Plasma Fibrinogen Levels in Normal and Sick Cows

B. J. McSherry, F. D. Horney and J. J. deGroot*

SUMMARY

Mean plasma fibrinogen levels were determined in 133 normal calves, bulls, non-pregnant and pregnant cows. These were 508, 505, 660, and 581 mg per 100 ml of plasma respectively. The levels in 233 sick cows were often greatly increased. This appeared to be related to inflammation and tissue destruction. Lower than normal levels were sometimes seen in liver disease and terminal states.

RÉSUMÉ

Les taux moyens de fibrinogène plasmatique furent déterminés chez 133 animaux normaux: veaux, taureaux, vaches gravides et non-gravides. Ces taux se révélèrent respectivement de 508, 505, 660 et 581 mgm par 100 cc de plasma; chez 233 vaches malades, ils s'avérèrent souvent fortement augmentés. Ce phénomène semble relié à l'inflammation et à la destruction tissulaire. On observa parfois des taux inférieurs à la normale dans des affections hépatiques et à la veille de la mort.

INTRODUCTION

Fibrinogen, one of the plasma proteins has a molecular weight of 340,000 and is classed as a globulin (52). The study of this protein began before the turn of the century and aided by modern techniques continues today. Differences at the molecular level have been demonstrated between the fibrinogen of man, horse, dog, and cow (40, 60) and it is likely that such differences also occur in the fibrino-peptides released by the action of thrombin on fibrinogen (38). Many inflammatory states are accompanied by increased plasma fibrinogen levels, and in certain diseases of man there is an increase in a fibrinogen-like protein that is precipitated by heparin (59). It has been reported that cattle suffering from Bracken poisoning produce a fibrinogen differing in chromatographic characteristics from the normal (17, 37). This change in plasma protein was related to streaking observed in blood films made from cows with Bracken poisoning (17, 37). The reported half life for fibrinogen is 2.1 to 6.1 days in man, (1, 31, 41, 61, 62) and 2.5 to 4.5 days in the dog (1, 31, 41, 56).

Early workers produced liver damage in dogs and concluded that this organ was the site of fibrinogen production (28, 67, 68). This view was supported by clinical experience but only in relatively recent years has definite proof that this is so been obtained. The perfusion of isolated rat livers with radio isotopes confirmed the dominant role of the liver in fibrinogen biosynthesis (46, 47). When fresh human liver slices were incubated *in vitro* fibrinogen was produced (61). Data obtained with the fluorescent antibody technique showed that in the dog the hepatic parenchymal cell is the production site of fibrinogen and that neither the Kupffer cells, nor cell types found in the spleen, bone marrow, lymph nodes or circulating blood produced this protein (20). By means of immunochemical and cellular fractionation procedures, it has been shown that in the dog and cow, fibrinogen was formed in the microsomes of the liver parenchymal cells and then stored in the soluble part of the cell until required (5).

Fibrinogen is not confined to the plasma in the vascular channels but is found in lymph vessels, connective tissue and interstitial spaces (26, 27). It has been variously stated that the intravascular fibrinogen constitutes 50 to 84 per cent of the total with the remainder being outside the vascular channels (1, 31, 41, 56, 62).

Fibrinogen is the sole precursor of fibrin and as such plays a dominant role in coagulation. It has been suggested that by promoting surface phagocytosis fibrinous exudates contribute to antibacterial defenses (39). The peptides released when fibrinogen is acted on by thrombin have a physiological activity on smooth muscle and may help to control the blood flow in the capillary bed (38). Neutrophils can

*Department of Pathology (McSherry) and Department of Clinical Studies (Horney and de Groot), Ontario Veterinary College, University of Guelph, Guelph, Ontario.

Present address of J. J. deGroot: Meerweg 7A. Zoetermeer, Holland.

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phagocytize fibrin, fibrinogen, or their breakdown products (4, 55), and evidence has been presented to show that profibrinolysin is synthesized by the eosinophils of the bone marrow and is then released to the tissues when necessary (6, 55).

Normal levels of plasma fibrinogen are well documented in man and the dog but not in other species. In even moderate inflammatory states plasma fibrinogen may increase and it is likely that many "high normal" values have resulted from undetected sub-clinical condition. Normal plasma fibrinogen levels in man are 200-400 mg per 100 ml (10, 21, 29, 52, 53, 57) and similar values are found in dogs (19, 22,-23, 58, 60, 67, 68). Normal values for the monkey, sheep, goat, cat, raccoon, oppossum, chicken and duck have also been reported (13, 19, 35, 60). Normal ox plasma contains twice as much fibrinogen as does that of man or the dog (13, 35, 60). In 1922 and 1925 the plasma fibrinogen levels in calves and cows of various ages and stages of pregnancy were recorded (34, 36). These values, other than for some very high ones that were likely due to unsuspected infections, are in agreement with those published by later workers indicating the cow has a normal plasma fibrinogen level of 450-750 mg (13, 60, 65).

Day to day variation of the plasma fibrinogen levels in normal man and dog is not marked (23, 29, 42, 58). Pregnancy is accompanied by a 20 to 25 per cent increase in man and the dog (10, 14, 21, 23, 51), but in cows it is said not to produce a uniform change (36). It is not affected by repeated bleeding, hemorrhage, transfusions of blood or Lockes solution or by changes in type or amount of diet (23, 24, 64, 65). There are no marked changes due to age, exercise, or sex (29, 53). Increases in body temperature, total white count, or the giving of anaesthetics are not *per se* accompanied by increased plasma fibrinogen (29,-42, 52, 58). The level is the same in both venous and arterial blood but with falling blood pressure there is a tendency for it to decline (12, 58, 64).

Increases in plasma fibrinogen may accompany tissue inflammation whether traumatic, bacterial, chemical or neoplastic in origin (29). High values are reported in instances of cell injury without an inflammatory response and in some afebrile diseases (29). In man the highest reported levels occur in lobar pneumonia and septicemia (21, 25, 42, 48, 51). Elevated levels are also described in moderate liver damage (10, 21, 67), myocardial infarction (44), nephrosis (10), sterile abscesses (25), x-ray damage (25, 52) and many other states. It has been said that failure of plasma fibrinogen to increase during acute inflammatory states suggests a poor prognosis (29).

Plasma fibrinogen levels in sick animals are not well documented (11). In dogs, distemper, peritonitis, wound infections, pneumonia, surgery and cellulitis have been associated with elevated levels (22, 25, 58). In cows a moderate increase attributed to tissue injury was noted following injection of *B. abortus* vaccine and a definite increase followed abortion (36). No change was noted following the immunization of cows against foot and mouth disease (66). Fibrinogen levels up to 2000 mg per 100 ml were reported in the later stages of Bracken poisoning (15, 16, 17, 42).

Fibrinogenopenia occurs in a variety of clinical conditions. Liver damage with subsequent inability to produce fibrinogen is one of the major causes (8, 10, 21, 25, 28, 42, 68). Liver disease must be severe before this happens (29). Acquired fibrinogenopenia is also seen in conditions having as their basis the rapid removal of fibrinogen from the circulation due to increased destruction by fibrinolysins or following release of thromboplastin into the circulation. This may happen in obstetrical accidents, shock, extensive cancer, in particular of the prostate, bladder, or pancreas, and as a complication of major pulmonary or abdominal surgery (8, 10, 43, 52, 57). It is of interest that there is little if any fibrinolytic activity in the cow's lung (2,-3, 50). Congenital afibrinogenopenia, while rare, is recognized in man (8, 26) and a case has been described involving four related calves one of which had a plasma fibrinogen level of 32 mg (7).

The relationship of the time of onset of the inflammatory process or tissue damage to the increase in plasma fibrinogen has been reported (29, 48). The fibrinogen level increases within 24 hours of tissue injury. In chronic reactions the fibrinogen generally remains high as long as the disease is present and active, while in an acute condition it reaches its peak and then declines.

The erythrocyte sedimentation rate serves as a valuable diagnostic test for inflammation in some species but is not demonstrable in cattle (9, 49, 54). As one of the main

TABLE I. Plasma Fibrinoge n Levels in 113 Normal Cows

Group	Number of Animal	Fibrinogen Mg %	
		Range	Mean and SD
Calves new born to ten weeks of age	22	280 — 800	508 ± 122
Bulls nine to 12 months of age	15	250 — 760	505 ± 156
Heifers and non-pregnant adult cows	27	380 — 1120	660 ± 172
Cows pregnant three to eight months	49	320 — 1350	581 ± 225

causes of a fast sedimentation rate is an increase in plasma fibrinogen (18, 30, 45) the demonstration of an increase in this protein in sick cattle might serve the same diagnostic function as a fast sedimentation rate does in other species.

METHODS AND MATERIALS

One hundred and thirteen animals were used to determine normal values. Twenty-two were calves varying in age from newborn to ten weeks, 15 were bulls aged nine to 12 months, 27 were non-pregnant heifers and cows and 49 were cows pregnant three to eight months. All were apparently clinically normal but this was not confirmed by a thorough examination.

Plasma fibrinogen was determined on 160 cows presented to the University Clinic with a variety of clinical disorders. In each case the diagnosis was arrived at by clinical examination supplemented by extensive laboratory tests, and often by exploratory surgery. Animals that died were subjected to detailed necropsy. Samples for fibrinogen estimations were taken at the time of the first clinical examination and in some cases at varying intervals thereafter. The fibrinogen levels presented here are those recorded when the animal was first examined.

Blood samples from 18 cows involved in two herd outbreaks of virus diarrhoea were tested for plasma fibrinogen. These animals were all acutely ill and six subsequently died making it possible to confirm the diagnosis.

Fifty-five steers being used in a study of naturally occurring pneumonia (63) were made available for this study. They were examined daily for evidence of pneumonia over a period of 30 days and samples for fibrinogen were taken on these days. Thirty-three developed pneumonia while 22 did not.

Whole blood was collected from the jugular vein into dipotassium ethylenediaminetetracetate. When the fibrinogen values were not determined on the day of collection the samples were frozen. Plasma fibrinogen was determined by applying the Biuret reaction to the fibrin clot produced by adding thrombin to diluted plasma (36).

RESULTS

The plasma fibrinogen values found in the 113 normal animals are presented in Table I. The mean values for the calves and bulls were 508 and 505 mg fibrinogen per 100 ml respectively. There were no values over 800 mg. The mean value for the 27 non-pregnant cows was 660 mg per 100 ml. Six animals in this group had individual values of 819, 820, 840, 920, and 1120 mg per 100 ml. The mean value for the 49 pregnant cows was 581 mg per 100 ml. Seven of these had individual values of

TABLE II. Clinical Cases with Normal or Subnormal Plasma Fibrinogen Levels

Diagnosis	No. of Cases	Fibrinogen Mg %
None — presumed normal	8	540 — 800
Sick — no diagnosis	2	325 and 700
Lymphosarcoma	8	310 — 780
Peritonitis	10	540 — 800
Necrotizing Mastitis	1	440
Metritis	4	500 — 725
Displaced Abomasum	6	310 — 800
Liver Damage	8	50 — 740
Nutritional	4	275 — 580
Miscellaneous	9	350 — 800

TABLE III. Plasma Fibrinogen Levels in 87 Sick Cows Where the Level was Greater than 800 mg per 100 ml

Diagnosis	No. Cases	Fibrinogen Mg %		
		Mean	Range	Individual Values
Peritonitis	34	1414	840 — 3125	
Pericarditis	8	1416	925 — 1675	925, 1235, 1275, 1325 1610, 1640, 1650, 1675
Pneumonia	8	1300	875 — 2300	850, 875, 1025, 1180 1200, 1430, 1550, 2300
Enteritis	7	980	840 — 1220	840, 840, 850, 920 1130, 1120, 1220
Endocarditis	5	1300	940 — 1550	940, 1180, 1350, 1525, 1550
Liver Damage	5	1060	850 — 1260	850, 940, 1050, 1120, 1260
Nephritis	4	1430	1260 — 1775	1260, 1350, 1360, 1775
Mastitis	3	1180	875 — 1500	875, 1175, 1500
Virus Diarrhoea	3	1500	1340 — 1900	1340 — 1375 — 1900
Lung Abscess	3	1020	940 — 1175	940 — 1050 — 1175
Displaced Abomasum	3	950	900 — 1025	900 — 900,1025
Ruptured Bladder	2	—	— —	1050 — 1160
External Abscess	2	—	— —	1100, 1100
No. Diagnosis	3	1100	1025 — 1180	1025 — 1100 — 1180

820, 840, 960, 1020, 1120, 1160, and 1350 mg per 100 ml.

Eight hundred mg per 100 ml was arbitrarily selected as the upper limit of normal for fibrinogen in cattle. Using this figure the 160 clinically sick animals were divided into two groups. Group 1 (sixty animals) had values below and Group 2 (100 animals) had values above 800 mg.

The plasma fibrinogen values of 800 mg or less of the sick animals are presented in Table II. Eight of these while admitted as sick were considered to be clinically well during their entire stay, and two animals while obviously sick were discharged without a definite diagnosis being made. Eight animals had advanced lymphosarcoma and one of these had a total white count of 500,000. Nine of the ten cases of peritonitis were associated with reticulitis and eight of these were terminal. The animal with necrotizing mastitis died within 24 hours of the sample being taken. All eight cows with advanced liver damage died and the clinical diagnosis was confirmed at necropsy. In five of these an inflammatory process complicated the picture. Three of the eight cows with liver damage had plasma fibrinogen levels of less than 200 mg, the lowest being 50 mg per 100 ml. None of the six cases of displaced abomasum were complicated by peritonitis. The four animals with nutritional problems included two calves with rickets and two with a malabsorption syndrome leading to emaciation and death. The nine cases listed under miscellaneous included two cases of ketosis, two cases of milk fever and single cases of poliocencephalomalacia, uremia, thrombocytopenia, oesophageal obstruction and nasal head catarrh.

The 100 sick cows with plasma fibrinogen greater than 800 mg per 100 ml are presented in Tables III and IV. Table III lists the cases where there was more than one animal with the same diagnosis while Table IV gives single cases.

Thirty-four cases were associated with peritonitis; four of these followed surgical procedures and the remainder were due to traumatic reticulo peritonitis. Of these 34 animals, 70 per cent had values over 1,000 mg, 50 per cent over 1,300 mg and 10 per cent over 2,000 mg of fibrinogen. The pericarditis lesions were in all cases traumatic in origin, and seven of these eight had

TABLE IV. Plasma Fibrinogen Levels in 13 Sick Cows Where the Level was Greater than 800 mg per 100 ml

Diagnosis	Fibrinogen Mg %
Muscle Necrosis	850
Intussusception	910
Dystocia	980
Muscular Dystrophy	990
Laminitis	990
Spinal Injury	1000
Anemia	1130
Post Surgery	1210
Fat Necrosis	1500
Indigestion	1600
Meningitis	1800
Calf Diphtheria	2095
Septicemia	2300

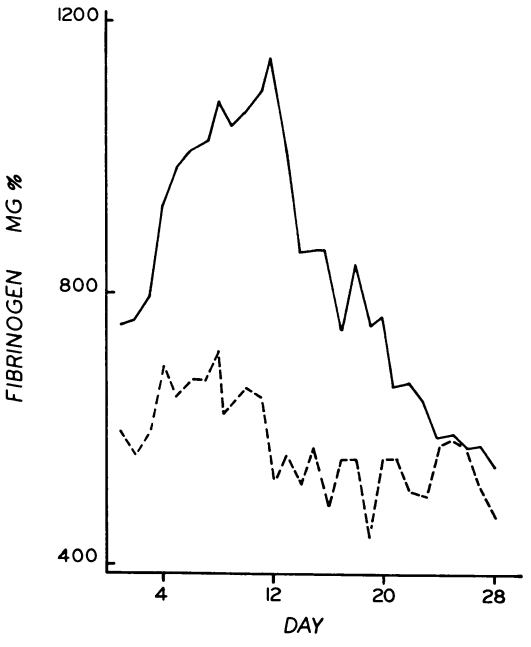

Fig. 1. Fibrinogen levels in 55 steers observed for evidence of pneumonia following shipping. The average daily levels of 33 steers developing (solid line) and 22 not developing (broken line) pneumonia are indicated.

plasma fibrinogen levels over 1200 mg. One case of pneumonia was diagnosed as acute fibrinous pneumonia; the other seven were related to septicemia, aspiration of foreign material or embolic from infections elsewhere in the body. The cases listed under enteritis were variously due to mycotic rumenitis, and abomasitis, Johnes disease, Salmonella infection, and one case described as gastro intestinal erosion. The three cases of virus diarrhoea all had prominent gastro intestinal erosions. The endocarditis lesions were chronic and arthritis was present in all cases. The five cases of liver damage included three with multiple liver abscesses, and two with extreme fatty degeneration. One of the cows with mastitis (fibrinogen 875 mg) was very toxic and died shortly after being admitted. The four cases of nephritis included three with amyloid kidneys and one with pyelonephritis. In three instances a cause for the high plasma fibrinogen was not determined. The animal with muscular dystrophy had a serum S.G.O.T. level of 3,700 Reitman-Frankel units.

The 18 cows with virus diarrhoea were acutely ill when the samples were taken and all had high temperatures. The plasma fibrinogen levels were between 275 and 750 mg with a tendency to be at the low end of normal or subnormal.

When the average fibrinogen levels of the 55 steers used in a study of pneumonia were examined there was a distinct difference between the 33 that did and the 22 that did not subsequently develop pneumonia. Thirty-seven per cent of those that developed pneumonia had high levels of fibrinogen at the start of the study as compared to less than 5 per cent of the other 22. As shown in Fig. 1, the 33 animals that developed pneumonia also had a subsequent increase in plasma fibrinogen.

In numerous clinical cases the plasma fibrinogen was determined daily over the course of an illness, and it was observed that with a favourable clinical response the level rapidly returned to normal. With a unfavourable response the level either remained high or would become subnormal. Two such cases are illustrated in Fig. 2.

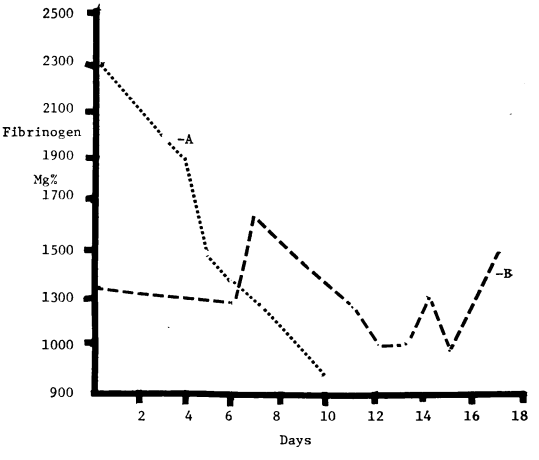

Fig. 2. Plasma fibrinogen levels in a calf with acute infection that responded well to treatment (A) and a cow with pericarditis that did not respond to therapy and died on Day 17 (B).

DISCUSSION

The normal plasma fibrinogen levels reported in this paper for healthy cattle agree with previously published figures of 450-750 mg per 100 ml (13,34,36,60,65). These are almost twice as high as reported for other species. Variations due to age, sex, or pregnancy were not noted. Every healthy cow likely has its own individual value

which does not fluctuate greatly and while 800 mg was selected as the upper limit of normal, it is recognized that for many sick animals this may in reality be a significant elevation from normal. The very high values that are sometimes encountered in apparently normal cattle are undoubtedly due to undetected inflammatory processes.

Cattle have a great capacity to produce fibrinogen and do so in response to a variety of stimuli the foremost of which appear to be inflammation and tissue destruction. The values encountered in many sick cows during this study were generally higher than those seen under similar circumstances in man.

Not all animals presented as sick had high fibrinogen levels. However, of the 60 animals in this category at least 33 either were not sick or had conditions that would not likely be associated with tissue destruction or inflammation, while eight others had advanced liver disease. Many of the remainder had overwhelming infections. It is obvious that lymphosarcoma by itself will not increase plasma fibrinogen. The same clinical entity (i.e. virus diarrhoea) can at times cause either a high or low plasma fibrinogen level. It has been suggested that the lack of fibrinogen response in some virus diseases may be due to inadequate stimulus to production (29).

While many diseases were associated with elevated plasma fibrinogen, peritonitis, and pericarditis tended to produce the most consistent change. However, the cases recorded were naturally very much influenced by the type of disease submitted to the clinic. It would appear that while a high level indicates that inflammation or tissue destruction is present this should be regarded as a non-specific response comparable to the sedimentation rate in other animals. A low plasma fibrinogen level in a sick animal is a poor prognostic sign. In experimental work the plasma fibrinogen can be of value in following the course of an induced infection. Since this data was compiled many more plasma fibrinogen levels have been determined on sick cows and the results confirm its usefulness as a laboratory test in this species.

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