Heart Imaging in the Diagnosis of Pheochromocytoma and Assessment of Catecholamine Uptake

The report in this issue of the *Journal* by Nakajo and co-workers of an inverse relationship between the accumulation of [^{131}I]metaiodobenzylguanidine (I-131 MIBG) in the heart and circulating and urinary catecholamines and their metabolites is a fascinating and exciting new finding (*1*). It dramatically demonstrates in a visual manner the ability of excess circulating catecholamines to affect the uptake and metabolism of catecholamines in the myocardium. Not only is this new finding of some diagnostic interest with respect to pheochromocytoma, but also it may have potential application to better understanding of catecholamine metabolism in vivo.

A radioiodinated analog of the adrenergic blocking agent guanethidine, I-131 MIBG (*1*), has an affinity for the adrenal medullae and adrenergic nerves (*2–4*). Its affinity for chromaffin tissue has proven valuable in the scintigraphic localization of pheochromocytoma and the identification of adrenal medullary hyperplasia (*5,6*). Since I-131 MIBG may be stored in a manner similar to norepinephrine (*3*), it probably concentrates in adrenergic nerves of the myocardium and has permitted imaging of the human heart (*7*). It is noteworthy that the authors found that the uptake of I-131 MIBG in the salivary gland depends on an intact sympathetic innervation. Furthermore, they have pointed out that certain drugs (e.g. reserpine and tricyclic antidepressants), which interfere with I-131 MIBG uptake in the heart (*3,8,9*), and severe adrenergic neuropathy, which impairs the adrenergic uptake mechanism, can prevent visualization of the heart as well as of the salivary glands by I-131 MIBG. These findings strongly suggest that uptake and storage of I-131 MIBG by adrenergic nerves is responsible for scintigraphic visualization of the heart.

Catecholamine storage sites consist mainly of "specific" (neuronal) and "nonspecific" (extraneuronal) sites; neuronal uptake by sympathetic nerves ($uptake_1$) and extraneuronal uptake ($uptake_2$) have been identified (*10–12*). Nakajo and co-workers indicate that residual radioactivity in images of the heart obtained 24 or 48 hr after injection of I-131 MIBG is consistent with the concept that it is stored in the neuronal compartment, since nonspecific extraneuronal accumulation of guanethidine (a drug similar to I-131 MIBG) decreases rapidly with time (*13,14*) and probably would not account for the increased activity in the cardiac images observed in normal subjects 1 or 2 days after administration of I-131 MIBG. Furthermore, since it has been found that pheochromocytomas concentrate only 2% or less of the administered dose (*5*), nonvisualization of the heart by I-131 MIBG in patients harboring a pheochromocytoma cannot, therefore, be explained by sequestration of the tracer in the tumor (*1*).

Nakajo et al. suggest that competitive uptake by the heart of I-131 MIBG with circulating catecholamines may explain nonvisualization of the myocardium in patients with pheochromocytoma who have significantly elevated plasma catecholamines (*1*). Uptake of excess catecholamines could potentially compete with and consequently inhibit the uptake of I-131 MIBG that would ordinarily occur in patients with normal concentrations of plasma catecholamines. In support of their suggestion they cite the fact that guanethidine, an analog of MIBG, inhibits uptake of radiolabeled norepinephrine by the rat heart in vivo and in vitro (*15,16*) and that prior treatment with norepinephrine or epinephrine prevents uptake of radiolabeled guanethidine (*17*). They further speculate that the rate of norepinephrine turnover in neurons and its release into the circulation in patients without pheochromocytoma may also influence adrenergic nerve uptake of circulating catecholamines and I-131 MIBG. They suggest, however, that catecholamine metabolites are probably not resposible for inhibiting I-131 MIBG uptake, since uptake of its analog, guanethidine, is not inhibited by normetanephrine (*17*).

Nonvisualization of the heart at 24 and 48 hr after injection of I-131 MIBG was found to have an accuracy of 80% and 59%, respectively, in the detection of pheochromocytoma. On the other

hand, visualization of the heart was found to be more accurate in excluding the presence of a pheochromocytoma. At 24 and 48 hr visualization accurately excluded the presence of pheochromocytoma 93% and 97% of the time, respectively. One would, therefore, feel much more secure in excluding rather than establishing the presence of a pheochromocytoma when using the technique of heart visualization in patients suspected of harboring this tumor. The use of I-131 MIBG scintigraphy to locate pheochromocytomas has been reported to be highly accurate and reliable and of particular value in the identification of small tumors and those that are extraadrenal (*5,6*). As indicated by Nakajo and co-workers, the intensity of heart uptake can be a helpful adjunct in the diagnosis of pheochromocytoma; nonvisualization of the heart occurred in one of their patients whose pheochromocytoma failed to be detected by I-131 MIBG imaging. It must be appreciated, however, that about 45% of patients with pheochromocytoma have paroxysmal episodes of hypertension, and the tumors in some of these patients secrete only periodically, thus plasma catecholamines are not constantly elevated in these subjects (*18*). In these latter patients uptake of I-131 MIBG would probably not be inhibited and would permit visualization of the heart despite the presence of a pheochromocytoma. To what extent such patients have been represented in the current study is unclear. It is possible that with a larger study group, the specificity of cardiac visualization in excluding pheochromocytoma may be less than found here.

The use of I-131 MIBG to localize a pheochromocytoma and to image the heart is a most interesting technique that may improve the ability to establish or exclude the presence of a pheochromocytoma. Since the likelihood of visualization of the tumor itself is very high, however, it is uncertain to what extent imaging of the heart will add to the accuracy of the diagnosis of pheochromocytoma. To this time the diagnostic use of I-131 MIBG has remained experimental and the published experience is limited. Transmission computerized tomography has proven extremely valuable in localizing pheochromocytoma (*19*) and is a particularly attractive radiographic modality since it is noninvasive. Occasionally, angiography may be useful in localizing a pheochromocytoma not identified by a TCT study, particularly when the tumor is relatively small and extraadrenal in location. Ultrasonography may demonstrate that a lesion is cystic; however, this finding is of no value in the differential diagnosis since pheochromocytomas can be solid or cystic (*18*). A biochemical diagnosis, i.e., elevated plasma or urinary catecholamines or their metabolites, has always been considered essential in establishing the presence of a pheochromocytoma. It appears, however, that scintigraphic imaging with I-131 MIBG may be a sensitive and specific method for both the diagnosis and localization of pheochromocytoma. This nuclear medicine technique may also be particularly helpful in identifying those patients with the multiple endocrine Type 2 syndromes, since it provides functional as well as anatomic evidence of subtle adrenal medullary abnormalities (*6*). Sisson and co-workers have found scintigraphic localization of pheochromocytoma more accurate than TCT scan (*5*).

The potential in vivo use of I-131 MIBG for studying catecholamine metabolism and for investigating adrenergic influences on the heart appears promising but remains to be explored. Certainly from the report by Nakajo et al. it seems that the effect of drugs or an adrenergic neuropathy on the catecholamine uptake mechanism may be assessed in vivo by studying the effect on heart intensity images caused by administration of I-131 MIBG. The mechanism whereby excess circulating catecholamines inhibit I-131 MIBG uptake remains somewhat obscure, since we and our colleagues have found that in experimental pheochromocytoma in the rat, marked elevations of plasma norepinephrine were not accompanied by a significant increase in tissue norepinephrine in the heart or other organs or tissues (*20,21*) except in erythrocytes (*22*). One might have anticipated that in the presence of markedly increased circulating catecholamines, a significant accumulation of tissue catecholamines would have occurred. Since this was not the case, it appears that inhibition of I-131 MIBG uptake by excess circulating catecholamines may not be explained simply by a reduced storage capacity in adrenergic nerves or other tissues that might result from an excess storage of catecholamines. Further studies are required to clarify the mechanisms involved in uptake inhibition with the major possibilities being competitive inhibition and/or diminished function of the amine uptake pumps.

It has recently been found that the excess circulating catecholamines in a rat model harboring pheochromocytoma cause diminished function of beta adrenergic receptor mechanisms in a variety of tissues including the heart (*23,24*, G. Tsujimoto, W. M. Manger, B. B. Hoffman, unpublished results). It is interesting to speculate that uptake mechanisms might also be desensitized in

patients with pheochromocytoma. Quite separately, the present work by Nakajo et al. hints at the possibility that I-131 MIBG may be useful as a tool to investigate autonomic dysfunction in man.

WILLIAM MUIR MANGER
New York University Medical Center
New York, New York
BRIAN B. HOFFMAN
Stanford University School of Medicine
and VA Medical Center
Palo Alto, California

ACKNOWLEDGMENT

This work was supported in part by the National Hypertension Association, Inc.

REFERENCES

1. NAKAJO M, SHAPIRO B, GLOWNIAK J, et al: Inverse relationship between cardiac accumulation of meta-[^{131}I]iodobenzylguanidine (I-131 MIBG) and circulating catecholamines in suspected pheochromocytoma. *J Nucl Med* 24:1127-1134, 1983
2. WIELAND DM, WU J-L, BROWN LE, et al: Radiolabeled adrenergic neuron-blocking agents: Adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J Nucl Med* 21:349-353, 1980
3. WIELAND DM, BROWN LE, ROGERS WL, et al: Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 22:22-31, 1981
4. WIELAND DM, BROWN LE, TOBES MC, et al: Imaging the primate adrenal medulla with [^{123}I] and [^{131}I]-metaiodobenzylguanidine: Concise communication. *J Nucl Med* 22:358-364, 1981
5. SISSON JC, FRAGER MS, VALK TW, et al: Scintigraphic localization of pheochromocytoma. *N Engl J Med* 305:12-17, 1981
6. VALK TW, FRAGER MS, GROSS MD, et al: Spectrum of pheochromocytoma in multiple endocrine neoplasia. A scintigraphic portrayal using ^{131}I-metaiodobenzylguanidine. *Ann Intern Med* 94:762-767, 1981
7. KLINE RC, SWANSON DP, WIELAND DM, et al: Myocardial imaging in man with I-123 meta-iodobenzylguanidine. *J Nucl Med* 22:129-132, 1981
8. LINDMAR R, LOFFELHOLZ K: Neuronal and extraneuronal uptake and efflux of catecholamines in the isolated rabbit heart. *Naunyn-Schmiedebergs Arch Pharmacol* 284:63-92, 1974
9. MICHELL JR, OATES JA: Guanethidine and related agents. I. Mechanism of the selective blockade of adrenergic neurons and its antagonism by drugs. *J Pharmacol Exp Ther* 172:100-107, 1970
10. IVERSEN LL: Uptake of circulating catecholamines into tissues. In *Adrenal Gland Handbook of Physiology.* Blaschko H, Sayers G, Smith AD, eds., Vol VI, Sec. 7, Endocrinology Washington DC, Am Physiol Soc, 1975, pp 713-722
11. IVERSEN LL, SALT PJ, WILSON HA: Inhibition of catecholamines uptake in the isolated rat heart by haloalkylamines related to phenoxybenzamine. *Br J Pharmacol* 461:647-657, 1972
12. TRENDELENBURG U: The extraneuronal uptake and metabolism of catecholamines in the heart. In *The Mechanism of Neuronal Extraneuronal Transport of Catecholamines.* Paton DM, ed. New York, Raven Press, 1976, pp 259-280
13. CHANG CC, COSTA E, BRODIE BB: Interaction of guanethidine with adrenergic neurons. *J Pharmacol Exp Ther* 147:303-312, 1965
14. MAITRE L, STAEHELIN M: Guanethidine uptake and noradrenaline depletion in noradrenaline storage particles of the rat heart. *Biochem Pharmacol* 20:1233-1242, 1971
15. HERTTING G, AXELROD J, PATRICK RW: Actions of bretylium and guanethidine on the uptake and release of [^{3}H]-noradrenaline. *Br J Pharmacol* 18:161-166, 1962
16. IVERSEN LL: Inhibition of noradrenaline uptake by drugs. *J Pharm Pharmacol* 17:62-64, 1965
17. BRODIE BB, CHANG CC, COSTA E: On the mechanism of action of guanethidine and bretylium. *Br J Pharmacol* 25:171-178, 1965
18. MANGER WM, GIFFORD RW JR: *Pheochromocytoma.* New York, Springer-Verlag, 1977, p 339
19. STEWART BH, BROWN EL, HAAGA J, et al: Localization of pheochromocytoma by computed tomography. *N Engl J Med* 299:460-461, 1978
20. MANGER WM, HULSE MC, CHUTE RN, et al: Tissue and blood catecholamines (CA) In *Experimental Pheochromocytoma. Federation Proceedings* 41, March 1982
21. BUU N, KUCHEL O, MANGER WM: Storage and turnover rate of catecholamines (CA). In *Experimental Pheochromocytoma: A Study with New England Deaconess Hospital (NEDH) Pheochromocytoma Rats:* in press
22. MANGER WM, HULSE MC, FORSYTH MS, et al: Effect of pheochromocytoma and hypophysectomy on blood pressure and catecholamines in NEDH rats. *Hypertension* 4:Suppl II, 200-207, 1982
23. SNAVELY MD, MOTULSKY HJ, MOUSTAFA E, et al: β adrenergic receptor subtypes in the rat renal cortex: selective regulation of β adrenergic receptors by pheochromocytoma. *Circ Res* 51:504-513, 1982
24. TSUJIMOTO G, MANGER WM, HOFFMAN BB: Pheochromocytoma and the regulation of β adrenergic receptors. *Federation Proceedings*, Vol 42, Abstract 6285, p 1365, 1983