until the disorder was apparent). In all cases the test became negative with spontaneous or steroid-induced resolution.

It is concluded that the circulating substance responsible for a positive test is not the product of the P.C.S. but is closely related to its pathogenesis. No evidence was obtained concerning the nature of the individual susceptibility which is a feature of this condition.

It is a pleasure to thank Professor C. Barwell and Dr. R. G. White for their helpful advice and for providing us with laboratory facilities.

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SERUM CHOLESTEROL LEVELS AFTER MYOCARDIAL INFARCTION

BY

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Although absolute proof is lacking that hypercholesterolaemia is a cause of atheroma, lowering of the serum cholesterol is regarded by many as a useful objective in the management of ischaemic heart disease. Patients who have had a myocardial infarction are particularly eligible for such therapy. It is known that the serum cholesterol falls after myocardial infarction (Biörck *et al.*, 1957), but the pattern of the fall and of the subsequent rise has not been clearly established, and it is not certain how long after an infarct maximum levels are attained. Such information is necessary in order to time the start and so assess the maximum efficiency of hypocholesterolaemic therapy.

The aims of this study were threefold: firstly, to observe in detail the serum cholesterol level after myocardial infarction; secondly, to establish how long after an infarct maximum levels were reached; and, thirdly, to detect any possible relation between change in cholesterol level and other disordered blood levels.

Methods

The problem was investigated in two phases, the first including the 22 days after an acute myocardial infarction, and the second the period from the 22nd day until the 20th week. Serum cholesterol was estimated in duplicate by Henly's (1957) modification of the method of Zlatkis *et al.* (1953) and the mean value taken. If duplicates varied by more than 15 mg. the estimation was repeated.

Phase I

The subjects were 14 men aged 42 to 65, who were admitted on the first day of a first myocardial infarction, so far as this could be determined from the history, and who had no evidence of reinfarction during the 22-day period of observation. All had electrocardiographic proof of acute myocardial infarction. Nine were treated with anticoagulants (phenindione with heparin initially, then phenindione alone). In five patients anticoagulants were contraindicated because of a history of dyspepsia or proved peptic ulcer. Two of the patients had intravenous nor-adrenaline for 24 hours because of severe hypotension.

Serum cholesterol was estimated on the 1st, 3rd, 6th, 9th, 12th, 15th, and 22nd days of the illness. On the first day

blood was taken as soon after admission as possible, and on the subsequent days at 9 a.m. The erythrocyte sedimentation rate (E.S.R.) and packed cell volume (P.C.V.) were measured frequently during this period. In 10 of the patients the serum glutamic oxaloacetic transaminase (S.G.O.T.) levels were estimated on the first, second, and third days of the illness.

Serum cholesterol was also estimated in a controlled group of seven men of comparable age, on the 1st, 3rd, 6th, and 12th days of admission. These seven comprised four minor haematemeses not requiring transfusion, two with acute myocardial ischaemia not amounting to infarction, and one cerebral infarction.

Phase II

Serum cholesterol was estimated in 10 male patients, satisfying the clinical criteria already described, on the 22nd and 29th days after infarction, and at follow-up visits 8 and 12 weeks after the infarction. Six of these 10 were also seen during the 20th week after infarction. All had discontinued anticoagulant therapy on discharge from hospital at the 29th day and were on no special dietary management. At out-patient visits blood was withdrawn between 11 and 11.30 a.m., the patients having had a light breakfast at 8 a.m.

Results

Phase I

The serum cholesterol levels, maximum percentage fall in cholesterol, maximum E.S.R., and highest S.G.O.T. readings of the infarct patients are recorded in Table I, and the cholesterol results are charted in Fig. 1. The results in Table I are grouped according to whether the patients received anticoagulants or not. The cholesterol readings of the control group are given in Table II and charted in Fig. 1.

There is a sharp fall in the serum cholesterol level after a myocardial infarction. This reaches its lowest about the 6th day and is highly significant (mean difference = 65.0 mg.; S.E. of mean = 7.05; $P < 0.001$). The fall seems to occur immediately, and even by the third day the mean fall of 35.7 mg. is significant (S.E. of mean = 5.2; $P < 0.001$). This

TABLE I.—Serum Cholesterol Levels, Highest E.S.R., and Highest S.G.O.T. Reading for 14 Patients During the First 22 Days After an Acute Myocardial Infarction

Case No.	Serum Cholesterol (mg./100 ml.)							Maximum Fall in Cholesterol	Maximum E.S.R. (mm. 1 hr.)	Maximum S.G.O.T. (Units)
	Day 1	Day 3	Day 6	Day 9	Day 12	Day 15	Day 22			
Anticoagulants										
1	324	254	232	229	285	256	267	29.2	58	—
2	232	215	209	196	250	215	216	15.5	7	—
3	278	245	234	207	234	237	256	25.5	54	—
4	210	190	145	121	120	166	172	42.8	88	200
5	304	250	202	200	182	225	290	40.2	96	66
6	227	203	189	220	186	205	237	18.1	26	200
7	220	203	194	196	200	201	224	11.8	20	140
8	225	180	122	105	97	112	164	57.0	94	740
9	276	254	188	215	240	301	315	32.6	60	152
Mean	255.1	222.0	190.6	187.7	199.3	213.1	238.0			
No Anticoagulants										
10	233	216	174	165	191	176	173	29.2	86	320
11	290	255	224	210	219	206	274	27.6	56	—
12	232	176	154	159	222	226	229	31.5	118	250
13	242	222	194	209	197	236	247	19.8	56	170
14	305	236	228	259	261	325	305	25.2	11	118
Mean	260.4	221.0	194.8	200.4	218.0	233.8	245.6			
Overall mean	257.2	221.5	192.2	192.4	206.4	220.5	240.8			

TABLE II.—Serum Cholesterol Results for Seven Patients During the First 12 Days of Hospital Admission with an "Acute" Medical Condition

Diagnosis	Serum Cholesterol (mg./100 ml.)			
	Day 1	Day 3	Day 6	Day 12
Haematemesis	142	120	171	166
"	241	230	213	210
"	188	177	209	211
"	168	186	176	138
Acute myocardial ischaemia ..	144	153	134	175
"	180	174	182	201
Cerebral infarction	154	135	128	146
Mean	173.9	167.9	173.3	178.1

FIG. 1.—Curve of mean serum cholesterol levels for control and myocardial infarction patients; data from Tables I and II.

low level is maintained until about the ninth day, when it may begin to rise again, but the increase is not significant until the 15th day, when the average rise from the 9th day is 28.1 mg. (S.E.=7.8; $P<0.01$). The subsequent mean increase of 20.3 mg. from Day 15 to Day 22 is also significant (S.E.=6.1; $P<0.01$).

By the 22nd day the mean cholesterol level had not attained the average level on admission, but the mean difference of 16.4 mg. is not significant (S.E.=7.9; $P>0.05$). Although the difference is not significant for the group, it may still be significant for certain individuals within the group. Case 8, for example, whose serum cholesterol level dropped from 225 to 97 mg. and whose reading at the 22nd day was only 164 mg., ultimately reached a level of 254 mg. eight weeks after his infarct.

A separate comparison of the figures for the anti-coagulant and no-anticoagulant groups shows that the cholesterol fall is independent of the administration of anticoagulants. Considering the no-anticoagulant group alone, the mean fall of 39.4 mg. from Day 1 to Day 3 is significant (S.E. of mean=10.2; $P<0.02$), as is the mean fall of 26.2 mg. from Day 3 to Day 6 (S.E. of mean=5.6; $P<0.01$).

The mean cholesterol levels of the seven control subjects show no significant variation during the first 12 days of hospital admission.

Some of the infarct patients showed a slight fall in the P.C.V. in keeping with the transient fluid retention which sometimes follows a myocardial infarction, and others

FIG. 2.—Relation between maximum percentage fall in serum cholesterol after myocardial infarction and maximum E.S.R. (14 patients). ($r=0.74$, $P<0.01$.) FIG. 3.—Relation between maximum percentage fall in serum cholesterol and highest S.G.O.T. reading (10 patients). ($r=0.64$, $P<0.05$.)

showed a slight rise. However, changes in P.C.V. were much too slight to explain the falling cholesterol levels on the basis of simple dilution due to an expanding plasma volume.

In Figs. 2 and 3 the maximum percentage fall in serum cholesterol for each subject is charted against his maximum

E.S.R. and S.G.O.T. respectively. The correlation coefficient (r) for Fig. 2 is 0.74 ($n-2=12$; $P<0.01$), and for Fig. 3 is 0.64 ($n-2=8$; $P<0.05$).

Phase II

The serum cholesterol levels of the 10 patients studied during this period are given in Table III. The first four subjects are Cases 4, 5, 9, and 14 of Table I.

TABLE III.—Serum Cholesterol Results for 10 Patients From the 22nd Day to the 20th Week After an Acute Myocardial Infarction

Case No.	Serum Cholesterol (mg/100 ml.)				
	Day 22	Day 29	Week 8	Week 12	Week 20
4	172	207	221	194	—
5	290	274	316	285	—
9	315	378	380	417	—
14	305	327	262	274	—
15	195	162	217	199	181
16	198	200	195	218	214
17	221	228	272	184	224
18	260	252	310	261	230
19	311	313	309	316	296
20	289	323	299	248	296
Means	255.6	266.4	278.1	259.6	—
Means for Cases 15-20	245.7	246.4	267.0	237.7	240.7

The mean readings for this group might suggest that the cholesterol level continues to rise until the eighth week after the acute infarction, and indeed this may be true in certain cases. But the mean difference of 22.5 mg. between the levels at the 22nd day and the eighth week is not significant (S.E. of mean = 10.4; $P>0.05$). The mean level at the 12th week shows that the apparent trend upwards has ceased, and this figure of 259.6 mg. lies between the mean levels at the 22nd and 29th days after infarction.

The further follow-up of six of these patients until the 20th week shows that no significant development in cholesterol trends has occurred.

Discussion

This study has established that after a myocardial infarction there is a sudden and significant fall in the serum cholesterol. The lowest levels are reached about the sixth to ninth day of the illness. The return to pre-infarction levels begins some time after the ninth day and continues until some time near the 22nd day. Although proof is lacking from the group figures it is likely that in some patients the rise continues beyond this point, and this is probably the case in those who have experienced the most profound fall in cholesterol levels.

The fall is independent of anticoagulant therapy. This is in keeping with the reports of various authors. Although heparin has a marked effect on the serum lipoproteins (Nikkilä, 1952) it has none on the total serum cholesterol (Soffer and Murray, 1954; Kuo *et al.*, 1956; Herbert *et al.*, 1959). The last group of authors also studied the effect of phenindione and the coumarin compounds nicoumalone (acenocoumarin) and ethyl biscoumacetate on the total serum cholesterol. They found that the coumarins produced a temporary elevation but that phenindione had no effect.

There seems to be a relationship between the degree of fall in the cholesterol level and the rise in E.S.R. The relationship with S.G.O.T. levels, though less obvious, is apparently significant. The poorer correlation here may be explained by the fact that S.G.O.T. levels change more rapidly than the E.S.R. and only frequently repeated readings within the first 72 hours of the infarction are likely to uncover the true maximum S.G.O.T. level. If there is an aetiological relationship between these three readings

—serum cholesterol, E.S.R., and S.G.O.T.—it may rest in the degree of myocardial damage. Elevated S.G.O.T. levels are certainly proportional to the mass of infarcted myocardium (LaDue *et al.*, 1954; LaDue and Wroblewski, 1955), and though a similar relationship has not been systematically sought between E.S.R. and degree of myocardial damage, elevation of the E.S.R. does depend on necrosis of the myocardium as opposed to ischaemia (Wood, 1936; Riseman and Brown, 1937). Further considerations are mere speculation, but the fall in serum cholesterol could perhaps be due to release of a tissue enzyme which inhibits the hepatic biosynthesis of cholesterol or enhances its breakdown.

It is difficult to select a control group which is wholly adequate for a study like this. Many of the acute cases admitted are clearly unsuitable, and emergency admission we regarded as an essential criterion for such a group. Few acute illnesses compare with myocardial infarction in acuteness of onset in management and in general progress. In some respects, however, a control group is unnecessary in a sequential study such as this in that each patient is his own control.

From a practical point of view this investigation shows that where an evaluation of hypocholesterolaemic therapy is contemplated in patients who have had a myocardial infarction, ideal control levels of serum cholesterol should probably be taken on the 29th day and about the eighth week after the acute event. We have data from three patients not included in the results of this study which indicate that reinfarction has the same effect on the cholesterol level as the initial event.

If hypocholesterolaemic agents are to be given before a patient is discharged from hospital and the fall in serum cholesterol has not been gross—perhaps not more than 30% of the level on admission—readings at the 22nd and 29th days might be adequate, but readings on the 1st and 29th days are probably better. Alternatively, if the suggestion of Thompson *et al.* (1959) that four or five cholesterol estimations at different times of the same day are more representative of the range of cholesterol levels in any one person, the 29th day (the day just before discharge in most uncomplicated cases where the patients have made a good recovery) should be chosen. However, where the fall in cholesterol level has been considerable—and this seems especially likely with the most severe degrees of infarction—it would be better to wait until the eighth week of the illness.

No direct evidence is presented in this paper in explanation of the sudden fall in serum cholesterol after a myocardial infarction. It falls after other forms of acute physical stress such as surgery (Kyle *et al.*, 1952) and pneumonia (McQuarrie and Stoesser, 1932) even although in this latter group a steady diet was maintained. Smokers have significantly though not grossly higher cholesterol levels than non-smokers (Gofman *et al.*, 1955; Bronte-Stewart, 1956), and withdrawal of tobacco may reverse this difference. This is hardly the reason, however, because some of our subjects were non-smokers and the recovery rise in cholesterol occurred while all were being forbidden to smoke, as part of the routine management. All infarct patients are given light diet during the early days of their illness, but information on the effect of calorie restriction on the serum cholesterol level is conflicting. Walker *et al.* (1953) claimed that small diets reduced the serum cholesterol by a mean value of 17 mg./100 ml. in a group of 39 subjects. On the other hand, Moore *et al.* (1954) found that loss of weight due to dietary restrictions was often associated with an increase in serum cholesterol, and indeed

some of the subjects in Walker's group showed a rise in cholesterol levels, although their weights fell.

We believe that the fall in serum cholesterol which occurs after a myocardial infarction is directly due to the infarction. Possible mechanisms for the fall are increased breakdown, increased excretion via the bile, or impaired biosynthesis. Regarding the last suggestion, the demonstration by Rosin (1961) of impaired liver function within 24 hours of a myocardial infarction may be relevant.

Summary

Serum cholesterol levels were followed serially in 20 male patients admitted to hospital on the first day of a first myocardial infarction. Fourteen of these were studied during the first 22 days—10 until the 12th week—and six were followed up the fifth month.

The serum cholesterol falls rapidly after a myocardial infarction. It reaches its lowest levels about the sixth to ninth day and begins to rise again some time after the ninth to the twelfth day. Baseline control levels prior to hypocholesterolaemic therapy should not be taken earlier than the 22nd to 29th day after infarction, and when the clinical syndrome has been severe readings up to the eighth week after infarction may be more reliable.

The reason for the fall is not known, but it may be related to the severity of the myocardial damage.

We wish to thank Professor L. J. Davis, now retired, for encouragement in this work and for permission to study patients under his care. We are also grateful to Professor E. M. McGirr for reading this paper and for his helpful suggestions.

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THE MAIN CAUSE OF INCREASED DEATH RATE FROM DISEASES OF THE HEART: 1920 TO 1959

BY

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The great increase in the registered death rates from diseases of the heart since about 1924 is very striking, especially when compared with the steadiness of these rates during the preceding 50 years. At least some of this increase is generally accepted as due to the greater number of older persons in the population; and this has been influenced largely by the number of young lives that were saved by the better control of infectious diseases and tuberculosis, though also by changes in the birth rates.

The great decrease in the death rates from all causes combined is equally well known, but not perhaps the times at which this decrease occurred. There had been little change for 40 years up to 1880, when the death rate fell to a lower level, near which it stayed for 15 years. In 1895 it fell again, and this time continuously until 1925, since when the fall has been much smaller. This fall was mainly due to the reduced number of deaths of younger patients.

Most figures quoted for diseases of the heart are the "crude death rates" (with or without adjustments that may have been made by the Registrar-General)—that is, the rate found from a simple comparison of the total number of deaths in a year with the corresponding total live population. For the deaths from all causes I have used the standardized death rates, taken from the sources given in Table I.

As just stated, the fall in the death rate from all causes was mainly due to the reduced number of deaths of younger patients from infectious diseases and tuberculosis. If we assume that the mean age of all the subjects whose lives were saved was 20 years (see below), that one-quarter of them died from diseases of the heart, and that the average

age of death for these subjects was 60 years, then the main effect of the fall of the death rate from all causes in 1880–95 would not be reflected in the rise in the death rate from diseases of the heart until 1920–35. The true state of affairs is, of course, much more complicated than this, but if we consider the items separately it should be possible to reach some approximation to the truth and then see how much correspondence there is between our calculations of the expected numbers of deaths from heart disease and the actual registered numbers. This should give us some indication of whether the apparent increase in the death rate from diseases of the heart is a real increase or whether it can all be explained by the older age of the population.

We shall consider (1) the changes in the death rates from all causes from 1838 to 1930, (2) the age of the subjects whose lives were saved, (3) the age at death of subjects with diseases of the heart, and (4) the inevitable effect of these three factors on the death rate from heart disease, particularly after 1920.

Fall in Death Rate from All Causes: 1838–1930

The Registrar-General in his *Annual Report for 1910* (p. xxviii) reviewed the fall in the death rate from all causes since 1838, when his statistics started, after corrections for variations in the age and sex constitution of the population. He stated that it reached its peak in 1846–50 and then fell gradually and intermittently until 1891–5, and after this at a faster rate.

The peak in 1846–50 was so small that the following statement is almost equally true and more convenient for my calculations. The death rate varied within narrow limits with little significant change from 1838 to 1870, and