Brand-Miller et al hypothize that Europeons have the lowest incidence of diabetes because the selection pressure for genes producing insulin resistance was relaxed first in Caucasians as a result of the increasing amount of dietary carbohydrate after the agricultural revolution. They expect the prevalence of genes producing insulin resistance to be lower in the European population and any other group exposed to high carbohydrate intake for sufficiently long. They further hypothise that ethnic groups have a very high incidence in diabetes, because they are (still) genetically insulin-resistant, and their β cells are not able to secrete enough insulin to overcome the insulin resistance.

In contrast, I have proposed that ethnic groups have a high incidence in obesity and diabetes, because their β cells are more susceptible to hypertrophy and dysregulation due to high-insulinogenic nutrition, while Europeans have lower rates, because their β cells have become less susceptible.

Thus, these are two completely different hypotheses, having in common only dietary changes in human evolution (facts that are common knowledge). I did not see the need to cite a hypothesis that is completely different from mine. Though, I probably should have put this into the discussion. But to the best of my knowledge the pathomechanism I have proposed has not been published before elsewhere.

The fact that numerous formulations and sentences are similar has several reasons. First, I would like to state that there are similarities, because a part of both papers deals with the same topic: Paleolithic nutrition and nutritional changes due to the introduction of agriculture, and that several of the sentences are cited almost verbatim from the same reference (Garn: "What did our ancestors eat.")[2]—by Brand-Miller et al as well as by me (like: "Neanderthals were cold-climate hunters of large game and subsisted primarily on game during the coldest periods," "Homo erectus was a hunter"). Some phrases like "postulate a critical role," or "lines of evidence" I have used intentionally because I thought that these were typical American English phrases.

Another reason for the similarities is that I have made a mistake. When I read the publication of Brand-Miller et al, I found their hypothesis to be different from what I wanted to propose but I found some of the facts concerning the dietary changes in human nutrition very helpful in the article and therefore extracted them, intending to rephrase them later. But after some time, going through the manuscript again and again, the words began to sound more and more familiar to me. I simply have forgotten about the fact that I had taken these lines from their publication. I did not intentionally use these sentences; this obviously would be a really stupid thing to do, that must be revealed immediately (which has been the case), and I certainly am capable of writing a paper by using my own formulations. So, I can only say that I am really sorry for the mistake I have made and that I am sorry for not having cited the publication of Brand-Miller et al and discussed the differences.

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Inflammation and Pathogenesis of Diabetic Nephropathy

To the Editor:

We have read with great interest the article by Moriwaki et al[1] published in the May 2003 issue of *Metabolism.* In this study, the authors analyzed the serum levels of the pro-inflammatory cytokines interleukin-18 (IL-18) and tumor necrosis factor-alpha (TNF-α) in type 2 diabetes mellitus patients. They found that serum IL-18 and TNF-α levels were increased in these patients, especially in those with nephropathy. In spite of these findings, they concluded that the cause-effect relationship between IL-18 or TNF-α and type 2 diabetes mellitus or diabetic nephropathy remain undetermined. However, the results by Moriwaki et al are of relevance.

Diabetic nephropathy, especially in the context of type 2 diabetes, has become the principal cause of renal failure, with renal disease as a major cause of morbidity and mortality in diabetic population. Metabolic and hemodynamic factors have been classically considered as the responsible for the development of renal lesions in patients with type 2 diabetes mellitus. However, nowadays, the factors determining the pathogenesis of diabetic nephropathy appears incomplete.

Recent studies have shown that chronic subclinical inflammation is an essential component of the insulin resistance syndrome.[2,3] Moreover, the findings of increased plasma levels of inflammatory parameters, including C-reactive protein (CRP), sialic acid, fibrinogen, interleukin-1, interleukin-6, and TNF-α, have led to the conclusion that type 2 diabetes includes an inflammatory component.[4-8]

Concerning the relationship between inflammation and nephropathy in type 2 diabetes mellitus, previous studies have reported that serum levels of pro-inflammatory markers are greater in patients with increased urinary albumin excretion with respect to normoalbuminuric diabetic subjects.[5,9] In a previous study, we showed a significant and positive relationship between serum TNF-α levels and urinary protein excretion in type 2 diabetic patients with overt nephropathy and chronic renal failure.[10] Furthermore, the Insulin Resistance Atherosclerosis Study has recently demonstrated a significant association between inflammatory markers (CRP and fibrinogen) with urinary albumin excretion in type 2 diabetic patients with microalbuminuria.[9]

Finally, we have just performed a study in type 2 diabetic patients to test the hypothesis that inflammatory parameters are independently associated to urinary albumin excretion.[11] In this study, only type 2 diabetic patients without potential confounding factors, including acute illness, severe proteinuria (urinary protein excretion $>$ 1 g/d), hypertension (defined as a systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg), renal insufficiency (defined as a serum creatinine level $>$ 1.3 mg/DL), cigarette smoking, treatment with aspirin or statins, and past medical history of clinical cardiovascular disease (cardiac, cerebral, or peripheral vascular disease) were included. Our results show that urinary TNF-α levels are increased in type 2 diabetic patients with respect to normal controls, and further-

Table 1. Independent Predictors of Urinary Albumin Excretion in Type 2 Diabetic Patients

Parameter	Correlation Coefficient	*P*
Glycated hemoglobin	0.27	<.05
Urinary tumor necrosis factor-α	0.36	<.01
Time of diabetes	0.42	<.001
C-reactive protein	0.50	<.001

more, urinary TNF-α excretion increased as diabetic nephropathy progressed. Simple univariate analysis showed that serum TNF-α was significantly related to urinary albumin excretion, but multiple regression analysis demonstrated that CRP and urinary TNF-α were independent predictors of urinary albumin excretion (Table 1).

An interesting aspect of our study was that although both serum and urinary TNF-α levels were greater in patients with diabetes with increased urinary albumin excretion, there was no significant correlation between these parameters.[11] That urinary excretion of TNF-α did not correlate with serum levels suggests that this cytokine can be produced within the kidneys. It is known that in these organs, endothelial, mesangial, glomerular, and tubular epithelial cells are able to produce cytokines. Moreover, in vitro studies have demonstrated increased expression of TNF-α messenger RNA in glomeruli of diabetic rats.[12]

In conclusion, serum and urinary inflammatory parameters have been shown to be independent predictors of urinary albumin excretion in type 2 diabetic patients. Interestingly, our recent studies suggest the production of pro-inflammatory cytokines within the kidneys. Therefore, in addition to metabolic and hemodynamic factors, inflammation is introduced as a potential pathogenic mechanism of diabetic nephropathy, with locally released cytokines, such as TNF-α, in the development of renal lesion through several mechanisms, including direct cellular injury, alteration of the glomerular protein permeability barrier, and development of intrarenal inflammatory damage.[11]

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REPLY

To the Editor:

We would like to thank Drs Navarro and Mora for their calling to attention the possible involvement of IL-18 in diabetic nephropathy in our study. Although IL-18 may play a role in the pathophysiology of diabetic nephropathy, besides the roles of TNF-α and IL-6, there are several problems with such a conclusion. First, as pointed out, the patients had several confounding factors, such as hypertension, cigarette smoking, and treatment with statin or aspirin, which may have been partly responsible for the increased serum IL-18 concentration in our diabetics, and we did not exclude these factors completely. However, since an acute rise in blood glucose level increases serum IL-18,[1] it is certain that IL-18 is related to diabetes. Second, though serum IL-18 increased with the progression of albuminuria, a multiple regression analysis of independent predictors of urinary albumin excretion was not performed in our study. Since IL-18 is a pro-inflammatory cytokine, inflammation within the kidney may be an independent factor for albumin excretion. Third, we did not measure IL-18 concentration in urine, although the urinary excretion of IL-18 is known to correlate with disease activity in patients with a minimal change nephrotic syndrome.[2] Moreover, it has been reported that the urinary excretion of IL-6 does not reflect its serum concentration,[3] which was also observed for TNF-α in the study of Navarro et al. Therefore, the serum concentration of IL-18 does not necessarily reflect the urinary excretion of IL-18, which is considered to be derived from its concentration in the