A R T I C L E

Bleeding, clotting, cancer

The balance between bleeding and clotting is easily disturbed. The condensation and dissolution of the clotting protein, fibrinogen/fibrin, is a continuous process, sensitive to changes in stress, nutrition, and hormones. Clots form, locally or systemically, when fibrin is formed faster than it is dissolved. When fibrin is destroyed faster than it can be replaced, blood vessels become too permeable, and bleeding can occur more easily.

Mental stress, exercise, estrogen, and serotonin activate both the formation and dissolution of clots.

Bleeding and clotting are not only very closely related with each other, such that a given stress can induce either or both, but the condensation and dissolution of the clotting protein are involved in edema, multiple organ failure, and the growth of cancers. The growth of tumors is as directly related to the clotting system as are thromboses and hemorrhages.

Disordered clotting contributes to maladaptive inflammation and to the "diseases" of aging and degeneration.

Metabolic energy is the basic defense against the stress reactions that disrupt circulation, healing, and growth.

"*It is commonly known that the ESR (red cell sedimentation rate) of cancer patients is always high*."

"*Thus far, completely unagglutinated blood has been found only in strictly healthy animals and men. No severely ill person has yet been seen who did not have intravascular agglutination of the blood and visibly pathologic vessel walls*." *Melvin H. Knisely, et al.**, 1947**)*

When science became a sort of “profession,” in the 19th century, the old “natural philosophy” of Newton’s time began to subdivide into many specialties. At that time, medicine had some general theories to account for deviations from good health, such as the theory of the four humors and their balance, but as those general theories disappeared, they weren’t replaced by any single scientific understanding of the nature of good health and disease. Medical education has convinced doctors and the public that the reasons for suffering, disability and death are mostly known, and that when medical experts agree to give a condition a name, there must be some clear scientific evidence behind that disease name.

That mystique of diagnosing disease (specific, concrete, reified disease) was so strong that when Hans Selye noticed (in the 1930s) something that underlies all sickness (he first called it the “syndrome of being sick”), he was disregarded and disrespected, at least until his dangerous perceptions could be trimmed, distorted, and subsumed under some proper medical categories. **Selye observed that stress causes internal bleeding (in lungs, adrenals, thymus, intestine, salivary and tear glands, etc.),** but instead of trying to understand what that means for the control of sickness, the medical schools and journals have offered concrete, fragmentary, and false explanations for his observations. “Stomach acid” causes bleeding in the stomach and duodenum**;** stuff leaking out of the brain gets the blame for some cases of systemic bleeding, stuff leaking out of the uterus, for other cases, and so on. Selye’s observations have been rendered harmless (to medicine) by these falsely concrete explanations. While conventional medicine propagated its medical fantasies, it characterized Selye’s work as “controversial.”

In many cases, “diagnosis” consists of what could, at best, be called an educated guess, with no attempt to find evidence to support it.

Obviously, if every doctor in the country is guessing wrong about certain deadly conditions, lots of people will die, and no one will see the need to even study the subject, since it has a definite name and an explanation that seems to satisfy.

Instead of finding pseudo-reasons for the bleeding abnormalities caused by stress, it would be good to look freshly at the nature of blood and its circulation. It might turn out that it's a way to expand our understanding of the stress reaction.

Most people are aware of some of the variations of bleeding and clotting that occur commonly. Bleeding gums, nose-bleeds, menstruation and its variations, and the spontaneous bruising (especially on the thighs) that many women have premenstrually, are familiar events that don't seem to mean much to the medical world. Sometimes nose-bleeds are clearly stress-related, but the usual "explanation" for that association is that high blood pressure simply blows out weak blood vessels. Bleeding gums are sometimes stress related, but high blood pressure is seldom invoked to explain that problem.

The whole issue of blood vessel fragility is usually disposed of as a "genetic trait," or a result of old age. This is part of a general tendency to think of the blood vessels as an anatomically fixed, "congenital," and genetically determined system. At least until recently, nearly all physicians have called aneurysms "congenital defects." But varicose veins are merely low-pressure analogs of arterial aneurysms, and they obviously develop under specific conditions, such as pregnancy and malnutrition. Spider veins are another anatomical variation that commonly appears under the influence of estrogen. Subarachnoid hemorrhages, which can put pressure on the brain, are usually considered to result from a ruptured aneurysm, and these hemorrages are twice as common in women as in men, and probably result from a hormone imbalance.

Menstrual bleeding is a good place to start the investigation of bleeding problems, since its relatively harmless abnormalities are physiologically related to some very serious health problems, such as pregnancy bleeding, abruptio placentae, and eclampsia. Women who die from eclampsia have been found to have massively clotted blood vessels in their brains, but the variety of names for the pregnancy disorders have prevented most people from thinking of pregnancy as a time when there is a high risk of the "thrombohemorrhagic disorders," a time when the clotting system is under stress. (For about fifteen years after Selye coined the term, only he and some Russians were publishing research on it, and Americans still don't show much interest in the subject.)

Women with a chronic menstrual problem resulting from progesterone deficiency often continue to bleed each month even when they are pregnant, and these women tend to develop toxemia, and to have a high incidence of pregnancy complications, and to deliver premature, poorly developed babies.

In 1933 James Shute was recommending the use of vitamin E for preventing the clotting problems associated with pregnancy, that often lead to miscarriage. He based his work on animal studies, that led to vitamin E's being known as the "fertility vitamin." Later, his sons Wilfred and Evan reported that vitamin E could prevent heart attacks, birth defects, complications of diabetes, phlebitis, hypertension, and some neurological problems.

Later, referring to the decades of hostility of the medical establishment to vitamin E, Dr. Shute said "...an obstetrician was unduly hardy and audacious to try it." The spectrum of vitamin E's protective effects (like those of aspirin) has been consistently misrepresented in the medical literature.

Hematomas in many organs (pituitary, kidney, pancreas, liver, even around the abdominal muscles) can occur because of hormone imbalances in these difficult pregnancies. Tom Brewer's demonstration that a good diet, with abundant protein, can prevent and cure pregnancy toxemia, is practically unknown in the medical world, though a protein deficiency has been shown to increase the risk of blood clots under many other circumstances besides pregnancy.

Abruptio placentae (premature detachment of the placenta) has often been blamed on the use of vitamin E, because of vitamin E's reputation

for preventing abnormal clotting, though the evidence tends to suggest instead that vitamin E (like aspirin) reduces the risk of pregnancy-related hemorrhaging.

One of the deadly clotting conditions related to childbirth has been called “pregnancy anaphylaxis,” but it is more often called “amniotic fluid embolism,” despite the fact that amniotic fluid injected intravenously is harmless (Petroianu, et al.), and only by grinding up and injecting massive amounts of the pregnancy membranes can the clotting system be disturbed. The term is really a criminal misnomer, serving to blame a preventable clotting/shock disorder on the patient.

“Consumption coagulopathy” refers to the bleeding that follows excessive activation of the clotting system, combined with a defensive dissolving of the clots, when finally the fibrinogen or other elements of the clotting system have been depleted, consumed. A blood test can show when clot degradation products are being produced too rapidly, even while a person has no symptoms, so there should be time for the accelerated clotting to be controlled, before major thromboses and bleeding and shock have developed.

In 1936 Albert Szent-Gyorgyi reported that some chemicals in lemon juice, which he called vitamin P (or citrin), would prevent purpura, subcutaneous capillary bleeding. By 1938, he had decided that citrin, (which he now called bioflavonoid) probably wasn’t a vitamin, and that its action was more like that of a drug, substituting for a natural regulatory factor that was missing. Later research has confirmed that view, showing that the bioflavonoids inhibit the enzyme hyaluronidase, which degrades the “ground substance” of connective tissues. At least one natural endogenous inhibitor of hyaluronidase has now been identified. The basement membrane that surrounds and unites the endothelial cells of capillaries is largely hyaluronic acid and collagen. It isn’t thrombogenic (Buchanan, et al.), despite the common belief that collagen is intrinsically a clot instigator. The breakdown of this ground substance is involved in growth and reproduction, so an excess of bioflavonoids in the diet could conceivably interfere with fertility and fetal development. Some bioflavonoids have been prescribed for menstrual problems, and are probably useful when the physiological inhibitor isn’t adequate.

Hyaluronidase is activated by shock, and also by estrogen. Both hyaluronidase and estrogen have been used in plastic surgery to “expand” tissue, weakening it and allowing it to be enlarged. During aging, hyaluronic acid (the major water-retaining component of connective tissue that’s broken down by hyaluronidase) decreases in the connective tissues, but increases in the blood stream. Shock allows hyaluronic acid to increase in the serum. Fragments of degraded hyaluronic acid are pro-inflammatory.

In the 1940s Hans Selye studied the steroid hormones in a comprehensive way, defining their actions and interactions. At that time he found that progesterone protected broadly against stress, and that a large dose of estrogen created a condition that duplicated the initial shock phase of the stress reaction. Later animal studies showed that estrogen quickly causes enlargement of the adrenal glands, followed by bleeding, and, with large and continuous doses, death of the adrenal cells.

Estrogen promotes vascular permeability by a variety of mechanisms. Serotonin, histamine, lactic acid, and various cytokines and prostaglandins contribute to the leakage stimulated by estrogen, trauma, irradiation, poisoning, oxygen deprivation, and other factors that can induce shock. Even exercise, mental stress, and aging can increase the tendency of capillaries to leak.

Progesterone and cortisol protect against shock and stress partly by maintaining the resistance and integrity of the capillaries, preventing leakage of blood materials into the tissues. The maintenance of the capillary barrier probably also prevents substances from the extracellular matrix from triggering the clotting systems.

Clots are formed when soluble fibrinogen polymerizes, condenses, and becomes insoluble. Even before the particles of fibrin become insoluble, a clot-dissolving system is continuously breaking it down into small peptides. These peptides tend to cause capillaries to leak. If a massive amount of fibrinogen and fibrin leak out of capillaries, clots are formed

outside capillaries, and the peptides released in the process of cleaning up this debris contribute to further leakage, and to inflammation. The inflammation stimulates the production of collagen-rich connective tissue, and a fibrotic tissue replaces the functional tissues. Many of Hans Selye's experiments explored the conditions in which inflammation, exudation, and fibrosis developed, sometimes ending with calcification of the region.

The presence of fibrin in the extracellular matrix interferes with the differentiated functioning of cells, which depend on their contact with a normal matrix. When healing and regeneration occur in the normal matrix, the remodeling of the tissue involves the breakdown of collagen, which releases peptides with antiinflammatory, antiangiogenic and antiinvasive actions. When fibrin is present, the remodeling process releases peptides that increase cell growth, invasiveness, inflammation, and the production of new blood vessels, which in turn become leaky.

Leakage of fluid out of the blood is one of the main features of shock, and at first it is mainly the loss of water and volume that creates a problem, by reducing the oxygenation of tissue and increasing the viscosity of the remaining blood. Blood becomes more concentrated during strenuous exercise, during the night, and in the winter, increasing the viscosity, and increasing the risk of strokes and other thrombotic problems. The absence of light causes the metabolic and hormonal changes typical of stress.

Tom Brewer and his associates showed that pregnancy toxemia involves inadequate blood volume, and that using extra sodium can alleviate the symptoms, including preventing albuminuria, one of the most characteristic signs of toxemia/preeclampsia. (Besides causing loss of albumin through leaky capillaries, estrogen also inhibits its synthesis by the liver**;** the loss of colloid osmotic pressure in hypoalbuminemia has many consequences, including disturbances of blood lipids.) Estrogen's action in toxemia of pregnancy is paralleled by the fact that blood viscosity is highest at the time of ovulation during the normal monthly cycle.

In the healthy person, some of the fibrin that is constantly being formed is deposited on the inside of blood vessels (and on the surfaces of blood cells), and this layer forms an important part of the capillary's resistance to leaking. A.L. Copley, who pioneered the study of hemorrheology, called this the "endoendothelial layer." This layer probably contains albumin, too, in close association with the (carbohydrate) "glycocalyx" of the endothelial cell surface. Disturbances that accelerate the formation and dissolution of the fibrin layer can be detected by an increase in the concentration of the fibrin degradation products (FDP, or D-dimers) in the blood, even before any symptoms have appeared.

Although Selye described shock as the first (potentially lethal) phase of stress, usually followed by the corrective adaptive processes, it's useful to think of aging in terms of a lingering partial state of shock, in which adaptation is less than perfect.

The loss of blood volume through leaky capillaries tends to be self-aggravating. The concentrated and viscous blood doesn't flow as well through the capillaries, and this energy deprivation leads to increased leakiness of the cells, and to swelling of the endothelial cells, decreasing the internal diameter of the small blood vessels. The energy-deprived state increases lactic acid, adrenaline, and free fatty acids, all of which contribute to increased leakiness and impaired circulation.

In the bowel, the capillary malfunction increases the absorption of endotoxin, which intensifies the systemic energy problem. (Polyunsaturated oils, especially fish oil, damage the bowel capillaries, allowing more endotoxin to be absorbed.)

In the uterus, increased viscosity of the blood impairs the delivery of oxygen and nutrients to the fetus, retarding its development. Dilution of the blood under the influence of progesterone reduces the hematocrit, helping to compensate for the viscosity**;** in toxemic pregnancies this isn't sufficient to maintain normal viscosity and perfusion.

In the brain, hyperviscosity contributes to dementia. In the lung, to edema and reduced oxygenation ("shock lung," "wet lung," respiratory distress**;** this lung edema is a major cause of mortality in pregnancy). In the pancreas, to inflammation, and to the release of proteolytic enzymes,

impairing the clotting system even more.

During the development of cancer, hyperviscosity (and the associated hypoxia) contributes to the tumor's deranged metabolism, tending to increase its production of ammonia, clotting factors, and other stress-inducing toxins.

Factors that increase the fluidity of the blood protect against all of the thrombohemorrhagic conditions, and are especially protective against the estrogen-promoted cancers. Progesterone decreases the production of fibrinogen, and increases the volume of the blood and the flexibility of the red blood cells, increasing the ability of blood to flow freely, and it also decreases the leakiness of capillaries. Hypothyroid people (who tend to have low progesterone and high estrogen) are highly susceptible to heart disease and cancer, and have abnormally viscous blood. Hyperthyroid people have unusually fluid blood. Hypothyroidism increases the leakiness of capillaries, and decreases the amount of albumin in the blood. Albumin itself decreases the permeability of blood vessels.

In hypothyroidism and under the influence of estrogen, there is a chronic increase of free fatty acids, and the free fatty acids are an important factor in increasing the production of fibrinogen (Pickart), and in blocking fibrinolysis (Lindquist, et al.). If the body's stores of fat are largely polyunsaturated fats, the free fatty acids will combine with the fibrin as it polymerizes, making the clots especially resistant to dissolution.

In the 1940s, Melvin Knisely noticed that all seriously sick people had "sludged" blood, that can be observed microscopically in the small blood vessels on the surface of the person's eye. The cells tend to stick together, producing a sludgy appearance and slow flow. This probably corresponds to increased viscosity of the plasma, increased red cell sedimentation rate, increased fibrinogen, decreased albumin, and decreased thyroid and progesterone. Clumped red cells, when separated under the microscope, appear to be bound together by fine filaments, possibly of fibrin.

Aspirin is known to have a variety of anticancer activities, including the prevention of metastasis, and some people have reasoned that the clotting process simply helps migrating cancer cells to become anchored. However, the clotting process is normally part of the healing and repair processes, and I think the role of the fibrin clotting system in cancer is that the breakdown products of fibrin are growth-promoters, and that their presence in the extracellular matrix in large quantity, distorting the normal composition of the matrix, is what causes the formation of a tumor. It's the leakage of the fibrin into the extracellular matrix that leads to the development of tumors.

Heparin, a natural anticoagulant, is currently being tested as an anticancer agent.

All of the factors that promote stable oxidative energy production protect against the coagulative derangements, largely by preventing capillary leakage, and it now seems that these processes protect against cancer as well as protecting against all of the stress-related degenerative and inflammatory diseases.

Since hyperventilation can increase capillary leakage and cause the blood to become more concentrated, breathing carbon dioxide (breathing in a bag) should help to restore capillary function.

Since the blood becomes more concentrated, viscous, and clottable during the night (especially during long winter nights), the risk of a heart attack or stroke would probably be reduced by drinking orange juice before getting out of bed (and at bed-time), to dilute the blood and decrease adrenaline and the free fatty acids, which contribute to the increased tendency to form clots in the morning. (Assanelli, et al., discuss the importance of adrenaline in morning/winter sudden death; Antoniades and Westmoreland show that the availability of glucose can override major promoters of clotting and bleeding.)

Things to reduce the stress-related coagulopathies: Sugar and niacin to minimize the liberation of fatty acids, progesterone and thyroid to protect against estrogen and to avoid hypoglycemia (which increases adrenaline and free fatty acids and accelerates clotting), magnesium and

gelatin (or glycine), to protect against intracellular calcium overload and hypoxia, and vitamin E and salicylic acid for antiinflammatory effects, are major nutrients that protect the circulatory system against clotting, bleeding, edema, and tumefaction.

Even on the mornings that you don't drop dead, there is reduced adaptive capacity and functional impairment before eating breakfast. For example, men who went for a run before breakfast were found to have broken chromosomes in their blood cells, but if they ate breakfast before running, their chromosomes weren't damaged.

REFERENCES

Vet Rec. 1988 Apr 2;122(14):329-32. **Relationships between the erythrocyte sedimentation rate, plasma proteins and viscosity, and leucocyte counts in thoroughbred racehorses.** Allen BV. "The influence of plasma proteins on erythrocyte aggregation was studied in a population of young thoroughbred racehorses, using the 60 minute erythrocyte sedimentation rate (ESR) with and without haematocrit standardisation. The ESR **was correlated inversely with the haematocrit, but directly with fibrinogen, plasma viscosity and serum total globulins.** When ESR values were standardised to a common haematocrit the correlation coefficients for the same plasma protein factors were increased. Albumin levels showed a strong direct relationship with **haematocrit which accounted for the inverse correlation found between albumin and ESR.** The haematocrit standardised ESR showed no significant correlation with albumin levels." "The high correlation (r = 0.75) found between fibrinogen levels and haematocrit standardised ESR suggests that differences in this acute phase protein influence the degree of red cell aggregation and rouleaux formation in the horse."

Ann N Y Acad Sci. 1976;275:28-46. **Metabolic influences in experimental thrombosis.** Antoniades HN, Westmoreland N. Studies presented in this report demonstrate that intravascular coagulation and thrombosis in the whole animal can be greatly influenced by noncoagulation factors, such as metabolic, endocrinologic, and nutritional states. **Injection of a partially purified human serum procoagulant fraction produced no significant clotting abnormalities in normal fed rats; however, injection of an identical preparation in fasted, diabetic, and obese rats produced hypercoagulability of blood, thrombosis, and hemorrhage. Glucose injection in fasted rats and insulin injection in diabetic rats reversed their susceptibility to thrombosis.** The concentrations of serum free fatty acids were shown to be elevated in the susceptible animals; however, they returned to normal in fasted and diabetic rats after injections of glucose and insulin, respectively. Infusion of free fatty acid-albumin preparations in normal fed rats rendered the animals susceptible to thrombosis when challenged with the serum procoagulant fraction.

Cardiologia. 1997 Jul;42(7):729-35. **[Circadian variation of sudden cardiac death in young people with and without coronary disease]** Assanelli D, Bersatti F, Turla C, Restori M, Amariti ML, Romano A, Ferrari M. "To clarify whether sudden cardiac death has a circadian rhythm in young people we have studied 40 patients < 45 years who died in Brescia between 1984 and 1993 of sudden cardiac death showing at autopsy features of coronary artery disease (CAD) and 12 patients aged < 30 years who died of sudden cardiac death without autoptic features of CAD. We observed a circadian rhythm in the hours of the morning in the two groups, more evident in patients without CAD. In patients **with autoptic features of CAD, we also observed a higher rate of events during the winter months. We would like to stress the importance of the adrenergic** system as a trigger able to produce the event."

An R Acad Nac Med (Madr). 2002;119(1):163-73; discussion 173-4. **[HELLP syndrome and hemorrhagic gestosis]** Botella Llusia J. In the year 1817, Charlotte daughter of Georges IV and princess of Wales, died on an unknown condition with uteroplacental hemorrhage **and fetal death called at the time "Uteroplacental Apoplexy" and later "Abruptio Placentae". This affection was described in the classical books as an hemorrhagic complication of labor. In 1961 we have at first related the Abruptio with acute toxemia (preeclampsia) and have proposed the term "Gestosis hemorragica" to design** it. In 1982 Weinstein has described the called HELLP syndrome (Hemolysis, Elevated liver Enzymes, at Low Platelets) which basically is the same pathological picture as the described by us as "hemorrhagic toxemia". The aim of the paper is to demonstrate the identity of both syndromes and to claim for the priority of our definition.

Thromb Haemost. 1987 Aug 4;58(2):698-704. **The basement membrane underlying the vascular endothelium is not thrombogenic: in vivo and in vitro studies with rabbit and human tissue.** Buchanan MR, Richardson M, Haas TA, Hirsh J, Madri JA.

Am J Physiol Heart Circ Physiol. 2003 Mar;284(3):H1028-34. Epub 2002 Nov 21. **Endotoxemia stimulates skeletal muscle Na+-K+-ATPase and raises blood lactate under aerobic conditions in humans.** Bundgaard H, Kjeldsen K, Suarez Krabbe K, van Hall G, Simonsen L, Qvist J, Hansen CM, Moller K, Fonsmark L, Lav Madsen P, Klarlund Pedersen B.

Thromb Haemost. 2001 Jul;86(1):334-45. **Tissue factor--a receptor involved in the control of cellular properties, including angiogenesis.** Chen J, Bierhaus A, Schiekofer S, Andrassy M, Chen B, Stern DM, Nawroth PP. **"Tissue factor (TF), the**

major initiator of blood coagulation, serves as a regulator of angiogenesis, tumor growth and metastasis."

Thromb Res Suppl. 1983;5:105-45. **The physiological significance of the endoendothelial fibrin lining (EEFL) as the critical interface in the 'vessel-blood organ' and the importance of in vivo 'fibrinogenin formation' in health and disease.** Copley AL. "The author's theory of the **endoendothelial fibrin lining (EEFL) . . .** localizes the homeostasis between steady fibrin formation and deposition, or 'fibrination', and continuous fibrinolysis in the more or less immobile portion of the plasmatic zone next to the vessel wall. In 1971, the author advanced, in relation to the EEFL, the theory of **fibrinogen gel clotting without thrombin action or 'fibrinogenin' formation in vivo.**" "The EEFL of the vessel-blood organ is considered by the author as the crucial critical interface between the blood and the vessel wall. **It is the primary barrier, followed by the endothelium (comprising the endothelial cells and the interendothelial cement substance which contains or is identical with 'cement fibrin') and the basement membrane for the exchanges between the blood, the vessel wall and its surrounding tissues and spaces. The EEFL acts as anticoagulant, is antithrombogenic, maintains vascular patency and aids cardiac action by decreasing significantly the apparent viscosity of blood,** referred to in the literature as the 'Copley-Scott Blair phenomenon'. A new concept of leukocyte emigration traversing the capillary wall is presented, affecting focal fibrinolysis of the EEFL and of fibrin contained in the interendothelial cement substance and in the basement membrane. The physical property of capillary (or vascular) permeability is related to the existence of the EEFL, since, as found by Copley et al, both fibrinopeptides, liberated in the transition of fibrinogen to fibrin, and plasminopeptides, freed in the conversion of plasminogen to plasmin, enhance capillary permeability. Capillary fragility, which is antagonistic to capillary permeability, is in great part due to fibrinolytic action on fibrin as a constituent of the basement membrane."

Am J Obstet Gynecol. 1995 Apr;172(4 Pt 1):1291-8. **Blindness associated with preeclampsia and eclampsia.** Cunningham FG, Fernandez CO, Hernandez C.

East Afr Med J. 2002 Apr;79(4):181-3**. Haemorheological changes during the menstrual cycle.** Dapper DV, Didia BC.

Cancer Res. 2001 Feb 1;61(3):795-8. **Tumor hypoxia, the physiological link between Trousseau's syndrome (carcinoma-induced coagulopathy) and metastasis.** Denko NC, Giaccia AJ.

Lab Invest 1998 Jun;78(6):657-68. **Development of porous defects in plasma membranes of adenosine triphosphate-depleted Madin-Darby canine kidney cells and its inhibition by glycine.** Dong Z, Patel Y, Saikumar P, Weinberg JM, Venkatachalam MA

Arterioscler Thromb Vasc Biol. 1997 Nov;17(11):2692-7. **Seasonal variations of rheological and hemostatic parameters and acute-phase reactants in young, healthy subjects.** Frohlich M, Sund M, Russ S, Hoffmeister A, Fischer HG, Hombach V, Koenig W.

Respir Physiol Neurobiol. 2003 Oct 16;138(1):37-44. **Lactate as a modulator of hypoxia-induced hyperventilation.**Gargaglioni LH, Bicego KC, Steiner AA, Branco LG.

Am J Vet Res. 1994 Jun;55(6):854-61. **Hemorheologic alterations induced by incremental treadmill exercise in Thoroughbreds.** Geor RJ, Weiss DJ, Smith CM.

Vopr Pitan. 1995;(1):7-11. **[Effects of dietary fat on permeability of the protective intestinal barrier to**

macromolecules in experimental anaphylaxis][Article in Russian]

Gmoshinskii IV, Ermekpaeva RA, Lysikov IuA, Kulakova SN, Mazo VK, Morozov IA.

Am J Physiol Cell Physiol 2000 Nov;279(5):C1495-505. **Calcium regulates estrogen increase in permeability of cultured CaSki epithelium by eNOS-dependent mechanism.** Gorodeski GI.

J Reprod Med. 2002 Dec;47(12):1021-4. **Documentation of amniotic fluid embolism via lung histopathology. Fact or Fiction?** Hankins GD, Snyder R, Dinh T, Van Hook J, Clark S, Vandelan A.

Klin Wochenschr. 1990 Jun 5;68(11):559-64. **[Hemodynamic and hemorheologic findings in patients with pregnancy-induced hypertension: comparison of pre-eclampsia and chronic hypertension]** Heilmann L, Schmid-Schonbein H.

Zentralbl Gynakol. 1986;108(7):393-402. **[Changes in flow properties of the blood in pregnancy]** Heilmann L.

Eur J Vasc Surg. 1992 Jan;6(1):36-40. **Claudication induces systemic capillary endothelial swelling.** Hickey NC, Hudlicka O, Simms MH.

Blood. 2001 Mar 15;97(6):1697-702. **Serotonin induces the expression of tissue factor and plasminogen activator inhibitor-1 in cultured rat aortic endothelial cells.** Kawano H, Tsuji H, Nishimura H, Kimura S, Yano S, Ukimura N, Kunieda Y, Yoshizumi M, Sugano T, Nakagawa K, Masuda H, Sawada S, Nakagawa M.

Br Med J (Clin Res Ed). 1984 Nov 24;289(6456):1405-8. **Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter.** Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. **"Six hours of mild surface cooling in moving air at 24 degrees C with little fall in core temperature (0.4 degree C) increased the packed cell volume by 7% and increased the platelet count and usually the mean platelet volume to produce a 15% increase in the fraction of plasma volume occupied by platelets. Little of these increases occurred in the first hour. Whole blood viscosity increased by 21%; plasma viscosity usually increased, and arterial pressure rose on average** from 126/69 to 138/87 mm Hg."

Acta Chir Scand. 1976;142(1):20-5. **Induction of endogenous fibrinolysis inhibition in the dog. Effect of intravascular coagulation and release of free fatty acids.** Lindquist O, Bagge L, Saldeen T. "In all groups subjected to infusion of thrombin an increase in plasma free fatty acids (FFA) was observed. The role of this increase for the development **of fibrinolysis inhibition was tested by infusion of norepinephrine alone and in combination with nicotinic acid. Norepinephrine caused an increase of FFA after 2 hours and in urokinase inhibitor activity after 24-48 hours.** Both of these were diminished by high doses of nicotinic acid, indicating that the release of FFA rather than intravascular coagulation might be the principal mechanism underlying the occurrence of fibrinolysis inhibition following trauma."

Matrix Biol. 2002 Jan;21(1):31-7. **Inhibitors of the hyaluronidases.** Mio K, Stern R. "Because of increased interest in hyaluronidases and their hyaluronan substrate, a study of these inhibitors was undertaken recently. **The predominant serum inhibitor is magnesium-dependent.…**"

Vopr Onkol. 1991;37(9-10):992-7. **[Blood coagulation disorders and tumor growth]** [Article in Russian] Mkrtchian LN, Shukurian SG, Sarkisian OM, Magakian AG, Khachaturova TS, Ambartsumian AM.

Usp Fiziol Nauk. 1989 Oct-Dec;20(4):94-109. **[The physiologic coagulation fibrinolytic system of the body and thrombohemorrhagic theory in oncology]** [Article in **Russian**] Nadiradze ISh, Machabeli MS.

Arch Gynecol Obstet. 2002 Nov;267(1):7-10. **Sex hormones, hemostasis and early pregnancy loss.** Nelson DB, Ness RB, Grisso JA, Cushman M. "This study was designed to determine the association between coagulation factors and spontaneous abortion adjusting for sex steroids and to examine the influence of sex hormones on coagulation factors early in pregnancy." "The relationship between coagulation factors and spontaneous abortion was reduced after adjustment for progesterone suggesting that **progesterone mediates the relationship between low levels of coagulation factors and spontaneous abortion. Progesterone seems to be the primary marker for a spontaneous abortion among women seeking emergent care.**"

Toxicol Pathol. 1992;20(1):71-80. **Pathogenesis of blood-filled cavities in estrogen-induced anterior pituitary tumors in male Sprague-Dawley rats.** van Nesselrooij JH, Hendriksen GJ, Feron VJ, Bosland MC.

Arch Int Physiol Biochim. 1983 Jul;91(2):81-5. **Effects of the administration of progesterone and adrenal medullectomy on the plasma fibrinogen levels in rats with surgical injury (laparotomy).** Palma JA, Gavotto AC, Villagra SB.

Pediatr Crit Care Med. 2000 Jul;1(1):65-71. **Administration of autologous fetal membranes: Effects on the coagulation in pregnant mini-pigs.** Petroianu GA, Toomes LM, Maleck WM, Friedberg C, Bergler WF, Rufer R. "**A hallmark of the so-called amniotic fluid embolism is the induction of coagulation defects. Entry of meconium-free autologous amniotic fluid into the circulation, however, is innocuous.**" "Animals received 2 g FM [fetal membranes] (shredded and suspended in lactated Ringer's solution) via an ear vein. **However, the full clinical picture of amniotic fluid embolism and disseminated intravascular coagulation could not be elicited despite the high dose of FM used.**"

Am J Physiol. 1976 Apr;230(4):996-1002. **Free fatty acids and albumin as mediators of thrombin-stimulated fibrinogen synthesis.** Pickart LR, Thaler MM. "Mobilization of FFA in mice, triggered with an injection of thrombin, was followed within 24 h by a 2.5-fold increase in fibrinogen synthesis and a 30% increase in plasma fibrinogen concentration." "Injection of exogenous defatted albumin into mice before thrombin injection prevented the FFA-associated rise in fibrinogen synthesis and plasma concentration." "These studies indicate that the FFA/ALBUMIN RATIO MAY PLAY A MAJOR ROLE IN THE REPLENISHMENT OF FIBRINOGEN AFTER PERIODS OF RAPID DEFIBRINOGENATION."

Thromb Haemost. 1995 Jul;74(1):391-5. **Tissue factor expression in human leukocytes and tumor cells.** Rickles FR, Hair GA, Zeff RA, Lee E, Bona RD. **"Tissue factor (TF) exists in a cryptic form [i.e. without procoagulant activity (PCA)] in peripheral blood monocytes and quiescent tissue macrophages but is expressed constitutively in most human tumor cells."** "The regulation of TF synthesis in cells is complex and new information from transfection studies suggests that changes in cellular glycosylation pathways impair cell surface expression of functional TF." "The importance of carbohydrate modification of TF is reviewed."

Nature 138: 32 (1936). Selye, H. **A Syndrome produced by diverse nocuous agents.**

Int J Microcirc Clin Exp. 1996 Sep-Oct;16(5):266-70. **Hyperventilation enhances transcapillary diffusion of sodium fluorescein.** Steurer J, Schiesser D, Stey C, Vetter W, Elzi MV, Barras JP, Franzeck UK.

Lancet. 1991 Jul 6;338(8758):9-13. **Seasonal variations in fibrinogen concentrations among elderly people.** Stout RW, Crawford V. "Mortality and morbidity in elderly people are higher in winter than in summer months, with seasonal variations in rates of both fatal and non-fatal myocardial infarction and stroke." "Significant seasonal effects were found for fibrinogen, plasma viscosity, and HDL cholesterol (p less than 0.003, Bonferroni adjustment). Plasma fibrinogen concentrations showed the greatest seasonal change and were 23% higher in the coldest six months compared with summer months. Fibrinogen was significantly (p less than 0.05) and negatively related to core body temperature and all measures of environmental temperature." "Those living in institutions had greater changes in plasma fibrinogen than those living in the community. The seasonal variation in plasma fibrinogen concentration is large enough to increase the risk of both myocardial infarction and stroke in winter."

Akush Ginekol (Mosk). 1989 Jan;(1):43-6. **[Coagulative activity of the amniotic fluid]** [Article in **Russian**] Tersenov OA, Mikhaleva IV, Usol'tseva VA, Byshevskii Ash. "An ultracentrifugation study has shown thromboplastin to be the only blood coagulating agent, present in the amniotic fluid (AF). **Its AF level shows no correlation to the rate of intrapartum or early postpartum thrombohemorrhagic complications...."**

Metabolism. 1989 May;38(5):471-8. **Effects of hypothyroidism on vascular 125I-albumin permeation and blood flow in Rats.** Tilton RG, Pugliese G, Chang K, Speedy A, Province MA, Kilo C, Williamson JR. "Effects of hypothyroidism on vascular 125I-albumin permeation and on blood flow were assessed in multiple tissues of male Sprague-Dawley rats rendered hypothyroid by dietary supplementation with 0.5% (wt/wt) 2-thiouracil or by thyroidectomy." "After 10 to 12 weeks of thiouracil treatment, **125I-albumin permeation was increased significantly in the kidney, aorta, eye (anterior uvea, choroid, retina), skin, and new granulation tissue**...."

Clin Nutr. 2001 Aug;20(4):351-9. **Effect of eicosapentaenoic acid (EPA) on tight junction permeability in intestinal monolayer cells.** Usami M, Muraki K, Iwamoto M, Ohata A, Matsushita E, Miki A.

Carcinogenesis. 2003 Jun;24(6):1009-13. Epub 2003 Mar 28. **Tissue factor signal transduction in angiogenesis.** Versteeg HH, Peppelenbosch MP, Spek CA. **Tissue factor (TF), a 47-kDa transmembrane glycoprotein, is a principal regulator of oncogenic neoangiogenesis and controls therefore the cancerous process.** Although originally identified as a component of the coagulation cascade, it has become clear that TF functions as a cytokine-like receptor and this notion was confirmed by the discovery of coagulation-independent actions of TF (which include regulation of tumour growth, embryonic and oncogenic blood vessel formation as well as regulation of inflammation and sepsis). In accordance, TF-mediated signal transduction events are readily detected and the elucidation of the underlying molecular mechanisms has recently seen spectacular progress and it is now understood that the role of TF in angiogenesis is both coagulation-dependent and independent. The recent evidence for this emerging insight will be the subject of this review.

Semin Thromb Hemost. 2003 Jun;29(3):317-20. **Occurrence of components of fibrinolytic pathways in situ in laryngeal cancer.** Wojtukiewicz MZ, Sierko E, Zacharski LR, Rozanska-Kudelska M, Zimnoch L.

Semin Thromb Hemost. 2003 Jun;29(3):239-46. **Malignancy as a solid-phase coagulopathy: implications for the etiology, pathogenesis, and treatment of cancer.** Zacharski LR.

Thromb Res. 2003 Jun 1;110(4):213-4. **Heparin treatment of malignancy: the case for clinical trials in colon cancer.** Zacharski LR.

Anticancer Res. 2003 May-Jun;23(3C):2789-93. **Low-molecular-weight heparin in oncology.** Zacharski LR, Loynes JT.

Cancer Lett. 2002 Dec 1;186(1):1-9. **Anticoagulants in cancer treatment: malignancy as a solid phase coagulopathy.** Zacharski LR.

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