded me negative results; and that it bears a very close resemblance to that variety of Rheumatism which is recognised to be of toxic and not bacterial origin - the Rheumatism which is produced by the injection into the human body of anti-toxic sera which are derived from the horse.

APPENDIX

As an appendix to this paper I should like to quote the history of four cases in which rheumatic arthritis was present in conjunction with a bacterial infection which appeared to be localised, and in which the arthritis might be with reason considered to be of toxic origin.

CASE A - Female, aged 53, who had suffered from a chronic rheumatic affection of the finger joints for some years was found to be the subject of a chronic senile endometritis. This was dealt with successfully and the patient has not suffered since then from any active manifestations in the joints, although, from previous attacks, there is still some thickening of the

joints of the fingers.

CASE B - Precisely similar to Case A, save that the woman was 49 years of age. The cure of the endometritis was followed immediately by the cessation of the rheumatism. In this case and in Case A there was no question of the possibility of gonorrhea. Both women were elderly unmarried ladies of good repute.

CASE C - A young woman, aged 28, who was the subject of a moderate degree of puerperal septicaemia, suffered for some days from pain and swelling in the right wrist and finger joints accompanied by considerable myalgia in arms and back. The joint symptoms appeared as local infection began to pass off.

CASE D - A young woman, aged between 25 and 30, was brought under a surgeon's notice suffering from a double pyosalpinx. When operated on, all the joints of the fingers of both hands were painful, tender and enlarged, and in some instances even reddened. Within 24 hours after the operation, which was successful in curing the patient, all traces of pain, tenderness and swelling had disappeared from the fingers.

Case B was the only case in which I was able to conduct a bacteriological examination of the blood, but in this case I examined the blood on three successive days, using the same technique which I used in the cases of Scarlatinal Rheumatism, and on all occasions the results were negative.
