THE EFFECT OF HEPARIN ON THE PLASMA CHOLESTEROL

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THE existence of some connection between heparin and blood lipoids was suggested by the work of Chargaff *et al.* (1941) and of Hahn (1943). The former workers demonstrated that heparin could rupture the bond uniting globulin with lipoid material in " lipoproteins," itself combining with the globulin. The latter observed that intravenous injection of hepærin was followed, in dogs, by a rapid disappearance of alimentary lipamia.

The importance of the plasma cholesterol concentration in relation to the concentration of other lipins at once suggested that heparin might have some influence on this, and in the course of a more general investigation of cholesterol metabolism the opportunity arose of testing this point.

METHODS AND RESULTS

Subjects.—The subjects were 19 patients suffering from xanthomatosis, nephrotic syndrome, coronary infarction or pulmonary infarction.

Chemical Methods.—Total cholesterol was determined by the method of Sackett (1925) adapted for use with a Spekker photoelectric absorptiometer ; free cholesterol by Sperry's method (1934) as modified by Delphine H. Clarke (1945).

Procedure.—After a sample of venous blood had been withdrawn, heparin was given intravenously in therapeutic doses and further samples of blood were withdrawn at the same time each day for five days. Free and total cholesterol were determined in the plasma separated from each sample. In 14 cases a further sample of plasma was analysed after an interval of six weeks, and in the remaining five the daily analysis was continued to the fifth or sixth day.

Results.—The results are summarised in Table IA which shows that in every instance the administration of heparin was followed by a prompt fall in the total concentration of cholesterol in the plasma and a proportionate fall in the concentration of free cholesterol. These falls were greater in those patients with marked hypercholesterolæmia.

Five patients, one with xanthomatosis, the others cases of nephrotic syndrome, had initial plasma total cholesterol concentrations ranging from 323 to 532 mg. per 100 ml. plasma (the normal range determined in this laboratory is 195 ± 25), and these fell by 120 to 232 mg. in twenty-four hours during which the patients had each received 30,000 units of heparin given in divided doses (12,000 units initially followed by 6,000 units at six-hour intervals). The free cholesterol concentrations, initially absolutely high but forming the normal proportion of the total, fell similarly, so that the ratio free total cholesterol was

unaltered. During the second twenty-four-hour period, in spite of further administration of 10,000 units of heparin (one dose), there was no further decrease in the plasma concentration of free or total cholesterol. During the third twenty-four-hour period, with no further

TABLE Ia

No.	Diagnosis.	Cholesterol Before Heparin.			Cholesterol 1st day (24 hours) after 30,000 units Heparin.			Cholesterol 2nd day (24 hours) after 10,000 units Heparin.			Cholesterol 3rd day No Heparin.			Cholesterol 4th day No Heparin.			Cholesterol 5th day No Heparin.			Cholesterol 6th day No Heparin.		
		mg. %.		F. %.	mg. %.		F. %.	mg. %.		F. %.	mg. %.		F. %.	mg. %.		F. %.	mg. %.		F. %.	mg. %.		F. %.
		T.	F.		T.	F.		T.	F.		T.	F.		T.	F.		T.	F.		T.	F.	
1*	Xanthomatosis	520	125	24	324	94	28	300	84	28	230	70	30	245	70	28	444	130	29	450	130	28
2	Nephrotic syndrome	514	130	25	300	80	26	305	80	26	300	84	24	375	100	26	425	120	27	...	...	...
3	Nephrotic syndrome	532	150	28	300	84	24	285	75	26	290	74	25	285	74	25	400	100	25	...	...	...
4	Nephrotic syndrome	323	88	27	200	60	30	205	58	28	215	62	28	220	62	28	300	80	26	...	...	...
5	Nephrotic syndrome	425	120	28	250	72	28	245	70	28	265	75	28	275	75	27	400	120	30	...	...	...

* Received tromexan throughout in addition to heparin (on the first and second days only).

TABLE Ib

No.	Diagnosis.	Heparin.	Cholesterol Before Heparin.			Cholesterol 24 hours after Heparin.			Cholesterol 48 hours after Heparin.			Cholesterol 6 weeks after Heparin.		
			Total.	Free.	%.	Total.	Free.	%.	Total.	Free.	%.	Total.	Free.	%.
6	Coronary infarction	8,000 units *statim* 6,000 units 6 hourly	245	70	28	200	55	27	220	62	28	250	67	26
7	Coronary infarction	8,000 units *statim* 6,000 units 6 hourly	230	68	29	200	53	26	210	55	26	238	68	28
8	Coronary infarction	10,000 units *statim* 6,000 units 6 hourly	220	60	27	189	60	31	200	56	28	216	62	28
9	Coronary infarction	8,000 units *statim* 6,000 units 6 hourly	230	68	29	202	60	29	200	55	27	235	66	28
10	Coronary infarction	10,000 units *statim* 10,000 units 4 hourly	250	67	26	190	56	29	210	55	26	257	67	26
11	Coronary infarction	10,000 units *statim* 10,000 units 4 hourly	200	55	27	170	48	29	175	48	27	209	57	27
12	Coronary infarction	10,000 units *statim* 10,000 units 4 hourly	211	53	25	190	54	28	192	54	28	216	59	27
13	Coronary infarction	10,000 units *statim* 10,000 units 4 hourly	200	75	37	176	66	37	...	...	...	220	76	35
14	Coronary infarction	10,000 units *statim* 10,000 units 6 hourly	268	70	26	250	70	28	255	70	27	275	80	29
15	Coronary infarction	8,000 units *statim* 6,000 units 6 hourly	235	85	36	205	70	34	210	70	33	230	80	35
16	Coronary infarction	8,000 units *statim* 6,000 units 6 hourly	230	70	29	202	60	29	...	...	...	235	68	29
17	Coronary infarction	10,000 units *statim* 10,000 units 6 hourly	255	65	25	204	52	25	...	...	...	260	74	28

administration of heparin, the total cholesterol concentration remained unaltered but thereafter there was a rapid rise towards the initial level, which in two cases had been practically reattained on the fifth day. The concentrations of free cholesterol behaved similarly except that the restoration of the initial concentration was more nearly complete on the fifth day.

The 14 patients with coronary or pulmonary infarction had received

no heparin prior to the observations reported in Table IB and IC and had just been admitted to hospital with a fresh coronary thrombosis or pulmonary embolism. The initial total cholesterol concentration ranged from 200 to 268 mg. per 100 ml., *i.e.* in or slightly above the upper half of the normal range, and free cholesterol formed the normal percentage of the total. Each of these patients received heparin in divided doses for twenty-four to forty-eight hours. Twenty-four hours after the last dose of heparin, the total cholesterol had fallen by amounts, ranging from 21 to 60 mg. per 100 ml. plasma, which were not proportionate either to the heparin dosage or to the initial level. The free cholesterol values fell proportionately. For therapeutic purposes,

TABLE IC

No.	Diagnosis.	Cholesterol Before Heparin.			Cholesterol 24 hours after Heparin.				Cholesterol 48 hours after Heparin.			Before Discharge 6 weeks after Heparin.		
		Total.	Free.	%.	Dose.	Total.	Free.	%.	Total.	Free.	%.	Total.	Free.	%.
18	Pulmonary infarction	255	70	27	10,000 units *statim* 10,000 units 6 hourly	210	55	26	215	60	27	257	67	26
19	Pulmonary infarction	250	67	26	10,000 units *statim* 10,000 units 6 hourly	208	55	26	218	60	27	245	70	28

Tromexan Only

No.	Diagnosis.	Cholesterol Before Tromexan.			Cholesterol 24 hours after Tromexan.				Cholesterol 48 hours after Tromexan.			Cholesterol 72 hours after Tromexan.			Cholesterol 96 hours after Tromexan.		
		T.	F.	%.	Dose.	T.	F.	%.	T.	F.	%.	T.	F.	%.	T.	F.	%.
1	Coronary infarction	180	54	30	Tromexan 1·2 gm. Next day 0·9 gm.	187	57	30	190	58	30	185	57	30	187	55	29

administration of heparin was followed by treatment with tromexan but this had, of course, no effect on the figures just quoted. Forty-eight hours after cessation of the heparin treatment, and twenty-four hours after the first dose of tromexan the concentration of cholesterol in the plasma were substantially unaltered. Daily determinations of the plasma cholesterol then ceased but six weeks later the concentration had, in all cases, returned to the initial level.

These results showed the profound influence of heparin on the plasma cholesterol concentration but did not indicate whether tromexan had a similar effect. The apparent absence of effect of tromexan in the cases quoted in Tables IB and IC is not conclusive, because as is shown in Table IA the fall in plasma cholesterol produced during twenty-four hours administration of heparin was not increased when the drug was given for a second period of twenty-four hours.

Other cases, however, show quite clearly that tromexan does not lower the plasma cholesterol level. Thus, in case 1 (Table IA) the plasma cholesterol concentration rose towards the normal level at the same time as in the other cases of this group although this patient

alone was receiving tromexan. Further, during continued administration of tromexan for six more days, the plasma cholesterol was maintained at 450 mg. per 100 ml. More clear cut, however, is the evidence from a patient, suffering from coronary thrombosis, who received tromexan therapeutically for about three weeks, but was at no time given heparin; the plasma cholesterol did not fall below the initial level of 190 mg. per 100 ml. on the second day of tromexan nor on any of three other occasions.

Conclusions

It is evident that heparin is capable of lowering markedly the concentration of cholesterol in the plasma, that this effect is produced equally in free and esterified cholesterol, that it is greater when hypercholesterolæmia exists than when the cholesterol level is normal, and that when the lowering has been produced continued administration of heparin has no further effect. The other anticoagulant tested, tromexan, had no such action.

The 12 patients in these series who were suffering from coronary thrombosis had plasma cholesterol concentrations which were not significantly above the normal range, although all were above the normal average. The free cholesterol formed the normal proportion of the total. Similar figures have been obtained by the authors in some 50 other cases to be reported elsewhere. This observation, in agreement with that of Hall, Morrison and Cheney (1948), does not support the idea that hypercholesterolæmia is the cause of coronary atheroma. Nevertheless, the metabolism of cholesterol may well undergo profound alteration without marked change in the plasma concentration and the bulk of evidence relating the occurrence of atheroma with abnormal cholesterol metabolism is too great to be ignored. It is tempting, though highly speculative, to relate the stability of cholesterol in the plasma, the concentration of heparin or similar amino-sugar esters, and the mast cells which many workers believe to be concerned in the production of such substances. Much indirect evidence indeed, can be adduced to lend plausibility to such a speculation, but until direct evidence is found, it is wiser to be content with drawing attention to the possible relation with all that it implies.

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