SERUM CHOLESTEROL IN RHEUMATIC DISEASES

BY

M. G. LONDON,* M.D.

K. D. MURDEN,† M.D., M.R.A.C.P.

Honorary Clinical Assistants, University Rheumatism Centre, Manchester Royal Infirmary

J. V. HEWITT, M.Sc.

Biochemist, Empire Rheumatism Council Field Unit

A recent study of population samples showed that women who had osteoarthritis tended to have above-average serum cholesterol (Kellgren, 1961). This interested us in studying the serum cholesterol in patients with other rheumatic diseases.

In a study of the causes of death in 130 patients with rheumatoid arthritis Cobb *et al.* (1953) found less than the expected number of deaths from myocardial infarction. If an elevated serum cholesterol is related to the development of coronary artery disease, as suggested (Keys *et al.*, 1952; Bronte-Stewart *et al.*, 1955; Albrink *et al.*, 1961; Kannel *et al.*, 1961), and if patients with rheumatic disease have a lower incidence of coronary artery disease, then we might expect to find lower serum cholesterol in such patients. We therefore decided to study the serum cholesterol in patients with rheumatic disease, comparing the results with appropriate mean values obtained from two population surveys.

Methods

The figures used as representative of normal cholesterol values in the north-west of England were arrived at by estimating the serum cholesterol in blood samples obtained during surveys of random samples of the populations of the town of Leigh and the rural area of Wensleydale; details of these population samples are published elsewhere (Ball and Lawrence, 1961). All the patients with rheumatic diseases studied were seen either in the out-patient clinic or in the wards of the Manchester Royal Infirmary and the Devonshire Royal Hospital, Buxton. The patients with pulmonary disease were in the wards of the Monsall and Baguley Hospitals and were studied by the kind permission of Dr. W. Robinson, consultant chest physician. Serum cholesterol determinations were all performed by the method of Sackett. Sedimentation rates (Westergren) were performed at the time of the serum cholesterol determination. All serum cholesterol on ward patients were determined the day after admission. No patients were included in this study who were pregnant at the time of the cholesterol determination or who were known to have thyroid disease, idiopathic diabetes mellitus, liver disease, familial hypercholesterolaemia, or nephrosis. Unless stated otherwise, the patients

studied were those consecutively seen during periods in 1959 to 1962.

Results

Inflammatory Disease

In Figs. 1-4 are shown the mean serum cholesterol and 95% limits of normal distribution in relation to age and sex for the population samples; as in fact the lower tail of the distribution was generally shorter than the upper tail, this by no means provides exaggerated contrasts. Superimposed on these graphs are represented the single determinations of serum cholesterol for 314 patients with inflammatory polyarthritis, excluding gouty arthritis. It can be seen that the mean serum cholesterol of ward patients and out-patients of both sexes is lower than the population mean for the appropriate age and sex. It can also be seen that this difference is most striking in the ward patients.

FIG. 1

FIG. 2

FIG. 1.—Serum cholesterol of 93 female ward patients with inflammatory polyarthritis (dots) superimposed on a graph wherein the centre curve represents the mean serum cholesterol, and the outer two curves the 95% limits of normal distribution for 1,133 women in two population surveys. FIG. 2.—Serum cholesterol of 48 male ward patients with inflammatory polyarthritis superimposed on a graph wherein the centre curve represents the mean serum cholesterol, and the outer two curves the 95% limits of normal distribution for 1,083 men in two population surveys.

FIG. 3

FIG. 4

FIG. 3.—Serum cholesterol of 90 female out-patients with inflammatory polyarthritis shown as in Fig. 1. FIG. 4.—Serum cholesterol of 83 male out-patients with inflammatory polyarthritis shown as in Fig. 2.

*Fellow of the National Foundation, New York. Supported in part by a travel grant from the Wellcome Research Foundation.

†Supported by a grant from the Nuffield Foundation.

The same observation of low serum cholesterol values in inflammatory polyarthritis was observed when the results of the determinations were analysed according to disease category (Fig. 5). Again, also, the ward patients, represented for the most part by patients with rheumatoid arthritis, had the lowest mean values. However, the patients with Reiter's disease, all of whom were out-patients, did not differ significantly from the general population nor from a group of patients with miscellaneous conditions seen in the out-patient clinic (degenerative disk disease, traumatic synovitis, arthralgia, peripheral neuropathy, shoulder-hand syndrome, etc.).

Serum cholesterol determinations were also done on serum from 39 ward patients with chronic inflammatory pulmonary disease. Thirty-three of these had chronic bronchitis or bronchiectasis with purulent sputum and six had active pulmonary tuberculosis. The mean serum cholesterol of this group was also significantly below the appropriate mean for the population (Fig. 5).

The common feature that distinguishes ward patients from out-patients and the Reiter's group from the other patients with inflammatory polyarthritis is the severity of the disease and degree of inflammatory change.

FIG. 5.—Mean deviations of serum cholesterol from the appropriate population means by disease categories. (111 rheumatoid arthritis in-patients; 99 rheumatoid arthritis out-patients; 12 systemic lupus erythematosus, 5 panarteritis nodosa, 4 systemic sclerosis, and 11 psoriatic arthritis patients; 49 patients with ankylosing spondylitis; 23 with Reiter's disease; 23 with miscellaneous conditions; 39 with chronic inflammatory pulmonary disease; 54 with osteoarthritis; and 30 with gouty arthritis.)

Ward patients usually have greater constitutional illness than out-patients, and patients with Reiter's disease usually have a benign illness. It would therefore appear that not only is the serum cholesterol low in patients with inflammatory polyarthritis but those with the most severe illness have the lowest cholesterol value.

That this observation is not restricted to inflammation in joints is borne out by the similarly low serum cholesterol values found in patients with active pulmonary inflammation.

Disease Activity

A correlation was found between the serum cholesterol and the sedimentation rate, the cholesterol being lower with higher rates of sedimentation. This correlation did not exist in each individual case, but when the mean deviations of cholesterol values from the appropriate population means for a group of patients with low rates of sedimentation (0–20 mm. per hour) were compared with a group with high sedimentation rates (over 60 mm. per hour) marked differences were noted (see Table, a). The differences were significant in patients with S.C.A.T.-positive rheumatoid arthritis and S.L.E. ($P < 0.01$), S.C.A.T.-negative rheumatoid arthritis, and psoriatic arthritis and Reiter's disease ($P < 0.05$).

We also studied 40 patients with varying types of inflammatory polyarthritis who had two serum cholesterol determinations at intervals of three weeks to three years. Twenty-four of these patients had rheumatoid arthritis, eight Reiter's disease, five systemic lupus erythematosus, two ankylosing spondylitis, and one panarteritis nodosa. Disease activity was estimated as severe, moderate, or little or none on the basis of the sedimentation rate, loss of weight, and the clinical impression of the examiner. The disease activity was estimated at the time of both serum cholesterol determinations and the change in disease activity between the two determinations was also estimated. In all instances the disease activity was greatest at the time of the first determination, and either diminished or

Mean Deviations of Serum Cholesterol from the Appropriate Population Means (Related to E.S.R.) in Patients with Inflammatory Polyarthritis

(a) By Disease Categories

E.S.R. Levels (mm./1 hr. Westergren)	S.C.A.T.-positive R.A. and S.L.E.		S.C.A.T.-negative R.A. and Psoriasis		Ankylosing Spondylitis		Reiter's Disease		P.N. and S.S.*	
	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population
0–20	35	–34.6	24	–30.6	15	–33.0	12	+9.6	3	+53.3
21–40	47	–51.0	27	–25.8	14	–30.0	4	–1.3	2	–45.0
41–60	34	–56.0	10	–56.5	8	–56.3	3	–25.0	2	–35.0
61+	42	–70.6	14	–64.6	10	–68.0	4	–50.0	2	–65.0
Total	158	–53.7	75	–38.7	47	–43.6	23	–7.2	9	–14.4
61+ minus 0–20		–36.0		–34.0		–35.0		–59.6		–118.3

(b) Treated and not Treated with Steroids

E.S.R. Levels (mm. / hr. Westergren)	On Steroids. 56 In- and 28 Out-patients		Not on Steroids				Total Patients with Inflammatory Polyarthritis		
			85 In- and 45 S.C.A.T.- positive Out-patients		98 S.C.A.T.- negative Out-patients				
	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population	No.	Mean Chol. ± Population	Total Range of Chol. ± Population
0-20	22	-26.2	29	-23.2	38	-24.1	89	-24.3	-170 to +225
21-40	17	-37.4	46	-50.5	31	-21.1	94	-38.4	-145 „ +115
41-60	21	-61.4	25	-64.6	11	-14.1	57	-53.9	-165 „ +70
61+	24	-75.7	30	-66.5	18	-59.4	72	-67.8	-190 „ +45
Total	84	-51.4	130	-50.8	98	-28.5	312	-44.0	-190 „ +225
61+ minus 0-20		-49.5		-43.3		-35.3		-43.5	

* Panarteritis nodosa and systemic sclerosis. S.C.A.T. = Sheep-cell agglutination test.

remained unchanged. It was observed that the serum cholesterol rose most markedly in those patients whose disease activity diminished most markedly; in those exhibiting moderate or little diminution of disease activity the serum cholesterol showed correspondingly lower increase. The differences in the mean rise of serum cholesterol between the first and the second and between the second and the third group are both highly significant ($P < 0.001$) (Fig. 6).

FIG. 6.—Disease activity related to the serum cholesterol in groups of patients with two cholesterol determinations (see text), showing a mean increase in serum cholesterol in proportion to the amount of diminution in disease activity. Numbers in parentheses refer to the number of patients in each group.

Though more refined measures of disease activity, such as loss of weight, grip strength, estimated volume of actively inflamed connective tissue, haemoglobin, serum protein, etc., are available it is difficult to apply these indices with accuracy to a retrospective analysis. However, it would appear from our data that the serum cholesterol varies with disease activity—rising towards “normal” when the activity of the disease diminishes and falling when the activity increases.

Effect of Medications

The serum cholesterol of patients taking prednisolone was compared with that of a group of patients with relatively similar disease severity (ward patients and S.C.A.T.-positive out-patients who were not receiving this medication). Both groups were studied in relation to their sedimentation rates, and no significant difference was apparent between the two groups. As shown in the Table (b), those with high sedimentation rates had much lower mean serum cholesterol, in both the steroid and the non-steroid group ($P < 0.01$).

Aspirin in a dosage of 4–6 g. daily has been shown to lower the serum cholesterol in hypercholesterolaemic patients (Alexander and Johnson, 1956; Alexander *et al.*, 1959; Reid, 1961). A consecutive group of patients admitted to the wards were therefore questioned about their daily consumption of aspirin prior to admission. The maximum dose taken was 4.8 g. and the mean 2.5 g. daily.

To investigate the possible effect of aspirin in this dosage 13 patients with rheumatoid arthritis at the rehabilitation hospital in Buxton were studied. Those patients were selected because their disease activity was relatively static. In all cases the initial serum cholesterol was determined after aspirin had been withdrawn for one week. The prescribed dose of aspirin was then given for two weeks and a second cholesterol determined. Seven patients received from 1.5 to 4.2 g. daily. In these patients the change in serum cholesterol ranged from –30 to +25 mg./100 ml., with a mean change of –2 mg./100 ml. Four patients received 4.8 g. of

aspirin daily and the range of serum cholesterol change was –15 to +5 mg./100 ml., with again a mean change of –2 mg./100 ml. Two patients took 6 g. of aspirin daily for the two-weeks test period, and in one the serum cholesterol fell 40 mg./100 ml. and in the other it remained unchanged.

It would appear that neither prednisolone nor aspirin in the doses taken by our patients played any significant part in the low serum cholesterol we found.

Gout and Osteoarthritis

Fifty-seven patients with osteoarthritis, in 10 of whom the disease was predominantly monoarticular, and 30 patients with gout in various stages of the disease were studied. The mean values for serum cholesterol in both groups were above the appropriate population means, but the results are not as impressive as we expected to find. In regard to osteoarthritis, this might be explained by the fact that a sizable segment of the relevant population samples used as “normal” also had osteoarthritis.

Discussion

Our data suggest that the serum cholesterol is influenced by inflammatory disease and the amount of activity or inflammation present. This effect of inflammation on the serum cholesterol has been noted before, but it does not appear to be widely appreciated. Chauffard *et al.* (1911) noted a direct relationship between the severity of an infection and the degree of depression of the serum cholesterol. Similar observations were made by Stern (1920) while studying patients with scarlet fever, by Archard *et al.* (1928), and by Stoesser (1940). In a study of serum cholesterol, diet, and coronary artery disease in South Africa, it was noted that the mean serum cholesterol was lower in those subjects who had a sedimentation rate greater than 10 mm. per hour as compared with those with sedimentation rates less than 10 mm. per hour (Bronte-Stewart *et al.*, 1955). However, the differences were not statistically significant and no obvious cause was found for the higher sedimentation rates. Thomas and Eisenberg (1959) noted a transient fall in serum cholesterol in three students during an acute influenzal infection. Three patients with arthritis studied by Mann and White (1953) showed a rise in serum cholesterol when their clinical condition improved and sedimentation rates fell, an observation very similar to ours. Though the serum cholesterol was noted to be low in patients with “atrophic” arthritis by Hartung and Bruger (1935), no correlation was found with the sedimentation rate.

The mechanism by which inflammatory disease produces a lowering of serum cholesterol has never to our knowledge been satisfactorily explained. Mann and White (1953) found that A.C.T.H. given to dogs produced a fall in serum cholesterol, whereas cortisone did not produce this effect. From their studies they concluded that disease acts as a stress phenomenon, that a physiological response to stress is a lowering of the serum cholesterol, and that this action is mediated by way of the adrenal gland but not through the action of cortisone. This could not be mediated through the action of hydrocortisone either, as it had been shown that this steroid also fails to depress the serum cholesterol (Hetzel *et al.*, 1957). Even if this explanation were applicable, one would have to explain the action of psychic stress in another manner, as it has been repeatedly shown that under such influences the serum

cholesterol does not fall but actually rises (Friedman *et al.*, 1958; Friedman and Rosenman, 1959; Dreyfuss and Czaczkes, 1959; Hammarsten *et al.*, 1957; Thomas and Eisenberg, 1959).

Could the serum cholesterol be depressed simply because of the loss of weight, so often an accompanying feature of chronic inflammation? It has been pointed out that cachectic states resulting from prolonged periods of starvation are often associated with a low serum cholesterol (Adlersberg and Sobotka, 1958), and this has also been observed experimentally in studies on dogs (Mann and White, 1953). However, significant loss of weight is not always an accompanying feature of inflammation in our patients in spite of the lowering of the serum cholesterol; and indeed some patients, especially if on steroid therapy, tend to be overweight during periods of disease activity and still show a lowered cholesterol. It would also seem unlikely that this explanation would be applicable in patients with acute infections who have been shown to have lowered cholesterol values.

The influence of corticosteroids on the serum cholesterol has been studied by a number of investigators. We noted no significant alteration of the serum cholesterol in our patients that could be solely attributed to the administration of prednisolone. Though A.C.T.H. has been shown to lower the serum cholesterol (Conn *et al.*, 1950; Kyle *et al.*, 1952; Oliver and Boyd, 1956), the results of treatment with cortisone have been variable. Conn *et al.* (1950) and Sprague (1950) did not observe any alteration of the serum cholesterol on administration of cortisone, whereas Kyle *et al.* (1952) found variable responses. In patients who had coronary disease with high initial cholesterol values and who were not ill with any inflammatory disease Oliver and Boyd (1956) were able to demonstrate a fall on treatment with cortisone. Adlersberg *et al.* (1950, 1951) and Adlersberg (1957), on the other hand, showed a rise in serum cholesterol on treatment with cortisone. However, many of their patients were acutely ill with rheumatic diseases. Those who showed a rise in cholesterol on treatment with cortisone also showed simultaneous diminution in disease activity; those who did not improve or whose clinical state worsened exhibited little change in the serum cholesterol. Their results, though interpreted differently, actually parallel our studies.

Aspirin was more universally taken by our patients than corticosteroids. However, the doses of daily aspirin were only moderate, and on studying the effects of such doses on the serum cholesterol we did not note any consistent changes. Alexander and Johnson (1956), Alexander *et al.* (1959), and Reid (1961) have shown that high doses of aspirin lower the serum cholesterol in hypercholesterolaemic patients, but no depression of serum cholesterol was found when similar doses were used in normocholesterolaemic patients (Austen *et al.*, 1958; Alexander *et al.*, 1959). On the other hand, in a study in which only 1.5 g. of aspirin was given daily to 10 patients, all showed a fall in serum cholesterol (Eidlitz, 1960). This observation was not confirmed by our study of three patients and may be partially explained by the fact that most of the patients investigated by Eidlitz had modest rises of the initial serum cholesterol, whereas our patients did not.

Summary

Serum cholesterol has been estimated in patients with rheumatic diseases for comparison with similar data

found in random samples of the population. In patients with inflammatory polyarthritis the serum cholesterol was significantly lower than in the general population. The amount by which the cholesterol was lowered was found to be related to the severity of the disease and the amount of disease activity. This relationship was not altered by corticosteroid therapy.

Low serum cholesterol values were also found in patients with inflammatory disease in the chest. The cholesterol tended to be higher than in the general population in patients with gout and osteoarthritis.

Aspirin, in doses usually taken by our patients, did not have any consistent effect on the serum cholesterol.

It is concluded that inflammation tends to lower the serum cholesterol. In that patients with inflammatory polyarthritis have a lowered serum cholesterol and appear also to have a lowered incidence of coronary artery disease, it is suggested that a profitable line of investigation might be a study of the possible inhibitory action of inflammation on the development of coronary artery disease.

We thank Professor J. H. Kellgren for help and encouragement and Miss F. Bier for help with the statistical analysis.

REFERENCES

- Albrink, M. J., Meigs, J. W., and Man, E. B. (1961). *Amer. J. Med.*, **31**, 4.
 Adlersberg, D. (1957). *Ibid.*, **23**, 769.
 — Schaefer, L. E., and Drachman, S. R. (1950). *J. Amer. med. Ass.*, **144**, 909.
 — (1951). *J. clin. Endocr.*, **11**, 67.
 — and Sobotka, H. (1958). In *Cholesterol*, edited by R. P. Cook, p. 397. Academic Press, New York.
 Alexander, W. D., and Johnson, K. W. M. (1956). *Clin. Sci.*, **15**, 593.
 — Macdougall, A. I., Oliver, M. F., and Boyd, G. S. (1959). *Ibid.*, **18**, 195.
 Archard, A., Grigaut, A., Le Blanc, A., and David, M. (1928). *J. Physiol. Path. gén.*, **26**, 415. Cited by W. R. Bloor in *Biochemistry of the Fatty Acids*. Reinhold, New York, 1943.
 Austen, F. K., Rubini, M. E., Meroney, W. H., and Wolff, J. (1958). *J. clin. Invest.*, **37**, 1131.
 Ball, J., and Lawrence, J. S. (1961). *Ann. rheum. Dis.*, **20**, 235.
 Bronte-Stewart, B., Keys, A., and Brock, J. F. (1955). *Lancet*, **2**, 1103.
 Chauffard, A., La Roche, G., and Grigaut, A. (1911). *Sem. méd. (Paris)*, **31**, 577. Cited by W. R. Bloor in *Biochemistry of the Fatty Acids*. Reinhold, New York, 1943.
 Cobb, S., Anderson, F., and Bauer, W. (1953). *New Engl. J. Med.*, **249**, 553.
 Conn, J. W., Vogel, W. C., Louis, L. H., and Fajans, S. S. (1950). *J. Lab. clin. Med.*, **35**, 504.
 Dreyfuss, F., and Czaczkes, J. W. (1959). *Arch. intern. Med.*, **103**, 708.
 Eidlitz, M. (1960). *Lancet*, **2**, 1123.
 Friedman, M., and Rosenman, R. H. (1959). *J. Amer. med. Ass.*, **169**, 1286.
 — and Carroll, V. (1958). *Circulation*, **17**, 852.
 Hammarsten, J. F., Cathey, C. W., Redmond, R. F., and Wolf, S. (1957). *J. clin. Invest.*, **36**, 897.
 Hartung, E. F., and Bruger, M. (1935). *J. Lab. clin. Med.*, **20**, 675.
 Hetzel, B. S., Williams, R., and Lander, H. (1957). *Aust. Ann. Med.*, **6**, 218.
 Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N., and Stokes, J. (1961). *Ann. intern. Med.*, **55**, 33.
 Kellgren, J. H. (1961). *Brit. med. J.*, **2**, 1.
 Keys, A., Fidanza, F., Scardi, V., and Bergami, G. (1952). *Lancet*, **2**, 209.
 Kyle, L. H., Hess, W. C., and Walsh, W. P. (1952). *J. Lab. clin. Med.*, **39**, 605.
 Mann, G. V., and White, H. S. (1953). *Metabolism*, **2**, 47.
 Oliver, M. F., and Boyd, G. S. (1956). *Lancet*, **2**, 1273.
 Reid, J. (1961). In *Drugs Affecting Lipid Metabolism*, edited by S. Garattini and R. Paoletti, p. 423. Elsevier, London.
 Sprague, R. G. (1950). Personal communication. Cited by Conn *et al.*, 1950.
 Stern, G. (1920). *Z. Kinderheilk.*, **25**, 129. Cited by W. R. Bloor in *Biochemistry of the Fatty Acids*. Reinhold, New York, 1943.
 Stoesser, A. V. (1940). *Proc. Soc. exp. Biol. (N.Y.)*, **43**, 168.
 Thomas, C. B., and Eisenberg, F. F. (1959). *Bull. Johns Hopk. Hosp.*, **104**, 14.