EXPERIMENTAL ARTHRITIS IN THE RABBIT. A CONTRIBUTION TO THE PATHOGENY OF ARTHRITIS IN RHEUMATIC FEVER.

By HAROLD KNIEST FABER, M.D.

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The significance of experimental arthritis in the rabbit has for many years been a matter of dispute. This may be attributed to the lack of data bearing upon the mechanism involved in the production of the lesions. It may be of interest to scrutinize the literature for facts which may relate to the conditions under which arthritis is, or fails to be, produced.

The first to produce arthritis in animals with pure cultures of streptococci was Loeffler (1), who published his results in 1884. Making cultural examinations of the exudate in the throats of patients with scarlet fever and diphtheria he isolated, besides the bacillus which now bears his name, several strains of streptococci, or micrococci, as he called them. Two of these strains, one from a fatal case of scarlet fever, the other from a fatal case of diphtheria, produced suppurative arthritis upon intravenous inoculation in 9 out of 12 rabbits. With Fehleisen's original strain of *Streptococcus erysipelatis* and by the same method he then produced a similar arthritis in 2 out of 3 rabbits. Smears from the pus in all cases showed abundant organisms and cultures made from 13 of them showed growth in 4, or 30 per cent—a high figure, considering the relatively crude methods employed. Most of the rabbits died.

Attention is called to the following points in Loeffler's work. There was between the time of injection and the development of arthritis an incubation period of 4 to 8 days, during which the animals were apparently normal. Arthritis followed only those injections which were given intravenously. Subcutaneous injections were followed by local infection usually ending in death without the evolution of joint lesions. The cultures, as shown by the mortality, were highly virulent. The infecting organism could be easily demonstrated in smears from the joint exudate and in a considerable percentage the cultures were also positive.

The streptococcus isolated by Wassermann (2) gave similar results, though it was probably not so virulent. The results are not reported in detail.

The diplococcus of Poynton and Paine (3) produced arthritis in 4 out of 9 rabbits injected (original report). The incubation period was 2 to 4 days. Two of the affected rabbits died on the 10th and 20th days, respectively, and two were killed. Only one recovered. Smears and cultures from the joint exudate were constantly positive. Here again the strain was evidently highly virulent.

Meyer (4) cultivated streptococci from tonsillar crypts of patients with rheumatic fever and produced arthritis in rabbits with these strains. The incubation period was 6 to 8 days and it was usually possible to demonstrate the organisms in numbers by smear and culture. Protocols and details are lacking.

Cole (5) in 1904 made a more careful study of experimental streptococcal arthritis. Using several strains isolated from widely varying conditions he produced with all a definite arthritis in rabbits,—also by intravenous inoculation. The organisms could usually be easily demonstrated in the joint exudate by smear and culture.

The most careful study of the one injection arthritis produced with virulent streptococci was made by Jackson (6). Using a highly virulent streptococcus isolated from the milk epidemic in Chicago she studied the joint reaction histologically at different periods after the injection. This report shows that 2 hours after injection streptococci could be found in the vessels of the periarticular tissues, that at 10 hours intravascular collections of leucocytes were present, while at 24 hours exudation and migration of leucocytes into the joint cavity had occurred. There is then a refractory period following the arrival of organisms at the joint during which no evident inflammatory reaction occurs, and this we may call the incubation period. It must be inferred that this reaction depends for its promptness and severity upon the virulence of the infecting organism. This is in accordance with the experiments of Dreyer (7) who found that the degree of reaction after injection of organisms into the joint of the rabbit is a good measure of their virulence. The point of most interest to us in Cole's paper is, however, the fact that two of his rabbits, inoculated with a less virulent strain, developed arthritis only after a second injection. In one of these rabbits smears and cultures were negative from all the affected joints except one and in this both smear and culture were positive. In several of the other animals spontaneous recovery occurred and in these Cole was able to provoke a relapse by another intravenous injection of the same organism. One attempt to cause a relapse with another strain of streptococcus failed.

Shaw (8) in 1904 and Schloss and Foster (9) in 1913 found that in monkeys arthritis occurred only after the second intravenous injection. Rothschild and Thalhimer (10) in 1913 note in their protocols that several of their rabbits with arthritis following intravenous inoculation of *Streptococcus mitis,* a slightly virulent organism, received five and six injections. In about one-third of these, cultures from the joint were positive.

It appears, then, that according to the virulence of the streptococcus used and possibly also according to the variety, two types of reaction may occur after intravenous inoculation. In one type, produced by streptococci of high virulence, the joint is attacked after the first injection. It is to be noted, however, that even in these instances a period of incubation is always observed. In this type of reaction cultures and smears from the affected joint are usually positive and the organisms are present in considerable numbers. In the second

type of reaction for which less virulent streptococci are used, no demonstrable joint lesion follows the first injection but a very definite arthritis does follow the second or, as will be shown, a still later injection. In other words the development of arthritis in these cases is conditioned probably upon some anterior process set up in the affected joint. In this type, cultures and smears from the joint frequently show no bacteria and, if bacteria are found, they are in much smaller numbers than in instances of the first type.

The number of definitely controlled and carefully reported experiments bearing upon the second type of reaction is quite small. A larger series is reported below.

In 1913 a Belgian investigator, Herry (11), reported a series of experiments which indicated the existence of a third type of reaction. In a remarkably large number of cases of rheumatic fever he was able to isolate a streptococcus from the blood or articular exudate. From this organism he obtained by a process of extraction with normal saline, desiccation, trituration, reextraction, and centrifugalization, an endotoxin soluble in water. By injection of this into the joint followed by an intravenous injection of the living organism 8 to 15 days later he was able to produce constantly in rabbits a definite arthritis in the joint originally treated. Cultures and smears from the joint were positive for about a week after the intravenous injection. Those experiments throw a clearer light upon the process of joint localization, but unfortunately they suffer from incompleteness.[1]

EXPERIMENTAL.

Experiments were therefore instituted with the object of treating joints with streptococci so that they might be more reactive to later intravenously injected streptococci and with the hope that arthritis might be made to localize in the joint so treated. It was thought that if this could be done the mechanism of joint localization might be partly explained.

[1] I have attempted without success to repeat Herry's experiments with extracts of the *S. mitis* used for the other experiments in this paper. Herry's method calls for the use of the supernatant fluid of a bacterial suspension after centrifugalization and it is probable that a certain number of organisms remained in this material. However, the author states that the same results may be obtained with endotoxin passed through a Chamberland filter. It should be stated that the subject of endotoxins in streptococci has been thoroughly studied and that present day opinion denies their existence. Herry's experiments are, however, illuminating.

A strain of *Streptococcus mitis seu viridans* was used for most of the experiments which was kindly lent by Dr. E. Libman of Mt. Sinai Hospital, New York. It was isolated by him from the blood of a patient with subacute endocarditis. It does not hemolyze blood, and grows on blood agar in small, discrete, dry, grayish colonies. It clouds glucose-ascitic agar. In broth it clumps and sinks to the bottom of the tube, leaving the medium clear. It is insoluble in rabbit bile and has no capsule. Since coming into our hands its pathogenicity for rabbits has been slight, a single intravenous inoculation of the contents of two 12 ounce Blake bottles of agar[2] failing to cause more than the slightest and most transient symptoms. This strain is designated No. 7. No. 4 is a similar organism from a similar source. No. 59 is a *Streptococcus viridans* obtained one year ago by Dr. Homer F. Swift from a case of pericarditis. It does not fall readily into any of the common groups of Andrewes and Horder. It is only slightly pathogenic for rabbits. Pn. I is a Type I pneumococcus isolated at the Hospital of The Rockefeller Institute. Pn. S. Afr. is a pneumococcus of Type IV isolated in South Africa from the Kaffir epidemic. The latter is not very pathogenic for rabbits. The *Bacillus typhosus* is a laboratory strain.

TABLE I.

Rabbits Receiving One Intravenous Injection of Streptococcus 7.

Rabbit No.	Amount injected.	Period of observation after injection.	Arthritis.	Remarks.
		days		
1	3 agar slants	49	0	
3	1 " slant	49	0	Intra-arterial.
5	⅓ Blake bottle	31	0	
6	¼ " "	39	0	
7	" " "	13	0	
9	" " "	39	0	
19	1 agar slant	14	0	
38	" " "	37	0	Slight limp on 16th day. No swelling or other evidence of arthritis.

Total ..... 8 rabbits.
Arthritis ..... 0.

[2] The surface of the medium in the average Blake bottle is equal to that of 10 agar slant tubes.

Rabbits of medium size (of 1,200 to 1,800 grams' weight), usually females, were used. All injections were given in the ear vein except one or two into the femoral artery. The latter method was found to have no localizing effect in the corresponding leg.

Table I shows the effect of one injection, Table II of two injections, and Table III of three or more injections.

TABLE II.

Rabbits Receiving Two Intravenous Injections of Streptococcus 7.

Rabbit No.	Amount of 1st injection.	Interval between 1st and 2d injections.	Amount of 2d injection.	Arthritis.	Period of observation after 2d injection.
		days			*days*
8	$\frac{1}{4}$ Blake bottle	9	$\frac{1}{3}$ Blake bottle	0	45
36	$\frac{1}{2}$ agar slant	6	1 " "	0	20
K	$\frac{2}{3}$ " "	15	$\frac{1}{3}$ " "	0	1
L	" " "	15	" " "	0	13

Total ..... 4 rabbits.
Arthritis ..... 0.

It appears that with the streptococci used two sensitizing doses were needed before any of the rabbits developed arthritis. Smears from the joint exudate in a few cases showed a few streptococci and in three cases the cultures were positive. Cultures were made in most of the cases by planting the fluid in tall tubes of glucose-ascitic agar and in the others in ascitic bouillon, both methods appearing to be equally efficacious.

The fluid in different rabbits varied from a thick, practically purulent exudate to one showing only a moderate opalescence. All the exudates examined, with the exception of that from Rabbit 17, were viscid. All contained numerous polymorphonuclear leucocytes, and some large mononuclear lymphocytes and large endothelial cells. The last named and occasionally the other two types of cell frequently contained inclusions which were interpreted as phagocyted cocci. They were Gram-negative and somewhat larger than the cocci injected. Unaltered cocci were rarely seen within the cells. It is interesting to note that similar inclusions were described by Bosc and Carrieu (12) and have been seen by the writer in cells in exudate from human rheumatic fever.

TABLE III.

Rabbits Receiving Three or More Intravenous Injections of Streptococci.

Organism.	Rabbit No.	Amount of 1st injection.	Interval between 1st and 2d injections.	Amount of 2d injection.	Interval between 2d and 3d injections.	Amount of 3d injection.	Interval between 3d and 4th injections	Amount of 4th injection.	No. of injections.	Arthritis.	Joint affected.	Remarks.
			days		*days*		*days*					
Streptococcus 7	14	$\frac{1}{2}$ Blake bottle	9	$\frac{1}{2}$ Blake bottle	63	$\frac{1}{4}$ Blake bottle	—	—	3	+	Both knees	Positive culture from joint fluid.
" "	15	" " "	9	" " "	63	" " "	—	—	3	+	" "	Positive culture from joint fluid.
" "	16	$\frac{1}{3}$ " "	1	$\frac{1}{3}$ " "	1	$\frac{1}{3}$ " "	33	$\frac{1}{3}$ Blake bottle	4	0	—	
" "	17	" " "	1	" " "	1	" " "	33	$\frac{1}{3}$ Blake bottle	4	+	Left wrist	Joint attacked 23 days after 3d injection. After recovery, a 4th injection caused a relapse.
" "	24	" " "	3	" " "	1	" " "	27	$\frac{1}{3}$ Blake bottle	4	0	—	
" "	25	" " "	3	" " "	1	" " "	27	$\frac{1}{3}$ Blake bottle	4	0	—	
" "	J	1/10 Blake bottle each day for 8 days.				Arthritis on 8th day			8	+	Both knees	
" 59	48	3 cc. broth culture	2	3 cc. broth culture	1	3 cc. broth culture	—	—	3	0	—	
" "	77	1 agar slant	1	1 agar slant	1	1 agar slant	—	—	3	+	Right shoulder	Positive culture from oint fluid.
" 4	49	4 cc. broth culture	3	" " "	1	" " "	—	—	3	0	—	

Total rabbits injected with Streptococcus 7..... 7. Arthritis..... 4.
" " " " " 59..... 2. " ..... 1.
" " " " " 4..... 1. " ..... 0.

The next series of experiments was made in an attempt to sensitize a joint with streptococci so that arthritis in that joint would follow a later intravenous injection of the same organism.

The left knee was used in all cases. The injections were made by the following technique:

> A suspension of the organism was made by scraping the surface of an agar growth into sterile salt solution. In a few cases a broth culture was employed. The suspension was drawn into a syringe and the needle inserted through the patellar ligament just below the patella. It was carefully pushed proximally, avoiding the bone surfaces as much as possible until it was felt to slip forward easily. This indicated that the point of the needle was in the synovial pocket under the quadriceps. The suspension was slowly injected and a little of it made to flow back into the syringe by pressure over the lower part of the quadriceps (piston test). This was returned to the joint and the needle quickly withdrawn.

After a few trials it was possible to inject the joint without infecting any of the periarticular tissues, thus giving a sharply localized reaction. This procedure caused an arthritis which usually subsided in 2 to 4 weeks, the joint and its contents returning to their normal state as far as could be determined microscopically. Dead bacteria were rapidly phagocyted, while the living resisted destruction and removal for a longer time. In all but a few cases dead bacteria were used for sensitization.

At a varying period after the inflammation and its products had been shown by examination of the synovial fluid to have disappeared an intravenous injection of the same organism was given. The results are given in Table IV.

The exudate in all cases except Rabbit 84 failed to show growth and recognizable streptococci were seen in the smears only once. The picture seen in the smears had the same characteristics as in the cases of successive intravenous inoculation without direct sensitization. In Rabbit 58 a second intravenous injection after the reaction following the first had subsided was also followed by a transient articular reaction.

The effect of similar procedure with other bacteria was then investigated with the results shown in Table V.

The condition of susceptibility in a joint to intravenous injections of streptococci has been referred to as one of sensitization, but it

TABLE IV.

Rabbits Receiving an Intravenous Injection of Streptococcus 7 after Treatment of the Left Knee with the Same Organism.

Rabbit No.	Amount injected into knee.	Interval.	Amount injected intravenously.	Arthritis (gross signs).	Joint fluid.	
					Culture.	Smear.
		days				
26	$\frac{1}{6}$ Blake bottle, living	53	2 cc. broth culture	+	0	
34	1 cc.,* killed	28	1.5 cc. broth culture	+	0	P.n.l. +++ Inclusions +
35	" " living	28	1.5 cc. broth culture	+	0	P.n.l. +++ Inclusions +
45	0.2 " "	15	1 agar slant	+	0	P.n.l. ++ A few cocci.
53	0.5 " killed	60	2 cc.	+	0	P.n.l. ++ No bacteria.
58	0.2 " "	35	$\frac{1}{2}$ agar slant	+	0	P.n.l. +++
58†		65	1 " "	+	0	P.n.l. ++ No bacteria.
61	" " "	19	" " "	+	0	P.n.l. ++ No bacteria.
65	10 mg. dried cocci, precipitated with alcohol	17	" " "	+	0	P.n.l. +
66	10 mg. dried cocci, precipitated with alcohol	31	2 cc.	+	0	P.n.l. ++
84	0.2 cc., killed	36	$\frac{1}{2}$ Blake bottle	0§	+	No p.n.l. No inclusions.
111	" " "	14	" " "	+	0	P.n.l. ++++ Inclusions +
112	" " "	14	" " "	±	0	P.n.l. ++ Inclusions +
113	" " "	14	" " "	++	0	P.n.l. +++ Inclusions +
114	" " "	14	" " "	+	0	P.n.l. +++ Inclusions +
115	" " "	14	" " "	++	0	P.n.l. ++ Inclusions +

Total rabbits treated with Streptococcus 7..... 15. Arthritis..... 14.

* Unless otherwise specified, figures given indicate amounts of a bacterial suspension consisting of the contents of a Blake bottle agar growth at 24 hrs. taken up in 10 cc. of normal saline. The total is equivalent to the growth on 10 agar slants.

† 65 days after the arthritis following the 1st intravenous injection had subsided a 2d intravenous injection was given and was likewise followed by marked inflammation of the joint.

§ 4 days later slight reddening and swelling of the joint appeared and polymorphonuclear leucocytes were found in the fluid, but the culture showed no growth.

TABLE V.

Rabbits Receiving Intravenous Injections of Streptococcus 59, Bacillus typhosus, or Pn. S. Afr. after Treatment of the Left Knee with the Homologous Organism.

Rabbit No.	Amount injected into knee.	Interval.	Amount injected intravenously.	Arthritis (gross signs).	Joint fluid. Culture.	Joint fluid. Smear.	Organism.
		days					
69	⅓ agar slant, killed	16	2 loops	0	−	−	*B. typhosus.*
91	0.5 cc., killed	29	½ agar slant	0	+	Some blood No excess cells	" "
92	" " "	31	⅔ " "	0	0	Normal, except that one cell shows inclusions	" "
93	" " "	31	" " "	0	0	Normal, except for one small clump of bacilli	" "
95	" " "	29	⅔ " "	0	0	Normal	" "
72	1 mg. bacteria sensitized by Gay's method	21	⅔ " "	±	0	Cells increased, 80% p.n.l.	S. 59
73	1 mg. bacteria sensitized by Gay's method	29	1 " "	+	+	No bacteria P.n.l. ++ Inclusions +	" "
83	0.2 cc., killed	35	½ Blake bottle	0	0	A few p.n.l. Inclusions +	" "
85	0.2 cc.	35	" " "	0	0	A few p.n.l. Inclusions +	" "
96	0.5 "	31	1 " "	0	0	Normal	Pn. S. Afr.
97	" "	31	1 broth tube	0	0	A few p.n.l. No inclusions	" " "

Total rabbits treated with B. typhosus	5.	Arthritis	0.
" " " " Streptococcus 59	4.	"	2.
" " " " Pn. S. Afr.	2.	"	0.

may be fairly asked whether any inflammation of the joint may not predispose to later joint affections. In other words, is the predisposing factor simply a non-specific inflammation or is it a specific sensitization? In order to answer this question a series of control experiments were made by injecting one sort of bacteria into the knee and following this with an intravenous injection of another sort (Table VI). By using two closely related strains of streptococci two doubtful (certainly very slight) reactions were obtained. By crossing with streptococcus and pneumococcus no reactions were obtained. It seems fair to conclude from these experiments that the reaction is due to a specific sensitization showing some evidence of a

TABLE VI.

Attempts at Cross-Sensitization.

Rabbit No.	Inoculation into knee. Amount.	Inoculation into knee. Organism.	Interval.	Intravenous inoculation. Amount.	Intravenous inoculation. Organism.	Arthritis.	Joint fluid. Culture.	Joint fluid. Smear.	Remarks.
			days						
52	0.5 cc. susp., killed by heat	Streptococcus 7	69	$\frac{2}{3}$ agar slant, living	Streptococcus 59	?	0	Moderate number cells, 90% p.n.l. No bacteria	Slight or absent palpable swelling of knee.
67	10 mg. bacteria precipitated with alcohol	" "	24	$\frac{1}{4}$ " " "	Pn. II	0	0	Normal	No swelling.
76	0.2 cc. susp., killed by heat	" 59	21	$\frac{2}{3}$ " " "	Streptococcus 7	?	0	Moderate number cells, 90% p.n.l. No bacteria	Very doubtful palpable swelling of knee.
83	0.2 cc. susp., killed by heat	" 7	35	$\frac{1}{2}$ Blake bottle, living	" 59	0	0	Few cells. Rare p.n.l. No inclusions	No swelling or other gross evidence of arthritis.
84	0.2 cc. susp., killed by heat	" 59	35	" " " "	" 7	0	0	Normal. No p.n.l. No bacteria	No swelling or other gross evidence of arthritis.
106	0.3 cc. susp., killed by heat	Pn. S. Afr.	14	$\frac{1}{5}$ " " "	" "	0	0	Rare cells. 3 p.n.l. seen. No bacteria	No swelling or other gross evidence of arthritis.
107	0.3 cc. susp., killed by heat	" " "	14	" " " "	" "	0	0	Rare cells. 1 p.n.l. seen. No bacteria	No swelling or other gross evidence of arthritis.
108	0.3 cc. susp., killed by heat	" " "	14	" " " "	" "	0	0	No excess cells No bacteria	No swelling or other gross evidence of arthritis.
109	0.3 cc. susp., killed by heat	" " "	14	" " " "	" "	0	0	Very few cells. No p.n.l. No bacteria	No swelling or other gross evidence of arthritis.
110	0.3 cc. susp., killed by heat	" " "	14	" " " "	" "	0	0	A few cells. About 10% p.n.l. No bacteria	No swelling or other gross evidence of arthritis.

Total rabbits tested for heterologous sensitization 10
" " showing joint reaction ..... 2 (doubtful).

group specificity comparable with the group agglutinations of certain bacteria.

Pathological Anatomy.

The arthritis following intravenous inoculation alone and that following intravenous inoculation after local sensitization presented the same gross and microscopic picture. An exception must be made in the case of Rabbits 14 and 15, in which a chronic arthritis with the continued presence of demonstrable living streptococci in the exudate followed the last injection. Here erosions in the articular cartilages were found. In the other rabbits the joint at autopsy showed the following changes: The synovial surface was moderately congested, the villi usually more so than the other parts. An excess of stringy fluid was usually present. The capsule was somewhat swollen. In cases which had reacted severely there was occasionally found after inflammation a small amount of inspissated exudate in the upper angle of the joint cavity. Sections showed a marked leucocytic infiltration of the villi and to a slighter degree of the subendothelial layer of the capsule. Examination of the adjacent cartilage and bone failed to show any noticeable change. Examination of the articular and periarticular tissues for bacteria by the Gram stain did not reveal the presence of organisms after a careful search. The vessels of the capsule and of the villi were moderately distended but no thrombi were seen. The reaction as seen under the microscope appeared to be mainly in the villi with the synovial membrane also playing a part.

DISCUSSION.

It is believed that the above experiments may throw some light upon the mechanism of acute arthritis. It seems to be established that the first attack of a highly virulent streptococcus can cause an arthritis and that the arthritis so produced is usually of a severe type with an exudate containing large numbers of viable organisms.

On the other hand, streptococci of lower virulence are frequently not able to produce arthritis at the first attack but at this time prepare the way for such an effect in a later attack.

It seems to be clearly proved that this preparatory or sensitizing process is, within narrow limits, a strictly specific one; *i. e.,* the organism used for the exciting, intravenous injection must be the same as that used for the sensitizing, intra-articular injection, else the reaction fails to occur.

It further appears that this preparation may be made by the introduction into the joint of the organism, living or dead, and it seems fair to conclude that the arthritis produced by successive intravenous injections results from a similar process; *i. e.,* a preliminary deposit of organisms in the joint leading to sensitization but not to gross inflammatory lesions, the latter resulting from a subsequent deposition of organisms. It is also shown that this reaction in a sensitized joint may be repeated several times in the same animal.

A close analogy between this reaction and the relapses in rheumatic fever can readily be drawn. Relapses are so common in this disease as to be one of its distinguishing characteristics. Thus in the figures given by Mosler and Valentin (13) 60 out of the 142 cases studied were suffering from their second or a later attack at the time of admission to the hospital. Cole produced 8 successive attacks, each followed by recovery, in a single rabbit.

Without assuming the specificity of any one organism the conception of relapsing arthritis as the effect of a virus upon an homologously sensitized joint may be fairly applied to the relapsing cases of human rheumatic fever.

The reaction of a sensitized joint in rabbits inoculated intravenously may properly be designated as an induced relapse and it will be seen from the protocol of Rabbit 17 that a second relapse can be induced by a second intravenous injection. From the ease and constancy with which lesions can be induced in sensitized joints by the method above outlined it is strongly suggested that the relapses, if not the primary arthritis, in rheumatic fever result from a virus reinvading the blood stream and provoking a reaction in a previously sensitized locus.[3]

[3] It may not be too wide a step to pass from the consideration of the effects induced in the joints to the phenomena observed in the endocardium and possibly even the myocardium in rheumatic fever. That they too are of relapsing nature is admitted; and that they also result from sensitization may be suggested.

In respect to the primary attack an analogy may be drawn from the fact above noted, that in rabbits and monkeys there is needed either a period of incubation, or, in most cases, a series of injections of the exciting organism before the joint is attacked. This fact suggests the hypothesis that some degree of sensitization, or of heightened activity on the part of the fixed cells is necessary before a definite and marked tissue reaction occurs.

It is not desired to state any opinion as to the identity of the organism causing rheumatic fever. In view of the fact that several different organisms can cause arthritis in the rabbit, that several different organisms can cause arthritis in man, and that the clinical manifestations of rheumatic fever vary widely it may well be that no one organism is constantly at fault. Nevertheless the streptococcus, and in most cases a member of the *viridans* group, has been the one most often found when cultures are positive. Further, this organism shows greater and more constant arthrotropic properties than any other now known. The preponderance of the evidence now available, therefore, is with the streptococcus. At this point the case must rest until further proof is offered.

SUMMARY.

By a process of sensitization described it was found possible to cause arthritis in rabbits constantly after one intravenous injection of the streptococcus.

This reaction is specific.

By intravenous inoculation, without previous sensitization, of the streptococcus used in these experiments it was possible to cause arthritis in rabbits only after three or more injections.

An analogy is suggested between the arthritis induced by sensitization and the relapses in human rheumatic fever.

A further analogy is suggested between the development in rabbits of arthritis after repeated intravenous injections and the development of the primary lesion in human rheumatic fever.

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