REPLY: Following the recent publication of our paper on MIBG uptake in patients with left ventricular hypertrophy secondary to aortic stenosis (*1*), Glowniak has commented on some of the article's conclusions.

First, he has suggested that the decrease in myocardial uptake of ^{123}I-MIBG seen in these patients could be linked to the fact that the mean age of these patients is higher than in the control group (62 ± 16 yr versus 30 ± 15 yr).

In general, a relationship has not yet been established between age and sympathetic nerve activity (*2*). Whereas Veith (*3*) and Esler (*4*) have actually demonstrated an increase in plasma norepinephrine in normal elderly patients, which reaches a maximum of 45% in patients older than 50 yr when compared to those under 30 yr (*4*) or 54% in healthy elderly subjects (68 ± 5 yr) when compared to healthy young volunteers (27 ± 6 yr) (*3*), this increase in plasma norepinephrine in elderly patients does not seem to result from an increase in sympathetic nervous tone (*4*). Other factors might have an influence, such as dietary salt (*5*). On the other hand, the sympathetic nervous outflow of norepinephrine to all organs is not uniform, and local organ-specific increases or decreases in sympathetic activity can occur (*2*). Thus, the increase in plasma norepinephrine concentration sometimes measured in elderly patients cannot be attributed to an increase in cardiac sympathetic nervous activity.

Similarly, a decrease in MIBG uptake linked to an increase in plasma norepinephrine concentration in elderly patients without any elevation in cardiac sympathetic nervous activity does not seem conclusively plausible. Indeed, only two studies have demonstrated an inverse relationship between myocardial uptake of ^{123}I-MIBG and plasma norepinephrine concentration. One study is by Nakajo (*6*), who demonstrated a significant relationship between the four grades of MIBG heart intensity and plasma norepinephrine concentration ($r = -0.56$; $p < 0.01$) without observing this relationship in patients with pheochromocytoma ($n = 28$; $r = -0.35$). The other study by Glowniak (*7*) was carried out on six patients with idiopathic congestive cardiomyopathy where only septum uptake of ^{123}I-MIBG showed a strong correlation with plasma norepinephrine concentration ($r = -0.798$), whereas that for total left ventricular uptake was poor ($r = -0.395$). None of the other studies performed on patients with congestive heart failure, even severe, demonstrated such a relationship (*8–10*).

It is true that no study has yet been published regarding the relationship between age and myocardial uptake of ^{123}I-MIBG. In most studies, patients in the control groups have an average age inferior to that of the patients studied and comparable to that of our study (*8,11,12*). Only Merlet (*9*) and Glowniak (*7*) used a control group of a similar age to that of the patients studied. By using 10 controls in our initial study on myocardial uptake of ^{123}I-MIBG in patients with myocardial infarction treated by the same technique (*13*), we obtained the following results 4 hr postinjection:

Group 1	16–24 yr	(20 ± 3 yr; n = 7): 1.92 ± 0.18
Group 2	25–39 yr	(33 ± 6 yr; n = 5): 1.69 ± 0.08
Group 3	40–62 yr	(49 ± 8 yr; n = 5): 1.70 ± 0.07.

The mean myocardial uptake of ^{123}I-MIBG of Group 1 was higher ($p < 0.05$) than that of Groups 2 and 3. There was also greater intersubject variation. The subjects of Group 3, whose mean age is closer to that of our patients, showed a higher mean myocardial uptake of ^{123}I-MIBG than that of our left ventricular hypertrophy patients ($p < 0.001$).

Thus, the hypothesis of a decrease in myocardial uptake of ^{123}I-MIBG in patients with left ventricular hypertrophy associated with an increase of sympathetic nervous activity related to age or to an elevation in plasma norepinephrine concentration has not been substantiated.

Second, Glowniak questions the decrease of myocardial uptake of ^{123}I-MIBG in patients treated with digoxin when compared to untreated patients. All our patients were in Class II of the NYHA classification for exertional dyspnea, but none showed any evidence of cardiac failure during isotopic tests. Clinically, they could not be considered as suffering from severe heart failure. Cardiac glycosides are relatively weak inotropic agents and have a modest effect upon cardiac failure secondary to ventricular volume overload (*14*), especially upon left ventricular ejection fraction (*15,17*). Therefore, treatment with digoxin can not explain that left ventricular ejection fraction was normal in patients, reaching 56%–80% (0.71 ± 0.13). Heart failure was not more severe in our treated patients than in the untreated ones. Furthermore, intravenous administration of digoxin (acute administration) has been shown to decrease plasma norepinephrine concentration in patients with severe heart failure (*18*). Therefore, competition for the transporter between norepinephrine and MIBG can not be accepted. Finally, a recent study by Ferguson (*19*) demonstrated sympatho-inhibition after intravenous administration of cedilamid-D in eight patients with moderate to severe heart failure (NYHA Class III–IV).

In total, it has been shown that therapeutic doses of digoxin or its analogues have a moderate positive inotropic effect in man and that they lead to a sympatho-inhibition in patients with congestive heart failure. For all the authors, the mode of action is an inhibition of Na-K-ATPase. This is based on the experimental studies cited in our article (*1*), which were performed in vitro or in animals. From these data, all authors have agreed that interspecies variations exist and that the doses of ouabain which inhibit Na-K-ATPase differ from one species to another. Glowniak (*20*) has argued that the adrenal chromathin cells' model, which requires high doses of ouabain to inhibit norepinephrine and MIBG uptakes, is questionable. In any case, the model of sodium-dependent transporter (uptake-1) remains the model currently in use.

It is true, however, that the most convincing argument of demonstrating an inhibition of myocardial uptake of ^{123}I-MIBG by digoxin would be to measure myocardial uptake of ^{123}I-MIBG before and after treatment in control subjects. However, French legislation and medical ethics prohibit such practice.

Thus, the important decrease in myocardial uptake of ^{123}I-MIBG seen in patients treated with digoxin cannot be explained by the severity of cardiac failure in these patients, because no clinical or hemodynamic criteria differentiate them significantly from untreated patients. However, the mode of action of cardiac glycosides in vitro and the clinical result obtained after intravenous injection of such agents both suggest a direct effect of digoxin upon myocardial uptake of ^{123}I-MIBG.

With regard to the results relating to the effects of amiodarone, it is true that an effective action of this drug upon ^{123}I-MIBG uptake can not be concluded from the three patients entered into the study.

Lastly, Glowniak discusses issues relating to heart transplant patients. Our aim was to determine the importance of extraneuronal cardiac uptake in man rather than examine any eventual sympathetic reinnervation following transplant. The fact that this extraneuronal uptake of ^{123}I-MIBG is 13% of the total uptake and not 8.7% (*10*) does not in any way affect the conclusion drawn, i.e., extraneuronal uptake of ^{123}I-MIBG is low in humans, contrary to the results obtained in animals.

Furthermore, it is impossible to claim that "a large body of

literature indicates that there is sympathetic reinnervation of the heart after 15 mo following cardiac transplantation." Wilson et al. (*21*) have shown that 39 of 50 patients, who had been subjected to a heart transplant more than a year before, had a significant release of norepinephrine following tyramine administration, suggesting a sympathetic reinnervation of the heart. In this group, the mean time since cardiac transplant was 40 ± 3 mo, whereas it was 30 ± 6 mo in the 11 patients considered to be denervated.

Studies with ^{11}C-hydroxyephedrine (HED) (*22*) did not show any gradual uptake of this marker with time in the transplanted heart. Two groups were studied, corresponding to 4.4 ± 2–3 mo or 42±22 mo after transplantation. In this study, a significant increase of ^{11}C-HED retention was demonstrated in the basal and mid-ventricle segments in patients with late transplant. Furthermore, in five patients who had received transplants 62 ± 2 mo, catecholamines could not be detected in endomyocardial biopsies (*23*). Fallen (*24*) could show clinical evidence of functional reinnervation in only 1 of 9 patients 33 mo after cardiac transplantation. In humans, only the very recent study by Dae (*25*) demonstrates an anterior and basal cardiac uptake of MIBG in 4 of 10 patients 13 ± 1.2 mo after cardiac transplant. In dogs, sympathetic reinnervation is functional 6 mo after autotransplantation or homo-transplantation (*26*) and 9 to 12 mo after surgical denervation (*27*). Therefore, it seems that the rate of reinnervation of a transplanted heart is very slow in humans (*22,28*).

Six months after surgical cardiac denervation in dogs (*29*), myocardial uptake of tritiated norepinephrine was increased by 57% when compared to control values taken in the left atrium. However, it was 35% in the basal section of the left ventricle but 7% only in the apex. Furthermore, the experimental model used is more distant from the allo-transplantation performed in humans. Similarly, an epicardial application of phenol or performing a transmural myocardial infarct in dogs produce only a regional denervation which cannot be compared to an allo-transplantation (*30*).

In conclusion, most authors agree with the statement that sympathetic reinnervation is possible but develops very slowly following cardiac transplantation in humans. Most of the data presently available indicate that reinnervation probably needs more than 33 mo to occur. Therefore, there is little evidence to indicate reinnervation in our patients who have been subjected to surgery 15 ± 10 mo before.

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