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IN RESPONSE: We appreciate that Dr. Liebmann and associates took the trouble to write to us about our Editors' Notes for the article by Du and colleagues. We said that "many unnecessary deaths could probably be prevented by following the National Institutes of Health guidelines." Liebmann and associates' citation of our statement omitted the word "probably," a word that we chose with care to be sure that readers understood that we were making a conjecture rather than a conclusion based on established fact. Our conjecture would have been more informed if we had estimated the number of women who might have benefited from adjuvant therapy, as we have tried to do for this response.

The NIH guidelines in force in 1991 to 1997, the dates of Du and colleagues' study, recommended chemotherapy for women with node-positive tumors or node-negative tumors with poor prognostic features. For our estimate, we confined ourselves to node-positive tumors, since Du and colleagues' study lacked information about the latter group. In the New Mexico study, 1660 women 50 to 69 years of age received a diagnosis of stage I, stage II, or stage IIIA breast cancer between 1991 and 1997 and did not receive adjuvant chemotherapy. The article did not provide the number of node-positive women who did not receive chemotherapy. To provide an upper bound on this number, we assumed that 34% of women who did not receive chemotherapy had node-positive disease, the same proportion as in all women in the New Mexico study (in fact, <34% of women who did not receive chemotherapy had node-positive disease, as seen in Du and colleagues' Table 2). According to this assumption, 564 of the 1660 women who did not receive chemotherapy would have had node-positive disease. According to data from the Early Breast Cancer Trialists' Collaborative Group (1), the absolute gain in 10-year survival was 3% for 50- to 69-year-old women with node-positive disease (46% to 49%). Therefore, the potential gain in 10-year survival from receiving recommended chemotherapy was no more than 17 women. This number is smaller than we supposed when we wrote the Editors' Notes, and we would frame our comment more judiciously now.

The Editors

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A Rash Decision

TO THE EDITOR: It was with great interest and pleasure that we read "A Rash Decision" by Georganna Davis (1), an essay we think was intended to convey the angst and insecurity of the author, a medical student, when evaluating a puzzling patient early in her career and making a diagnosis not shared by her venerated mentor. Although we were able to appreciate and relate to the emotions she evoked, we were left with what we feel was an unintended message. Although the patient seemed to have a very severe tinea infection, the experienced physician preceptor was either too busy to perform a potassium hydroxide wet mount preparation or, more alarmingly, didn't even entertain the diagnosis in a patient with a scaly rash.

In the present climate of managed care and decreasing remuneration, financial pressures may dictate that primary care physicians see more patients and spend less time on issues they feel are not important. Although this is not proven, we fear that primary care providers may not place skin disease high among their priorities when they are asked to perform so many other functions, such as chronic disease management, cancer screening, and prevention of cardiovascular disease and death. An alternative explanation for the preceptor's initial misdiagnosis is the overall poor performance of primary care providers with respect to the diagnosis and treatment of cutaneous disease (2, 3). This is of great importance since 6% of all outpatient encounters involve some symptom affecting the hair, skin, or nails (4), and most patients are seen by nondermatologists (5). Although we don't know why the preceptor didn't make the correct diagnosis in this case, either of our postulated reasons is both telling and disquieting.

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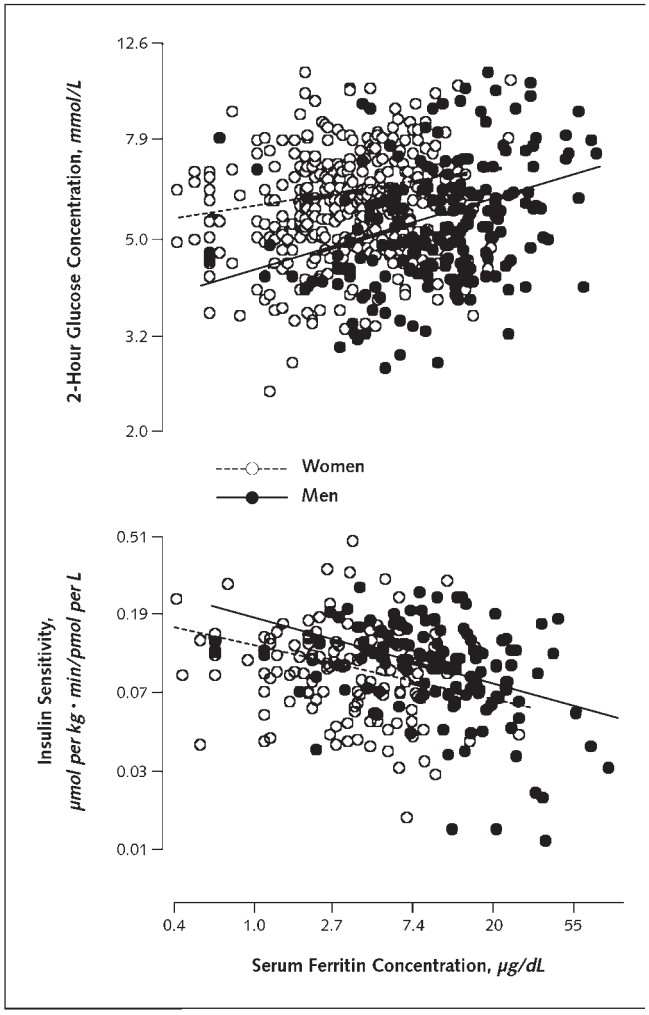
Clinical Observations

Association of High Serum Ferritin Concentration with Glucose Intolerance and Insulin Resistance in Healthy People

TO THE EDITOR: *Background:* Increasing evidence points to an association between increased body iron storage and type 2 diabetes mellitus, even outside the context of hemochromatosis (1, 2). A small intervention study provided preliminary evidence that bloodletting, which resulted in 50% reduction of serum ferritin concentrations, improved glycemia and insulin sensitivity in patients with type 2 diabetes (3). However, interpretation of mechanistic studies in patients with overt type 2 diabetes mellitus are complicated because glycemic control itself influences serum ferritin concentrations (glycosylated ferritin has a longer serum half-life) and primary effects on insulin sensitivity or β-cell function can no longer be studied.

Figure. **Correlation of serum ferritin concentrations with 2-hour glucose concentration (*top*) in 538 nondiabetic persons and insulin sensitivity (*bottom*) in 257 nondiabetic persons.**



Data were derived from least-square linear regression analyses performed on log-transformed data. For 2-hour glucose concentration in all participants, men, and women, $r = 0.08$ ($P = 0.049$), $r = 0.32$ ($P < 0.001$), and $r = 0.13$ ($P = 0.002$), respectively. For insulin sensitivity in all participants, men, and women, $r = -0.22$ ($P < 0.001$), $r = -0.35$ ($P < 0.001$), and $r = -0.22$ ($P = 0.02$), respectively. Mean serum ferritin concentrations (±SE) were 154 ± 9 μg/L in men and 46 ± 2 μg/L in women ($P < 0.001$). To convert serum ferritin concentration from μg/dL to μg/L, multiply by 10.

Objective: To analyze the relationship between iron variables and glucose tolerance, insulin sensitivity, and β-cell function in nondiabetic persons.

Methods: Five hundred thirty-eight nondiabetic participants (202 men, 336 women), were given a 75-g oral glucose tolerance test. The mean age (±SD) of participants was 35 ± 11 years, and mean body mass index (±SD) was 26.1 ± 5.8 kg/m^2. Insulin sensitivity (mean glucose infusion rate divided by the mean serum insulin concentration) was measured in 257 persons by using a euglycemic–hyperinsulinemic clamp, and β-cell function (mean plasma C-peptide concentration during the first 10 minutes) was measured in 69 participants by using a square-wave hyperglycemic clamp (glucose level, 10 mmol/L). Participants with clinical or laboratory signs of acute infection or liver disease were excluded. Multivariate linear regression analysis on log-transformed values was used. An institutional review board approved the research, and informed consent was obtained.

Findings: Serum ferritin level was positively correlated with 2-hour glucose concentration and negatively correlated with insulin sensitivity (**Figure**). These associations remained statistically significant ($P = 0.02$ and $P = 0.003$, respectively) after transferrin saturation, age, sex, body mass index, waist-to-hip ratio, leukocyte count, and C-reactive protein level were included as covariates in a multivariate linear regression analysis. There was no significant correlation between serum ferritin concentration and either estimated (from the oral glucose tolerance test) or measured β-cell function ($P > 0.2$).

Discussion: High serum ferritin level (even high-normal serum ferritin level) is an independent, albeit weak, predictor of poor glucose tolerance. This association seems to be secondary to an association with insulin resistance but not with β-cell dysfunction. Mechanisms through which iron causes insulin resistance with ultimate impact on glucose homeostasis probably exist in the liver (4). However, muscle and fat cannot be excluded. Iron is a potent pro-oxidant, and reactive oxygen species have been shown to interfere with insulin signaling at the cellular level (5). Conversely, insulin resistance may be the cause rather than the consequence of disturbances in iron metabolism, as recently reviewed (6). Finally, although we adjusted for leukocyte count and C-reactive protein level, we cannot entirely exclude the possibility that serum ferritin level is an additional marker of subclinical inflammation, which itself may be a risk factor for type 2 diabetes mellitus (7).

Nevertheless, in view of the sustained improvement in insulin sensitivity after bloodletting (3), it appears possible that iron overload is a weak but effective etiologic factor in the pathogenesis of insulin resistance and type 2 diabetes. It is quite plausible that the unhealthy diets in affluent western societies contribute to diabetes risk not only through excess fat intake but also through excess iron supply (for example, in meat or in iron-supplemented food). Moreover, the iron overload hypothesis partially explains the reduced risk for diabetes in premenopausal women and vegetarian societies (8).

Conclusion: It may become advisable to routinely screen for mildly elevated or even high-normal serum ferritin concentrations in the context of glucose intolerance. If prospective and interventional studies confirm an etiologic role of iron overload in the pathogenesis of insulin resistance and type 2 diabetes, reduced dietary iron intake, especially in men and postmenopausal women (9) with additional risk factors for type 2 diabetes, would appear to be a logical consequence. In the future, actively lowering body iron stores may become a tool in preventing type 2 diabetes in selected subgroups.

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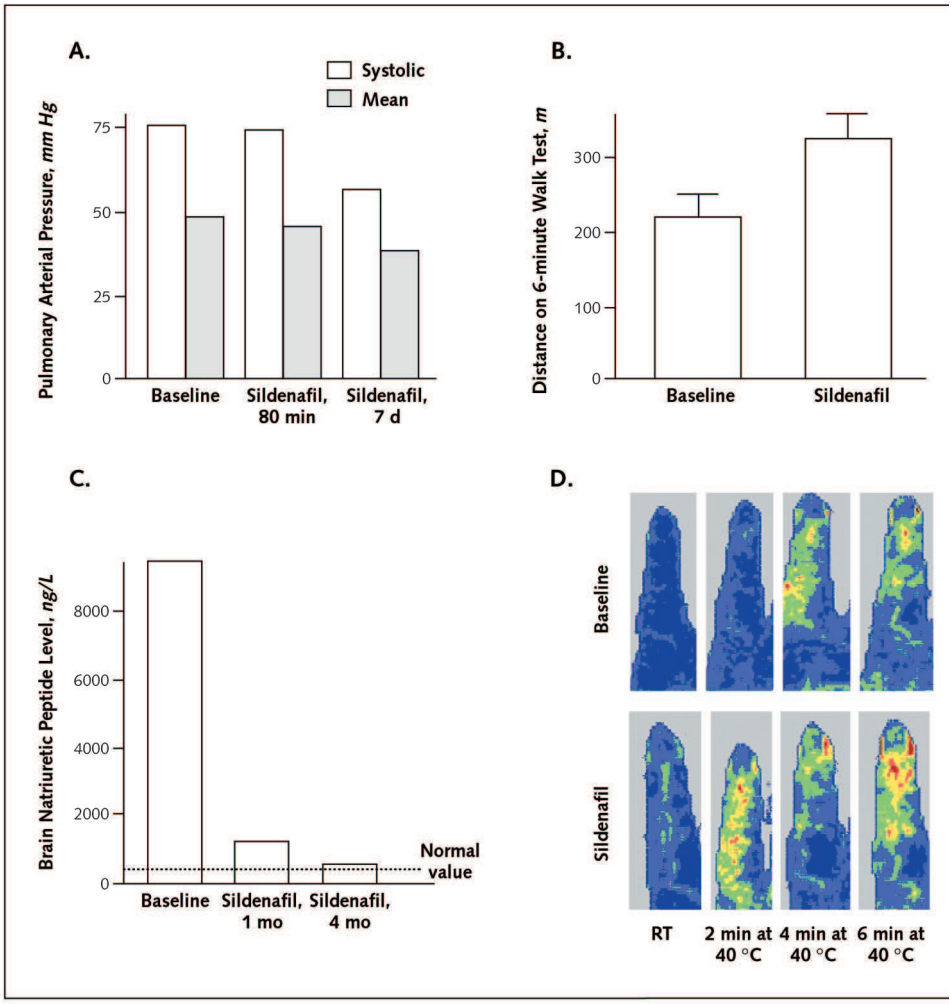
Sildenafil Improved Pulmonary Hypertension and Peripheral Blood Flow in a Patient with Scleroderma-Associated Lung Fibrosis and the Raynaud Phenomenon

TO THE EDITOR: *Background:* Systemic scleroderma is a connective tissue disease involving several organ systems. Up to 90% of affected patients have the Raynaud phenomenon, and mortality rates largely

Figure. **Effects of sildenafil treatment on pulmonary arterial pressure, 6-minute walk test, brain natriuretic peptide levels, and peripheral blood flow.**



A. Hemodynamic measurements of systolic and mean pulmonary arterial pressure during right-heart catheterization before, 80 minutes after, and 1 week after initiation of sildenafil treatment. **B.** Distance on a 6-minute walk test performed at baseline and after initiation of sildenafil treatment. Data represent mean values (±SD) from 3 independent 6-minute walk tests performed on separate days before and after initiation of sildenafil treatment. **C.** Brain natriuretic peptide levels at baseline and after 1 and 4 months of sildenafil treatment. **D.** Laser flux Doppler of the finger at room temperature (*RT*) and in warm water before (*upper panel*) and after (*lower panel*) initiation of sildenafil treatment.