In this issue of *Circulation*, Regitz et al.\(^1\) provide evidence that the transplanted human heart remains denervated for as long as 5 years after transplantation. These authors measured myocardial catecholamines in right ventricular septal endomyocardial biopsies taken from 24 orthotopically transplanted hearts and found measurable norepinephrine levels in only two samples, both of which were from subjects who had had their transplant within 18 months. High-performance liquid chromatography assay with electrochemical detection was used and was sufficiently sensitive to detect levels of norepinephrine as low as 20 ng/g/wet wt tissue, which is 1–2% of the norepinephrine content of innervated, nonfailing human heart.\(^1,2\) The data confirm an earlier ultrastructural analysis that found a marked and sustained reduction in nerve density in transplanted human hearts that were examined 1–12 years after surgery.\(^3\) The findings are also consistent with several investigations\(^4–6\) that have demonstrated denervation physiology and pharmacology in the transplanted human heart.

The observations of Regitz et al.\(^1\) are important because of the issue of whether reinnervation can occur in the transplanted human heart. This question arises in part because of data from models of surgical denervation that have demonstrated functional autonomical reinnervation in the majority of animals examined 3–6 months after autotransplantation or allotransplantation.\(^7,8\) In addition, reports\(^9\) and anecdotes of the reestablishment of sensory innervation in cardiac transplant recipients continue to appear in the form of angiina pectoris in subjects with documented graft atherosclerosis. Moreover, recent work measuring “myocardial production” of norepinephrine in response to tyramine provocation\(^10\) suggests that cardiac release of norepinephrine can occur in subjects more than 1 year after transplan-

In view of these observations suggesting that reinnervation routinely occurs in the setting of surgical denervation, the data of Regitz et al.\(^1\) are perhaps surprising.

An update of our own series that includes aliquots from left and right ventricular free wall of transplant recipients undergoing retransplantation\(^2,11\) indicates that of 16 left and right ventricular chambers examined, six had norepinephrine levels of more than 50 ng/g/wet wt tissue, suggesting reinnervation. However, tissue neuropeptide Y levels were undetectable in all samples (unpublished data), including those with elevated norepinephrine levels. Because neuropeptide Y is colocalized with norepinephrine in adrenergic nerve terminals, it is therefore somewhat unclear whether an elevated tissue norepinephrine level implies reinnervation. Additionally, Regitz et al.\(^1\) report relatively high levels of tissue epinephrine in the two samples that contained norepinephrine. Because epinephrine is not a cardiac neurotransmitter in humans, the possibility is raised that the myocardial catecholamines measured in their two subjects were deposited in the heart from the circulation. As pointed out by Regitz et al.,\(^1\) circulating norepinephrine levels are only about 0.1% of tissue levels and therefore could not produce measurable tissue levels by simple blood contamination, but it is possible that systemically originating norepinephrine and other catecholamines could be concentrated in cardiac tissue by “uptake-2”\(^12\) or some other kind of sequestration system. Such neuronally independent uptake of systemically administered norepinephrine has been demonstrated in the denervated, transplanted canine heart.\(^13\)

Therefore, the measurable myocardial norepinephrine levels present in 8% of Regitz et al.'s subjects offer only equivocal evidence of reinnervation. In contrast, the absence of measurable norepinephrine in 22 of 24 tissue samples measured by Regitz et al.\(^1\) appear to be good evidence for a lack of routine reinnervation in the transplanted human heart. Collectively, the data reported by Regitz et al.\(^1\) and other investigators indicate that the reinnervation rate in cardiac transplant recipients is quite low, and it remains unclear whether adrenergic reinnervation can actually occur.

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The opinions expressed in this editorial comment are not necessarily those of the editors or of the American Heart Association.

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The state of cardiac denervation in the posttransplant patient has important clinical, physiological, and pharmacological consequences. The clinical consequences of denervation include the inability of the cardiac transplant recipient to sense cardiac pain, which means that all ischemia will be silent. Because the development of graft atherosclerosis is a major problem in the cardiac transplant population, effective surveillance must use intensive and costly measures such as routine angiography. Another clinical consequence of cardiac denervation is a slowly developing exercise response due to the lack of adrenergic innervation. As recently reported by Stephenson et al.,\textsuperscript{14} the exercise capacity of transplant patients can be quite blunted and is in the range of New York Heart Association class II or III heart failure. Ordinarily, these patients' submaximal exercise capacities are sufficient to maintain routine daily activities, but some subjects do complain of markedly reduced exercise tolerance.

The physiological and pharmacological consequences of denervation are fascinating and have interested investigators for more than 100 years.\textsuperscript{15,16} The general observation is that surgical interruption of autonomic innervation results in a heightened response to the neurotransmitter that has been lost. The changes that occur are the result of both the presynaptic consequences of nerve loss and postsynaptic changes involving the respective receptor-effector system. With regard to adrenergic innervation, both presynaptic and postsynaptic changes have been described in animal models of surgical denervation,\textsuperscript{17,18} including a transplant model.\textsuperscript{19} The presynaptic changes are due to loss of the neuronal catecholamine uptake system (uptake-1),\textsuperscript{17,18} whereas the postsynaptic changes appear to be due to changes in \( \beta \)-adrenergic receptors.\textsuperscript{18,19}

Interestingly, in the transplanted human heart, adrenergic supersensitivity appears to be mediated solely by the presynaptic component\textsuperscript{20} and is therefore limited to catecholamines with a high affinity for the neuronal uptake system. This is the basis for the transplanted human heart's supersensitivity to noradrenaline and epinephrine.\textsuperscript{6} Although one study in the transplanted human heart did describe a heightened heart rate response to isoproterenol, which would imply postsynaptic supersensitivity,\textsuperscript{20} another study carried out under more stringent pharmacological conditions did not demonstrate isoproterenol supersensitivity.\textsuperscript{6} Additionally, in orthotopically transplanted hearts, total \( \beta \)-receptor density measurements\textsuperscript{6,21,22} and isoproterenol stimulation of adenylate cyclase\textsuperscript{21} have not demonstrated the upregulation in \( \beta \)-adrenergic receptors or isoproterenol supersensitivity that was described in heterotopically positioned, nonworking animal cardiac transplants.\textsuperscript{19} Finally, the contractile response to the \( \beta \)-agonist dobutamine, which like isoproterenol has a relatively low affinity for uptake-1, is the same in transplant recipients as in innervated normal controls.\textsuperscript{23} In other words, the available data indicate that the orthotopically positioned human cardiac allograft develops denervation supersensitivity that is exclusively presynaptic in origin.

Denervation physiology dictates a different approach to both electrophysiological and inotropic pharmacotherapy of the transplant recipient. Because preganglionic cholinergic efferents and afferent nerves have been interrupted, the atiroventricular blocking ability of digitalis is much reduced,\textsuperscript{24} and the anticholinergic effects of quinidine\textsuperscript{25} or atropine\textsuperscript{4} are not manifest. One practical consequence is that atrial flutter, a common arrhythmia in the postoperative cardiac surgical setting and a common arrhythmia in transplant recipients, may be treated with quinidine alone without fear of accelerating atrioventricular conduction, whereas digoxin is a relatively ineffective antiarrhythmic. Additionally, atropine will not speed atrioventricular conduction or sinus rate\textsuperscript{4} in transplant recipients with heart block.

The issue of optimal inotropic support is important in the denervated human heart in both postoperative cardiac surgical settings and settings in which systolic function is compromised by rejection. The absence of neuronal norepinephrine stores beyond the early postoperative period in the transplanted human heart means that "indirect acting" catecholamines are much less effective inotropic agents in transplant recipients.\textsuperscript{2} Therefore, the commonly used agent dopamine will essentially be only a dopaminergic and \( \alpha \)-adrenergic agent in cardiac transplant patients. Additionally, because of the loss of uptake-1, systemically delivered epinephrine will have a higher \( \beta \)-to-\( \alpha \) or inotrope-to-vasoconstrictor ratio than in an innervated setting,\textsuperscript{6} and this catecholamine is therefore more effective in supporting pump function in the transplanted heart. Finally, the transplanted human heart contains an unexpectedly high percentage and density of \( \beta _1 \)-adrenergic receptors,\textsuperscript{22} which means that nonselective \( \beta \)-agonists, such as epinephrine, isoproterenol or dobutamine, should be used for maximal inotropic stimulation; \( \beta _1 \)-selective agents such as norepinephrine will not lead to occupancy of the entire \( \beta \)-receptor population at doses that can be administered clinically.

Because the question of reinnervation has not been completely resolved, particularly in subjects more than 1 year after transplantation, additional studies need to be done. In view of the potential for selective reinnervation to occur as shown experimentally,\textsuperscript{8} these studies should ultimately focus on cholinergic, adrenergic, and afferent nerve systems. As first appreciated in earlier investigations,\textsuperscript{26} the human heart transplant patient continues to be a "living laboratory" that is readily accessible to cardiac physiologists and pharmacologists.

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The surgically denervated, transplanted human heart.
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_Circulation_. 1990;82:658-660
doi: 10.1161/01.CIR.82.2.658

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/82/2/658.citation

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