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Dear Dr. Shine:

Please regard this letter and enclosures as a formal complaint on the actions and the report of the IOM committee on Multiple Sclerosis: Current Status and Strategies for the Future, project # BNBH-H-99-01-A. I appreciate you taking on the task of reviewing this complaint and of deciding if any further action is necessary. I can think of no one more appropriate at IOM for doing this and I look forward to hearing your comments on what I believe is a very important matter for the all persons affected by MS as well as for IOM.

To summarize, I believe that the IOM committee which was charged with recommending areas of future research for MS did not act in a sufficiently objective manner when deciding which areas of research to include in their formal recommendations and which to exclude. I reached this conclusion on the fact that they did not recommend that future research be done on nutritional factors and MS despite the fact there is a very robust database implicating various nutritional factors in the onset and progression of MS. The diversity and cohesiveness of this database argues very strongly that nutritional factors are very plausible causal factors for MS. To me a plausible causal factor for MS is one for which there is a reasonable amount of data which demonstrates that the factor is compatible with the available data on MS pathogenesis and/or epidemiology which has been compiled over the last 50 years. Of course one would want to see a solid theoretical underpinning for any plausible cause. Thus for MS, a plausible cause would have to have a reasonable theoretical foundation as well as diverse supporting data such that it helped to explain 1) the activation or lack of suppression of autoaggressive, myelin-sensitive T cells and/or 2) the distinctive geographic variation in MS prevalence. Furthermore there can be no available data that clearly negate the likelihood of the factor playing a role in MS etiology and pathogenesis

I would hope you agree that for any serious disease of unknown cause, research into plausible causes is critical and should be of the highest priority. The fact that the committee chose not to include a recommendation for research into what I believe are plausible and testable causal factors in MS indicates to me that subjective, self-interest rather than objective science and a genuine concern for the welfare of persons with MS guided the committee members in their decisions. Clearly, to substantiate this charge, it will be necessary to show that nutritional factors are indeed plausible causal factors for MS because, if they are, then there can be no acceptable excuse for not including a formal recommendation for future research in this area in the report. With this letter and attached documents I hope to convince you that specific nutritional factors are plausible causal factors for MS. Once this is accepted then I believe there will be a need for a revision of the report such that it includes an appropriate formal recommendation for nutritional research in MS.

I am a geological research scientist and I have been involved in scientific research through industrial, academic and governmental settings for 33 years. Over this time I have been a project leader, a conference organizer, the author of numerous peer-reviewed papers, a science administrator, an editor-in-chief of a scientific journal, the editor of a number of symposium volumes and, of special importance for this matter, a member of innumerable scientific committees. I mention this to let you know that I am well

aware of all the scientific and non-scientific aspects of research, of the various pitfalls, frustrations and strategies associated with major research efforts, and the workings and machinations of scientific committees.

I became involved in the science of multiple sclerosis when my 18-year-old son was diagnosed with MS almost 6 years ago. At that time I decided that the best thing I could do was to read as much of the scientific literature on MS as possible so as to determine as many plausible causal factors as possible. I wanted to ensure my son was doing everything possible in terms of safe and science-based therapies that have a reasonable chance of affecting disease progression. In geology, because we deal with the past, one can know very little with certainty and I am very comfortable with using my best (simplest) interpretations of the current data base, with all the attendant uncertainties, to guide my actions. Of course in the attempt to affect disease progression, I had nothing to gain and all to lose by subjectively favoring one plausible cause over another or by ignoring any proposed cause without properly evaluating its plausibility. Such evaluation was done by comparing each proposed causal factor with all the constraints provided by the extensive MS database and to select only those which are compatible with the data.

On the basis of the above methodology, I reached the conclusion that the simplest explanation (Occam's razor and all that) for all the available data was that MS is a multi-factorial autoimmune disease that involves four main causal factors. These are:
1) genetic susceptibility
2) common infectious agents contracted throughout life
3) novel proteins derived from foods for which humans have limited evolutionary experience (i.e. less than 10,000 years).
4) a deficiency in vitamin D and omega 3 essential fatty acid.

As you may know, factors one and two are widely accepted as probably being part of MS etiology. However a model using only these two factors cannot satisfactorily explain MS etiology because it leaves unexplained the highly distinctive geographic variation of MS prevalence as revealed by many epidemiological studies. Using only factors one and two was also at odds with a Darwinian perspective of MS and that is a very important consideration if one believes in evolution. In geology, I would not think of trying to explain a given phenomenon without placing it in a historical context. The need for such a Darwinian approach (i.e. evolutionary biology as a foundation of any hypothesis) seems to be slowly infiltrating the medical world although I expect that many medical researchers are not yet even aware of it, let alone using it. It certainly is not yet part of the mainstream MS research effort.

The addition of factors three and four is compatible with the established immunology of MS, allows the epidemiology of MS to be explained very well and also satisfies the problem raised by the Darwinian approach. Finally, factors three and four are also included in order to satisfy the results from a variety of studies of MS and other closely related cell-mediated autoimmune diseases such as IDDM and rheumatoid arthritis. Overall I think the fact that only four causal factors are necessary to adequately explain the very large and very varied MS database, especially given the many factors which have been proposed, is somewhat surprising and is definitely satisfying. Certainly William of Occam would have been pleased with such a result.

With this as background, I am sure you can imagine how pleased I was when I read 18 months ago that IOM had been commissioned by the National MS Society to "review current knowledge about the cause and treatment of multiple sclerosis and develop a strategic plan to guide future investments". I was most interested in the statement in the published project scope that said "in particular to identify the resources and strategies from disciplines not generally considered to be involved in MS research, but that might expand the intellectual and technological resources from which researchers might draw in the fight against MS". This was certainly a bold statement for MS research that has been mired in a deep and narrow rut for many years when it comes to causal factors. This lack of advancement in understanding cause is undoubtedly one of the main reasons that no effective therapies have been devised for MS despite

many years of effort and hundreds of millions of dollars of funding. One can only imagine what the state human health and longevity would be today if infectious agents had not been identified as the cause of many serious diseases. The mind boggles at the thought of modern medicine applying the same strategies currently in use for MS (treat the symptoms and try to manipulate biochemical reactions) to bacterial infectious diseases.

I was also energized by the statement in the project scope that said "2) exploring opportunities for innovations that have prospects for creating significant scientific and clinical advances, and 3) identifying areas that have not previously been involved in MS and might contribute new insights." There is no doubt that MS research is in need of some new directions.

After I read the documents describing the project, it seemed clear that the Committee would be extremely interested in receiving submissions that documented the need for research into plausible causal factors of MS which were currently receiving very little research attention. I hope you agree that there is no more important field of research because, only through the identification of such factors, will the etiology of MS be determined and strategies for preventing MS be developed. Also the identification of causal factors will also be very important for devising effective therapies for greatly slowing or halting disease progression. I assumed the Committee chairman and members shared this common sense conclusion which is axiomatic.

Accordingly, I sent the Committee, by way of the chairman, Dr. Richard Johnston, submissions that provided referenced information on evidence that implicates food proteins and vitamin D supply in MS. These submissions are included with this letter to allow you to gain an appreciation of the robust database that supports the role of nutritional factors in MS. I would emphasize that the medical literature references for the statements below are found in these attached documents which are numbered.

For food proteins, this evidence includes:

1) A theoretical concept, Paleolithic nutrition, which allows one to deduce that various nutrients in foods recently added to the human diet (< 10,000 years ago) have the potential to cause biochemical failures in genetically susceptible persons due to a lack of genetic compatibility (natural selection at work). This concept certainly has held up for heart disease, stroke, cancer and one autoimmune disease (celiac) and its application to autoimmune disease in general is reasonable. Notably it provides a reasonable theoretical underpinning as well as a Darwinian perspective for the role of various food proteins in MS. [enclosures 4,5]

2) A theoretical model for the role of food proteins in cell-mediated autoimmune disease has been developed using RA as an example. [enclosure 4]

3) Epidemiology reveals a close correlation (R= .84) between milk consumption and MS prevalence [enclosure 1]

4) Peptides from milk proteins have been found to be molecular mimics of self-antigens in myelin [enclosures 2,3]

5) T cells that are activated by milk proteins cross react with self-antigens in myelin [enclosure 3]

6) Injection of the mimicking peptide from milk precipitates EAE (animal MS) in laboratory animals [enclosure 2,3]

7) T cells reactive with milk proteins are very common in persons with MS but very rare in healthy controls [enclosure 2]

8) NOD mice immunized with MOG do not develop EAE when fed an elemental diet but do develop EAE when fed the same diet plus milk. [enclosure 1]

9) Proteins from milk, soy and wheat precipitate IDDM and RA, cell-mediated autoimmune diseases closely related to MS, in laboratory animals. [enclosures 1,2,4]

10) Peptides from various food proteins are mimics of self-antigens in IDDM and RA and T cells activated by these peptides cross react with self antigens. [enclosures 1,2,3,4]

11) Small clinical trials in Crohn's and RA have shown that avoidance of milk, grains and legumes results in major symptom improvements. [enclosures 1,4]

12) Proteins from gluten are the known cause of a cell-mediated autoimmune disease, celiac disease. Notably this is the only cell-mediated autoimmune disease for which the causal factor is established. [enclosures 1,4]

For vitamin D, the evidence includes:

1) MS systemically becomes more common as vitamin D supply systematically decreases with increasing latitude. This is most important because vitamin D supply provides by far the best explanation for the pronounced N-S gradient in MS prevalence. [enclosures 5,6,8]

2) MS rates are significantly lower in coastal communities that eat a lot of fish (the main dietary source of vitamin D), as compared with that of neighboring farming communities. [enclosures 5,6]

3) Immunological studies show that vitamin D hormone suppresses inflammatory reactions which characterize MS. [enclosures 5,6]

4) Six months of vitamin D supplementation in MS patients significantly lowered the level of an inflammatory cytokine (IL-2) and significantly increased the level of a suppressor cytokine (TGF)

5) Injection of vitamin D hormone prevents and halts EAE progression in laboratory animals. [enclosure 6]

6) There is a very close, inverse correlation between seasonal changes in MRI-determined disease activity and seasonal changes in vitamin D supply and consequent blood levels of circulating hydroxyvitamin D. [enclosure 7]

7) Individuals with a high exposure to sunlight have a significantly lower risk of MS but a significantly higher risk of skin cancer. This finding was independent of country of origin, age, sex, race, and socioeconomic status. [enclosure 6]

Evidence for the role of omega 3 EFA in MS is not as abundant and includes:

1) Immunological studies show omega 3 EFA suppresses inflammatory reactions in vivo and in vitro.

2) Omega 3 EFA suppresses EAE in laboratory animals.

3) A recent, small clinical trial demonstrated that omega 3 EFA supplements (fish oil) significantly reduced MS exacerbations.

4) Increased omega 3 intake has been shown to be beneficial in RA and Crohn's

It is worth noting that intakes of both vitamin D and omega 3 EFA were much higher for most of human history and it is only recently that intakes of these immune suppressants have been drastically declined due to migration to higher latitudes (>350) and to dietary changes.

From a Darwinian perspective of MS, one would assume that genetics and natural selection acting over two million years of evolution would have resulted in ways of controlling infection-driven autoimmunity (i.e. the production of autoaggressive immune cells) in humans such that it rarely advanced to uncontrolled autoimmune disease. The common occurrence of autoimmune disease today is an anomaly

in terms of evolutionary biology and this is why a genetic-infectious agent model for MS is not entirely compatible with a Darwinian perspective. However, one possible explanation for this anomaly is that the established balance between the activation and suppression of infection-activated autoaggressive, immune cells has been upset by the relatively recent (in terms of evolution) addition of immune-activating, novel proteins from foods introduced by agriculture. The associated large decline in the intakes in vitamin D and omega 3 EFA would have also been contributing factors for tipping the balance from well controlled autoimmunity to uncontrolled autoimmune disease. It follows that MS may well be the result of autoimmune reactions stimulated by proteins from both infectious agents and "new" foods in combination with the failure to suppress such reactions due to a chronic deficiency in vitamin D and omega 3 EFA. Such a Darwinian deductive model certainly is compatible with all the diverse inductive data listed above as well as the entire MS database in general.

Given all of the above, it seems to me there is an urgent need for a major research effort which determines beyond a doubt if these nutritional factors are involved in MS or not and if they can provide a means of preventing and/or halting disease progression.

Very important considerations in all this are:

1) No responsible researcher, including each of the IOM Committee members, can say with confidence that consumption of proteins from dairy, grains and legumes does not contribute to MS progression. All that can be said with our current data is that food proteins may well be playing a role in MS or they may not be. Given that most persons with MS are consuming potentially pathogenic proteins every day, it would seem imperative that this question be answered definitively as soon as possible. As an analogy, if there is a reasonable chance that a town's water supply is contaminated, I hope you agree that the best thing to do would be to issue a warning and then to undertake a thorough testing program to decide the issue beyond a reasonable doubt.

2) Nutritional factors, unlike infectious agents and genes, are relatively easy and cheap to manipulate. Thus there is a reasonable chance that a cheap, safe and effective therapy for MS might be developed by such manipulation. It would basically entail an avoidance of potentially pathogenic food proteins and an increase in vitamin D and omega 3 EFA intake. There is very abundant anecdotal evidence that such a nutritional regime is very effective for halting MS progression. However, such anecdotal data are not worth much and proper clinical trials are required to determine the efficacy of such a regime for MS. The promise of such a therapy is reason enough for a major research effort into nutrition and MS and fits perfectly with the project scope statement- "exploring opportunities for innovations that have prospects for creating significant scientific and clinical advances". How many other research initiatives considered by the Committee offered the promise of such a therapy?

The IOM Committee had all the above data and reasoning available to them and I fully expected that they would formally recommend the need for future research into nutritional factors and MS. It clearly fit their project scope statements like a glove! Given all the above, what rational, objective scientist who wanted to determine the cause and an effective therapy for MS would not make such a recommendation. It was not like the Committee was bombarded with numerous plausible and readily testable causes for MS and had to choose between them. I doubt if they received any other proposal that outlined an innovative, new clinical approach that had a solid scientific rationale. I expect the nutritional factors concept was the only such one they received and thus one might have predicted they would have fallen over themselves as they put the need for such crucial research at the top of their list. There is no more important research than that into plausible causal factors of MS and anyone who disagrees with this has no appreciation of the history of the fight against disease.

I was stunned when I read the report of the Committee and found that they did not include a formal recommendation for nutritional factors among the many recommendations for future research. The report contained only one page on nutrition and MS and it was buried in a large chapter on Disease

Measurement and Management. Notably it even contains some simple errors such as referring to omega 3 EFA as omega 6 EFA, a completely different substance. Clearly the Committee had little regard for the concept of nutrition and MS. Needless to say it was very bothersome to me that the Committee had essentially ignored the need for research on plausible, testable causal factors for MS and I could not think of a single scientific reason why they would do this. I wrote the committee chairman, Dr Johnston, and asked for the reasons why the Committee chose to exclude a formal recommendation for research into nutrition and MS given all the solid evidence linking the two and the potential huge benefits such research might yield (eg. effective therapies for prevention and/or halting progression). His reply (see enclosure 9) was very revealing through its superficial and rhetorical nature.

Dr. Johnston stated that the strength of the quality of the evidence was not sufficient but provided no supporting arguments for such a sweeping statement. The bogus nature of such a claim is readily seen when all the evidence linking nutritional factors to MS is examined in toto. All the evidence provided is in peer-reviewed, mainstream medical journals and includes data from epidemiology, animal experiments, theoretical considerations, immunological studies, and small clinical trials. All the data are consistent and all point to an involvement of nutritional factors in MS onset and progression. One literally could not expect more data for new plausible causal factors of MS. Any more data and a concerted research effort would have already been initiated. One of the main goals of the committee was to identify new and innovative areas of research. In contrast, Dr Johnston suggests that nutritional factors were ignored because it is not an established research field ("All of us who do research that is innovative and that questions the status quo face this challenge"). The committee advertises that it is looking for innovative research from new areas and then rejects a well-supported concept because it is innovative and not status quo. The credibility and integrity of the IOM committee on MS and perhaps even that of IOM are greatly strained by such conflicting statements.

Dr Johnston also claimed that the Committee was limited in the number of formal recommendations it could make and, that on the basis of scientific merit, there was no room in the report for a recommendation on nutrition and MS. This is an unsupportable excuse. As I have emphasized, research into plausible causes of MS has to be regarded as the highest priority and, as I hope I have demonstrated, nutritional factors are indeed plausible causal factors. Thus there is no scientific justification for saying there is no room in the report for a recommendation on nutritional factors. Furthermore, a recommendation for research on nutritional factors could have readily been included in recommendation 4 in the "causes, courses and treatments" section. This recommendation dealt with "pathogens" which is certainly one of the plausible environmental causes of MS. Recommendation 4 should have dealt with all plausible environmental causes of MS and thus included a discussion of nutritional factors. I would note that if one objectively compares the evidence for the involvement of "pathogens" in MS with that of nutritional factors it is clear that the types of evidence are very similar (theoretically reasonable, animal experiments, immunological studies, molecular mimics). In fact the evidence supporting nutritional factors is perhaps somewhat more convincing because they provide a reasonable explanation for the geographic variance of MS prevalence whereas pathogens do not. Furthermore, as discussed earlier, nutritional factors allow a much more reasonable Darwinian perspective.

Finally, Dr Johnston claimed that the one page discussion of diet and MS in the report provided a way of recommending research in this field. Such a claim is hollow and I've seen such a "damning by faint praise" strategy used in science on a number of occasions. Dr Johnston and anyone with any experience in these matters know full well that the only recommendations that will receive any attention are those in the formal section. I am sure he is also aware that any research field that did not make it into the formal list is very likely doomed to funding obscurity for the foreseeable future. By not including a recommendation for nutritional research in the formal list and by superficially addressing the entire issue with one, well-buried page, the Committee has purposefully relegated the subject of nutritional research for MS to the "little or no value" category. And it is this decision which indicates to me, and hopefully any responsible scientist, that the Committee was acting with subjective self-interest rather than scientific objectivity.

The obvious question is "Why didn't the Committee act with reasonable objectively?" and this is not easily answered. Most scientists, including both you and I, are very aware through long experience that self-interest is rampant on most committees especially where funding and future research directions are the main topics. Objectivity is the first casualty when one's research career and/or funding is under a threat or even a perceived threat. Thus one can surmise that the Committee members lacked the required scientific objectivity to appraise the need for nutritional research for various reasons. One reason is that there was no one on the Committee with any expertise on nutrition and disease. Thus there was no one to advocate for such research and to explain its value, and this in itself is usually enough to doom a given subject to a quick, superficial discussion and an exclusion from further consideration. The fact that no one with nutritional expertise was selected for the Committee biased it from the onset against nutritional research. I would further note that the individual research fields of each of the Committee members are all well represented in the list of formal recommendations. I doubt if this is by chance, good fortune or even objective analysis alone. A second reason is possibly the general prejudice against nutritional research and the use of nutritional strategies for fighting disease that exists in many corners of conventional medicine. The very fact that nutritional therapies are commonly referred to as "alternative" medicine and are lumped with a wide variety of bizarre therapies for which no scientific data exist, demonstrates a subtle and ingrained prejudice against the role of nutrition in disease.

A more complex reason involves the relationship between the MS research community and the pharmaceutical companies which market drugs for MS. I am sure you are aware of the general problems associated with potential conflicts of interest which exist due to the financial ties between medical researchers and pharmaceutical companies. Notably the academic community strives very hard to eliminate any potential problem. The potential for conflict between nutritional research and the pharmaceutical industry is illustrated by Celiac Disease that, like MS, is a cell mediated autoimmune disease. As you know, nutritional research led to the identification of a major role for a nutritional factor in Celiac Disease and this then led to an effective nutritional therapy for controlling an otherwise very serious disease. Because of this there are currently no pharmaceuticals prescribed for Celiac Disease. Undoubtedly the pharmaceutical companies are well aware that the same situation might well result if nutritional research led to the identification of one or more nutritional factors in MS etiology and thus one can safely surmise that pharmaceutical companies would not be supportive of such research. I think it would be worthwhile to determine if any of the Committee members are, or have been, the recipients of grants from pharmaceutical companies. If any have financial ties to such companies then a conflict of interest may exist and this may have led to unacceptable subjectivity when it came to considering nutritional research for MS. There may well be other reasons why the Committee did not act with sufficient objectively towards the concept of nutritional research for MS. The reasons will likely never be known but that does not detract from the fact that the Committee did indeed act very subjectively by excluding a recommendation for research in this field. One does not objectively ignore the need for research into plausible causal factors of MS.

In closing, I would again emphasize that the validity of this entire complaint turns on the question of whether or not sufficient data relating nutritional factors to MS exist so as to establish them as plausible causal factors worthy of research. To me, the database greatly exceeds that required for the acceptance of the interpretation that there is a reasonable chance that nutritional factors are involved in MS. If you accept this, then clearly the report is tainted and must be withdrawn and not re-released until a suitable and comprehensive formal recommendation for research into nutrition and MS is included.

In this regard I would point out that I believe in its present form the report does more harm than good. My reasoning for this is that all the recommendations for research cover areas that currently have a concerted effort already in place. There are no recommendations for new, innovative research; a very strange result given the project scope statements. Thus, if the report did not exist, the current MS research effort would not be affected. Basically all the report has done is to give the MS research community, whose members dominated the Committee, a stamp of approval to keep doing what they are doing. This in itself is not

harmful although its value is questionable. However, by excluding a recommendation for the need for nutritional research, the report has ensured that less research will be done in this field than what might have been done otherwise. If nutritional factors are indeed important causal factors in MS, and the available information indicates they may well be, the report is actually very harmful and will delay the solution to the MS puzzle for many years.

If you can look at the existing database and say without hesitation that there is not a reasonable chance that nutritional factors are involved in MS, then this matter is finished as far as IOM is concerned. There is no room for waffling on this. Either the available data are sufficient in your estimation or they are not. When making this decision I hope you will seriously weigh the long-term as well as the short-term consequences of your action. I would also ask you to consider what you would do if you had a loved one diagnosed with MS. Now that you are aware of the available information linking MS and nutrition, would you disregard it (insufficient data) or apply it (sufficient data)? Would you feel comfortable allowing that person to consume potentially pathogenic food proteins and to not have a higher intake of vitamin D and omega 3 EFA until future research demonstrated these are not factors in MS? Your answer to this should provide you with a very objective appraisal of the strength of the database. As I previously mentioned, one cannot afford to be subjective in such a scenario.

Thank you very much for reviewing this complaint. I await your decision on this important matter that may affect all those currently with MS and all those who will be diagnosed with MS in the foreseeable future.

Yours truly,

Dr Ashton F. Embry