Medical Hypotheses 6: 545-557, 1980

FATTY ACIDS, FIBRINOGEN AND BLOOD FLOW: A General Mechanism For Hyperfibrinogenemia And Its Pathologic Consequences

L.R. Pickart and M. Michael Thaler,* Department of Pediatrics, University of California, San Francisco, CA., 94143.

ABSTRACT

Plasma fibrinogen is elevated in various stressful states and conditions in which active mobilization of free fatty acids (FFA) occurs. Reduction of plasma FFA by an assortment of hypolipidemic drugs is consistently followed by a decrease in the accompanying hyperfibrinogenemia. A direct link between FFA and fibrinogen has been demonstrated in animals, and in experiments employing incubated liver slices. Based on these clinical and experimental observations, we postulate that hepatic fibrinogen synthesis is stimulated by FFA. Since fibrinogen is a major determinant of whole blood viscosity, erythrocyte aggregation, and sludging of red cells in terminal and pre-terminal blood vessels, we propose that microcirculatory blood flow may be impaired in the presence of chronically elevated plasma FFA levels. Consequently, hypolipidemic drugs may be effective in prevention of circulatory complications associated with FFA-induced hyperfibrinogenemia.

INTRODUCTION

Fibrinogen and the Microcirculation. Blood flows through the microcirculation in man as a pulsatile column, behaving as a solid during no-flow periods and as a liquid during flow. These non-Newtonian (thixotropic) flow characteristics are primarily due to alternating formation and dissolution of cellular aggregates (rouleaux) formed by the interaction between erythrocytes and plasma fibrinogen at the low flow velocities (0.1 to 0.5 cm/sec) in human arterioles and capillaries (1,2). The force required for propulsion of the blood column (yield shear stress) in the microcirculation is a direct squared function of the plasma fibrinogen concentration (3). Moreover, fibrinogen is the major determinant of plasma viscosity (3,4). An increase in blood viscosity due to hyperfibrinogenemia results in elevated peripheral vascular resistance which, in turn, reduces tissue perfusion (1,4,5,6). Thus, plasma fibrinogen exerts an inhibitory effect on blood flow in the microcirculation by a complex mechanism involving rouleaux formation, plasma viscosity, and possibly, fibrinogen-induced changes in red cell deformability (1).

Dependence of red cell aggregation on plasma fibrinogen is species-related, being observed in man, dog and elephant, and absent or greatly attenuated in sheep and goats (7). Indeed, limb and brain perfusion has been strikingly enhanced in man and dog by enzymatic defibrinogenation (2,8), fibrinogen-lowering drugs (9), or venesection (10).

A gradual increase in mean plasma fibrinogen concentration from an average of 230 mg/dl at 20 years, to 350 mg/dl at 70 years of age normally occurs during aging in man (11). However, a 10 to 20-fold increase in fibrinogen production may be induced within several hours after acute injury or stress, resulting in a 2 to 3-fold rise in plasma fibrinogen within 48 hours (12,13,14). Persistent elevations in plasma fibrinogen are also commonly observed in many chronic disorders, including those listed in the Table.

CONDITIONS IN WHICH BOTH PLASMA FFA (OR FFA/ALBUMIN RATIO) AND FIBRINOGEN ARE INCREASED*

African Trypanosomiasis (63,64)	Nephrosis (23)
Ascorbic Acid Deficiency (23)	Pneumonia (71,72)
Cigarette Smoking (23)	Pregnancy (20,73)
Cobalt Poisoning (65,66)	Severe Mental Stress (23)
Diabetes (23)	Silicosis (74)
Electroshock (23)	Starvation (48 hours) (25)
Endotoxin (23)	Surgery (20,75)
Fat, Excess in Diet (23)	Thrombin Injection (23)
Malaria (67,68)	Tissue Damage (19,75)
Mercury Poisoning (69)	X-ray Radiation (19,76)
Myocardial Infarction (24)	Zinc Deficiency (77,78)
Neoplastic Disease (20,70)	Zinc Poisoning (79)

*Listed in alphabetical order, with references in parentheses.

Hyperfibrinogenemia has been causally implicated in increased sludging of blood, development of hypoxic lesions in various tissues, low blood flow rates and congestive heart failure (,4, 5,6), as well as localized necrosis (15,16), rejection of kidney transplants (1), metastatic extension of tumors (17,18, 19), and thromboembolism (2,20,21). The known effects of various stresses and injuries on blood fibrinogen levels and yield shear stress are illustrated graphically in Fig. 1.

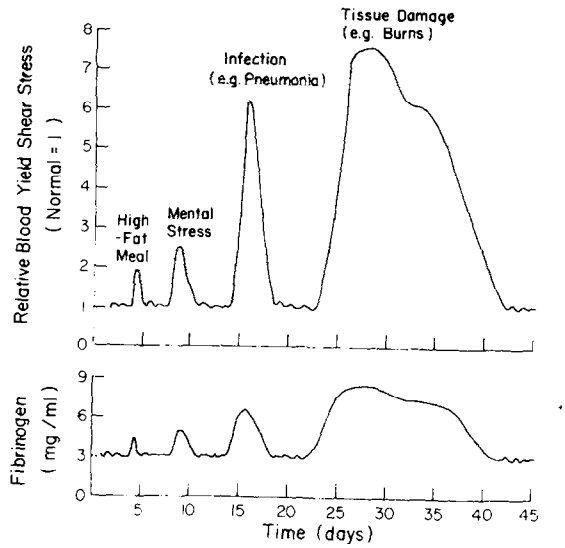

Fig. 1. The relationship between plasma fibrinogen levels commonly observed in representative conditions, and corresponding yield shear stress values. The width of individual peaks denotes approximate duration of hyperfibrinogenemia in each condition.

Fibrinogen-induced circulatory derangements which reduce tissue perfusion appear to be especially dangerous in patients with atherosclerosis, or in diabetics with microangiopathic lesions whose vascular bed is incapable of adequate compensatory vasodilation or is already maximally expanded. A highly significant relationship between mortality or morbidity and plasma fibrinogen has been demonstrated in coronary artery disease (22) and in diabetes mellitus (23). A prospective study of diabetic patients revealed that elevation of plasma fibrinogen above 400 mg/dl was a reliable indicator of future cardiovascular complications (23). Furthermore, fibrinogen (as fibrin) is the major plasma protein deposited in developing atheromatous plaques, and changes in blood hemorrheology due to aberrations of fibrinogen metabolism have been proposed as essential in the development of atherosclerotic lesions (24). These observations indicate that chronic hyperfibrinogenemia may predispose to development of circulatory deficiency in various common vascular disorders.

HYPOTHESIS

We propose that hepatic fibrinogen production is stimulated by increased intrahepatic uptake of FFA from plasma. Consequently conditions associated with acute or chronic lipolysis, or excessive dietary intake of fat, induce elevations in plasma fibrinogen. The resultant hyperfibrinogenemia raises the viscosity of plasma, which leads to increased resistance to peripheral blood flow, microcirculatory sludging and suboptimal tissue perfusion. Ultimately, chronic hypoperfusion may induce compensatory polycythemia, with further impedance to blood flow in arterioles and venules. The postulated relationship between FFA, fibrinogen and blood flow is shown schematically in Fig. 2.

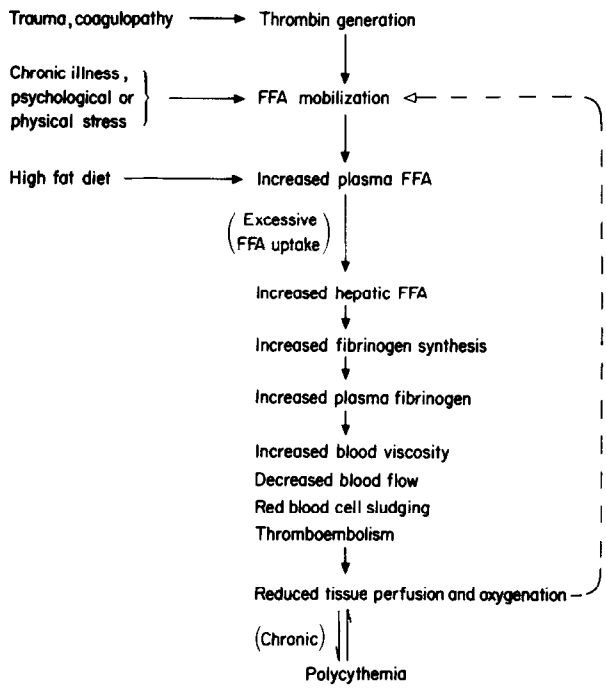

Fig. 2. Proposed relationship between FFA and fibrinogen metabolism, and pathophysiological consequences.

EVIDENCE FOR THE HYPOTHESIS

1. Role of FFA in Fibrinogen Synthesis. Our studies on the regulation of fibrinogen production in the mouse (25,26) and man (11,27) have shown that plasma FFA play a major role in induction of hyperfibrinogenemia. A rise in plasma fibrinogen concentration and fibrinogen synthetic rate occurs in association with mobilization of FFA in rats with an experimentally induced hepatoma (28), as well as following thrombin administration (29). Inhibition of lipolysis by pretreatment with clofibrate suppressed the development of hyperfibrinogenemia, and blocked the enhancement of fibrinogen synthesis in these widely disparate experimental situations (28,29). Investigations of fibrinogen synthesis in vitro revealed that intrahepatic FFA concentrations are directly related to hepatic fibrinogen synthesis and release (26,27). The rapid rise in FFA which occurs in fasted obese patients is accompanied by a concomitant increase in plasma fibrinogen (30). Elevations of both FFA and fibrinogen coexist in a wide variety of diseases and stressful conditions (Table 1). Moreover, it is pertinent that corticotropin (31) and prostaglandin (32), hormones which have been suggested as physiologic stimulators of fibrinogen production, induce a rise in fibrinogen synthesis only at pharmacological doses which trigger massive FFA mobilization (33,34).

Albumin is the major carrier of FFA in the circulation. Hence, the FFA/albumin molar ratio modulates the availability of FFA for transport into liver and other tissues, in a fashion analogous with other lipophilic metabolites (e.g. bilirubin). Fibrinogen synthesis and plasma concentrations have been shown to vary with plasma FFA/albumin molar ratios (26). The synthesis and export of several other proteins is similarly enhanced by a rise in the plasma FFA/albumin ratio (35,36,37). These observations suggest that intrahepatic FFA concentrations may regulate the production of certain proteins by the liver, and their release into the circulation during periods of stress.

2. Effect of Hypolipidemic Agents on Fibrinogen Metabolism in Man. Treatment of human subjects with antilipidemic agents of wide biochemical and structural diversity induces uniform reductions in plasma fibrinogen concentrations, as shown in Fig. 3. Allyl propyl disulfide, the active principle from oil of garlic, reduces plasma FFA in humans (38) and blocks the rapid rise in fibrinogen detectable in human subjects 3 hours after a meal containing 100 grams of butter (39). Acetylsalicylic acid has been shown to lower both FFA and fibrinogen in atherosclerotic patients (40). Since aspirin has no effect on the half-life of fibrinogen in man (41), the reduction in fibrinogen plasma concentrations by this agent is most likely due to decreased synthesis of the protein. The fatty acid analog beta-benzalbutyrate reduces plasma FFA (42) and fibrinogen concentration in patients with hyperlipidemia without affecting plasma cholesterol, triglycerides, plasminogen, alpha-macroglobulins, fibrinogen degradation products or euglobulin lysis time (43). Another fatty

acid analog, clofibrate, has been shown to induce concurrent decreases in resting FFA and fibrinogen concentrations in patients with angina pectoris (44). Clofibrate also partially suppresses the rise in fibrinogen which follows surgical insertion of plastic venous grafts in rabbits (45). While some of the effects of clofibrate may be due to displacement of thyroxine from albumin and consequent alterations in hepatic energy metabolism, an analog of clofibrate without effect on thyroxine metabolism (I.C.I. 55, 897) causes a reduction in plasma fibrinogen which is apparently mediated through a decrease in FFA availability to tissues. A second clofibrate analog (I.C.I. 55, 695) also decreased fibrinogen levels in humans (44). Tetranictonoylfructose is cleaved in the intestine and releases nicotinic acid, a catecholamine antagonist which lowers plasma FFA and fibrinogen (46). Etofibrate, a compound of clofibrate and nicotinic acid, reduces elevated fibrinogen concentrations in humans with primary hyperlipidemia and is effective at a smaller dosage than clofibrate (47).

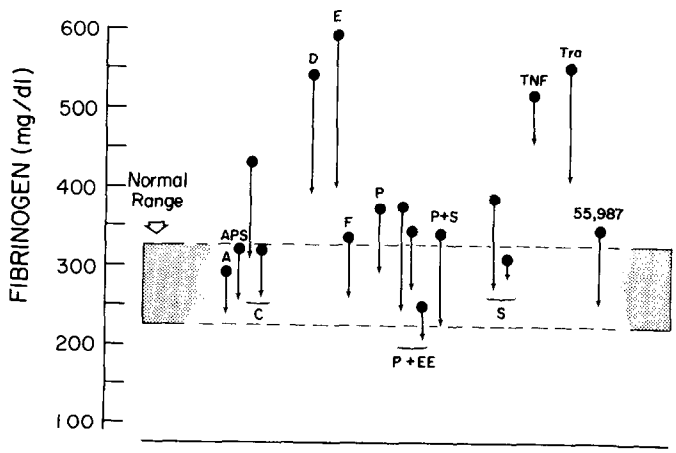

Fig. 3. Effect of antilipidemic agents on plasma fibrinogen concentrations in man. The closed circles represent plasma fibrinogen levels at initiation of therapy; length of arrows represents the decline in plasma fibrinogen induced by hypolipidemic agents. A = aspirin, APS = allyl propyl disulfide, C = clofibrate, D = dextran sulfate, E = etofibrate, F = furbazol, P = phenformin, P + EE = phenformin plus ethylestrenol, P + S = phenformin plus stanazol, S = stanazol, TNF = tetranicotinoyl-fructose, Tra = trasylol, 55, 897 = a clofibrate analog. References are cited in text.

Synthetic analogs of testosterone such as ethylestrenol, furazabol and stanazol, lower serum triglyceride concentrations and increase fat oxidation in man (48). Ethylestrenol has been shown to reduce the elevation in plasma fibrinogen associated with myocardial infarction (49), while similar effects were observed with furazabol in patients with acute injury (limb fractures) (50). Stanazol also reduces plasma fibrinogen (51). The antifibrinogenemic effect of these anabolic steroid hormones is considerably amplified when used in combination with the FFA suppressive agent phenformin (52), which, by itself, also lowers plasma fibrinogen (49,51,53-56). Ethylestrenol and phenformin, when administered together, decrease fibrinogen synthesis in man (55). Prolonged administration of the FFA-binding agent, dextran sulfate, has been reported to reduce the elevated plasma fibrinogen concentrations present in constitutional hyperlipidemia (57). The kallikrein-trypsin inhibitor, trasylol, induces a decline in both fibrinogen and FFA in humans (58,59). Finally, plasma FFA and fibrinogen concentrations may be extremely elevated in uncontrolled diabetes; both are rapidly reduced with insulin (60,61).

CONCLUSIONS

The proposed relationship between FFA and fibrinogen suggests that the circulatory complications associated with a variety of diseases and stressful chronic disorders may be significantly influenced by drugs which decrease mobilization of FFA from depot fat, or reduce hepatic uptake of FFA from plasma. These postulates can be experimentally evaluated with various antilipidemic agents which have recently become available, and with infusions of plasma albumin. Such therapeutic trials may be especially indicated in patients with impairment of microcirculatory blood flow due to arteriosclerotic changes, microangiopathic lesions, or increased peripheral resistance. Beyond the known undesirable effects of excessive fat intake on development of arteriosclerosis and coronary artery thrombosis, our hypothesis points toward an additional mechanism whereby dietary fat may be involved in the pathogenesis of cardiovascular disease. The proposed direct link between FFA and hyperfibrinogenemia suggests that inadequate tissue perfusion due to hyperviscosity and other deterrent actions of fibrinogen on microcirculatory blood flow may intensify the deleterious consequences of atheromatous and thrombotic lesions.

Erasistratus (300 B.C.) reported that excessive food intake alters the fluid properties of blood, an effect which he considered responsible for many diseases (62). As treatment, Erasistratus recommended restricted dietary intake, and exercise. The postulated relationship between fat, fibrinogen, and blood flow may finally justify this ancient physician's observations and his thoroughly up-to-date advice.

This work was supported by USPHS grant HD03148.

References

1. Dintenfass L. In Rheology of Blood. Buttersworth, London, 1976.

2. Dormandy J, Reid HL. Controlled defibrinogenation in the treatment of peripheral vascular disease. Angiology 29: 80, 1978.

3. Merrill EW. Rheology of blood. Physiol. Rev. 49: 863, 1969.

4. Dintenfass L. A preliminary outline of the blood high viscosity syndromes. Arch. Int. Med. 118: 427, 1966.

5. Replogle R, Meiselman H, Merrill E. Clinical implications of blood rheology studies. Circ. 36: 148, 1967.

6. Gordin R, Snyder G, Tritel H, Taylor W. Potential significance plasma viscosity and hematocrit variations in myocardial ischemia. Amer. Heart J. 87: 175, 1974.

7. Chien S, Usami S, Dellenback RJ, Bryant CA. Comparative hemorheology-hematological implications of species differences in blood viscosity. Birheology 8: 35, 1971.

8. Gustafsson L, Appelgren HE, Myrvold HE. Flow improvement after defibrinogenation. J. Surg. Res. 22: 113, 1977.

9. Jarrett PEM, Morland M, Browse NL. Treatment of Raynaud's phenomenon by fibrinolytic enhancement. Lancet 2: 523, 1978.

10. Thomas DJ, Duboulay GH, Marshall J, Pearson TC, Tussell RWR, Symon L, Wetherley-Mein G, Zilka E. Effects of hematocrit on cerebral blood flow in man. Lancet 2: 941, 1977.

11. Pilgeram LO, Pickart L. Turnover rate of autologous plasma fibrinogen-^{14}C in subjects with coronary thrombosis. Thromb. Diath. Haemorr. 21: 402, 1969.

12. Regoeczi E. Fibrinogen. p 133 in Structure and Function of Plasma Proteins. vol. I. (AC Allison, ed) Plenum Press, New York, 1974.

13. Reeve EG, Franks JJ. Fibrinogen synthesis, distribution and degradation. Semin. Thromb. Hemostasis 1: 129, 1974.

14. Workman EF, Lundblad RL. The role of the liver in biosynthesis of the non-vitamin K-dependent clotting factors. Sem. Thromb. Hemostasis 4: 15, 1977.

15. Bicher HI. Pathological significance of intravascular red cell aggregation. p 19 in Blood Cell Aggregation in Thrombotic Processes. C. Thomas, Springfield, Ill., 1972.

References (cont.)

16. Ball G, Goldman L. Chronic ulcerative colitis, skin necrosis, and cryfibrinogenemia. Ann. Int. Med. 85: 464, 1976.

17. Hoover H, Ketcham A. Techniques for inhibiting tumor metastases. Cancer 35: 5, 1975.

18. Hilgard P, Thornes, RD. Anticoagulants in the treatment of cancer. Eurpo. J. Cancer 12: 755, 1976.

19. Heyes H, Gluck D. Die bedeuting des fibrins/fibrinogens fur wachstum und metastasierung von malignomen. Klin. Wschr. 55: 1079, 1977.

20. Sirs JA. Erythrocyte flexibility, blood fibrinogen, and surgery. p 59 in Thromboembolism (A. Nicolaides, ed) Univer sity Park Press, Baltimore, 1975.

21. Wessler S. Factors in the initiation of deep venous thrombosis. p. 9. Ibid.

22. Bottiger LE, Carlson LA. The Stockholm prospective study 2. p 158 in Early Phases of Coronary Heart Disease (J. Waldenstrom, T Larsson, N Ljungstedt, eds) Nordiska Bokhandelns Forlag, Stockholm, 1973.

23. Wardle E, Piercy D, Anderson J. Some chemical indices of diabetic vascular disease. Postgr. Med. J. 49: 1, 1973.

24. Copley AL. Fibrinogen, platelets and a new theory of atherogenesis. Thrombosis Res. 14: 249, 1979.

25. Pickart L, Pilgeram LO. The role of thrombin in fibrinogen biosynthesis. Thromb. Diath. Haemorr. 17: 358, 1967.

26. Pickart L, Thaler MM. Free fatty acids and albumin as media tors of thrombin-stimulated fibrinogen synthesis. Am. J. Physiol. 230: 996, 1976.

27. Pilgeram LO, Pickart L. Control of fibrinogen synthesis: the role of free fatty acid. J. Atheroscler. Res. 8: 155, 1968.

28. Pickart L, Thaler MM. Suppression of tumor-associated hyperfibrinogenemia and free fatty acidemia with p-phenoxybenzalbutyrate (clofibrate). Cancer Res. 39: 3845, 1979.

29. Pickart L, Thaler MM. Suppression of acute phase induction of fibrinogen synthesis with a hypolipidemic agent (clofibrate). Biochem. J. (submitted).

30. Dimitrescu C, Mihalache N. Correlation between plasma lipids, plasma fibrinogen, and fibrinolytic activity in acute fasting obese patients. Med. Interna. (Rom.) 21: 1093, 1969.

31. Atencio AC, Lorand L. Effect of ACTH on biosynthesis of fibrinogen in the rabbit. Am. J. Physiol. 219: 1161, 1970.

32. Carlson TH, Wentland SH, Leonard BD, Ruder MA, Reeve CB. Effects of prostaglandin E_2, analogs, fatty acids and indomethacin on fibrinogen level. Am. J. Physiol. 235: H223, 1978.

33. Havel RJ. The automatic nervous system and intermediary carbohydrate and fat metabolism. Anesthesiology 29: 720, 1968.

34. Bergstrom S, Carlson LA, Eklund L, Oro L. Effect of prostaglandin E_1 on blood pressure, heart rate and concentration of free fatty acids in man. Proc. Soc. Exp. Biol. 118: 110, 1965.

35. Rodbell M. Regulation of release of protein by lipolytic hormones and insulin. J. Biol. Chem. 241: 3909, 1966.

36. Ruderman NB, Richards KC, DeBourges V, Jones AL. Regulation of production and release of lipoprotein by the perfused rat liver. J. Lipid Res. 9: 613, 1968.

37. DeLeiris J, Opie LH, Lubbe WF. Effect of free fatty acids on enzyme release in experimental myocardial infarction. Nature 253: 746, 1975.

38. Augusti K, Benaim M. Effect of essential oil of onion (allyl propyl disulfide) on blood glucose, free fatty acid, and insulin levels in normal subjects. Clin. Chim. Acta. 60: 121, 1975.

39. Bordia A, Bansal HC, Arora SK, Singh SV. Effect of essential oils of garlic and onion on alimentary hyperlipidemia. Atheroscler. 21: 15, 1975.

40. Matsuo T, Ohoki Y. Study of fibrinolytic activity induced by aspirin ingestion in patients with atherosclerosis. Kobe J. Med. Sci. 21: 17, 1975.

41. Clagett G, Brier D, Rosoff B, Schneider PB, Salzman EW. Effect of aspirin on postoperative platelet kinetics and venous thrombosis. Surg. Forum 25: 473, 1974.

42. Piccardo M, Onori L. Activity of sodium beta-benzalbutyrate on the blood level of FFA and triglycerides in man. G. Arterioscler. 5: 223, 1967.

43. Mannucci P, Maggi C, Gioventu M, Marchi E, Terruzzi AB. Betabenzal butyric acid, a new antiadhesive drug. Acta Univ. Carol. Med. Monogr. 53: 409, 1972.

44. Stone M, Thorp J, Wain J. Experimental and clinical evaluation of two "Atromid-S" analogues in relation to their differential mode of action. p 151 in Lipids, Lipoproeins, and Drugs. (D. Kritchevsky, ed) Plenum Publishing Co., New York, 1975.

45. Postlethwaite JA. The importance of plasma fibrinogen in vascular surgery. Ann. Royal College Surg. 58: 457, 1976.

46. Benaim M, Dewar H. The effect of tetranicotinyl fructose (Bradilan) on fibrinolytic activity, platelet stickiness, and some other parameters. J. Int. Med. Res. 3: 423, 1975.

47. Spottl F, Froschauer J. Influence of etofibrate on plasma fibrinogen and plasminogen concentrations in patients with different forms of primary hyperlipoproteinemia. Atheroscler. 25: 293, 1976.

48. Gribbin H, Matts S. Mode of action and use of anabolic steroids. Brit. J. Clin. Practice 30: 3, 1976.

49. Chakrabarti R, Fearnley GR. Penoformin plus ethyloestrenol in survivors of myocardial infarction. Lancet 2: 556, 1972.

50. Karacharov AT. The effect of anabolic steroid preparations on the blood coagulation. Klinch. Meditsina. 49 (no. 10): 131, 1971.

51. Davidson J, Lochhead M, McDonald G, McNicol GP. Fibrinolytic enhancement by stanazolol: a double blind trial. Brit. J. Haem. 22: 543, 1972.

52. Kissebah AH, Adams PW, Wynn V. Inter-relationship between insulin secretion and plasma free fatty acid and triglyceride transport kinetics in maturity onset diabetes and the effect of phenethylbiguanide (phenformin). Diabetologia 10: 119, 1974.

53. Chakrabarti R, Fearnley GR. Pharmacological fibrinolysis in diabetes mellitus. Diabetologia 10: 19, 1974.

54. Isacson S, Nilsson I. Effect of treatment of combined phenformin and ethylestrenol on coagulation and the fibrinolytic system. Scand. J. Haemat. 7: 404, 1970.

55. Hickman J. Pharmacological enhancement of fibrinolytic activity and ^{125}I-fibrinogen survival. J. Clin. Path. 23: 797, 1970.

56. Grabowski VR, Bielawiec M, Kiersnowska B, Lukjan H, Perzanowski A, Mysliwiec M, Korfel B, Rogowski F. Untersuchungen uber den ^{131}J-fibrinogenumsata bei der aktivierung der blutfibrinolyse. Zschr. Inn. Med. 31: 1025, 1976.

57. Akazawa Y, Koide M, Yamadori E. Correlation between plasma fibrinogen level and vascular complications of diabetes. p 189 in Diabetes in Asia, Excerpta Medica, 1976.

58. Godal HC, Skaga E. Effect of trasylol in fibrinogen and on fibrinogen-like substances after major surgery. Acta Chir. Scand. Suppl. 376: 41, 1967.

59. Heller W, Moerl F. Behavior of plasma lipids after fractures and effect of proteinase inhibitor trasylol. Med. Welt 36: 2076, 1967.

60. Schulz F, Knobloch H. Fibrinogen in diabetes mellitus. Deut. Z. Verdauungs Stoffwech Slekraukh 15: 218, 1955.

61. West GS, Todd WR, Mason HS, Von Vruggen JT. p 115 in Textbook of Biochemistry, Davis, Philadelphia, 1966.

62. Longrigg J, Erasistratus. p 382 in Dictionary of Scientific Biography. vol. 4. (CC Gillipsie, ed) C. Scribner's Sons, New York, 1971.

63. Assoku RKG, Tizard IT, Nielsen KH. Free fatty acids, complement activation, and polyclonal B-cell stimulation as factors in the immunopathogenesis of African trypanosomiasis. Lancet 2: 956, 1977.

64. Boreham DFL, Facer CA. Fibrinogen and fibrinogen/fibrin degradation products in experimental African trypanosomasis. Int. J. Parasitol 4: 143, 1974.

65. Eaton RP. Cobalt chloride-induce hyperlipidemia in the rat: effects on intermediary metabolism. Am. J. Physiol. 222: 1550, 1972.

66. Lober M, Krantz S. Investigations on some chemical properties on plasma fibrinogens and fibrins from normal and cobalt-treated rabbits. Acta Biol. Med. Germ. 34: 1573, 1975.

67. Angus MGN, Fletcher KA, Maegraith BG. Studies on the lipids of plasmodium knowlesi-infected rhesus monkeys. Ann. Trop. Med. Parasitol. 65: 155, 1971.

68. Alecrim IC, Leao MA. Electrophoresis of proteins of serum of rats innoculated with plasmodium berghei. An. Fac. Med., Univ. Fed. Pernambuco 28/29: 9, 1968.

69. Galasinski W, Worowski K, Niewiarowski S, Franecki G. Turnover of ^{131}I-fibrinogen in mercury chloride intoxicated dogs. Thromb. Diath. Haemorr. 18: 268, 1967.

70. Carter AC, Lefkon BW, Farlin M, Feldman EB. Metabolic parameters in women with metastatic breast cancer. J. Clin. Endocrin. Metab. 40: 260, 1975.

71. Danilchik VS, Kovaleva IA, Kishkurno SP. Lipid spectrum of the blood of newborns with pneumonia. Vopr. Ohkr. Materin. Det. 22: 82, 1977.

72. Vakalyuk PM, Berezhnitsky MN, Shvedenko LA. The biochemical criteria of the activity of the process in chronic pneumonia. Klin. Med. (Moscow) 49 (12): 23, 1972.

73. Iwasa Y. Significance of human placental lactogen estimated by radioimmunoassay in the studies of placental function and maternal lipid metabolism. Yonago Acta Med. 19: 138, 1975.

74. Szabo I, Dianiello L, Nemes I, Gelepu E, Mody E, Makai M, Szabo L, Adorjan E, Popa V. The prothrombinic factors in silicosis. Acad. Rep. Populare Romine, Filiala Cluj, Studii Cercetari Med. 11: 331, 1960.

75. Warner WA. Release of free fatty acids following trauma. J. Trauma 9: 692, 1969.

76. John DW, Miller LL. Effect of whole-body x-irradiation on net synthesis of albumin fibrinogen, alpha$_1$-acid glycoprotein and alpha$_2$-globulin (acute phase globulin) by the isolated perfused liver. J. Biol. Chem. 243: 268, 1968.

77. Quarterman J, Florence G. Glucose tolerance and plasma levels of free fatty acids and insulin in the zinc-deficient rat. Brit. J. Nutr. 28: 75, 1972.

78. Parry W, Pacey J. Abnormal blood coagulation in zinc-deficient lambs. I. R. C. S. Med. Sci. 3: 523, 1975.

79. Guga A. Coagulation and fibrinolysis during acute poisoning with zinc. Biol. Sluzby. Sanit. Epidemiol. Wojewodztwa Katowickiego 15: 405, 1973.