Causes of Ferritin Elevation

To the Editor Drs VanWagner and Green[1] analyzed the case of a 46-year-old man with inflammatory arthritis presenting with an elevated ferritin level of 2556 µg/L. Of the potential causes of ferritin elevation, the authors primarily considered hereditary hemochromatosis, which was the final diagnosis, as well as excess iron supplementation, frequent blood transfusions, obesity, alcohol consumption, hematologic disorders, and inflammatory arthritis.

Although I agree that these conditions are frequently associated with hyperferritinemia, malignancy should also be considered as a potential source of elevated serum ferritin levels, especially in middle-aged men. Ferritin is variably overexpressed in tissues from a large number of malignancies, including hepatocellular carcinoma, hematologic malignancies, and breast and pancreatic cancers, and is frequently associated with liver metastases.[2] A recent study investigated the underlying etiology of markedly elevated ferritin levels in patients treated at a tertiary care medical center and concluded that cancer was the most frequent condition (24%), followed by iron overload syndromes (22%).[3] In patients with cancer, the mean ferritin level was found to be 2850 µg/L, a value similar to that reported by VanWagner and Green.[1]

The potential underlying mechanisms of hyperferritinemia in patients with cancer include a chronic inflammatory state, increased cancer-related transcription of H-ferritin, and localized release into the bloodstream from ferritin-rich macrophages that accumulate in cancer tissue.[2] The accumulation of ferritin in certain cancers is so enhanced that an innovative diagnostic strategy based on magnetoferritin nanoparticles has been proposed for targeting tumors.[4]

According to the most recent statistics, cancer is the leading cause of death in men aged 40 to 59 years.[5] The incidence of hematologic and liver malignancies is gradually increasing in US men, with as many as 68 300 new cases of blood cancers and 24 600 new cases of liver cancers each year. As such, the presence of occult cancer should not be discounted in the differential diagnosis of hyperferritinemia.

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply Dr Lippi raises the important point that an elevated serum ferritin level may also be associated with underlying malignancy; it is true that ferritin may be elevated in a broad variety of other disease processes, as we noted in our JAMA Diagnostic Test Interpretation article. Elevated serum ferritin levels are commonly encountered in general practice and many elevations may be due to non-iron overload conditions.

The patient described was a relatively healthy middle-aged man who was unexpectedly noted to have a markedly elevated ferritin level. The cited investigation by Moore et al[1] retrospectively studied the underlying etiology of markedly elevated serum ferritin levels in a large group of patients at a tertiary care medical center, including patients with a range of cancers, infections, inflammatory conditions, and renal diseases.[1] This study population is distinctly different from the relatively healthy patient described in our article.

Therefore, we believe that the approach outlined in our report, including *HFE* gene testing, remains the most appropriate diagnostic approach, albeit with the recognition that cancers and other disease processes remain possible as a cause of a markedly elevated ferritin.

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Prevention of Noncommunicable Diseases

To the Editor We agree with Dr Yach and Mr Calitz[1] in their Viewpoint on the changing landscape of prevention of noncommunicable diseases that increased and more targeted research on prevention, adequate infrastructure at the National Institutes of Health (NIH), public-private partnerships, and use of up-to-date health technology tools are needed. In addition, we would like to add another perspective.

Epidemiological research has linked exposures early in life to adult health and disease.[2] These exposures span a range including socioeconomic conditions, toxic exposures, and birth weight as a proxy for early adversities. Data sug-

gest that the origins of the most recalcitrant (and costly) noncommunicable diseases begin in childhood. The biological, environmental, and psychosocial conditions under which children develop not only affect their health at the present moment but set them up for poor health outcomes that manifest decades later.

For example, studies of adverse childhood experiences show that toxic psychosocial stressors during childhood, such as abuse, neglect, parents with mental health conditions, having an incarcerated parent, and parental separation or divorce, were associated with higher incidences of ischemic heart disease, liver disease, chronic obstructive pulmonary disease, and depression when these children became adults, even after controlling for factors such as age, sex, and education.[3] A growing body of evidence shows that these psychosocial stressors contribute to physiological dysregulation, known as allostatic load. Alterations in stress hormone profiles, inflammatory mediators, and immune regulation contribute to allostatic load and are precursors to noncommunicable diseases.[4]

Adverse childhood experiences are not the only toxic childhood stressors that may contribute to adult chronic illness. More recent data suggest that other adversities, such as witnessing violence, living in an unsafe neighborhood, being bullied, or experiencing discrimination, are additional childhood stressors that may also contribute to adult adverse outcomes.[5]

A key strategic prevention priority must address the contextual childhood precursors that lay the groundwork for chronic conditions. Studies of the effects of toxic stressors and childhood adversities show that a life-course approach to prevention is necessary.

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In Reply We agree with Drs Pachter and Cheng about the value of research into the early origins of chronic diseases. Further progress requires greater investment in large-scale birth cohort studies to better understand the complex interactions of genetic, environmental, and social factors and their trajectories over time.

Birth cohort studies in South Africa have yielded novel and valuable insights for policy makers. Examples include raised blood pressure in Soweto children by 5 years of age and higher levels of respiratory infections in children younger than 2 years resulting from poor air quality from coal burning.[1] The goals of such research reflect what we think is a needed shift in the goal of NIH research: to promote and enhance health over the lifespan. The current justification for NIH funding based on breakthrough cures undermines more significant funding opportunities for research leading to sustained health gains and reduced disparities.

However, prevention science should not focus solely on children. Today, life expectancy at age 50 years in leading countries is almost another 40 years to age 90 years and will soon approach 100.[2] The historic emphasis on prevention programs for childhood needs to adapt to this reality. Childhood vaccines, optimal nutrition, active living, mental stimulation, and a tobacco-free environment have relevance for prevention programs for individuals older than 50 years.

Public and private research has led to efficacious new medications and vaccines. Nonetheless, levels of adherence for chronic disease medications and recommended adult vaccines remain extremely low.[3,4] The multibillion dollar investment in developing efficacious treatments is often failing to have its full effect on population-level health outcomes because of persistent knowledge gaps in implementation science and the use of new insights such as behavioral economics.

Furthermore, true breakthroughs in prevention are required for 2 categories of disease that are increasingly prevalent due to the aging population: mental health and musculoskeletal disorders. For both, diagnoses are often available before effective cures have been found or prevention options identified. The result is increasing health care costs with few gains to health.

Prevention science also needs to reach beyond the medical and traditional health care sectors. One promising area involves research aimed at defining guidelines that interior designers, architects, and town planners can use to design buildings and cities that actively promote health.[5]

Reversing the lagging health of the United States will require a tangible financial commitment to the value of prevention science and a portfolio that emphasizes health across the lifespan.

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