OBSERVATIONS ON THE PLASMA FIBRINOGEN CONTENT AFTER MYOCARDIAL INFARCTION

By ELIZABETH GILCHRIST, M.A., B.Sc., Ph.D.
Department of Clinical Chemistry
and
JOHN A. TULLOCH, M.C., M.D., M.R.C.P.E.
Department of Cardiology
Royal Infirmary, Edinburgh

FIBRINOGEN is one of the proteins normally present in plasma, and is constantly utilised within the body. In the healthy adult approximately 6 g. are synthesised by the liver and are metabolised each day (Everett, 1946). Much larger quantities are formed in the presence of inflammation, which with injury is the most powerful stimulus to fibrinogen production. The stimulus does not depend on bacterial products, as sterile or aseptic inflammatory processes have the same effect. Meyers (1948) has shown that myocardial infarction is followed by a rise in plasma fibrinogen. He suggests that determination of the fibrinogen levels in the plasma may be a valuable guide to the progress of the reparative process in the infarcted area. The present investigation was undertaken to determine (*a*) the frequency with which increase in the plasma fibrinogen content occurs after a coronary thrombosis, and (*b*) the relation, if any, of the clinical severity of the case with the degree and duration of the changes observed.

MATERIAL

Forty-two patients were studied during forty-five attacks of coronary thrombosis—33 males, 3 of whom have been observed during two attacks, and 9 females. All were inpatients in the Royal Infirmary, Edinburgh, and all showed electrocardiographic evidence of recent myocardial infarction. Serial estimations of plasma fibrinogen content were carried out at frequent intervals during the period of hospitalisation. Seven patients were treated conservatively, while anti-coagulants were employed in the remaining 38 patients. Seven deaths occurred during the period of observation; 2 of these patients were treated conservatively, and 5 received anti-coagulants. In addition, plasma fibrinogen estimations were carried out on 10 healthy male adults as controls, and to establish the normal for the method used.

METHOD

Blood samples were collected at 9 a.m. each day, except on the day of admission. A clean venepuncture was performed; blood was withdrawn into a dry sterile all-glass syringe and was immediately transferred to a specially prepared glass tube graduated at 6 ml. and contain-

ing the optimum amount of oxalate—30 mg. to 6 ml. of blood.* Thorough mixing of the oxalate powder with the blood was ensured by corking the tubes and inverting gently several times. Hæmolysis was avoided.

Fibrinogen was estimated by the following method. To 2 ml. of plasma there were added 30 ml. of 0·9 per cent. sodium chloride and 1 ml. of 2·5 per cent. calcium chloride, and the mixture was incubated overnight at 37° C. The clot which had formed was collected on a fine glass rod and dried on a filter paper, care being taken that none was lost. The nitrogen content was estimated by the micro-kjeldahl method, and the fibrinogen content calculated using the factor 6·25. The accepted figures for the normal range of plasma fibrinogen is

TABLE I

This Illustrates the Distribution of the Maximum Plasma Fibrinogen Levels Observed in 32 Patients with a Recent Coronary Thrombosis, and their Relationship to the Severity of the Attack as Divided Clinically into Three Grades, Mild, Moderate and Severe

Maximum Plasma Fibrinogen.	Number of Cases of Coronary Thrombosis.			
	Total.	Clinical Assessment.		
		Mild.	Moderate.	Severe.
0·30-0·39 g. per cent.	1	1	...	...
0·40-0·49 ,,	3	2	...	1
0·50-0·59 ,,	10	9	1	...
0·60-0·69 ,,	9	5	2	2
0·70-0·79 ,,	6	1	3	2
0·80-0·89 ,,	1	...	1	...
0·90-0·99 ,,	2	...	1	1
Total . . .	32	18	8	6

between 0·2 and 0·4 g. per cent. In the 10 control cases investigated the results obtained by the method above varied from 0·24 to 0·32 g. per cent.

Discussion

The time after the acute attack at which the patients first came under observation varied widely: thus 3 cases were already in hospital at the time of their coronary occlusion, while, at the other extreme, one patient was not admitted until twenty-two days after the infarct had been sustained. The cases studied fall into two groups: (*a*) 32 patients investigated from within one to five days after the onset, and (*b*) 13 patients admitted between the eighth and twenty-second day after the infarct. In 30 of the 32 cases in group (*a*) the plasma showed a rise in fibrinogen content to abnormally high levels during the first or second weeks after the myocardial infarction, the highest recorded level being 0·98 g. per cent. From Table I it will be seen that in the majority of cases the

* These tubes were prepared by adding 0·5 ml. of 6 per cent. sodium oxalate to each tube and drying them in an oven at 100° C. till the oxalate remained as a powder.

maximum figure lay between 0·50 and 0·79 g. per cent. In the remaining 2 cases of this group the highest levels were at the upper limit of normal, viz., 0·39 and 0·40 g. per cent respectively. Since in these patients the first estimations of fibrinogen were lower, a minor rise did occur. Six patients were examined on the day of the attack, 11 on the second day and 15 between the third and fifth day after the infarct occurred. Of the 6 patients seen on the first day, 3 were examined within three to six hours after the onset and at that time showed normal fibrinogen levels. The other 3 patients were not examined till ten to seventeen hours had elapsed and these all showed abnormally high levels. Of the 11 patients seen for the first time on the second day, all had plasma fibrinogen levels above the normal range, while of the remaining 15 patients examined for the first time between the third and fifth day after the acute incident, only 3 gave first readings still within the normal range, viz., 0·36 and 0·38 and 0·39 g. per cent.

TABLE II

The Day on which the Maximum Plasma Fibrinogen Level was Recorded in 32 *Cases of Coronary Thrombosis, is Shown*

Day After Onset.	Number of Cases.	Day after Onset.	Number of Cases.
2nd	2	9th	1
3rd	3	10th	0
4th	3	11th	2
5th	7	12th	2
6th	5	13th	0
7th	4	14th	2
8th	1	15th	0

respectively. These figures are near the upper limit of the normal range and may have been high for the patients in question, so that the rise though slight may have started.

The times at which the highest levels occurred and the subsequent fall started varied considerably in different patients. Reference to Table II will show that the common peak period lay between the fifth and the seventh day after the attack. In a few cases the highest level was attained more slowly and occurred between the tenth and the fourteenth day of the illness. As the samples of blood for estimations were not withdrawn every day but with a few days' interval between, it is possible that in some cases the highest level of plasma fibrinogen reached may have been missed. This must be borne in mind when considering the results. It would appear, however, that in general there is a rapid rise in plasma fibrinogen to a maximum during the first week after the infarct occurs.

In all the cases studied this steep rise in the early stages of the disease was succeeded by a gradual return of the plasma fibrinogen levels to within normal limits during the succeeding weeks. This is

illustrated in Fig. 1. The fall occurs over a varying period of time. Excluding the 2 patients who showed only a slight rise within the limits of normal and 5 patients who died during the first few weeks, 25 cases remain for analysis. Nine of these showed a return of the plasma fibrinogen to within the normal range during their stay in hospital, *i.e.* within six weeks after the attack. The duration of the abnormal levels in these patients ranged from fifteen to thirty-six days after the occurrence of the coronary thrombosis. The maximum level attained

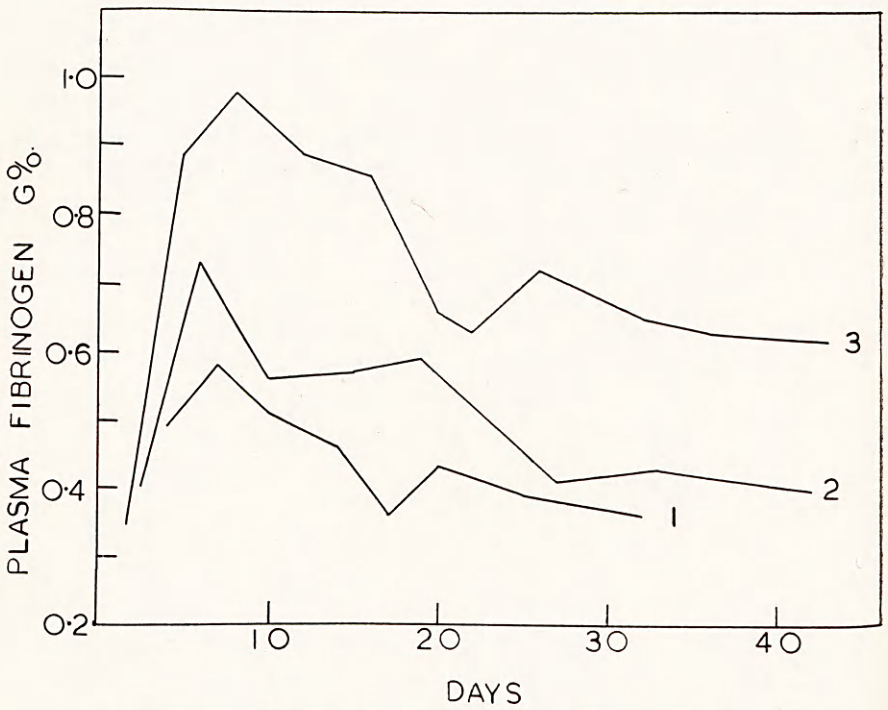

FIG. 1.—The changes in plasma fibrinogen content observed in 3 cases of coronary thrombosis are illustrated. The extreme variation in the magnitude of the increase in plasma fibrinogen and its duration are well known. Clinically Case 1 had a very mild attack; Case 2 was moderately severe; while Case 3 was seriously ill.

was under 0·6 g. per cent. in 6 of the 9 cases, and was lower than that reached in the other 16 cases of the group under consideration. These 16 cases had not only a higher maximum level—only 3 showed a figure under 0·6 g. per cent.—but the return to normal was much slower. The final reading prior to discharge from hospital was still above the normal level. Nine of these 16 cases have been followed up six weeks after their discharge from hospital, *i.e.* they were under observation for three months after the coronary thrombosis had occurred. Five had returned to normal plasma fibrinogen levels at that time, and 4 were still above normal, viz. 0·41, 0·43, 0·44 and 0·49 g. per cent. respectively. As already stated 5 of the patients died, 4 in congestive

heart failure and 1 suddenly and unexpectedly. In these cases the serial levels of fibrinogen did not differ materially from those obtained in the patients who survived.

Comparison of the rise in plasma fibrinogen levels with the severity of the coronary thrombosis—the latter being assessed on clinical grounds in all cases by the same physician—shows that the more severe attacks tend to be associated with the higher levels of fibrinogen in the plasma (Table I). Determination of blood sedimentation rate was done throughout the course of the illness in all the patients, and it was found that in most cases the B.S.R. changed in a fashion roughly

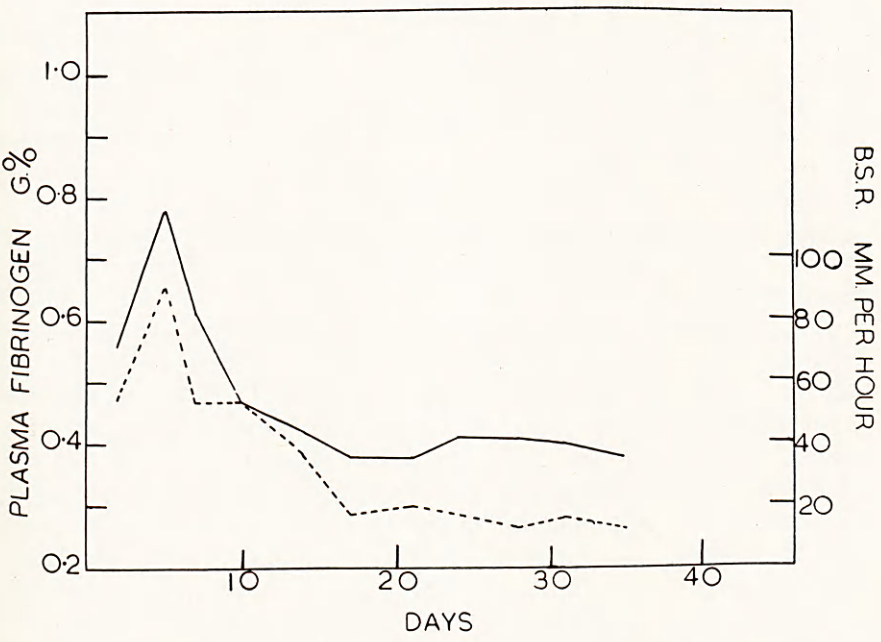

FIG. 2.—Serial observations made on the plasma fibrinogen content (continuous line) and on the blood sedimentation rate (dotted line) in one moderately severe case of coronary thrombosis are illustrated.

parallel with the rise and subsequent fall in fibrinogen. The closeness of the correlation has not, however, been mathematically examined. Fig. 2 illustrates this point; the curves shown by these two factors tend to be parallel to each other, although the fall in plasma fibrinogen may lag behind that of the B.S.R. Comparison of individual cases shows that a particular plasma fibrinogen level is not associated with a particular B.S.R. reading and *vice versa*; thus a B.S.R. of over 100 mm/hr. has been observed with plasma fibrinogen levels of 0·63 and 0·43 g. per cent.; while B.S.R.s of approximately 50 mm/hr. occurring two weeks after the infarct have been associated with plasma fibrinogen levels ranging from 0·41 to 0·78 g. per cent.

The 13 patients in group (*b*) were first investigated between the

eighth and twenty-second day after the coronary thrombosis was sustained. These have been analysed separately. One patient died on the twelfth day, while 12 survived. All received tromexan. All but one showed abnormally high plasma fibrinogen levels from the beginning of examination. Eleven patients admitted between the eighth and nineteenth days showed a rise in plasma fibrinogen level during the first few days of their investigation, the increase observed varying from 0·03 to 0·27 g. per cent. The maximum level was observed on the twelfth and thirteenth days after the infarct in 3 patients; on the seventeenth day in 2; and between the twentieth and twenty-fourth days in 6 cases. Thereafter the fibrinogen levels fell gradually towards normality. Two cases admitted on the thirteenth and twenty-second days respectively showed no such initial rise in fibrinogen content during the first few days after admission. As in group (*a*) one-third (4 of the patients) showed plasma fibrinogen levels within the normal range in twenty-four to thirty-six days after the infarct, while two-thirds (8 patients) still showed fibrinogen levels greater than 0·40 g. per cent. at the time of their discharge from hospital. Three of these latter 8 patients have been examined six weeks after their discharge, and in 2 the fibrinogen levels were still high, being 0·40 and 0·41 g. per cent. respectively.

The fibrinogen estimations recorded in the patients in group (*b*) differ in one important respect from these obtained in the group (*a*) patients. The rise in plasma fibrinogen content in the 11 patients described above occurred at a time when, in the group (*a*) patients, the fibrinogen levels had begun to fall. Some factor other than the myocardial infarct, and common to all cases would therefore appear to be involved. Tromexan administration may be this factor, as all cases were so treated. Dicoumarol is known to influence fibrinogen production by the liver (Irish and Jaques, 1945), temporarily stimulating fibrinogen production when administered in moderate dosage, and damping down fibrinogen production when given in massive dosage. It is therefore possible that tromexan administration in therapeutic dosage may temporarily stimulate fibrinogen production by the liver. This is at present under investigation. In the group (*a*) patients who received tromexan (24 cases) or dicoumarol (1 case) this effect of the coumarol drug may be overshadowed by the more powerful stimulus of the myocardial infarct. The 7 patients in group (*a*) who were treated conservatively differed in no respect from those receiving anti-coagulants, except in so far as the maximum level recorded did not exceed 0·79 g. per cent. The numbers involved are too small to draw definite conclusions.

Summary

An increase in plasma fibrinogen content occurs after myocardial infarction. The maximum increase is detected about one week after the acute episode, and is succeeded by a gradual fall in plasma fibrinogen

levels. In one-third of all cases, the level has returned to within normal limits by the sixth week after the onset, but in the remaining two-thirds, the readings are still abnormal at this time. Plasma fibrinogen estimation may therefore be an additional aid in establishing in retrospect the diagnosis of coronary thrombosis. In some cases the levels may still be abnormally raised three months after the acute incident. The more severe cases tend to show the greatest rise in plasma fibrinogen, and in these a longer time elapses before a normal level is restored. Patients observed from the onset react similarly whether treated conservatively or with anti-coagulants. Patients first treated with anti-coagulant therapy from the eighth day after the attack, or later, show a further rise in plasma fibrinogen content from an already abnormally high level. This may be related to tromexan administration.

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