DRAFT

The Root Cause in the dramatic rise of Chronic Disease

NOTE to Readers: *I am seeking one or two scientists to take the following research and paper forward. There are really two papers here. One is a paper that strengthens the scientific connection between peroxynitrite and at least forty fast-growing chronic diseases. The second paper is a translation of the science that can be offered to the American people, who remain unaware of the root cause of the dramatic increase of chronic disease and conditions in the US. More than 170 million Americans are currently suffering from diseases and conditions that can be vastly improved or even reversed by reducing levels of peroxynitrite through moderate changes in lifestyle, the immediate environment and diet plus non-prescription supplementation. While scientists recognize the pivotal role of peroxynitrite in disease, few policy makers and physicians are aware of the opportunity they have to heal a nation suffering from chronic diseases. The annual cost of just forty fast-growing diseases is more than $2.5 trillion. With increased awareness and action this cost to society can be reduced to a fraction by simply implementing the knowledge we already have.*

- **Richard Lear**

richardlear@alumni.brown.edu

Growth of Chronic Disease

There has been unprecedented growth in a new class of chronic diseases in the US since 1990. Four categories of disease have virtually exploded: autoimmune, neurological, metabolic and inflammatory. Meanwhile, there has been a similar uptick in reproductive conditions like infertility and a half dozen psychiatric disorders.

While the major health threats of the 20th century: cardiovascular disease, infectious disease and cancer, are barely growing, at least forty chronic diseases and disorders have more than doubled in the past generation. Many of these *new age* diseases weren't even on our radar until the 1980's.

In a single generation, there has been a dramatic acceleration* in the prevalence of diseases and disorders like autism (2094%), Alzheimer's (299%), COPD (148%), diabetes (305%), sleep apnea (430%), celiac disease (1111%), ADHD (819%), asthma (142%), depression (280%), bipolar disease in youth (10833%), osteoarthritis (449%), lupus (787%), inflammatory bowel disease (IBD – 120%), chronic fatigue syndrome (11027%), fibromyalgia (7727%), multiple sclerosis (117%) and hypothyroidism (702%).

The values for these increases were derived from scientific literature; that they are over-precise is a given. These generational increases in prevalence are offered to convey a clearer picture of the spectacular increase in chronic disease.

Diseases of Civilization

These are the so-called *diseases of civilization*. None are associated with an identifiable pathogen. Root causes remain elusive. Since genetics of humans have remained substantially unchanged over time, most believe these diseases are linked to our diet, lifestyle and/or environment.

The impact from *germless disease* in America is staggering. In a population of 322 million, there are now more than 700 million instances of the forty fast-growing chronic diseases and medical conditions tracked in this article (See Table 1). Americans are suffering from an average of 2.1 chronic diseases per person across this select group. *Annual* economic impact, which includes medical costs, lost income and medical research is estimated to be just over $2.5 trillion (see Table 1).

The *Smoking Gun*

While controversy remains over possible external causes, one internal biological trigger may already be known. A single molecule produced by the body called *peroxynitrite* is associated with much of this sudden explosion of disease. In January 2007 three leading scientists, funded by the National Institutes of Health (NIH), published, "Nitric Oxide and Peroxynitrite in Health and Disease,"[1] This paper details the massive destructive capabilities of peroxynitrite ($ONOO^-$).

The lead author, Dr. Pal Pacher, who has authored 260 peer-reviewed publications, is among the top 50 most-cited researchers in the pharmacology and toxicology fields worldwide. He is joined by Ph.D.'s Joseph Beckman and Lucas Liaudet. Beckman is Principal Investigator and Burgess and Elizabeth Jamieson Chair in Healthspan Research, Linus Pauling Institute at Oregon State University. Lucas Liaudet, who is affiliated with University Hospital at Lausanne, has published more than 200 peer-reviewed papers with over 10,000 citations.

Together, this team details the cytotoxic effects, tissue damage and biochemical disruption of peroxynitrite and then systematically connects the molecule to more than 60 chronic diseases. Among them: neurodegenerative disorders, heart disease, vascular disease, accelerated aging, hypertension, inflammatory disease, cancer, stroke, arthritis, IBS, kidney disease, liver disease, Alzheimer's, MS and diabetes.

Until now many in the scientific community has been reticent to propose a unifying factor that explains the dramatic rise of so many seemingly unrelated diseases. Yet, there is growing evidence that peroxynitrite may just be that elusive *factor*. I recently asked Dr.

Pacher, if it would be hyperbole to call peroxynitrite a "smoking gun" for chronic disease. Without hesitation he replied, "Absolutely not!"

Though peroxynitrite is not strictly a free radical, it acts as both an *oxidative* and *nitrative* agent, causing extensive cellular damage, while disrupting at least 97 *critical* biological processes (see appendix). This molecule is set loose by the combination of two free radicals, one of which is nitric oxide (NO). Among the most studied molecules in the body, nitric oxide is known to be critical to almost every cellular function. When found in close proximity, it combines with superoxide (O2) to create peroxynitrite ($ONOO^{-}$). In turn, peroxynitrite catapults our sensitive biochemistry into unimaginable chaos.

Left unchecked, *peroxynitrite* single-handedly creates high levels of oxidative stress (OS), nitrative stress (NS), mitochondrial dysfunction (MD) and autonomic dysfunction (AD) while triggering *cytokine storms*, which then lead to chronic systemic inflammation (CI). By stealing electrons from important biological actors like lipids (essential fats), proteins and enzymes, peroxynitrite wreaks havoc on cellular integrity and function, upends ATP (energy) production, interferes with ion messaging and disrupts key neurotransmitters. Meanwhile the prolific anion recklessly damages DNA, which leads to downstream genotoxic effects and cultivates an ideal biological environment for disease.

The *Chronic Disease State*

Our research tracks forty fast growing diseases and conditions which share a common biological profile. The following five biofactors, which are all triggered by peroxynitrite[1], emerge as common constituents of what may ultimately serve to define the *chronic disease state* (see Table 1):

- Oxidative Stress (OS)
- Nitrative stress (NS)
- Chronic Inflammatory State (CI)
- Mitochondrial Dysfunction (MD)
- Autonomic Dysfunction (AD)

In their paper, *Pacher et al* build *the* theoretical case for how a complex series of biochemical disruptions, triggered by peroxynitrite, sets in motion a lethal combination of *oxidative* and *nitrative stress*. Free radicals and nitrative agents like *nitrotyrosine* disrupt a broad array of biological systems, which, in turn, leads to a self-reinforcing *vicious cycle* of chronic inflammation, mitochondrial dysfunction and autonomic dysfunction. The expected outcome predicts disequilibrium, biological chaos and the emergence of disease.

Sections and Graphics on 1) Oxidative Stress; 2) Mitochondrial Dysfunction; 3) Chronic Inflammation; 4) Autonomic Dysfunction; and 5) Neurological Disease will be added here.

DATA on Chronic Disease and Medical Conditions

In our survey of the literature, the real life drama plays out precisely as Pacher, Beckman and Liaudet have predicted. We are now facing an alarming level of fast-growing diseases for which there has been no warning. Peroxynitrite sits conspicuously at the heart of this unexpected health drama. A single prolific molecule emerges as a central antagonist and prime mover in the unprecedented rise in chronic disease. The synchronicity of the theoretical science on peroxynitrite and the extraordinary real-world impacts we have experienced to human health leaves little question as to the root cause of the dramatic rise in chronic disease in the US.

The following data tracks the *generation growth* of forty chronic diseases and conditions plus the key biological associations with peroxynitrite and the concomitant biofactors and economic costs.

Table 1 tracks a new class of chronic diseases and medical conditions which have dramatically risen since 1990. The focus of this data is strictly on germless, chronic diseases that share the following common factors:

- Each more than doubled in prevalence since 1990.
- Each is associated in scientific studies with:
    - Peroxynitrite
    - Oxidative Stress (OS)
    - Nitrative Stress (NS)
    - Mitochondrial Dysfunction (MD)
    - Chronic Inflammation (CI)
    - Autonomic Dysfunction (AD)

Our research primarily draws from studies cited or published by the Centers for Disease Control (CDC), PubMed and/ or the National Institutes of Health (NIH). Though we found data for some diseases were out of date – more than five years old – we supplement our data from scientific studies from other nations like Canada, the UK, Ireland or Denmark to fill in the gaps. Through this process we discovered the existence of a generally *unrecognized epidemic* of chronic disease, which we estimate affects more than 170 million Americans.

Generation Growth

This paper tracks the secular growth of chronic disease from 1990-2015 – a single generation. One challenge in calculating growth across a generation arises from the paucity of data available that precisely covers the 25 year period. Consequently, we have been compelled to identify data which best contrast *partial* time segments during this period. Despite the potential shortcomings of this convention, solid evidence of an upward secular trend still emerges, signifying the steady increase in prevalence of chronic disease in the US.

As a means for revealing the underlying growth of prevalence of disease, we have created a category called *Generation Growth*. This metric serves to normalize the data for comparison by extrapolating growth across partial time intervals to reflect expected growth over the 25 year period. In some cases this approach may overestimate actual growth; and in others it may underestimate it. Additionally much of the data utilized in our calculations are estimates for the prevalence of disease. Thus it is challenging to create precise empirical results. Nonetheless the extraordinary acceleration of multiple chronic conditions demonstrate clear secular trends for a new class of chronic diseases.

Secular Trends

On balance the data reveals an accelerating upward trend for autoimmune, inflammatory, metabolic and neurological/ neurodegenerative diseases that cannot be simply explained by an aging population. Nor can it be easily explained by a trend within the medical community to more aggressively diagnose chronic disease and disorders. The uptick in a new class of chronic diseases and disorders confirms what most of us have already been observing anecdotally in families and communities for some time.

It should be noted that this paper primarily tracks *prevalence* of disease but also employs *incidence* statistics, depending on the available science. Prevalence measures the percentage (%) of the population affected by each disease. Incidence signifies the % of new cases reported each year. The percentages listed in Table 1 represent absolute changes in proportions over a particular time interval, which vary.

Societal Impacts

The economic and social impacts from these new diseases is substantial. The US is spending more than $2.5 trillion annually on these 40 diseases, which includes medical costs, lost income and research. The human suffering and societal costs are incalculable. Conservative estimates show more than 700 million instances of these fast-growing chronic diseases across the US population in 2016.

It is important to mention that a*ffected population* figures are provided for each of the forty diseases and disorders but likely underestimate actual levels. The data in our chart reflect statistics that both precede the publication date of each study and some that are already years out of date. Both factors serve to underestimate current levels, especially for dramatically growing diseases. Assuming an average of four instances of disease per person, the data suggest at least 175 million people are affected by at least one of these forty chronic diseases. This equates to approximately 53% of the US population. As context, the CDC reports that 48.7%[2] of the population has taken a prescription drug in the past 30 days. Data follows:

Table 1.

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxy nitrite	Tyrosine Nitration	OS	CI	MD	AD
1	Neurological[3]	**ADD/ ADHD**	5,312,000[4]	139%[4]	204.5[5,6]	204.5[7]	42.5[8,9]	N/A	.045[6]	1[10]	1[10]	3[10,11,12]	1[13]	1[14]	1[15]
2	Inflammatory	**Allergic Rhinitis**	60,000,000[16]	79%[17]	17.51[6,18]	17.5[18]	17.5[18]	N/A	.006[6]	2[19,20]	3[16,20,21]	2[16,22]	2[16,22]	1[23]	1[24]
3	Inflammatory	**Allergies - Food**	16,474,300[25]	104%[25]	24.88[6,26]	24.8[26]			.035[6]	1[16]	1[16]	1[27]	2[28,29]	1[30]	1[31]
4	Neurological[32]/ Inflammatory[33]	**Alzheimer's**	4,700,000[34]	299%[34,35]	227.2[6,36]	226.6[36]	186[36]		.562[6]	12[1,37,38,39,40,41,42,43,44,45,46,47]	9[37,38,39,41,42,43,44,45,46,47]	7[37,39,40,42,43,44,47,48]	3[43,49,50]	4[43,47,51,52,53]	1[54]
5	Mental Health	**Anxiety**	40,000,000[55]	104%[55]	42.3[56]	42.3[56]				2[57,58]	1[59]	2[60,61]	1[62]	1[63]	1[64]
6	Mental Health	**Panic Disorder**	6,000,000[65]	263%[56,66]	Incl. In Anx.[56]	Incl. In Anx.[56]				1[58]	1[67]	1[60]	1[62]	1[63]	0
7	Inflammatory	**Osteoarthritis**	27,000,000[68]	449%[69]	153.3[70]	153.3[70]	83.6[70]	69.7[70]		4[71,72,73,74]	1[75]	1[76]	2[77,78]	1[79]	1[80]
8	Inflammatory	**Asthma**	25,500,000[81]	142%[81]	62.1[6,82]	61.9[82]	56[82]	5.9[83]	.241[6]	7[1,74,84,85,86,87,88]	4[74,84,88,89,]	4[84,85,88,90]	3[84,88,91]	1[92]	2[31,93]
9	Neurological[94]	**Autism Spectrum Disorder**	4,664,280[95]	2094%[95,96]	268.2[6,97]	268[97]	126[97]		.188[6]	5[98,99,100,101,102]	4[98,99,100,101]	4[98,99,100,103]	4[98,99,100, 103]	3[98,100,103]	1[104]
10	Autoimmune	**Autoimmune Disease**	(24,114,643) [†105]	221%[†]	100.8[6,106]	100.8[106]	100[106]		.822[6]	9[1,46,74,107,108,109,110,111,112]	7[46,75,107,108,111,112,113]	1[114]	2[107,115]	1[116]	1[117]
11	[Neurological] [118,119,120]	**Bipolar Disorder** (youth)	768,481[121]	10833%[121]	151.0[122]	151[122]	30.7[122]	120.3[122]		3[123,124,125]	2[124,125]	3[123,124,126]	3[123,126,127]	2[123,128]	1[129]
12	Vision	**Cataracts**	20,500,000 [130]	480%[130]	10.7[131]	10.7[131]	10.7[131]			7[132,133,134,135,136,137,]	5[135,136,138,139,140]	3[133,134,136,141]	1[142]	1[143]	1[144]

[†] Autoimmune diseases tracked in this paper include Alzheimer's, Celiac, CFS, Type 1 Diabetes, Lupus, MS and IBD. Total affected for these diseases are tallied in the totals. However, the total affected listed for autoimmune disease is not included in final totals, as that number includes diseases not tracked in this paper. .

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	Tyrosine Nitration	OS	CI	MD	AD
										[138]					
13	Autoimmune/ Inflammatory	**Celiac Disease**	3,000,000[145,146]	1111%[147]	24.65[6,148]	24.65[148]	24.65[148]			5[46,74,149,150,151]	4[46,149150,152]	1[149]	1[149]	1[153]	1[154]
14	Inflammatory	**Chronic Fatigue Syndrome**	8,077,200[155]	11027%[155,156]	51.0[6,157]	51[157]	14[157]	37[157]	.005[6]	5[158,159,160,161,162]	2[161,162]	2[162,163]	1[164]	2[162,165]	1[166]
15	Genetic	**Congenital Heart Disease*** **(CHD)**	2,000,000[167]	143%[168]	78.7[169]	78.7[169]	78.7[169]			1[170]	1[170]	1[171]	1[172]	1[173]	1[174]
16	Inflammatory[175]	**COPD**	3,862,335[176]	148%[176]	50.1[6,177]	50[177]	30[177]	20[177]	.107[6]	9[178,179,180,181,182,183,184,185,186]	7[178,179,180,181,182,183,187]	1[188]	1[189]	1[190]	1[191]
17	Mental Health	**Depression**	20,304,560[192]	280%[192]	192.3[6,193]	191.9[193]	86.4[193]		.396[6]	5[194,195,196,197,198]	3[194,195,196]	4[198,199,200,201]	4[195,200,202,203]	3[199,200,204]	1[205,]
18	Metabolic	**Diabetes Mellitus**	29,100,000[206]	305%[207]	246.0[6,208]	245[208]	176[208]	69[208]	1.011[6]	10[1,71,209,210,211,212,213,214,215,216]	8[46,210,211,212,213,214,217,218]	2[211,219]	2[220,221]	2[211,222]	1[223]
19	Autoimmune[224]/ Metabolic	**Diabetes Type 1**	Incl. in Diabetes Mellitus[206]	144%[225]	Incl. in Diabetes Mellitus[6,208]	Incl. in Diabetes Mellitus[208]	Incl. in Diabetes Mellitus[208]		Incl. in Diabetes Mellitus[6]	9[1,46,74,209,210,211,213,214,216]	6[46, 210,211,213,214,218]	1[226]	1[227]	1[222]	1[228]
20	[Neurological][229][Inflammatory][230]	**Erectile Dysfunction**	18,000,000	150%[231]	1.0[232]					5[233,234,235,236,237]	3[233,234,235]	1[238]	1[239]	1[240]	1[241]
21	Neurologic[242,243]	**Fibromyalgia**	6,345,959[244]	7727%[6,245]	37.7[246]	37.7[246]	37.7[246]		.010[6]	2[158,247]	2[158,247]	1[248]	1[249]	1[248]	1[250]
22	Autoimmune/ Inflammatory	**Inflammatory Bowel Disease (IBD)**	1,150,000[251]	120%[6,252]	11.9[6,253,254]	11.8[254]	6.3[254]	5.5[253]	.125[6]	8[1,74,112,255,256,257,258,]	5[112,255,256,257,260]	2[257,261]	2[257,262]	2[263,264]	1[265]

* It is thought that the growth in prevalence of congenital heart disease may be largely due to increased longevity.

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	Tyrosine Nitration	OS	CI	MD	AD
										259					
23	[Inflammatory]	**Hypertension**	92,799,900[266]	223%[6,266]	73.6[267]	73.4[267]			.216[6]	5[1,74,268,269,270]	3[268,269,271]	2[268,272]	2[268,273]	2[268,274]	1[275]
24	Renal	**Kidney Stones**	28,620,000[276]	246%[277]	5.3[278]	5.275[278]	4.5[278]	0.775		1[279]	2[279,280]	1[281]	1[282]	1[283]	1[284]
25	Inflammatory	**Kidney Disease: ESRD**	871,000[285]	413%[285]	32.0[286]	32[286]	32[286]			2[74,287]	1[287]	1[288]	1[289]	1[290]	1[291]
26	[Inflammatory][292,293]	**Leukemia**	327,520[294]	588%[294]						1[295]	1[296]	1[297]	1[298]	1[299]	1[300]
27	Autoimmune/ Neurological/ Inflammatory	**Lupus (SLE)**	563,542[301]	787%[6,282]	9.9[302]	9.77[302]	5.8[302]	3.97[302]	.099[6]	3[1,74,108]	2[75,108]	1[303]	1[304]	1[305]	1[117]
28	Inflammatory[306,307]	**Melanoma**	996,587[308]	145%[308]	3.349[309]	3.349[309]	3.349[309]			2[74,310]	1[310]	1[311]	1[312]	1[311]	1[313]
29	Autoimmune[224]/ Inflammatory	**Multiple Sclerosis**	2,100,000[314]	117%[6,314]	10.1[315]	10[315]	10[315]		.102[6]	7[146,47,74,107,111,316,317]	6[46,47,107,111,316,317]	1[47,318]	4[107,317,319,320]	2[47,321,322]	1[323]
30	Metabolic	**Obesity**	110,736,980[324]	260%[6,325,326]	215.9[6,327]	215[327]	161.3[327]		.857[6]	1[328]	2[328,329]	1[330]	2[220,331]	1[332]	1[333]
31	Mental Health/ Neurological	**Psychosocial: Attentional Problems**		819%[334]						1[10]	1[10]	3[10,11,12]	1[13]	1[14]	1[15]
32	Mental Health/ Inflammatory	**Psychosocial: Emotional Problems**		2500%[334]						5[98,99,100,101,102]	4[98,99,100,101]	4[98,99,100,103]	4[98,99,100,103]	3[98,100,103]	1[104]
33		**SLEEP Disturbances**	112,966,706[††335]		164.133[†][† 6,336]	163.9[††][336]	13.9[†† 336]	150[†† 337]	.233[6]	3[338,339,340]	6[329,338,339,340,341,342]	5[340,341,343,344,345,]	6[341,344,346,347,348,349]	3[340,350,351,]	3[352,353,354]
34	Neurological[355]	**Sleep Apnea**	[47,835,000][†† 336,356]	430%[336,356]	[420][†† 336, 357]	[420][†† 336, 357]	[115][†† 336]	[305][†† 357]		1[339]	4[329,341,342,339]	2[341, 344]	3[341,344,348]	1[350]	1[358]

[††] We use only statistics for *Sleep Disturbances* for "total affected" and "costs." While totals for Sleep Apnea and Insomnia combine for $533 Billon, which is $359 B more than Sleep Disturbances alone, we've adopted the $164 B total for Sleep to cover all categories of sleep tracked.

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	Tyrosine Nitration	OS	CI	MD	AD
35		**Sleep: Dissatisfaction**	[43,370,400] †† 359	165%[359]						1[340]	1[340]	1[340]	2[346,347]	1[350]	1[354]
36	[Neurological] [360]	**Sleep: Insomnia**	[61,228,800] †† 361	123%[361]	[113.9] †† 336	[113.9] †† 336		100†† 336		1[340]	1[340]	1[340]	1[349]	1[340]	1[354]
37	[Inflammatory] [362,363]	**Squamous Cell Cancer**	322,762[364]	177%[364]						2[74,365]	3[365,366,367]	1[368]	1[369]	1[370]	1[371]
38	Neurological	**Stroke**	6,800,000[372]	262%[372] (age 20-54)	34.3[6,373,374]	34.3[373,374]	34[373,374]		.300[6]	2[1,47,74,209,375]	1[47,375]	1[47,376]	1[377]	1[47,378]	1[379]
39	Metabolic[380]/ Inflammatory	**Thyroid Dysfunction**	20,000,000 [381]	233%[381]	4.3[382,383]	4.3[382,383]	4.3[382,383]			1[384]	1[384]	1[385]	1[386]	1[387]	1[388]
40	Metabolic[380]/ Inflammatory/ [Autoimmune[224]]	**Hypothyroidism**	Incl. above	702%[389]						1[384]	1[384]	1[385]	1[386]	1[387]	1[388]
	All Diseases		**Total Affected**	**AVG Generation Growth Rate**	**TOTAL COSTS ($B)**	**Total Economic Burden ($B)**	**Care Cost ($B)**	**Lost Productivity/ Indirect Costs ($B)**	**Research ($B)**						
			703,978,755	**1,142%**	**$2,508**	**$2,503**	**$1,276**	**$1,227 (estimate)**	**$5.36**						

Note: In compiling the data for this paper, we reviewed 190 diseases and chronic conditions, most of which have shown steady growth in the past twenty-five years. We chose the forty chronic diseases based on the metric of doubling in prevalence over the course of a generation.

Appendix: Sample biological impacts of peroxynitrite:

Excerpts from "Nitric Oxide and Peroxynitrite in Health and Disease." (Some citations included in this paper will reflect numbering systems of both papers).

NITRATIVE STRESS

- **Creates nitrative stress:** peroxynitrite readily yields nitrotyrosine in yields of 3–14%. Nitrosative stress produces products such as nitrosothiols and nitrosamines, but nitrotyrosine and nitrotryptophan are more stable products and indicative of a *more intense oxidative stress.* This stress is better characterized as *nitrative stress*[1].
- **Tyrosine nitration**: represents a major cytotoxic pathway in the nervous system, possibly contributing to neurodegenerative disorders. Mitochondria are particularly vulnerable targets of oxidative stress and protein nitration in neurodegeneration (1135). [390]
  - Myeloperoxidase reacts rapidly and directly with peroxynitrite to produce nitrogen dioxide and efficiently catalyzes tyrosine nitration (400, 1112). [391,392]
  - When peroxynitrite acts as an oxidant, it produces nitrite and hydroxide ion rather than isomerizing to nitrate. Consequently, the major decomposition products of superoxide and peroxynitrite formation in the phagosome are ultimately hydrogen peroxide and nitrite. These are also substrates for myeloperoxidase and can be a significant source of tyrosine nitration (158,668, 1113) [393,394,395]
  - It will be the rare exception to find nitrotyrosine being formed without peroxynitrite being a major intermediate.
  - Tyrosine nitration has been identified in at least 50 human diseases and more than 80 conditions modeled in animals, as reviewed recently (476),[74] and these figures are continuously increasing.
- **Peroxynitrite damages complex I in the mitochondria** (919, 1062) [396,397]and might further amplify injury. One of the major consequences of peroxynitrite production within mitochondria is nitration and inactivation of mitochondrial Mn-SOD (826, 827, 830). [398,399,400]
- **Nitration of tyrosine**: In most reported studies, nitration of tyrosine has been associated with a significant loss of function of the nitrated protein. An important example of loss of enzyme activity is that of mitochondrial Mn-SOD, which was the first protein found to be nitrated in vivo. Nitration of a single tyrosine residue (Tyr-34) leads to complete enzyme inactivation (830)[400], with the possible consequence to favor peroxynitrite generation in this organelle, due to the impaired dismutation of $O_2^{\bullet-}$. In vivo, nitration of Mn-SOD has been detected in rodent (828)[401] and human (826)[398] rejected kidney allographs, in cerebrospinal fluid of patients with amyotrophic lateral sclerosis as well as Alzheimer's and Parkinson's diseases (27),[402]and in hearts from humans with diabetes (1397)[403] and from mice exposed to cigarette smoke (691)[404], and it has also been associated with vascular aging (1311)[405].
- **Peroxynitrite nitrates and inhibits Mn-SOD** (830) [400], thereby preventing the breakdown of locally produced superoxide, which further fuels the formation of peroxynitrite.
- **Tyrosine nitration** affects protein structure and function, resulting in the generation of antigenic epitopes, changes in the catalytic activity of enzymes, altered cytoskeletal organization, and impaired cell signal transduction (1132)[406], and is thus increasingly considered as a central aspect of peroxynitrite-mediated cytotoxicity.

- **In vivo, nitration of Mn-SOD has been detected** in cerebrospinal fluid of patients with ALS, Alzheimer's disease, and Parkinson's disease (**27**)[402].
- **Tyrosine Nitration and the heart**: In the heart, nitration of several critical proteins has been proposed as a major mechanism of cardiac dysfunction (**995**, **1300**)[407,408]. Thus both creatine kinase (**740**[409], **877**[410], **878**[411], **883**[412]), a critical energetic controller of cardiomyocyte contractility, and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2A) (**789**[413], **1397**[403]) are rapidly inactivated by tyrosine nitration. Peroxynitrite also nitrates and inactivates the voltage-gated K^+ channels in the coronary endothelium, which may foster cardiac dysfunction by imparing coronary flow reserve (**754**)[414], and nitrates several important structural protein in cardiomyocytes such as desmin, myosin heavy chain, and α-a
- **Tyrosine Nitration and Neurodegenerative Diseases such as Parkinson's**: Tyrosine nitration represents a major cytotoxic pathway in the nervous system, possibly contributing to neurodegenerative disorders. α-Synuclein, a neuronal presynaptic protein, undergoes oligomerization upon peroxynitrite-mediated nitration, forming Lewy bodies, the hallmark of Parkinson's disease (**22**)[415], and nitrated α-synuclein has been detected both in experimental and human Parkinson's disease (**443**, **1042**)[416,417].
- **Tyrosine Nitration and Dopamine**: Peroxynitrite further contributes to Parkinson's disease through nitration (and cysteine oxidation) of tyrosine-hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (**103**, **720**, **721**, **1005**). [418,419,420,421]
- **Tyrosine Nitration : Neurological Diseases: Alzheimer's and ALS:** Peroxynitrite nitrates the microtubule-associated tau protein, inducing tau aggregation, a critical mechanism of Alzheimer's disease (**1073**, **1074**)[40,422], while peroxynitrite-mediated nitration of neurofilament L may be involved in the alterations of motor neurons in amyotrophic lateral sclerosis (**247**).[423]
- **Peroxynitrite disabling of several cytoskeletal proteins** by nitration represents a further major cytotoxic effect attributed to peroxynitrite. Tubulin nitration by peroxynitrite or by direct incorporation of free nitrotyrosine has been reported in cell lines derived from intestine (**54**),[424] neurons (**1269**),[425] and muscle (**199**),[426] resulting in the loss of normal physiological functions
- **Peroxynitrite disorganizes actin polymerization through actin nitration**, and via the nitration of profilin (**658**,**659**),[427,428] an important actin-binding protein. These effects have been associated with platelet dysfunction (**659**),[428] disruption of both intestinal (**55**) and endothelial barrier function (**940**),[429] as well as impaired migration and phagocytosis of activated polymorphonuclear cells (**221**).[430]
- **High concentrations of peroxynitrite enhance nitrotyrosine formation** (which is generally not reversible) and downregulates phosphotyrosine signaling, suggestive of a direct competition between nitration and phosphorylation of tyrosine at high peroxynitrite concentrations. (839)[431]

OXIDATIVE STRESS

- **Produces hydroxyl radical**: Beckman et al. (75) [432] showed peroxynitrite was a far more effective means of producing hydroxyl radical than the widely accepted reaction of reduced iron with hydrogen peroxide (known as the Fenton reaction or the iron-catalyzed Haber-Weiss reaction). These results were confirmed by Hogg et al. using systems to cogenerate superoxide and NO (287, 559). [433,434]
- **Produces Nitrogen Dioxide →** produces oxidation products like those found in cigarettes and air pollution: peroxynitrite produced nitrogen dioxide, which could lead to novel oxidation products

that were previously only suspected to occur after exposure to cigarette smoke or to air pollution.

- **Acts as a strong oxidant:** Peroxynitrite itself is also a strong oxidant and can react directly with electron-rich groups, such as sulfhydryls (1056) [435], iron-sulfur centers (182), [436] zinc-thiolates (245), [437] and the active site sulfhydryl in tyrosine phosphatases (1254). [438]
- **Peroxynitrite oxidizes glutathione**. In addition to protein-bound thiol, peroxynitrite can directly oxidize low-molecular-weight thiols, most notably reduced glutathione (GSH). GSH thereby serves as an efficient endogenous scavenger of peroxynitrite and plays a major role in the cellular defense against this species (**31**).[439] Accordingly, the susceptibility of cells to peroxynitrite toxicity largely depends on the amount of intracellular GSH. GSH depletion enhances peroxynitrite toxicity and tissue injury during circulatory shock (**258**,**278**),[440,441] and a relationship between GSH depletion and enhanced peroxynitrite toxicity has also been proposed as contributing to the development of some neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis (**847**, **1321**).[442,443]
- **Combines with CO2 to create toxic carbonate radical**. The direct reaction of peroxynitrite with CO_2 ($4.6 \times 10^4\ M^{-1} \cdot s^{-1}$ at 37°C) gives rise to an unstable product (nitrosoperoxycarbonate, $ONOOCO_2^-$), which rapidly homolyzes into the $CO_3^- \cdot$ (carbonate radical) and $NO_2 \cdot$ (**34**).[444] Carbonate radical is likely to be more toxic than hydroxyl radical and yields many of the same types of oxidation commonly attributed to hydroxyl radical. Thus carbon dioxide redirects much of the peroxynitrite produced in vivo towards radical mechanisms (**16**).[445]
- **Reacts with carbon dioxide to create the *carbonate radical*;** a significant biological oxidant**.** Carbon dioxide reacts with peroxynitrite to form a transient intermediate nitrosoperoxycarbonate that rapidly decomposes homolytically to nitrogen dioxide and carbonate radical. Carbonate radical is more selective than hydroxyl radical but will initiate many of the damaging reactions commonly attributed to hydroxyl radical in the biological literature and is perhaps more significant as a biological oxidant (873).[446]
- **Peroxynitrite exacerbates oxidative damage to mitochondrial proteins.** Peroxynitrite targets cytochrome *c*, the nitration of which significantly impairs its redox properties. Notably, cytochrome *c* nitration increases its peroxidatic activity, leading to the generation of hydrogen peroxide and exacerbation of oxidative damage to mitochondrial proteins (**178**, **627**).[447,448]
- **Peroxynitrite may alter protein structure and function** by reacting with various amino acids in the peptide chain. The most prevalent reaction is that with cysteine, making thiol oxidation a major modification introduced by peroxynitrite (**1056**, **1057**).[435,449] The direct second-order reaction of peroxynitrite with thiols (particularly with the anion form, RS^-) results in the formation of an intermediate sulfenic acid (RSOH), which then reacts with another thiol, forming a disulfide (RSSR) (**16**).[445] Thiols may also be oxidized by the radicals formed from peroxynitrite, generating thiyl radicals (RS·). Thiyl radicals may react with oxygen and promote oxidative stress by propagating free radical reactions (**334**).[450] They will also react with NO to form nitrosothiols.
- **Modifies proteins** containing a heme prosthetic group, such as hemoglobin (106) [451], myoglobin (540) [452], or cytochrome *c* (1275) *[453]*, oxidizing ferrous heme into the corresponding ferric forms.
- **Neurodegenerative: Alzheimer's. Peroxynitrite directly oxidizes methionine**, forming methionine sulfoxide, and to a lesser extent, ethylene and dimethyldisulfide (**16**).[445] These modifications may participate in immune defenses by inactivating glutamine synthetase (**90**)[454] and the molecular chaperone GroEL (**673**)[455] in bacteria. Met oxidation also inhibits α1-

antiproteinase, which then loses its ability to inactivate proteases, most notably elastase (**1368**).[456] Methionine oxidation is reversed by methionine sulfoxide reductase, an enzyme whose reduced expression in the brain is associated with the development of Alzheimer's disease (**1199**).[457]

- **Peroxynitrite can also oxidize tryptophan** (**16**),[445] yielding *N*-formylkynurenine, oxindole, hydropyrroloindole, and nitrotryptophan,
- **Peroxynitrite modifies histidine**, which inactivates copper and **oxidize tryptophan**. (through a radical mechanism, forming a histidinyl radical, a mechanism involved in the inactivation of Cu,Zn-SOD by peroxynitrite (**15**, **1403**, **1404**).[458,459,460]

MITOCHONDRIAL DYSFUNCTION

Mitochondria are involved in many vital processes, e.g., energy production, calcium homeostasis, and the control of various biosynthetic pathways. They also play essential roles in cell death mechanisms. Disruption of mitochondrial functions is implicated in a great number of disease processes, such as diabetes, atherosclerosis, ischemic heart diseases, stroke, aging, and neurodegenerative diseases.

Peroxynitrite may affect every critical function of the Mitochondria. The pivotal role of peroxynitrite in such derangements is increasingly recognized, as it can react with key components of mitochondria and thus may affect virtually every critical function of these organelles.

- **Peroxynitrite formation in Mitochondria**. Mitochondria can produce both NO, by the activity of a Ca^{2+}-sensitive mitochondrial NOS (mtNOS) (**140**, **528**), and superoxide, following the partial reduction of oxygen within the mitochondrial matrix due to the natural leak of electron from the respiratory chain.
- **interruption of electron transfer at cytochrome oxidase increases the leakage of electrons leading to enhanced formation of superoxide within the mitochondrial matrix and generation of peroxynitrite**. A major physiological function of NO in the mitochondria is to regulate oxygen consumption by reversibly inhibiting cytochrome-*c* oxidase (complex IV of the electron transport chain) via competition with oxygen for the binuclear binding site (**1001**). In conditions of high NO production (e.g., during inflammation, reperfusion injury, or neuronal hyperactivation), the interruption of electron transfer at cytochrome oxidase markedly increases the leakage of electrons from the respiratory chain, resulting in enhanced formation of superoxide within the mitochondrial matrix and generation of significant amounts of peroxynitrite (**143**, **147**, **533**).
- **Peroxynitrite nitrates and inhibits Mn-SOD** (**830**), thereby preventing the breakdown of locally produced superoxide, which further fuels the formation of peroxynitrite.
- **Mitochondrial toxicity of peroxynitrite** results both from direct oxidative reactions and from free radical-mediated damage (**1058**, **1059**), secondary to peroxynitrite reacting with CO_2, giving rise to $CO_3^- \cdot$ and $NO_2\cdot$ radicals. The latter reaction is particularly favored within mitochondria, which are the main organelles where CO_2 is produced during decarboxylation reactions (**1058**, **1059**).
- **Peroxynitrite inactivation of Mn-SOD triggers cardiac failure and CNS pathology that includes mitochondrial vacuolization and oxidized lipid deposits**. Serious consequences arise from the genetic knockout of Mn-SOD, which is generally lethal in the neonatal period. In addition to causing cardiac failure, the mitochondrial Mn-SOD knockout mouse suffers CNS pathology that includes mitochondrial vacuolization and oxidized lipid deposits. Conversely, genetically induced

increased expression of mitochondrial Mn-SOD or induction of the enzyme during stress has been shown to protect mitochondria and cells from oxidative stress. The inactivation of Mn-SOD by peroxynitrite will make mitochondria more vulnerable in neurodegeneration

- **Peroxynitrite damages complex I in the mitochondria** (**919**, **1062**)[396,397] and might further amplify injury. One of the major consequences of peroxynitrite production within mitochondria is nitration and inactivation of mitochondrial Mn-SOD (**826**, **827**, **830**). [398]
- **Peroxynitrite exerts significant inhibition to most components of the electron transport chain,** including complex I (NADH dehydrogenase) (**146**, **919**, **1016**) [396], complex II (succinate dehydrogenase) (**111**,**1092**), complex III (cytochrome *c* reductase) (**489**, **1016**), and complex V (ATP synthetase) (**177**,**1058**, **1059**), through mechanisms involving, to various extents, cysteine oxidation, tyrosine nitration, and damage of iron sulfur centers, as extensively reviewed in References **1058** and**1059**
- **Peroxynitrite exacerbates oxidative damage to mitochondrial proteins.** Peroxynitrite targets cytochrome *c*, the nitration of which significantly impairs its redox properties. Notably, cytochrome *c* nitration increases its peroxidatic activity, leading to the generation of hydrogen peroxide and exacerbation of oxidative damage to mitochondrial proteins (**178**, **627**).
- **Permeability transition pore (PTP) induces mitochondrial swelling and rupture of the outer membrane** with subsequent efflux of proapoptotic molecules. Depending on the degree of MPT, cells may either recover (minimal MPT) or die by apoptosis (moderate or transient MPT, with maintained ATP production) or necrosis (widespread and irreversible MPT, leading to severe ATP depletion) (**982**,**984**, **1356**).
- **Increased superoxide production in mitochondria** should render them vulnerable when exposed to NO (**532**)[47]
- **Peroxynitrite impairs energy metabolism** by inhibiting the tricarboxylic acid cycle enzyme aconitase, located in the mitochondrial matrix, via oxidative disruption of the 4Fe-4S center of the enzyme (**182**, **511**), as well as mitochondrial creatine kinase, which is present in the intermembrane space (**1197**).
- **Peroxynitrite oxidizes Nicotinamide nucleotide transhydrogenase, which allows formation of NADPH** from NADH and NADP. This mitochondrial protein is oxidized, nitrated, and inactivated by peroxynitrite (**403**). The ensuing depletion of NADPH reduces the mitochondrial ability to regenerate GSH, contributing to the amplification of oxidative stress within the organelle.

INFLAMMATION

- **Activates NFκB and stimulates interleukin (IL**). –a series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (**391**, **640**, **674**, **1476**). [461,462,463,464] These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions. Matata et al. (**851**) [465] also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (**851**)[465].

- **Inflammatory Disease: Demyelination**: Peroxynitrite may play a critical role in inflammatory diseases of the nervous system by initiating peroxidation of myelin lipids, leading to demyelination (1155,1175, 1313).
- **Peroxynitrite activates NFκB** A series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (391, 640, 674, 1476). These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions.
- Matata et al. (851) [465] also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (851). [465]
- **Enhances inflammatory cell recruitment**
- **Peroxynitrite activation of proinflammatory cytokines activates nitric oxide.** Enhanced NO production due to induced expression of iNOS by proinflammatory cytokines is instrumental in the pathophysiology of inflammation**.**

IMMUNITY

- **Negatively affects normal immune response**: the impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo.
- **Autoimmune: Lupus, arthritis and glomerulonephritis:** the modulation of tyrosine kinase-dependent signaling, peroxynitrite and cell signaling, and the generation of new epitopes on proteins, to which T and B lymphocytes are not rendered tolerant. A number of nitrotyrosine-carrying proteins have thus been shown to elicit both humoral and cellular immune responses in mice (102, 966), and recent findings indicate that nitrated proteins may be involved in the development of autoimmune diseases such as systemic lupus erythematosus, arthritis, and glomerulonephritis (571, 671).
- **The impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions**. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo (137).

DNA DAMAGE

- Peroxynitrite can damage DNA by introducing oxidative modifications in both nucleobases and sugar-phosphate backbone (for review, see Refs. 160, 945). Among the four nucleobases, guanine is the most reactive with peroxynitrite due to its low reduction potential (1422). The major product of guanine oxidation is 8-oxoguanine, which further reacts with peroxynitrite, yielding cyanuric acid and oxazolone (945). Ultimately, guanine oxidation by peroxynitrite results in guanine fragmentation, a critical step towards mutagenesis and carcinogenesis (160, 945).

- **Peroxynitrite can nitrate guanine**, yielding 8-nitro-guanine, which leads to the formation of abasic sites that can be cleaved by endonucleases in vivo to give DNA single-strand breaks (160, 945,1422).
- **The formation of DNA single-strand breaks** represents a critical aspect of peroxynitrite-mediated cytotoxicity, since they represent the obligatory trigger for the activation of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) (1243), a pathway ultimately related to the induction of cell death and tissue inflammation, as developed in detail in the next section.

ENDOTHELIAL DYSFUNCTION

- **Prostacyclin synthase (PGI_2 synthase) is another important target of peroxynitrite** that is inactivated by a specific nitration of Tyr-430 (1130). PGI_2 synthase is rapidly nitrated in arterial walls during inflammatory processes (39), through a mechanism involving CD40 ligand-dependent increases in vascular peroxynitrite generation (290). The consecutive loss of PGI_2 synthesis may be a significant contributor to endothelial dysfunction in many pathological conditions, e.g., diabetes (1473), atherosclerosis (290), and ischemia-reperfusion (1468) and may play an important role in the phenomenon of nitrate tolerance (549).

INACTIVATES ENZYMES

- **The oxidation of critical cysteine residues by peroxynitrite inactivates many enzymes** involved in cellular energetic processes, including glyceraldehyde-3-phosphate deshydrogenase (157, 1192), creatine kinase (703), complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), and complex III (cytochrome *c* reductase) as well as complex V (ATP synthase) from the mitochondrial respiratory chain (1058, 1059, 1062). [397]
- **Cysteine oxidation by peroxynitrite may result in enzyme activation** instead of inhibition, as demonstrated for matrix metalloproteinases (MMPs), which have been recently implicated as an important mechanism of peroxynitrite-dependent toxicity in heart disease (994,1085, 1345) and stroke (495).

EPITHELIAL DAMAGE

- **Cause airway hyperresponsiveness and airway epithelial damage**. .
- **Inhibits pulmonary surfactant.** Asthma is characterized by increased airway hyperresponsiveness, airway epithelial shedding, and inflammation. (2) [466]

NEUROTRANSMITTER DISRUPTIONS

- **Tyrosine Nitration and Dopamine**: Peroxynitrite further contributes to Parkinson's disease through nitration (and cysteine oxidation) of tyrosine-hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (103, 720, 721, 1005).

LIPID PEROXIDATION

- **Lipid Peroxidation**: A major aspect of peroxynitrite-dependent cytotoxicity relies on its ability to trigger lipid peroxidation in membranes (1055), liposomes, and lipoproteins by abstracting a hydrogen atom from polyunsaturated fatty acids (PUFA). Resulting products include lipid hydroperoxyradicals, conjugated dienes, and aldehydes (311). Such radicals in turn attack neighboring PUFAs, generating additional radicals which propagate free radical reactions and the degeneration of membrane lipids (560, 1055), causing membrane permeability and fluidity changes with significant biological consequences (1075).
- **Oxidizing agent toward LDL leading to atherogenesis.** Peroxynitrite acts as a potent oxidizing agent towards low-density lipoprotein (LDL) (742,1287). Peroxynitrite-modified LDL binds with high affinity to scavenger receptors leading to the accumulation of oxidized cholesteryl esters and foam cell formation, which represent a key early event in atherogenesis (465, 498, 558).
- **Secondary oxidative insults:** peroxynitrite with membrane lipids may lead to the formation of various nitrated lipids, with potential biological properties as mediators of signal transduction both under physiological and pathological conditions (50), and of several intermediates products, including isoprostanes and 4-hydroxynonenal that can further trigger secondary oxidative insults (311)

APOPTOSIS

Once the level of cellular damage inflicted by peroxynitrite supersedes any possibility of repair, the cell eventually dies via one of the two main pathways of cell demise, necrosis or apoptosis. Necrosis is associated with loss of cellular ATP, leading to membrane disruption, release of noxious cellular debris, and the development of secondary inflammation. In contrast, apoptosis occurs in a well-choreographed sequence of morphological events characterized by nuclear and cytoplasmic condensation with blebbing of the plasma membrane. The dying cell eventually breaks up into membrane-enclosed particles termed apoptotic bodies, which are rapidly ingested and degraded by professional phagocytes or neighboring cells, without inducing any inflammatory response.

- **Cell Death: Apoptosis from cell signals**: In addition to directly targeting the mitochondria, peroxynitrite can also activate cell death mechanisms through the modulation of various cell signal transduction processes. The role of mitogen-activated protein kinases (MAPKs) and Akt (protein kinase B) deserves some comment here, though more details on these cascades are given in section V. MAPKs comprise three distinct members, ERK, JNK, and p38, whose activation regulates many critical cellular functions, notably apoptosis, and which are strongly activated by peroxynitrite in vitro

- **Peroxynitrite mediated apoptosis across cell types:** in HL-60 cells (773), PC12 cells (367), fibroblasts (1064), SN 4741 dopaminergic neurons (1148), SH-SY5Y neuroblastoma cells (1101), primary neurons (115, 370, 664, 665), astrocytes (1452) and oligodendrocytes (1439), endothelial cells (319, 1339), beta islet cells (309, 1210), neutrophils (408, 1267), chondrocytes (1366), cardiomyocytes (30, 750), and renal tubular cells (13).
- **Peroxynitrite acts via mitochondrial permeability transition (MPT**) (29), which is a prominent feature of peroxynitrite-mediated cell death. MPT describes the permeabilization of the inner mitochondrial membrane by a multiprotein complex termed the permeability transition pore, which is composed of the adenine nucleotide translocase (ANT), cyclophilin D (CyP-D) and the voltage-dependent anion channel (VDAC). Formation of the permeability transition pore is triggered by calcium overload or by oxidative modifications of critical thiol groups within the ANT, allowing its interaction with CyP-D. The permeability transition pore results in the

dissipation of mitochondrial membrane potential ($\Delta\psi_m$), cessation of electron transfer and ATP production, and the secondary production of reactive oxygen species within the mitochondria, which further amplify the phenomenon.

- **Permeability transition pore (PTP) induces mitochondrial swelling and rupture of the outer membrane** with subsequent efflux of proapoptotic molecules. Depending on the degree of MPT, cells may either recover (minimal MPT) or die by apoptosis (moderate or transient MPT, with maintained ATP production) or necrosis (widespread and irreversible MPT, leading to severe ATP depletion) (982,984, 1356).
- **Permeability transition pore (PTP) opening in response to peroxynitrite** has been documented in isolated mitochondria (118, 142, 1127, 1326), where it is likely to occur as a consequence of peroxynitrite-mediated oxidation of cysteine-bound thiols in the ANT (1326).
- **Calcium overload enhances PTP opening by peroxynitrite** suggest that calcium-dependent sensitization of certain mitochondrial proteins to oxidative/nitrative damage is critical for apoptosis to proceed following peroxynitrite exposure (142).
- **Peroxynitrite causes dissipation of mitochondrial potential** (216, 758, 1148, 1332, 1339), **mitochondrial efflux of cytochrome** *c* (758, 1339), and **caspase activation** (1148, 1339) occurred to various extents in different cells exposed to endogenously produced or exogenously added peroxynitrite

CELL SIGNALING and PEROXYNITRITE

The concept of cell signaling defines the ability of cells to detect changes in their environment to generate an appropriate physiological response (1362). In the past few years, significant experimental efforts have been put forward to explore the relationships between cellular oxidative processes and the modulation of cell signal transduction, collectively grouped under the concept of “redox signaling” (848). The early observation that NO could regulate many critical cell signaling processes through *S*-nitrosylation of critical cysteine residues in proteins was a milestone discovery in our understanding of redox regulation of signal transduction (1200). Soon thereafter, the identification of peroxynitrite's ability to nitrate tyrosine residues rapidly focused attention on phosphorylation cascades, as this protein modification was found to inhibit cell signaling processes relying on tyrosine phosphorylation. Although this view was initially strongly considered, it proved to be overly simplistic, as peroxynitrite often promoted phosphotyrosine signaling in many instances. Further evidence was gathered that, in many different cell systems in vitro, peroxynitrite behaved as a potent modulator of an array of cell signal transduction pathways, independently from its ability to nitrate tyrosine. After a brief summary of the main cell signal transduction pathways, these emerging aspects of peroxynitrite biology are discussed in detail.

Most extracellular signals are sensed by two major families of cell membrane receptors, G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (1362). GPCRs interact with G proteins (guanine nucleotide binding proteins), which act on several downstream effectors to generate second messengers such as inositol trisphosphate, cyclic nucleotides, or Ca^{2+}, which in turn modulate the degree of protein phosphorylation. GPCRs also activate small G proteins (Ras and Rho families) that lie upstream of the MAPK superfamily of proteins (see below) (for review, see Refs. 98, 497). Receptor tyrosine kinases (RTKs) are transmembrane glycoproteins consisting of at least 13 families, e.g., receptors for insulin and growth factors. Upon binding by specific ligands, RTKs create docking sites for specific phosphotyrosine binding domains to recruit and activate downstream effectors, including Ras-MAPKs, phosphatidylinositol 3-kinase (PI3K), and protein kinase C. RTKs control most fundamental cellular processes such as cell proliferation, differentiation, and cell survival, and abnormal RTKdependent signaling has been linked to a number of disease processes, notably cancer and cardiovascular diseases (for review, see Refs.577, 1129).

MODULATION of CELL SIGNALING by PEROXYNITRITE

- **Peroxynitrite induced nitration tyrosine residues can impair signaling processes** depending on tyrosine phosphorylation. Early in vitro studies using peptide substrates showed that phosphorylation of critical tyrosine residues within these peptides was markedly inhibited by peroxynitrite-mediated tyrosine nitration (463, 702), and further results indicated that tyrosine nitration blocked downstream signaling in intact cell systems in vitro
- In the human neuroblastoma SH-SY5Y cells, the **peroxynitrite generator SIN-1 triggered the nitration of the focal adhesion protein p130^{cas}, resulting in the blockade** of its phosphorylation and interfered with the assembly of focal adhesion complexes (1100).

- **Peroxynitrite-dependent nitration of a key tyrosine residue (Tyr686) interferes with its phosphorylation and prevents binding to the protein-tyrosine phosphatase SHP-2.** Nitration of tyrosine residue (Tyr686) within the cytoplasmic domain of the adhesion molec interferes with its phosphorylation by src family protein kinases, and prevents its binding to the protein-tyrosine phosphatase SHP-2 ule platelet-endothelial cell adhesion molecule-1 (PECAM-1), interferes with its phosphorylation by src family protein kinases, and prevents its binding to the protein-tyrosine phosphatase SHP-2 (941).

- **The impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions**. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo (137).

- **Nitrotyrosine disrupts complex chain of signal transduction**. Nitrotyrosine formation in human platelets inhibited tyrosine phosphorylation in response to thrombin, thereby preventing their activation (795, 896) [467,468]. Under certain conditions, competition between nitration and phosphorylation on a single tyrosine residue may completely disrupt a complex chain of signal transduction, as recently shown in primary rat hepatocytes. These cells undergo apoptotic cell death upon stimulation with CD95 (Fas) ligand. Activated CD95 then promotes the formation of a death-inducing signal complex (DISC), committing the cell to apoptosis.

- **Irreversible inhibition of PTPs by very low concentrations of peroxynitrite** has been demonstrated both in cells (791, 839) and purified enzymes (175, 1254). All PTPs contain a conserved cysteine residue, which forms an intermediate phosphocysteine with the phosphatase substrate of the PTP, and oxidation of this critical cysteine has been shown to inactivate the PTPs (1254). Peroxynitrite anion is structurally similar to phosphate anion, so that the extreme vulnerability of PTPs to peroxynitrite-mediated inactivation is consistent with attraction of peroxynitrite to the active site of the enzyme and subsequent oxidation of this essential cysteine (1254).

- **Peroxynitrite targets NRTK family member Src,** as a preferential target of peroxynitrite. Src family members participate in a variety of signaling processes, including mitogenesis, T- and B-cell activation, cell differentiation and proliferation, as well as cytoskeleton restructuring, through the activation of an array of downstream effectors such as PI3K, phospholipase C, and FAK (1087).
- In human red blood cells, the src kinase *hck* was activated by peroxynitrite via cysteine oxidation, whereas another src kinase, *lyn*, was activated through a mechanism involving the inhibition of Tyr527 binding to the SH2 domain (838, 840).

MAPK SIGNALING

- **Peroxynitrite activates MAPKS.** MAPKs (ERK, JNK, and p38) are all activated by a dual phosphorylation at a specific tripeptide motif, mediated by a conserved protein kinase cascade, involving MAP kinase kinase kinases (MKKK or MEKK) and MAP kinase kinases (MKK or MEK) (328). The upstream signaling pathways leading to MKKK activation largely depend on the activation of growth factor receptors and small G proteins, such as Ras, Rac, and Cdc42 (328, 848). Downstream targets of MAPKs include an array of proteins as well as transcription factors, whose activation regulates virtually every critical cellular function, especially apoptosis, cell proliferation, and inflammatory genes expression.

ERK PATHWAY

- **Peroxynitrite potently activates ERK**. ERK is involved in the signaling pathways triggered by growth factors and their receptors, via the successive activation of the small G protein ras, Raf-1 kinase and MEK 1 (1434). ERK can also be activated by various extracellular stresses, including oxidants and free radicals (848). In vitro, peroxynitrite potently activated ERK in fibroblasts (57, 1434), neutrophils (735, 1477), endothelial and vascular smooth muscle cells (1307), neural cells (191, 638, 645, 1099), and cardiomyocytes (1024), through strikingly distinct and cell-specific mechanisms
- **ERK activation by peroxynitrite** (up to 200 μM) has been associated with the upregulation of surface expression of the β_2-integrins CD11b/CD18 and increased neutrophil adhesion to endothelial cells (1477), as well as an enhanced oxidative burst upon stimulation (735). These data then support a potential role of peroxynitrite in mediating excessive neutrophil trafficking and superoxide generation under inflammatory conditions.
- With respect to peroxynitrite stimulation, it is noticeable that all studies performed so far have indicated a proapoptotic role of ERK. Indeed, peroxynitrite-induced apoptosis in primary rat astrocytes (1420), human SH-SY5Y neuroblastoma cells (1099), human bronchial epithelial BEAS-2B cells (922), and primary murine neurons (645) was associated with the activation of ERK and was significantly attenuated by MEK-ERK pathway inhibitors

JNK PATHWAY

- JNK exists as three distinct isoforms, activated in response to many different environmental stresses via a signaling cascade involving the small G proteins ras and rac, several MAPKKKs, MAPKK, MKK1, and MKK4, linked together by various scaffold proteins in specific signaling modules (198, 291). Activated JNK phosphorylates the protoconcogene product c-*jun*, allowing its homodimerization or heterodimerization with c-*fos* to form the active transcription factor

AP-1. JNK is involved in the regulation of inflammation and cell death, with both pro- and antiapoptotic reported functions (198, 291).

- JNK activation in response to peroxynitrite has been reported in many different cell types (23,450, 922, 1024, 1128, 1162).
- Go et al. (450) showed that endogenously produced peroxynitrite was responsible for the activation of JNK triggered by laminar shear stress in endothelial cells (450).
- JNK activation by peroxynitrite was causally linked to apoptotic cell death in murine alveolar C10 cells, as cells expressing a dominant negative mutant of JNK1 were protected from peroxynitrite-mediated apoptosis (1162).

P38MAPK

- The p38 family consists of at least five different isoforms: α, β_1, β_2, γ, and δ, whose activation by environmental stress is controlled by several MAPKKKs as well as MKK3 and MKK6. The activation of p38 has been linked with apoptotic cell death and mitotic arrest in a great variety of cells exposed to different oxidants and free radicals (848).
- Peroxynitrite is extremely efficient in activating p38, as shown by the very early (within minutes) phosphorylation of p38 upon peroxynitrite stimulation, even at low concentrations (<10 μM) in cardiomyocytes (1024), endothelial (350, 450) and vascular smooth muscle cells (1307), hepatocytes (414, 1128), bronchial epithelial cells (922), and neural cells (120, 638, 965, 1120, 1440).

PKC pathway

- PKC represents a family of phospholipid-dependent serine/threonine kinases involved in signaling pathways regulating cell growth and differentiation, cell death, immune response, transcriptional regulation, and stress responsiveness (notably oxidative stress) (458, 848). PKC-mediated cellular effects are both tissue and isoform specific. PKC exists as 11 different isoforms, subdivided in three distinct subgroups (classical PKC α, βI, βII, γ; novel PKC δ, ε, η, θ; and atypical PKC λ, ι, ζ), separated upon their particular mechanism of activation (45).
- **Peroxynitrite has been associated with a significant reduction of the activity of PKC α, β, ε, and ζ in neuronal cells**, and the degree of this inhibition correlated completely with the degree of tyrosine nitration within the enzyme (689). Importantly, PKC is essential for a number of aspects of neuronal functions including synaptic plasticity, learning, and memory. Decreased PKC activity may contribute to several neurodegenerative disorders (66, 689), which are also associated with increased peroxynitrite generation (1284). PKC inhibition might thus represent one of the mechanisms linking peroxynitrite in the brain with neurodegeneration.

NFκB

- NFκB is a crucial transcription factor activating inflammatory and antiapoptotic genes in response to immunostimulation.
- A series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (391, 640, 674, 1476).

These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions.

- Matata et al. (851) [465] also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (851). [465]

CELL SIGNAL TRANSDUCTION

- **Disrupts complex chain of signal transduction** Nitrotyrosine formation in human platelets inhibited tyrosine phosphorylation in response to thrombin, thereby preventing their activation (795, 896) cross ref. Under certain conditions, competition between nitration and phosphorylation on a single tyrosine residue may completely disrupt a complex chain of signal transduction.
- **Peroxynitrite-mediated activation of ERK** committed bronchial (922) and neural cells (645, 1099, 1420) to apoptotic cell death,
- **Peroxynitrite mediated activation of JNK**, p38, or both triggered a similar outcome in murine alveolar cells (1162), cerebrocortical neurons (120), and PC12 cells (1148), respectively.
- **Peroxynitrite creates the release of free Zn^{2+}** by peroxynitrite, possibly due to oxidation of Zn^{2+}-sulfur bridges in mitochondrial and cytosolic proteins (120, 245, 1469), could play an essential role in initiating these responses (120, 1439, 1440).
- **Peroxynitrite activates MAPKs**: peroxynitrite activation of MAPKs has been associated with significant inhibition of protein kinase B (Akt), a serine-threonine protein kinase whose activation represents a powerful protective mechanism to limit apoptosis in various stress conditions, including oxidative stress (848).
- **Peroxynitrite blocks the activation of Akt in macrophages** (536), adipocytes (949), PC12 cells (1148, 1193), and endothelial cells (353, 485–487, 1471), through a mechanism involving nitration and inactivation of phosphatidylinositol 3-kinase, the upstream signaling intermediate in the Akt pathway (353, 536).

NECROSIS

- **High concentrations of Peroxynitrite have been associated with necrosis.** Whereas apoptosis is a typical consequence of low to moderate concentrations of peroxynitrite, exposure of cells to higher concentrations of the oxidant has been associated with necrosis (115,1334). Studies investigating this process have established that peroxynitrite-dependent cell necrosis is not a purely passive phenomenon, but instead is mediated by a complex process involving DNA damage and activation of the DNA repair enzyme PARP-1 (1243). PARP-1 is a member of the PARP enzyme family consisting of PARP-1 and many additional poly(ADP-ribosylating) enzymes. PARP-1 detects and signals DNA strand breaks induced by a variety of genotoxic insults, including ionizing radiations, alkylating agents, oxidants (essentially hydrogen peroxide, peroxynitrite, and possibly nitroxyl anion), and free radicals (mainly carbonate or hydroxyl radical) (299, 696, 1230).

- **PARP-1: peroxynitrite inducees DNA strand breakage leading to PARP activation.** An important function of PARP-1 is to allow DNA repair and cell recovery in conditions associated with a low degree of DNA damage. Upon severe DNA injury, overactivation of PARP-1 depletes the cellular stores of NAD^+, an essential cofactor of the glycolytic pathway, the tricarboxylic acid cycle, and the mitochondrial electron transport chain (762, 769, 1227, 1243). As a result, the loss of NAD^+ leads to a marked decrease in the cellular pools of ATP, resulting in cellular dysfunction and cell death via the necrotic pathway (503, 765) (Fig. 7). This intriguing mode of cell response to acute genotoxic stress led Berger (86) to propose the “suicide hypothesis” of PARP activation, which can be regarded as a way to eliminate cells after irreversible DNA injury. Evidence has been gathered that both exogenous and endogenously generated peroxynitrite potently induce DNA strand breakage leading to PARP activation in a variety of cell types, including pulmonary (1239) and intestinal epithelial cells (666), vascular endothelial and smooth muscle cells (430,1233), fibroblasts (1240), macrophages (1462), and cardiomyocytes (444, 987, 992), to cite just a few examples.

- A vast amount of experimental studies have then established that the **PARP-1 pathway of cell death plays pivotal roles in tissue injury** and organ dysfunction in virtually every disease process accompanied by oxidative/nitrosative stress: ischemia-reperfusion, localized and systemic inflammation, diabetes, and circulatory shock to name but a few (for extensive recent reviews on this topics, see Refs.248, 254, 373, 624, 821, 959, 995, 997, 1228, 1245, 1306).
- **PARP-1 and nuclear factor kappa B (NFκB**). The second additional role of PARP-1 is its involvement in the upregulation of inflammatory processes. The absence of functional PARP-1 (either genetic or pharmacological) alleviated the expression of a host of proinflammatory mediators, including cytokines, chemokines, adhesion molecules and enzymes (e.g., iNOS, COX-2), and it also reduced tissue infiltration with activated phagocytes in experimental models of inflammation, circulatory shock, and ischemia-reperfusion (see Refs. 361, 765, 1230 for review). The proinflammatory function of PARP was initially believed to reflect exclusively its role as an inducer of cell necrosis, which promotes inflammation via the spilling of noxious cellular debris into neighboring tissues. However, this concept was reviewed after the demonstration by Oliver et al. (973) of a functional association between PARP-1 and the proinflammatory transcription factor nuclear factor kappa B (NFκB).

Results (in process)

We tallied 704 million instances of disease from 40 fast-growing diseases at an annual cost to Americans of $2.5 trillion. While these numbers are staggering, they are likely substantially understated. There are hundreds of chronic diseases and medical conditions which are not tracked in this paper. There is also limited access to current data. Few meta-studies since 2011 could be found for the diseases we tracked in this paper and economic impact data for the past 4-7 years are sparse. Thus we are left with only an impression of the actual impacts of chronic disease in America. As the growth of chronic disease is clearly both a human and economic problem, it could be valuable for US agencies to more systematically collect or sponsor acquisition of appropriate disease data. One idea is to gather more current data annually through incentives for those filing annual tax returns. Self-reported illness could provide a more vivid picture of the state of our national health.

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New Age of Chronic Disease:		Selected Generation Growth	
Autism	**+ 2094%**	**Alzheimer's**	**+ 299%**
Diabetes	**+ 305%**	**Autoimmune**	**+ 221%**
Sleep Apnea	**+ 430%**	**ADHD**	**+ 819%**
Bipolar Disorder	**+10833%**	**Asthma**	**+ 142%**
Osteoarthritis	**+ 449%**	**Fibromyalgia**	**+ 7727%**
Depression	**+ 280%**	**Hypothyroidism**	**+ 702%**