

MEMORIAL SLOAN-KETTERING CANCER CENTER

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February 1, 1979

Mr. J. Stenmark
American Iron and Steel Institute
1000 16th Street, N.W.
Washington, D.C. 20036

Dear Mr. Stenmark:

Last fall your medical advisory committee requested further background about Dr. Maria de Sousa's research on the role of iron in the immune system, and a copy of Dr. de Sousa's curriculum vitae and list of scientific publications. We had this information sent to your Assistant Mr. Peter Hernandez to forward to the committee. Since we had not heard from the American Iron and Steel Institute during the interim, I assume that you are still deliberating about our previous request for support of this research. Therefore I would now like to bring you up to date about some very important recent findings Dr. de Sousa and associates are making which convince me still further that iron is a very important and all too neglected currency in the body economy and defense against disease.

Regulation by Iron and Iron-Binding Proteins of the Development of White Blood Cells.

One of the major research goals of this institution is to understand how the various disease-fighting white blood corpuscles develop from a single precursor in the bone marrow and how this development, in the case of blood disorders like leukemia, becomes abnormal. Throughout the course of this research, many peptide molecules have been discovered which appear to regulate these processes, turning on the development of certain lines of cells, and turning them off at appropriate times in response to the needs of the body to combat disease. One of these proteins is an inhibitory factor in the development of granulocytes, a crucial variety of white blood cells. The identity of this inhibitory protein, designated CIF (colony inhibitory factor) was unknown.

Based upon the discoveries of receptors for iron-binding proteins (transferrin and lactoferrin) on lymphocytes and an intuition seen only in truly brilliant scientists, Dr. de Sousa postulated that CIF was one or the other

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of these iron-binding proteins. This prediction was correct and it saved us years of research to discover the identity of CIF. It also pointed out clearly that iron and iron-binding proteins truly are far more important in regulating the immune system than we realized. A copy of Dr. de Sousa's published report of this discovery is enclosed.

Regulation of the Expression of Cell Surface Markers by Iron.

If, as Dr. de Sousa postulated, a buildup of iron in the wrong place in the body was a reason for the abnormal distribution of certain white blood cells in various diseases of uncertain origin like Hodgkin's disease, and if receptors for iron and iron-binding proteins existed on the surfaces of these white blood cells, it was logical to suspect that iron might influence the behavior of lymphocytes by directly interacting with them at their surface membrane.

To test this notion, Dr. de Sousa examined the effect of iron and transferrin upon the ability of lymphocytes to bind foreign (sheep) red blood cells - a classical test for the expression of characteristic markers of certain lymphocytes. She found that iron directly inhibited binding of sheep red blood cells to lymphocytes and thus masked their outer surface. It was as if iron were blunting the teeth of our best guard dogs. In addition, iron-binding agents like transferrin or the iron-grabbing drug desferal removes iron and prevents its interference with lymphocyte function and expression. Some of these results are described in the enclosed recent publication. These findings are crucial because they strongly suggest that iron can interfere with the expression of a characteristic function of lymphocytes. What's more, this is the first time anyone has shown that iron can modulate the expression of cell surface components in immune cells.

Genetic Susceptibility to the Effects of Iron on Immune Function

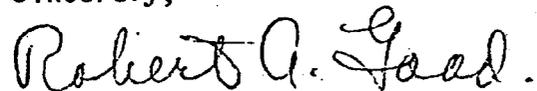
One of the early suggestions by Dr. de Sousa was that certain individuals may be genetically more susceptible to the effects of excess iron upon their immune function than others. Recently Williams and colleagues in England reported an association between certain genes of the major histocompatibility complex (HLA genes) and an iron storage disease known as idiopathic hemochromatosis. Since the HLA genes are expressed on the surface of lymphocytes and can be detected and characterized by the way lymphocytes of one person react to those of another (by a testtube assay called the MLC reaction), Dr. de Sousa speculated that differences in the way people react to iron may reside in these genes. These differences should therefore be detectable by determining how iron affects the expression of these genes in various people using the MLC test.

Indeed, very recent experiments completed by Dr. de Sousa, have shown that there are significant differences between people with different HLA types in their reaction to iron. If these results can be further borne out they will herald the first discovery of genetic control of iron binding by mammalian cells and thus a genetic basis for the way iron affects the immune system and potentially causes disease. If this is the case, we can screen people for this iron susceptibility and advise them about exposure to excess iron.

These are truly fundamental discoveries and they have been made under very difficult financial conditions. As you know, federal grant support is usually given to well established projects through a bureaucratic process that frequently stifles the rapid expansion of exciting new findings like Dr. de-Sousa's. Because I am more convinced than ever that this research is leading us to new and vital understandings about iron's role in our immune function and the way we combat disease, I would once again urge you to consider providing financial backing for this research until such time as we can secure longer term support from the National Cancer Institute. Although the annual budget for this work is about \$100,000, we would welcome half this amount per year from the American Iron and Steel Institute for two or three years.

The number of times Dr. de Sousa's hunches about iron and the immune system have been correct convince me that she is opening a major new field of biomedical science that will greatly influence our understandings not only of disease but also the role of iron in the evolution of our defenses against disease. I do hope the American Iron and Steel Institute would want to join in partnership with her in her efforts to learn more about this truly pivotal element.

Sincerely,



Robert A. Good, Ph.D., M.D.
President and Director

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Enclosures