lated to long-term metabolic control, whereas microaneurysms represent irreversible anatomical lesions.

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ADDRESS CORRESPONDENCE TO HARRY DORCHY, MD, PHD, HÔPITAL UNIVERSITAIRE DES ENFANTS REINE FABIOLA, UNIVERSITE LIBRE DE BRUXELLES, AVENUE JJ CROCQ, 15-B 1020 BRUXELLES, BELGIQUE.

TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS.

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Response to Dorchy

I appreciate Dr. Dorchy's comments and am sorry that my characterization of the capillary microaneurysm as "the hallmark of diabetic retinopathy and its earliest reliable sign" may have seemed unfair to him or dismissive of the pioneering fluorescein angiographic studies he and his collaborators have published over the years.

In the table in Dr. Dorchy's letter, 18% of eyes in which the initial stage of retinopathy was observed had only fluorescein leakage, whereas 31% had only microaneurysms (1). However, two other commonly observed lesions, characterized as "between the stages of clear absence and definite presence" were excluded from this analysis, namely, "microaneurysm-like spot dilatations" (present in 52% of eyes) and "focal capillary dilatations" (present in 49% of eyes). Both of these lesion types are beautifully illustrated in the paper, and I suspect many observers would agree with me that the authors are probably being overly conservative in excluding them from the microaneurysm category. To be counted as a microaneurysm, a lesion had to be at least as large as a 65-μm reference spot. Even to be counted as a microaneurysm-like spot dilatation, a lesion had to be at least as large as a 45-μm spot. If microaneurysm-like spot dilatations and/or focal capillary dilatations were included as microaneurysms, I suspect that substantially >31% of eyes would be classified as having only microaneurysms and substantially <18% as having only fluorescein leakage. If so, results might not be very different from those reported by the Diabetes Control and Complications Trial (Table 1) (2), which were the basis for my statement that "when the number of microaneurysms in an eye exceeds 10, fluorescein angiography usually demonstrates retinal capillary abnormalities, consisting of capillary dilation, capillary nonperfusion (capillary dropout), and/or focal fluorescein leakage from microaneurysms or more diffuse leakage from capillaries (3)."

I commend Dr. Dorchy and his collaborators for their important contributions. Fluorescein angiography has played an important role in advancing our knowledge of diabetic retinopathy. Currently, however, I find little clinical need for it, except to guide photocoagulation treatment of diabetic macular edema.

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Table 1—*Presence of LK, D, and/or LS in field 2F fluorescein negative of rapid series eye compared with number of microaneurysms detected in field 2F negative of same eye

	Microaneurysms in field 2F fluorescein negative (*n*)						
LK, D, or LS	0	1	2	3–5	6–10	≥11	Total
None	181	30	11	24	7	13	266
Questionable	2	1	1	2	1	8	15
LK (no D or LS)	0	0	0	1	5	12	18
D (±LK, no LS)	0	0	1	1	2	6	10
LS (±LK, ±D)	0	0	0	1	0	10	11
Total	183	31	13	29	15	49	320

*Rapid series eye indicates the eye photographed at ~1 frame/s during the transit of fluorescein dye through the retinal vasculature.

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LK, FLUORESCEIN LEAKAGE; D, CAPILLARY DILATATION; LS, CAPILLARY LOSS.

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Effect of Pancreatic Elastase on Diabetic Nephropathy

Pathological change of diabetic nephropathy is characterized by a thickening of the glomerular basement membrane. Although blood glucose and BP are important factors in the control of diabetic nephropathy, the two factors alone may be insufficient in slowing the course of the disease (1). Elastase is a pancreatic enzyme that hydrolyzes elastin and regulates the metabolism of elastin in arterial walls and connective tissues (2). Pancreatic elastase showed an inhibitory effect on the thickening of the glomerular basement membrane in experimental diabetic animals (3). We studied the inhibitory effect of pancreatic elastase on nephropathy in diabetic patients whose blood glucose and BP remained stable.

Thirty-six (14 men and 22 women) nonobese NIDDM patients with >10 yr diabetes duration were studied. Of the patients, 50% were maintained on diet and sulfonylurea and 50% on diet and insulin. All patients had diabetic retinopathy and showed >100 mg/g creatinine of the urinary albumin index from >7 mo before the study. Hypertension was found in 27 of 36 patients and was normalized or corrected by administration of anti-hypertensive drugs, whose doses and sorts were not changed in >3 yr. We gave the patients either 10,800 U of pancreatic elastase (Eisai, Tokyo, Japan) b.i.t. (group 1, $n = 23$) or 300 mg of dilazep dihydrochloride (group 2, $n = 13$), a drug known as an antiplatelet agent, three times a day for 12 mo. The data were analyzed by Duncan's multiple range test. Data were shown as means ± SE.

BMI, FBG, HbA_{1c}, sBP, dBP, and total cholesterol levels remained constant in both groups during the study. In group 1, the albumin index dropped significantly after 2 mo and remained at this level for up to 12 mo. No significant changes were seen in albumin index with group 2. Serum levels of creatinine and urinary levels of NAG (NAG-I) and β_2MG (β_2MG-I) did not change in either group (Table 1). No abnormalities were noted in general laboratory findings, including hematology and chemistry, during the study.

Table 1—*Clinical characteristics of study subjects before and after administration of pancreatic elastase (group 1) or dilazep dihydrochloride (group 2)*

	Group 1		Group 2	
	Before	12 mo after	Before	12 mo after
Age (yr)	63.1 ± 1.7	64.1 ± 1.7	63.8 ± 2.6	64.8 ± 2.6
BMI (kg/m^2)	22.4 ± 0.4	22.5 ± 0.4	22.1 ± 0.4	22.2 ± 0.5
FBG (mM)	6.8 ± 0.2	7.0 ± 0.2	6.5 ± 0.2	6.6 ± 0.3
HbA_{1c} (%)	8.0 ± 0.1	8.0 ± 0.2	7.7 ± 0.1	8.1 ± 0.2
sBP (mmHg)	145 ± 2	139 ± 4	145 ± 2	142 ± 2
dBP (mmHg)	81 ± 2	79 ± 3	82 ± 2	80 ± 3
Total cholesterol (mM)	5.4 ± 0.1	5.1 ± 0.1	5.2 ± 0.1	5.2 ± 0.2
Creatinine (μM)	79.9 ± 3.4	84.8 ± 3.5	78.9 ± 4.8	83.1 ± 6.2
Albumin index (mg/g creatinine)	509.5 ± 82.8	281.7 ± 64.6*	524.7 ± 100.8	429.8 ± 118.2
NAG-I (U/g creatinine)	18.0 ± 1.5	17.9 ± 2.1	19.1 ± 2.1	18.2 ± 2.8
β_2MG-I (μg creatinine)	1235.3 ± 345.1	1055.9 ± 301.7	1237.4 ± 382.8	1049.4 ± 303.9

Data are means ± SE.
*$P < 0.01$.

A significant inhibitory effect of pancreatic elastase on increased albuminuria in diabetic patients was discovered. During the course of the study, body weight, blood glucose, HbA_{1c}, and BP levels remained unchanged. The decreased albuminuria, therefore, was not the result of changes in these factors. However, pancreatic elastase did not affect urinary levels of either NAG or β_2MG, reflecting renal tubular function. This result may indicate pancreatic elastase does not act on the tubular basement membrane, but mainly on the glomerular basement membrane.

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