THE PLASMA CHOLESTEROL IN CORONARY DISEASE

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NUMEROUS attempts have been made to demonstrate a causal relationship between hypercholesterolæmia and atherosclerosis, but no such relationship has been clearly shown to exist although, equally, it has not been disproved.

Evidence yielded by a frontal attack—comparison of the plasma cholesterol levels in persons with and without clinical evidence of atherosclerosis—is inconclusive. Mjassnikow (1924) found that whereas 25 controls had serum cholesterol concentrations ranging from 120 to 170 mg. per 100 ml., 14 patients suffering from angina pectoris had concentrations ranging from 190 to 440 mg. per 100 ml. plasma. Similarly clear differences have been found by others, but this is not the general experience and a considerable overlap is a more usual finding. Thus Davis, Stern and Lesnick (1937) found this when comparing 59 patients suffering from angina pectoris with 54 normal controls, although about one-fifth of the patients had plasma cholesterol concentrations above the highest figure found in the normal group. Steiner and Domanski (1943) also found considerable overlapping with, however, significantly higher figures for the serum cholesterol in patients with coronary arteriosclerosis; they noticed fluctuations in the serum cholesterol concentrations in their patients. That age may be a factor was pointed out by Learman and White (1946) and by Morrison, Hall and Chaney (1948) who noted a greater tendency to hypercholesterolæmia among patients with coronary disease below the age of sixty than among older patients. A similar tendency was noted by Collen (1949) and by Geier (1949); this last author states that whereas none of 16 healthy subjects had a plasma cholesterol concentration exceeding 300 mg. per 100 ml., this level was exceeded by 43 per cent. of patients with coronary artery disease and under fifty-five years old, but by only 16 per cent. of similar patients over fifty-five years old.

These results, which form a fair cross section of those reported in the literature, show that hypercholesterolæmia, in the sense of a plasma cholesterol concentration distinctly above the normal maximum, does not necessarily precede coronary artery disease. However, the normal range is so wide that the figure found in a patient with coronary arteriosclerosis may well represent a personal hypercholesterolæmia—*i.e.* be above that previously customary for the individual concerned. It is, however, striking that such tendency to hypercholesterolæmia (in the general sense) as exists is greater in the younger patients.

Histological examination of normal, atheromatous and sclerotic arteries shows that deposition of cholesterol in the vessel walls is an important part of the disease process (Virchow, 1924; Aschoff, 1924; and Leary, 1944).

A similar conclusion is given by the animal experiments of Anitschow (1924), Weinhouse and Hirsch (1940), Leary (1941), Mukherjee (1948) and others. However, although it would appear that hypercholesterolæmia may aid abnormal deposition of cholesterol in vessel walls, it has not been shown to be an essential factor, and, indeed, Duff (1935) claimed to have observed that injury to the vessels seemed to precede the deposition of cholesterol.

On the whole, it appears likely, as Peters and Van Slyke (1946) suggest, that "cholesterol accumulates in the walls of the arteries when these are affected by degenerative processes or suffer local injuries." Such a deposition might be aided by hypercholesterolæmia or, without actual elevation of the plasma cholesterol level, by a decreased stability in solution either of the cholesterol alone or of the colloidal solutes in general (Alvarez and Neuschlosz, 1931; Eck and Desbordes, 1934; Hueper, 1944; etc.). It is particularly significant that Eck and Desbordes (1935) found the stability of the plasma cholesterol to decrease with advancing age; this suggests that deposition might tend to occur at a lower plasma cholesterol concentration in old than in younger persons.

The observations recorded in this paper were undertaken with the objects: (1) of adding to the volume of evidence suggesting some relationship (possibly indirect or secondary) between the plasma cholesterol concentration and the occurrence of coronary infarction; (2) of finding, by determining both free and total cholesterol, whether other metabolic disturbances in the liver might be implicated; (3) of investigating similarly the plasma cholesterol in groups of patients of ages comparable to those with coronary disease but suffering from other abnormalities, some of which could be expected to involve arterial degeneration.

Methods

Total cholesterol was determined in plasma separated from oxalated venous blood withdrawn (in the case of the hospital patients) at 10-11 a.m., about three hours after breakfast. The method used was that of Sackett (1925) adapted for use with a Spekker absorptiometer.

Free cholesterol was determined in the same plasma samples by Clarke and Marney's (1945) modification of the digitonin precipitation method described by Schoenheimer and Sperry (1934).

This combination of methods was chosen as being more convenient than using the digitonin method before and after hydrolysis. That it is reliable is indicated by the fact that the ratio of free to total cholesterol obtained by its use agrees well with the ratio reported by other methods.

Normal Controls

As normal controls, blood was obtained from 50 healthy subjects (blood donors) within the age range of twenty to sixty, and including both men and women, between whom there seems to be no significant difference in plasma cholesterol level (Kounts, Sonnenberg, Hofstatter and Wolff, 1945). The blood was withdrawn during the afternoon, two to three hours after a light lunch.

The mean values, ranges, and standard deviations are given in Table I. The standard deviations are not strictly accurate since the distribution curve is slightly skew.

TABLE I

The Plasma Cholesterol in Normal Subjects

	Total Cholesterol mg. per 100 ml. Plasma.	Free Cholesterol mg. per 100 ml. Plasma.	$\frac{F}{T} \times 100$.
Mean	195	52	26·5
S.D.	25·6	7·6	1·24
Maximum found	242	69	29
Minimum found	129	36	24
Range for 90 per cent. of observations	161-235	42-61	...

The mean figure for total cholesterol agrees well with those in the literature derived from a study of 50 or more subjects. With this restriction Sunderman and Boerner (1949) list means from 194-235 mg. cholesterol per 100 ml. plasma, with a composite mean of about 200. The range in our series was smaller than some previously reported (*e.g.* Peters and Man (1943) record a mean of 194 with S.D. = 35·6 but a maximum individual observation of 320), although the S.D. does not differ very greatly from those reported.

The free cholesterol concentration in the series reported here agrees well, both as regards absolute value and ratio to total cholesterol with that reported by Sperry (1936) and by Peters and Man (1943). As in their series the range of variation was very small—much less than has been reported by certain other earlier workers.

Results in Recent Coronary Infarction

The subjects were 52 patients (50 males and 2 females) aged between forty-two and seventy-two who had been admitted to hospital because of coronary infarction. The blood for examination was withdrawn, in every case, within twenty-four hours of the attack, and usually before the administration of any anti-coagulant drug. The diagnosis was in all cases confirmed by clinical and electrocardiographic examination.

The data are summarised in Table II. The means and standard deviations are such as to suggest no clearly significant differences from the normal controls. Nevertheless, there is a tendency for the coronary infarction patients to have slightly higher plasma cholesterol

levels (both total and free) than the normal subjects. This tendency is shown for total cholesterol in the distribution diagram (Fig. 1*a*)

TABLE II

The Plasma Cholesterol in Acute Coronary Infarction

	Total Cholesterol mg. per 100 ml. Plasma.	Free Cholesterol mg. per 100 ml. Plasma.	$\frac{F}{T} \times 100$.
Mean	212	62	29
S.D.	39·2	13·5	3·3
Maximum found	305	117	0·38
Minimum found	129	40	24
Range for 90 per cent. of observations .	152-275	42-92	25-37

in which there is evident a distinct bunching of the coronary infarction patients in the upper levels, and in which it is obvious that the distribution curves are skew. Examined in this way, it can be seen that

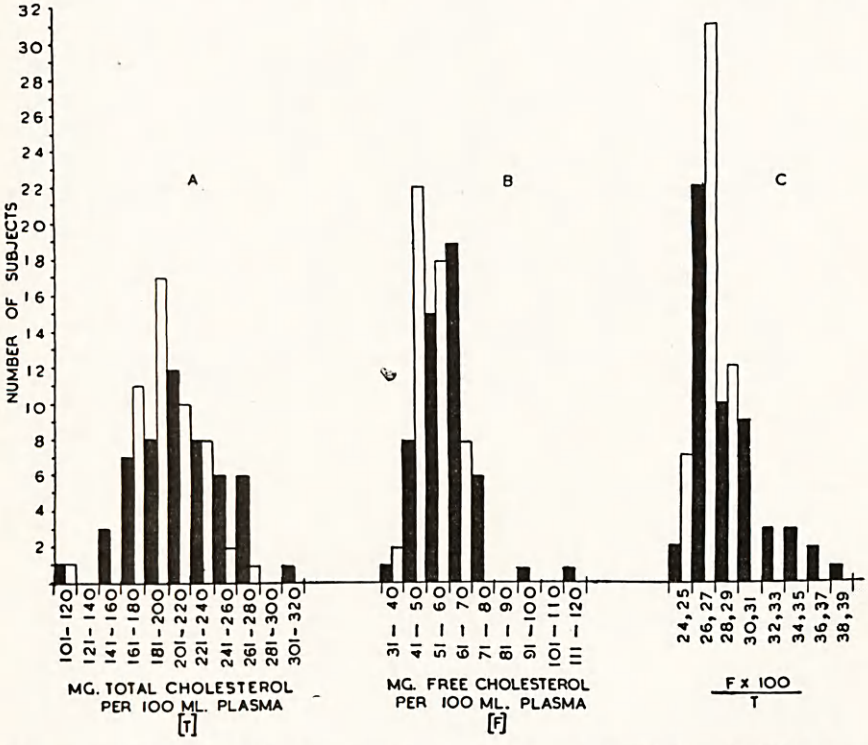

FIG. 1.—The total plasma cholesterol (A), the free cholesterol (B), and the ratio (C) in cases of acute coronary infarction (black columns), and in healthy subjects (white columns).

only 22 per cent. of the normal subjects, but 40 per cent. of the coronary infarction patients, had a total plasma cholesterol concentration over 220 mg. per 100 ml. It is still clearer in the case of the free cholesterol (Fig. 1*b*).

The mean proportion of the total cholesterol existing in the free state is nearly the same for the two groups of subjects, but among the coronary infarction patients the range is rather greater (Fig. 1*c*). Although 38 of the 52 patients had $\frac{F}{T} \times 100$ above the normal mean, the rather high average in this group is partly due to the inclusion in this group of 6 patients with $\frac{F}{T} \times 100$ above 34. In three of these functional liver damage was demonstrated by clinical examination and by the cephalincholesterol flocculation test; the others showed no clinical signs of hepatic disease but unfortunately tests of function were not done. One of these had suffered several previous thromboses and had a total plasma cholesterol of 305 mg. per 100 ml. with a free cholesterol of 117 mg. per 100 ml.—the highest figures in the series; another was a chronic bronchitic of seven years standing; the third had, at the time of the coronary thrombosis, arterial occlusion at other sites.

It has already been mentioned that several American workers have noted a greater tendency to hypercholesterolæmia among the younger than among the older patients with coronary disease. The results reported here support this (Table III) so far as total cholesterol is concerned. The patients over sixty years of age show no significant tendency to increased total cholesterol, but 20 out of 27 had a free

TABLE III

The Plasma Cholesterol in Recent Coronary Infarction—Effect of Age

	Total Cholesterol mg. per 100 ml. Plasma.		Free Cholesterol mg. per 100 ml. Plasma.		$\frac{F}{T} \times 100$.	
Age.	Over 60.	Under 60.	Over 60.	Under 60.	Over 60.	Under 60.
Mean	199	229	57	68	28	29
Range	129-250	189-305	42-73	52-117	...	...
Number in group . . .	27	25	27	25	...	...
Number above *Normal* mean .	13	21	20	18	...	...

cholesterol concentration in the plasma above the normal mean. The patients under sixty years of age, however, had a mean total plasma cholesterol of 229 mg. per 100 ml. (normal mean 195) and 21 of them, out of 25, were above the normal mean. The free cholesterol in this group was rather similar to that in the older group, although the mean value was high—possibly because it included the patients with demonstrable liver deficiency; 18 of the 25 were above the normal mean. The age difference, therefore, was not clearly demonstrated in the case of the free cholesterol.

Results in Angina Pectoris without Recent Infarction

The results from 20 patients with angina pectoris but without evidence of recent coronary infarction are summarised in Table IV.

The patients were drawn mainly from those attending the Out-Patient Department. Some were known to have had acute coronary infarction some months previously but others provided no evidence

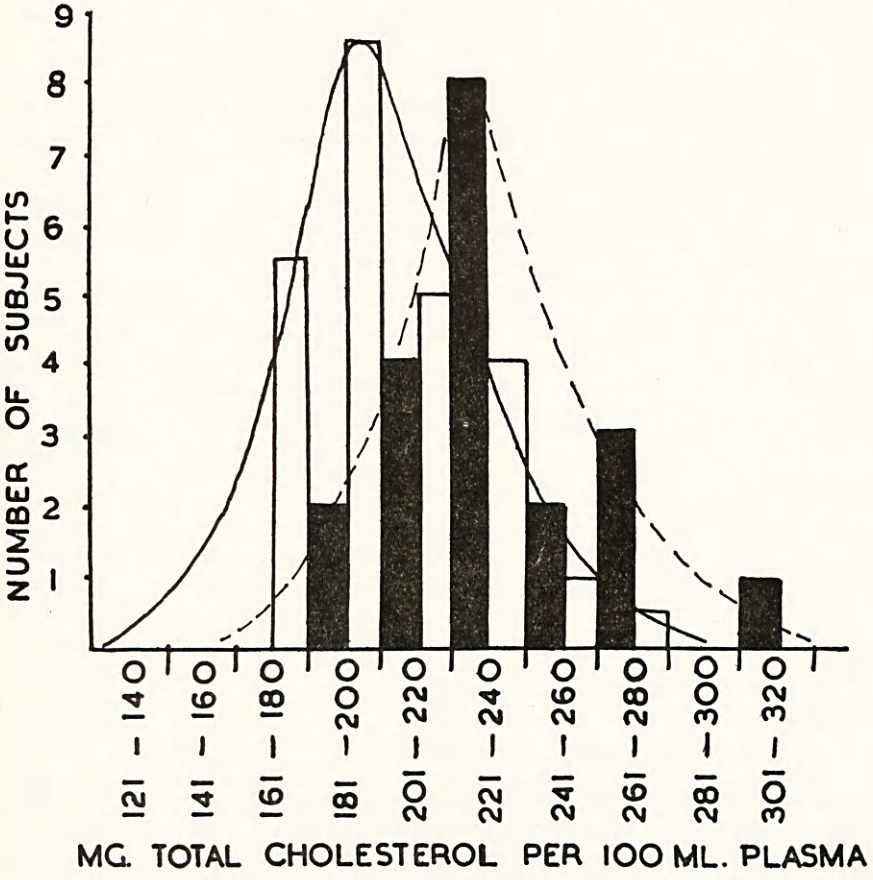

Fig. 2.—The total plasma cholesterol in cases of angina pectoris (black columns) and in healthy subjects (white columns). For the latter, the number of individuals represented by each column is twice the number indicated on the scale.

of infarction. All had suffered recurrent attacks of pain over a period of several months, and in some instances of more than a year (four years in one instance). Those patients who had no history of acute infarction were submitted to an exercise tolerance test with electrocardiographic confirmation of the diagnosis.

It is evident that these patients showed a much greater tendency to hypercholesterolæmia than did those with acute coronary infarction. The mean value for the total plasma cholesterol was 234·7 mg. per 100 ml. (normal 195) and, although many of the values were within

the normal range, Fig. 2 shows a clear shift of the distribution curve. Of the 20 patients in the group, 19 had plasma cholesterol in concentration greater than the normal mean.

Moreover, analysis of the 52 cases of acute coronary infarction supports the conclusion that the occurrence of anginal pain is a more important factor in relation to hypercholesterolæmia than the actual coronary infarction. Of these cases, 12 gave a history of previous attacks of pain ; the total plasma cholesterol ranged from 250-305 mg. per 100 ml., with a mean of 269·5.

The free cholesterol concentration in the plasma showed a similar general, and indeed proportional, increase above the normal ; the ratio of free cholesterol to total cholesterol was consequently unchanged from that shown in the normal controls.

Table IV shows also that the age effect found in acute coronary infarction does not exist in the group of patients with angina pectoris

TABLE IV

The Plasma Cholesterol in Angina Pectoris without Recent Infarction

	Total Cholesterol mg. per 100 ml. Plasma.		Free Cholesterol mg. per 100 ml. Plasma.		$\frac{F}{T} \times 100$.	
Age.	Over 60.	Under 60.	Over 60.	Under 60.	Over 60.	Under 60.
Mean	240	226	65·5	64	27	27
Range	204-314	185-270	57-80	46-86	...	...
Number in group . . .	12	8	12	8	...	...
Number above *Normal* mean .	12	7	12	6	...	...
Mean	234·7		61·4		26	
Range (for 90 per cent. of cases)	200-271		54-80		...	
Total range	185-314		46-86		...	

but without recent infarction. There is, however, a suggestion that the tendency to hypercholesterolæmia in this group of patients is roughly related to the time which had elapsed since the first attack of anginal pain.

Since many of the patients in this group were old and all were over fifty years of age, the question of hypertension obviously arose. Among the patients with acute coronary infarction those giving a history of previous pain (*i.e.* those with the greatest tendency to hypercholesterolæmia) had relatively high blood pressure, and among the patients with angina but no acute infarction there was some suggestion of a rough correlation between blood pressure and plasma total cholesterol concentration. There was, however, no clear-cut relationship, but it was obviously desirable to measure the plasma cholesterol in a group of hypertensive patients without evidence of coronary disease.

Results in Hypertension without Evidence of Coronary Disease

The plasma cholesterol concentration was examined in 44 hypertensive subjects (24 men and 20 women) of all ages. Every subject had systolic blood pressure above 180 mm. Hg. or a diastolic pressure above 90 mm. Hg. (or both). The general results are summarised in Table V and Fig. 3.

TABLE V*a*

The Plasma Cholesterol in Hypertension

	Total Cholesterol mg. per 100 ml. Plasma.	Free Cholesterol mg. per 100 ml. Plasma.	$\frac{F}{T} \times 100$.
Mean	213	67	31
S.D.	50·5	17·5	...
Maximum found	325	122	50
Minimum found	109	42	25
Range for 90 per cent. of observations	110-309	53-110	26-44
Number above *Normal* mean	27	41	40

TABLE V*b* and *c*

The Plasma Cholesterol in Hypertension

	Total Cholesterol mg. per 100 ml. Plasma.		Free Cholesterol mg. per 100 ml. Plasma.		$\frac{F}{T} \times 100$.	
(*b*) Effect of Age						
Age.	Over 60.	Under 60.	Over 60.	Under 60.	Over 60.	Under 60.
Mean	195	215	69	69·8	36·8	32
Range	152-266	110-309	65-80	53-110	31-44	26-44
(*c*) Effect of Sex						
	Male..	Female.	Male.	Female.	Male.	Female.
Mean	211	214	65	73	31	34

The figures for total cholesterol are very similar to those found in the patients with recent coronary infarction, though the range was rather greater and there was the same tendency for the higher figures to occur among the younger patients. There was no sex difference (Table V*c*). The free cholesterol was distinctly higher, on the whole, than among the normal controls or even the patients with coronary disease, but the age difference appeared to have vanished. The tendency to increased free cholesterol concentration was so marked that the ratio Free : Total was considerably above the values found in the groups previously examined. This change in the ratio was

actually more marked in the older patients (over sixty) in contradistinction to the total hypercholesterolæmia which was more marked in the younger (below sixty) patients (Table V*b*). It is tentatively suggested that this alteration in the Free : Total ratio may be ascribed to the effect of arteriosclerotic changes on the functional efficiency of the liver. No such decreased efficiency could be demonstrated by the cephalin-cholesterol flocculation test, except in two cases, with $\frac{F}{T} \times 100$ of 35 and 50 respectively, but this does not, of course, suffice to negative the suggestion. It is worth mentioning in this connection that

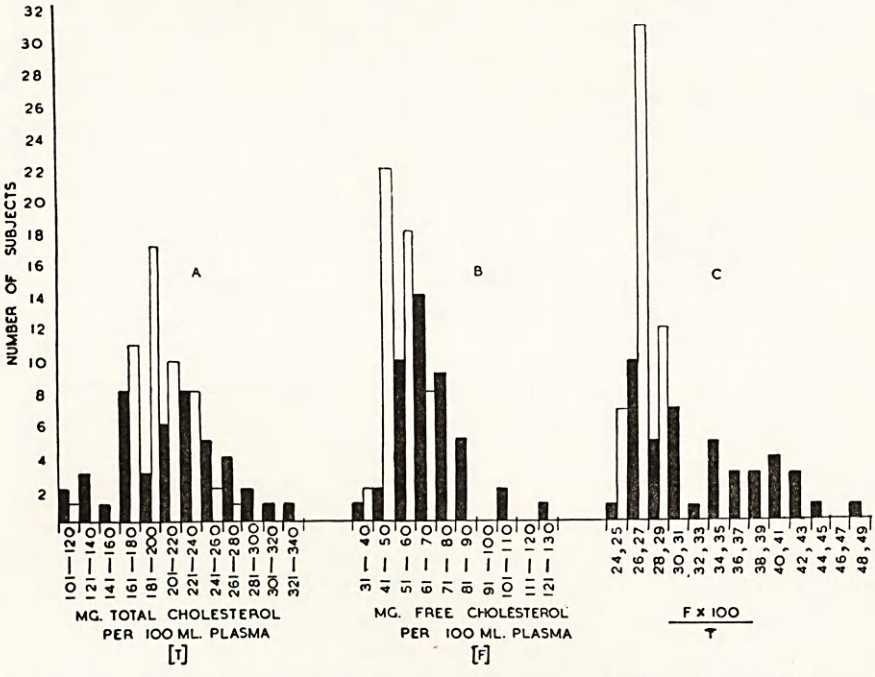

FIG. 3.—The total plasma cholesterol (A), the free cholesterol (B), and the ratio (C) in hypertensive subjects (black columns), compared with healthy subjects (white columns).

McMichael (1950) has, in one post-mortem case, demonstrated pathological changes in the liver of a severely hypertensive patient who also showed an old healed pyelonephritis and the belief has been expressed that such changes may be associated with a lowered hepatic blood flow.

The discrepancy between the total cholesterol-age relationship and the ratio-age relationship suggested that duration of hypertension rather than age might be the determining factor, and the figures were re-examined accordingly. When the patients were classified in this way, taking five years duration of hypertension as the standard, the results were as shown in Table VI. It appears that the tendency to a total hypercholesterolæmia is rather greater among the patients

in whom the hypertension is of relatively short duration, but it must be emphasised that this tendency has not been shown to be statistically

TABLE VI

Hypertension

	Total Cholesterol mg. per 100 ml. Plasma		Free Cholesterol mg. per 100 ml. Plasma.		$\frac{F}{T} \times 100$.	
	Over 5 Years Duration.	Under 5 Years Duration.	Over 5 Years Duration.	Under 5 Years Duration.	Over 5 Years Duration.	Under 5 Years Duration.
Mean	204	228	78	65	38	28
Range	110-300	109-323	53-122	38-88	32-50	25-35
Number in group	20	24	20	24	20	24
Number above *Normal* mean	7	20	20	21	20	20

significant. With the same *caveat*, though with rather more assurance, it can be suggested that the concentration of free cholesterol, and, even more markedly, the Free : Total ratio is more abnormal in the long duration group of patients. The progressive change of the ratio with increasing duration of hypertension is shown even more clearly in Table VII*a*. The abnormality of the Free : Total ratio is progressive, becoming very much greater among the patients with hypertension of over five years duration, and it should be noted that this coincides

TABLE VII

	No. of Cases.	$\frac{F}{T} \times 100$.	
		Mean.	Range.
(*a*) Duration of Hypertension in Years			
0- 2	13	28·0	25-31
2- 4	11	30·5	26-37
5-10	10	36·8	32-40
10-15	10	41·0	37-50
(*b*) Age in Years			
40	8	27·5	26-29
41-50	12	32·0	26-37
51-60	18	35·5	25-43
61-70	5	38·0	30-50
70	1	31·0	31

with electrocardiographic evidence of progressive left ventricular hypertrophy. Naturally, the longer duration patients tend to be found among the older ones but a similar classification on the basis of age by decades (Table VII*b*) showed a much less clear progression

in the Free : Total cholesterol ratio, the ranges overlapping much more completely although the means increased. It is justifiable to conclude that, although age and duration of hypertension are not completely independent, the latter is the more important and possibly the fundamental factor.

Since some degree of renal inefficiency is almost inseparable from hypertension of long duration, it was necessary to find whether the abnormalities in the plasma cholesterol were associated with this rather than with the mere elevation of the blood pressure. In most of the cases, renal function was tested by the urea range test. Only two gave a completely normal range (*i.e.* 3·5 per cent. urea to below 0·5 per cent. urea) and it was therefore necessary to choose arbitrarily some lower standard which could be taken as representing a " considerable " degree of functional impairment ; this standard was fixed at 2·5 per cent. urea, those failing to concentrate to this level being regarded as showing impairment of renal function. Eighteen patients fell in this group, and the figures for plasma cholesterol (Table VIII) are practically indistinguishable for those of the whole hypertensive group shown in Table VII. Evidently, impairment of

TABLE VIII

Hypertension with Impaired Kidney Function Tests

	Total Cholesterol mg. per 100 ml. Plasma.		Free Cholesterol mg. per 100 ml. Plasma.		$\frac{F}{T} \times 100$.	
	Over 5 Years Duration.	Under 5 Years Duration.	Over 5 Years Duration.	Under 5 Years Duration.	Over 5 Years Duration.	Under 5 Years Duration.
Mean	207	192	79·8	68	38	28
Range	136-300	209-257	53-122	57-80	34-44	26-31
Number in group . . .	12	6	12	6	12	6
Mean for whole group . .	217		71		32	

renal functional efficiency is not, in these patients, a factor in the abnormality of cholesterol metabolism which leads to a very slight tendency to hypercholesterolæmia combined with a much more definite increase in the proportion of the total cholesterol which remains in the free state.

Results in Congestive Heart Failure

The consideration that the tendency to increase in $\frac{F}{T} \times 100$ in the cases discussed in the preceding sections of this paper might be explained by some degree of liver functional efficiency due to interference with the circulation with consequent diminution of the supply of metabolites (including oxygen) to the cells, led to the examination

TABLE IX

Congestive Heart Failure

Case No.	Number of Attacks.	Etiology.	Liver Enlargement.		Acute Phase.					Complete Recovery Phase.			
			During Illness.	After Recovery.	Ascitis.	Spleen.	Total Cholesterol mg. per 100 ml. Plasma.	Free Cholesterol mg. per 100 ml. Plasma.	$\frac{F}{T} \times 100$.	Total Cholesterol mg. per 100 ml. Plasma.	Free Cholesterol mg. per 100 ml. Plasma.	$\frac{F}{T} \times 100$.	Cephalin-Cholesterol Test.
1	One	Rheumatic	++	−ve	−ve	−ve	160	55	34	188	50	26	−ve
2	Two	Rheumatic	+++	−ve	+	−ve	155	70	46	209	57	27	−ve
3	One	Rheumatic	++	−ve	−ve	−ve	142	50	35	216	59	27	−ve
4	Two	Rheumatic	++	−ve	−ve	−ve	129	46	35	200	57	28	−ve
5	One	Rheumatic	+	−ve	−ve	−ve	257	80	31	Not examined but very early failure case			Nil
6	Two	Rheumatic	+++	...	−ve	−ve	150	70	46	...	Not examined	...	...
7	Two	Rheumatic	++	...	−ve	−ve	147	58	39	...	Not examined	...	...
8	Multiple	Rheumatic	+++	+	−ve	−ve	140	57	43	170	67	39	+ve
9	Multiple	Rheumatic	+++	+	+	+	146	60	42	155	55	35	−ve
10	Multiple	Hypertensive	+++	+	+	−ve	136	57	42	150	56	37	−ve
11	Multiple	Hypertensive	+++	+	+	+	164	73	44	184	70	38	+ve
12	Multiple	Hypertensive	+++	+	−ve	−ve	161	65	40	185	65	35	+ve
13	Multiple	Hypertensive	+++	+	−ve	−ve	160	80	50	170	70	41	+ve

of patients with congestive heart failure. In these there is a similar disturbance which could well lead to a similar apparent diminution in liver functional efficiency and indeed, the condition of " cardiac cirrhosis " has been described as a late phenomenon in recurrent congestive heart failure.

The relevant data from 13 cases are summarised in Table IX. There is an obvious diminution in the total plasma cholesterol during the acute phase of congestive failure and, since the free plasma cholesterol is not similarly reduced, the abnormality consists in a reduction of the combined cholesterol. This, of course, gives an apparent increase in $\frac{F}{T} \times 100$, such as is commonly found associated with liver disease. The clinical examination of the patients during this phase showed a rough correlation between the degree of liver enlargement and the abnormality of $\frac{F}{T} \times 100$, but none between this abnormality and the number of previous attacks.

After clinical recovery the same patients were re-examined. Those who had had not more than two previous attacks of congestive heart failure showed an increase in the total plasma cholesterol to the normal level with a return of $\frac{F}{T} \times 100$ to normal. In these patients the liver had returned to normal size and the cephalin cholesterol test gave a negative result. The patients with several previous episodes showed a much smaller increase in the total plasma cholesterol, a continuing high value for $\frac{F}{T} \times 100$, residual liver enlargement and, in most cases, flocculation in the cephalin-cholesterol test.

These results strongly suggest that the circulatory failure in these patients produces impairment of the hepatic functional efficiency and that long continuation or repetition of the condition leads ultimately to cellular damage. It cannot be concluded definitely that the similar derangement of the plasma cholesterol associated with hypertension and with coronary disease is also due to liver inefficiency. Since, however, these other conditions involve vascular changes which must be expected to affect the liver in the same way as does congestive heart failure, the conclusion is at least probable that liver inefficiency plays a part.

Discussion

This suggestion, that vascular degenerative changes slowly produce some abnormality of cholesterol metabolism is strengthened by the finding that in angina pectoris the tendency to hypercholesterolæmia is roughly proportional to the period over which anginal pains have been observed, and that, in the same subjects there is a rough parallelism between the plasma cholesterol and the blood pressure. It seems that the level of the plasma cholesterol and the degree

of hypertension alike may be governed by the extent of the degenerative lesions in the blood vessels, which is a function of duration. On this basis, an acute coronary infarction may occur without widespread degenerative arterial changes, and consequently with little elevation of the plasma cholesterol. This is not to deny the proposition that the atheromatous lesion involves the deposition of cholesterol or cholesterol esters derived from the plasma ; it is in agreement with the idea that there is some inherent or at least primary fault in the sub-intimal tissues ; but it suggests that given this primary fault, the development of the lesion may begin without pre-existing hypercholesterolæmia to which, however, it may lead in the course of time. This hypothesis of the sequence of events is equally consistent with the frequent occurrence of atheromatous changes in diabetes with hypercholesterolæmia and in nephrosclerosis without constant hypercholesterolæmia. The suggestion that hypercholesterolæmia is the sequel to, rather than the cause of, atheromatous changes does not oppose, but is indeed supported by the distribution of these changes in the vascular system, a distribution which led Anrep, Davis and Volhard (1931), Gregg (1934), Johnson and Di Palma (1939), Moschkowitz (1942) and others to develop the theory that atheromatous change is the result of excessive localised intravascular pressure.

The actual production of thrombi may be attributed to some abnormality of the clotting mechanism which is potentiated by the local injury to the artery wall (although it is not clear whether such a clotting abnormality must necessarily be postulated). It is fairly well established (Wright, 1948) that the mast cells of the liver and the walls of the smaller blood vessels produce heparin ; others (*e.g.* Jorpes, Holmgren and Wilander, 1937 ; Levene and Lopez-Suarez, 1918) have extracted a heparin-like substance from the wall of the aorta, and Faber (1946, 1949) has ascribed to this substance the accumulation of cholesterol in the aorta wall of hypertensive patients with a normal plasma cholesterol. Although the observations are not yet sufficiently complete for detailed publication, we have found mast cells in the walls of the aorta and coronary artery of normal human subjects. In 3 patients who had died accidentally but were found, *post mortem* to have atheromatous changes in the aorta and the coronary artery, we failed to detect the presence of mast cells in these sites. If the local disappearance or deficiency of mast cells is found to be associated regularly with atheroma a causal relation between the two may eventually be established. In the meantime it is permissible to speculate whether a deficiency of heparin, produced in this way, may so alter the coagulability of the blood as to produce a tendency to thrombus formation at least on a favourable surface. It is permissible further to speculate whether a prolonged deficiency of heparin may be a factor in the hypercholesterolæmia which is associated with atheromatous changes of long duration ; this is in agreement with the observation (Basu and Stewart, 1950) that injection of heparin produces

a decrease in the plasma cholesterol concentration. Much very indirect evidence supports the hypothesis that deposition of cholesterol in the sub-intimal tissues of the atheromatous vessel is concentrated in and destroys the mast cells, but in the absence of more direct evidence it is not justifiable to pursue these speculations further.

There are, of course, many other possibilities—such as that there may be, associated with atheromatous changes, an alteration in the concentration of a specific cholesterol-globulin complex without much immediate change in the total cholesterol of the plasma—but there is little profit in discussing these since the observations we have made neither support nor deny them. But, whatever the mechanism, our observations indicate that increase in the plasma cholesterol concentration follows the atheromatous changes (being, therefore an effect and not a cause) and that this increase does not necessarily involve a defect in the cholesterol esterifying mechanism.

In hypertension the position may be a little different. Again, duration is the important factor. The mechanism, associated with vascular change, may slowly tend to an increase in the total plasma cholesterol, but this tendency is less marked than is found in the patients with anginal pains and atheromatous rather than arteriosclerotic changes. The hypertensive patients whose abnormality is of long duration show rather an increase in the free cholesterol with a consequent rise in the value of $\frac{F}{T} \times 100$ which is of the same order as is found consistently associated with hepatic functional deficiency. Although few hypertensive patients have any such deficiency demonstrable by other function tests, it is noteworthy that some degree of fatty infiltration of the liver is a common post-mortem finding in such patients. Moreover, a similar increase in $\frac{F}{T} \times 100$ has been found in cases of congestive heart failure (Hawkins, 1934; Cantarrow, 1935; Epstein, 1936), in which, as we have found, repeated failures may lead to a deficiency demonstrable in other ways—" cardiac cirrhosis." There is a strong suggestion that the abnormality of the plasma cholesterol in hypertension, whilst in part due to the causes which produce vascular degeneration, is partly the result of " hypertensive liver deficiency "—a supply lack in the earlier stages which, as in congestive heart failure, may lead ultimately to actual cellular damage.

It is, however, clear that on the evidence presented the abnormalities of the plasma cholesterol in angina pectoris, in hypertension and in congestive heart failure cannot all be ascribed solely to the effect of hepatic deficiency. For whereas in the first two of these conditions there is a slight tendency for the total cholesterol to be raised and a more marked tendency for the free cholesterol to be increased with a consequential change in the ratio, congestive heart failure is characterised by a decrease in the total cholesterol with no change

in the free cholesterol. It is the disproportionate change in the free and total cholesterol concentrations with an increase in $\frac{F}{T} \times 100$ which in all these conditions suggests hepatic functional impairment as a common factor. This, however, seems to be superimposed on other effects which may be due to diverse causes. It is possible that in congestive heart failure the hepatic damage may have progressed so far as the result of markedly defective blood supply that the liver can no longer synthesise cholesterol adequately whereas minor degrees of damage (such as can, at most, exist in the other cases studied) affect rather the esterifying and possibly the excretory powers. On the evidence available, however, it is more reasonable to suppose that the atheromatous changes in the blood vessels themselves produce conditions which tend to disturb the normal plasma cholesterol distribution and that the circulatory deficiency causes impairment of the hepatic functions which lead to further abnormalities in the plasma cholesterol.

Summary

1. In 50 healthy subjects, men and women aged twenty to sixty, the total plasma cholesterol (T) was $195 \pm 25{\cdot}6$ mg. per 100 ml., the free cholesterol (F) $52 \pm 7{\cdot}6$ mg. per 100 ml., and $\frac{F}{T} \times 100$ was $26{\cdot}5 \pm 1{\cdot}24$.

2. In 52 patients with acute coronary infarction, T was 212 ± 39, F was $62 \pm 13{\cdot}5$ and $\frac{F}{T} \times 100$ was $29 \pm 3{\cdot}3$. A slight tendency to hypercholesterolæmia, more marked in the free cholesterol, and in the patients below sixty years of age was more clearly shown by the distribution diagrams.

3. Patients with angina pectoris but without recent coronary infarction showed a much clearer tendency to hypercholesterolæmia, with age playing no important part, but with the plasma cholesterol level roughly related to the duration of the condition. In the 20 patients of this group the mean T was 234·7 (range 185-314), F was 61·4 (range 46-86), and $\frac{F}{T} \times 100$ was 26.

4. The figures for the total plasma cholesterol in 44 patients with hypertension but no evidence of coronary disease were very similar to those in acute coronary infarction—T was $213 \pm 50{\cdot}5$—although the "scatter" was greater. However, F was higher at $67 \pm 17{\cdot}5$ and so, consequently, was $\frac{F}{T} \times 100$ at 31. Of these patients 24 were men and 20 were women but as in the normal controls there was no sex difference in the plasma cholesterol level. The plasma cholesterol tended, on the whole, to increase with the age of the patient, but was much more closely related to the duration of the hypertension; this applied to

the free cholesterol and to $\frac{F}{T} \times 100$ even more clearly than to the total cholesterol. There was no clear correlation with renal efficiency.

5. Patients with congestive heart failure showed a marked diminution in the total plasma cholesterol with return to normal levels on recovery except in those patients who had suffered several previous acute attacks. The free cholesterol was not similarly reduced, so that $\frac{F}{T} \times 100$ was high. These changes were roughly correlated with the duration of the condition and with evidence of hepatic functional impairment.

6. It is suggested that degenerative changes in the vascular system slowly produce abnormalities in the cholesterol level of the plasma partly by interference with the functional efficiency of the liver and partly by interference with the supply of heparin from the mast cells which, normally present in the wall of the aorta and of the coronary artery were found to be absent from these sites in 3 cases with atheromatous changes.

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