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Research Article

THE EFFECT OF ANTI-RHEUMATIC DRUGS ON THE ARTHRITIS AND IMMUNE BODY PRODUCTION IN SERUM DISEASE

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Serum sickness, the group of symptoms which follows the administration of foreign serum to human beings, was first extensively observed and recorded clinically by Von Pirquet and Schick (1) and later by other groups of workers. These studies concerned themselves entirely with the clinical and serological aspects of the disease; but up to the present little or no attempt has been made to obtain a method of treatment to prevent or lessen the severity of this illness. The present study was undertaken, therefore, with this in view. This work was suggested by the findings of Boots and Swift (2), who showed that in patients with serum sickness the involved joints contained a cellular exudate in which the proteins of the horse serum could be demonstrated. They also pointed out that salicylates had little effect upon the course of the illness when administered after the onset of arthritis.

During the past two years we have studied the serum-treated patients in this Hospital to determine, first the influence of the early institution of anti-rheumatic therapy upon the course of the disease, and, second the effect of such therapy upon the antigen and antibody content of their sera.

Neocinchophen, because of its anti-exudative influence in acute rheumatic fever (3) and the ease with which it is tolerated by patients, was employed in the first twenty-five cases; it was replaced by aspirin in the last nine. Depending upon the age and weight of the patient and his tolerance for the agent, neocinchophen was used in amounts of 8 to 10 grams daily, aspirin in doses of 5 to 6 grams. Drug treatment was usually begun from 24 to 48 hours after the last serum injection, and continued for 10 to 14 days. As the advantages of

early and prolonged therapeusis quickly became evident, this schedule was strictly followed with the exception of four instances in which either dosage or duration was insufficient. As identical results were obtained with both drugs, the two series have been analyzed as one group. All patients were carefully examined daily for the appearance of lymphadenopathy, urticaria and arthritis, and the signs and symptoms, whether positive or negative, were charted along with the temperature and pulse records. The degree of intensity of the respective manifestations was recorded by using the − sign, or one or more + signs, according to their severity.

As different observers have reported variations in the frequency of the individual manifestations of serum disease, we have thought it best to use as controls for this series the incidence of the various symptoms in the patients treated in this Hospital previous to the time of this study. In this way the elements of dosage of serum and type of infection—lobar pneumonia—for which it was given were constant. The records of 65 such controls were analyzed and compared with those of 34 patients subjected to anti-rheumatic therapy. In 30 of the latter, treatment was continued for a sufficient period; in 3 others its premature cessation was in each instance quickly followed by the development of arthritis. One of these is represented as the case of severe arthritis in the column marked "Treated" of table 1; in one there was moderate and in another a slight arthralgia. In a fourth patient, moderate arthritis developed because of insufficient, even though adequately prolonged, treatment.

Table 1 shows the frequency and severity of arthritis in these two groups. Of the treated patients, over 82 per cent showed little or no arthritis as compared with only 50 per cent in the untreated group. The percentages with moderately severe arthritis were about the same in each series, i.e., 14.6 per cent of the treated patients and 15.2 per cent of the untreated. Further, it will be noted that only the one patient mentioned above, who was insufficiently treated, or 3 per cent of the treated patients, had a severe arthritis, compared with over 30 per cent among those untreated. Thus, as is well shown in this table, the lessening in the frequency and severity of the arthritis in the treated patients is quite evident. No comparison as to the duration of joint involvement in the two series has been attempted.

In table 2 is given the comparison of the degree and frequency of urticaria in the same two groups. Of the untreated patients, 7.7 per cent showed little or no urticaria as compared with 11.8 per cent of those treated; 31.9 per cent of the untreated patients showed a mild to moderate urticaria as compared with 14.7 per cent of the treated;

TABLE 1

Comparison of arthritis in treated and untreated patients

	Untreated patients		Treated patients	
Degree of severity	Number	Per cent of total	Number	Per cent of total
−	27	40.9	22	64.7
±	6	9.0	6	17.7
+	5	7.6	2	5.9
++	5	7.6	3	8.7
+++	12	18.2	0	0
++++	8	12.1	1	3.0
No mention	3	4.5		
Totals.....	66	100 per cent	34	100 per cent

TABLE 2

Comparison of frequency and severity of urticaria in treated and untreated patients

	Untreated patients		Treated patients	
Degree of severity	Number	Per cent of total	Number	Per cent of total
−	2	3.0	4	11.8
±	3	4.7	0	0
+	11	16.7	2	5.9
++.	10	15.2	3	8.8
+++	24	36.4	10	29.4
++++	16	24.0	15	44.1
Totals.....	66	100 per cent	34	100 per cent

while 60.4 per cent of the first series showed severe urticaria as compared with 73.5 per cent of the second.

Although there was little difference in the frequency of urticaria in the two series, this symptom was more intense among the treated patients. As shown in the table, the number of patients with severe urticaria was 13 per cent less among those not receiving anti-rheumatic

drugs. Whether these drugs, which are known occasionally to cause exudative dermatoses in susceptible individuals, may exert a synergic influence and thus increase the severity of the exudation into the skin of patients with serum disease, is a question we cannot answer with certainty. Such an explanation is, however, not unreasonable. But in spite of this statistical evidence, the great comfort resulting from the nearly complete elimination of arthritis more than counterbalances this undesirable effect.

Adenopathy was present with sufficient frequency to demonstrate that the therapy was apparently without effect upon its incidence. As only rarely is it a source of discomfort to the patient, it will not be further considered. Febrile reactions of varying intensity were quite regularly observed. How far they were influenced by the well-known antipyretic effect of the drugs employed it would be unprofitable to conjecture at the present time.

As soon as it was evident that a definite anti-arthritic influence of anti-rheumatic drugs could be demonstrated in serum sickness, it became desirable to determine whether there was any parallelism between this phenomenon and the immunological manifestations of the disease.

The sera of twenty treated patients were therefore studied with respect to the elimination of horse serum and the appearance of anti-horse precipitin. For this purpose blood was obtained as soon as anti-rheumatic therapy was instituted, or just prior thereto, and at intervals thereafter of four to seven days during the remainder of the hospitalization. In a number of instances it was possible to procure further specimens at varying intervals following discharge.

Since the early studies of Hamburger and Moro (4) various observers (5) have commented upon the antigen-antibody relationships in serum disease. Longcope and Rackemann (6) observed that in this condition anaphylactin and precipitin for horse serum appeared in the blood stream shortly before recovery, and that the occurrence of antibody in high titer was accompanied by rapid diminution or complete disappearance of the circulating antigen. In the serum of patients who failed to develop serum sickness such antibodies were not found. In their opinion the neutralization or destruction of the antigen by these antibodies was the determining factor in recovery.

More recently Mackenzie and Leake (7), following a careful study of nineteen patients to whom serum had been administered, were able to distinguish three types of serological behavior. In the largest group were included those individuals who suffered from severe serum disease, and in whose sera precipitin appeared. Under these conditions the horse serum was found to disappear from the circulation near the end of the disease, at a time when the precipitin was present in high titer. In the second group were included a few patients who failed to develop serum disease, and in whose sera no precipitin could be demonstrated. In these patients the antigen persisted in the blood stream for extended periods of time. The third group was intermediate: its members, although suffering from serum disease, produced antibodies only in low titer, and antigen could consistently be demonstrated in their sera, though in reduced concentration with the passage of time.

In spite of differing theoretical interpretations, there has been no dispute concerning the actual serological findings of untreated serum disease. It has therefore seemed permissible to utilize the observations of Longcope and Rackemann and of Mackenzie and Leake as controls upon the results reported in this study, especially as the amounts of unconcentrated serum administered were practically the same in the different groups.

METHODS

Anti-sera were prepared by daily subcutaneous injections into rabbits of undiluted horse serum in doses of 0.2 cc. As soon as a precipitin titer of 1:40,000 or better was obtained the animals were exsanguinated, usually one week following the final injection, and the sera were stored in the ice-box without preservative. To avoid confusion from the possible presence of antigen in the blood stream at the time of bleeding, each serum was titrated in ascending dilutions against each of the others. No serum was used with which any suspicion of clouding was observed.

To test for the presence of antigen (horse serum) in the patients' sera, 0.2 cc. of a mixture of equal parts of anti-serum and normal salt solution was placed into each of a series of small tubes, and the human serum to be tested was added in 0.2 cc. amounts in dilutions ranging from 1:2 to 1:200,000. All readings were expressed in terms of the final dilutions of human serum resulting. In view of the small amount of anti-human precipitin present in most high titer rabbit anti-horse sera, many control series were made with sera from healthy subjects.

In addition, as a check against deterioration of the precipitin, normal horse serum was titrated against the anti-serum employed each day that tests were carried out. The same anti-serum was always utilized for testing the entire series of bleedings from any given patient.

The same general technique was followed in testing the sera of patients for the presence of antibody (anti-horse precipitin). Into each of a series of small tubes was placed 0.2 cc. of the undiluted human serum, and normal horse serum was added in 0.2 cc. amounts in dilutions ranging from 1:2 to 1:200,000. Results were expressed in terms of the final dilutions of horse serum. A control series were always employed in which serum from a normal human subject was tested against the same dilutions of horse serum.

All tests were incubated in the water-bath at 37°C. for a period of two hours, following which they were left over night in the ice-box. Readings were made upon the following morning.

Usually the sera were tested within a few days of the bleeding. A few specimens were preserved in the ice-box for periods varying up to five weeks before being titrated. Several comparative observations revealed no significant differences in the results obtained before and after the lapse of such an interval.

RESULTS

With respect to their immunological behavior, our series of treated and serologically tested cases may easily be divided into three groups.

Of these the first corresponds with group 2 of Mackenzie and Leake, and includes those patients, four in number, in whom there was little or no evidence whatever of serum disease. The sera of these individuals failed consistently to reveal the presence of antibody, and the titer of the antigen remained at a high level throughout their stay in the hospital, showing but a slight diminution toward the time of discharge. Two of these four were observed at intervals following their discharge; in one case the antigen had disappeared from the blood stream at the end of three months, while in the other traces were still present at the end of two and a half months. Antibody was not detected at any time. Chart 1 represents a typical member of this group.

The second group, the largest of all, comprises those patients, eleven in number, in whom signs of serum disease were indubitably present, but who through adequate therapy failed to develop arthritis. Chart 2 shows a typical example of this group. Four of them failed to show precipitin during their hospitalization, while in three others

it was present during this period only in evanescent traces. In three more it was found to the extent of 1:40, while in only one instance was a titer of 1:250 reached. In only one of the seven who developed antibody did this appear in detectable amounts prior to the subsidence of the initial urticaria. The antigen (horse serum) titer in the serum remained high throughout the entire period, apparently quite uninfluenced by the development of small amounts of precipitin;

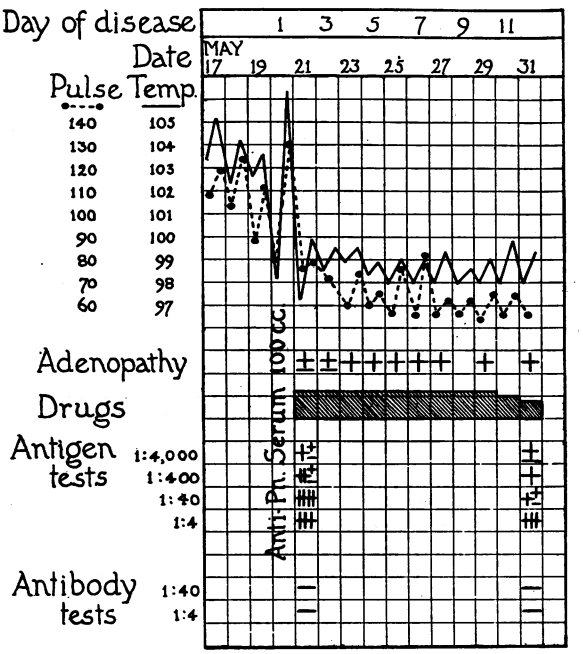

CHART 1. NO SERUM DISEASE; NO ANTIBODY FORMATION

Patient received 6 gm. aspirin per day over period indicated

toward the end of the hospitalization there was some diminution in the figure, but no more than was observed in the cases of the first group. Seven of these patients were observed at intervals for three months following discharge; in five instances there was complete disappearance of antigen by the end of this period, while in the sixth case only traces were found. The seventh patient still harbored demonstrable amounts of horse serum at this time, but at the end of two more

months this had vanished. With a single exception, and that questionable, precipitin was never demonstrated during the follow-up period.

Into the third group may be placed five patients in whom arthritis of varying degrees of severity developed.

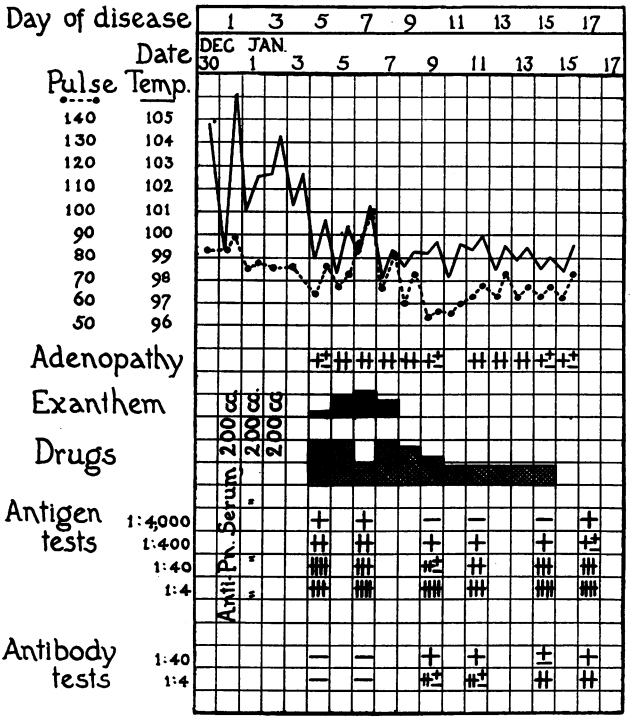

CHART 2. SERUM DISEASE; NO ARTHRITIS; LOW ANTIBODY FORMATION

Patient received neocinchophen maximum 10 gm. per day. Each large block represents 5 gm.

In the first case there was present on three separate days a mild arthralgia characterized principally by stiffness and vague pains, with but little resemblance to the severe arthritis of serum sickness; hence there was a reasonable doubt as to whether the symptoms should be so construed. At no time was antibody present in this patient's serum, and the antigen titer remained high during her hospitalization.

The second patient was one in whom moderately severe arthritis developed on the twenty-fifth day following serum administration.

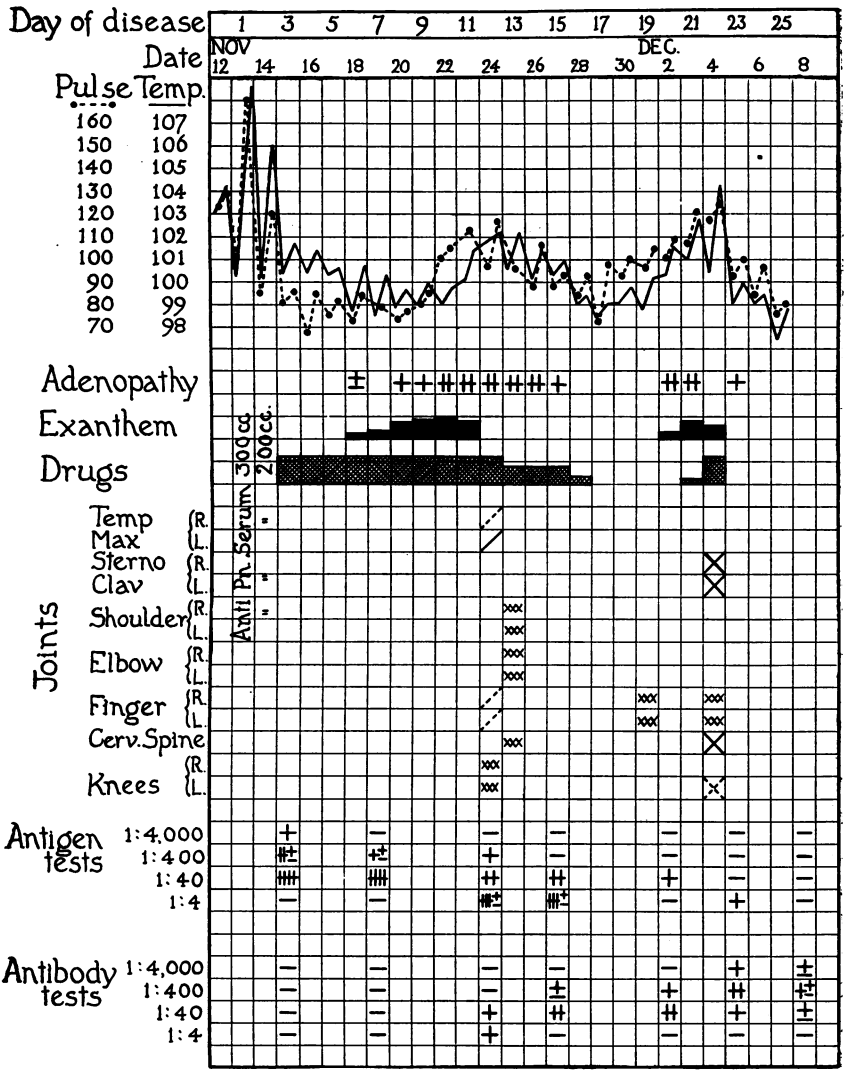

CHART 3. SERUM DISEASE; MILD ARTHRITIS; MODERATE ANTIBODY FORMATION

Patient received neocinchophen 6 gm. per day over period indicated. ╱ represents pain. ╲ represents tenderness. xxx represents stiffness.

Throughout the preceding period the antigen titer had remained high; immediately following the subsidence of the arthritis, however, a sharp drop was found to have taken place, and three weeks later only traces of horse serum could be demonstrated. At no time was it possible to detect precipitin. This was the only occasion upon which arthritis of any severity appeared in the face of adequate anti-rheumatic therapy.

The other three patients suffered moderately severe arthritis as the result of insufficient treatment. In each case antibody appeared closely upon the subsidence of the urticaria, and at the time of the arthritis had reached a titer of about 1:400. During the period of the arthritis a sharp drop took place in the antigen curve, though it

TABLE 3

Relationship between development of antibodies and appearance of arthritis

	Number of patients	Therapy		Precipitin		
		Adequate	Inadequate	None	1:4 to 1:250	1:400 or higher
No serum disease	4	4		4	0	0
Serum disease without arthritis	11	11		4	7	0
Serum disease with arthritis	5	2		2*	0	0
			3	0	0	3
Totals	20	17	3	10	7	3

* Arthritis very slight in one case.

never reached the base line. Following the arthritis the antibody titer remained at 1:400 and in the case of one patient, shown on chart 3, who suffered a relapse, it reached the figure of 1:4,000. Both antigen and antibody disappeared from the serum of one patient by the end of a month, and from that of a second by the end of two months. With one exception the formation of circulating antibody in titer approximating 1:400 seemed to be the necessary condition for the development of arthritis. The significance of this fact will be discussed below.

In table 3 are presented in condensed form the relationships in these drug treated patients between the existence of arthritis and the development of circulating antibody.

DISCUSSION

The foregoing observations have revealed two rather interesting phenomena. Early, adequate and sufficiently prolonged administration of aspirin or neocinchophen to patients who have received large amounts of anti-pneumococcus horse serum usually results in the prevention of one clinical manifestation of serum disease—the arthritis. Under similar therapeutic conditions there is a failure on the part of the patient to develop circulating antibodies in a concentration comparable with that shown by unmedicated controls. The conclusion seems justified, therefore, that there is some causal relationship between these two facts. It is important that the drugs be started soon after the serum treatment is discontinued; for we have frequently observed the occurrence of severe arthritis when the drugs were not given until later, even though the patients were saturated to the point of toxicity, and also when the medication was insufficiently prolonged. The clinical effect, therefore, is somewhat different from that observed in rheumatic fever, in which a severe arthritis usually disappears shortly after the exhibition of full therapeutic doses.

The observations of Boots and Swift (2) indicate that the so-called arthralgia is a true inflammatory process, or at least is characterized by the presence of cellular exudate in the synovial fluid. It is interesting, further, to note that not all of the clinical manifestations of serum disease occur simultaneously, but that fever, adenopathy and urticaria usually precede the arthritis. In those rare cases in which there is a relapse of the serum disease the skin manifestations ordinarily differ from those seen in the first attack. The primary skin rash is practically always urticarial in nature; the second, if such occurs, is very finely macular or maculopapular, often situated about the hair follicles, apparently involving, therefore, some of the special organs of the skin rather than the skin as a whole. In an occasional case of the latter type which we have had the opportunity to study the precipitin titer at the time of the relapse has been distinctly higher than at the time of the first bout.

Opie (8) has shown that there is a rough parallelism between the intensity of the Arthus phenomenon and the concentration of precipitin in the sera of rabbits immunized either actively or passively to a soluble foreign protein. He concurs with the opinion, expressed

by others, that the inflammatory process is a reaction to an irritating compound which is formed by the local union of antibody and antigen. Several years ago one of us (9) showed that salicylate medication during the course of immunization partially inhibited antibody production in rabbits. The present observations seem to indicate that the two anti-rheumatic drugs used have a similar effect in human beings. If, however, all of the symptoms of serum disease were dependent upon the concentration of circulating antibodies it would be expected that drug treated patients would be practically free from any manifestation of the disease. Such is not the case; hence another explanation is required.

In recent years the view has been gaining ground that the cells of the reticulo-endothelial system play the chief rôle in the production of antibodies. Aschoff (10) and his co-workers have shown that not all of the cells of the body or even of the reticulo-endothelial system react similarly towards parenterally introduced particulate dyes or carbon particles. Certain groups of cells take up these particles readily, other groups do not react until after a more prolonged or intense exposure to the dye. Those of the skin stain very readily with trypan blue. It is probable that they absorb soluble proteins contained in foreign serum even more easily, and react by the production of antibodies. According to the theory of sessile and free antibodies a certain concentration of antibodies must be attained in the cells before they are set free into the tissue juices, and are detectable in the serum. Coördinating our observations with this theory we are led to the following explanation of the observed phenonena: The drugs so alter conditions that antibodies are discharged into the blood stream in very small amounts or not at all. This effect might follow either a lowered intracellular concentration or an altered permeability of the cell membrane. It seems, however, that antibodies must exist in the cells, for at a certain time the tissues give evidence of the presence of some irritating substance which probably results from the union in the cells of antigen and antibody, in sufficient concentration. In other words, the urticaria is an evidence of the active immunization of the reticulo-endothelial cells of the cutaneous tissue.

The fact that the arthritis in this disease appears later and practically only when there is a fairly high concentration of antibodies in the

serum, suggests that the cells of the articular tissue must be passively sensitized with antibodies before they are in a condition to show an inflammatory reaction. In other words, while the irritating substance that stimulates the inflammatory reaction may be the same in both the skin and joints, in the case of the former it is the result of active immunization of the cells, while in the latter it is the result of passive immunization. When for any reason this passive sensitization does not take place the patient remains free from arthritis. Support is given to this theory by the type of dermatitis observed in relapsing serum disease. Here, again, another type of cell seems to be involved than that taking part in the primary urticaria, and, as above mentioned, there is usually a concomitant high concentration of antibodies in the patient's serum. It is probable that the tissues of the skin involved in the relapse have been passively sensitized in the same manner as have those of the joints.

Another possibility must be considered. Dale and Hartley (11) have shown that when an animal is injected with a mixture of antigens the maximum time of immunization or sensitization may be different for each individual antigen. It is well established that serum contains several distinct antigenic proteins, and it is possible that the urticaria is attributable to a toxic antigen antibody complex involving one serum protein and the arthritis to a similar complex involving another. It is also possible that the depressing influence of the drugs on antibody formation is more powerful against the more slowly forming hypothetical arthrotropic antibody. If this were true one would expect with a complex antigen such as horse serum to demonstrate two curves or a curve with two peaks, one at the time of urticaria and another at the time of arthritis. Such a complex curve is rarely if ever found. We are, therefore, more inclined to the theory of active sensitization of the skin and passive sensitization of the joints as an explanation of the observed phenomena.

SUMMARY

1. If, immediately following the discontinuance of serum therapy, neocinchophen or aspirin in adequate dosage is given to patients and continued throughout the usual period of serum disease, arthritis is usually prevented even though other manifestations of serum disease occur.

2. The serum of patients treated in this manner usually fails to contain anti-horse serum precipitin, and only rarely shows a precipitin concentration above 1:40.

3. Usually a precipitin content of 1:400 is necessary before the patient shows arthritis.

4. The theory is advanced that urticaria in serum disease is the result of active sensitization of the skin which is not prevented by the drug treatment, while the arthritis is the result of passive sensitization of the joints which is inhibited when the circulating antibodies in the serum are kept to a low concentration by the anti-rheumatic drugs.

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