

REVERSIBLE CARDIOMYOPATHY WITH PHEOCHROMOCYTOMA

BY JOHN G. WISWELL, M.D. AND (*by invitation*) REX M. CRAGO, M.D.

BALTIMORE

In patients with pheochromocytoma life-threatening cardiac arrhythmias, pulmonary edema, myocardial infarction or shock may occur at any time spontaneously or during operative removal of the tumor. In 1909, myocardial damage was observed in rabbits after administration of adrenaline¹ and since that time, there have been several reports of pathologic changes in the hearts of animals given catecholamines. In 1958, human cardiac lesions were described after administration of nor-epinephrine² and in several patients who died with a pheochromocytoma.^{3, 4} Histochemical and electron microscopic changes induced by isoproterenol in rats and morphologic cardiac findings in patients given catecholamines or in those with pheochromocytoma have been described.³⁻⁵ Early lesions consists of infiltration with polymorphonuclear leukocytes, lymphocytes and histiocytes, small hemorrhages and edema. Later, there are focal degeneration and necrosis of myofibrils and fibrosis. The alterations are most numerous in the inner two-thirds of the left ventricle. The lesions are similar to those associated with coronary artery disease⁶ and may result from an inability of the coronary circulation to meet the enhanced metabolic needs imposed upon the myocardium by catecholamines or by a direct effect on the coronary arteries themselves.

PATHOLOGIC STUDIES

In the present series of 13 patients with pheochromocytoma, five died before the diagnosis was made. One was a 60 year old man with normal blood pressure who had a laparotomy for empyema of the gall bladder. During and after the operation there were several episodes of hypotension treated with large amounts of vasopressors. At autopsy, one week postoperatively, a pheochromocytoma was found

From the Division of Endocrinology and Metabolism, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland.

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FIG. 1. Acute necrosis of myofibrils in the myocardium.

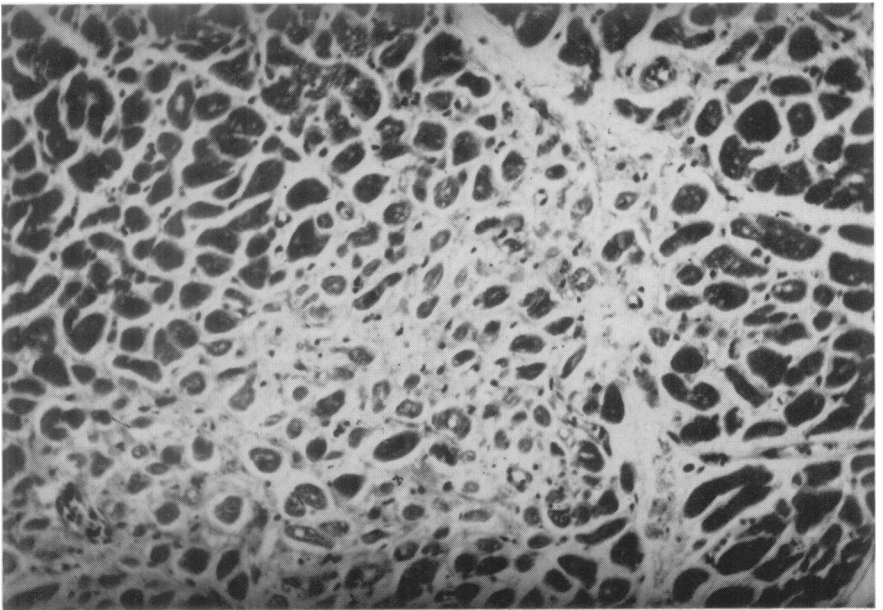


FIG. 2. Focal myocardial fibrosis.

within the right kidney. In the heart there were focal areas of acute necrosis of the myofibrils which probably developed because of the treatment with vasopressors (fig. 1). Another patient, a 45 year old male, presented with congestive heart failure and blood pressures ranging from 130/80 to 190/110. He died of a pulmonary embolus; a pheochromocytoma was found in the left para-aortic region outside the adrenal gland. There were focal areas of myocardial fibrosis (fig. 2). In the other three patients who died, there were similar myocardial lesions. The coronary arteries showed only minimal degrees of atherosclerosis.

ELECTROCARDIOGRAPHIC CHANGES

In animals and humans given catecholamines, various abnormalities of the electrocardiogram may occur.^{7, 8} These consists of elevation or depression of ST segments, flattening or inversion of the T-waves and ectopic arrhythmias. In 1944, Mackeith described left axis deviation and inversion of T-waves in a patient with pheochromocytoma and there have been other subsequent similar reports.⁹⁻¹¹ These elec-

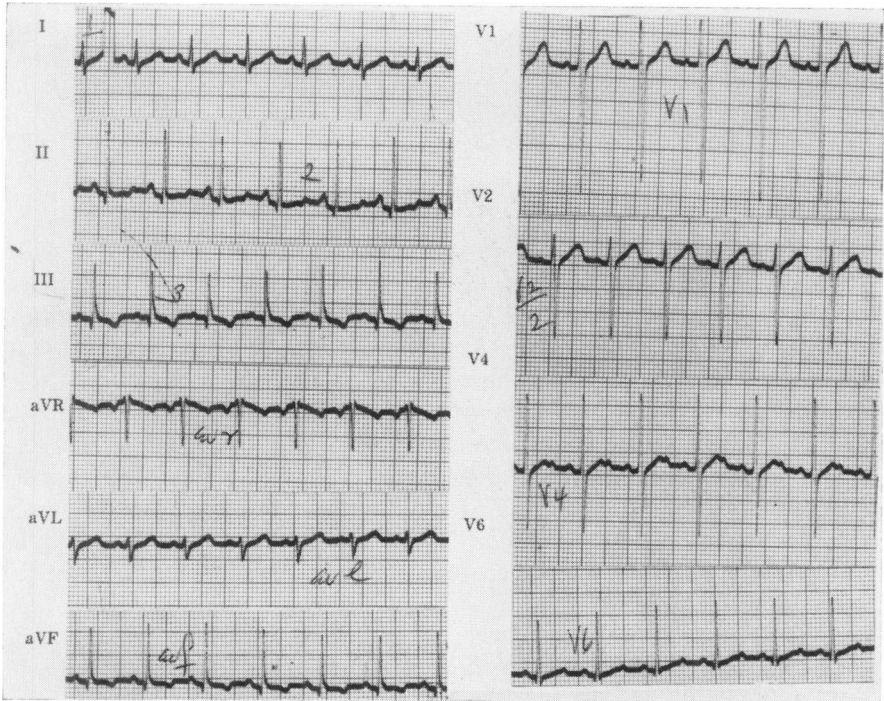


FIG. 3. Preoperative electrocardiogram in 14 year old male.

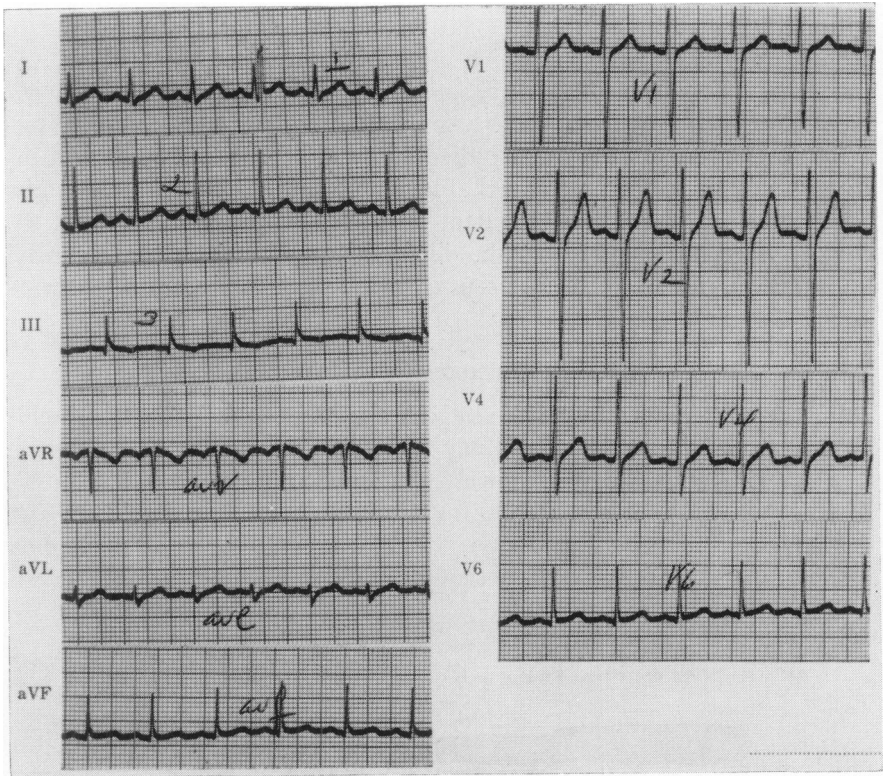


FIG. 4. Postoperative electrocardiogram in 14 year old male.

trocardiographic changes are very like those found in patients with coronary insufficiency together with patterns secondary to the hypertension, and they may reflect the presence of catecholamine cardiomyopathy. Since they occur in young patients with pheochromocytoma and disappear following removal of the tumor, they may not indicate coronary disease, but may be due to functional or early pathologic changes which are potentially reversible.

The preoperative electrocardiogram of a 39 year old female with paroxysmal hypertension revealed an A-V nodal escape rhythm with not much change in the ST or T segments. Nine days following a difficult operation, T-waves changes had appeared, but five weeks later the electrocardiogram was normal. In 1959, a 10 year old boy had four pheochromocytomas removed at one operation. Four years later, mild hypertension returned and the electrocardiogram showed a diphasic T-wave in Lead 2, inverted T-waves in Leads 3 and AVF (fig. 3). Blood pressure was approximately 140/90 and SGOT was 24 units. Ten days postoperatively there was improvement in the T-waves and

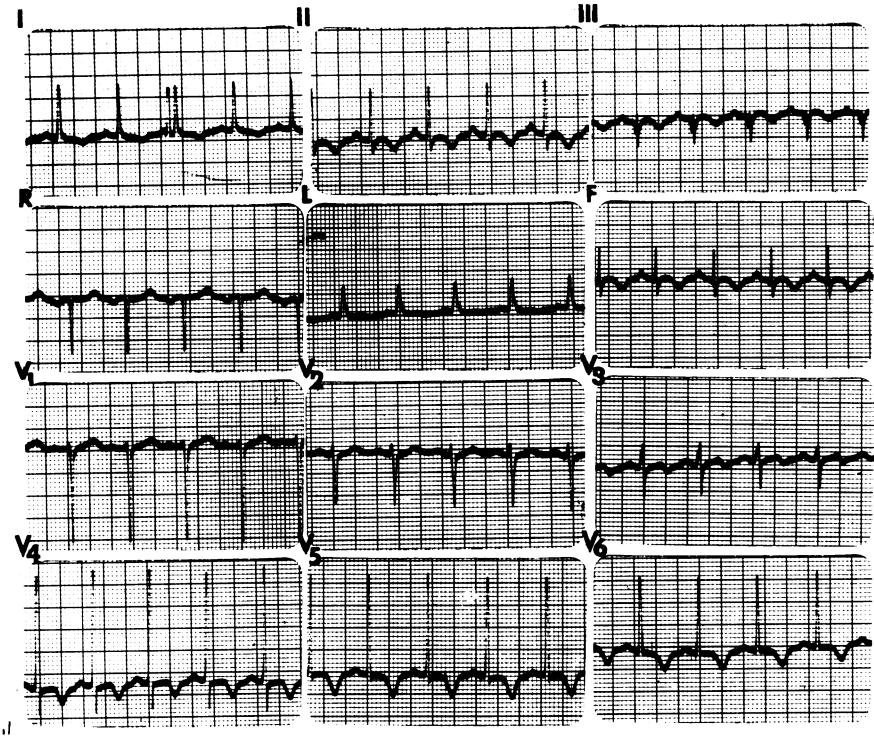


FIG. 5. Pre-treatment electrocardiogram in 21 year old female.

the tracing was just about normal (fig. 4). The electrocardiogram of a 52 year old male with persistent hypertension and a diastolic pressure of 120 to 130 revealed evidence of left ventricular hypertrophy and ST and T-wave changes compatible with myocardial ischemia. One week postoperatively there was slight decrease in the degree of T-wave inversion with blood pressure 140/110. It was not until two years later, however, that his electrocardiogram returned to normal at which time his blood pressure was 140/90. The preoperative electrocardiogram of a 56 year old female with varying degrees of hypertension demonstrated some left ventricular hypertrophy with non-specific ST and T-wave changes in Leads 1, 2, 3, AVL and AVF. Six days postoperatively there was significant improvement in the T-waves. In two other patients with paroxysmal hypertension the electrocardiograms were normal.

EFFECTS OF ADRENERGIC BLOCKING DRUGS

If these electrocardiographic abnormalities represent functional or early myocardial pathologic changes, it would seem important to attempt

their reversal in the preoperative period which might ensure less risk to the patient during surgery. In the cardiovascular system, alpha receptors are stimulated by norepinephrine resulting in an elevation of blood pressure through arteriolar constriction; beta-receptors are stimulated by epinephrine leading to an increase in cardiac automaticity and contractility. Myocardial hemorrhages, cardiac arrhythmias and electrocardiographic abnormalities induced by epinephrine in dogs can all be prevented by dual blockade with phenoxybenzamine and propranolol, alpha and beta-adrenergic blocking agents, respectively.¹² Phenoxybenzamine has been used in a few patients with pheochromocytoma prior to surgery¹³ and also for prolonged therapy in patients with malignant pheochromocytoma.¹⁴ In the past two years there have been three reports of the combined use of phenoxybenzamine and propranolol preoperatively.¹⁵⁻¹⁷ In only one instance were the drugs given for more than a few days in order to correct the electrocardiographic abnormalities.

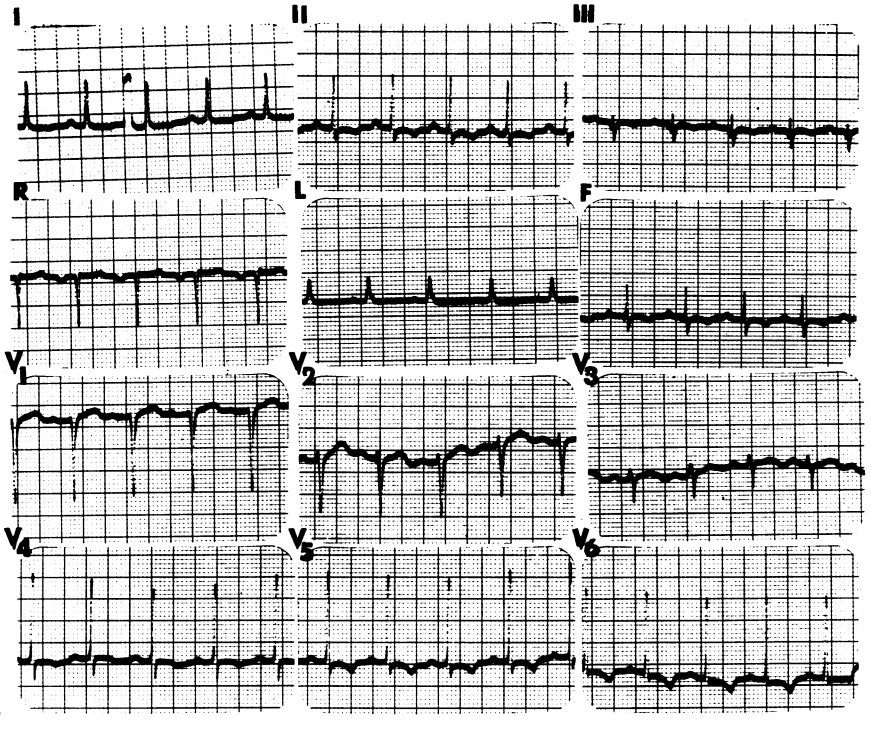


FIG. 6. Electrocardiogram during therapy with phenoxybenzamine.

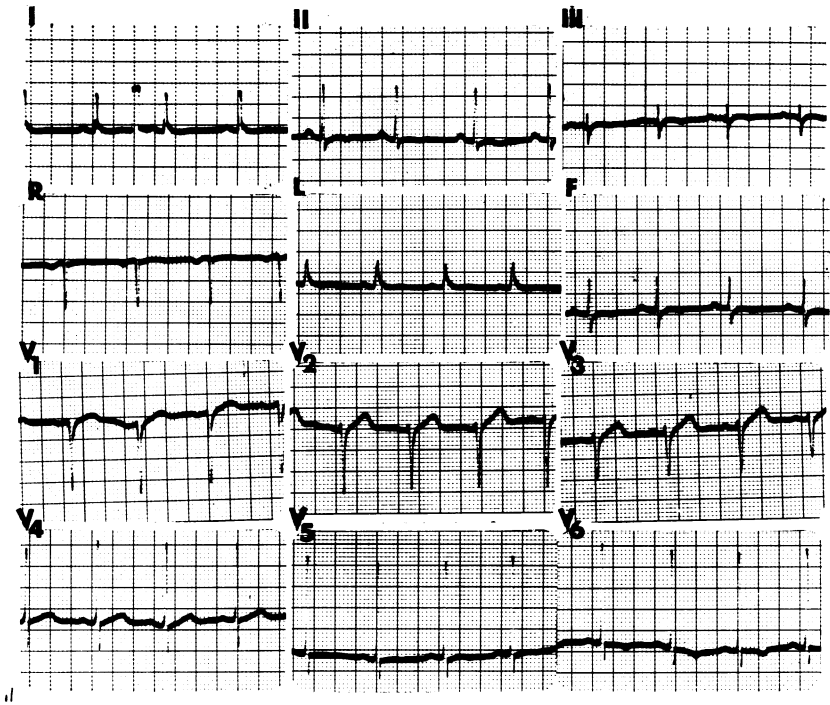


FIG. 7. Electrocardiogram during therapy with phenoxybenzamine and propranolol.

A 21 year old female presented with a blood pressure of approximately 180/120 and the electrocardiogram revealed a sinus tachycardia, some left ventricular hypertrophy, and inverted T-waves in Leads 2, 3, AVF, V-4, V-5 and V-6 (fig. 5). SGOT varied from 33 to 56 units. Daily 24-hour urinary norepinephrine varied from 170 to 723 $\mu\text{g.}$, epinephrine from 6 to 63 $\mu\text{g.}$ and VMA from 8.2 to 17.2 mg. Infusion of 1250 $\mu\text{g.}$ of tyramine intravenously resulted in elevation of 50 mm. Hg. in systolic blood pressure. Therapy with phenoxybenzamine was instituted and continued for four and one-half weeks in doses of 30 mg. twice daily. With the alpha receptors blocked, tachycardia and arrhythmia may occur because of excessive beta-adrenergic stimulation. Indeed, in this patient a protodiastolic gallop and an increasing cardiac rate appeared, but no other signs of congestive heart failure developed and she was, therefore, digitalized. The electrocardiogram during treatment with phenoxybenzamine revealed disappearance of the inversions of the T-waves and of the pattern of left ventricular hypertrophy (fig. 6). SGOT had decreased to 13 units. Eleven days prior to operation, propranolol was added to the

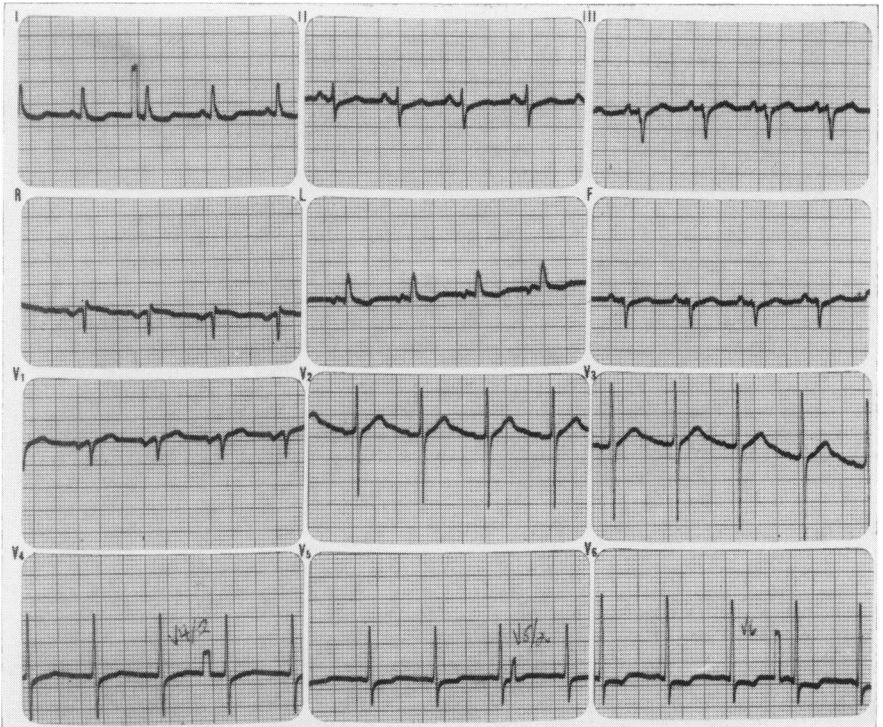


FIG. 8. Pre-treatment electrocardiogram in 54 year old male.

therapeutic program in doses of 20 mg. every eight hours. On this regime the cardiac rate was approximately 70 per minute and blood pressure 140/90. The electrocardiogram showed now a normal sinus rhythm and further improvement in the configuration of the T-waves (fig. 7). Infusion of 2500 μ g. of tyramine caused no increase in blood pressure. The blood volume, which originally was low, returned to normal during therapy. The patient did have three spontaneous attacks of hypertension prior to operation, indicating that the adrenergic blockade was incomplete. (Additional data on this patient have been recorded previously.¹⁸)

The electrocardiogram of a 54 year old male with paroxysmal hypertension showed sinus tachycardia, some left ventricular hypertrophy and ST and T-wave changes in Leads 1, V-4, V-5 and V-6 (fig. 8). His blood pressure was approximately 140/90 and SGOT 32 units. He was treated with phenoxybenzamine 10 mg. twice daily for eight days and propranolol 20 mg. twice daily for six days prior to operation. His blood pressure on this regimen remained about 120/70 and a preoperative

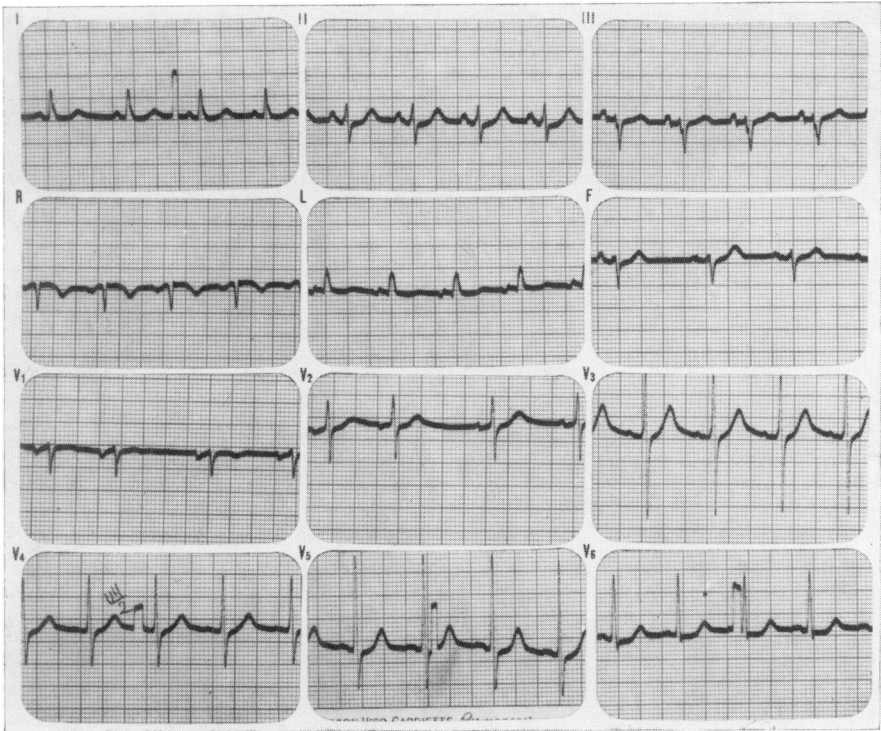


FIG. 9. Electrocardiogram during therapy with phenoxybenzamine and propranolol.

electrocardiogram revealed improvement in the ST and T-wave changes with T becoming upright in Leads 1 and V-4 to V-6 (fig. 9). SGOT prior to operation had decreased to 18 units.

DISCUSSION

The presence of tachycardia, cardiac arrhythmia, cardiomegaly or electrocardiographic abnormalities are suggestive of cardiomyopathy in patients with pheochromocytoma. The improvement in the electrocardiograms of these two patients under dual therapy with alpha and beta blockade was greater than could be accounted for on the basis of relief of hypertension alone. The optimal duration of the preoperative treatment with these blocking drugs is not clearly established, but the treatment should be continued until maximum control of blood pressure and improvement in the electrocardiogram occur prior to operation. Elevated levels of SGOT in the serum, as well as electrocardiographic changes, may indicate the degree of cardiac myopathy. Complete alpha and beta adrenergic blockade should not be attained

because of increased sensitivity to the hypotensive effects of anesthesia and hemorrhage and increased venous oozing during surgery. Both drugs can be given until the time of surgery. Since phenoxybenzamine has a prolonged effect, further administration during the operation should not be necessary. Episodes of hypertension or arrhythmia due to manipulation of the tumor can be controlled with intravenous phentolamine and propranolol. It appears that this type of combined therapy may induce improvement in cardiac function with consequent less risk to the patient during surgery.

SUMMARY

In a series of 13 patients with pheochromocytoma, myocardial lesions were demonstrated at autopsy in five. Electrocardiographic abnormalities were present in six patients and improved following removal of the tumor. Electrocardiograms in two patients with paroxysmal hypertension were normal. In two patients treated with alpha and beta adrenergic blocking drugs, electrocardiographic changes improved significantly prior to operation. It is suggested that patients with pheochromocytoma may have cardiomyopathy which may be improved by therapy with adrenergic blocking drugs prior to operative removal of the tumor.

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DISCUSSION

DR. LEWIS DEXTER (Boston): How much phenoxybenzamine do you give?

DR. WISWELL: Up to about 60 milligrams a day in divided doses. We don't think that you should achieve a complete blockade, which I think brings us to one or two points. If the blockade is complete, there may be increased sensitivity to the hypotensive effects of anesthesia and hemorrhage and increased venous oozing during surgery. One has to be careful not to produce those.

DR. GEORGE R. CAHILL (Boston): How close to the time of operation do you continue the blockade keeping in mind the fact that the patient might experience blood loss during the operation with a hypotensive response?

DR. WISWELL: In the first place, one can easily overcome the blockade by giving norepinephrine. The phenoxybenzamine can be given up to just a few hours pre-operatively. Secondly, the blood pressure and cardiac rate during operation can be controlled by intravenous phentolamine and propranolol which are short acting drugs.