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BETA-HAEMOLYTIC STREPTOCOCCI AND ANTISTREPTOLYSIN-O TITRES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND A MATCHED CONTROL GROUP

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Since 1935 several reports have dealt with the antistreptolysin-O (ASO) titre in rheumatoid arthritis (RA). The mean and the upper ASO values were first established in a group of normal subjects and in patients with no history of recent streptococcal illness, and subsequently the distribution of the ASO titres was recorded in patients suffering from RA. Table I summarizes the results of Blair and Hallman (1935), Dawson and Olmstead (1936), Longcope (1936), Goldie and Griffiths (1936), Bunim and McEwen (1940), Winblad (1941), Westergren and Stavenow (1947), van Loghem-Langereis (1950), Oker-Blom and Widholm (1952), Quinn and Liao (1952), Jacqueline, Eyquem, and Jochem (1954), Otten and Westendorp Boerma (1959). These results are very divergent; most studies show higher ASO titres in patients with RA, but the significance of this difference is variable. Moreover, in most of the reported studies, the control group was not matched to the patient group with regard to age distribution; the controls were often physicians or laboratory-workers and were investigated at different seasons of the year. All these factors might influence the ASO titres. Furthermore, no data were available about the epidemiology of β-haemolytic streptococci in RA, nor about the antibody response of such patients in long-term studies. The behaviour of RA patients in the case of a common bacterial infection is a worth-while study, since in recent years much stress has been laid on possible immunological disturbance in rheumatoid disease, and since experimental and clinical evidence favours the hypothesis that bacterial infection may be responsible for the origin of the rheumatoid factor (Eyquem, Guyot Jeannin, and Podliachouk, 1959; Abruzzo and Christian, 1961; Svartz, 1962; Williams and Kunkel

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TABLE I

ANTISTREPTOLYSIN-O IN RHEUMATOID ARTHRITIS
SUMMARY OF REPORTED DATA, 1935-59

Year	Authors	Control Group		RA Group	
		No. of Subjects	Per cent. Raised Titres	No. of Subjects	Per cent. Raised Titres
1935	Blair and Hallman	5	0> 100 U	45	33
1936	Dawson and Olmstead	91	5 (mean 62 U)	151	not stated (mean 51 U)
	Longcope	55	2	55	46
	Goldie and Griffiths	50	2	60	25
1940	Bunim and McEwen	39	3	72	15
1941	Winblad	61	20	178	31
1947	Westergren and Stavenow	346	15·9	41	29·3
1950	van Loghem-Langereis	144	10·4	224	23·6
1952	Oker-Blom and Widholm	86	41	48	23
	Quinn and Liao	32	6·2	56	10·7
1954	Jacqueline and others	115	7·8	393	56·2
1959	Otten and Westendorp Boerma	100	16	100 (Rose +) 100 (Rose −)	16 39

1962). For these reasons we decided to make a combined bacteriological and serological study and to determine the ASO level and to take a nose and throat swab monthly, for 6 months, in a group of RA patients and in a control group without rheumatoid arthritis (NRA).

Methods

Selection of Patients

RA and NRA patients were selected between January 9 and March 15, 1961. All attended our outpatients department at least once a month. Both groups had the same age and sex distribution. In cases of sore throat no penicillin was given.

All RA patients suffered from definite rheumatoid arthritis according to the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). Activity of the disease was not taken into account. Half of the patients were treated with gold, the other half received acetylsalicylic acid, antimalarial drugs, pyramidon, or phenylbutazone. Only two patients received a short course of prednisone because of gold dermatitis. Eleven of these patients had to be hospitalized in the course of the study.

In the control group, cervical syndrome or disk lesion was diagnosed in thirteen cases, painful shoulder in eleven, osteo-arthritis in ten, lumbar disk lesion in nine, myalgia in seven, and "tennis elbow" in two; there were three miscellaneous cases and five with no abnormality. Three of these patients were hospitalized during the study.

Completion Rate.—63 RA patients and sixty NRA patients fulfilled the criteria and were followed for 6 months, the completion rate being 95 and 93 per cent. respectively. Due to the relatively long selection period, the first patients were seen from January to June and the last patients from March to August. Since 95 per cent. of the RA patients were admitted to the study in January and February whereas 75 per cent. of the control group were admitted in February and March, and since it was considered of utmost importance that both groups should be examined strictly simultaneously, only the data obtained from March to June were taken into account for most of the calculations. In order to obtain a more valuable statistical analysis, we required for the March-to-June data a 100 per cent. completion rate, and in this way were able to include 54 RA patients and 55 NRA patients. The age and sex distribution remained the same in both groups after the loss of respectively nine RA and five NRA patients (Table II).

Plan of the Study

Once a month each patient was asked about possible symptoms of streptococcal illness. A nose swab was introduced into each nostril; for the throat, we used two cotton wool swabs mounted on one cork stopper; both tonsils were swabbed with such a double throat swab; in the beginning of the study, before being swabbed, the tonsils of the patients were expressed with a wooden tongue spatula; later on, only swollen tonsils were first expressed.

A blood sample was drawn for determination of the ASO titre. The first blood sample was also used for the determination of the rheumatoid factor, antinuclear factors, total serum protein, and serum protein electrophoresis.

Once during the study, *x*-rays were taken of the sinuses in order to avoid a bias due to a greater incidence of infection foci of possible streptococcal origin in one group or the other.

Laboratory Methods

Swabs.—Within 15 minutes to 3 hours the swabs arrived in the laboratory.

The nose swabs were inoculated on a 5 per cent. defibrinated sheep's blood agar plate and subsequently immersed in sheep's blood broth.

The double throat swabs were inoculated in the following way. One swab was inoculated on two sheep's blood agar plates and then immersed into a sheep's blood broth; after 24 and 48 hrs' incubation at 37° C., a sample of this broth was inoculated on two blood agar plates. The other swab was immediately put into a fluid Pike's broth, a sample of which was inoculated on two blood agar plates after 24 and 48 hrs' incubation at 37° C. From each pair of blood agar plates, one was incubated aerobically and the other anaerobically. Group B and

TABLE II

AGE AND SEX DISTRIBUTION OF RA AND NRA GROUPS AT THE START OF THE STUDY AND AFTER THE LOSS OF FOURTEEN PATIENTS

Age (yrs)	At the Start				After the Loss of 14 Patients			
	RA		NRA		RA		NRA	
	M	F	M	F	M	F	M	F
20-29	1	4	1	3	1	3	1	3
30-39	3	6	4	4	3	5	3	4
40-49	8	8	9	6	8	7	8	5
50-59	9	10	7	8	8	9	7	7
⩾60	7	7	9	9	6	4	8	9
	28	35	30	30	26	28	27	28
Total	63		60		54		55	

Group F streptococci appeared to grow better in an anaerobic medium. Further details about the techniques used are to be published elsewhere (Lorrier, 1964). Representative colonies were subcultured and grouped according to the technique of Lancefield (1933). Special care was taken not to overlook Group F colonies which are smaller than the colonies of other groups. Group A streptococci were typed by the slide agglutination method of Griffith (1934) supplemented in some by the micro-precipitin method of Swift, Wilson, and Lancefield (1943). The technique used was that advocated by the Streptococcus Reference Laboratory, Colindale, Great Britain.

Blood Analyses

A.S.O. Titration.—The method of Rantz and Randall (1945) was used with slight modifications. Sheep cells were used instead of rabbit cells. A two-fold ASO variation was considered as significant.

Rheumatoid Factor.—This was demonstrated by the Waaler-Rose test modified by Valkenburg (1963). A titre of 1/32 was considered positive.

Anti-nuclear Factors.—These were demonstrated by the Coons' fluorescent antibody method using human granulocytes as described by Alexander, Bremner, and Duthie (1960).

Total Serum Protein was measured by biuret method.

Paper Electrophoresis.—Amidoschwarz was used for the staining of the serum proteins; the quantity of dye bound on the various protein fractions was measured colorimetrically after elution.

Radiography.—The *x* rays of the paranasal sinuses were obtained by a mandibulo-occipital view of the head with open mouth.

Results

Bacteriological Findings

Prevalence.—This signifies the number of subjects presenting a positive culture for β-haemolytic streptococci at a certain time (point prevalence) or during a certain period (period prevalence); whether the recovered streptococcus had been acquired before or during the study is not taken into account.

From March to June (period-prevalence), β-haemolytic streptococci were found in thirty of the 54 RA patients and in 21 of the 55 NRA patients (Table III). This difference has no statistical significance. Group A streptococci were recovered in eight RA patients and two NRA patients; this four-fold difference in prevalence does not reach a 5 per cent. significance level because of the small numbers involved and the necessity to apply Yates' correction for calculation. When Groups A, C, and G streptococci are combined—they are all known for their pathogenicity and their ability to produce streptolysin-O (Todd, 1939)—the difference between 23 RA patients and nine NRA patients is significant at the 1 per cent. level.

There was no great monthly variation in point prevalence (Table IV). For Groups A, C, and G streptococci there was some tendency to increase from March to June, for Groups B, D, E, F, and H streptococci, some tendency to decrease.

The statistically significant difference between RA

TABLE III

NUMBER OF SUBJECTS PRESENTING AT LEAST ONE POSITIVE CULTURE FOR β-HAEMOLYTIC STREPTOCOCCI DURING THE MARCH-TO-JUNE PERIOD (PERIOD PREVALENCE)

Group	No. of Subjects Examined	Number of Subjects with Positive Cultures									
		All Streptococcus Groups	Group								Groups
			A	B	C	D	E	F	G	H	A + C + G
RA	54	30	8	6	12	1	0	6	5	1	23
NRA	55	21	2	9	6	0	1	8	2	0	9
P			<0·10 >0·05								0·01

TABLE IV

SUBJECTS PRESENTING A POSITIVE CULTURE FOR β-HAEMOLYTIC STREPTOCOCCI EACH MONTH DURING THE MARCH-TO-JUNE PERIOD (POINT PREVALENCE)

Positive Cultures	Subjects	March	April	May	June
ACG	RA	11	13	17	16
	NRA	2	3	5	5
	P	<0·05	<0·05	<0·01	<0·05
BDEF	RA	7	8	4	6
	NRA	12	9	10	6
	P	n.s.*	n.s.*	n.s.*	n.s.*

*n.s. = No significant difference

and NRA patients as regards Groups A, C, and G was found each month.

Acquisition Rate.—This is defined as the number of newly-occurring streptococci per 100 patients per month:

$$\text{Acquisition rate} = \frac{\text{No of acquisitions} \times 100}{\text{No of patients} \times \text{No of months of follow-up}}$$

It is obvious that the longer the observation period, the more accurate the calculation of the acquisition rate. We therefore analyzed on this point the data obtained for 6 months. The RA group comprises 358 patient-months, the control group 332. The acquisition rates for the different streptococcal groups are listed in Table V. Although there is a two or three-fold difference between the two patient groups for some streptococcal groups, this difference should not be considered important because the absolute numbers are small. For this reason the figures presented in Table V are not well suited to statistical analysis. Nevertheless, if one wants to perform statistical analysis, one can combine Groups A, C, and G on one hand and Groups B, D, E, F, and H on the other; acquisition rates can be considered as percentages and compared as such. In that case no statistically significant difference is found. Acquisition rates were also calculated for the March-to-June period with quite similar results.

The monthly variations in the acquisition rate are shown in Fig. 1 (opposite). The highest levels are found in February, there is a sharp decline in March, rather constant figures from March to June, and a further decline in July. The levels for August and for the control group in February are related to only three or eleven subjects; it is preferable not to attribute any importance to them. Throughout the whole study, the curves of acquisition rate of RA and NRA parallel each other; even the greatest monthly difference (February) is not statistically significant.

Clinical Symptoms (sore throat and pain on swallowing).—These were presented by seven patients in each group; three RA patients had a concomitant positive culture for streptococcus group A and a two-fold ASO increase; one other RA patient and one NRA patient showed recovery* of a Group C streptococcus without ASO variation; one further RA patient and one NRA patient had a subsequent ASO rise without isolation of any streptococcus. From the fourteen patients with clinical symptoms, seven (2 RA and 5 NRA) showed no laboratory evidence of streptococcal infection.

Streptococci were recovered without clinical symptoms but with concomitant ASO variations ten times in the RA group and six times in the NRA group. With neither clinical symptoms nor ASO variation they were recovered 44 and 31 times respectively. ASO variations without symptoms and without recovery of streptococcus occurred fifteen and eleven times respectively. Streptococcus recovery and/or ASO variation were often seen more than once in a single patient.

Lastly, eighteen RA patients and eighteen NRA patients presented neither clinical nor bacteriological nor serological evidence of infection.

Disappearance Rate.—For these calculations the 6 months' data are also used. Not only the newly-acquired streptococci, but all recovered cocci are taken into account. These calculations can give only an approximation of the real disappearance rate, as for many streptococci the acquisition, the disappearance, or both took place before or after the observation period. Table VI (opposite) shows the approximate mean duration of the recovery periods of the different streptococci. It is clear that

* "Recovery" includes all streptococci cultured, not only the newly-acquired ones.

TABLE V

ACQUISITION RATES FOR THE DIFFERENT STREPTOCOCCAL GROUPS DURING THE 6 MONTHS' PERIOD

Streptococcal Groups	RA		NRA	
	No. of Acquisitions	Acquisition Rate	No. of Acquisitions	Acquisition Rate
A	4	1·34	3	1·09
C	8	2·68	6	2·18
G	9	3·02	3	1·09
A + C + G	21	7·04	12	4·36
B	6	2·01	2	0·73
F	9	3·02	7	2·54
DEH	2	0·67	1	0·36
B + F + D + E + H	17	5·70	10	3·63
Total	38	12·74	22	7·99

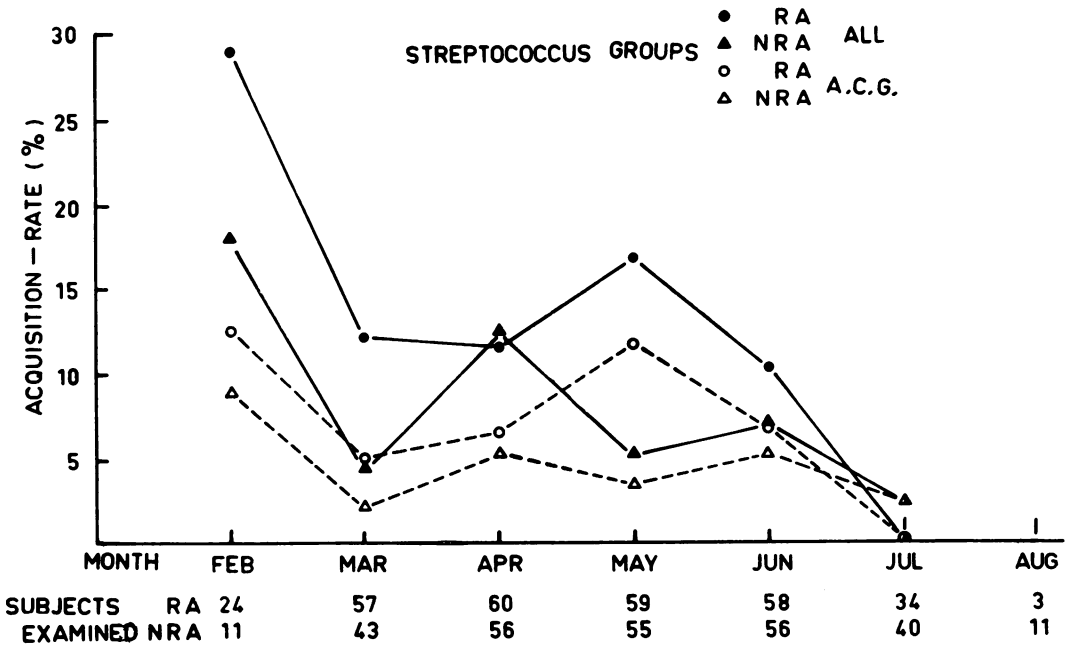

Fig. 1.—Monthly variations of acquisition rate for β-haemolytic streptococci.

TABLE VI

APPROXIMATE MEAN DURATION OF RECOVERY PERIODS OF STREPTOCOCCAL GROUPS (MTHS)

Streptococcal Group	RA	NRA	Ratio RA:NRA
A	3·45	2·25	1·53
B	2·83	4·08	0·69
C	2·93	1·87	1·56
F	1·60	2·33	0·68
G	2·30	1·66	1·38

Groups A, C, and G were recovered for a longer period in the RA group than in the NRA group, and that the reverse is true for Groups B and F.

Serological Data

The distribution of the ASO values for the March-to-June period is shown in Table VII. The highest antibody titre seen during the period is considered for each patient. No significant difference appears between the RA and NRA subjects ($\chi^2_{(4)} = 8{\cdot}312$; $0{\cdot}10 > P > 0{\cdot}05$). However, a titre above 300 U

TABLE VII

DISTRIBUTION OF ASO TITRES, SHOWING FOR EACH PATIENT THE HIGHEST TITRE OBSERVED FROM MARCH TO JUNE

ASO Titres	RA	NRA	Totals	
<100 U	17	18	44	
100 U	2	7		
150 U	14	12	26	99
200 U	6	10	16	
300 U	6	7	13	
400 U	2	1	10	10
600 U	4	0		
800 U	2	0		
1200 U	1	0		
Total	54	55		109
χ^2 (degrees of freedom)			$\chi^2_{(4)} = 8{\cdot}312$	$\chi^2_{(1)} = 7{\cdot}209$
P			$0{\cdot}05 < P < 0{\cdot}10$	$0{\cdot}005 < P < 0{\cdot}01$

was observed in only one NRA patient as opposed to nine RA patients; this difference in the distribution of titres above 300 U is statistically significant ($\chi^2_{(1)} = 7{\cdot}209$; $0{\cdot}01 > P > 0{\cdot}005$).

The distribution of the ASO titres is not the same for each month separately. In March and in April there is no significant difference at the 5 per cent. level for the distribution of all titres or for that of the higher titres (>300 U).

On the contrary, in May and June, the two groups differ statistically from each other, both for all titres ($0{\cdot}02 > P > 0{\cdot}01$) and for the higher titres, which are more frequent in the RA group. Titres of 300 U and even of 200 U can now be included among the higher values.

The time factor is illustrated in Fig. 2, in which the proportion of patients with an ASO value above 150 or 200 U is plotted against time. These percentages are greater in the RA group than in the NRA group. In the RA group they show only a slight decline from March to June, but in the control group there is a sharp decline from the beginning to the end of the study: the seasonal influence is thus more marked in the controls than in the RA patients.

Influence of Treatment.—Since more than half of the patients with RA received gold salts, a possible influence of the heavy metal upon the serological reaction has to be considered. In fact, the same distribution of ASO values is seen in the gold-treated patients as in the other RA patients.

Relationship with Gamma Globulins, Rheumatoid Factor, and Anti-nuclear Factors.—No correlation could be demonstrated between the ASO titres on the one hand, and the gamma globulin level and the presence of rheumatoid or anti-nuclear factors on the other.

So far serological data have been analyzed by comparing individual titres. A more dynamic study should include a comparison of the antibody curves. For this purpose too, the 6 months' data are much better suited than the 4 months' data. A two-fold variation in titres is considered to be significant. The RA group shows twelve two-fold ASO increases, and the NRA group only four.

X-ray Examination of the Sinuses

Radiological examinations of sinuses showed no difference in the distribution of pathological features that might be due to the presence of foci where streptococci could be harboured.

X rays of the sinuses are available in 53 subjects of

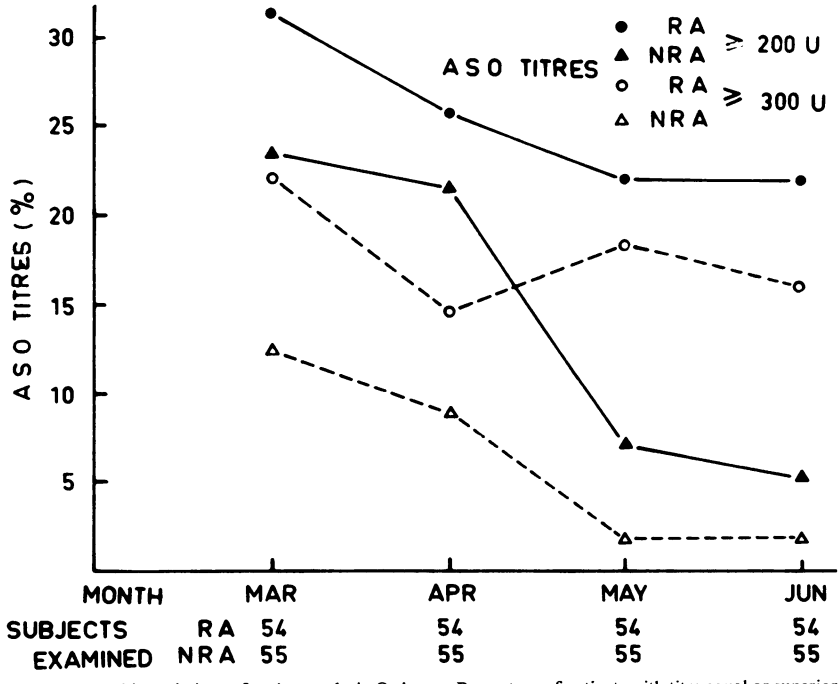

Fig. 2.—Monthly variations of antistreptolysin O-titres. Percentage of patients with titre equal or superior to 200 U and 300 U plotted against time.

both groups; definite pathological changes compatible with sinus infection were observed in 13 per cent. of the RA patients and 19 per cent. of the NRA patients.

Discussion

The results may be summarized as follows:

(1) Throughout the whole observation period, β-haemolytic streptococci of Group A, C, or G are recovered significantly more often in RA than in NRA patients.

(2) The acquisition rate of all groups of β-haemolytic streptococci is 1·6 times greater in the RA than in the NRA group, but this has no statistical significance.

(3) The elimination rate of β-haemolytic streptococci Group A, C, or G is reduced in the RA group.

(4) Raised ASO titres (>150 U) do not occur more frequently in the RA group, but higher titres (>300 U) do. Two-fold ASO variations occur with a slightly greater frequency in the RA group, but this has no statistical significance.

(5) No correlation is found between ASO level and gold treatment, rheumatoid factor, anti-nuclear factors, or serum gamma globulin level.

(6) No difference is found between the two groups as regards radiological examination of sinuses.

Studies of the epidemiology of β-haemolytic streptococci should last at least one year, as there is a marked seasonal influence. This ideal condition could not be met in this study. However, as the purpose was to compare two groups of patients, it was not necessary to have a one-year follow-up, provided both groups were studied simultaneously, and the monthly acquisition rate of streptococcus was recorded. For Group A streptococci, a rate of 1·34 (RA) or 1·09 (NRA), constant throughout a whole year, would mean respectively 0·16 and 0·13 acquisitions per patient per year. These figures are lower than those reported in the literature for persons of comparable age: James, Badger, and Dingle (1960) reported 0·21 acquisitions per patient per year and Zanen, Ganor, and van Toorn (1959) reported 0·24. From the work of Valkenburg, Goslings, Bots, de Moor, and Lorrier (1963), it is known that in 1959 and in 1960 in the neighbourhood of Leyden streptococcal pharyngitis had its peak incidence in November. If the total acquisitions parallel the number of clinical infections, it may be stated that this study was carried out in a low acquisition period; it may be supposed that a one-year study would have revealed higher acquisition rates, probably in the same range as 0·21 and 0·24.

Although Group A, C, and G streptococci are not acquired significantly more often in RA patients than in controls, the prevalence of these groups of streptococci is definitely higher in the RA group. That means that not many more pathogenic streptococci enter into either group, but that the chance to recover one of them is definitely greater in the RA group. Only one explanation can be afforded: RA patients do not eliminate their pathogenic streptococci as quickly as controls. We should have liked to verify this hypothesis by measuring the real mean duration of occurrence of streptococci, but for this a longer follow-up would have been necessary. It is difficult to obtain repeated throat swabs from patients for a prolonged period, especially from control subjects who would otherwise be discharged. We do not therefore know the true mean elimination period, but the approximate value obtained agrees with the other observed facts of nearly equal acquisition rate and different prevalence. It should be emphasized that all streptococcal groups are acquired 1·6 times more often in the RA group and that only A, C, and G streptococci have a definitely higher prevalence in RA subjects. In the NRA group non-pathogenic streptococci are eliminated more slowly than in the RA group and the reverse is true for pathogenic streptococci. So the higher prevalence of A, C, and G streptococci in the RA subjects is mainly due to a lower elimination rate.

In the literature, figures for the elimination period of β-haemolytic streptococci are reported only for Group A. From the work of Zanen and others (1959) and James and others (1960) we may deduce that, in healthy adults of comparable age, 33 per cent. of Group A streptococcus acquisitions last for more than 4 months. In the RA patients of the present study, 45 per cent. of acquisitions lasted for more than 4 months and this figure might have been even greater if the follow-up period had been as long as that of the other studies.

What is the significance of the reduced ability of RA patients to eliminate pathogenic streptococci? There are three possible explanations:

(*a*) The reduced elimination of β-haemolytic streptococci is the consequence of the chronic disease which lowers the resistance to all kinds of invading agents.

(*b*) β-haemolytic streptococci are one of the aetiological factors of rheumatoid disease or at least of the rheumatoid factor.

(*c*) Both facts are the result of some immunological disturbance.

In the first hypothesis, a higher acquisition rate of β-haemolytic streptococci might also be expected, at least when the disease is active. In this study more acquisitions were observed in the RA group, but

without statistical significance; the observed difference might be purely fortuitous but it is also possible that it would become significant if the study were repeated on a larger scale. It should be remembered that the grade of activity of the disease was not taken into consideration.

In considering the second hypothesis, the work of Williams and Kunkel (1962) should be cited. These authors noticed the occurrence of the rheumatoid factor in 50 per cent. of 44 patients suffering from subacute bacterial endocarditis. There is also experimental evidence that rheumatoid factor might be induced by bacterial agents. Eyquem and others (1959) produced a rheumatoid factor-like substance by immunizing rabbits with various micro-organisms; among others Group C and fourteen types of Group A streptococci were used; five other types of Group A, and Groups B, E, F, H, K, L, O, P, Q, gave negative results; Group G was not used. Svartz (1962) claimed to have produced not only the rheumatoid factor in sixteen out of forty white rats, but also mild arthritis in two out of three pigs (Svartz, 1961) sensitized with Group B streptococci. It is remarkable that Eyquem had negative results with Group B, and that our RA patients acquired Group B streptococci more often than controls, but eliminated them quickly so as to give a lower prevalence.

Summary and Conclusions

The antistreptolysin-O titre has been determined and a throat and a nose swab have been taken monthly for 6 months in a group of patients with rheumatoid arthritis and a control group. At any moment of the study the prevalence of β-haemolytic streptococci of Groups A, C, and G was significantly higher in the patients with rheumatoid arthritis than in the controls. This was due in part to a slightly higher acquisition rate, but mainly to a reduced elimination rate. Equal numbers of raised antistreptolysin-O titres (>150 U) were found in both groups, but significantly more higher titres (>300 U) in the rheumatoid patients; this seems to agree with the lower elimination rate, as prolonged infection leads to higher antibody response.

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Les streptocoques β-hémolytiques et les titres d'antistreptolysine-O chez des malades atteints d'arthrite rhumatismale et chez des témoins assortis

RÉSUMÉ

On a déterminé le titre d'antistreptolysine-O et on a fait des prélèvements dans la gorge et dans le nez tous les mois pendant six mois chez des malades atteints d'arthrite rhumatismale et dans un groupe de témoins. À tout moment de cette étude l'incidence des streptocoques hémolytiques— du groupe A, C et G était appréciablement plus grande chez les malades atteints d'arthrite rhumatismale que chez les témoins. Cela était dû en partie à l'acquisition un peu plus fréquente, mais surtout à l'élimination ralentie. On a trouvé un nombre égal de titres augmentés d'antistreptolysine-O (>150 U) dans les deux groupes, mais il y avait plus de titres appréciablement élevés (>300 U) chez les malades rhumatisants; cela semble s'accorder avec l'élimination plus lente, étant donné qu'une infection prolongée mène à la création augmentée de l'anticorps.

Los estreptococos β-hemolíticos y los valores de antistreptolisina-O en enfermos con artritis reumatoide y en testigos apareados

SUMARIO

El valor de antistreptolisina-O fué determinado y las secreciones nasales y faríngeas fueron examinadas mensualmente durante seis meses en un grupo de enfermos con artritis reumatoide y un grupo de testigos. Durante el tiempo entero de la investigación la incidencia de los estreptococos hemolíticos-β del grupo A, C y G fué significativamente mayor en los enfermos con artritis reumatoide que en los testigos. Esto se debió en parte a la adquisición algo más frecuente, pero principalmente a la eliminación más lente. En ambos grupos se encontró un número igual de valores aumentados de antistreptolisina-O (150U), pero hubo un mayor número de valores apreciablemente elevados (300 U) en los reumáticos; esto parece acordarse con la teoría de eliminación más lenta, ya que una infección prolongada provoca una respuesta más fuerte del anticuerpo.