The Relationship Between Thimerosal and Autism:

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The statements below summarize my professional opinions concerning the role of thimerosal in causing autism and related developmental disorders. These opinions reflect my knowledge of relevant molecular and metabolic mechanisms in the context of neurological disorders, gained from my personal research and from my reading and from my awareness of the research and clinical experience of others.

My qualifications include:

1. Education: *B.S. Degree in Pharmacy (SUNY at Buffalo, 1970), Ph.D. Degree in Pharmacology (University of Miami, 1975), Post-doctoral Training (University of Leuven, Belgium, 1975/6). Research interest: Molecular Signaling Mechanisms of Neurotransmitter Receptors.*

2. University Professor: *Professor of Pharmacology (School of Pharmacy, Northeastern University, Boston, Massachusetts, 1976-present). Research interests: Structure and Function of G protein-coupled Receptors, Dopamine-stimulated Phospholipid Methylation, Regulation of methionine synthase.*

3. Publications: *Sixty three peer-reviewed original research articles and book chapters, and a monograph entitled: "Molecular Origins of Human Attention: The Dopamine-Folate Connection".*

4. Memberships: *American Society for Pharmacology and Experimental Therapeutics, Society for Biological Psychiatry, Society for Neuroscience.*

Signed

Richard C. Deth, Ph.D Date: August 24, 2007

SUMMARY

Thimerosal (ethylmercury thiosalicylate) has been utilized as a preservative in a number of medical products, particularly those of biological origin, including certain vaccines. Ethylmercury is readily released from thimerosal in solution and is considered to be the primary active species for its preservative function and, similar to other organomercurials, it is a potent neurotoxin. A significant role for thimerosal in causing and/or contributing to autism and other neurological disorders is, in my profession opinion, well-supported by studies of its distribution and elimination and by studies of its metabolic and neurological actions. These studies, including experimental findings from my own laboratory, show that the effects of thimerosal closely parallel metabolic abnormalities found in autistic children, including its ability to induce a state of oxidative stress and impaired methylation status. In brain, and in neurons in particular, these metabolic abnormalities interfere with mechanisms that are critical for normal attention and cognitive abilities, accounting for major symptoms of autism. Congruence between attributes of thimerosal and the features of autism provide convincing evidence that thimerosal exposure represents an important risk factor for autism, particularly in individuals possessing certain risk-inducing polymorphisms. Autistic children possess a higher frequency risk-inducing genetic variants in thimerosal-sensitive pathways, making them more vulnerable than others to its neurotoxic effects. These polymorphisms introduce risk by adversely impacting the capacity for mercury detoxification or elimination, or the ability to sustain redox or methylation balance and/or the ability to synchronize activity of neuronal networks. While thimerosal is capable of causing widespread metabolic disruption in all cell types, the special vulnerability of neuronal cells to oxidative stress increases the prominence of neurological consequences at levels of exposure associated with vaccine administration.

THIMEROSAL: GENERAL ATTRIBUTES

Thimerosal (ethylmercury thiosalicylate) is essentially a molecular delivery system for ethylmercury, the organomercurial which is readily released from the parent molecule in solution. Ethylmercury in turn gives rise to inorganic mercury as it undergoes dealkylation. Like other organomercurials, most notable of which is methylmercury, ethylmercury is toxic to most life forms, including different cell types in complex organisms such as humans. Indeed, it is this broad potential for toxicity that has led to the use of thimerosal as a vaccine preservative. Methylmercury is considered to be one of the most toxic non-radioactive substances and a general threat to human health (1). There is no *a priore* reason to assume that ethylmercury does not share a similar level of toxic risk as methylmercury, since they are close chemical analogs sharing many physical and chemical properties.

Toxic effects of organomercurials are typically chronic due to retention of released inorganic mercury, which can remain in tissues for many years, especially in protected compartments such as the brain, and the rate of release of inorganic mercury from ethylmercury is greater than the rate for methylmercury. Initial claims of thimerosal safety based upon a lack of entry into the brain are patently false, as demonstrated by the important study of Burbacher *et al.*, carried out in infant non-human primates (2). In that study, thimerosal was administered intramuscularly at weekly intervals as a vaccine, at doses comparable to human infants, and levels of mercury were assessed in blood and brain compartments and compared to orally administered methylmercury, which simulated food intake. Thimerosal-derived ethylmercury was cleared more readily from blood compartment and did not achieve as high a level in brain as methylmercury, although significant entry of thimerosal-derived ethylmercury into the brain was observed. Despite more rapid clearance of the parent ethylmercury compound, brain inorganic mercury levels were higher after thimerosal treatment, indicating a higher rate of release from ethylmercury. Moreover, this inorganic mercury showed no significant clearance during the period of study. Thus a greater proportion of thimerosal-derived mercury remains in the brain long-term than is the case for methylmercury. Accordingly, at equal doses, thimerosal carries a higher risk of producing neurological impairments than methylmercury.

Thimerosal is toxic to human cortical neurons and neuronal cells grown in culture (3-5). Thimerosal caused 50% of cells to die after 48 hrs at concentrations between 5 and 100 nM, depending upon the level of nerve growth factor (5). The mechanism of thimerosal-induced cell death appears to involve activation of apoptosis (3,4), similar to methylmercury (6). Patterns of urinary porphyrins in autistic subjects are consistent with effects of mercury exposure (7).

THIMEROSAL AND SULFUR METABOLISM

Sulfur metabolism is a major locus of toxic action for heavy metals, including, but not limited to, mercury and thimerosal. Indeed, thiol compounds containing reduced sulfur are named "mercaptans" for their ability to "capture" mercury, and thimerosal itself consists of mercury bound to the sulfur moiety of thiosalicylate. Thus sulfur metabolism is the single most important system to examine for a contribution of thimerosal to autism. Despite this obvious relationship, earlier reviews of thimerosal safety failed to investigate whether or not thimerosal affected sulfur metabolism and/or whether sulfur metabolism was altered in autistic children exposed to thimerosal (8). Indeed, these studies did not specifically investigate autistic children or the metabolic effects of thimerosal.

Sulfur metabolism serves several critical roles. These include: 1. Maintenance of cellular reduction/oxidation (redox) status. 2. Support of methylation (single-carbon transfer) reactions. 3. Detoxification and elimination

of heavy metals and xenobiotics. 4. Formation of sulfate. Each of these aspects of sulfur metabolism is abnormal in autistic children (9,10), consistent with a toxic influence of thimerosal. Moreover, thimerosal affects these processes with exceptionally high potency, making it the most likely candidate for causing these abnormalities, especially since a specific source of exposure (i.e. immunization with thimerosal-containing vaccines) can be identified.

1. Effects on Cellular Redox Status:

Almost all cellular functions are affected by shifts in the prevailing redox status, the propensity for gain and loss of electrons. Homeostasis, the ability to maintain a favorable metabolic set-point, is closely linked to maintenance of normal redox status. The cysteine-containing tripeptide glutathione (GSH) serves as the primary intracellular antioxidant, and is maintained at a remarkably high concentration, providing a reservoir of metabolic reducing equivalents (11). The ratio of reduced to oxidized forms of GSH (GSH/GSSG) can be as high as 100, but when the rate of GSH oxidation exceeds the rate of its formation, this ratio can be dramatically reduced, creating a state of oxidative stress. Oxidative stress, reflected as a decreased GSH/GSSG ratio (9,10), or an increase in oxidative stress marker levels (12-15) has been well-documented in autism (for reviews see 16-18). Inflammation is a clinical condition in which oxidative stress plays a major role, and the presence of neuroinflammation with activation of microglia has been documented in post-mortem brain samples from autistic (19). In monkeys treated with thimerosal, mercury deposits were found associated with activated microglia cells (20).

Thimerosal significantly reduces cellular levels of GSH in cultured neuronal cells (21-23). *In vitro* studies in our laboratory using human neuronal cells revealed decreases of approximately 40% at a concentration of 10 nM (24). This concentration is 3-fold lower than the plasma concentration of mercury following administration of a single dose of a thimerosal-containing vaccine (25). The threshold effect for thimerosal reduction of GSH is approximately 0.1 nM, indicating a remarkably potent influence on cellular redox status in human neuronal cells.

When doses of thimerosal were administered to different strains of mice at doses and times similar to infant vaccinations, significant neuropathy and developmental disturbances were only observed in the strain harboring genetic deficits in redox-related enzymes (26). Furthermore, up-regulation of the neuronal cysteine transporter EAAT3 in hippocampus was observed in response to thimerosal in this same strain, consistent with an adaptive response to oxidative stress. Thus thimerosal administration produces a pattern of pathology and metabolic disturbance that mirrors some features of autism, in a genetically vulnerable strain of mice.

2. Effects on Methylation

Cells have evolved a large number of adaptive mechanisms to maintain their homeostatic redox set-point (i.e. their GSH/GSSG ratio). Important among

these is redox-dependent regulation of the methylfolate and vitamin B12-dependent enzyme methionine synthase, which uses methylfolate-derived methyl groups to catalyze conversion of homocysteine to methionine. Via multiple mechanisms, oxidative stress inhibits methionine synthase activity, increasing diversion of homocysteine to GSH synthesis via the transsulfuration pathway. Studies in my laboratory demonstrated potent inhibition of neuronal methionine synthase by thimerosal (27), with half maximal inhibition occurring at approximately 1 nM, 30-fold below the plasma concentration produced by a thimerosal-containing vaccine. While other heavy metals (e.g. lead and arsenic) also partially inhibit methionine synthase, mercury and thimerosal are distinguished by their ability to cause complete inhibition. Subsequent investigation revealed that inhibition of methionine synthase was caused by a reduction of GSH levels, limiting synthesis of the active methylcobalamin form of vitamin B12, which is required for activity of the neuronal form of the enzyme (24).

In addition to its methylation of homocysteine, methionine synthase is also required for transferring folate-derived methyl groups to the D4 dopamine receptor, supporting its unique ability to carry out methylation of membrane phospholipids in response to dopamine (28,29). The latter phospholipid methylation (PLM) mechanism allows dopamine to affect the fluid properties of the membrane of neuronal cells, which appears to be intimately involved in dopamine-dependent synchronization of neuronal networks during attention and cognition (30,31). Since this mechanism is absolutely dependent upon activity of methionine synthase, it is highly sensitive to oxidative stress. We have reported that thimerosal potently inhibits dopamine-stimulated PLM, causing half-maximal inhibition at concentrations well below plasma levels produced by immunization with thimerosal-containing vaccines (27).

Children with autism exhibit evidence of impaired methylation, consistent with lower activity of methionine synthase (9,10), and they also exhibit impaired synchronization of neural networks in conjunction with impaired attention and cognition (32-34). Taken together these observations are consistent with thimerosal-induced oxidative stress as a cause of autism-associated neurocognitive deficits.

Accumulation of homocysteine following inhibition of methionine synthase also causes accumulation of S-adenosylhomocystine, a general inhibitor of methylation reactions. Thus agents that induce oxidative stress, such as thimerosal, exert a broad influence on almost two hundred different methylation reactions, including methylation of DNA, which is responsible for epigenetic control over gene expression. Abnormal patterns of DNA methylation are generally recognized as an important contributor to developmental disorders (35,36), and cellular redox status may be a controlling factor in regulating differential gene expression during development (37). Thus thimerosal-induced inhibition of methionine synthase can not only impair molecular mechanisms of

attention and cognition, but can also adversely impact the processes that guide brain development. Thimerosal's ability to cause oxidative stress and impaired methylation is similar to actions of methylmecury and/or other toxic xenobiotics which induce oxdative stress and disrupt signaling pathways that guide development (38).

Thimerosal's ability to cause severe oxidative stress is likely to be the same mechanism by which it kills or inhibits the growth of a wide range of organisms, forming the basis for its use as a preservative. Recognizing this, only its dilution in tissues and body fluids (approximately 1 : 3000 in a 7 lb infant) protects human cells from experiencing the same effects. However, not all human cell types are equally sensitive to its toxic effects and neuronal cells in the brain are most vulnerable to thimerosal. This vulnerability is evident in the extreme potency of thimerosal in causing inhibition of methylation and methionine synthase.

Other roles for methylation that are of particular significance in autism include metabolic inactivation of neurotransmitters by catechol-O-methyltransferase, regulation of nitric oxide synthesis by arginine-N-methyltransferase and synthesis of creatine, which supports energy distribution. Each of these metabolic pathways are reported to function abnormally in autism, consistent with thimerosal-induced impairment of methylation (10, 39-41).

3. Effects on Detoxification

GSH plays a central role in protecting cells from harmful effects of heavy metals and xenobiotics (e.g. pesticides and herbicides) by directly binding them or their metabolites. While the amount of vaccine-derived thimerosal (e.g. 25 μg/dose) is too small to cause a stoichiometric depletion of plasma GSH, thimerosal interferes with cellular production of GSH, contributing to the approximately 40% lower plasma levels in autistic children (9,10). These lower plasma levels increase the circulation time of heavy metals, including thimerosal-derived ethylmercury, as well as xenobiotics. As a consequence, there is an increased opportunity for their transfer across the blood-brain barrier into the central nervous system. In the case of vaccine-derived thimerosal, successive doses can gradually increase the retention of mercury in the brain as the efficiency of peripheral detoxification decreases. Release of inorganic mercury in the brain is particularly harmful, since organomercurical forms (i.e. ethylmercury and methylmercury) have the ability to leave the central nervous system after exposure has ceased and blood levels fall, whereas the ability of inorganic mercury to leave is greatly lower (2). Since inorganic mercury is more readily released from ethylmercury than from methylmercury, thimerosal carries a greater risk of creating a long-term brain burden of mercury.

4. Formation of Sulfate

Sulfate is produced by successive oxidation of cysteine, initially catalyzed by the enzyme cysteine dioxygenase. The latter reaction functionally competes with GSH synthesis, and under conditions of oxidative stress, such as that

induced by thimerosal, cysteine dioxygenase activity is diminished by its ubiquitination and subsequent proteolytic destruction (42). This destruction represents another adaptive metabolic response to preserve GSH levels under stressful conditions, and it reduces sulfate availability for a number of cellular reactions. Of particular importance is sulfation of dihydroepiandrosterone (DHEA), which limits DHEA availability for synthesis of androgens. During oxidative stress, lower sulfate levels lead to an increase of DHEA and augmentation of androgen synthesis, with multiple adverse endocrine and hormonal consequences. Among these consequences is a decrease in diversion of homocysteine to GSH synthesis, which is a feature of the male gender (43). The 4:1 predominance of autism in males *vs.* females is well-established (44), and it has been proposed that excessive male traits may be a feature of autism (45). Thimerosal effects on sulfur metabolism can contribute to such a pattern.

GENETIC VULNERABILITY TO THIMEROSAL

Based upon the above, it is clear that thimerosal exerts its toxic effects via actions on sulfur metabolism. Across the population, individuals harboring genetic differences adversely affecting resistance to oxidative stress or its consequences will exhibit a greater vulnerability to thimerosal, or other similar-acting agents. Recent studies have revealed a number of mutations and single-nucleotide polymorphisms (SNPs) that are associated with autism. Collectively these genetic features begin to define the subpopulation that is at greater risk for autism than the general population. Importantly, a number of autism-associated SNPs directly or indirectly affect sulfur metabolism, redox status and methionine synthase-dependent methylation activity (11,46-48). Accordingly these genetic features will synergize with the potent toxic effect of thimerosal on sulfur metabolism to produce a greater level of oxidative stress and impaired methylation at any given level of exposure. Important examples of these genetic risk factors are:

1. **Methionine synthase reductase:** Reactivates methionine synthase after cobalamin oxidation.
2. **Methylenetetrahydrofolate reductase:** Provides methylfolate for methionine synthase.
3. **Transcobalamin 2:** Brings cobalamin (vitamin B12) into cells.
4. **Reduced folate carrier:** Brings folate into cells.
5. **Glutathione-S-Transferase M1:** Inactivates xenobiotics.
6. **Paraoxonase-1:** Hydrolyzes homocysteine thiolactone and xenobiotics.
7. **Adenosine deaminse:** Regulates methylation cycle activity.

Additional autism-associated genes affect the ability to produce synchronized neuronal network oscillations and can also synergize with thimerosal toxicity:

1. **Catechol-O-methyltransferase:** Inactivates dopamine.
2. **Reelin:** Helps to build neural networks.

3. Hepatocyte growth factor/scatter factor: Helps build neural networks.
4. Neuroligin: Helps build neural networks.

Since each of these autism-associated genetic variants affects a thimerosal-sensitive pathway related to redox status and the capacity for neuronal synchronization, they lend strong support to a role of thimerosal in causing autism.

TREATMENT OF AUTISM

If thimerosal does indeed contribute to autism via its ability to cause oxidative stress and impaired methylation, then treatment approaches that reverse these conditions would be clinically beneficial. Indeed, the administration of agents that support methionine synthase activity (e.g. methylcobalamin, betaine or folinic acid) have been reported to reduce abnormal levels of sulfur metabolites in autistic children, in conjunction with improved clinical status (9). Similarly, measures that reduce oxidative stress or remove heavy metals are reported to bring clinical improvement in autism (7,49). Notably, our lab studies show that thimerosal-induced inhibition of methionine synthase activity can be reversed by supplying either methylcobalamin or GSH. While more extensive clinical testing is needed to confirm and extend these early reports, my personal contact with autism families has convinced me that therapies which improve methylation and decrease oxidative stress can benefit a substantial proportion of children with autism. The fact that improvements in an otherwise "untreatable" disorder occur when antidotes to thimerosal are administered is perhaps the most important evidence for its role in causing autism.

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A. Personal Data:

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1965-1970	Bachelor of Science (Pharmacy) S.U.N.Y. at Buffalo
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1975-1976	Catholic University of Leuven (Belgium)

B. Professional Experience

1972-1976	Registered Pharmacist, State of Florida
1976-1981	Assistant Professor of Pharmacology, Northeastern University, Boston, MA
1981-1982	Section Leader, Pharmacology
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1982-1986	Director, Pharmacy Program
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III. Memberships:

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Society for Neuroscience
American Association of Colleges of Pharmacy
American Society of Pharmacology and Experimental Therapeutics
Society of Biological Psychiatry

IV. Research Interests:

1. D_4-dopamine receptor-mediated phospholipid methylation and its role in psychiatric illnesses.
2. Regulation of methionine synthase activity
3. Molecular recognition and Receptor/G-protein coupling events.
4. α_1-Adrenergic and α_2-adrenergic coupling events in vascular tissue.

V. Teaching Experience

Undergraduate:

Responsible for course coordination and lectures for several undergraduate pharmacology courses for pharmacy students. Lecture areas have included: Autonomic Pharmacology, Neuropharmacology, Cardiovascular Pharmacology, G.I. Pharmacology, Autacoids, Diuretics, Anesthetic drugs, Diabetes management, G.I. pharmacology, Endocrine pharmacology, Anti-inflammatory drugs.

Graduate:

Offered graduate lectures in the areas of molecular modeling, cardiovascular pharmacology and physiology, neuropharmacology and receptor pharmacology

Graduate Student Advisees:

- Thirteen Ph.D. Thesis Students
- Three M.S. Thesis Students
- Service on numerous thesis committees

Continuing Education:

Numerous presentations, primarily in cardiovascular pharmacology, receptor pharmacology and new drug updates.

VI. Administrative Experience:

1980-1982	Pharmacology Section Leader, Northeastern University (5 Faculty members)
1982-1986	Director, Pharmacy Program-Northeastern University (22 Faculty members, 8 Staff members)
1990-1992	Chairman, Department of Pharmaceutical Sciences, Northeastern University (16 Faculty members, 2 Staff members)

VII. Service Activities:

A. Program Level

-Coordinated Pharmacology/Toxicology Seminar and Journal Club Series
-Graduate Admissions Committee
-Curriculum Committee
-Professional Education Committee
-Ad Hoc Drug Abuse
-Faculty Advisor to Rho Chi Honor
-Faculty Advisor to Student Pharmaceutical Association

B. College Level

-Graduate Committee
-Executive Committee
-Scholarship and Awards Committee
-Tenure and Promotion Committee
-Biomedical Colloquium Committee

-Honors Program Committee
-Professional Affairs Committee
-Drug Education Committee

C. University Level

-Undergraduate Admissions Committee
-Graduate Council
-Research Council
-Faculty Senate
-University Undergraduate Curriculum Committee
-Drug Abuse Certificate Program Development
-Health Reorganization Steering Committee
-Health Professions Recruitment Committee
-Dean Search Committee
-Long-Range Planning Committee
-Health Colleges Merger Committee

D. Community Service

- Member of the Newton Drug Abuse Task Force
- Member of the State Commission on Alcohol and Drug Abuse Education
-Presented numerous drug abuse educational programs
-Presentation of 3-D molecular visualization programs to area high school students and teachers
-Established Fenway Senior Citizens visitation program for pharmacy students
-Former Scoutmaster (Cub Scout Pack 210, Waban, MA)
-Soccer Coach (Newton Youth Soccer League)

VIII. Journal Referee

Journal of Pharmacology and Experimental Pharmacology
Life Sciences
Hypertension
European Journal of Pharmacology
Science
Circulation Research
American Journal of Physiology
Molecular Pharmacology
American Journal of Physiology
Biological Psychiatry
Neuropsychopharmacology

IX. Grant Reviewer

National Science Foundation
National Heart Lung and Blood Institute
Massachusetts Heart Association

X. Grant Support

Current:

1. Autism Research Institute: "Methylcobalamin requirement for methionine synthase" ($58,000) 5/1/04 – 4/30/05.
2. SafeMinds: "Abnormal methylation events in autism" ($60,000) 7/15/03 – 7/14/05.
3. Forest Laboratories Inc.: "NMDA receptor modulation by D4 dopamine receptors: The role of phospholipid methylation ($73,433) 11/1/04 – 10/31/05.

4. Cure Autism Now: "Glutathione-dependent synthesis of methylcobalamin: A target for neurodevelopment toxins" ($117,880) 1/15/05 – 1/14/07.

Pending:

1. Nancy Lurie Marks Foundation: "Impaired methionine synthase activity in autism" ($135,780) 2/1/05 - 1/31/07.
2. NIH- "Methionine synthase, methyl-B12 synthesis and autism" ($1,080,322) 7/1/05 – 6/30/08.

XI. Publications:

A. Articles:

1. Chang, K.J., Deth, R.C., Triggle, D.J.: "Cholinergic antagonism among stereoisomers of a series of substituted 1,3 dioxolanes". J. Med. Chem., 15, 243-249 (1972).

2. Van Breemen, C., Farinas, B.R., Casteels, R., Gerba, P., Wuytack, R., Deth, R.C.: "Factors controlling cytoplasmic Ca^{2+} concentration". Phil. Trans. Roy Sci., Lond, B 265, 57-71 (1973).

3. Deth, R.C., Van Breemen, C.: "Relative contributions of Ca^{2+} influx and cellular Ca^{2+} release during drug induced activation of the rabbit aorta". Pflugers Arch: 348, 13-22 (1974).

4. Van Breemen, C., Deth, R.C.: "La and excitation contraction coupling in vascular smooth muscle (pp. 26-31) in "Ionic actions of vascular smooth muscle", edit by E. Betz, Springer-Verlag Berlin (1976).

5. Deth, R.C., Van Breemen, C.: "Agonist-induced release of intracellular Ca^{2+} in rabbit aorta". J. Membrane Biology, 30, 363-380 (1977).

6. Deth, R., Casteels, R.: "A study of releasable Ca^{2+} fractions in smooth muscle cells". J. General Physiology, 69, 401-419 (1977).

7. Deth, R.C.: "The effect of Lanthanum and reduced temperature on Ca^{2+} efflux from the rabbit aorta". Am. J. Physiol. (Cell Physiology) 3 (3), C139-C145 (1978).

8. Deth, R.C. and Lynch, C.J.: "The binding of ^{3}H-ouabain to Na-K ATPase sites in arterial smooth muscle". Pharmacology 21, 29-37 (1980).

9. Deth, R.C. and Lynch, C.J.: "Mobilization of a common source of smooth muscle Ca^{2+} by norepinephrine and methylxanthines". Am. J. Physiol. 240, C239-C247 (Cell Physiology) (1981).

10. Deth, R.C. and Lynch, C.J.: "Inhibition of alpha-receptor-induced Ca^{2+} release and Ca^{2+} influx by Mn^{2+} and La^{3+}". Eur. Pharmacol. 71, (1981).

11. Lynch, C.J., Deth, R.C. and Steer, M.L.: "Simultaneous loss and reappearance of alpha-adrenergic responses ^{3}H-prazosin binding sites in rat liver after irreversible blockage by phenoxybenzamine". B.B.A., 757, 156-163 (1983).

12. Awad, R. land Deth, R.C.: "Alpha-adrenergic subtype associated with receptor binding, Ca^{2+} release and contractile events in the rabbit aorta". J. Pharmacol. Exp. Ther. 227, 60-77 (1983).

13. Lynch, C.J. and Deth, R.C.: "Release of a common source of intracellular Ca^{2+} by alpha-adrenergic agonists and dinitrophenol in rat liver slices". Pharmacol. 28, 74-85 (1984).

14. Deth, R.C., Smart, J.L., Lynch, C.J. and Walsh, R.: "Lack of correlation between ^{3}H-ouabain binding and Na-K ATPase inhibition in rat aorta". Eur. J. Pharmacol. 99, 45-55 (1984).

15. Lynch, C.J., Guarino, J.J., Deth, R.C. and Steer, M.L.: "The effect of sucrose-feeding on alpha-adrenergic response in the rat liver". Am. J. Physiol. 246, E344-E349 (1984).

16. Danthuluri, N.R. and Deth, R.C.: "Phorbol ester-induced contraction of arterial smooth muscle and inhibition of α-adrenergic response". Biochem. Biophys. Res. Comm. 125, 1103-1109 (1985).

17. Lynch, C.J., Steer, M.L., Connors, M.R., Schatz, R.A. and Deth, R.C.: "Evidence for a decrease in the efficiency of beta-receptor coupling to adenylate cyclase in liver membranes from sucrose fed rats". Biochem. Pharmacol. 34, 623-629 (1985)

18. Tumas, J., Deth, R.C. and Loner, R.A.: "Effects of nisoldipine on myocardial infarct size, hemodynamics, and myocardial performance". J. Cardiovasc. Pharmacol. 7, 383-391 (1985).

19. Campbell, M.D., Honeyman, T.M. and Deth, R.C.: "Correlation between ^{32}P-labelling of phosphoinositides and agonist-induced contraction and Ca^{2+} fluxes in arteries". Eur. J. Pharmacol. 116, 129-136 (1985).

20. Danthuluri, N.R., and Deth, R.C.: "Acute desensitization to angiotensin II: Evidence for a requirement of agonist-induced diacylglycerol production during tonic contraction of rat aorta". Eur. J. Pharmacol. 126, 135-139 (1986).

21. Lynch, C.J., Steer, M.L., Smart, J.L. and Deth, R.C.: "Differences in the role of Na^{+}/K^{+} ATPase during α_1-adrenergic events in rat and rabbit aorta". Pharmacology 33, 221-234 (1986).

22. Campbell, M.D., Danthuluri, N.R. and Deth, R.C.: "Differences in phospholipid incorporation of ^{32}P relevent to α_1-receptor coupling events in rat and rabbit aorta". Biochem. Biophys. Res. Comm. 141, 1213-1221 (1986).

23. Wick, P.F., Keung, A.C., Bowler, J.J. and Deth, R.C.: "Alpha-1 adrenergic coupling events induced by full and partial agonists in rabbit aorta". J. Pharmacol. Exp. Ther. 241, 458-464 (1987).

24. Gupta, S., Campbell, M.D., Cragoe, E.J., Jr. and Deth, R.C.: "Influence of ANF on receptor-initiated phosphoinositide metabolism and ^{22}Na uptake in arteries". Proc. Congress on Biologically Active Arterial Peptides 1, 252-255 (1987).

25. Jagadeesh, G. and Deth, R.C.: "Different affinity states of alpha-1 adrenergic receptors defined by agonists and antagonists in bovine aorta plasma membranes". J. Pharmacol. Exp. Ther. 243, 430-436 (1987).

26. Danthuluri, N.R., Berk, B.C., Brock, T.A., Cragoe, E.J., Jr., and Deth, R.C.: "Protein kinase C-mediated intracellular alkalinization in rat and rabbit aortic smooth muscle cells". Eur. J. Pharmacol. 141, 403-506 (1987).

27. Deth, R.C., Payne, R.A. and Peecher, D.M.: "Influence of furosemide on rubidium-86 uptake and alpha-adrenergic responsiveness of arterial smooth muscle". Blood Vessels 24, 321-333 (1987).

28. Smart, J.L. and Deth, R.C.: "Influence of α_1-adrenergic receptor stimulation and phorbol esters on hepatic Na^+/K^+ ATPase activity". Pharmacology 37, 94-104 (1988).

29. Danthuluri, N.R. and Deth, R.C.: "Contractile effects of ammonium chloride in relation to agonist-induced intracellular alkalinization". Am. J. Physiol. (Heart and Circ.) H867-H875 (1989).

30. Ek, T.P. and Deth, R.C.: "Reduced EIPA sensitive Na/H exchange in SHR arteries". Hypertension 12, 331 (1988).

31. Ek, T.P., Campbell, M.D. and Deth, R.C.: "Reduction of norepinephrine-induced tonic contraction and phosphoinositide turnover in arteries of spontaneously hypertensive rats: A possible role for protein kinase C". Am. J. Hypertension 2, 14-18 (1988).

32. Jagadeesh, G. and Deth, R.C.: "Phorbol ester-induced modulation of agonist and antagonist binding to α_1 adrenergic receptor in bovine aorta". J. Pharmacol. Exp. Ther. 247, 196-202 (1988).

33. Gupta, S., Campbell, M.D., Cragoe, E.J., Jr. and Deth, R.C.: "Influence of ANF on 32P-phospholipid labelling and EIPA-sensitive ^{22}Na uptake in rabbit aorta". J. Pharmacol. Exp. Ther. 248, 991-996 (1989).

34. Jagadeesh, G. and Deth, R.C.: "Modulation of bovine aortic alpha-1 receptors by Na^+ 5'guanylylinidophosphate, amiloride and ethyl-isoprophylamiloride for receptor G-protein precoupling". J. Pharmacol. Ther. 252, 1184-1196 (1990).

35. Tian, W. and Deth, R.C.: "Species differences in chloroethylclonidine antagonism at vascular alpha-1 adrenergic receptors". J. Pharmacol. Exp. Ther. 253, 877-883 (1990).

36. Deth, R.C., Lesburg, C., Li, S., Cragoe, E.J., Jr.: "Influence of amiloride derivatives on arterial contractility". J. Pharmacol. Exp. Ther. 253, 530-536 (1990).

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39. Jagadeesh G., Tian, W., and Deth, R.C.: "Agonist-induced modulation of agonist binding to alpha-1 adrenoceptors in bovine aorta". Eur. J. Pharmacol. 208, 163-170 (1991).

40. Aburto, T.K., Jinsi, A. and Deth, R.C.: "Involvement of protein kinase C activation in alpha-2 adrenergic receptor-mediated contractions of rabbit saphenous vein". Eur. J. Pharmacol. 277:24-34 (1995).

41. Jagadeesh, G. and Deth, R.C.: "Protein kinase C modulation of antagonist and agonist binding at alpha-2 adrenergic receptors". J. Pharmacol. Exp. Ther. 262, 775-783 (1992).

42. Tian, W. and Deth, R.C. : "Precoupling of Gi/Go-linked receptors and its allosteric regulation by monovalent cations". Life Sciences. 52, 1899-1907 (1993).

43. Tian, W.-N., Lanier, S.H., Duzic, E. and Deth, R.C.: "Determinants of alpha-2 adrenergic receptor activation of G-proteins: Evidence for a precoupled R/G state". Mol. Pharmacol. 45:524-531 (1994).

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47. Tian, W.-N., Duzic, E., Lanier, S.M. and Deth, R.C.: "Receptor reserve for α_{2D}-adrenergic receptor-regulated G-protein activation in PC12 cell membranes". Pharmacol, 52: 252-262 (1996).

48. Jinsi, A., Paradise, J. and Deth, R.C.: "A tyrosine kinase regulates α–adrenoceptor-stimulated contraction and phospholipase D activation in the rat aorta." Eur. J. Pharmacol. 302: 183-190 (1996)

49. Liu, Y.-F., Deth, R.C. and Devys, D.: "SH3 domain-dependent association of Huntingtin with epidermal growth factor receptor signaling complexes". J. Biol. Chem. 272: 8121-8124 (1997).

50. Jinsi-Parimoo, A. and Deth, R.C.: "Reconstitution of α_{2D}-adrenergic receptor coupling to phospholipase D in a PC12 cell lysate". J. Biol. Chem. 272: 14556-14561 (1997).

51. Sharma, A., Kramer, M., Wick, P.F., Liu, D., Chari, S., Shim, S., Tan, W.-B., Ouellette, D., Nagata, M., DuRand, C., Kotb, M. and Deth, R.C.: "Dopamine D_4 receptor-mediated methylation of membrane phospholipids and its implications for mental illnesses such as schizophrenia". Molecular Psychiatry 4: 235-246 (1999).

52. Jinsi-Parimoo, A. and Deth, R.C.: "Protein kinase C and tyrosine kinase-dependent coupling of alpha-2A/D adrenergic receptors to phospholipase D". Pharmacol. 60: 19-26 (2000).

53. Tian, W.-N., Miller, D.D. and Deth, R.C.: "Bidirectional allosteric effects of agonists and GTP binding at $\alpha_{2A/D}$-adrenergic receptors". J. Pharmacol. Exp. Ther. 292: 664-671 (2000).

54. Tian, W.-N. and Deth, R.C.: "Differences in efficacy and Na^+ sensitivity between α_{2B} and α_{2D} adrenergic receptors" Pharmacology 61: 14-21 (2000)

55. Zhao, R., Chen, Y., Tan, W., Waly, M., Malewicz, B., Stover, P., Rosowsky, A. and Deth, R.C.: "Influence of single-carbon folate and *de novo* purine synthesis pathways on D4 dopamine receptor-mediated phospholipid methylation." J. Neurochem. 78: 788-796 (2001)

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57. Deth, R.C., Sharma, A. and Waly, M.: "Dopamine-stimulated solid-state signaling: A novel role for single-carbon folates in human attention." In: Proc. 12th Int. Symp. Chem. Pteridines and Folates. Kluwer Academic Press (2002).

58. Zhu Q., Qi, L-J., Abou-Samra, A., Shi, A. and Deth, R.C.: "Protein kinase C-dependent constitutive activity of α2A/D-adrenergic receptors." Pharmacol. 71: 80-90 (2004).

59. Waly, M., Banerjee, R., Choi, S.W., Mason, J., Benzecry, J., Power-Charnitsky, V.A, Deth, R.C. "PI3-kinase regulates methionine synthase: Activation by IGF-1 or dopamine and inhibition by heavy metals and thimerosal" Molecular Psychiatry 9: 358-370 (2004).

60. Deth, R.C., Kuznetsova, A. and Waly, M.: "Attention-related signaling activities of the D4 dopamine receptor" in *Cognitive Neuroscience of Attention*, Michael Posner Ed., Guilford Publications Inc., New York (2004).

61. Kuznetsova, A.Y., and Deth, R.C.: "A model for gamma oscillations induced by D4 dopamine receptor-mediated phospholipid methylation." J. Neurophysiology (Revision Under Review).

62. Waly, M., Power-Charnitsky, V., Deth, R.C.: "Reduced activation of phospholipid methylation by the seven-repeat variant of the D4 dopamine receptor." Mol. Psychiatry (Submitted)

63. Waly, M, and Deth, R.C.: "Methylcobalamin-dependent methionine synthase activity and its relationship to autism." (In Prep.)

XI. Monograph:

Deth, R.C. "Molecular Origins of Attention: The Dopamine-Folate Connection" Kluwer Academic Publishers (April, 2003)

XII. Patents:

1. "Compositions and methods for diagnosing schizophrenia" Inventor: Richard C. Deth; Patent# 5686255; Date of issue: Nov. 11, 1997. Claims restricted to the diagnosis of schizophrenia and related psychiatric disorders with novel laboratory tests involving D4 dopamine receptor-mediated phospholipid methylation.

2. "Compositions and methods for diagnosing schizophrenia" Inventor: Richard C. Deth; Patent# 5,738,998; Date of issue: April 14, 1998. Claims restricted to the use of novel assays for the discovery of new therapeutic entities.

3. "Methods and materials for the diagnosis and treatment of schizophrenia and related disorders" Inventor: Northeastern University/Richard C. Deth; Patent# 6,080,549; Date of issue: June 27, 2000.

4. "Methods of identifying and determining the effectiveness of therapeutic processes or agents for the treatment of schizophrenia and related disorders" Inventor: Northeastern University/Richard C. Deth; Patent# 6,773,892; Date of issue: August 10,2004.

XIII. Congressional Testimony:

1. U.S. House of Representatives, Committee on Government Reform, Subcommittee on Human Rights and Wellness; "The Vaccine Additive Thimerosal and Autism". September 8, 2004.

2. U.S. House of Representatives, Committee on Appropriations, Subcommittee on Labor, Health and Human Services and Related Agencies; "The Link Between Thimerosal and Autism". October 5, 2004.

CERTIFICATE OF SERVICE

I hereby certify that on August 27, 2007, I served the foregoing **Expert Report from Sander Greenland, M.A., M.S., Dr.P.H, and Expert Report from Richard Deth, Ph.D** on the following individual(s):

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