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Correspondence

Would Montagnier please clarify whether HIV or oxidation by the risk factors is the primary cause of AIDS?

In the view of one of the most eminent retrovirologists, Howard Temin, ''when an experiment is challenged no matter who it is challenged by, it's your responsibility to check. That is an ironclad rule of science, that when you publish something you are responsible for it...even the most senior professor, if challenged by the lowliest technician or graduate student, is required to treat them seriously and consider their criticisms. It is one of the most *fundamental aspects* of science'' [1] (emphasis in original).

At the beginning of the HIV/AIDS era we proposed a non-HIV theory. This states the cause of AIDS is the oxidation induced by the risk factors including malnutrition to which patients in the AIDS risk groups are chronically exposed [2,3]. In 1990, the journal *Research in Immunology*, an *Institut Pasteur* publication, opened its ''columns to Dr. P. Duesberg and Dr. L. Montagnier, who have agreed to discuss the matter of whether HIV is the causative agent of AIDS'' and ''invited other contributions on this topic''. In our contribution entitled ''Oxidative Stress, HIV and AIDS'' we wrote ''As long ago as 1983, one of us (E.P.-E.) proposed that oxidative mechanisms are of critical significance in the genesis of AIDS (acquired immune deficiency syndrome). A prediction of this hypothesis was that the mechanisms responsible for AIDS could be reversed by the administration of reducing agents, especially those containing sulphydryl groups (SH groups). The discovery of HIV resulted in a broadening of this hypothesis in that it considered oxidative stress as a principal mechanism in both the development of AIDS and expression of HIV'' [4]. In the same contribution as well as earlier [5] we presented evidence that cellular activation is an oxidative phenomenon. Montagnier did not respond to Peter Duesberg or to us.

However, more than ten years after we proposed the oxidative theory of AIDS, and fully aware of it, in 1997 Montagnier wrote ''In AIDS pathogenesis, oxidative stress *is proposed* as a metabolic alteration that favours disease progression by inducing both viral replication and apoptotic death...Indeed, evidence that oxidative stress induces, while antioxidants inhibit, HIV replication and apoptosis suggests the use of these molecules as an antiretroviral therapy to reduce cell death in AIDS patients'' [6] (emphasis in original).

In two papers, one published in 1991 and the other in 1993, Montagnier proposed that ''In HIV-infected patients, the loss of CD4+ cells is associated with lymphocyte activation, but this activation does not result in cell proliferation, as it does normally, but rather in cell death by a mechanism known as programmed cell death'', or apoptosis. When he tried to prove that HIV causes apoptosis he found that in HIV infected, activated cultures the cells died from apoptosis. But, ''Intriguingly'' the same phenomenon was observed in activated (stimulated) but non-infected cultures. In other words, apoptosis was caused by the activating agents not HIV. Despite this, Montagnier concluded: ''These results demonstrate that HIV infection of peripheral blood mononuclear cells leads to apoptosis''. Regarding the mechanism by which HIV cause decrease in CD4 cells (Acquired Immune Deficiency, AID) Montagnier and his colleagues wrote: ''In vitro and in vivo, soluble gp120 might interact with CD4 receptors on uninfected cells leading to an abortive cell activation and thus triggering apoptosis'' [7,8].

In his book *Virus* Montagnier stated that in AIDS patients ''The phenomenon [oxidative stress] is massive, and occurs at an early stage'', its cause is HIV but opportunistic agents and other infections

may contribute to it. And, ''we know that the products of this stress can trigger cellular apoptosis''. Although we were the first and only group to put forward an oxidative theory of AIDS, for which he was made personally aware, as early as 1991 he claimed that only ''Dröge in Germany and Leonard and Lena Herzenberg in the United States'' are interested in this phenomenon. (Dröge and the Herzenberg's proved two predictions of our oxidative theory of AIDS). And in 1991 Dröge wrote ''However, we do agree with Papadopulos-Eleopulos and colleagues on the basic interpretation that a distorted balance of oxidants and antioxidants may play a key part in the immuno-pathology of HIV/SIV infection'' [9]. Instead of acknowledging our work Montagnier stated: ''It would be a tribute to their [dissidents] courage and honour to abandon it [questioning the role of HIV], in the face of the overwhelming evidence'' [10].

In 1995, we presented detailed evidence on the relationship between activation, apoptosis and oxidation [11]. In the same year, Montagnier gave an interview, where he stated that in progression to AIDS ''oxidative stress is a key factor...I strongly believe that one important factor is the activation of the T-helper cells. Consecutive T-cell receptor stimulation induces T-cell depletion by apoptosis. Recognising the importance of apoptosis in AIDS progression may have dramatic implications for developing new treatments for AIDS. Apoptosis may induce oxidative stress. We know also that oxidative stress can mediate apoptosis... Being able to reduce apoptosis to a normal rate in lymphocytes of HIV-infected individuals would put HIV infection in a class with mononucleosis and other chronic infections, where cell death does occur, but the immune system goes back to normal after a period of time. In the middle and later stages of HIV infection, apoptosis is a chronic and permanent problem. Antioxidants including NAC might slow the rate of apoptosis'' [12].

In a talk he gave to the European Parliament, 8th December 2004, Montagnier said that the cause of the ''clinical phase of opportunist infections and cancers which result in death [AIDS] '' is principally due to a decline in the numbers of T4 cells. The decline in T4 cells is due to their ''propensity to die from apoptosis''. In turn apoptosis is due to ''potent oxidative stress''. Significantly, with the exception of African patients, Montagnier, unlike us, does not address the cause of the oxidation in the AIDS risk groups (HIV expression cannot be both the result and the cause of oxidation). In regard to African patients he said that the oxidative stress ''exists even in the non-infected individuals because of malnutrition'' [13] (our translation from French). That is, the cause of AIDS is oxidation, not an infectious retrovirus.

Since in the name of ''HIV'', a virus whose existence Montagnier is said to have proven in May 1983, millions of people are suffering, does Montagnier not have a scientific and moral responsibility to respond to his critics?

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Endogenous secretory RAGE as a potential biochemical screening tool for erectile dysfunction

Dear Editor,

Recent results have shown a linear increment in the prevalence of erectile dysfunction (ED) with a linear impairment of endothelial function score, as well as with the number of components of the metabolic syndrome (MS) [1]. Interestingly, a growing body of evidence has clearly indicated that the MS may be extremely significant in the pathogenesis of erectile dysfunction [2,3]. Working from these assumptions, the availability of a reliable biochemical marker for several components of the metabolic syndrome would be of great interest as a screening tool for ED, especially in an epidemiological setting. In this context, we speculate that evaluation of plasma levels of endogenous secretory receptor for advanced glycation end products (esRAGE) may represent a potentially useful laboratory marker for ED.

There are at least three theoretical reasons whereby esRAGE could act as a biomarker for ED. Firstly, there is evidence that levels of esRAGE are strongly and inversely associated with subclinical atherosclerosis [4], a well-known risk factor for ED [2]. Secondly, levels of esRAGE measured in plasma are inversely related to a number of components of the metabolic syndrome, including body mass index, blood pressure parameters, triglycerides, HbA1c, or insulin resistance index [4]. Of note, esRAGE levels are inversely associated to all these parameters [4], each of which being in turn related to ED [2,3]. Third, the soluble decoy esRAGE is capable of neutralizing the action of advanced glycation end product (AGEs) on vascular endothelial cells, thereby acting as a protective factor for endothelial dysfunction [5]. Notably, a role for AGEs in ED has been postulated through quenching nitric oxide [6]. In addition, AGEs have been shown to be elevated in diabetic human penile tissue, thus indicating a direct role for advanced glycation end products in the pathogenesis of ED [6].

Since evaluation of circulating esRAGE levels requires only a minimally invasive venous blood sampling, we believe that future epidemiological studies aiming to test our hypothesis of a reduced level of this molecule in ED would be highly desirable.

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