# Autonomic systems

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*Historically, functions such as reason, emotion, and instinct were associated with particular nervous structures, and there was a reluctance to think that consciousness, like instinct, could be based on "reflexes." Eventually, this led to the idea of an autonomous nervous system which produced emotions and adjusted the body's functions, while the "central nervous system" was the seat of conscious thought, perception, and behavior.*

*Our individual cells have a degree of autonomy, consisting of the ability to sense their situation, integrate stimuli, and act adaptively. Their behavior is intelligently adaptive. The cells that make up the nervous system have this basic capacity for complex adaptive integration, but they also have the specialized role of serving as links between cells, and between cells and the environment.*

*The integration of the organism is most complete when the energy of each cell is optimal. The "autonomic nervous system," including nerves that are closely associated with the diverse organs and tissues, is easiest to understand as a system for integrating and optimizing energy throughout the organism.*

*This view suggests new ways of understanding imbalance in these nervous functions, and the diseases that develop under the imbalanced conditions--e.g., asthma, polycystic ovaries, menopausal symptoms, some skin diseases, multiple sclerosis, heart disease, and tumors.*

*Every organ has its own intrinsic nerve net, and the cortex of the brain adjusts each system to meet the adaptive needs of the organism.*

*When every cell is functioning optimally, and the organism is adapted to its environment, there is little need for intervention by the "transmitter substances."*

People like Walter Cannon and Wilhelm Reich popularized the idea of the autonomic nervous system, but they were just systematizing ideas that had been developing since the beginning of the century. Their views were the context in which Selye's idea of stress developed.

The anatomical components of the nervous system that were called the sympathetic ("fight or flight," adrenergic) system and the parasympathetic ("vegetative") system are still important factors in physiological thinking, and despite the great complexity that has grown up around them, there is still a tendency to identify the systems with polarities of mood or emotion. The idea of polarities is useful, but it easily leads to error.

(The sympathetic system includes a chain of ganglia along the spine, and its functions include dilating the pupils and accelerating the heart. The parasympathetic system is also called the cranio-sacral system, from the location of its ganglia, and among its functions are slowing the heart and constricting the pupils. However, despite several decades of research, the actions of "sympathetic" and "parasympathetic" nerves in most organs aren't understood.)

If the "adrenaline side" of the nervous system is responsible for the reactions to pain and threat, reactions of fear and rage, then the opposite side tends to be given attributes such as peace and pleasure, and the fact that these oppositions are often true has led to a climate in which the adrenergic reactions are seen as "bad," and the opposite reactions as "good." When adrenalin was identified as an agent of the sympathetic nervous system, there was a search for the "opposing" agent of the parasympathetic system. Histamine was an early candidate, before acetylcholine was discovered to be the main parasympathetic agent. This view of histamine was fostered by the older idea of "trophic nerves," which easily became identified with the parasympathetic system. When acetylcholine was identified as the transmitter or agent of the parasympathetic system, it tended to take on many of the qualities, including the "trophic" functions, that had grown up around the idea of the parasympathetic system, but the emphasis on acetylcholine led to a general neglect of the associations of histamine, and the mast cells that produce much of it, with the autonomic nervous system. (The current trend seems to be emphasizing a close integration of mast cell function with nervous function.) Nitric oxide has recently been identified as another parasympathetic "transmitter." Nitric oxide and histamine are both very important factors in degenerative inflammatory diseases, but their association with the parasympathetic nervous system has given them an aura of benevolence.

I think it's useful to compare the autonomic nervous system with the pituitary, not just because some of the pituitary hormones are called "trophic" hormones (e.g., luteotrophic, adrenocorticotrophic), but because their important adaptive functions can themselves be the cause of serious problems. An excess of the thyroid stimulating hormone, for example, causes degeneration and cancer development in the thyroid gland, and animals deprived of their pituitary gland, but given thyroid, live longer than intact animals.

If slaves are starved and beaten frequently, they aren't very productive, they don't live long, and they might rebel. Workers that are healthy and working for a common goal that they understand are more productive. Cells that are well energized perform their functions with minimal cues, but deprived cells that have to be forced to function are likely to die unexpectedly, or to reproduce inappropriately, or to change their identity.

Professors often make a strong impression on their students, but, especially in technical or scientific fields, they usually do this by controlling the discourse, so that radical questioning is excluded. What they don't know "isn't knowledge." Under the pressure of "getting a professional education," students appreciate organizing principles and mnemonic devices, but this gives traditional ways of systematizing knowledge tremendous power that, in practice, is far more important than mere

experimental results. (Experiments that don't acknowledge the ruling metaphors are almost universally considered inadmissable, unpublishable.)

Some obvious questions about the autonomic system have been commonly ignored or minimized by physiologists. If "stress" is the stimulus that causes the sympathetic system to increase its activity, what is the stimulus for increased activity of the parasympathetic system? What accounts for the relative balance between the two sides of the system, or their imbalance? The fact that the answers aren't obvious has left the questions largely to psychiatrists and psychologists. Wilhelm Reich, who tried to provide answers in terms of developmental interactions between the organism and its environment, found that the question led him to investigate psychosomatic disease, sexual repression, cancer, and fascism, with disastrous results for himself.

Chinese medicine was familiar with many of the functions of the autonomic nervous system at a time when western medicine was organized around "the humors." It's easy for contemporary "western" people to see that the "winds" and the hot and cold principles of Chinese tradition are metaphors, but they are reluctant to see that their own system has grown up within very similar traditional metaphoric polarities.

The successes of even a good metaphor can cause people to neglect details that could support a more complete and accurate image of reality.

Contemporary science carries a load of bad metaphors, because the educational system doesn't tolerate a critical attitude. Potentially, a good metaphor (e.g., Vernadsky's suggestion that an organism is "a whirlwind of atoms") could blow away many bad metaphors, but the present organization of science is tending in the other direction**:** Commercial interests are creating a culture in which their metaphors are replacing the traditional science in which there was a certain amount of honest intellectual exploration.

In talking about consciousness, sleep, stress, biological rhythms, aging, and energy, I have often focussed on the efficient use of oxygen for energy production by the mitochondria, i.e., cellular respiration. Every situation demands a special kind of adaptation, and each kind of adaptation requires a special distribution of cellular and organic activity, with its supporting local respiratory activity.

There is a lot of local self-regulation in the adapting organism, for example when the activated tissue produces increased amounts of carbon dioxide, which dilates blood vessels, delivering more oxygen and nutrients to the tissue. But the distribution of excitation, and the harmonious balancing of the organism's resources and activities, is achieved by the actions of the cortex of the brain, acting on the subordinate nerve nets, adjusting many factors relating to energy production and use.

On the level of the mitochondria, adrenaline and acetylcholine have slightly different effects. (Metabolic studies with isolated mitochondria are so remote from the normal cellular condition that their results are nothing more than a hint of what might be occurring in the cell.) Acetylcholine appears to shift the proportion of the fuels used (increasing the oxidation of alpha-ketoglutarate, with the production of carbon dioxide) and increasing the efficiency of energy conservation (phosphorylation, producing ATP) so that less oxygen is needed, while adrenaline increases the rate of oxygen consumption (and succinate oxidation). This would be consistent with F. Z. Meerson's conception of the parasympathetic function as one of the "stress limiting" systems.

On the level of the whole cell, organ, and organism, the parasympathetic function limits oxygen consumption in a variety of ways, including the reduction of blood flow. Acetylcholine, like histamine and serotonin, activates glycolysis, the conversion of glucose to lactic acid, which provides energy in the absence of oxygen.

The effects of a little adrenaline, and a lot of adrenaline, are very different, with a high concentration of adrenaline decreasing the efficiency of phosphorylation. In the stressed heart, this effect of excess adrenaline can be fatal, especially when it is combined with adrenaline's acceleration of clotting, liberation of fatty acids, and frequently of calcium, and constriction of blood vessels.

Seventy years ago, autonomic control of blood vessels seemed to be a matter of nerve fibers that constrict them, and other fibers that cause them to dilate, but that idea hasn't worked for a long time.

Ever since I noticed that the students in our physiology lab who tried to use adrenaline to revive their rats weren't successful, I have wondered about the television shows in which adrenaline is given to patients with heart problems. Under some conditions adrenaline does increase circulation to the heart, but extreme stress doesn't seem to be among those conditions.

Too much serotonin, histamine, acetylcholine, and polyunsaturated fatty acids, like too much adrenalin, can cause spasms of the coronary arteries, along with disturbances of mitochondrial respiration. In stress, these substances are almost sure to be present in excess. (Anti-serotonin drugs are effective for a variety of heart problems, and other degenerative diseases.)

By increasing the production of lactic acid and the loss of carbon dioxide, exaggerated nervous stimulation (especially the excess of acetylcholine, histamine, and serotonin) can cause a variety of problems, including generalized vasoconstriction and systemic alkalosis, as well as increased intracellular alkalinity. This metabolic pattern is characteristic of many kinds of stress, including cancer. (Elsewhere, I have referred to this pattern as "relative hyperventilation.") The metabolic effects probably account for some of the "paradoxical" effects of the autonomic agents.

When nutrition and thyroid function, light, atmospheric pressure, and other conditions are favorable, the autonomic transmitters (e.g., acetylcholine, histamine, serotonin, adrenalin) and pituitary hormones and other "signal substances" are kept within safe limits.

Because the substances released from various cells under the influence of the autonomic nerves (histamine and serotonin, for example) stimulate cell division, injuries which produce clots and vascular spasms will also stimulate the formation of new blood vessels, a process that is essential for the adaptation of tissues to prolonged stress.

These stress-induced agents are appropriately included in the "vegetative" (parasympathetic) nervous system, because they promote vegetation, i.e., the proliferation of substance.

Adrenaline, and the sympathetic nerves, have the opposite function, of restraining cell division, and they also oppose the pro-inflammatory functions of those parasympathetic agents.

Estrogen tends to shift autonomic balance toward the parasympathetic side, away from the sympathetic/adrenergic. Recalling that stress, hypothyroidism, and aging increase the activity of aromatase in various tissues, with local production of estrogen, and that tissue-bound estrogen stays at a high level in postmenopausal women despite the lower level of estrogen in the serum, it's worthwhile looking at the effects of estrogen on the various components of the so-called autonomic nervous system.

One injection of estrogen can induce a large increase in the number of sympathetic nerves in the ovaries. At menopause, a similar "invasion" of sympathetic nerves occurs. The polycystic ovary (which is even more common after menopause than before, and some studies have found the condition in 20% of premenopausal women) responds to estrogen by producing nerve growth factor(s), and growing a large number of new sympathetic nerves. Although the hyperestrogenism associated with the polycystic ovary syndrome has many harmful effects, the invasion of the ovary by adrenergic nerves apparently protects it from the development of cancer.

Parasympathetic nerves, pituitary hormones and mast cells activate the ovaries. The number of mast cells in the ovaries is increased by the pituitary hormones (including the thyroid stimulating hormone), and by estrogen (Jaiswal and Krishna, 1996). Estrogen is the most potent of these hormones in causing the cells to release histamine. The overgrowth of the sympathetic nerves in the polycystic ovary causes the number and activity of mast cells to decrease, possibly as a protective adaptation against excessive stimulation from the many pro-inflammatory factors. The mast cells are needed for the follicles to rupture, so their suppression prevents ovulation.

The nervous system is closely involved in controlling the growth of tissues, and it has been argued (R.E. Kavetsky reviewed the subject in his book, emphasizing the role of depression in development of cancer) that cancer results from reduced activity of the sympathetic nerves, or unopposed action of the parasympathetic system. That stress has a role in cancer is acknowledged by the scientific establishment, but the nervous system's direct involvement in the regulation of cellular metabolism, cell division, and other processes that are central to the cancerous state is either flatly denied or simply ignored.

Although mast cells have been known to be a common component of tumors for many years, it is only recently that antihistamines and other antiinflammatory drugs have been recognized as valuable therapies in cancer. The whole issue of the role of nerves in tumor development and physiology has been submerged by the mystique of the "intrinsically bad cancer cell."

In Alzheimer's disease, there has been a great investment in the doctrine that drugs to promote the function of cholinergic (acetylcholine forming) nerves will restore lost mental function, or at least retard the progression of the disease. The success of ***anti***cholinergic drugs in treating several degenerative brain diseases is probably embarrassing to the companies whose cholinergic-intensifying drugs aren't very successful. Conveniently for them, these formerly "anticholinergic" drugs are now being called anti-excitotoxic or anti-glutamatergic drugs. There is no serious conflict in the terminology, since the cholinergic processes (like the serotonergic processes) are closely associated with excitotoxic nerve damage. The cholinergic drugs will probably be sold as long as their patents are effective, and then will be quietly forgotten.

The modern conception of pharmacology, with receptors and transmitters turning functions on or off, has turned into an unproductive and dangerous scholasticism. No one will ever successfully count the number of transmitter angels dancing on the variable sites of the variable receptor molecules. The functional "meaning" of a receptor or transmitter changes according to circumstances, and the effect of activating a particular nerve depends on surrounding conditions, and on preceding conditions. Each cell integrates stimuli adaptively.

If no reflex is simply mechanical and innate, then all reflexes are conditional. (M. Merleau-Ponty argued against the validity of the reflex concept itself, because of this conditionality.) P. K. Anokhin's concept of the "Acceptor of Action" (described in my book, ***Mind and Tissue***) provides an image in which we can see the "set-points" for the relatively "autonomic" reflexes as reflections of the general needs of the organism. The local tissue reflexes, the organ reflexes, the spinal reflexes, etc., are variable, according to their energetic resources, and according to the way in which they are organized under the influence of the cerebral cortex and the environment.

The reality is more complex than the philosophy of the drug industry imagines, but the solutions of problems can be much simpler, if we think in terms of energetic support, rather than the over-concretized interventions of the pharmacologists. In hypothyroidism, it is common for there to be an excess of adrenalin/noradrenalin, serotonin, histamine, and some of the pituitary hormones. Correcting thyroid function can immediately correct many problems, but especially when the energy deficiency has caused anatomical adjustments (redistribution of blood vessels and mast cells, for example) it's important to make the environment supportive in as many ways as possible.

In polycystic ovaries, menopausal symptoms, arthritis, angina pectoris, multiple sclerosis, some kinds of dementia, migraine, and emphysema, the relief achieved with a simple improvement of cellular energy can be rapid and complete. Presumably a similar process of biological reorganization is involved in the occasional spontaneous regression of tumors.

Although I don't think the autonomic nervous system, with its sympathetic and parasympathetic divisions, exists in the way

it has traditionally been conceived, the idea can be useful if we think of using drugs and other factors in ways that tend to ***"quiet an overactive autonomic nervous system."***

## References


Am J Emerg Med 1989 Sep;7(5):485-8. **Coronary artery spasm induced by intravenous epinephrine overdose.** Karch SB. A 27-year-old man was accidentally given 2 mg intravenous epinephrine instead of 2 mg naloxone. He immediately developed chest pain, nausea, and diaphoresis. An ECG taken shortly after the epinephrine administration showed widespread ischemia. Forty-five minutes later the tracing still showed an early repolarization pattern, but ST elevation was less marked and the patient was asymptomatic. Serum potassium was 3.2 mEq/L and serum catecholamines, drawn approximately 20 minutes after the epinephrine administration, were 10 times normal (dopamine, 173 ng/L; epinephrine, 1,628 ng/L; norepinephrine, 1,972 ng/L). There are seven other reports of intravenous epinephrine overdose in the English literature. Two of the previously reported cases had 12-lead ECGs within the first hour. In both there was evidence of transient ischemia similar to that observed in this case. Most of the patients had symptoms consistent with angina, **and several developed pulmonary edema. These findings suggest that, in humans, large intravenous doses of epinephrine are likely to produce coronary artery spasm and may decrease coronary artery perfusion.**

Res Exp Med (Berl) 1987;187(5):385-93. **Possible interaction of platelets and adrenaline in the early phase of myocardial infarction.** Seitz R, Leising H, Liebermann A, Rohner I, Gerdes H, Egbring R. "**It is known that in most cases of transmural acute myocardial infarction a platelet clot originates within a coronary artery. In acute myocardial infarction patients increased levels of the plasma catecholamines adrenaline and noradrenaline as well as the platelet release proteins platelet factor 4 and beta-thromboglobulin have been reported."**

Anesthesiology 1991 Jun;74(6):973-9. Comment in: Anesthesiology. 1992 Mar;76(3):475. **Magnesium inhibits the hypertensive but not the cardiotonic actions of low-dose epinephrine.** Prielipp RC, Zaloga GP, Butterworth JF 4th, Robertie PG, Dudas LM, Black KW, Royster RL. Intravenous magnesium supplementation is often used to control cardiac arrhythmias and coronary artery vasospasm resulting from disturbances of magnesium homeostasis after coronary artery bypass surgery. Many such patients also require inotropic drug support of depressed myocardial function. However, increased serum magnesium concentrations directly depress cardiac contractility in animals and may interfere with catecholamine actions. To determine whether small intravenous doses of magnesium sulfate ($MgSO_4$) interfere with the cardiotonic actions of epinephrine, we examined the hemodynamic effects of $MgSO_4$ and epinephrine infusion in 17 cardiac surgical patients on their 1st postoperative day in a prospective, controlled study. In 11 patients, infusion of $MgSO_4$ (7-mg.kg-1 bolus followed by 10 mg.kg-1.h-1 as a continuous infusion) increased serum magnesium concentrations by 44% (mean +/- standard error of the mean [SEM] of 0.8 +/- 0.1 to 1.2 +/- 0.1 mM; P less than 0.01) but had no significant effect on heart rate; mean arterial, central venous, or pulmonary arterial occlusion pressures; or cardiac output. Epinephrine infusion (30 ng.kg-1.min-1) significantly increased cardiac index (2.7 +/- 0.1 to 3.1 +/- 0.21.min-1.m-2; P less than 0.05); this effect was not altered by $MgSO_4$ administration (n = 11). However, $MgSO_4$ significantly blunted epinephrine's hypertensive action and prevented a significant increase in mean arterial pressure during concurrent $MgSO_4$-epinephrine administration. Six placebo control patients were given two sequential infusions of epinephrine separated by a placebo infusion to rule out an effect of time on the hemodynamic response to epinephrine. Mean arterial pressure and cardiac index responses to epinephrine were identical before and after placebo infusion.

Jpn Heart J 1979 Jan;20(1):75-82. **Inhibition of constrictor responses of dog coronary artery by atropine. A possible effectiveness of atropine on variant form of angina pectoris.** Sakanashi M, Furukawa T, Horio Y. A possible effectiveness of atropine on variant form of angina pectoris was investigated using the left circumflex coronary arterial strips of dogs. Acetylcholine 10(-5)--10(-3) Gm/ml dose-dependently constricted the isolated arterial strips during potassium-contracture in 6 cases, and repetitive applications of acetylcholine could produce the similar contractions to the control. In 18 strips atropine 10(-6) Gm/ml significantly depressed the contractions of coronary arteries induced by acetylcholine 10(-5)--10(-3) Gm/ml. In 5 arterial strips atropine 10(-6) Gm/ml **significantly inhibited norepinephrine-induced responses** of these arteries, and by 10(-5) Gm/ml further suppression of the responses was obtained. The **results suggest that atropine may suppress the contractile responses of the coronary artery induce by acetylcholine and nonrepinephrine through a muscarinic-receptor blocking action and simultaneously partly through an adrenergic alpha-receptor blocking action.**

Eur J Clin Pharmacol 1981;20(4):245-50. **Effect of long-term beta-blockade with alprenolol on platelet function and fibrinolytic activity in patients with coronary heart disease.** Jurgensen HJ, Dalsgaard-Nielsen J, Kjoller E, Gormsen J.

C R Seances Soc Biol Fil 1987;181(3):242-8. **[Adrenaline activates oxidative phosphorylation of rat liver mitochondria through alpha 1-receptors].** Breton L, Clot JP, Bouriannes J, Baudry M. We studied the effects and mode of action of epinephrine on the oxidative phosphorylation of rat liver mitochondria. With either succinate or beta-hydroxybutyrate as substrate, i.v. injection of 1.5 microgram/100 g epinephrine increased the respiratory rates by 30-40% in state 3 (with ADP), and by 20-30% in state 4 (after ADP phosphorylation), so that the respiratory control ratio (state 3/state 4) changed little. The respiratory stimulation by epinephrine was maximal 20 minutes after its injection. The action of epinephrine on mitochondria was blocked by pretreatment of the animals with the alpha 1-antagonist prazosin but not by treatment with the beta-antagonist propranolol. I. v. injection of 10 micrograms/100 g phenylephrine evoked the same mitochondrial response as epinephrine. I. v. administration of 50 micrograms/100 g dibutyryl cyclic AMP enhanced glycaemia but did not affect mitochondrial respiration. Epinephrine therefore has an alpha 1-type of action on mitochondrial oxidative phosphorylation.

Biochimie 1975;57(6-7):797-802. **Effects of catecholamines on rat myocardial metabolism. I. Influence of catecholamines on energy-rich nucleotides and phosphorylated fraction contents.** Merouze P, Gaudemer Y. 1. The influence of catecholamines (adrenaline and noradrenaline) on energy metabolism of the rat myocardium has been studied by incubating slices of this tissue with these hormones and by following the levels of the different phosphorylated fractions and adenylic nucleotides. 2. Similar effects are obtained with both hormones, adrenaline being more effective. 3**. Catecholamines decrease significantly the total amount of phosphate while Pi content increases during the first 10 minutes of incubation; labile and residual phosphate contents increase at the beginning of incubation and decrease to the initial values afterwards. 4. ATP and ADP levels decrease significantly** with both hormones; however, the effect of noradrenalin on the ATP level needs a longer time of incubation. **The ATP/ADP ratios decrease after 5 minutes incubation and the total adenylic nucleotide content is severely decreased (35 per cent with adrenalin, after 20 minutes incubation). 5. Similar results have been obtained with other tissues; these results can explain the decrease of aerobic metabolism we observed under the same conditions.**

Eur J Pharmacol 1982 Jul 30;81(4):569-76**. Actions of serotonin antagonists on dog coronary artery.** Brazenor RM, Angus JA. **"Serotonin released from platelets may initiate coronary vasospasm** in patients with variant angina. If this hypothesis is correct, serotonin antagonists without constrictor activity may be useful in this form of angina. We have investigated drugs classified as serotonin antagonists on dog circumflex coronary artery ring segments in vitro. Ergotamine, dihydroergotamine, **bromocriptine, lisuride, ergometrine, ketanserin, trazodone, cyproheptadine and pizotifen caused non-competitive antagonism of serotonin concentration-response** curves. In addition, ketanserin, trazodone, bromocriptine and pizotifen inhibited noradrenaline responses in concentrations similar to those required for serotonin antagonism. All drugs with the exception of ketanserin, cyproheptadine and pizotifen

showed some degree of intrinsic constrictor activity." "Of the **drugs tested, ketanserin may be the most useful in variant angina since it is a potent 5HT antagonist, lacks agonist activity and has alpha-adrenoceptor blocking activity."**

Arch Mal Coeur Vaiss 1983 Feb;76 Spec No:3-6. **Role of autonomic nervous system in the pathogenesis of angina pectoris.** Yasue H. "The attacks of vasospastic angina or coronary spasm can be induced by injection of epinephrine, cold pressor test, Valsalva maneuver, and exercise." "The attacks of vasospastic angina can also be induced by injection of methacholine, a parasympathomimetic agent, and this reaction is suppressed by atropine, a parasympathetic blocking agent. Thus, **parasympathetic nervous system also seems to play a role in the production of vasospastic angina. The attacks of vasospastic angina can be easily induced by adrenergic or parasympathetic stimuli from midnight to early morning but is** usually not provoked by these stimuli in the daytime. Thus, there is circadian variation in the reactivity of coronary arteries to adrenergic or parasympathetic stimuli. There are also weekly, monthly and yearly variations of the reactivity of coronary arteries to these stimuli. Thus, **alpha adrenergic or parasympathetic activity is not the sole factor in the production of vasospastic angina.** Angina pectoris caused by increased myocardial oxygen demand is induced by infusion of isoproterenol, a beta adrenergic stimulant, and is suppressed by propranolol but not by phentolamine."

Nippon Yakurigaku Zasshi 1986 Mar;87(3):281-90. **[Vasoconstrictor responses of isolated pig coronary arteries].** [Article in Japanese] Ikenoue K, Kawakita S, Toda N. **"In helical strips of pig coronary arteries, histamine, serotonin, acetylcholine and a stable analogue of thromboxane A2 (9, 11-epithio-11, 12-methano TXA2: s-TXA2) produced a dose-dependent contraction. The histamine-induced contraction** was suppressed by treatment with chlorpheniramine, suggesting an involvement of H1 receptors. **Contractile responses to serotonin were attenuated by not only ketanserin, an S2 antagonist, but also by cinanserin and methysergide.**" "Contractile responses to histamine were potentiated by treatment with low concentrations of serotonin or s-TXA2. Contractile responses to serotonin were also potentiated by low concentrations of histamine or s-TXA2. Removal of the endothelium from pig coronary arterial strips potentiated contractions induced by serotonin, histamine and norepinephrine. These results suggest that, in addition to damaged endothelium, **integrating action of endogenous vasoconstrictors, including histamine, serotonin, TXA2 and norepinephrine, may play an important role in producing coronary vasospasm."**

Jpn Heart J 1987 Sep;28(5):649-61**. The role of parasympathetic nerve activity in the pathogenesis of coronary vasospasm.** Suematsu M, Ito Y, Fukuzaki H. To evaluate the role of the autonomic nervous system, especially the parasympathetic nervous system, in the initiation mechanism of vasospastic angina pectoris (AP), the coefficient of R-R interval variation (CV) on the electrocardiogram (ECG) and plasma catecholamine concentration were measured in 25 patients with vasospastic AP, 10 patients with effort AP and 12 control subjects. CV which has been recognized as reflecting parasympathetic nervous system activity was calculated from 100 consecutive heart beats on the ECG and represented as the percentage of standard deviation of the R-R interval per mean R-R interval. Repeated measurements of **plasma catecholamine concentration revealed higher values at any sampling point throughout a day in patients with vasospastic AP than those in** control subjects. A distinctly higher CV was observed at night in the vasospastic AP group. **This elevated CV was abolished by atropine sulfate (1.5 mg/day per os). Pilocarpine injection (1.3 mg/10 kg B.W. subcutaneously) induced a marked increase** in CV that preceded the occurrence of chest pain and/or ischemic ECG changes in 5 patients with vasospastic AP. The **increment in CV at 10 min after pilocarpine administration was greater in vasospastic AP than in control subjects (p less than 0.05). It is concluded that enhanced parasympathetic activity may play a role in the initiation of coronary vasospasm associated with sympathetic hyperactivity.**

Science 1984 Mar 30;223(4643):1435-7. **Coronary arteries of cardiac patients are hyperreactive and contain stores of amines: a mechanism for coronary spasm.** Kalsner S, Richards R. Coronary arteries from hearts of cardiac patients contain significantly higher concentrations of histamine than do those from noncardiac patients. The coronary vessels of cardiac patients are also hyperresponsive to histamine and serotonin. These differences between groups of patients suggest an explanation for coronary artery spasm in heart disease.

Fed Proc 1985 Feb;44(2):321-5. **Coronary artery reactivity in human vessels: some questions and some answers.** Kalsner S. "It is now clear that human coronary arteries in vitro contract to acetylcholine but that relaxation is the only response observed in dog coronary vessels. **Acetylcholine is as powerful a constrictor of human coronary arteries, in terms of tension induced, as 5-hydroxytryptamine (5-HT) or histamine and is a substantially more powerful constrictor than norepinephrine.** Field stimulation of coronary artery strips caused a vasoconstriction that was partially antagonized by atropine (3.45 X10(-6) M)." "Coronary tissue from cardiac patients also contains stores of 5-HT and histamine, and the histamine levels are substantially increased above the values in vessels from noncardiac patients. Coronary artery spasm or contraction **probably can be initiated by diverse intrinsic and extrinsic influences, including autonomic discharge from either the parasympathetic or sympathetic nervous system or from histamine or 5-HT, and probably no one agent or entity is causative in all cases."**

Ann N Y Acad Sci 1969 Oct 14;164(2):517-9. **Induced carcinogenesis under various influences on the hypothalamus.** Kavetsky RE, Turkevich NM, Akimova RN, Khayetsky IK, Matveichuck YD.

Kavetsky RE, (editor) ***The Neoplastic Process and the Nervous System*,**Kiev, 1958.

Ann N Y Acad Sci 1966 Jan 21;125(3):933-45. **On the psychophysiological mechanism of the organism's resistance to tumor growth.** Kavetsky RE, Turkevich NM, Balitsky KP.

Patol Fiziol Eksp Ter 1971 Sep-Oct;15(5):3-10. **[Role of disorders in intra-cellular and neuro-humoral regulation in the development of the tumor process].** [Article in Russian] Kavetskii RE, Balitskii KP.

Mil'man, M.S., **The sympathetic nervous system and the source of tumors,** Problems of Oncology IX, 162-173, 1936.

Obstet Gynecol Surv 1977 May;32(5):267-81. **Estrogen and endometrial carcinoma.** Knab DR. "1. It has become evident that the estrogen secreting tumors of the ovary are associated with endometrial carcinoma, but this association is most easily observed in the postmenopausal patient where the incidence of carcinoma has been **reported at 10.3% (1. 02) to 24% (83). 2. The most consistent association of endometrial carcinoma is with polycystic ovarian disease, where 19 (34), 21 (152), and 25% (150) of young women with endometrial carcinoma had Stein-Leventhal syndrome (67).** 3. A very significant discovery became known in 1967 when the peripheral aromatization of delta4 androstenedione to estrone was reported by Kase (94) and MacDonald (111,112). Since that time we have learned that endometrial carcinoma patients have an increased peripheral conversion (139) (0.1% compared to 0.027%), which is similar to that found in obese and aging patients, by Hemsell, et al (77). This can be 2 to 4 times greater than the young adult or the patient without cancer." "Similarly patients with polycystic ovary disease, hyperthecosis and lipoid cell tumors of the ovary demonstrate androgen excess with extraglandular conversion to estrone (2). 4. It has become apparent that the principal estrogen in the postmenopausal patient is estrone and that the estrone-estradiol ratio in the serum is higher in postmenopausal women with corpus cancer than similar patients without cancer (135)." "5. With the lack of ovarian estrogen there is a relative excess of adrenal testosterone, dihydrotestosterone and delta4 androstenedione, the available precursors of extraglandular estrone (1). 6. With the passage of time **it appears that endometrial carcinoma is associated with hypothalamic "hyperactivity"** (31)...."

Endocrinology 2000 Mar;141(3):1059-72. **An increased intraovarian synthesis of nerve growth factor and its low affinity receptor is a principal component of steroid-induced polycystic ovary in the rat.** Lara HE, Dissen GA, Leyton V, Paredes A,

Fuenzalida H, Fiedler JL, Ojeda SR. A form of polycystic ovary (PCO) resembling some aspects of the human PCO syndrome can be induced in rats by a single injection of estradiol valerate (EV). An increase in sympathetic outflow to the ovary precedes, by several weeks, the appearance of cysts, suggesting the involvement of a neurogenic component in the pathology of this ovarian dysfunction. The present study was carried out to test the hypotheses that this change in sympathetic tone is related to an augmented production of ovarian nerve growth factor (NGF), and that this abnormally elevated production of **NGF contributes to the formation of ovarian cysts induced by EV. Injection of the steroid resulted in increased intraovarian synthesis of NGF** and its low affinity receptor, p75 NGFR. The increase was maximal 30 days after EV, coinciding with the elevation in sympathetic tone to the ovary and preceding the appearance of follicular cysts. Intraovarian injections of the retrograde tracer fluorogold combined with in situ hybridization to detect tyrosine hydroxylase (TH) messenger RNA-containing neurons in the celiac ganglion revealed that these changes in NGF/p75 NGFR synthesis are accompanied by selective activation of noradrenergic neurons projecting to the ovary. The levels of RBT2 messenger RNA, which encodes a beta-tubulin presumably involved in slow axonal transport, were markedly elevated, indicating that EV-induced formation of ovarian cysts is preceded by functional activation ofceliac ganglion neurons, including those innervating the ovary. Intraovarian administration of a neutralizing antiserum to NGF in conjunction with an antisense oligodeoxynucleotide to p75 NGFR, via Alzet osmotic minipumps, **restored estrous cyclicity and ovulatory capacity in a** majority of EV-treated rats. These functional changes were accompanied by restoration of the number of antral follicles per ovary that had been depleted by EV and a significant reduction in the number of both precystic follicles and **follicular cysts. The results indicate that the hyperactivation of ovarian sympathetic nerves seen in EV-induced PCO is related to an overproduction of NGF and its low affinity receptor in the gland. They also suggest that activation of this neurotrophic-neurogenic regulatory loop is a component of the pathological process by which EV induces cyst formation and anovulation in rodents. The** possibility exists that a similar alteration in neurotrophic input to the ovary contributes to the etiology and/or maintenance of the PCO syndrome in humans.

Acta Physiol Hung 1996;84(2):183-90. **Effects of hormones on the number, distribution and degranulation of mast cells in the ovarian complex of mice.** Jaiswal K, Krishna A. The changes in the number and degranulation pattern of mast cells varied with the types of hormonal treatment and ovarian compartment. **Luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH) and 17-beta estradiol (E2) treatment caused increase (P < 0.05) in the number of mast cells** in the hilum as compared with the controls. Increase (P < 0.05) in the number of mast cells in the whole ovarian complex was observed only following FSH and E2 treatment. All the hormones used in the present study increased the percentage degranulation of mast cells in the hilum. However, only LH, FSH and E2 increased the percentage degranulation of mast cells in other compartments of the ovary (medulla, bursa and cortex). TSH and ACTH failed to cause any increase in the percentage degranulation of mast cells in these compartments. The present findings indicate E2 to be the most potent among the hormones tested in causing degranulation of mast cells in all ovarian compartments.

Fertil Steril 2001 Jun;75(6):1141-7. **Increase in nerve fibers and loss of mast cells in polycystic and postmenopausal ovaries.** Heider U, Pedal I, Spanel-Borowski K. OBJECTIVE: To quantify nerve fibers and mast cells in human ovaries at different functional stages. DESIGN: Retrospective study. SETTING: Research laboratory of the university. SPECIMEN(S): 8 human ovaries in the follicular (cyclic) phase, 7 polycystic ovaries, and postmenopausal ovaries with (n=5) or without (n=7) hyperthecosis. MAIN OUTCOME MEASURE(S): Single- and double immunohistology for the S100 antigen in glial cells of autonomic nerve fibers, for chymase and tryptase in mast cells, and for the common leukocyte antigen on leukocytes. Histometric evaluation was also performed. INTERVENTION(S): None. RESULT(S): Polycystic ovaries contained significantly more S100-positive nerve fibers in the corticomedullary region than did cyclic ovaries (mean +/- SD per 2-mm(2) area, 476 +/- 136 and 224 +/- 133; P<.01). Postmenopausal ovaries with or without hyperthecosis had the highest density of nerve fibers. In cyclic and polycystic ovaries, more tryptase-positive mast cells than chymase-positive mast cells were found in the interstitial cortex and the medulla. In cyclic ovaries, areas with a moderate density of nerve fibers contained many mast cells. Hence, **with increasing nerve fiber density in polycystic ovaries, the number of mast cells decreased strikingly compared with cyclic ovaries (p<.001). Almost no mast cells were seen in postmenopausal ovaries** with and without hyperthecosis. The number of leukocyte antigen-positive leukocytes was similar in all groups. CONCLUSION(S): The high density of nerve fibers in polycystic and postmenopausal ovaries, together with a conspicuous decrease in mast cells, indicates altered neuroimmune communication.

Endocrinology 1993 Dec;133(6):2696-703. **Ovarian steroidal response to gonadotropins and beta-adrenergic stimulation is enhanced in polycystic ovary syndrome: role of sympathetic innervation.** Barria A, Leyton V, Ojeda SR, Lara HE. Experimental induction of a polycystic ovarian syndrome (PCOS) in rodents by the **administration of a single dose of estradiol valerate (EV) results in activation of the peripheral sympathetic neurons that innervate the ovary. This activation is evidenced by an increased capacity of ovarian nerve terminals to incorporate and release norepinephrine (NE), an increase in ovarian NE content, and a** decrease in ovarian beta-adrenergic receptor number in the ovarian compartments receiving catecholaminergic innervation. The present experiments were undertaken to examine the functional consequences of this **enhanced sympathetic outflow to the ovary.** The steroidal responses of the gland to beta-adrenergic receptor stimulation and hCG were examined in vitro 60 days after EV administration, i.e. at the time when follicular cysts are well established. EV-treated rats exhibited **a remarkable increase in ovarian progesterone and androgen responses to isoproterenol, a beta-adrenergic receptor agonist, with no changes in estradiol responsiveness. Basal estradiol release was, however, 50-fold higher than the highest levels released from normal ovaries at any phase of the estrous cycle.** The ovarian progesterone and androgen responses to hCG were enhanced in EV-treated rats, as were the responses to a combination of isoproterenol and hCG. Transection of the superior ovarian nerve (SON), which carries most of the catecholaminergic fibers innervating endocrine ovarian cells, dramatically reduced the exaggerated responses of all three steroids to both beta-adrenergic and gonadotropin stimulation. SON transection also reduced the elevated levels of ovarian NE resulting from EV treatment and caused up-regulation of beta-adrenoreceptors. Most importantly, SON transection restored estrous cyclicity and ovulatory capacity. The results indicate that the increased output of ovarian steroids in PCOS is at least in part due to an enhanced responsiveness of the gland to both catecholaminergic and gonadotropin stimulation. The ability of SON transection to restore a normal response indicates that the alteration in steroid output results from a deranged activation of selective components of the noradrenergic innervation to the ovary. These findings support the concept that **an alteration in the neurogenic control of the ovary contributes to the etiology of PCOS.**

Wilderness Environ Med 2001 Spring;12(1):8-12. **Alterations in autonomic nervous control of heart rate among tourists at 2700 and 3700 m above sea level.** Kanai M, Nishihara F, Shiga T, Shimada H, Saito S. "RESULTS: Both HF and LF heart rate variability **decreased according to the elevation of altitude**." "CONCLUSIONS: **At 2700 and 3700 m, the activity of the autonomic nervous system measured by heart rate variability was decreased** in untrained office workers. The sympathetic nervous system was dominant to the parasympathetic at 3700 m. These alterations in the autonomic nervous system might play some role in physical fitness at high altitudes."

Acta Neuroveg (Wien) 1967;30(1):557-63. **[Neuroautonomic reactivity of the skin during high mountain climate treatment of skin diseases].** [Article in German] Chlebarov S.

Munch Med Wochenschr 1966 Mar 18;108(11):589-92. **[Changes of the neurovegetative reactivity of the skin after Alpine climatic therapy].** [Article in German] Borelli S, Chlebarov S.

J Appl Physiol 1978 May;44(5):647-51. **Mechanism of the attenuated cardiac response to beta-adrenergic stimulation in chronic hypoxia.** Maher JT, Deniiston JC, Wolfe DL, Cymerman A. **"A blunting of the chronotropic and inotropic responses of the heart to beta-adrenergic stimulation occurs following chronic exposure to hypobaric hypoxia."** "Neither monoamine oxidase

activity nor norepinephrine level of any region of the heart was altered by chronic hypoxia. However, a twofold increase (P less than 0.001) **in catechol O-methyltransferase activity above sea-level values was found in both the atria and ventricles of the hypoxic animals.** Thus, the attenuation in cardiac responsiveness to beta-adrenoceptor stimulation in chronic hypoxia appears unrelated to the level of vagal activity, but may be attributable to enhanced enzymatic inactivation of catecholamines."

Acta Physiol Scand 1976 Jun;97(2):158-65. **Effects of respiratory alkalosis and acidosis on myocardial excitation.** Samuelsson RG, Nagy G. In anesthetized dogs electrocardiogram and monophasic action potentials (MAPs) were recorded from the right atrium and the right ventricle by intracardiac suction electrode technique. The animals were subjected, by means of ventilation with CO2 and hyperventilation, to periods of respiratory acidosis and respiratory alkalosis, respectively. **Pronounced respiratory acidosis induced an increased sympathetic activity** followed by a decrease in heart rate and prolongation of the A-V conduction time whereas the shape and duration of the atrial and ventricular MAPs remained unaltered. Arterial hypoxia in combination with pronounced respiratory acidosis did not influence the MAP durations. Respiratory **alkalosis resulted in an increased sympathetic influence on the heart activity** whereas the shape and duration of the atrial and the ventricular MAPs remained unaffected. **During pronounced hyperventilation with increasing central venous pressure an increased parasympathetic influence** on the heart activity with decrease in the heart rate, prolongation of the A-V conduction time and shortening of the atrial MAP duration was recorded.

Biull Eksp Biol Med 1978 Nov;86(11):525-8. **[Effect of neuromediators on acid-base status].** [Article in Russian] Lazareva LV, Bazarevich GI, Makarova LV. A relationship between the state of adrenergic, cholinergic, and serotoninergic systems, on the one hand, and the acid-alkaline balance of the organism, on the other hand, was revealed in sharp and chronic experiments on dogs. A surplus of each of the mediators was accompanied by respiratory alkalosis, and its deficiency--by combined respiratory and metabolic acidosis.

Can J Physiol Pharmacol 1987 May;65(5):1078-85. **Pathophysiology of pH and Ca2+ in bloodstream and brain.** Somjen GG, Allen BW, Balestrino M, Aitken PG. The highlights of the literature and our work on tetany and hyperventilation are reviewed. Our studies concern the following: (1) the changes of [Ca2+] in circulating plasma caused by respiratory and "metabolic" acidosis and alkalosis; (2) critical plasma [Ca2+] levels associated with signs of tetany and neuromuscular blockade; (3) changes in cerebral [Ca2+]o caused by hypo- and hyper-calcaemia, and the changes in cerebral [Ca2+]o and pHo caused by acute systemic acidosis and alkalosis; and (4) effects of changing [Ca2+]o and pHo levels on synaptic transmission in hippocampal formation. Our main conclusions are (1) changes of plasma [Ca2+] caused by "metabolic" pH changes are greater than those associated with varying CO2 concentration; (2) acute systemic [Ca2+] changes are associated with small cerebral [Ca2+]o changes; (3) the decreases in systemic and cerebral [Ca2+]o caused by hyperventilation are too small to account for the signs and symptoms of hypocapnic tetany; (4) moderate decrease of [Ca2+]o depresses and its increase enhances synaptic transmission in **hippocampal formation; and (5) H+ ions in extracellular fluid have a weak depressant effect on neuronal excitability. CO2 is a strong depressant, which is only partly explained by the acidity of its solution. CO2 concentration is a significant factor in controlling cerebral function.**

J Hirnforsch 1991;32(5):659-664. **Normalization of protein synthesis and the structure of brain dystrophic neurons after the action of hypoxia, 10% NaCl and organ-specific RNA.** Polezhaev LV, Cherkasova LV, Vitvitsky VN, Timonin AV N. I. Vavilov Institute of General Genetics, USSR Academy of Sciences, Moscow. It was shown previously (Polezhaev and Alexandrova, 1986) that hypoxic hypoxia causes mass (up to 30%) diffuse dystrophy of brain cortex and hippocamp neurons in rats, disturbances in the higher nervous activity, reduction of protein, RNA synthesis in neurons and of DNA synthesis in the whole brain cortex. Transplantation of embryonic nervous tissue (ENT) in one of the hemispheres normalizes all the above abnormalities observed in some neurologic and mental diseases in humans. However, transplantation may entail injuries of parenchyma and brain blood vessels. This forces researchers to search for another biological method similar by its action but safer and simpler. ENT transplantation has a dual action: 1) formation of biologically active substances (BAS) releasing from the ENT transplant and from the host brain nervous tissue upon operation; 2) establishment of synaptic connections between the transplant and host neurons. Previously we (Vitvitsky, 1987) described the isolation of BAS from rat forebrain in the form of organ-specific RNA. The latter was injected intraperitoneally several times to post-hypoxic rats in which 30 min prior to that the blood-brain barrier (BBB) was opened by injecting intravenously and intraperitoneally 10% NaCl solution without damaging the host brain. At the beginning 10% NaCl increased the destruction of brain cortical neurons and then stimulated protein synthesis in them. RNA injections stimulated the synthesis in cortical neurons and normalized their structure. Thus, we propose a safe and simple method for normalization of dystrophic neurons which can be used after certain improvement for curing neurodegenerative and neuropsychic diseases in humans.

Group processes

The trouble with writing and painting is that they are considered to be solitary and individualistic activities. In the 20th century, the idea developed that they were "expressive," rather than communicative, as if there could be any sane distinction between those. The result was that much of 20th century poetry and painting was insane. The products of insanity aren't necessarily worthless, but they are less than they could be.

When the writer and painter are in close contact with responsive people, their product is adjusted to, and enriched by, the reactions they evoke.

J Cardiovasc Pharmacol 1987;10 Suppl 2:S94-8; discussion S99. **The effect of beta-blockade on platelet function and fibrinolytic activity.** Winther K. Department of Clinical Chemistry, Rigshospitalet, Copenhagen, Denmark. Two groups of hypertensives and a group of migraine sufferers were tested during treatment with the nonselective beta-blocker propranolol and the beta 1-selective metoprolol. During treatment with propranolol, an increased platelet aggregability and a decrease in platelet content of cyclic AMP were seen when compared with metoprolol treatment. In addition, propranolol treatment increased the plasma level of adrenaline as well as the euglobulin clot lysis time. types of monoamine oxidase, adrenaline

45: Br J Pharmacol 1982 Feb;75(2):269-86 Coronary vasoconstrictor and vasodilator actions of arachidonic acid in the isolated perfused heart of the rat. Belo SE, Talesnik J. The administration of arachidonic acid (AA) to the isolated perfused heart of the rat usually produced biphasic coronary responses characterized by initial vasoconstriction followed by prolonged vasodilatation. However, some responses were predominantly vasoconstrictor or vasodilator. The non-steroidal anti-inflammatory agents (NSAA) indomethacin (1-5 mg/l) and naproxen (12.5-25 mg/1) reversibly inhibited both phases of the response induced by AA. Pretreatment of animals with indomethacin (5 mg/kg) or naproxen (25 mg/kg) daily, resulted in unaltered coronary response to AA. Subsequent addition of NSAA to the perfusate produced inhibition of the AA effect. Short infusions of acetylsalicylic acid at low concentrations (2.9 micrograms/ml), dipyridamole (0.6 micrograms/ml) and sulphinpyrazone (28.7 micrograms/ml) selectively inhibited the vasoconstrictor phase of the response to AA. It was confirmed that metabolic coronary dilatation induced by cardiostimulation was inhibited by prolonged AA administration; this effect was prevented by NSAA pretreatment. Reactive hyperaemic responses to short lasting occlusions of coronary inflow **were unaffected by NSAA. Linolenic, linoleic, dihomo-gamma-linolenic and oleic acid usually produced decreases in coronary flow which were unaffected by NSAA, dipyridamole or sulphinpyrazone. Intra-aortic injections of AA, prostacyclin (PGI2) and prostaglandin E2 (PGE2) in the intact rat produced a dose-dependent decrease in blood pressure with the AA response inhibited by indomethacin. PGI2** and PGE2 produced long lasting coronary vasodilatation in the isolated heart. The coronary actions of AA appear to be due to its transformation, within the easily accessible vascular wall, into prostaglandin and thromboxane-like **substances. We suggest that a vasoconstrictor thromboxane A2-like substance may be responsible for coronary vasospasm. Coronary insufficiency may**

**also result from an inhibition of compensatory metabolic coronary dilatation by increased synthesis of PGE2 within the myocardial cell.**

42: Br Heart J 1983 Jan;49(1):20-5 **Platelet reactivity and its dependence on alpha-adrenergic receptor function in patients with ischaemic heart disease.** Yokoyama M, Kawashima S, Sakamoto S, Akita H, Okada T, Mizutani T, Fukuzaki H. We studied 57 patients admitted to hospital with ischaemic heart disease, including nine patients with variant angina, to evaluate platelet reactivity and its dependence on alpha-adrenergic receptor function. The threshold concentration for biphasic platelet aggregation in response to adrenaline and adenosine diphosphate was measured in fresh platelet rich plasma. There were age related alterations in platelet responsiveness to adrenaline. In 27 age matched control subjects platelets showed adrenaline induced aggregation at a concentration higher than 0.1 mumol. The threshold concentrations for adrenaline and adenosine diphosphate were 0.91 mumol and 4.68 mumol. In 16 patients with acute infarction, 14 with old infarction, nine with effort angina, and nine with rest angina, mean values of platelet aggregation threshold for both adrenaline and adenosine diphosphate were not altered significantly when compared with control subjects. In contrast, the values for adrenaline and adenosine diphosphate in nine patients with variant angina were 0.012 mumol and 2.24 mumol and seven of them showed obvious platelet hyperactivity to adrenaline at a concentration lower than 0.1 mumol. The threshold concentration for adrenaline induced aggregation did not correlate with serum cholesterol and triglyceride levels.

Am Heart J 1985 Jun;109(6):1264-8. Reduction of plasma norepinephrine levels in response to brief coronary occlusion in experimental dogs. Haneda T, Arai T, Kanda H, Ikeda J, Takishima T. Although an increased plasma norepinephrine (NE) level is sometimes observed during angina pectoris, it is difficult to say whether sympathetic overflow is its cause. The left anterior descending coronary artery was occluded by intracoronary balloon for 3 minutes in 12 closed-chest anesthetized dogs. During occlusion, heart rate did not change but aortic pressure slightly decreased. Occlusion caused a significant reduction in both NE levels in the aorta (177 +/- 17 to 134 +/- 16 pg/ml, p less than 0.01) and in the great cardiac vein (GCV) 296 +/- 44 to 249 +/- 44 pg/ml, p less than 0.01). After surgical vagotomy, the occlusion increased NE levels in the aorta (227 +/- 44 to 278 +/- 43 pg/ml, p less than 0.01) and in GCV (384 +/- 76 to 444 +/- 81 pg/ml, p less than 0.01), showing the release of vagal inhibition. These results may be applicable to **patients with transient anterior myocardial ischemia; if plasma NE increases without marked hemodynamic changes, it is suggested that the sympathetic overflow is not a result but a possible cause of the ischemia.**

25: Exp Mol Pathol 1986 Apr;44(2):138-46 **Intimal thickening and the distribution of vasomotor nerves in the mechanically injured dog coronary artery.** Taguchi T, Ishii Y, Matsubara F, Tanaka K. Intimal injury and atherosclerotic change seem to be causative factors linked to spasm of the coronary artery. Intimal thickening was produced by mechanical injury to the endothelium of the canine coronary artery and we investigated the distribution of adrenergic, cholinergic, and peptidergic nerves in the coronary arteries. Although adrenergic and cholinergic nerves were not altered in **density, neuron specific enolase positive nerve fibers were increased in number in dogs killed 1 and 3 months after injury. Substance P-containing fibers were also increased at 3 months after the induced injury.**

24: J Am Coll Cardiol 1986 Jul;8(1 Suppl A):42A-49A **Mechanisms of coronary spasm of isolated human epicardial coronary segments excised 3 to 5 hours after sudden death.** Vedernikov YP. Isolated segments of epicardial coronary artery with and without severe atherosclerotic lesions excised from human hearts 3 to 5 hours after sudden coronary death demonstrated spontaneous contractile activity that was dependent on the external calcium level and was inhibited by calcium antagonists and activation of beta-adrenoceptors (isoproterenol and high concentrations of norepinephrine). Isoproterenol, with a median effective dose (ED50) of 6.3 X 10(-7) M, relaxed coronary segments that had been precontracted with 30 mM **potassium. Stimulation of the alpha-adrenoceptors activated spontaneous contractions and increased tension. Norepinephrine ED50 (in the presence of 10(-6) M propranolol) was 2.3 X 10(-7) M, and tension at a maximal concentration of 10(-4) M was 385.4 +/- 51.4 mg. The ED50 for acetylcholine and histamine, the potent activators of coronary segment tone and phasic contractility, was 3.98 X** 10(-7) and 8.9 X 10(-7) M, respectively; the maximal increase in tension was 1,079.5 +/- 175 (at 10(-4) M) and 1,131.3 +/- 302 mg (at 10(-5) M), respectively. Acetylcholine and histamine increased whereas high concentrations of norepinephrine failed to inhibit rhythmic activity and tension of coronary artery segments with severe atherosclerotic lesions. Membrane electrogenic mechanisms and ways of activating the contractile elements of human coronary artery smooth muscle are discussed.

Pharmacol Rev 2000 Dec;52(4):595-638. **The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system.** Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. Inflammatory Joint Diseases Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA. The brain and the immune system are the two major adaptive systems of the body. During an immune response the brain and the immune system "talk to each other" and this process is essential for maintaining homeostasis. Two major pathway systems are involved in this cross-talk: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This overview focuses on the role of SNS in neuroimmune interactions, an area that has received much less attention than the role of HPA axis. Evidence accumulated over the last 20 years suggests that **norepinephrine (NE) fulfills the criteria for neurotransmitter/neuromodulator in lymphoid organs.** Thus, primary and secondary lymphoid organs receive extensive sympathetic/noradrenergic innervation. Under stimulation, NE is released from the sympathetic nerve terminals in these organs, and the target immune cells express adrenoreceptors. Through stimulation of these receptors, locally released NE, or circulating catecholamines such as epinephrine, affect **lymphocyte traffic, circulation, and proliferation, and modulate cytokine production and the functional activity of different lymphoid cells.** Although there exists substantial sympathetic innervation in the bone marrow, and particularly in the thymus and mucosal tissues, our knowledge about the effect of the sympathetic neural input on **hematopoiesis, thymocyte development, and mucosal immunity** is extremely modest. In addition, recent evidence is discussed that **NE and epinephrine, through stimulation of the beta(2)-adrenoreceptor-cAMP-protein kinase A pathway, inhibit the production of type 1/proinflammatory cytokines,** such as interleukin (IL-12), tumor necrosis factor-alpha, and interferon-gamma by antigen-presenting cells and T helper (Th) 1 cells, whereas they **stimulate the production of type 2/anti-inflammatory cytokines such as IL-10** and transforming growth factor-beta. Through this **mechanism, systemically, endogenous catecholamines may cause a selective suppression of Th1 responses and cellular immunity, and a Th2 shift toward dominance of humoral immunity. On the other hand, in certain local responses, and under certain conditions, catecholamines may actually boost regional immune** responses, through induction of IL-1, tumor necrosis factor-alpha, and primarily IL-8 production. Thus, the activation of SNS during an immune response might be **aimed to localize the inflammatory response, through induction of neutrophil accumulation and stimulation of more specific humoral immune responses, although systemically it may suppress Th1 responses, and, thus protect the organism from the detrimental effects of proinflammatory cytokines and other products of activated macrophages.** The above-mentioned immunomodulatory effects of catecholamines and the role of SNS are also discussed in the context of their clinical implication in certain **infections, major injury and sepsis, autoimmunity, chronic pain and fatigue syndromes, and tumor growth.** Finally, the pharmacological manipulation of the sympathetic-immune interface is reviewed with focus on new therapeutic strategies using selective alpha(2)- and beta(2)-adrenoreceptor agonists and antagonists and inhibitors of phosphodiesterase type IV in the treatment of experimental models of autoimmune diseases, fibromyalgia, and chronic fatigue syndrome.

Am J Physiol Cell Physiol 2000 Nov;279(5):C1665-74. **beta-adrenergic receptor/cAMP-mediated signaling and apoptosis of S49 lymphoma cells.** Yan L, Herrmann V, Hofer JK, Insel PA. Department of Pharmacology, University of California, San Diego, La Jolla,

California 92093-0636, USA. **beta-Adrenergic receptor (betaAR) activation and/or increases in cAMP regulate growth and proliferation of a variety of cells and, in some cells, promote cell death. In the current studies we addressed the mechanism of this growth reduction** by examining betaAR-mediated effects in the murine T-lymphoma cell line S49. Wild-type S49 cells, derived from immature thymocytes (CD4(+)/CD8(+)) undergo growth arrest and subsequent death when treated with agents that increase cAMP levels (e.g., betaAR agonists, 8-bromo-cAMP, cholera toxin, forskolin). Morphological and biochemical criteria indicate that this cell death is a result of apoptosis. In cyc(-) and kin(-) S49 cells, which lack G(s)alpha and functional protein kinase A (PKA), respectively, betaAR activation of G(s)alpha and cAMP action via PKA are critical steps in this apoptotic pathway. S49 cells that overexpress Bcl-2 are resistant to cAMP-induced apoptosis. We conclude that betaAR activation induces apoptosis in immature T lymphocytes via G(s)alpha and PKA, while overexpression of Bcl-2 prevents cell death. betaAR/cAMP/PKA-mediated apoptosis may provide a means to control proliferation of immature T cells in vivo.

Carcinogenesis 2001 Mar;22(3):473-9. **Beta-adrenergic growth regulation of human cancer cell lines derived from pancreatic ductal carcinomas.** Weddle DL, Tithoff P, Williams M, Schuller HM. Carcinogenesis and Developmental Therapeutics Program, College of Veterinary Medicine, University of Tennessee, 2407 River Drive, Knoxville, TN 37996, USA. Exocrine ductal carcinoma of the pancreas has been associated with smoking, and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) causes this cancer type in laboratory rodents. Current knowledge on the growth regulation of this malignancy is extremely limited. Recent studies have shown overexpression of cyclooxygenase 2 (COX 2) and 5-lipoxygenase (5-lipox) in exocrine pancreatic carcinomas, **suggesting a potential role of the arachidonic acid (AA) cascade in the regulation of this cancer type. In support of this interpretation, our data show high basal levels of AA release in two human cell lines derived from exocrine ductal pancreatic carcinomas.** Both cell lines expressed m-RNA for beta2-adrenergic receptors and beta1-adrenergic receptors. Radio-receptor assays showed that beta2-adrenergic receptors predominated over beta1-adrenergic receptors. beta2-Adrenergic antagonist ICI118,551 **significantly reduced basal AA release and DNA synthesis** when the cells were maintained in complete medium. DNA synthesis of the cell line (Panc-1) with an activating point mutation in codon 12 of the ki-ras gene was significantly stimulated by NNK when cells were maintained in complete medium and this **response was inhibited by the beta-blocker ICI118,551, the COX-inhibitor aspirin, or the 5-lipox-inhibitor MK-886.** The cell line without ras mutations (BXPC-3) did not show a significant response to NNK in complete medium. When the assays were conducted in serum-free medium, both cell lines demonstrated increased DNA synthesis in response to NNK, an effect inhibited by the beta2-blocker, aspirin, or MK-886. Panc-1 cells were more sensitive to the stimulating effects of NNK and less responsive to the inhibitors than BXPC-3 cells. Our findings are in accord with a recent report which has identified NNK as a beta-adrenergic agonist and suggest beta-adrenergic, AA-dependent regulatory pathways in pancreatic cancer as a novel target for cancer intervention strategies.

Shock 2000 Jul;14(1):60-7. Terbutaline prevents circulatory failure and mitigates mortality in rodents with endotoxemia. Wu CC, Liao MH, Chen SJ, Chou TC, Chen A, Yen MH. Department of Pharmacology, National Defense Medical Center, Taipei, ROC, Taiwan. Septic shock is characterized by a decrease in systemic vascular resistance. Nevertheless, regional increases in vascular resistance can occur that may **predispose mammals to organ dysfunction, including the acute respiratory** distress syndrome. In the host infected by endotoxin (lipopolysaccharide, LPS), the expression and release of proinflammatory tumor necrosis factor-alpha (TNFalpha) rapidly increases, and this cytokine production is regulated by agents elevating cyclic AMP. In this report, we present evidence that **terbutaline, a beta2-agonist, inhibits TNFalpha production and enhances interleukin-10 (IL-10) release in the anesthetized rat treated with LPS. In addition, an overproduction of nitric oxide (NO, examined by its metabolites nitrite/nitrate) by inducible NO synthase (iNOS, examined by western blot analysis) is attenuated by pretreatment of LPS rats with terbutaline. Overall,** pretreatment of rats with terbutaline attenuates the delayed hypotension and prevents vascular hyporeactivity to norepinephrine. In addition, pretreatment of mice with terbutaline also improves the survival in a model of severe endotoxemia. The infiltration of polymorphonuclear neutrophils into organs (e.g., lung and liver) from the surviving LPS mice treated with terbutaline was reduced almost to that seen in the normal controls. These findings suggest that the inhibition of TNFalpha and NO (via iNOS) production as well as the increment of IL-10 production contribute to the beneficial effect of terbutaline in animals with endotoxic shock.

Ann Endocrinol (Paris) 1977;38(6):421-6. [Hyperestrogenism in the woman during the reproductive period]. [Article in French] Kuttenn F.

Br J Obstet Gynaecol 1976 Aug;83(8):593-602. Polycystic ovarian disease. Duignan NM. **Sex hormone binding globulin (SHBG) capacity was reduced in 9 of 31 patients with polycystic ovarian (PCO) disease and the mean level in PCO patients was significantly less (p less than 0.001) than normal. Serum testosterone levels** were elevated in 21 of 32 PCO patients and the mean level was significantly elevated (p less than 0.001). Serum androstenedione values were raised in 17 of 31 patients and the mean value was also significantly raised (p less than 0.001). Serum dehydroepiandrosterone sulphate (DHAS) concentrations were elevated in only 2 of 14 patients. Urinary 17-oxo and 17-oxogenic steroids were normal in all patients studied. Basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were normal but LH release following injection of luteinizing hormone-releasing hormone (LH-RH) was enhanced. A highly significant negative correlation (r=--0.449; p less than 0.01) was found between the logarithm of testosterone and the logarithm of LH levels. Serum prolactin concentrations were elevated in 4 of 21 PCO patients. Thyroid-stimulating hormone (TSH) values were normal. Eighteen of 20 patients ovulated following treatment with clomiphene and nine became pregnant. Five of 12 of patients treated with oestrogen/progesterone preparations noticed an improvement in their hirsutism. It is **suggested that the normal cyclical release of LH is inhibited in PCO** disease by a negative feedback by androgens to the hypothalamus or the pituitary, and that wedge resection should be reserved for patients in whom other forms of treatment have failed.

Nouv Presse Med 1976 Apr 10;5(15):975-9. [Secretion of gonadotropins during sleep. Changes during secondary amenorrheas]. [Article in French] Passouant P, Crastes de Paulet A, Descomps B, Besset A, Billiard M. 4 females with secondary amenorrheas underwent sleep polygraphic recordings together with blood samples for measurements of LH, FSH and GH, 3 normal females served as controls. Among normal subjects LH and FSH secretion showed a pulsating pattern around the time of ovulation, appearing as secretory episodes throughout the night, without any relationship with sleep stages. In amenorrheas, 3 types of abnormalities could be identified: the first was a lack **of secretory episodes of LH and FSH associated with an abnormal pattern of GH (9 subjects). The second was an hypersecretion of LH and a decrease of FSH secretion together with a normal secretion of GH in 4 subjects with a Stein-Leventhal syndrome. The last one was an hypersecretion of LH and FSH** together with a normal pattern of GH in a subject with an early menopause. These results are discussed according to the present data on the part of neurotransmission in the regulation of ovulation and the 2 types of sleep. Furthermore secretory abnormalities of LH and FSH together with a disconnection between GH secretion and the stages of sleep lead to question the possibility of interrelationships in the secretory mechanisms of these different hormones.

Cancer 1997 Feb 1;79(3):494-9. Comment in: Cancer. 1997 Oct 1;80(7):1360-2. Association of Stein-Leventhal syndrome with the incidence of postmenopausal breast carcinoma in a large prospective study of women in Iowa. Anderson KE, Sellers TA, Chen PL, Rich SS, Hong CP, Folsom AR. Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, USA. BACKGROUND: The Stein-Leventhal syndrome (SLS), first described in 1935, is characterized by infertility, hyperandrogenization, and obesity. Because this phenotype represents an aggregation of risk factors for postmenopausal breast carcinoma, and because in general, a hormonal imbalance underlies the disorder, the authors examined the association between self-reported SLS and breast carcinoma incidence in a cohort of 34,835 cancer-free women assembled in 1986 and followed through 1992. METHODS: All participants were between the ages of 55 and 69 and held a valid Iowa driver's license. A total of 472 women in the cohort (1.35%) reported a history of SLS at baseline. Incident cases of breast carcinoma were identified annually using the State Health Registry of Iowa. Data were analyzed using Cox proportional hazards regression. RESULTS: During

the follow-up period, there were 883 incident breast carcinomas, 14 among women reporting a history of SLS. Women with SLS were more likely than women without SLS to report fertility problems and menstrual irregularities, but there were no significant differences observed regarding body mass index (BMI). Although women with SLS were 1.8 times as likely to report benign breast disease than women without SLS ($P < 0.01$), they were not more likely to develop breast carcinoma (relative risk [RR] = 1.2; 95% confidence interval [CI] = 0.7-2). Adjustment for age at menarche, age at menopause, parity, oral contraceptive use, BMI, waist-to-hip ratio, and family history of breast carcinoma lowered the RR to 1 (95% CI = 0.6-1.9. CONCLUSIONS: Despite the high risk profiles of some women with SLS, these results do not suggest that the syndrome per se is associated with an increased risk of postmenopausal breast carcinoma.

Am J Epidemiol 1991 Oct 15;134(8):818-24. Comment in: Am J Epidemiol. 1992 Aug 1;136(3):372-3. Polycystic ovaries and the risk of breast cancer. Gammon MD, Thompson WD. Division of Epidemiology, Columbia University School of Public Health, New York, NY. Data from a case-control study that was conducted between 1980 and 1982 were analyzed to investigate the possible association between polycystic ovaries and the risk of breast cancer. The multicenter, population-based study included in-home interviews with 4,730 women with breast cancer and 4,688 control women **aged 20-54 years. The age-adjusted odds ratio for breast cancer among women with a self-reported history of physician-diagnosed polycystic ovaries was 0.52 (95% confidence interval 0.32-0.87). The inverse association was not an artifact of infertility, age at first birth, or surgical menopause. Because women with this syndrome have abnormal levels of certain endogenous hormones, the observation of a low risk of breast cancer in this group may provide new insights into hormonal influences on breast cancer.**

Clin Endocrinol (Oxf) 1996 Mar;44(3):269-76. Polycystic ovaries in pre and post-menopausal women. Birdsall MA, Farquhar CM. Department of Obstetrics and Gynaecology, National Women's Hospital, Auckland, New Zealand. **OBJECTIVE: Polycystic ovaries have been diagnosed in more than 20% of premenopausal women using ultrasound. The aim of this study was to determine whether polycystic ovaries exist in post-menopausal women. DESIGN: Two groups of** women were studied; group 1 consisted of 18 post-menopausal volunteers and group 2 comprised 142 women, 94 of whom were post-menopausal who had recently undergone coronary angiography. MEASUREMENTS: Transabdominal and transvaginal ultrasound scans were performed and measurements made of uterine area, endometrial thickness and ovarian volume. The morphological appearance of the ovaries was also noted. Fasting blood samples were taken. Medical and menstrual questionnaires were completed. RESULTS: Polycystic ovaries were found in 8/18 **(44%) of group 1 and 60/142 (42%) in group 2. Polycystic ovaries were detected in 35/94 (37%) of the post-menopausal women in group 2. Post-menopausal women with polycystic ovaries had larger ovaries containing more follicles compared with post-menopausal women with normal ovaries. Post-menopausal women with** polycystic ovaries had higher serum concentrations of testosterone and triglycerides than had post-menopausal women with normal ovaries. CONCLUSIONS: Polycystic ovaries can be detected in post-menopausal women and have some of the same endocrine abnormalities which are evident in premenopausal women with polycystic ovaries, that is, raised serum concentrations of testosterone and triglycerides.

Cancer Causes Control 1996 Nov;7(6):605-25. Comment in: Cancer Causes Control. 1996 Nov;7(6):569-71. Nutrition, hormones, and breast cancer: is insulin the missing link? Kaaks R. International Agency for Research on Cancer, Lyon, France. Breast cancer incidence rates are high in societies with a Western lifestyle characterized by low levels of physical activity, and by an energy-dense diet rich in total and saturated fat and refined carbohydrates. Epidemiologic studies, so far mostly on postmenopausal women, have shown that breast cancer risk is increased in hyperandrogenic women, with decreased levels of plasma sex-hormone binding globulin, and with increased levels of testosterone and of free estrogens. This paper describes the role of hyperinsulinemia as a hysiologic link between nutritional lifestyle factors, obesity, and the development of a hyperandrogenic endocrine profile, and reviews evidence that may or may not support the theory that chronic hyperinsulinemia is an underlying cause of breast cancer. An hypothesis is presented, stipulating that breast cancer risk is increased not only in hyperandrogenic postmenopausal women, but also in premenopausal women with mild hyperandrogenism and normal (ovulatory) menstrual cycles. The author suggests further investigation as to whether there is a positive association between risk of breast cancer before menopause and ubclinical forms of the polycystic ovary syndrome (PCOS), and to what extent iet and physical activity during childhood, by modulating the degree of insulin esistance during adolescence, may or may not be determinants of a PCO-like hyperandrogenic endocrine profile persisting into adulthood.

Akush Ginekol (Mosk) 1990 Sep;(9):61-3. [The therapeutic effect of parlodel in the polycystic ovary syndrome]. [Article in Russian] Soboleva EL, Komarov EK, Potin VV, Svechnikova FA. Parlodel (2.5-50 mg/day) has been given for 1 to 7 days to 33 patients with the polycystic ovary syndrome (POS). The ovulatory menstrual cycle returned in 10 (30%) patients and 4 of them conceived. Pretreatment cycle disturbance persisted in 6 (18%) patients. **Parlodel reduced mid-follicular mean blood LH levels** to values of normal women. Some decrease in blood testosterone levels occurred only in the second phase of the cycle. Estradiol test in 6 patients showed normal positive and negative feedbacks in the hypothalamic-pituitary-ovarian axis. Parlodel treatment reduced basal and estradiol stimulated pituitary gonadotropin secretion. It is suggested that parlodel may be used in ovulation induction in a proportion of POS patients.

polycystic menopausal sympathetic estrogen parasympathetic, antimitochondrial, both can have a protective function, though in excess the inhibition itself is toxic.

Mast cells: hair growth, angiogenesis, cancer, MS, asthma. Nervous control of insulin,7:

Am J Obstet Gynecol 1993 Nov;169(5):1223-6. Comment in: Am J Obstet Gynecol. 1994 Dec;171(6):1673 **Excessive estradiol secretion in polycystic ovarian disease.** Benjamin F, Toles AW, Seltzer VL, Deutsch S. Department of Obstetrics and Gynecology, Queens Hospital Center, Jamaica, NY 11432. Polycystic ovarian disease is both a hyperestrogenic and a hyperandrogenic syndrome, and all studies have shown that hyperestrogenemia is the result of an elevation of estrone with plasma estradiol levels in the normal follicular range. Because a literature search failed to reveal any report of polycystic ovarian disease with significantly elevated estradiol levels, we report a case in which the plasma estradiol was so massively elevated as to mimic an estrogen-producing neoplasm. This case also suggests that although polycystic ovarian disease is a very rare cause of such excessive estradiol production, it should be included in the differential diagnosis of estrogen-producing neoplasms.

Nephron 1983;33(4):253-6. **Influence of inhibitor of glucose utilization on the blood platelet function.** Tison P, Kubisz P, Cernacek P, Dzurik R. The **inhibition of glycolysis** by an inhibitor of glucose utilization isolated from urine of the uremic subjects reflects in: (1) decreased platelet **aggregation induced by adenosine diphosphate, adrenaline, or collagen,** respectively; (2) decreased platelet factor 4 release induced by the same inductors; (3) decreased availability of platelet factor 3, and (4) inhibition of retraction of reptilase clot. It is concluded that the inhibition of glycolysis by 'inhibitor of glucose utilization' contributes to the functional changes of platelets and thus to the alteration of hemostasis in uremic patients.

Energy: vasodilate, bronchoconstrict, secrete/leak, swell, grow, tumefy. Invasion by sympathetic balances the chronic stimulation by mast cells, platelets, pituitary hormones, locally formed estrogen, and the other mediators of stress.

Res Exp Med (Berl) 1987;187(5):385-93. **Possible interaction of platelets and adrenaline in the early phase of myocardial infarction.** Seitz R, Leising H, Liebermann A, Rohner I, Gerdes H, Egbring R. **It is known that in most cases of transmural acute myocardial infarction a platelet clot originates within a coronary artery. In acute myocardial infarction patients increased levels of the plasma catecholamines adrenaline and noradrenaline as well as the platelet release proteins platelet factor 4**

**and beta-thromboglobulin have been reported.** In this study, significantly higher values were found of platelet factor 4 (P less than 0.0001) and beta-thromboglobulin (P less than 0.002) in 17 acute myocardial infarction patients as compared to 17 control patients (on intensive care due to non-cardiac disorders), while the plasma levels of adrenaline and noradrenaline were not different. Positive correlations were obtained between the two catecholamines and the platelet products in the control group and between adrenaline and both platelet factor 4 (r = 0.715, P less than 0.01) and beta-thromboglobulin (r = 0.547, P less than 0.05) in the acute myocardial infarction patients. The data suggest that a stimulation of the platelets by adrenaline may facilitate in vitro activation during sampling in patients with high catecholamine load. On the other hand, a "preactivation" of the platelets by an increase of adrenaline might be of significance for thrombus formation in acute myocardial infarction.

Anesthesiology 1991 Jun;74(6):973-9. Comment in: Anesthesiology. 1992 Mar;76(3):475. Magnesium inhibits the hypertensive but not the cardiotonic actions of low-dose epinephrine. Prielipp RC, Zaloga GP, Butterworth JF 4th, Robertie PG, Dudas LM, Black KW, Royster RL. Intravenous magnesium supplementation is often used to control cardiac arrhythmias and coronary artery vasospasm resulting from disturbances of magnesium homeostasis after coronary artery bypass surgery. Many such patients also require inotropic drug support of depressed myocardial function. However, increased serum magnesium concentrations directly depress cardiac contractility in animals and may interfere with catecholamine actions. To determine whether small intravenous doses of magnesium sulfate ($MgSO_4$) interfere with the cardiotonic actions of epinephrine, we examined the hemodynamic effects of $MgSO_4$ and epinephrine infusion in 17 cardiac surgical patients on their 1st postoperative day in a prospective, controlled study. In 11 patients, infusion of $MgSO_4$ (7-mg.kg-1 bolus followed by 10 mg.kg-1.h-1 as a continuous infusion) increased serum magnesium concentrations by 44% (mean +/- standard error of the mean [SEM] of 0.8 +/- 0.1 to 1.2 +/- 0.1 mM; P less than 0.01) but had no significant effect on heart rate; mean arterial, central venous, or pulmonary arterial occlusion pressures; or cardiac output. Epinephrine infusion (30 ng.kg-1.min-1) significantly increased cardiac index (2.7 +/- 0.1 to 3.1 +/- 0.21.min-1.m-2; P less than 0.05); this effect was not altered by $MgSO_4$ administration (n = 11). However, $MgSO_4$ significantly blunted epinephrine's hypertensive action and prevented a significant increase in mean arterial pressure during concurrent $MgSO_4$-epinephrine administration. Six placebo control patients were given two sequential infusions of epinephrine separated by a placebo infusion to rule out an effect of time on the hemodynamic response to epinephrine. Mean arterial pressure and cardiac index responses to epinephrine were identical before and after placebo infusion.(

Jpn Heart J 1979 Jan;20(1):75-82. **Inhibition of constrictor responses of dog coronary artery by atropine. A possible effectiveness of atropine on variant form of angina pectoris.** Sakanashi M, Furukawa T, Horio Y. A possible effectiveness of atropine on variant form of angina pectoris was investigated using the left circumflex coronary arterial strips of dogs. Acetylcholine 10(-5)--10(-3) Gm/ml dose-dependently constricted the isolated arterial strips during potassium-contracture in 6 cases, and repetitive applications of acetylcholine could produce the similar contractions to the control. In 18 strips atropine 10(-6) Gm/ml significantly depressed the contractions of coronary arteries induced by acetylcholine 10(-5)--10(-3) Gm/ml. In 5 arterial strips atropine 10(-6) Gm/ml **significantly inhibited norepinephrine-induced responses** of these arteries, and by 10(-5) Gm/ml further suppression of the responses was obtained. The **results suggest that atropine may suppress the contractile responses of the coronary artery induce by acetylcholine and nonrepinephrine through a muscarinic-receptor blocking action and simultaneously partly through an adrenergic alpha-receptor blocking action.**

Eur J Clin Pharmacol 1981;20(4):245-50. **Effect of long-term beta-blockade with alprenolol on platelet function and fibrinolytic activity in patients with coronary heart disease.** Jurgensen HJ, Dalsgaard-Nielsen J, Kjoller E, Gormsen J. In 14 patients with coronary heart disease the effect of long-term treatment (mean 16 months, range 12-33) with alprenolol on platelet function and fibrinolytic activity was studied. While on the beta-blocker and two weeks after gradual withdrawal of it, the patients performed a bicycle-ergometer test and blood samples were obtained before and following exercise. Pre-exercise fibrinolytic activity, assessed by the euglobulin clot lysis time, was 183 +/- 27 min (mean +/- SEM) while on alprenolol as compared to 111 +/- 18 min (p less than 0.01) after its withdrawal. Activation of fibrinolysis following exercise was not significantly influenced by alprenolol. In patients treated with alprenolol, the pre-exercise threshold level of ADP, producing platelet aggregation was 3.3 muM (geometric mean) and 5.1 muM after stopping treatment (p less than or equal to 0.05). In patients receiving the beta-blocker, the ADP- threshold value dropped from 3.3 muM before exercise to 2.3 muM immediately after exercise (not significant). The corresponding values after withdrawal of alprenolol were 5.1 muM and 2.7 muM (p less than or equal to 0.02). Adrenaline - stimulated aggregation was not significantly influenced by alprenolol. Serotonin release from platelets following maximal ADP- and adrenaline stimuli was not significantly changed by exercise in patients on beta-blockade. After stopping treatment, ADP-induced serotonin release was 22 +/- 4.1% before and 15 +/- 4.7% after exercise (p less than 0.02). the corresponding values using the adrenaline stimulus were 29 +/- 5.7% and 17 +/- 4.7% (p less than 0.05). It is suggested that during physical stress alprenolol may protect platelets against aggregatory stimuli.

C R Seances Soc Biol Fil 1987;181(3):242-8. **[Adrenaline activates oxidative phosphorylation of rat liver mitochondria through alpha 1-receptors].** Breton L, Clot JP, Bouriannes J, Baudry M. We studied the effects and mode of action of epinephrine on the oxidative phosphorylation of rat liver mitochondria. With either succinate or beta-hydroxybutyrate as substrate, i.v. injection of 1.5 microgram/100 g epinephrine increased the respiratory rates by 30-40% in state 3 (with ADP), and by 20-30% in state 4 (after ADP phosphorylation), so that the respiratory control ratio (state 3/state 4) changed little. The respiratory stimulation by epinephrine was maximal 20 minutes after its injection. The action of epinephrine on mitochondria was blocked by pretreatment of the animals with the alpha 1-antagonist prazosin but not by treatment with the beta-antagonist propranolol. I. v. injection of 10 micrograms/100 g phenylephrine evoked the same mitochondrial response as epinephrine. I. v. administration of 50 micrograms/100 g dibutyryl cyclic AMP enhanced glycaemia but did not affect mitochondrial respiration. Epinephrine therefore has an alpha 1-type of action on mitochondrial oxidative phosphorylation.

Biochimie 1975;57(6-7):797-802. **Effects of catecholamines on rat myocardial metabolism. I. Influence of catecholamines on energy-rich nucleotides and phosphorylated fraction contents.** Merouze P, Gaudemer Y. 1. The influence of catecholamines (adrenaline and noradrenaline) on energy metabolism of the rat myocardium has been studied by incubating slices of this tissue with these hormones and by following the levels of the different phosphorylated fractions and adenylic nucleotides. 2. Similar effects are obtained with both hormones, adrenaline being more effective. 3**. Catecholamines decrease significantly the total amount of phosphate while Pi content increases during the first 10 minutes of incubation; labile and residual phosphate contents increase at the beginning of incubation and decrease to the initial values afterwards. 4. ATP and ADP levels decrease significantly** with both hormones; however, the effect of noradrenalin on the ATP level needs a longer time of incubation. **The ATP/ADP ratios decrease after 5 minutes incubation and the total adenylic nucleotide content is severely decreased (35 per cent with adrenalin, after 20 minutes incubation). 5. Similar results have been obtained with other tissues; these results can explain the decrease of aerobic metabolism we observed under the same conditions.**

Eur J Pharmacol 1982 Jul 30;81(4):569-76**. Actions of serotonin antagonists on dog coronary artery.** Brazenor RM, Angus JA. Serotonin released from platelets may initiate coronary vasospasm in patients with variant angina. If this hypothesis is correct, serotonin antagonists without constrictor activity may be useful in this form of angina. We have investigated drugs classified as serotonin antagonists on dog circumflex coronary artery ring segments in vitro. Ergotamine, dihydroergotamine, **bromocriptine, lisuride, ergometrine, ketanserin, trazodone, cyproheptadine and pizotifen caused non-competitive antagonism of serotonin concentration-response** curves. In addition, ketanserin, trazodone, bromocriptine and pizotifen inhibited noradrenaline responses in concentrations similar to those required for serotonin antagonism. All drugs with the exception of ketanserin, cyproheptadine and pizotifen showed some degree of intrinsic constrictor activity. Methysergide antagonized responses to serotonin competitively but also constricted the coronary

artery. The lack of a silent competitive serotonin antagonist precludes a definite characterization of coronary serotonin receptors at this time. However, the profile of activity observed for the antagonist drugs in the coronary artery differs from that seen in other vascular tissues. Of the **drugs tested, ketanserin may be the most useful in variant angina since it is a potent 5HT antagonist, lacks agonist activity and has alpha-adrenoceptor blocking activity.**

Arch Mal Coeur Vaiss 1983 Feb;76 Spec No:3-6. **Role of autonomic nervous system in the pathogenesis of angina pectoris.** Yasue H. The attacks of vasospastic angina or coronary spasm can be induced by injection of epinephrine, cold pressor test, Valsalva maneuver, and exercise. The attacks induced by these procedures can be suppressed by injection of phentolamine, an alpha adrenergic blocking agent in 80 per cent of the patients. On the other hand, propranolol, a beta adrenergic blocking agent, is not only ineffective in suppressing the attacks but aggravates the attacks in 50 per cent of the patients. Thus, alpha adrenergic receptors seem to play an important role in the production of vasospastic angina. The attacks of vasospastic angina can also be induced by injection of methacholine, a parasympathomimetic agent, and this reaction is suppressed by atropine, a parasympathetic blocking agent. Thus, **parasympathetic nervous system also seems to play a role in the production of vasospastic angina. The attacks of vasospastic angina can be easily induced by adrenergic or parasympathetic stimuli from midnight to early morning but is** usually not provoked by these stimuli in the daytime. Thus, there is circadian variation in the reactivity of coronary arteries to adrenergic or parasympathetic stimuli. There are also weekly, monthly and yearly variations of the reactivity of coronary arteries to these stimuli. Thus, **alpha adrenergic or parasympathetic activity is not the sole factor in the production of vasospastic angina.** Angina pectoris caused by increased myocardial oxygen demand is induced by infusion of isoproterenol, a beta adrenergic stimulant, and is suppressed by propranolol but not by phentolamine. So, beta adrenergic receptors play an important role in the production of angina pectoris caused by increased myocardial oxygen demand or organic angina pectoris.

Nippon Yakurigaku Zasshi 1986 Mar;87(3):281-90. [Vasoconstrictor responses of isolated pig coronary arteries]. [Article in Japanese] Ikenoue K, Kawakita S, Toda N. **In helical strips of pig coronary arteries, histamine, serotonin, acetylcholine and a stable analogue of thromboxane A2 (9, 11-epithio-11, 12-methano TXA2: s-TXA2) produced a dose-dependent contraction. The histamine-induced contraction** was suppressed by treatment with chlorpheniramine, suggesting an involvement of H1 receptors. Contractile responses to serotonin were attenuated by not only ketanserin, an S2 antagonist, but also by cinanserin and methysergide. Relaxation induced by serotonin in preparations treated with high concentrations of ketanserin were inhibited by cinanserin and methysergide. Norepinephrine contracted coronary arteries treated with propranolol. Contractile responses to norepinephrine were reversed to relaxations by prazosin, which were abolished by treatment with yohimbine. Contractile responses to histamine were potentiated by treatment with low concentrations of serotonin or s-TXA2. Contractile responses to serotonin were also potentiated by low concentrations of histamine or s-TXA2. Removal of the endothelium from pig coronary arterial strips potentiated contractions induced by serotonin, histamine and norepinephrine. These results suggest that, in addition to damaged endothelium, integrating action of endogenous vasoconstrictors, including histamine, serotonin, TXA2 and norepinephrine, may play an important role in producing coronary vasospasm.

Jpn Heart J 1987 Sep;28(5):649-61**. The role of parasympathetic nerve activity in the pathogenesis of coronary vasospasm.** Suematsu M, Ito Y, Fukuzaki H. To evaluate the role of the autonomic nervous system, especially the parasympathetic nervous system, in the initiation mechanism of vasospastic angina pectoris (AP), the coefficient of R-R interval variation (CV) on the electrocardiogram (ECG) and plasma catecholamine concentration were measured in 25 patients with vasospastic AP, 10 patients with effort AP and 12 control subjects. CV which has been recognized as reflecting parasympathetic nervous system activity was calculated from 100 consecutive heart beats on the ECG and represented as the percentage of standard deviation of the R-R interval per mean R-R interval. Repeated measurements of **plasma catecholamine concentration revealed higher values at any sampling point throughout a day in patients with vasospastic AP than those in** control subjects. A distinctly higher CV was observed at night in the vasospastic AP group. **This elevated CV was abolished by atropine sulfate (1.5 mg/day per os). Pilocarpine injection (1.3 mg/10 kg B.W. subcutaneously) induced a marked increase** in CV that preceded the occurrence of chest pain and/or ischemic ECG changes in 5 patients with vasospastic AP. The **increment in CV at 10 min after pilocarpine administration was greater in vasospastic AP than in control subjects (p less than 0.05). It is concluded that enhanced parasympathetic activity may play a role in the initiation of coronary vasospasm associated with sympathetic hyperactivity.**

Science 1984 Mar 30;223(4643):1435-7. **Coronary arteries of cardiac patients are hyperreactive and contain stores of amines: a mechanism for coronary spasm.** Kalsner S, Richards R. Coronary arteries from hearts of cardiac patients contain significantly higher concentrations of histamine than do those from noncardiac patients. The coronary vessels of cardiac patients are also hyperresponsive to histamine and serotonin. These differences between groups of patients suggest an explanation for coronary artery spasm in heart disease.

Fed Proc 1985 Feb;44(2):321-5. **Coronary artery reactivity in human vessels: some questions and some answers.** Kalsner S. Spasm of a conduit coronary artery, converting it into a major resistance vessel impeding myocardial blood flow, may have severe short- or long-term effects on cardiac rhythm and systolic ejection of blood. It is now clear that human coronary arteries in vitro contract to acetylcholine but that relaxation is the only response observed in dog coronary vessels. **Acetylcholine is as powerful a constrictor of human coronary arteries, in terms of tension induced, as 5-hydroxytryptamine (5-HT) or histamine and is a substantially more powerful constrictor than norepinephrine.** Field stimulation of coronary artery strips caused a vasoconstriction that was partially antagonized by atropine (3.45 X10(-6) M). An enhanced reactivity of the epicardial arteries of cardiac and older patients to several agonists was also observed and appears to provide a background against which a number of vasoactive agents might induce spasm. Coronary tissue from cardiac patients also contains stores of 5-HT and histamine, and the histamine levels are substantially increased above the values in vessels from noncardiac patients. Coronary artery spasm or contraction **probably can be initiated by diverse intrinsic and extrinsic influences, including autonomic discharge from either the parasympathetic or sympathetic nervous system or from histamine or 5-HT, and probably no one agent or entity is causative in all cases.**

Ann N Y Acad Sci 1969 Oct 14;164(2):517-9. **Induced carcinogenesis under various influences on the hypothalamus.** Kavetsky RE, Turkevich NM, Akimova RN, Khayetsky IK, Matveichuck YD.

Ann N Y Acad Sci 1966 Jan 21;125(3):933-45. **On the psychophysiological mechanism of the organism's resistance to tumor growth.** Kavetsky RE, Turkevich NM, Balitsky KP.

Patol Fiziol Eksp Ter 1971 Sep-Oct;15(5):3-10. [Role of disorders in intra-cellular and neuro-humoral regulation in the development of the tumor process]. [Article in Russian] Kavetskii RE, Balitskii KP.

Obstet Gynecol Surv 1977 May;32(5):267-81. **Estrogen and endometrial carcinoma.** Knab DR. 1. It has become evident that the estrogen secreting tumors of the ovary are associated with endometrial carcinoma, but this association is most easily observed in the postmenopausal patient where the incidence of carcinoma has been **reported at 10.3% (1. 02) to 24% (83). 2. The most consistent association of endometrial carcinoma is with polycystic ovarian disease, where 19 (34), 21 (152), and 25% (150) of young women with endometrial carcinoma had Stein-Leventhal syndrome (67). 3. A very significant discovery became known in** 1967 when the peripheral aromatization of delta4 androstenedione to estrone was reported by Kase (94) and MacDonald (111,112). Since that time we have learned that endometrial carcinoma patients have an **increased peripheral conversion (139) (0.1% compared to 0.027%), which is similar to that found in obese and aging patients, by Hemsell, et al (77).** This can be 2 to 4 times greater than the young adult or the patient without cancer. Estrone produced peripherally in normal postmenopausal women can amount to 40-60

microng/day and rise as high as 120-180 microng/day in the endometrial neoplasia group (39). Similarly patients with polycystic ovary disease, hyperthecosis and lipoid cell tumors of the ovary demonstrate androgen excess with extraglandular conversion to estrone (2). 4. It has become apparent that the principal estrogen in the postmenopausal patient is estrone and that the **estrone-estradiol ratio in the serum is higher in postmenopausal women with corpus cancer than similar patients without cancer** (135). Clearly, we must find the effect of this estrone excess at the nuclear "acceptor" level; and does this imbalance create a hormonal environment conducive to the development of endometrial carcinoma when age (an extremely important factor) and an oncogenic agent are added? 5. With the lack of ovarian estrogen there is a relative excess of adrenal testosterone, dihydrotestosterone and delta4 androstenedione, the available precursors of extraglandular estrone (1). 6. With the passage of time **it appears that endometrial carcinoma is associated with hypothalamic "hyperactivity"** (31) which exhibits immunologic-biologic dissociation of LH as previously observed in persistent trophoblastic disease when measuring hCG. The significance of this is still unknown. In a like fashion a significant number of the at risk polycystic ovary disease patients have an increased LH secretion. 7. Patient susceptibility is required as seen in animal experiments where prolonged administration of stilbestrol is used and still only rabbits and mice developed a malignant change. 8. Long term exogenous estrogen appears to have caused malignant changes in the endometrium, but it was universally given over a prolonged period (4 or more years). The recent retrospective studies demonstrate an association of oral estrogen therapy with endometrial cancer, but prospective studies investigating dose and duration of all estrogen preparations need to be undertaken. 9...

Endocrinology 2000 Mar;141(3):1059-72. **An increased intraovarian synthesis of nerve growth factor and its low affinity receptor is a principal component of steroid-induced polycystic ovary in the rat.** Lara HE, Dissen GA, Leyton V, Paredes A, Fuenzalida H, Fiedler JL, Ojeda SR. A form of polycystic ovary (PCO) resembling some aspects of the human PCO syndrome can be induced in rats by a single injection of estradiol valerate (EV). An increase in sympathetic outflow to the ovary precedes, by several weeks, the appearance of cysts, suggesting the involvement of a neurogenic component in the pathology of this ovarian dysfunction. The present study was carried out to test the hypotheses that this change in sympathetic tone is related to an augmented production of ovarian nerve growth factor (NGF), and that this abnormally elevated production of **NGF contributes to the formation of ovarian cysts induced by EV. Injection of the steroid resulted in increased intraovarian synthesis of NGF** and its low affinity receptor, p75 NGFR. The increase was maximal 30 days after EV, coinciding with the elevation in sympathetic tone to the ovary and preceding the appearance of follicular cysts. Intraovarian injections of the retrograde tracer fluorogold combined with in situ hybridization to detect tyrosine hydroxylase (TH) messenger RNA-containing neurons in the celiac ganglion revealed that these changes in NGF/p75 NGFR synthesis are accompanied by selective activation of noradrenergic neurons projecting to the ovary. The levels of RBT2 messenger RNA, which encodes a beta-tubulin presumably involved in slow axonal transport, were markedly elevated, indicating that EV-induced formation of ovarian cysts is preceded by functional activation ofceliac ganglion neurons, including those innervating the ovary. Intraovarian administration of a neutralizing antiserum to NGF in conjunction with an antisense oligodeoxynucleotide to p75 NGFR, via Alzet osmotic minipumps, **restored estrous cyclicity and ovulatory capacity in a** majority of EV-treated rats. These functional changes were accompanied by restoration of the number of antral follicles per ovary that had been depleted by EV and a significant reduction in the number of both precystic follicles and **follicular cysts. The results indicate that the hyperactivation of ovarian sympathetic nerves seen in EV-induced PCO is related to an overproduction of NGF and its low affinity receptor in the gland. They also suggest that activation of this neurotrophic-neurogenic regulatory loop is a component of the pathological process by which EV induces cyst formation and anovulation in rodents. The** possibility exists that a similar alteration in neurotrophic input to the ovary contributes to the etiology and/or maintenance of the PCO syndrome in humans.

Acta Physiol Hung 1996;84(2):183-90. **Effects of hormones on the number, distribution and degranulation of mast cells in the ovarian complex of mice.** Jaiswal K, Krishna A. The changes in the number and degranulation pattern of mast cells varied with the types of hormonal treatment and ovarian compartment. **Luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH) and 17-beta estradiol (E2) treatment caused increase ($P < 0.05$) in the number of mast cells** in the hilum as compared with the controls. Increase ($P < 0.05$) in the number of mast cells in the whole ovarian complex was observed only following FSH and E2 treatment. All the hormones used in the present study increased the percentage degranulation of mast cells in the hilum. However, only LH, FSH and E2 increased the percentage degranulation of mast cells in other compartments of the ovary (medulla, bursa and cortex). TSH and ACTH failed to cause any increase in the percentage degranulation of mast cells in these compartments. The present findings indicate E2 to be the most potent among the hormones tested in causing degranulation of mast cells in all ovarian compartments.

Fertil Steril 2001 Jun;75(6):1141-7. **Increase in nerve fibers and loss of mast cells in polycystic and postmenopausal ovaries.** Heider U, Pedal I, Spanel-Borowski K. OBJECTIVE: To quantify nerve fibers and mast cells in human ovaries at different functional stages. DESIGN: Retrospective study. SETTING: Research laboratory of the university. SPECIMEN(S): 8 human ovaries in the follicular (cyclic) phase, 7 polycystic ovaries, and postmenopausal ovaries with (n=5) or without (n=7) hyperthecosis. MAIN OUTCOME MEASURE(S): Single- and double immunohistology for the S100 antigen in glial cells of autonomic nerve fibers, for chymase and tryptase in mast cells, and for the common leukocyte antigen on leukocytes. Histometric evaluation was also performed. INTERVENTION(S): None. RESULT(S): Polycystic ovaries contained significantly more S100-positive nerve fibers in the corticomedullary region than did cyclic ovaries (mean +/- SD per 2-mm(2) area, 476 +/- 136 and 224 +/- 133; P<.01). Postmenopausal ovaries with or without hyperthecosis had the highest density of nerve fibers. In cyclic and polycystic ovaries, more tryptase-positive mast cells than chymase-positive mast cells were found in the interstitial cortex and the medulla. In cyclic ovaries, areas with a moderate density of nerve fibers contained many mast cells. Hence, **with increasing nerve fiber density in polycystic ovaries, the number of mast cells decreased strikingly compared with cyclic ovaries (p<.001). Almost no mast cells were seen in postmenopausal ovaries** with and without hyperthecosis. The number of leukocyte antigen-positive leukocytes was similar in all groups. CONCLUSION(S): The high density of nerve fibers in polycystic and postmenopausal ovaries, together with a conspicuous decrease in mast cells, indicates altered neuroimmune communication.

Endocrinology 1993 Dec;133(6):2696-703. **Ovarian steroidal response to gonadotropins and beta-adrenergic stimulation is enhanced in polycystic ovary syndrome: role of sympathetic innervation.** Barria A, Leyton V, Ojeda SR, Lara HE. Experimental induction of a polycystic ovarian syndrome (PCOS) in rodents by the **administration of a single dose of estradiol valerate (EV) results in activation of the peripheral sympathetic neurons that innervate the ovary. This activation is evidenced by an increased capacity of ovarian nerve terminals to incorporate and release norepinephrine (NE), an increase in ovarian NE content, and a** decrease in ovarian beta-adrenergic receptor number in the ovarian compartments receiving catecholaminergic innervation. The present experiments were undertaken to **examine the functional consequences of this enhanced sympathetic outflow to the ovary.** The steroidal responses of the gland to beta-adrenergic receptor stimulation and hCG were examined in vitro 60 days after EV administration, i.e. at the time when follicular cysts are well established. EV-treated rats exhibited a remarkable increase in ovarian progesterone and androgen responses to isoproterenol, a beta-adrenergic receptor agonist, with no changes in estradiol responsiveness. Basal estradiol release was, however, 50-fold higher than the highest levels released from normal ovaries at any phase of the estrous cycle. The ovarian progesterone and androgen responses to hCG were enhanced in EV-treated rats, as were the responses to a combination of isoproterenol and hCG. Transection of the superior ovarian nerve (SON), which carries most of the catecholaminergic fibers innervating endocrine ovarian cells, dramatically reduced the exaggerated responses of all three steroids to both beta-adrenergic and gonadotropin stimulation. SON transection also reduced the elevated levels of ovarian NE resulting from EV treatment and caused up-regulation of beta-adrenoreceptors. Most importantly, SON transection restored estrous cyclicity and ovulatory capacity. The results indicate that the increased output of ovarian steroids in PCOS is at least in part due to an enhanced responsiveness of the gland to both catecholaminergic and gonadotropin stimulation. The ability of SON transection to restore a normal response indicates that the alteration in steroid output results

from a deranged activation of selective components of the noradrenergic innervation to the ovary. These findings support the concept that an alteration in the neurogenic control of the ovary contributes to the etiology of PCOS.