A Unified Theory of the Causes of Monoclonal Gammopathy of Unknown Significance (MGUS) and Multiple Myeloma, with a Consequent Treatment Proposal for Long-term Control and Possible Cure

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Introduction

The etiology of Multiple Myeloma is generally acknowledged as obscure. The epidemiology presents a number of puzzles. Most cancers are the affliction of age. Myeloma is more remarkably so, with few cases under the age of 40, (0.3% under 30), 98% above this demarcation line and a median incidence age of 65 years. Whilst sporadic community and familial clusters have occurred, and indeed, even husband and wife cases, to date no evidence of genetic predisposition has been discovered. Failure to find a definitive environmental cause for the community clusters might suggest that such cases are simply random, given their statistical low incidence relative to Myeloma incidence in general. Myeloma also affects more men than women, more blacks than whites and at a relatively earlier age than whites, farmers more than the general population. A French study noted a 40% excess prevalence, age- and sex-adjusted, amongst farmers, relative to other occupations. Other at-risk groups include foresters, fishermen, veterinarians, teachers, anaesthesiologists, radiologists, and anyone exposed to ionizing radiation. Though the latter would seem an obvious risk factor, intriguingly the proportion of atom bomb victims at Hiroshima and Nagasaki who ultimately developed Myeloma seems relatively small, if still significant. Indeed, Myeloma is a rare cancer, accounting for no more than 1% of all cancers, and 10% of all haematopoietic malignancies; although its incidence, as with the majority of all cancers, is on the increase.

It now appears that Multiple Myeloma, though a B cell malignancy, very much conforms to what we know about the molecular biology of solid tumours, even down to the development of angiogenesis, albeit in the marrow. The oncogenesis of Myeloma takes place over several decades in the largely silent, pre-cancer condition known as Monoclonal Gammopathy of Unknown Significance (MGUS), where the clonal plasma cells are immortalized but not transformed. About 24% of people with MGUS go on to develop full blown Multiple Myeloma and/or other lympho-proliferative malignancy. MGUS and pre-Stage I Myeloma are relatively indolent, benevolent phases. Paradoxically, however, once in the active phase, Myeloma is lethal and without a known cure, with the exception of allogeneic transplants which carry a 41% mortality rate.

Moreover, paradoxes and problems abound in the pathology and treatment of Myeloma, a mystifyingly heterogenous disease, with survivals recorded ranging from a few months to nearly two decades. Conventional chemotherapy offers a median survival of 18 months to 2 years. Newer approaches of high-dose combination chemotherapy and autologous stem cell transplant have demonstrated an improved median survival of 3 to 4 years, with 20% alive at 5 years. Improvement is pertinent largely to a minority of patients who fit particular diagnostic criteria, including age less than 56 years, low β2 microglobulin,
low C-Reactive Protein, no deletion of chromosome 13 and a low Labeling Index. Myeloma, in fact, presents a therapeutic enigma. It does not respond to therapy as cancers generally do. It does not exhibit a dose-response effect; remission duration and survival does not appear directly related to Myeloma cell-kill; maintenance therapy does not necessarily prolong remission and survival duration; surviving Myeloma cells do not necessarily begin to grow and proliferate exponentially when treatment stops; and treatment can lower the M-protein to a plateau beyond which it will not fall lower despite continued therapy. Finally, in the rare cases where longterm survival is achieved beyond ten years, there is also the paradox that, alone of all hematopoietic malignancies, such longterm survival does not equal cure, and relapse is still, bafflingly, the rule.

Why? Why too, for instance, should Myeloma show “a special predilection for the spinal column”? Again, the mysterious, rare but recognized phenomenon of the plateau achieved without treatment, peculiar to Myeloma, in which the disease is still present but “spontaneously” becomes inactive, suggests an inner mechanism of control. If we knew what this mechanism involved, we might be able to access it and perhaps prolong the plateau indefinitely, as good as a cure. Similarly, in a tiny minority, about 4%, MGUS occasionally disappears altogether. If we knew why, as Robert Kyle has remarked, “If we could reverse MGUS, we could cure Myeloma.”

The Hypothesis

“Discovery”, said Albert Szent-Gyorgi, “is seeing what everybody else has seen and thinking what no-one else has thought.” Much of the information behind this hypothesis has been available for decades, if hitherto unlinked, and perhaps it will seem too simple. I believe that the fundamental cause of MGUS and Multiple Myeloma, without which all the diverse known risk factors, from benzene to paints and solvents, from hair dyes and asbestos, to pesticides and radiation, may not be potentiated, is a chronic, subtle, and sometimes perhaps not so subtle, deficiency of vitamin B12.

Evidence: Epidemiological, Biochemical and Genetic

Vitamin B12 deficiency is, like Multiple Myeloma, almost unknown under the age of 40. Barring inherited congenital B12 abnormalities, when it occurs in the young, particularly the black young, co-balamin deficiency manifests blatantly, as Pernicious Anaemia, and tends therefore to be promptly treated. However, even when treated, Pernicious Anaemia itself carries an increased risk for Myeloma, and MGUS is frequently present in Pernicious Anaemia. Blacks, who have a higher incidence of Pernicious Anaemia and MGUS, also have a higher incidence of Myeloma.

Subtle or insidious B12 deficiency, with no overt clinical manifestations and even in the presence of seemingly normal serum B12, is now a well-established phenomenon. B12 deficiency follows a discrete pathologic staging pattern, similar to iron deficiency, and the sub-clinical early stage can be effectively defined using the Deoxyuridine Suppression test. It is most prevalent in the elderly, for instance, 50% of Americans by age 65 do not have adequate B12 absorption, and can exist as an isolated deficiency, even in the well-nourished elderly, due to the increasing natural gastric atrophy of age, which significantly begins earlier in men than women, and leads to hypochlorhydria, achlorhydria, and sometimes loss of Intrinsic Factor, the B12 absorption medium, nowadays com-
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Pounded by the increasing long-term use of antacids in the elderly. Even in the presence of Intrinsic Factor, the separation of B₁₂ from its protein bound form in food can only take place at low gastric pH. A further contribution to B₁₂ deficiency in age may be made by an age-related alteration in the binding sites for B₁₂ on Transcobalamin II (TCII), the B₁₂ serum transport protein, which carries 20% of B₁₂, largely as Adenosylcobalamin (AdoCbl), to all tissues in the body. The 80% B₁₂ carried on TCII is apparently not directly bio-available. Thus, measuring total serum B₁₂ may be misleading. As regards true B₁₂ Sufficiency status, it is the percentage saturation of TCII that counts. In the normal elderly the Unsaturated B₁₂ Binding Capacity (UBBC) of TCII is considerably higher than in the young, in tandem with lower serum B₁₂ levels in general. Low serum levels of B₁₂ in Myeloma are well attested to and are viewed as an unexplained exception in cancer. Other non-haematological cancers in general appear to have normal B₁₂ status. Interestingly, it has been demonstrated that there is very similar erythrocyte total cobalamin in Myeloma patients and age-matched controls, both on average 50% lower than in younger controls. Moreover, lower levels of B₁₂ in Myeloma have been linked to greater degrees of immune paresis, a major Myeloma characteristic, also manifest in 30-40% of MGUS cases. One study cites a median level of 181.5 p mol/l B₁₂ amongst its patients, as well as a significantly higher frequency of hypo- and achlorhydria in levels below 160 p mol/l. Conversely, marked elevations of TCII UBBC characterize both MGUS and Myeloma in particular. The possible significance of this phenomenon has been effectively overlooked because TCII is also seen “only” as an acute phase reactant protein which transiently appears in infections and inflammatory conditions, such as rheumatoid arthritis (RA). I would maintain however that elevations of TCII in Myeloma signal an emergency need for more B₁₂ precisely because the lack of B₁₂ is causal to the crisis. This ascribes a beneficial rescue role, and meaning, to the term acute phase reactant. If we look at RA, which itself carries an increased risk for Myeloma, associated with increased production of Interleukin-6 and Interleukin-1β, it seems pertinent that it too is characterized by elevations of TCII and low serum B₁₂, that the Japanese have successfully treated RA with high doses of B₁₂ and other work demonstrates that, through inhibition of nuclear factor NF-κ-B, B₁₂ can substantially reduce both Interleukin-1β and Interleukin-6, the cytokines responsible for growth and proliferation in Myeloma and inflammation in RA. So an initial deficiency of B₁₂, mild or otherwise, may promote upregulation of IL-6 and thus an environment propitious to MGUS and Myeloma. In turn this may be compounded by low gastric acid impairing absorption of vital bone-building minerals over time. Since B₁₂ opposes IL-6, we can see why its relative absence in spinal fluid, normally high in B₁₂, would logically make the spinal cord vulnerable in Myeloma. Not inappropriately, current research into therapy for Myeloma is seeking to find ways of opposing IL-6. Subtle B₁₂ deficiency aside, there is some association of megaloblastic anaemia and low B₁₂ status in Myeloma. If this is not greater it may be because concurrent iron deficiency, common in Myeloma, due to haemolysis and hypochlorhydria, can mask megaloblastosis by lowering the MCV. Occasional alterations in B₁₂ status for the better, (perhaps due to random vitamin administration, alterations in stomach pH, antacid withdrawal, or the puzzlingly unexplained observation that lack of Intrinsic Factor Secretion sometimes reverses itself), may also conceivably explain both the “spontaneous” plateau phenomenon and rare long-term survival and relapse even after 10 years. Such relapses
might be expected because B\textsubscript{12} deficiency tends to increase with age and, unless blatant, go undetected and untreated. In this view also, the problems of Myeloma chemotherapy referred to earlier arise because the fundamental cause of Myeloma persists unaddressed.

The marked bias in Myeloma for males against females may be explained partly by delayed gastric atrophy in the latter, for whom the gene is not normally expressed till after the menopause, with the exception of black women,\textsuperscript{22} who notably have higher rates of Myeloma than white men, though still lower than black men. (Speculating further, it is possible that it is in the early or more active expression of the gastric atrophy gene that the true genetic link in familial Myeloma is to be found. In familial Myeloma the affected children of parents with Myeloma tend to get Myeloma at an earlier age;\textsuperscript{5} just as premature expression of the gastric atrophy gene in one generation leads to even more premature expression in the next.)\textsuperscript{22} Secondly, there is a life-long sex difference in cobalamin status. Women appear to have both higher serum B\textsubscript{12} levels and higher UBBC TCII.\textsuperscript{39,40} The latter may ensure relative protection. Women are also probably exposed to far fewer of the known occupational hazards than men, given traditional male domination of at-risk professions. The fact that blacks worldwide also have higher B\textsubscript{12} serum levels than whites, in spite of a lower dietary intake, as well as significantly higher TCII levels, attributed to a genetic enzyme polymorphism,\textsuperscript{24} might initially appear to contradict my argument. It may be however that these higher B\textsubscript{12} and TCII levels do not reflect blacks' true B\textsubscript{12} status and instead indicate a greater metabolic need for B\textsubscript{12}, so that the B\textsubscript{12} deficiency threshold may actually be considerably lower for blacks, rendering them more vulnerable. Gastric acid concentrations are also lower for blacks than whites;\textsuperscript{24} as are their mean haemoglobin and albumin levels,\textsuperscript{24} suggestive of a more precarious nutritional status, which might favour oncogenesis. Furthermore, there is the possibility of functional differences between the different allelic forms of TCII, since studies show different TCII alleles have different affinities for cobalamin.\textsuperscript{24} Blacks, moreover, have a greater tendency to form circulating immunoglobulin-TC complexes and there is a suggestion of greater frequency of genetic and acquired TC disorders in blacks, perhaps related to their higher TCII levels.\textsuperscript{24} Blacks also get Pernicious Anaemia at a much earlier age than whites and the course of the disease tends to be more accelerated.\textsuperscript{24}

Farmers, foresters, fishermen, veterinarians and anaesthesiologists all have increased incidence of Myeloma. Where is the B\textsubscript{12} link? All these professions have varying degrees of exposure to nitrous and nitric oxide. NO effectively inactivates B\textsubscript{12} for biochemical use by preventing reduction of hydroxocobalamin, thus it can cause B\textsubscript{12} deficiency even in the presence of abundant B\textsubscript{12}.\textsuperscript{41} B\textsubscript{12} is used biochemically to quench excess NO in the body, thus exposure to external NO would use up B\textsubscript{12} stores more rapidly.\textsuperscript{42} Farmers, fishermen and foresters are routinely exposed to N\textsubscript{2}O and NO in a relatively unregulated fashion through exposure to diesel combustion products, also a good source of carcinogens, such as polycyclic aromatic hydrocarbons. For farmers the link between Myeloma and diesel exposure, established if hitherto unexplained,\textsuperscript{8} is pointed up by the increased risk of farmers in higher diesel use farming, (arable, fruit and vegetable), and the risk is additional to exposure to pesticides and fertilizers,\textsuperscript{8} the latter incidentally being another potential if more limited source of N\textsubscript{2}O and NO, especially when stored indoors. In anaesthesiologists the risk for Myeloma initially appears partly hidden in modern statistics which show an increased risk for lymphoproliferative and haematopoietic malignancies in general. Contem-
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porary anaesthetic practice makes gas filtering units, checked daily, regulatory. However, the moment one looks at earlier anaesthetic practice decades, (where higher doses of N₂O and NO were routine), Eastern Bloc anaesthetics, or less regulated veterinary use of N₂O, the risk seems more apparent, and may arise in particular because, as with farmers, inactivation of B₁₂ is coupled with exposure to known mutagens and possible carcinogens, in other anaesthetic gases; i.e. exposure minus protection.

In a way the B₁₂ deficiency hypothesis may also explain Myeloma’s relatively low incidence. Raised homocysteine is a corollary of B₁₂ deficiency, particularly if folate and B₆ are also low. This being a major cardio-vascular risk factor, a substantial proportion of the elderly will die of heart disease, the West’s greatest killer, as well as of “old age”, other cancers etc. The Mayo Clinic’s large study of MGUS patients over 3 decades seems to make the point: whilst 25% developed Myeloma, and other blood cancers, 52% died, of mixed causes including heart disease. Thus the true potential of MGUS for Myeloma was not revealed. Perhaps it is those relatively well nourished persons with chronic, subtle B₁₂ deficiency, and thus relatively mild hyperhomocysteinaemia, whether or not they have past exposure to known risk factors, who linger on to run a small but increasing risk of Myeloma. Perhaps this explains the raised risk for teachers and clerical workers. By age 95 anyway the incidence of MGUS is 19%. Fortunately, by then, death usually intervenes.

B₁₂, the Second Secret of Life?

Every DNA synthesizing cell in the body contains receptors for TCII, the B₁₂ transport protein. B₁₂ is nature’s most complex non-polymer molecule, the most complex of the vitamins and enzymatic co-factors known to date, and the oldest known in life forms, “conjectured to have been part of the very beginning of metabolism as we know it today.” B₁₂’s coenzyme AdoCbl’s, remarkable chemical and biological reactivity lies in a unique, water-soluble, covalent carbon-cobalt bond. This renders B₁₂ one of the most potent physiological compounds, with a daily requirement of only 1µg in health. Modest as this seems, the role of B₁₂ is to protect every major organ and system in the body. As a methyl donor, it reduces homocysteine to methionine, thus protecting the heart and circulation. With major stores in the liver, B₁₂, like glutathione with which it shares a low molecular weight and ubiquity, protects that organ from the toxins it must continually deal with. The stomach, normally viewed as just a transit station for B₁₂, may be equally dependent, since B₁₂ deficiency in Pernicious Anaemia is correlated with a 3-fold increase in carcinoma of the stomach. High kidney stores of B₁₂ which protect the renal tubules, (and might conceivably have some role in the kidney’s production of erythropoietin), are ensured by megalin, an endocytosis mediating membrane protein and member of the lipoprotein receptor gene family, also expressed in varying absorptive epithelia, such as the CNS ependyma, inner ear and lung epithelia. A further receptor protein has recently been identified that appears to ensure high concentrations of B₁₂ in the adrenals. B₁₂ protects the integrity of the brain and central nervous system, as the neuropathies and dementias of deficiency demonstrate. Through its co-enzyme, AdoCbl, which mediates the isomerization of methylmalonyl Co-A to Succinyl Co-A, B₁₂ affects a critical point in the Krebs or Tricarboxylic Acid cycle, since succinyl Co-A represents a metabolic branch point wherein intermediates may enter or exit the cycle, leading ultimately to the release of Adenosine Triphosphate. In other words, B₁₂ is critical to the release of cellular energy, which is decreased in cancer. Thus a deficiency of B₁₂ may accelerate the course
of cancer, an acceleration characteristic of Myeloma in its active phase. B₁₂ is essential for effective haematopoiesis: it protects the marrow from deranged DNA synthesis, megaloblastic erythropoiesis and associated erythroid hypoplasia. Additionally, I would suggest that, by tightly regulating IL-6, B₁₂ safeguards the marrow from clonal plasma cell expansion or Myeloma. Animal experiments with exposure to nitrous oxide, which inactivates, B₁₂ have also demonstrated haematologic depression occurring at the level of the haematopoietic stem cell. Since Myeloma is now thought to evolve from a haematopoietic stem cell, such depression, though milder in mild B₁₂ deficiency states, might, if persistent, be very relevant to the haematopoietic stem cell's susceptibility to malignancy. The prior observation of increased immune paresis with greater occurrence of B₁₂ deficiency in Myeloma may also be pertinent to oncogenesis. (The proverbial immunity lowering effects of anaesthesia may well be due principally to B₁₂ inactivation by N₂O). By polyglutamating folate, B₁₂ traps folate within the cell, thus ensuring good DNA methylation, hypomethylation being linked to oncogenesis. B₁₂ may play an indirect role in cell growth and differentiation, vital in cancer chemoprevention, since it enhances tissue deposition of vitamin A, itself a growth regulator and differentiator, by enhancing betacarotene absorption and its conversion to vitamin A. B₁₂ may also play an oncogene regulatory role via its relationship to the production of the leucine-zipper motif of certain regulatory proteins, (the transcription factors Myc, Jun and Fos, Myc being relevant as expression of its close relative c-myc is amplified in Myeloma.) B₁₂ is apparently required for the isomerization of the branched chain amino acid β-leucine to leucine, which in turn contributes to the leucine-zipper motif. In B₁₂ deficiency β-leucine is elevated and leucine is low. The consequence may be mutations and disregulation of the regulatory oncogene protein: end result, a transformed cell. Though it is unclear at what stage c-myc is activated in Myeloma, it plays a central role in controlling proliferation, differentiation and apoptosis. Interestingly, there is a suggestion that the c-myc ligand up-regulates TC gene expression in Myeloma, and various haematological malignancies. This might be an attempt at self-correction.

Finally, if cancer is, amongst other things, the result of a radical loss of balance in the Redox equation, B₁₂ may be one of the body’s greatest weapons in preventing or redressing this state, as its coenzyme AdoCbl may be the non plus ultra of antioxidants. A notable B₁₂ chemist has found evidence pointing to the possibility that AdoCbl dependent enzymes may alternate between serving as “ultimate radical cages” and “ultimate radical traps”. An index of this effect might be seen in various trials on squamous metaplasia in chronic smokers. A double-blind trial using B₁₂ and folate, or placebo, showed significantly higher responses in atypia with B₁₂ than did trials with various retinoids.

Testing the Hypothesis

If this hypothesis is correct, then it should be theoretically possible to reverse MGUS, and thus prevent Myeloma, or even perhaps just prevent Myeloma, by the administration over time of large doses of intravenous B₁₂, as hydroxocobalamin. (Cyanocobalamin, being metabolically rather inactive, is not the cobalamin of choice.) The correct dose and schedule may be a matter for empirical experimentation. Since one is treating a disease, as well as a deficiency, it might take many months, even years, with dose adjustments upwards, to take effect. Titrating dose and schedule to an arbitrary low or short-term ceiling may be counterproductive. Nor, as indicated earlier, is the actual B₁₂ serum status of MGUS patients necessarily a guide, unless you measure the percentage B₁₂ saturation of TCII, and even...
then you must remember we are looking for a subtle, pre-clinical, chronic deficiency. Linus Pauling believed one could use B₁₂ in megadoses,⁶⁰ like his beloved Vitamin C, and indeed B₁₂ has a consummately safe toxicity profile. In the treatment of congenital TCII deficiencies, serum levels have been kept as high as 10,000 µg/ml or more, with no ill effects.²³ B₁₂ as hydroxocobalamin has been routinely used in France since the 1970s as an antidote to cyanide poisoning, requiring 5 grams intravenously at a time.⁶¹ The FDA has also given B₁₂ orphan drug status for this purpose.⁶⁰ Most tellingly perhaps, a major trial of B₁₂ for the treatment of neuroblastoma (with over 50% regression rates,) was undertaken in children at Great Ormond Street in the 1950s.⁶² The children, in the absence of any other treatment, were given 1000 µg every other day for 2 years or more, and many lives were considerably extended, by up to 8 years. Since B₁₂ is not strictly speaking a drug, and does not act in isolation, the inappropriate drugs testing paradigm should be abandoned.⁶³ It is essential to ensure good nutritional support for its maximum efficacy by the administration of a high dose multi-vitamin, multi-mineral formula alongside a healthy diet,⁶³ high in Omega-3 fatty acids. This should be begun at least 1 month before B₁₂ therapy.

It is probably unrealistic to assume that B₁₂ alone will cure Myeloma itself directly. It is nevertheless possible that continuous B₁₂ therapy, at 1000 µg daily, may control Myeloma indefinitely and render it a chronic and no longer lethal disease. This should work without conventional treatment, though it would complement bisphosphonates which have some anti IL-6 action. There is no reason why it should not be tried alongside or post-chemotherapy. I doubt whether B₁₂ will, in popular scientific parlance, “feed the cancer”, though there is a school of thought that espouses this view,⁶⁴ citing increased B₁₂ turnover in cancer as related to the need for more methyl donors and C1 units for increased nucleotide synthesis. I believe the opposite is true, in part because other non-haematologic cancers do not appear to have increased B₁₂ turnover, and because B₁₂ blocks both IL-1ß and IL-6 which really do feed Myeloma, and it may also down-regulate expression of c-myc, all with no side effects. This contention, and indeed this hypothesis, is based on my experience of and involvement with the case of an 8 year survivor of Myeloma, who eschewed chemotherapy in favour of the Gerson Therapy allied to “orthomolecular” approaches.⁶⁴ Following an empirical observation of Max Gerson that Myeloma and the leukaemias require more B₁₂ than other cancers,⁶⁵ and my own basic observation that the patient’s slightly raised MCV implied a need for B₁₂, in an attempt to ameliorate the patient’s anaemia,⁶⁴ I proposed to his GP that he should allow the patient to inject 1000 µg daily. The patient, initially diagnosed as Stage I Multiple Myeloma, has now done this for 8 years, and is alive, well and in remission. This may prove nothing. At the least it may suggest B₁₂ does not kill Myeloma patients. Further, raised MCVs indicating a need for B₁₂ are not uncommon in Myeloma.³² This may be another aetiological pointer that has been overlooked.

If this hypothesis is tested and proved, I would also venture that it might hold good for related haematological conditions, such as Waldenstrom’s Macroglobulinaemia, which also demonstrates raised TCII levels; amyloidosis and heavy chain diseases in general; other paraproteinaemias; chronic lymphocytic leukaemia, which like Myeloma is a clonal proliferation, sharing deletion of 13q14, the retinoblastoma gene, a remarkably similar age of onset and MGUS association; chronic neutrophilic leukaemia, which also has a MGUS connection; possibly even the lymphomas. It is noteworthy, for example, that low B₁₂ is a poor prognostic factor in AIDS,⁶⁶ a condi-
tion peculiarly prone to the lymphomas. Is this just a coincidence? Is this hypothesis just a series of coincidences? Of course, many correlations can lack causality. I have tried to link them nonetheless. The wider implications should now be explored. Myeloma remains unyielding, and the field is short of therapeutic ideas.

References


Myeloma Control and Prevention Trials Orthomolecular Oncology, a UK and overseas registered Charity (http://www.canceraction.org.gg), would like to co-ordinate multi-centre trials of the above Hypothesis. The trial protocol proposed will be published on our site April, 2002. This is a call for interested physicians everywhere who have MGUS or Myeloma patients to come forward and join this endeavour. Please contact me at: canceraction@gtonline.net