SIGNIFICANCE OF THE WAALER-ROSE TEST, STREPTOCOCCAL AGGLUTINATION, AND ANTISTREPTOLYSIN TITRE IN THE PROGNOSIS OF RHEUMATOID ARTHRITIS

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When the clinical picture of rheumatoid arthritis was defined by Garrod (1859) and practically the same syndrome was termed "rheumatisme articulaire chronique progressif" by Charcot (1874), these terms were used to designate a chronic arthritis, progressing unfavourably and resulting in some degree of permanent disability. Only in the last few decades has it become known that in some cases of rheumatoid arthritis there is complete recovery within a few months. Short and Bauer (1948) have pointed out that cases progressing favourably are by no means as rare as is commonly supposed.

In Anglo-Saxon countries cases progressing favourably are included in the rheumatoid arthritis group, whereas in France such cases are variously termed "rheumatisme articulaire subaigu", "rhumatisme articulaire subaigu curable", or "polyarthrite subaigue", and the term "polyarthrite chronique évolutive" is used exclusively for the types progressing unfavourably. Hence the terms rheumatoid arthritis and "polyarthrite chronique évolutive" are not synonymous, a point which is too often forgotten.

According to de Sèze and Ryckewaert (1954), 25 per cent. of patients suffering from "polyarthrite chronique évolutive" become complete invalids, and the remainder are partly able to continue their work, though about half of the latter suffer severe limitation of activity.

The usual prognosis in cases of rheumatoid arthritis is that 25 per cent. of patients recover, 25 per cent. are incapacitated, and the remaining 50 per cent. show improvement but do not recover completely. Short and Bauer (1948), however, believed that in many cases of rheumatoid arthritis the prognosis is more favourable than is commonly supposed, chiefly depending upon the duration of the disease at the time of the first examination. When the duration of the disease was less than 12 months, remission increased to 37 per cent.

Steinbrocker (1946) found that 90 per cent. of the cases of acute rheumatoid arthritis recovered, the only therapy being general medical treatment.

So far it has not proved possible to predict the course of the disease in early cases. A gradual onset with symmetrical involvement of fingerjoints has always been regarded with suspicion. Egelius, Hävermark, and Jonsson (1949) investigated the case histories of 200 patients suffering from advanced rheumatoid arthritis and noted this classical beginning in 37.5 per cent. Sclater (1943) noticed, in a group of 388 patients, an onset in the fingerjoints in 38 per cent. of female patients and in 26 per cent. of male patients; no attention was paid, however, to symmetrical involvement. The literature does not yield any information about the percentage of cases in which the disease started in the fingerjoints but developed favourably and resulted in recovery within a few months.

The relation of serological reactions to the prognosis of rheumatoid arthritis has been subjected to various investigations. Kellgren (1952) believed that a positive Waaler-Rose test was characteristic for cases of rheumatoid arthritis which were progressing unfavourably. Ball (1952) found the test positive in 55 per cent. of patients with pronounced x-ray changes, and in only 21 per cent. of patients with normal x-ray findings.

Present Investigations

Material.—Data were collected from 141 patients in the initial stage of the disease. A diagnosis of rheumatoid arthritis was made when several joints showed inflammatory symptoms, pain, swelling, and functional disorder. Only a few patients showed monoarthritis, or great pain in the hands and feet only at the time of the first examination, and in them swelling of other joints soon became apparent. Some patients suffered from disturbances of the locomotor system, extremely painful larger joints

and a significant increase in the erythrocyte sedimentation rate, conforming with the description of "pseudo-polyarthrite rhizomélisque" (Forestier and Certonciny, 1953).

Cases presenting difficulties of differentiation from rheumatic fever have not been included. Most patients felt quite well, and complaints of fatigue were by no means as frequent as is stated in many publications. Brief case histories of the patients are given in the thesis of one of us (Otten, 1958).

The patients were divided into two groups:

- (A) Duration of disease at time of first examination 1-3 months (106 patients).
- (B) Duration of disease at time of first examination 4-6 months (35 patients).

Method.—Antistreptolysin titre, streptococcal agglutination, and the Waaler-Rose test were performed at the time of the first examination and repeated once or several times subsequently. The technique was the same as that used by Otten and Boerma (1954), but in the last year of observation the Waaler-Rose test was performed with sensitized human O cells instead of with sheep red blood cells (Boerma, 1955; Meijer and Boerma, 1958).

A titre of 1:16 is considered positive in the Waaler-Rose test. Positive streptococcal agglutinations refer to L and O agglutination with titres of 1:40 or more, no value being attached to a positive titre of only one of these reactions.

Treatment.—Salicylate or amino pyrine was given first, and if no influence upon the disease was observed chrysotherapy was instituted. 32 of the 141 patients were clinically treated in this way during the first year.

Results

Group A

Of the 106 patients in this group, 29 had been ill for 1 month at the time of the first examination, 42 for 2 months, and 35 for 3 months. All 106 patients were observed for at least 1 year, 78 for 2 years, 40 for 3 years, and some for as long as 5 years.

In general the disease had had a gradual beginning, and complaints of fatigue or general malaise were rare.

Sex Differences.—We observed that the initial stage of rheumatoid arthritis was seen nearly as frequently in men as in women, *i.e.* in 48 males and 58 females. It was usually stated that rheumatoid arthritis is much more frequent in women, the ratio being about 2 or 3 to one.

At the end of the first year, 46 patients of the 106 in the series had joint involvement, at the end of the second year 34, and at the end of the third year 22 (Table I). Amongst these patients with continuing joint involvement, in whom the disease might be said to have become chronic, the proportion of women to men increased as time went on. Of the 46 patients under observation who had joint involvement at the end of the first year, 27 were women and nineteen were men; of the 34 patients at the end of the second year, 23 were women and eleven were men; of the 22 patients at the end of the third year, sixteen were women and only six were men.

We may conclude, therefore, that initial attacks of rheumatoid arthritis occur with practically the same frequency in both sexes, but that the chronic form is more often found in women.

TABLE I
RELATIONSHIP OF JOINT INVOLVEMENT TO WAALER-ROSE TEST IN 106 PATIENTS (GROUP A)
IN 3 YEARS FOLLOW-UP

Waller-Rose Test	Joint Involvement									
	Present at Initial Examination	At End of First Year			At End of Second Year			At End of Third Year		
		Present	Absent	Total	Present	Absent	Total	Present	Absent	Total
Positive	37	26	11	37	17 3	4 6	30	9 3	1 4	17
Negative	69	20	49	69	14 0	0 34	48	10 0	0 13	23
Total Patients	106	46	60	106	34	44	78	22	18	40

Table I shows that 26 of the 37 sero-positive patients still had joint involvement at the end of the first year; of 21 who were still under observation at the end of the second year 4 had recovered; and of 10 still under observation at the end of the third year 1 had recovered. The other eleven of the original 37 sero-positive patients had recovered by the end of the first year, but three of them had relapsed by the end of the second year, and three still had joint involvement by the end of the third year. The developments in the group of 69 sero-negative patients is set out in the same way, and shows a steady decline in joint involvement and no relapses.

Waller-Rose Test.—37 of the 106 patients (35 per cent.) had a positive Waller-Rose test within 3 months of onset of the disease. No difference was attributable to sex. The test proved to be very stable; once it was positive there might be minor fluctuations, but it was exceptional for it to become negative. Even in cases of complete remission for as long as 5 years the test remained positive.

Because a large number of the patients in whom the Waller-Rose test was negative recovered, there was an increase in the percentage of sero-positive patients with joint involvement from 35 per cent. in the initial stage to 57 per cent. at the end of the first year of observation, and by the end of the third year this had increased to approximately 80 per cent. In some cases the test became positive in the later stages of the disease. Only a few patients recovered after the first year of observation. More than half of the patients who showed joint involvement and a positive Waller-Rose test in the third year of observation had already become sero-positive during the first few months of the disease.

Course of the Disease.—Most of the patients recovered within a few months, but the others developed chronic rheumatoid arthritis. The prognosis was much better in patients with a negative Waller-Rose test than in those with a positive test. The patients were therefore divided into two groups: those with positive Waller-Rose test at the time of the first examination, and those with a negative test at the time of the first examination.

The term "recovery" is used when joint involvement, both manifest and functional, is no longer apparent, no notice being taken of the erythrocyte sedimentation rate or of subjective complaints, such as vague joint pains or morning stiffness. Table I shows the number of patients with joint involvement at the end of each year of observation.

At the end of the first year of observation, 30 per cent. in the sero-positive group had recovered compared with 71 per cent. in the sero-negative group (57 per cent. of the total). Once recovery had set in, no relapses were observed among the sero-negative patients, whereas relapses did occur among the sero-positive patients. Patients still manifesting joint involvement at the end of the first year seldom recovered; this applies to both sero-positive and sero-negative patients. The entire duration of the disease in patients who recovered during the first year of observation varied from 2 to 14 months (average 7). Although the hope of recovery for patients who still showed joint involvement at the end of the first year was small, no continuous progression was seen, and improvement has been

known to occur just as frequently as deterioration in the following years.

Antistreptolysin Titres.—The difference between the percentages of increased antistreptolysin titre in sero-positive patients and healthy persons was not significant, but the sero-negative patients differed significantly from both (Table II). In patients with a negative Waller-Rose test and an antistreptolysin titre of 300 U/ml. or more, rheumatoid arthritis developed favourably, but not more so than in patients of the same group with a normal or only slightly increased antistreptolysin titre.

TABLE II
ANTISTREPTOLYSIN TITRES IN A GROUP OF HEALTHY CONTROLS AND IN THE PATIENTS WITH POSITIVE AND NEGATIVE WALLER-ROSE TESTS (PER CENT.)

Antistreptolysin Titres (U/ml.)	Healthy Controls	Waller-Rose Test	
		Positive	Negative
≥ 300	4	8	20
200-300	12	8	19
< 200	84	84	61
Total ..	100	100	100

Streptococcal Agglutination.—Of 37 patients with a positive Waller-Rose test, 28 showed positive L- and O-agglutination with a titre of 1 : 40 or more. Of the 69 sero-negative patients, only eight had such a titre. The course of the disease in the latter group is shown in Table III.

TABLE III
STREPTOCOCCAL AGGLUTINATION AND THE COURSE OF THE DISEASE IN SERO-NEGATIVE PATIENTS

L- and O-Agglutination	Joint Involvement at End of First Year	
	Present	Absent
Positive ..	6	2
Negative ..	14	47

In five of the six patients who showed positive L- and O-agglutination and joint involvement at the end of the first year, the Waller-Rose test became positive later on. It is clear that the recovery percentage is significantly higher when the L- and O-agglutination is negative, and that these reactions have a prognostic significance.

Arthritis of the Fingerjoints.—This was frequently observed at the time of the first examination. The percentage in the sero-positive group was 81, and in the sero-negative group 58. No notice was taken

of symmetrical involvement. 60 per cent. of the sixty patients who recovered in the first year and 78 per cent. of the 46 patients who failed to recover had manifested involvement of the joints of one or more fingers at the time of the first examination. The prognostic value of involvement of the joints of the fingers is therefore slight.

Group B

The 35 patients in this group (27 females and 8 males) had had the disease at the time of the first examination for from 4 to 6 months. Of thirteen patients with a positive Waaler-Rose test, none recovered in the first year, but of 22 sero-negative patients eleven recovered. That the recovery percentage is lower than in Group A is mainly due to selection, since patients recovering within 4 months were not included in Group B. Increased antistreptolysin titres were again found more frequently in the sero-negative than in the sero-positive group. Arthritis of the joints of the fingers was seen in six of the eleven patients who recovered in the first year.

Discussion

To obtain a better insight into the prognosis of early rheumatoid arthritis clinical and serological examinations were made in the initial stage of the disease and repeated during a period of from 1 to 5 years. A considerable number of patients recovered during the first year of observation: in Group A 57 per cent., and in Group B 31 per cent. This confirms the opinion of Short and Bauer (1948) and of Duthie, Brown, Knox, and Thompson (1957), who state that the prognosis depends upon the duration of the disease at the time of the first examination. Initially the incidence of rheumatoid arthritis was almost equal in both sexes, but it reached the chronic stage more frequently in female patients, and at the end of the third year of observation joint involvement was found in sixteen women, but in only six men.

Involvement of the joints of the fingers proved to be of little prognostic value, since it was observed in the initial stage of the disease in 60 per cent. of the patients who recovered during the first year of observation.

More prognostic value could be attached to the Waaler-Rose and the streptococcal agglutination tests. The recovery percentage was much higher in sero-negative patients with normal agglutination titres, than in those who were sero-positive and had high agglutination titres. In Group A, 70 per cent. of the sero-negative patients and only 30 per cent.

of the sero-positive patients recovered. Similar findings were reported by Duthie and others (1957).

After the first year of observation, recovery was rare in both the sero-negative and sero-positive patients; the prognosis thus entirely confirms the description of "polyarthrite chronique évolutive" as put forward by the French clinicians. In Group A, 35 per cent. of the 106 patients were sero-positive when examined for the first time, but 80 per cent. were sero-positive of those observed for 3 years. A positive Waaler-Rose test thus appears to be characteristic of chronic rheumatoid arthritis. Patients with a positive Waaler-Rose test have been known to recover, but relapses are frequent. By improving our methods it might be possible to show that the test is positive in all chronic cases, but it is unlikely, in our opinion, that this will ever be seen in the initial stages, since this disease is not a unity but a syndrome. The French clinicians express this by using the terms "rhumatisme articulaire subaigu", "rhumatisme articulaire subaigu curable", or "polyarthrite subaigu" for the type of disease which progresses favourably.

Positive streptococcal agglutination in sero-negative patients had an unfavourable prognostic significance. These positive agglutinations may probably be attributed to a mechanism similar to that of the Waaler-Rose test, *i.e.* the agglutination of particles sensitized with a globulin. This globulin could be a small quantity of specific antibody against streptococci present in many human sera (Lamont-Havers, 1955). Increased antistreptolysin titres were found with greater frequency in sero-negative patients than in sero-positive patients. The clinical picture in these patients did not resemble that of rheumatic fever, and the prognosis was the same as that in patients with normal antistreptolysin titres. The significance of the increase in titre is not clear. Possibly there is some causal relationship between benign rheumatoid arthritis and streptococcal infections.

Summary

The course of rheumatoid arthritis was followed for 1 to 3 years in 141 patients who were first seen in the initial stage of the disease. In 106 patients the duration of the disease at the time of the first examination was 1 to 3 months (Group A), in 35 patients it was 4 to 6 months (Group B). In the first year of observation, 57 per cent. from Group A and 31 per cent. from Group B recovered.

Initial rheumatoid arthritis was seen with about the same frequency in both sexes, but the chronic form more often in women. The Waaler-Rose test was positive in 35 per cent. of the patients in the

initial stage, in 57 per cent. at the end of the first year of observation, and in 80 per cent. at the end of the third year of observation in patients who still had joint involvement.

In Group A, 71 per cent. of sero-negative patients recovered and only 30 per cent. of sero-positive patients. In Group B, half the sero-negative and none of the sero-positive patients recovered. Positive streptococcal agglutinations had an unfavourable prognostic significance in patients who were sero-negative.

If at the end of the first year of observation joint involvement was still present, recovery was rare, quite apart from the result of the Waaler-Rose test. Increased antistreptolysin titres occurred much more often in the sero-negative group than in the sero-positive group or in healthy persons.

The prognostic significance of arthritic involvement of the joints of the fingers was slight.

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Importance de la réaction de Waaler-Rose, des agglutinations streptococciques et du titre d'antistreptolysine dans le pronostic de l'arthrite rhumatismale

RÉSUMÉ

On étudia l'évolution de l'arthrite rhumatismale pendant 1 à 3 ans chez 141 malades vus pour la première fois à la période de début de la maladie. Chez 106 d'entre eux la maladie était présente depuis 1 à 3 mois (Groupe A) au moment du premier examen et chez 35 d'entre eux depuis 4 à 6 mois (Groupe B). Au cours

de la première année d'observation, 57% du groupe A et 31% du groupe B guérirent.

L'arthrite rhumatismale à la période initiale fut également répartie entre les deux sexes, mais la forme chronique fut plus fréquente chez les femmes. La réaction de Waaler-Rose fut positive chez 35% des malades à la période de début, chez 57% à la fin de la première année d'observation et chez 80% à la fin de la troisième année d'observation.

Dans le Groupe A, 71% des malades séro-négatifs et seulement 30% des séro-positifs guérirent. Dans le Groupe B, la moitié des séro-négatifs et aucun des séro-positifs guérirent. Les agglutinations streptococciques positives eurent une importance pronostique peu favorable chez des malades séro-négatifs.

Quand l'atteinte articulaire était encore présente à la fin de la première année d'observation, la guérison était rare, indépendamment du résultat de la réaction de Waaler-Rose. Les titres d'antistreptolysine augmentés se trouvaient beaucoup plus souvent chez les séro-négatifs que chez les séro-positifs ou des sujets sains.

L'importance pronostique de l'implication arthritique des articulations des doigts fut minime.

Importancia de la reacción de Waaler-Rose, de las agglutinaciones estreptocóccicas y del título de antiestreptolisina en la prognosis de la artritis reumatoide

SUMARIO

La evolución de la artritis reumatoide fué estudiada durante uno a tres años en 141 enfermos vistos por vez primera en al período inicial de la enfermedad. En 106 de ellos (Grupo A) el comienzo de la enfermedad antedatada la primera examinación de uno a tres meses, y en los 35 demás (Grupo B) de cuatro a seis meses. En el curso del primer año de observación, un 57% del Grupo A y un 31% del Grupo B recobraron.

La artritis reumatoide inicial fué observada con igual frecuencia aproximadamente en cada sexo, pero la forma crónica fué más frecuente en las mujeres. La reacción de Waaler-Rose fué positiva en un 35% de los enfermos en el período inicial, en un 57% al cabo del primer año de observación y en un 80% al cabo del tercer año de observación.

En el Grupo A, el 71% de los enfermos sero-negativos y sólo el 30% de los sero-positivos recobraron. En el Grupo B, la mitad de los sero-negativos y ninguno de los sero-positivos recobró. Las agglutinaciones estreptocóccicas positivas tuvieron una importancia pronóstica poco favorable para los enfermos sero-negativos.

Cuando la lesión articular estuvo presente hasta el cabo del primer año de observación, el restablecimiento fué raro, independientemente del resultado de la reacción de Waaler-Rose. Los títulos de antiestreptolisina aumentados se vieron más a menudo en los sujetos sero-negativos que en los sero-positivos o en sujetos sanos.

La importancia pronóstica de la implicación artrítica de las articulaciones de los dedos fué poca.