THE VALUE OF REPEATED COLLOIDAL GOLD TESTS IN RHEUMATOID ARTHRITIS

BY

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It has been shown by several workers that the colloidal gold test is positive in a proportion of cases of rheumatoid arthritis; in 76 per cent. of a series of twenty-four by Carter and MacLagan (1946), in 71 per cent. of a series of eleven by Rennie and Rae (1947), and in 61 per cent. of a series of a hundred by Fraser (1948). Although the latter performed 133 tests in the hundred cases, none of these workers made repeated observations on the same cases over a period to see whether the test altered with the passage of time or with changes in clinical condition. This present investigation was undertaken in order (a) to confirm the observation that the gold sol reaction was indeed positive in a proportion of cases of rheumatoid arthritis; (b) to see whether the test varied over a period of time or with a change in the clinical condition; and (c) to try to discover the significance of the test in the light of clinical and other observations.

Material and Technique

The patients in this series of cases all suffered from rheumatoid arthritis according to the accepted diagnostic criteria for that disease; sixty-five were in-patients, and five were out-patients of the Rheumatic Unit of the Northern General Hospital, Edinburgh, and two were from the general wards of the same hospital.

Serum for the test was obtained by centrifuging a specimen of venous blood which had been allowed to clot and then stored overnight in a refrigerator. The test was performed at weekly, fortnightly, or monthly intervals, depending whether the patient was in the wards or attending the follow-up clinic. The method of performing the test and the gold sol used were those recommended by MacLagan (1944). The reaction was allowed to stand for twenty-four hours at room temperature and the result then interpreted as follows: no precipitation as negative; slight precipitation, just visible on shaking as 1; slight colour loss as 2; more colour loss as 3; supernatant fluid just coloured as 4; and complete precipitation as 5.

The blood sedimentation rate was estimated on every occasion that a gold test was performed using Westergren's technique (1926), and the fall at the end of one hour was recorded.

TABLE 1
NUMBER OF TESTS DONE

Number of tests	Number of months between first and last test										
	1	2	3	4	5	6	7	8	9	10	11
1											
2	5	4		1	3						
3	3	1	4		1	1			1		
4	2	6	5	1	3	1					
5		1	2	2		1					
6			4		1		1				
7					1	2		1	1		
8											
9					1						1
10											
11				1		1					

The table shows the number of tests, the numbers of patients on whom they were performed, and the interval between the first and last test. The eight patients on whom only a single test was performed are omitted.

Results

The results in 72 cases are available for analysis. The number of observations and the period over which they were made are shown in Table 1. The age incidence is given in Table 2, and shows that the series is in keeping with the expected age incidence of the disease (Sclater, 1943).

Of the seventy-two cases in the series, thirty-five (49 per cent.) had always a negative test, and thirty-seven (51 per cent.) had one or more positive tests. This confirms the previous observations that the test is positive in a proportion of cases of rheumatoid arthritis. In eight cases, on which the test was only performed once, it was positive in five and negative in three. Of the remaining sixty-four

tested on more than one occasion, forty-three (50 per cent.) were always negative, eight (12.5 per cent.) were always positive, and twenty-four (37.5 per cent.) were sometimes positive and sometimes negative. The thirty-two patients who were consistently negative were tested, on an average, three times; the twenty-four in whom both positive and negative results were obtained were tested, on an average, six times. It is likely, therefore, that a proportion of the patients in the first group would have passed into the second if tested more often and over a longer period.

In the whole series there were forty-eight women and twenty-four men, an incidence of 2 : 1. The

analysis of the sixty-four cases in which the test was carried out more than once is presented in Table 3. It will be seen that there is no difference between the sexes in the results obtained.

The results were also examined critically to see whether they bore any relation to clinical activity, progress and prognosis, duration of the disease, tissue damage, gold therapy, and muscle biopsy findings.

Clinical Activity.—The cases were divided into two groups; active and inactive, according to the following criteria: the blood sedimentation rate, the state of the joints, and constitutional signs such as changes in weight and the presence or absence of fever and fatigue.

Sixty-two cases were considered to be active and ten to be inactive cases. Of the former, twenty-eight always had a negative test, and thirty-two had at least one positive test; of the latter, inactive cases, seven were always negative, and three had at least one positive test. Thus, although the number of results amongst the inactive cases was too small from which to draw conclusions, there were almost equal numbers of negative and positive results amongst the active cases, so that it can be concluded that a single test is of no value in deciding whether the case is active or not.

Progress and Prognosis.—Repeated tests appear to help in giving a prognosis. In Table 4 it can be seen that of the thirty-two cases observed more than once who gave at least one positive result fifteen went on to give negative reactions and improved clinically; eleven others, however, in spite of clinical improvement, continued to give positive reactions, although in seven of them there

TABLE 2
AGE INCIDENCE

Sex	Age groups						
	5-14	15-24	25-34	35-44	45-54	55-64	65-74 over 75
Females		1	4	14	12	8	6 1
Males		2	2	10	7	3	1

Female mean age = 48.8 years.
Male mean age = 42.7 years.

TABLE 3
SEX INCIDENCE

Sex	Positive tests		Negative tests		Varying tests	
	Cases	%	Cases	%	Cases	%
Female	5	12	23	53	15	35
Male	3	14	10	48	8	38

The single tests performed in eight cases are omitted.

TABLE 4
CLINICAL PROGRESS IN CASES WITH AT LEAST ONE POSITIVE TEST

Cases showing clinical improvement						Cases showing progressive deterioration					
Case No.	Final gold test negative					Case No.	Final gold test positive				
1	4	0	0			16	4	4	3	3	
2	4	1	1	0	0	17	0	5	4	3	
3	4	4	4	3	2 1 0	18	1	3	4	0 3 0 1	
4	5	3	4	1	0 0 0 0	19	4	1	1	3	
5	0	0	1	2	0 0 0 0 0 0 0	20	1	4	1	0 1 2	
6	3	0	0	1	0 0	21	1	1	1		
7	1	1	0	1	0 0 0	22	1	0	2		
8	1	0	0			23	0	0	1		
9	1	0	0	0	0	24	1	1			
10	1	1	1	0		25	0	0	1 2		
11	0	3	0			26	4	5	4 4 5		
12	0	2	3	3	0 0						
13	1	0	1	0							
14	3	0									
15	0	1	0	0	1 0

FIGURE.—Duration of disease.

was a tendency for the results of the test to be less strongly positive. Six cases that had very strongly positive tests, (all except one had a 5), remained clinically very active; these six were the most seriously ill of the whole series, one dying (Case 32) and another (Case 31) becoming moribund after being discharged home at her own request; four (Cases 27 to 30) ran into an active phase of the disease, Case 28, in particular, being severely affected.

There was one exception to this, Case 26; this man was not seriously affected, although his test results were consistently very strongly positive, and he made a good clinical recovery. It was thought, therefore, that some other cause might be responsible but full clinical investigation failed to reveal it. In this connexion, it may be mentioned that two other cases both had strongly positive results but were not suffering from severe arthritis. In one, the disease was of only six weeks' duration, and he had had syphilis and gonorrhoea less than twelve months previously; in the other, the duration was of several years, but he had a positive Wassermann reaction and was undergoing anti-syphilitic treatment while in the rheumatic unit. It is likely that these specific conditions were responsible for the positive results, and as the issue was confused they were omitted from the series.

It would appear, therefore, that in the absence of other pathological conditions, repeated strongly positive results, especially including some 5's, are of grave significance. It should be noted that undue

gravity need not be attached to a single 5, since, in Case 4, a marked clinical improvement took place with the test becoming less strongly positive and finally negative. A trend towards becoming negative, or several negative readings, are of good omen. In these cases where the results fluctuated from negative to various degrees of positivity, the outcome is presumably still in doubt.

An interesting case is number 12. This was a woman who was very upset and deteriorated clinically on learning of a motor accident to her husband while on his way to visit her; her test became positive within a few days, remaining so for two further weeks and became negative again at the end of a month.

Duration.—The relationship of the test to the duration of the disease is shown in Fig. 1. It will be seen that all the observations in cases of under six months' duration were negative; in cases of six to eleven months' duration there were two which had negative and two which had positive results; in Cases of one to three years' duration only ten had negative tests, whereas eighteen had positive, a ratio of nearly 1 : 2. In cases of over three years' duration, there were nearly equal numbers of positive and negative results.

It is concluded that most cases tested in the first six months of the disease will be negative, and that thereafter, there will be an increasingly greater number of positive results until about the third year, from which time onwards the numbers of negative and positive results will be approximately equal.

TABLE 5
BLOOD SEDIMENTATION RATES

Test results	Blood sedimentation rates in mm.			
	0-9	10-29	30-49	over 50
Negative	16	41	19	24
Positive	9	30	20	41

TABLE 6
RADIOGRAPHIC APPEARANCES

x-ray results	Gold results	
	Negative	Positive
Normal	7	2
Early changes of rheumatoid arthritis	14	15
Marked changes of rheumatoid arthritis	6	6
Advanced changes of rheumatoid arthritis	8	14

Sedimentation Rate.—Table 5 shows the number of blood sedimentation rates (BSR) associated with positive and negative gold results. It will be seen that there is a definite tendency for a low BSR to be associated with a negative gold and a high BSR with a positive one. On the other hand, there is clearly no absolute relation between the two tests, since both a normal and an elevated BSR have been found with either a positive or a negative gold test, as can be seen from the table. That is to say, whatever the circumstances are which determine the rate of sedimentation, they are not the same as those which determine the gold reaction, since the two results can be dissociated.

Degree of Arthritis.—The degree of arthritic change was assessed from the radiographs, which were available in every case. The appearances of the radiographs were classified as being normal, or showing the early, marked, or advanced changes of rheumatoid arthritis. Table 6 shows that the damage done is not related to the gold reaction except in so far as the early cases with no x-ray changes gave predominantly negative gold tests.

Gold Therapy.—Seven persons were under treatment with myochrysin during the period of observation, too small a number from which to draw any conclusions; the tests of four remained negative, two became less positive, and one changed from negative to positive and back again to negative. Fifty-seven cases had had gold therapy at some time prior to admission, and of these, thirty had a positive and twenty-seven a negative test.

Muscle Biopsy.—A muscle biopsy was performed on twenty-six cases; no relationship was found between these results and the gold test.

Discussion

In this series, 51 per cent. of the cases gave a positive gold reaction on at least one occasion. Higher figures have been given elsewhere; 76 per cent. (Carter and MacLagan, 1946), 71 per cent. (Rennie and Rae, 1947), and 61 per cent. (Fraser, 1948). None of these workers stated whether the cases were early or late, active or inactive. It may be that the explanation of the smaller percentage in this series is that earlier and less seriously affected cases were available for examination.

Like Fraser (1948), no relationship was found between the results of the test and the age at examination, sex, and degree of arthritic change. His

statement, however, that there is a definite relationship between the results of the test and the blood sedimentation rate can only be accepted with reservations since it has been shown that, while there is admittedly a tendency for a low BSR to be associated with a negative gold, and a high BSR with positive gold, the two can be completely dissociated; they must, then, be due to different mechanisms, and therefore impart different information. It has been shown, by Ham and Curtis (1938), that the BSR can be influenced by (a) changes in the red cells, and (b) quantitative changes of the plasma proteins. A decrease or an increase of any of the plasma proteins may cause a change in the BSR, but unless that change happens, for the time being, to be the same as that causing a positive gold reaction, the two tests will not run in parallel.

The serum protein changes responsible for a positive gold test were first thought to be purely quantitative, resulting in a reversed albumin/globulin ratio. Gray (1940), however, showed that this was not so, since positive results could be obtained in the presence of a normal globulin level and a normal albumin/globulin ratio, while negative results could occur with an elevated globulin ratio and a low or inverted albumin/globulin ratio. In 1942 Gray further showed that the test depended upon the gamma globulin fraction; by adding increasing amounts of electrophoretically pure gamma globulin to serum, he found that the test became increasingly positive, whilst the addition of electrophoretically pure albumin inhibited this. This has since been confirmed by Kabat and others (1942), who also showed (1943) that the test depends on qualitative as well as quantitative changes, in that different albumin preparations vary in their inhibitory power. MacLagan and Bunn (1947) showed that the alpha and beta globulins could also inhibit the reaction.

Electrophoretic studies of twenty-three cases of rheumatoid arthritis were made by Perlmann and Kaufman (1946) and in one case by Dole and Rothbard (1947). The former found that the alpha globulins became elevated early in the disease and the gamma globulins later. This might explain why the gold test is negative in the first six months or so, and when the gamma globulins become elevated later, the test may become positive. An explanation of why so many cases continue to give a negative reaction while just as clinically active as those giving a positive one, may well be that the effect of the elevated gamma globulins (if indeed they are always raised) is inhibited because one or other of the albumin, alpha, or beta fractions is also elevated sufficiently to inhibit the reaction.

Speculation as to why gamma globulins are increased in this disease is outside the scope of this paper, but three theories may be mentioned.

1. That the serum antibody level is raised in response to some unknown antigen, since it is known that some antibodies are attached to the gamma fraction (Enders, 1944).

2. That the liver is damaged and, by analogy with other conditions with liver damage, it is unable to break down the complex "storage" protein of high molecular weight, to the simpler albumin of small molecular weight, finding it easier to produce gamma globulin which has a large molecule (Wilensky, 1946).

3. That an abnormal protein, resulting from synovial or other articular damage, is circulating in the blood and is of the same order of molecular weight and electrophoretic mobility as the gamma globulins (Perlmann and Kaufman, 1946).

Whatever the true explanation may be, there is clearly need for further investigation of the serum protein fractions in rheumatoid arthritis, using a more direct method of measuring them than by the indirect means of showing a relatively increased serum level offered by the colloidal gold reaction. When this has been done in a similar series, it may be possible to explain the significance of this elevated gamma globulin.

Summary

1. The results of the colloidal gold test were studied in a series of seventy-two cases of rheumatoid arthritis of all degrees of activity, in which the age and sex incidence corresponded with that of other published series, and it was therefore considered to be a representative one.

2. Three types of result were obtained; those always positive, those always negative, those which were sometimes one and sometimes the other; and it was concluded that a single test was of no value in assessing clinical activity.

3. Repeated tests were of value in estimating progress and prognosis in that consistently negative tests, or tests tending to become less positive indicated a good prognosis; repeatedly strong tests, particularly if more than one 5 were obtained, indicated a bad prognosis; and tests which were sometimes positive and sometimes negative probably indicated that the outcome of the disease was still undecided.

4. It was shown that the disease had to be at least of six months' duration before the test became positive, and that for the next three years it was twice as often likely to be positive as negative;

thereafter, it was equally likely to be positive as negative.

5. It was demonstrated that the blood sedimentation rate and the gold test were unrelated, although frequently the causative mechanisms for each might simultaneously be in action so that the results might run in parallel.

6. No relationship was found between the results of the test and the age and sex of patients, the degree of arthritic change, or the gold therapy given.

7. It was shown from the literature that the test probably depended upon an elevated serum gamma globulin, but that it could be inhibited by sufficiently elevated serum albumin, alpha, or beta globulins. It was suggested that the explanation of persistently negative results in clinically active cases was that the reaction was being masked by one or more of these other fractions being also elevated.

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Valeur des Réactions à l'or Colloïdal Répétées dans l'Arthrite Rhumatismale

RÉSUMÉ

Les résultats des réactions à l'or colloïdal furent étudiés dans une série de soixante douze cas d'arthrite rhumatismale à tous les degrés d'activité; l'incidence de l'âge et du sexe y correspondait à celle des autres séries

publiées ; cette série peut donc être considérée comme représentative.

Trois types de résultats furent obtenus : les toujours positifs, les toujours négatifs et ceux qui étaient parfois l'un et parfois l'autre ; on conclut qu'une seule réaction était sans valeur pour déterminer l'activité clinique.

Les réactions répétées se sont montrées utiles pour évaluer le progrès et le pronostic ; ainsi les réactions constamment négatives ou celles qui tendaient à devenir moins positives indiquaient un pronostic favorable ; des réactions fortes répétées, surtout lorsqu'on obtenait plus d'un 5, indiquaient un pronostic mauvais ; et les réactions parfois positives et parfois négatives indiquaient probablement que l'évolution de la maladie n'était pas encore décidée.

Il fut démontré que la maladie devait être là depuis six mois au moins pour que la réaction devienne positive et que pendant les trois années suivantes il y avait deux

chances sur une qu'elle soit positive plutôt que négative ; plus tard les chances devenaient égales.

Il fut démontré qu'il n'y avait pas de rapport entre la sédimentation globulaire et la réaction à l'or, bien que souvent les mécanismes respectifs en cause pouvaient agir en même temps créant ainsi une évolution parallèle.

On n'a pas trouvé de rapport entre les résultats de la réaction et le sexe des malades, le degré des changes arthritiques ou l'intensité de la chrysothérapie.

On a montré, en se basant sur la littérature, que la réaction dépendait probablement de la gamma globuline du serum mais qu'elle pouvait être inhibée par l'albumine, par l'alpha- ou par la beta-globuline suffisamment élevées. On a suggéré que les résultats négatifs persistants dans des cas cliniquement actifs s'expliquaient par le fait que la réaction était masquée par l'augmentation simultanée d'une ou de plus de ces fractions.

SEVENTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

This Congress, the first to be held under the auspices of the Ligue Internationale contre le Rhumatisme since the war, was held in New York from May 30 to June 3, under the chairmanship of Dr. R. Freyberg, President of the American Rheumatism Association, who were hosts. After this, a large party of delegates visited the Annual Meeting of the American Medical Association in Atlantic City, and were afterwards taken on a tour of some of the leading centres of rheumatism research in the United States. These included Philadelphia, Boston, Buffalo, Ann Arbor, Chicago, The Mayo Clinic, and Washington, D.C. Some 600 delegates attended from no less than 26 nations ; at the inaugural meeting the audience numbered over 1,000, as it did at the session to which the paper by Drs. Hench, Kendall, Slocumb, and Polley was read, in which they officially announced the remarkable results they had obtained by the use of "Cortisone" (their original report was published in our last number). Five other distinguished physicians had been given 1 gramme of this substance for independent trial and they all personally confirmed similar results. These were Drs. R. Freyberg, E. Boland, P. Holbrook, E. Rosenberg, and Walter Bauer.

At the official banquet the following foreign rheumatologists were presented with Honorary Membership of the American Rheumatism Association.

Lord Horder (London, England), Dr. Charles W. Buckley (Buxton, England), Dr. George D. Kersley (Bath, England), Dr. R. G. Gordon (Bath, England), Dr. J. Barnes Burt (Bath, England), Dr. William Tegner (London, England), Dr. J. A. Glover (London, England), Dr. W. S. C. Copeman (London, England), Dr. Douglas H. Collins (Leeds, England), Prof. L. S. P. Davidson (Edinburgh, Scotland), Dr. Anibal Ruiz-Moreno (Buenos Aires, Argentina), Dr. P. Barcelo (Barcelona, Spain), Dr. Thore Gunnar Kahlmeter (Stockholm, Sweden),

Dr. Gunnar Edström (Lund, Sweden), Dr. Frederik Sundelin (Nyashamn, Sweden), Dr. Jacques Forestier (Aix-les-Bains, France), Dr. Matthieu Pierre Weil (Paris, France), Dr. J. van Breemen (Amsterdam, Holland), Dr. Med. Knud Brochner-Mortensen (Copenhagen, Denmark), Prof. Dr. Med. Cai Holton (Aarhus, Denmark), Dr. Ejnar V. Jarlov (Copenhagen, Denmark), Dr. Svend Clemmesen (Copenhagen, Denmark).

Some of these gentlemen were also elected to the Honorary Membership of the Danish Rheumatism Society.

At a meeting of the Ligue Internationale contre le Rhumatisme, held during the Congress, the following officers were elected for the next four years. President : Professor J. Jarlov (Denmark) ; Secretary General : Dr. W. Tegner (England) ; Treasurer : Mr. O. de Bornemann. President of the European Branch : Dr. W. S. C. Copeman (England) ; Secretary : Dr. G. Edström (Sweden) ; Treasurer : Mr. O. de Bornemann. The Honorary Membership of the Ligue was conferred upon the retiring Secretary General, Dr. J. Van Breemen (Holland), Professor Ralph Pemberton, who unfortunately died suddenly a few days later (an obituary notice appears at p. 256 of this issue), and Dr. Loring Swaim, who deputized for Dr. Pemberton throughout.

Over one hundred papers were read and five "panel" discussions were held. The standard of all these was exceptionally high and the Congress would have been a notable one even if the recent work on the adrenal and pituitary hormones had not been presented. The thanks of all who attended are due to the hosts, who must have worked untiringly for many months previously to render the Congress so successful in every aspect.

The proceedings are being published by the American Rheumatism Association towards the end of the year, and this *Journal* proposes by agreement with them, to publish a series of abstracts of certain of the most important papers together with certain of the other papers in full, of which only an abstract will appear in the Proceedings.

Of the organization of the social side we have nothing but praise. Lavish hospitality and kindness were enjoyed by all the delegates.

The next Congress (European) will be held in Spain in 1951, with a further International Congress in America again two years later.