

# The NeuroTransmission

*Helping practitioners address chronic symptoms,  
acute conditions, and practice effective wellness medicine.*

Volume 3, Issue 2 · May, 2009

Sanesco International • 866.670.5705

Online presentation available at [www.Sanesco.net](http://www.Sanesco.net)



## Editorial

### Editor-in-Chief:

R.W. Watkins, MD, MPH,  
FAAFP

### Medical Editor:

Denise Mark, MD

### Medical Editor:

Koren Barrett, ND

### Contributing Editor:

Christina Callahan

### Contributing Editor:

Connie Shoemaker, ND

Volume 3, Issue 2  
The NeuroTransmission  
is published by  
Sanesco International.

© Copyright 2009  
All Rights Reserved  
Sanesco International  
1010 Merrimon Ave.  
Asheville, NC 28804

866.670.5705

[www.Sanesco.net](http://www.Sanesco.net)

## Featured Author



R.W. Watkins, MD,  
MPH, FAAFP

## Cardiovascular Disease and the CSM Model

R. W. "Chip" Watkins, MD, MPH, FAAFP

*From 1995 to 2005, death rates from CVD declined 26.4%.  
This is certainly great news, isn't it? However, even though  
death rates from cardiovascular disease (CVD) have declined,  
the burden of disease remains high.*

**The 2005 overall death rate from cardiovascular disease (CVD) was 278.9 per 100,000, or roughly 1 of every 2.9 deaths in the United States. The preliminary mortality data for 2006 showed that CVD accounted for 34.2% of all deaths that year. It remains the leading cause of death in the country<sup>1</sup>**

(see Table 1).

About every 25 seconds, an American will have a coronary event, and about every minute someone will die from one. As many of us know, controllable risk factors for heart disease include smoking, high blood pressure, high blood cholesterol, diabetes, being overweight or obese, and physical inactivity.

On the basis of data from the latest National Health and Nutrition Examination Survey<sup>(2)</sup>, the prevalence of overweight (body mass index-for-age values at or above the 95th percentile) in children 6 to 11 years of age increased from 4.0% in 1971-1974 to 17.0% in 2003-2006. In addition, 62% of adults >18 years of age who responded to the National Health Interview Survey<sup>(3)</sup>, reported no vigorous activity lasting >10 minutes per session.

The basis of these neuro-endocrine changes, from an HPA-T perspective, is a pro-inflammatory state which sets the stage for heart disease and one of its main progenitor conditions, metabolic syndrome, by the up-regulation of the sympathetic nervous system. This occurs chiefly through a predominance of norepinephrine over

## Featured Author



Dr. Watkins earned his medical degree at East Carolina School of Medicine, and completed his internship and residency in Family Medicine at Florida Hospital, Orlando in 1989. He has a Master's in Public Health in Health Promotion and Nutrition from Loma Linda University in Loma Linda, California, with experience in both academic and corporate medicine.

Dr. Watkins enjoys a thriving integrative medical practice in Greensboro, NC and specializes in functional medicine with a focus on neuro-hormonal imbalances. He is a member of the American Academy of Family Physicians and President-Elect of the North Carolina Academy of Family Physicians, and a Clinical Assistant Professor at both the UNC School of Medicine and the Carolina School of Medicine.

Dr. Watkins has lectured on a wide variety of topics at the local, state, national and international levels. He has authored a number of articles and book chapters.

## Online Presentation

See Dr Watkins' presentation on Cardiovascular Disease and the CSM Model

online at [www.Sanescos.net](http://www.Sanescos.net)

epinephrine. This is particularly true if an already stressed HPA axis is stimulated further through the actions of CRF.

Much research suggests that both hypothalamic and extrahypothalamic CRF activate the locus ceruleus in the brain, leading to an increase in norepinephrine (4). In a study by Melia (5), results showed that

endogenous CRF is necessary for the induction of tyrosine hydroxylase in response to the stress paradigm and that exogenously administered CRF is sufficient for the regulation of this enzyme in non-stressed subjects. Thus, CRF is necessary to induce tyrosine hydroxylase which is the rate-limiting step in the production of catecholamines. Then, Koob, et al, showed that norepinephrine can enhance forebrain CRF activity, leading to higher activity of both norepinephrine and CRF in patients, possibly closing a feed-forward loop (6).

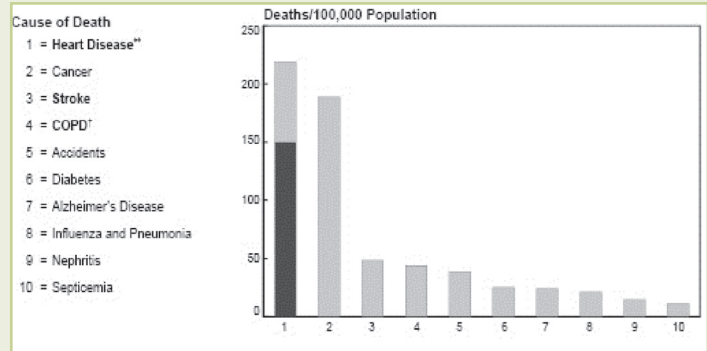
So when a person is stressed, there is an upregulation of catecholamines (particularly NE) and cortisol that occurs in a dance where the body is trying to balance the production of inflammatory cytokines with cortisol which attempts to turn down the gain on the inflammation. But there is a cost to the dance, particularly in light of adrenal fatigue and exhaustion. One can see these specific patterns in metabolic syndrome.

The typical pattern seen on the HPA profile in a patient with metabolic syndrome or hyperinsulinemia will show a high NE with usually a low epinephrine - indicating the decreased adrenal medullary activity noted in a study by Ward, et al (7). The researchers looked at the relationship between 24-hour urinary catecholamine excretion and serum lipid and lipoprotein levels examined among 6 male participants of the Normative Aging Study. Epinephrine excretion was positively correlated with the high-density lipoprotein cholesterol (HDL-C) level and the ratio of HDL-C to LDL-C and inversely correlated with the triglyceride level. Their data suggested that epinephrine plays an important role in regulating lipid and lipoprotein metabolism in humans.

In addition, decreased adrenal medullary activity (adrenal stress) may contribute to the dyslipidemia (increased triglycerides and decreased HDL-C) commonly observed among the obese. This is the typical lipid pattern in metabolic syndrome. They concluded that the sympathoadrenal system, along with hyperinsulinemia, might contribute to the increased cardiovascular risk associated with the insulin resistance syndrome.

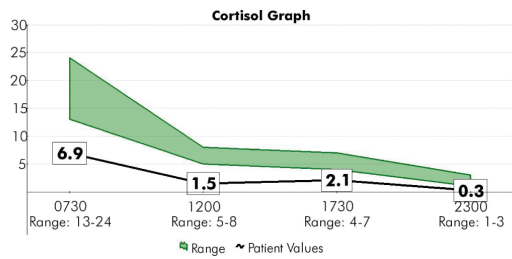
In a study by Troisi (8), the relationship of obesity to sympathetic nervous system activity was investigated. Sympathetic activity was assessed by measurement of 24-hour urinary norepinephrine excretion and level of obesity by BMI. They showed mean urinary norepinephrine excretion was higher in subjects classified as either hyperglycemic and hyperinsulinemic than the mean urinary norepinephrine excretion in normal subjects. There are many other studies looking at NE excretion and risk of metabolic syndrome and CHD. DePergola and colleagues (9) even suggested that insulin and noradrenaline cooperate independently to the development of the metabolic syndrome.

Table 1. 10 leading causes of death in the United States Source: Vital Statistics of the United States, NCHS



Marker	Values	Range
<b>INHIBITORY NEUROTRANSMITTERS</b>		
SEROTONIN	<b>125.0 (L)</b>	150-300 mcg/g Cr
GABA	<b>461.9 (L)</b>	550-750 mcg/g Cr
Marker	Values	Range
<b>EXCITATORY NEUROTRANSMITTERS</b>		
DOPAMINE	<b>105.9 (L)</b>	150-300 mcg/g Cr
NOR-EPINEPHRINE	<b>58.3 (H)</b>	20-45 mcg/g Cr
EPINEPHRINE	<b>6.4</b>	3-20 mcg/g Cr
GLUTAMATE	<b>34.5</b>	15-35 mcg/g Cr
<b>ADRENAL ADAPTATION INDEX</b>		
NOREPI/EPI RATIO	<b>9.1</b>	<10
<b>ADRENAL HORMONES</b>		
CORTISOL (0730)	<b>6.9 (L)</b>	13-24 nM
CORTISOL (1200)	<b>1.5 (L)</b>	5-8 nM
CORTISOL (1730)	<b>2.1 (L)</b>	4-7 nM
CORTISOL (2300)	<b>0.3 (L)</b>	1-3 nM
DHEA-s (0730)	<b>1.1 (L)</b>	2-10 ng/ml
DHEA-s (1730)	<b>1.1 (L)</b>	2-10 ng/ml
<b>OTHER MARKERS</b>		
CREATININE, URINE	<b>84.0</b>	

Creatinine is used to calculate results and is not intended to be used diagnostically.



*In CHD and metabolic syndrome there are typically higher levels of NE and lower levels of epinephrine, often with low levels of adrenal function.* This is part of the “perfect storm” for the propagation of inflammatory mediators. In a recent article, by Széleányi<sup>(10)</sup> it was demonstrated that the TNF- $\alpha$  response is in direct correlation with level of NE. Finally, Brunner, et al.<sup>(10)</sup> not only confirmed that there is relative cardiac sympathetic (NE and epi) predominance in CHD, but their group found several inflammatory markers to be strongly related to the metabolic syndrome, among them IL-6 and C-reactive protein.

One possible explanation for the patterns typically seen in metabolic syndrome (high NE, low epinephrine and low adrenal status) which is a preamble to CHD are due to years of excursions of the blood sugar with the body using epinephrine and cortisol to help sustain euglycemia. The adrenals (particularly the adrenal cortex) consequently get worn out and the patient is then left “running” on NE, often with concomitant anxiety, sleep difficulties and/or hypertension. This situation also sets the stage for increased inflammatory status.

Those who use the CSM<sup>®</sup> model see the above patterns on a regular basis. Currently, medical research involving multiple neurotransmitters and particularly their inter-relationships is limited. Until the time that such research becomes available, we are left to scour the literature and see glimpses of our model as researchers work to collate the bits and pieces of the whole. With time, we at Sanesco are sure that research will bear out the veracity of the CSM<sup>®</sup> model.

The discussion above gives an inkling of what the recent medical literature has to tell us about the state of the neuro-endocrine system in CHD. We believe that rebalancing the HPA-T axis is an important step in toning down the gain on the body’s sympathetic nervous system. This is done by providing adequate inhibitory NTs (serotonin and GABA) to counterbalance the NE and possibly epinephrine that are the result of ramping up of the sympathetic system. What we see clinically are products like Prolent, Lentra, and Tranquilent “standing in the gap” and in essence “cooling down” the excitatory NTs. This yields calmer patients who typically sleep better and are better able to handle the stress that can, over time, impact CHD risk.

In summary, CHD is the result of the interplay of numerous risk factors, not the least of which are increased sympathetic nervous system activity as evidenced by increased levels of NE in the urine often associated by low levels of urinary epinephrine. Concomitantly, there is often upregulation of the HPA axis with regard to adrenal function. After prolonged periods, this may lead to diminished adrenal function. The combination of these factors can lead to increased inflammation within the cardiovascular system often manifesting in higher levels of hs-CRP and fibrinogen, etc. The scenario discussed above may be part of the underlying cause of CHD - forming the antecedents and triggers that end up shaping the disease.

The prevention of CHD should be approached in a holistic and integrated manner with primary concerns centering on lifestyle and dietary choices. All risk factors should be addressed as comprehensively as possible and the underpinnings of sympathetic overdrive and inflammation must be taken into consideration as part of that comprehensive plan.

## References

1. <http://www.americanheart.org/presenter.jhtml?identifier=3000090>. Heart Disease and Stroke Statistics -- 2009 Update
2. <http://www.cdc.gov/nchs/nhanes.htm> NHANES 2005-2006
3. <http://www.cdc.gov/nchs/nhis.htm> National Health Interview Survey (NHIS)
4. Arlt J, Jahn H, Kellner M, Strohle A, Yassouridis A, Wiedemann K: Modulation of sympathetic activity by corticotropin-releasing hormone and atrial natriuretic peptide. *Neuropeptides* 2003; 37:362–368.
5. Melia KR, Duman RS: Involvement of corticotropin-releasing factor in chronic stress regulation of the brain noradrenergic system. *Proc Natl Acad Sci USA* 1991; 88:8382–8386.
6. Koob GF: Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiatry* 1999; 46:1167–1180.
7. Ward KD, Sparrow D, Landsberg L, The Relationship of Epinephrine Excretion to Serum Lipid Levels: The Normative Aging Study. *Metabolism*, 1994;43(4):509-513.
8. Troisi RJ, Weiss ST, Parker DR, et al: Relation of obesity and diet to sympathetic nervous system activity. *Hypertension* 17:669-677,1991.
9. De Pergola G, Giorgino F, Benigno R. Independent Influence of Insulin, Catecholamines, and Thyroid Hormones on Metabolic Syndrome. *Obesity* (2008) 16, 2405–2411.
10. Szelényi J, Vizi ES. The catecholamine cytokine balance: interaction between the brain and the immune system. *Ann N Y Acad Sci*. 2007 Oct;1113:311-24.
11. Brunner EJ, Hemingway H, Walker BR, Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. *Circulation*. 2002 Nov 19;106(21):2659-65.



### About Sanesco International

Sanesco International is a medical company with expertise in assessing and addressing neuro-hormonal imbalances affecting HPA-T axis function. Since inception in 2004, the Sanesco team remains committed to providing an effective clinical model with practical solutions to help practitioners address their patients' chronic symptoms, acute conditions, and to practice preventive medicine. **Contact one of our Practice Building Specialists today to learn how you can find more success with addressing your patients chronic symptoms and conditions.**

**1010 Merrimon Ave. • Asheville, NC 28804 • 866.670.5705 • [www.Sanesco.net](http://www.Sanesco.net)**