THE EFFECT OF CHRYSOTHERAPY ON THE SEDIMENTATION RATE IN RHEUMATOID ARTHRITIS

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INTRODUCTION

IN a disease such as rheumatoid arthritis the assessment of the results of any form of treatment is admittedly a matter of great difficulty. It is now generally accepted, however, that the blood sedimentation rate (B.S.R.) is an accurate index of the activity of the disease at any stage, and that any lasting improvement in the condition will be accompanied by a fall in the B.S.R. More and more reliance is being placed on this test to corroborate the clinical result of different kinds of therapy. For this reason it is a pity that in only a small proportion of the many papers which have appeared in the past few years on the gold treatment of rheumatoid arthritis has an attempt been made to assess the effect of this form of treatment on the B.S.R.

A fall in the B.S.R., in the majority of cases as a result of chrysotherapy, has been reported by Hartfall, Garland and Goldie (1937, 1938); by Parr and Shipton (1937); and by Copeman and Tegner (1937). The latter reported a preliminary rise in a small proportion of cases, and a subsequent fall; in certain patients, too, a preliminary fall was succeeded by a permanent increase in the B.S.R., and it was suggested that some degree of tolerance to gold therapy might be established. Forestier and Certoncin (1936) concluded, from a study of fifty cases, that a gradual fall in the B.S.R. was a favourable prognostic sign, whereas a stationary or increasing rate was unfavourable; clinical improvement was usually proportional to the fall in the B.S.R.

Saskin and Spanbock (1937) have studied the behaviour of the B.S.R. in twenty-two gold-treated cases of rheumatoid arthritis. In twelve instances where marked improvement was found the average B.S.R. was 47 mm. before treatment and 11 mm.

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after treatment. In ten cases where no improvement resulted the average B.S.R. was 49 mm. before treatment and 48 mm. after.

More recently Ellman and Lawrence (1938) have reported in detail on the change in the B.S.R. in a series of twenty control and forty gold-treated cases of rheumatoid arthritis, all of which received some form of physiotherapy. The B.S.R. became normal in twenty-two of the gold-treated and in five of the control cases. The conclusion reached by the authors was that physiotherapy produced no definite change in the B.S.R., whereas chryso-therapy caused a slowing of the rate. They appear to imply, therefore, that the B.S.R. will become normal in a proportion of cases without treatment.

The purpose of this paper is to discuss the effect of chryso-therapy on the B.S.R. in a series of 400 cases of rheumatoid arthritis selected from the files of the arthritis clinic of the Leeds Public Dispensary and Hospital. These cases have been under observation over a period varying from six months to four years, and have been included in previous publications (Hartfall and Garland, 1935, 1936; and Hartfall, Garland and Goldie, 1937, 1938). The following criteria have been used in their selection:

(1) The cases conform to the criteria proposed for the diagnosis of rheumatoid arthritis in the British Medical Association classification (1933). Although no attempt has been made to differentiate "primary" from "secondary" types, the majority fall into the primary group.

(2) Chrysotherapy has been the only form of treatment employed, and cases have not had any previous gold treatment before coming under observation.

(3) Each case has completed one course of treatment and has been observed afterwards for a period of at least three months.

(4) Estimation of the B.S.R. has been carried out before treatment and at the end of each course.

The gold salts employed have been lopion, parmanil, sol-ganal B, oleosum, myocrisin and crisalbine. No attempt will be made in this paper to differentiate between the effects on the B.S.R. of the individual preparations used; it is felt that the results observed were common to all gold salts, and any differences which may exist are so slight as not to affect the main argument.

Of the 400 cases, 116 had one course only, 154 had two, 77 had three, 42 had four, 8 had five, and 3 had six. No adequate

control series has been observed, but it may be stated that an attempt to overcome this defect by injecting a series of patients with sterile saline instead of gold salts had to be abandoned on humanitarian grounds owing to the uniformly bad results.

CLINICAL DATA, ETC.

Of the 400 cases, 308 were females and 92 males. Table I. shows the age distribution at the onset of arthritis and at the beginning of treatment.

TABLE I.—AGE DISTRIBUTION OF CASES

Age.	At Onset of Arthritis.		At Beginning of Treatment.	
	Number.	Per Cent.	Number.	Per Cent.
20 and under ..	18	4.5	4	1.0
21-30	66	16.5	28	7.0
31-40	108	27.0	78	19.5
41-50	115	28.75	101	25.25
51-60	74	18.5	129	32.25
61-70	17	4.25	56	14.0
71 and upwards ..	2	0.5	4	1.0
Total	400	100.0	400	100.0

It will be seen that the onset of the disease occurred under the age of forty in approximately half the cases. It has always been our experience at this clinic that rheumatoid arthritis is rather more frequently found in persons over forty than below this age.

METHOD.—The Westergren method has been used throughout in estimating the B.S.R. The disadvantages of this method have been discussed recently by Gibson (1938), who concludes that inaccuracies may occur in 5 to 10 per cent. of cases. This test has been found most convenient, however, especially in view of the large number of cases presenting themselves at the clinic each week. For the latter reason, too, no attempt has been made to correct the B.S.R. for any anæmia that may have been present; but as all cases showing clinical signs of anæmia were investigated from this point of view, and chrysotherapy commenced only when the blood count had become normal, it is probable that any error on this account will be negligible. Another possible source of error lies in the fact that in estimating the B.S.R. attention was not paid to such disturbing factors

as upper respiratory infections, menstruation, etc. The large number of cases examined, however, will tend to minimise any fallacies due to these.

The figure used as index of the B.S.R. in this paper is the average hourly reading. Thus, if S_1 be the first-hour reading and S_2 the reading at the end of the second hour, then the average hourly reading (S) is obtained from the equation:

$$S = \frac{S_1 + \frac{S_2}{2}}{2}.$$

In the majority of cases the average hourly reading approximates to the reading at the end of the first hour, as the fall in the second hour is about twice that in the first. In certain cases, however, where there is a lag in the first hour followed by a marked fall in the second hour, the average hourly reading appears to be a much fairer index and to overcome to a certain extent what is the principal disadvantage of the Westergren method—namely, the occasional initial delay in the sedimentation of erythrocytes. At the same time, the best way of expressing the B.S.R. as determined by the Westergren technique is to give both the first-hour and the second-hour readings, but for the purposes of this paper such a method is impracticable.

RESULTS

In Table II. the range of B.S.R. in the 400 cases is shown before and after treatment.

TABLE II.—B.S.R. BEFORE AND AFTER TREATMENT

<i>B.S.R.</i>	<i>Before Treatment.</i>		<i>After Treatment.</i>	
	<i>Number of Cases.</i>	<i>Per Cent.</i>	<i>Number of Cases.</i>	<i>Per Cent.</i>
0-10	44	11.0	164	41.0
11-20	99	24.75	134	33.5
21-30	85	21.25	57	14.25
31-40	64	16.0	26	6.5
41-50	43	10.75	7	1.75
51-60	26	6.5	6	1.5
61-70	15	3.75	2	0.5
71-80	12	3.0	3	0.75
81-90	7	1.75	1	0.25
91-100	5	1.25	—	—
Total	400	100.0	400	100.0

It will be seen from this table that 11 per cent. of the cases had an original B.S.R. of 10 or less before treatment. This agrees with the experience of Forestier and Certonciny (1936), who find that approximately 10 per cent. of all cases of rheumatoid arthritis have an approximately normal B.S.R. It is obvious from this table that gold therapy causes a marked slowing in the rate. Actually 36 per cent. of cases had a B.S.R. of 20 mm. or less before treatment as compared with 76 per cent. after treatment. If the B.S.R. gives an indication of the activity of the disease, gold treatment appears to slow down its activity or to arrest it altogether. These results, of course, are entirely in keeping with clinical findings, and afford further evidence of the value of this therapy.

It seems to be very important to find out at what stage this slowing takes place, and whether it is maintained in those cases observed over a long period. In Table III. the average B.S.R. before and after each course has been arranged according to the number of courses given.

TABLE III.—TABLE SHOWING AVERAGE B.S.R. AT END OF EACH COURSE GROUPED ACCORDING TO THE NUMBER OF COURSES GIVEN

<i>Number of Courses.</i>	<i>Number of Cases.</i>	<i>Average Initial B.S.R.</i>	<i>After First Course.</i>	<i>After Second Course.</i>	<i>After Third Course.</i>	<i>After Fourth Course.</i>	<i>After Fifth Course.</i>	<i>After Sixth Course.</i>
1 only ..	116	27.8	14.6	—	—	—	—	—
2 „ ..	154	30.8	15.1	14.9	—	—	—	—
3 „ ..	77	33.8	18.1	14.8	16.9	—	—	—
4 „ ..	42	37.1	19.0	22.4	17.0	20.5	—	—
5 „ ..	8	44.5	20.0	12.0	21.0	21.0	27.1	—
6 „ ..	3	39.0	22.0	43.0	26.0	39.0	28.0	23.0
Total ..	400	31.5	16.1	16.2	18.0	21.6	27.3	23.0

This table shows that the total average fall which takes place in the B.S.R. is entirely determined by the fall taking place at the end of the first course; there is no indication of any further reduction following subsequent courses. It is obvious, therefore, that the fall in the B.S.R. is quite independent of the number of courses given. This finding is surprising, and seems to be at variance with the clinical findings; as a general rule, the clinical improvement which takes place after the second and subsequent courses, though not so dramatic as that after the first, is nevertheless considerable; it has been previously

pointed out (Hartfall, Garland and Goldie, 1937) that results are better with multiple courses.

The explanation of this anomaly may be that the complete or partial arrest of the disease precedes by a considerable interval the abatement of clinical symptoms. It is only to be expected that patients will be left with pain and stiffness after the infective process has been arrested, especially when one considers the destruction of cartilage and replacement fibrosis which the disease leaves in its wake; this point emphasises more strongly than ever the importance of early treatment in rheumatoid arthritis.

In order to learn to what extent the B.S.R. is of prognostic significance in gold-treated cases of rheumatoid arthritis, some statistical analysis of the inter-relationships existing between the following factors has been carried out—viz., initial and final B.S.R., change in B.S.R., disability and clinical result. In a previous paper (Hartfall, Garland and Goldie, 1937) an attempt was made to classify cases into seven grades of disability, and the criteria laid down at that time have again been applied. Briefly, the seven grades represented increasing degrees of disablement varying from Grade 1, where the patient is still able to work, up to Grade 7, where the patient is completely bedridden. In order to save space, only those tables where a definite statistical relationship has been shown to exist will be published.

No association has been found to exist between the initial B.S.R. and clinical result, between initial disability and change in B.S.R., between disability and result, and between initial and final B.S.R. It thus appears that the chances of improvement are equal in slightly and severely disabled cases and in cases with high and low initial B.S.R.s. On the other hand, a significant association has been found to exist between disability and initial B.S.R., between clinical result and change in B.S.R., between final result and final B.S.R., and between initial B.S.R. and change in B.S.R.

The relationship between disability and initial B.S.R. is shown in Table IV. A slight but definite association has been shown to be present, cases in the higher grades of disability tending to show a higher B.S.R. That the association is only slight is to be expected. It would be unlikely that a large series of cases such as this would not include a number of cases where the activity of the disease was becoming arrested, but where marked

disability was left; conversely, patients with a short history and slight or moderate disability have often a high B.S.R. It is surprising, incidentally, how often one finds a high B.S.R. in apparently "burnt out" cases.

TABLE IV.—RELATIONSHIP BETWEEN INITIAL B.S.R. AND DISABILITY

<i>Grade of Disability.</i>	0-10.	11-20.	21-30.	31-40.	41-50.	51-60.	61-70.	71-80.	81-90.	91-100.	<i>Average.</i>	<i>Total.</i>
1	4	7	1	—	—	1	1	—	—	—	20.0	14
2	21	49	41	25	11	8	5	7	1	3	29.0	171
3	5	12	16	8	3	—	3	1	2	—	29.5	50
4	2	11	5	13	5	5	1	—	1	—	33.6	43
5	8	8	10	10	12	5	4	1	—	1	36.0	59
6	4	11	11	6	12	7	1	3	3	1	36.9	59
7	—	1	1	2	—	—	—	—	—	—	29.0	4
Total ..	44	99	85	64	43	26	15	12	7	5	31.5	400

Correlation coefficient $+0.1781$.

The relationship between clinical result and change in the B.S.R. is shown in Table V. The classification of the clinical results is the same as was made in a previous publication (Hartfall, Garland and Goldie, 1937).

TABLE V.—RELATIONSHIP BETWEEN CLINICAL RESULT AND CHANGE IN B.S.R.

Clinical Result.	Change in B.S.R.									Average Change.	Total.
	Minus.					Plus.					
	81 100	61 80	41 60	21 40	1 20	0 19	20 39	40 59	60 79		
Cured ..	2	1	1	10	15	1	—	—	—	— 24.3	30
Markedly im- proved	1	9	24	57	136	42	5	1	—	— 16.4	275
Moderately improved	—	2	5	9	17	8	1	—	—	— 16.6	42
Slightly im- proved ..	—	—	—	1	7	8	1	—	—	— 0.6	17
No improve- ment	—	—	4	4	13	12	1	1	1	— 5.7	36
Total ..	3	12	34	81	188	71	8	2	1	— 15.4	400

Correlation coefficient $+0.2180$.

A significant statistical association has been shown to exist between the factors, those cases with better results tending to show a greater fall in the B.S.R. The association is, however, not a very close one; it will be seen that a small proportion of the "markedly improved" cases show a rise in the B.S.R., and conversely a fall in the B.S.R. was observed in over half the cases who did not improve at all. The reason for such anomalous results is not at all clear. It is difficult, however, to rule out altogether the possibility that the improvement in some instances may be entirely psychological; the view has previously been stated that psychogenic factors play no part in the majority of rheumatoid arthritis cases (Hartfall, Garland and Goldie, 1937), but the psychological effect of injection therapy, together with contact with a group of cases showing undoubted improvement, may well explain a stationary or raised B.S.R. in a minority of patients who pronounce themselves "better." It is unlikely that minor intercurrent upsets such as upper respiratory infections or menstruation could be the sole cause of the raised B.S.R. in the "markedly improved" group, as a persistently high B.S.R. was found to exist throughout treatment in most of these cases. It has already been suggested that residual pain may be due to cartilage erosion and replacement fibrosis in a case in which the active disease has been arrested. This would be especially true of patients showing marked initial disability, and may well explain the fall in the B.S.R. occurring in a considerable proportion of patients showing no clinical improvement.

The association between change in B.S.R. and result might have been still closer had it been possible further to subdivide the "markedly improved" class. The difficulties involved in assessing the clinical results of treatment have already been emphasised, and a further subdivision of the "marked improvement" class has not been found practicable.

In most cases the clinical result tends to be proportional to the average fall in the B.S.R. It is significant that every case in the "cured" class had a normal B.S.R. after treatment, and the average fall in this group was greater than in any other class. The average fall in the "slight" and "no improvement" classes was very small.

The relationship between final B.S.R. and clinical result is shown in Table VI.

TABLE VI.—RELATIONSHIP BETWEEN FINAL B.S.R. AND CLINICAL RESULT

<i>Clinical Result.</i>	<i>Final B.S.R.</i>									<i>Average.</i>	<i>Total.</i>
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90		
Cured	29	1	—	—	—	—	—	—	—	4.9	30
Marked improvement	107	105	41	13	6	1	1	1	—	15.5	275
Moderate improvement	12	17	6	5	—	1	1	—	—	18.5	42
Slight improvement	5	5	2	4	—	1	—	—	—	21.0	17
I.S.Q. or worse ..	11	6	8	4	1	3	—	2	1	25.1	36
Total ..	164	134	57	26	7	6	2	3	1	16.1	400

Correlation coefficient +0.3169.

The association here has been shown to be somewhat closer than was the case in Table V. It would appear, then, from the above tables that clinical improvement is generally proportional to the fall in the B.S.R. and that the final B.S.R. gives some index of the clinical result. One must conclude, therefore, that the B.S.R. is of definite prognostic value as regards the extent of the fall and the final figure.

It has already been stated that no relationship exists between the initial and the final B.S.R. A significant association has, however, been shown to exist between the initial B.S.R. and the change in B.S.R. This is shown in Table VII., where it will be seen that that change is neatly proportional to the initial figure.

TABLE VII.—RELATIONSHIP BETWEEN INITIAL B.S.R., CHANGE IN B.S.R. AND THE FINAL B.S.R.

<i>Class Interval.</i>	<i>Initial B.S.R. (Mean).</i>	<i>Change in B.S.R. (Mean).</i>	<i>Final B.S.R. (Mean).</i>
0-10	5.0	+4.3	9.3
11-20	15.5	-2.5	13.0
21-30	25.5	-10.0	15.5
31-40	35.5	-19.1	16.4
41-50	45.5	-23.1	22.4
51-60	55.5	-34.5	21.0
61-70	65.5	-47.7	17.8
71-80	75.5	-53.0	22.5
81-90	85.5	-57.3	28.2
91-100	95.5	-77.0	18.5

Correlation coefficient between initial B.S.R. and change in B.S.R. +0.7940.

B.S.R. AND RELAPSE

Relapse has occurred eighty-one times in seventy-four cases. In thirty-three cases the immediately preceding B.S.R. was 10 mm. or less; it would appear from our findings, therefore, that a normal B.S.R. does not preclude the occurrence of relapse. On the other hand, there are many instances in the 400 cases where relapse has not occurred despite the fact that chrysotherapy has been discontinued when the B.S.R. was still high.

In fifty-one cases relapse was accompanied by an increase in the B.S.R. over the immediately preceding figure; the increase was 5 mm. or under in twenty cases, between 6 and 20 mm. in twelve, and over 20 mm. in eleven. In five cases the B.S.R. remained unchanged with the occurrence of relapse. In twenty-six instances a decrease in the B.S.R. as compared with the immediately preceding figure accompanied relapse. This decrease was 5 mm. or less in five cases and more than 20 mm. in three.

It is an interesting finding that the B.S.R. taken when relapse had actually occurred was 5 mm. or less in eight cases and between 6 and 10 mm. in seventeen cases. Attacks of acute fibrositis are, of course, common in rheumatoid arthritis, and it seems probable that the normal B.S.R. may be explained on the ground that the relapse in those twenty-five cases (and probably in many others) was not an actual flare-up of the arthritic lesion, but a fibrositis. Of the remaining cases, forty-eight had a B.S.R. of between 11 and 40 mm. and eight of 41 mm. and over.

B.S.R. AND TOXIC REACTIONS

Hartfall, Garland and Goldie (1937) have already pointed out that a proportion of the toxic reactions met with in chrysotherapy may be delayed for weeks or months after the end of the individual courses. As the 400 cases dealt with have been out-patients, and, further, as they have invariably been referred to their own doctors at the end of each course, no information is available regarding the B.S.R. in the majority of those cases having toxic reactions between courses. There is, however, sufficient information about toxic reactions during courses to make analysis worth while. In any case, it seems to be certain

that the B.S.R. would give little or no help in the prevention of toxic reactions which occur some time after the termination of a course, as the only means we have at the present time of averting reactions is the suspension of gold therapy.

In analysing the B.S.R.s associated with toxic reactions, only those taken two weeks or less before the onset of the toxic reaction have been considered. It is felt that if the B.S.R. is to be of any value in the avoidance of toxic reactions, as Savy (1935) has suggested, then any change must take place at least two weeks before their appearance, in order that the suspension of gold therapy may be effective.

The disturbances most frequently found involve the skin and consist of pruritus, erythemata, which may or may not be accompanied by desquamation and rarely exfoliative dermatitis. In all, there were six cases of pruritus alone where the B.S.R. was taken at the stated interval before its appearance. As these occurred in the early stages of the treatment, it might be expected that they would be associated with a high B.S.R. The actual figures found in the six cases were 4, 34, 7, 9, 9 and 40 mm., but in no case did this represent an increase over the previous B.S.R. In twenty-four cases of itching erythema the associated B.S.R. varied from 4 to 84 mm., the average being 18 mm. In three instances the figure associated with this type of reaction represented a slight increase over the previously found figure; but in view of the fact that in ten out of twenty-four cases the associated B.S.R. was less than 10 mm., it would appear that the B.S.R. will be of no value at all in foreseeing this type of reaction.

In the case of desquamating erythemata a similar state of affairs exists. In eleven such reactions the associated B.S.R. was under 10 mm. in eight cases, the figures for the other three cases being 32, 27 and 21 mm. Only in two of the latter three cases did the associated B.S.R. show any increase over that taken previously, and in both cases the difference was slight.

One case of exfoliative dermatitis had an associated B.S.R. of 29 mm.; this patient's B.S.R. was previously normal, but the increase from normal had taken place very gradually over about three months.

There was one case of herpes with an associated B.S.R. of 20 mm.; the preceding B.S.R. had been 38 mm.

In eight cases of sore mouth the associated B.S.R.s were 2, 2, 7, 22, 30, 22, 38 and 31 mm. In no case did the associated B.S.R. show any substantial increase over the preceding figure.

In three cases of diarrhoea the associated B.S.R. was 13, 12 and 5 mm.; in all three cases the B.S.R. was falling at the time of the toxic reactions. In ten cases of jaundice the associated B.S.R.s were 17, 18, 10, 12, 10, 15, 19, 18, 9 and 4 mm. The B.S.R.s in four cases of albuminuria were 6, 5, 41 and 38 mm. In one case of thrombocytopenic purpura the B.S.R., taken on the week of development of the purpura, was 5 mm.

From the above it will be seen that any type of toxic reaction can develop in association with either a normal or an abnormal B.S.R. It is apparent that the B.S.R. is of no help in the avoidance of even the most severe toxic reactions.

DISCUSSION

It is admittedly a great drawback that a series of control figures for untreated cases is not available; so far as I am aware no such series has yet been published. The difficulty of obtaining a satisfactory control group is undoubted, and whether one would be justified in withholding all forms of treatment in a progressive and crippling disease such as rheumatoid arthritis over a long period of time is highly debatable. The introduction of chrysotherapy has altered the prognosis of this disease to so great an extent that every patient should be given the opportunity of benefiting from this therapy at the earliest stage. It has been shown previously (Hartfall, Garland and Goldie, 1937) that the results of chrysotherapy become significantly worse the longer the disease has lasted before the institution of this form of treatment, and the rapidity with which severe crippling can take place makes early treatment imperative.

That gold treatment produces a marked fall in the B.S.R. is certain, and the higher the initial figure the greater the fall; the ultimate effect seems to be to reduce the figures to a common level. While the initial figure is valueless from a prognostic point of view, the change in the B.S.R. is of definite value. The greater the fall and the lower the final figure, the better, on an average, is the clinical result. It is unfortunate that the "marked improvement" class included such a large proportion of the 400 cases. Had it been found practicable to subdivide

this class still further, it is probable that a closer association between final B.S.R. and result would have been found.

One of the most interesting features which has emerged from the analysis of these figures is that the mean fall in the B.S.R. is entirely determined by the fall taking place at the end of the first course. Ellman and Lawrence (1938) have suggested that dosage should be reduced whenever the B.S.R. falls to normal figures, in order that toxic reactions occurring later on in the treatment may be avoided. On the basis of the figures presented here it might be suggested that reduction of dosage should take place after the first course; whether subsequent courses consisting of, say, half the amount of gold salt used in the first course would be effective in stabilising the B.S.R. at its new level and in maintaining clinical improvement is a matter for trial. If some of the severe reactions encountered in second and subsequent courses, especially the hæmorrhagic ones, could be avoided by this means, one of the greatest disadvantages of gold treatment would be removed.

It has already been stated that no information is available regarding untreated cases over a long period of time. In this paper, however, it has been shown that, although a close association exists between initial B.S.R. and change in B.S.R., there is no definite relationship between initial and final figures. This raises the possibility that in a considerable number of untreated cases the B.S.R. would show wide fluctuations. This hypothesis receives support from the fact that a considerable proportion of the 400 cases shows a moderate increase in the B.S.R. after chrysotherapy and a small proportion shows a considerable increase. An alternative hypothesis is the assumption that chrysotherapy produces a non-specific upset which usually causes a fall in the B.S.R., but may cause a rise. The present-day view on the action of gold suggests that the latter theory is the correct one.

It is unfortunate, but not altogether unexpected, that according to the above figures the B.S.R. is of little value in anticipating either relapse or severe toxic reactions. The most severe upsets such as jaundice, severe albuminuria and aplastic anæmia have been seen in the presence of a normal B.S.R. The utility of the test is thus considerably lessened from a practical point of view.

CONCLUSIONS

1. A study of the blood sedimentation rate has been made in 400 gold-treated cases of rheumatoid arthritis observed over a period of time up to four years.

2. A considerable fall in the blood sedimentation rate has resulted in a large proportion of cases.

3. No relationship has been found to exist between the initial blood sedimentation rate and the clinical result.

4. The extent of the fall is entirely determined by the fall taking place at the end of the first course.

5. Clinical improvement is generally proportional to the fall in the blood sedimentation rate.

6. The blood sedimentation rate is of no value in anticipating toxic action or relapse.

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