Biochemical Pharmacology, Vol. 18, pp. 317–326. Pergamon Press. 1969. Printed in Great Britain

FIBRINOGEN AND EXPERIMENTAL INFLAMMATION

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(*Received* 13 *February* 1967; *accepted* 5 *July* 1968)

Abstract—Plasma fibrinogen concentrations are useful indexes for the assessment of inflammation and its therapy. The increase in plasma fibrinogen concentrations is related to the magnitude of the inflammation. It occurs before clinical evidence of disease. In rats with granuloma pouches, fibrinogen appears to be sequestered in areas of granulomatous tissue formation. Heparin injections into local sites of inflammation lead to exsanguination. Local steroid injections are more efficacious than subcutaneous injections for the reduction of both the local inflammatory reaction and circulating fibrinogen. The exact role of fibrinogen in areas of inflammation is not known entirely. The physiologic factors controlling its increased synthesis by the liver in response to distant sites of inflammation are unknown.

THE LIVER is the main site for fibrinogen synthesis.[1,2] Fibrinogen is increased in many inflammatory diseases and may be of some importance in the pathogenesis of various diseases. The increase in plasma fibrinogen and its deposition as fibrin in synovial fluid[3] suggest that it plays an important role perhaps in the chronicity of many inflammatory diseases of joints. Fibrin deposition appears to play a pathogenic role in hypersensitivity gangrenosum.[4,5]

Neutrophils possess the capacity for incorporating and inactivating fibrin deposits in experimental microthrombosis of dogs and in humans with myocardial infarctions.[6] The increased production of these cellular constituents of blood in response to inflammation may result partly, therefore, from the increase in fibrinogen synthesis and its deposition as fibrin at sites of tissue damage.

Fibrinolytic drugs have been used successfully for the treatment of some patients with rheumatoid arthritis.[7] The prevention of fibrin deposition, with anticoagulent therapy in animals, inhibits the development of some forms of experimental nephritis.[8] On the hypothesis that all information about fibrinogen and its relationship to inflammation is not known, the following studies were undertaken to define partially its role in experimental inflammation of the rat.

MATERIALS AND METHODS

Animals. Sprague–Dawley male rats, weighing 175–200 g at the start of the experiments, were used.

D-α-*tocopherol-induced granuloma pouches.* The methods have been described.[9] Rats were anesthetized with 5-allyl-5-(2-cyclopenten-1-yl)-barbituric acid and the back of each was shaved with hair clippers. Air (25 ml) was injected with the appropriate syringe via a 23 gauge needle. D-α-tocopherol (Eastman) (0·5 ml) was injected into the lumen of the pouch with a No. 15 gauge needle. To prevent leakage of air

from the pouch, a small bulldog clamp was placed over the hole at the injection site for 5 min. Animals were sacrificed on either the eighth or ninth day after making the pouches. Exudates were removed in plain or heparinized sterile syringes, depending upon the type of sample required. Blood was removed from the dorsal aorta of anesthetized rats. Samples were centrifuged to obtain either plasma or serum.

Adjuvant-induced polyarthritis. The induction of polyarthritis by *M. butyricum* inoculations into the tail has been described and reviewed in numerous publications.[10-15].

Drugs. Aspirin, phenylbutazone, indomethacin and cortisol acetate were suspended in deionized water and given orally twice a day for 14 days. For local and subcutaneous injections into rats with granuloma pouches, cortisol was suspended in 0·1 ml saline and given once each day for 7 days.

Labeled fibrinogen and albumin. ^{125}I-albumin and ^{125}I-fibrinogen were purchased from Abbott Laboratories Chicago, Ill. The rat protein fractions had essentially the same specific activity: 107 μc/mg for rat albumin and 101 μc/mg for rat fibrinogen. These were dissolved in saline with unlabeled proteins to make a final concentration of approximately 10 mg fibrinogen or albumin per ml saline. The final dilutions were equivalent to 47 μc of labeled protein per ml. The diluted solutions (1·0 ml) were injected at 8 a.m. once each day into the tail vein of rats with granuloma pouches, starting on day 4 after the pouches were made and ending on day 7. Rats were anesthetized. Pouch walls, exudates and blood were removed on the eighth day.

All samples were dissolved in hot 1·0 N NaOH. Aliquots were taken for total protein determinations. Samples were placed in Diotol solution (Packard) and counted in a Packard liquid scintillation spectrometer. All samples were counted in duplicate. Appropriate corrections were made for background interference. Final results were expressed either as dpm/mg protein or as dpm total sample.

Determination of protein and other substrates in plasma, serum and exudates. Fibrinogen,[16] albumin,[17] electrophoresis patterns,[18] free fatty acids,[19] triglycerides,[20] amino acids,[21] glucose,[22] total protein,[23] and lactate[24] were determined in plasma, sera or exudates of rats (or in all three) by standard techniques. Sodium and potassium determinations of sera and exudates were done on a Perkin–Elmer flame photometer. Fibrinolytic activity of plasma and exudates was determined by established techniques.[25]

Protein and metabolic substrate patterns in rats with D-α-*tocopherol granuloma pouches and adjuvant-induced polyarthritis.* Within 24 hr after inoculation of 0·5 mg of *M.butyricum* into the tail and the introduction of D-α-tocopherol into air pouches of rats, significant increases occur in the plasma concentrations of fibrinogen. Arthritis does not develop in *M. butyricum*-inoculated rats for at least 12 days. Exudation of fluid does not occur for at least 4 days after the injection of D-α-tocopherol (Tables 1 and 2). The fibrinogen–albumin ratios increase in both diseases. The change is more pronounced in rats inoculated with *M. butyricum.* The polyarthritis of rats is a more severe inflammatory disease than the localized diseases occurring in response to D-α-tocopherol.

Comparisons were made between other groups of plasma proteins, fibrinogen and albumin. The rise in plasma fibrinogen is the most marked change occurring in both inflammatory diseases (Tables 3 and 4). Increases in alpha-2-globulins and betaglobulins also occur, but are not as great as those occurring in fibrinogen concentrations.

The protein concentrations of blood and exudates were compared quantitatively in the same animals (Table 5). Fibrinogen concentrations are lower in exudates than they are in plasma. Some of the other exudate protein concentrations are decreased slightly when compared to plasma. They are not as great, however, as the decrease in fibrinogen.

TABLE 1. PLASMA FIBRINOGEN–ALBUMIN CHANGES AFTER THE INJECTION OF *M. butyricum**

Time (hr)	Plasma fibrinogen (mg/100 ml plasma)	Albumin (g/100 ml plasma)	Fibrinogen: Albumin ratio	Arthritis
0	380 ± 23	2·85 ± 0·06	0·13	0/10
24	830 ± 15	2·12 ± 0·01	0·39	0/10
48	1420 ± 42	2·11 ± 0·02	0·67	0/10
72	1291 ± 84	1·55 ± 0·02	0·83	0/10
96	1372 ± 25	1·43 ± 0·03	0·96	0/10
168	1367 ± 51	1·44 ± 0·06	0·95	0/10
336	1242 ± 18	1·98 ± 0·04	0·63	9/10

* Ten rats per group; 0·5 mg *M. butyricum* in 0·1 ml mineral oil was inoculated into the tail on day 0. Values are given ± S.E.M.

TABLE 2. PLASMA FIBRINOGEN–ALBUMIN CHANGES IN RATS INOCULATED INTO AIR POUCHES WITH D-α-TOCOPHEROL*

Time (hr)	Fibrinogen (g/100 ml plasma)	Albumin (g/100 ml plasma)	Exudate (ml)	Pouch wall wt. (g)	Fibrinogen: Albumin ratio
0	0·43 ± 0·01	2·85 ± 0·06	0	0	0·15 ± 0·01
24	0·62 ± 0·08	2·62 ± 0·09	0	0	0·24 ± 0·03
48	0·92 ± 0·08	1·93 ± 0·07	0·2	0·75 ± 0·3	0·48 ± 0·05
72	0·74 ± 0·03	2·01 ± 0·08	0	1·27 ± 0·3	0·37 ± 0·02
96	0·60 ± 0·03	2·50 ± 0·1	4·0 ± 1·7	2·22 ± 0·4	0·24 ± 0·01
120	0·63 ± 0·09	1·98 ± 0·07	15·1 ± 2·8	4·14 ± 0·6	1·32 ± 0·04
144	0·70 ± 0·06	1·86 ± 0·05	20·8 ± 1·4	3·61 ± 0·3	0·38 ± 0·04
168	0·72 ± 0·05	1·86 ± 0·05	30·4 ± 2·9	5·40 ± 0·5	0·39 ± 0·03
240	0·71 ± 0·05	1·84 ± 0·02	39·0 ± 5·4	7·28 ± 0·9	0·39 ± 0·03

* Five rats per group; 25 ml air + 0·5 ml D-α-tocopherol into the pouch on day 0. Values are given ± S.E.M.

Various metabolic substrate concentrations (glucose, lactate, free fatty acids, Na^+ and K^+) were compared in plasma and in exudate fluids (Table 6). Glucose and lactate concentrations are somewhat reversed in exudates, suggesting merely a high rate of anaerobic glycolysis in the granuloma pouches. Part of the increased glycolysis occurs within the exudate fluid. Incubation *in vitro* causes the conversion of glucose to lactate under aerobic and anaerobic conditions.

These studies suggest merely that the rise in plasma fibrinogen accompanied by a fall in plasma albumin is one of the most marked and readily identifiable quantitative changes in certain chronic inflammatory processes. Fibrinogen may be sequestered in areas of tissue damage and inflammation. Its concentration is lower in inflammatory exudates than in the blood. Pouch fluids do not possess fibrinolytic activity (unpublished data).

TABLE 3. EFFECT OF ADJUVANT ON VARIOUS PROTEIN CONSTITUENTS IN PLASMA AND SERUM

Treatment	Arthritis	Total protein (g/100 ml)	Albumin (g/100 ml)	Total globulin (g/100 ml)	A:G ratio	Alpha-globulin (g/100 ml)	Beta-globulin (g/100 ml)	Gamma-globulin (g/100 ml)	Fibrinogen (g/100 ml)
Control rats (no adjuvant)	0/10	5·70 ± 0·02	2·66 ± 0·06	3·02 ± 0·07	0·88 ± 0·04	1·62 ± 0·02	0·77 ± 0·03	0·65 ± 0·07	0·44 ± 0·01
Adjuvant*	10/10	5·53 ± 0·07	1·34 ± 0·04	3·77 ± 0·06	0·32 ± 0·01	2·40 ± 0·05	1·26 ± 0·04	0·53 ± 0·04	1·19 ± 0·01
Per cent change		0	− 50	+ 124		+ 148	+ 164	− 19	+ 270

* *M. butyricum*, 0·5 mg per 0·1 ml mineral oil was injected into tail on day 0. Rats were exsanguinated for plasma determinations on day 15; ten rats per group. All values are given ± S.E.M.

TABLE 4. ELECTROPHORETIC PROTEIN PATTERNS IN PLASMA AND SERA OF RATS WITH D-α-TOCOPHEROL-INDUCED GRANULOMA POUCHES*

Treatment	Total prot. (g/100 ml)	Albumin (g/100 ml)	Total glob. (g/100 ml)	A:G ratio	Alpha-glob. (g/100 ml)	Beta-glob. (g/100 ml)	Gamma-glob. (g/100 ml)	Fibrinogen (g/100 ml)
None	5·38 ± 0·01	2·47 ± 0·09	2·91 ± 0·13	0·86 ± 0·06	1·60 ± 0·09	0·79 ± 0·05	0·52 ± 0·05	0·32 ± 0·02
Pouch-bearing	5·04 ± 0·06	1·94 ± 0·09	3·10 ± 0·06	0·63 ± 0·04	1·77 ± 0·03	0·97 ± 0·05	0·36 ± 0·01	0·81 ± 0·07
Per cent change	0	− 22	0	− 27	0	+ 123	− 31	+ 219

* Ten rats per group. Plasma for fibrinogen and serum for electrophoretic determinations were removed from rats on the eighth day after the inoculation of 25 ml air + 0·5 ml D-α-tocopherol. Values are given ± S.E.M.

TABLE 5. ELECTROPHORETIC PROTEIN PATTERNS AND FIBRINOGEN CONCENTRATIONS IN BLOOD AND POUCH EXUDATES OF RATS*

Type of specimen	Total prot. (g/100 ml)	Albumin (g/100 ml)	Total glob. (g/100 ml)	A:G ratio	Alpha-glob. (g/100 ml)	Beta-glob. (g/100 ml)	Gamma-glob. (g/100 ml)	Fibrinogen (g/100 ml)
Sera and plasma from pouch-bearing rats	5·04 ± 0·06	1·94 ± 0·09	3·10 ± 0·06	0·63 ± 0·04	1·77 ± 0·03	0·97 ± 0·05	0·36 ± 0·01	0·81 ± 0·07
Exudates from pouch-bearing rats	3·62 ± 0·07	1·57 ± 0·05	2·05 ± 0·08	0·76 ± 0·02	1·14 ± 0·03	0·64 ± 0·03	0·27 ± 0·07	0·24 ± 0·01
Sera and plasma from normal litter-mates	5·38 ± 0·10	2·47 ± 0·09	2·91 ± 0·13	0·86 ± 0·06	1·60 ± 0·09	0·79 ± 0·05	0·52 ± 0·05	0·37 ± 0·02
Per cent change in concentration of plasma to exudate	− 28	− 20	− 34		− 36	− 34	− 25	− 70

* Ten rats per group. Plasma for fibrinogen and serum for electrophoretic protein determinations were removed from rats on the eighth day after inoculation of 25 ml air and 0·5 ml D-α-tocopherol on day 0. Values are given ± S.E.M.

TABLE 6. OTHER SUBSTRATE DIFFERENCES IN SERA AND EXUDATES OF RATS WITH GRANULOMA POUCHES*

Specimen	Glucose (mg/100 ml)	Lactate (mg/100 ml)	Amino acid N (mg/100 ml)	Total protein (g/100 ml)	FFA (μ-equiv./L)	Triglycerides (mg/100 ml)	Na^+ (μ-equiv./L)	K^+ (μ-equiv./L)
Plasma	119·1 ± 3·4	13·0 ± 0·2	5·70 ± 0·01	5·49 ± 0·1	389 ± 10·4	45·8 ± 3·3	135 ± 13	5·6 ± 0·01
Exudates	100·0 ± 2·0	44·3 ± 1·1	6·70 ± 0·01	4·01 ± 0·1	574 ± 26·1	64·7 ± 6·8	137 ± 10	4·2 ± 0·03
Per cent change from plasma to exudate	− 16	+ 340	+ 118	− 27	+ 147	+ 141	0	− 25

* Ten rats per group. Rats were anesthetized and exsanguinated on the eighth day after inoculation of 25 ml air and 0·5 ml D-α-tocopherol on day 0. Values are given ± S.E.M.

Influence of size and magnitude of the inflammatory process upon plasma fibrinogen concentrations. Granuloma pouches of different sizes were made in groups of rats by the inoculation of 0–50 ml of air preceding the inoculation of 0·5 ml of D-α-tocopherol. Rats were anesthetized and the pouch fluids and granulomas were measured 8 days later. Plasmas were removed. The fibrinogen concentrations were determined. A quantitative relationship exists between all parameters (Table 7). The larger the

TABLE 7. INFLUENCE OF VARYING AMOUNTS OF AIR ON EXUDATION AND PLASMA FIBRINOGEN CONCENTRATIONS*

Amt. of air† (ml)	Exudate (ml)	Wall wt. (g)	Fibrinogen (g/100 ml)
0	0	0·250 ± 0·02	0·39 ± 0·01
5·0	14·5 ± 1·2	0·283 ± 0·15	0·42 ± 0·02
10·0	19·0 ± 2·0	0·395 ± 0·10	0·51 ± 0·04
20·0	25·8 ± 3·1	0·672 ± 0·20	0·65 ± 0·06
30·0	33·0 ± 2·5	3·780 ± 0·09	0·75 ± 0·04
50·0	32·0 ± 1·7	4·785 ± 0·10	0·83 ± 0·03
No treatment	0	0	0·38 ± 0·01

* Ten rats per group removed on day 8. Values are given ± S.E.M.

† Varying amounts of air were injected to make air pouch, followed by inoculation of 0·5 ml D-α-tocopherol into the air space.

initial air space in the tissues, the greater the other changes in plasma fibrinogen, pouch wall weights and exudates. Greater amounts of injected *M. butyricum* also produce increments in the plasma fibrinogen concentrations (Table 8).

TABLE 8. VARYING AMOUNTS OF *M. butyricum* AND EFFECTS ON FIBRINOGEN CONCENTRATIONS IN PLASMA*

M. butyricum (mg) in 0·1 ml mineral oil	Fibrinogen (g/100 ml)	Albumin (g/100 ml)	F:A ratio
0·025	0·39 ± 0·03	2·96 ± 0·02	0·13
0·050	0·52 ± 0·04	2·11 ± 0·01	0·40
0·100	0·63 ± 0·02	2·01 ± 0·03	0·31
0·200	0·68 ± 0·04	1·95 ± 0·01	0·35
0·400	0·77 ± 0·06	1·89 ± 0·03	0·40
0·800	0·79 ± 0·02	1·88 ± 0·02	0·42

* Ten rats per group. Rats were exsanguinated for plasma 96 hr after inoculation of *M. butyricum* into the tail. Values are given ± S.E.M.

Influence of anticoagulent therapy on exudation of fluids into granuloma pouches. Heparin increases the exudation of both fluid and fibrinogen into granuloma pouches of rats (Table 9). When high doses of heparin are injected locally, rats exsanguinate into the granuloma pouch.

Use of plasma fibrinogen concentrations for the assessment of oral anti-inflammatory drugs. Cortisol acetate, phenylbutazone, aspirin and indomethacin were given orally for 14 days in the prophylactic treatment of adjuvant-induced polyarthritis. Although

TABLE 9. LOCAL INJECTIONS OF HEPARIN INTO GRANULOMA POUCHES AND EFFECTS ON FLUID EXUDATION*

Treatment	(ml/pouch dose/ day × 7 days)	Exudate (ml)	Exudate Fibrinogen (g/100 ml)	Exudate Albumin (g/100 ml)	Comments
Saline	0·4	14·3 ± 2·5	0·21 ± 0·01	3·16 ± 0·1	
Heparin	0·1	21·3 ± 3·6			
	0·2	25·0 ± 2·2	0·45 ± 0·02	3·20 ± 0·1	1/10 (exsanguinated)
	0·4	36·6 ± 3·4	0·62 ± 0·01	3·18 ± 0·1	3/10 (exsanguinated)
	0·8				10/10 (exsanguinated)

* Air (25 ml) followed by 0·5 ml D-α-tocopherol on day 0. Exudates were removed on day 6. The heparin solution contained 1000 USP units/ml (Upjohn). Values are given ± S.E.M.

differences in milligram potency exist, the drugs exert dose-related inhibitory effects on the plasma fibrinogen concentrations (Table 10).

Distribution of ^{125}I-albumin and ^{125}I-fibrinogen in the exudates, plasmas and pouch walls of rats. Rats with D-α-tocopherol-induced granuloma pouches were injected intravenously with either ^{125}I-albumin or ^{125}I-fibrinogen. At the termination of the

TABLE 10. EFFECTS OF ANTI-INFLAMMATORY DRUGS ON PLASMA FIBRINOGEN CONCENTRATIONS*

Drug	Dose (mg/kg, P.O., b.i.d. × 14 days)	Fibrinogen (g/100 ml)	Per cent Inhibition	Visual arthritis score†	Per cent Inhibition
Vehicle (water) (No *M. butyricum*)		0·39 ± 0·01		0	
Vehicle (water) (*M. butyricum*)		1·36 ± 0·01		11·3 ± 1·2	
Phenylbutazone	8·8	0·88 ± 0·01	33	8·0 ± 0·9	30
	34·0	0·57 ± 0·02	58	6·1 ± 0·8	46
	72·0	0·36 ± 0·01	73	2·3 ± 0·7	80
Indomethacin	0·2	1·13 ± 0·03	17	8·8 ± 0·9	22
	0·4	0·96 ± 0·01	30	9·3 ± 0·9	18
	1·0	0·67 ± 0·01	51	3·3 ± 0·6	71
Aspirin	41·0	1·09 ± 0·01	20	10·6 ± 1·2	7
	82·0	0·74 ± 0·02	31	7·3 ± 0·9	36
	66·0	0·30 ± 0·01	78	0·8 ± 0·2	93
Cortisol acetate	5·0	0·96 ± 0·02	30	8·0 ± 0·7	30
	10·0	0·63 ± 0·02	50	5·2 ± 0·9	54
	15·0	0·41 ± 0·03	70	0·9 ± 0·02	92

* Ten rats per group. *M. butyricum* (0·5 mg) was inoculated into the tail in 0·1 mg mineral oil on day 0. Drugs were administered starting on day 1 and for 14 days thereafter. Animals were exsanguinated on day 15 or 16 hr after the last dosage of drug. Values are given ± S.E.M.

† Visual arthritis score: 1–4+ of each of the 4 appendages.

experiment, plasma, exudates and pouch walls were examined for ^{125}I. These levels were related to the total protein concentrations. Greater specific amounts of ^{125}I are present in the granuloma pouch walls of rats receiving labeled fibrinogen than of those receiving albumin (Table 11).

TABLE 11. DISTRIBUTION OF ^{125}I-LABELED FIBRINOGEN AND ALBUMIN IN RATS WITH GRANULOMA POUCHES*

Sample and type of determination	^{125}I-Albumin-treated rats	^{125}I-fibrinogen-treated rats	Fibrinogen: Albumin ratio
Plasma			
Total protein (g/100 ml)	5·17 ± 0·09	4·99 ± 0·08	
Albumin (g/100 ml)	1·73 ± 0·04	1·91 ± 0·06	
Fibrinogen (g/100 ml)	0·76 ± 0·04	0·65 ± 0·05	
dpm/mg plasma	73,579 ± 1502	78,101 ± 10,551	1·06
dpm/ml Total protein	1423 ± 24	1565 ± 81	1·10
Exudate			
Volume (ml)	17·3 ± 0·9	16·7 ± 2·6	
Total protein (g/100 ml)	3·86 ± 0·07	3·76 ± 0·07	
Albumin (g/100 ml)	2·22 ± 0·1	1·96 ± 0·20	
Fibrinogen (g/100 ml)	0·32 ± 0·02	0·28 ± 0·01	
dpm/ml Exudate	139,226 ± 1,555	131,577 ± 3,766	0·9
dpm/mg Protein	3606 ± 67	3499 ± 163	1·0
Granuloma pouch			
Weight (g)	4·55 ± 0·26	4·48 ± 0·37	
Total protein (mg/pouch)	331·0 ± 23·5	323·7 ± 28·6	
dpm/mg Total protein	8366 ± 665	18,807 ± 970	2·2
dpm/Pouch	2,765,500	6,093,450	2·2

* Ten rats per group. Values are given ± S.E.M.

DISCUSSION

Of various protein and metabolic substrates studied in two models of experimental inflammation, plasma fibrinogen concentration appears to offer the greatest contrast between control animals and those with inflammation. When the concentration of fibrinogen is analyzed across granuloma pouches, a marked difference is observed. The decreases suggest a high rate of utilization, degradation or sequestration or of all three. The experiments here do not solve any of these possibilities.

The plasma fibrinogen response to inflammatory stimuli occurs long before overt clinical evidence of disease. The mainenance of fibrinogen levels in the blood requires a high rate of synthesis by the liver and adequate means for its disposal. The physiologic factors controlling the synthesis of fibrinogen by the liver are unknown.

The local injection of cortisol directly into sites of inflammation normalizes the plasma fibrinogen levels more readily than its subcutaneous injection. Events occurring at sites of inflammation somehow control the synthesis of fibrinogen by the liver.

The importance of fibrinogen to the overall assessment of inflammatory activity is surmised from its inverse relationship to anti-inflammatory therapy. Both steroidal and nonsteroidal anti-inflammatory drugs lower the elevated fibrinogen concentrations in rats with adjuvant arthritis. The drug-induced effects are related primarily to their effects on the inflammatory reaction *per se* through unknown mechanisms. The drugs at pharmacologic doses do not exert effects on albumin and fibrinogen concentrations of so-called normal, healthy animals.

The relationship of this work to other investigations may have some importance. Fibrinogen has been found in all vertebrate species studied, including the cyclostome fishes.[26,27] It is a substrate for numerous proteolytic enzymes, including thrombin.

Fibrinogen is a clot-forming architectural substrate around which the hemostatic defense of vertebrates revolves. It contributes to rouleaux formation of the red blood cells and appears to contribute to phagocytosis by leukocytes through its conversion to fibrin.[6] The ability of fibrinogen to form polymeric fibrous structures is of major physiologic importance. It plays a role in tissue integrity and homeostasis by aiding perhaps in the "walling-off" process toward bacterial and chemical invaders. It aids in the formation of a matrix for new blood vessel formation in areas of tissue damage. Its increased synthesis is a nonspecific response to the tissue invasion and damage induced by a wide variety of equally nonspecific mediators.

Lack[3] believes that the persistence of fibrin at joint surfaces is indicative of the failure of an important physiologic mechanism; that fibrin is the initiator of pannus formation and subsequent fibrosis in rheumatoid arthritis. Under certain circumstances, fibrin poses as an antigen in autoimmune reactions. A permanent arthritis can be produced in rabbits by pre-immunization with heterologous fibrin, followed by its local injection into joints.[28] The products of elevated fibrinogen concentrations in certain areas of tissue damage may have some uncertain pathogenic significance in chronic inflammatory diseases.

The level of plasma fibrinogen is a useful guide in the management of acute myocardial infarction:[29] a raised level is a reliable indication of recent myocardial infarction and a return to normal corresponds with clinical recovery. Similarly, a fall in plasma fibrinogen levels of experimental animals in response to anti-inflammatory therapy indicates a decrease in tissue inflammation.

Although the analysis of fibrinogen concentrations in blood is a useful index for the assessment of inflammation and its therapy, the relatively high concentration of this protein fraction in the blood of normal animals limits its usefulness. The concentration of fibrinogen in the plasma of normal rats (0·35–0·5 g/100 ml) may indicate that tissue damage and repair are natural phenomena of everyday existence. A desirable biochemical endpoint for the analysis of inflammation and its therapy would be one which did not exist in normal organisms and appeared only in those with inflammation.

Fibrin accumulation, as a result of increased deposition or decreased lysis, may play a fundamental role in the production of atherosclerosis. Anti-inflammatory drugs have been used successfully for the prophylactic treatment of experimental atherosclerosis.[30] These discoveries may be related somehow to those reported here, wherein anti-inflammatory drugs lower effectively the elevated fibrinogen concentrations in response to inflammation.

Acknowledgement—The author gratefully acknowledges the technical assistance of Miss B. J. Bowman and Mr. T. Koslowske. The gifts of phenylbutazone and indomethacin were received from the Geigy Pharmaceutical Company and from Dr. Charles A. Winter of Merck respectively.

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