Bleeding, clotting, cancer

From the original article in 2006. Author: Ray Peat.

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.

I n 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.

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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."

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