Modification of Cardiovascular Responses by Propranolol*

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The introduction of propranolol (ICI 45,520) (1-isopropylamino-3- (1-naphthoxy)-2- propanol hydrochloride: inderal), a strong beta-adrenergic blocker with but weak intrinsic sympathetic activity, has resulted in extensive evaluation of the role of beta-adrenergic receptors in the regulation of the circulation (Black *et al.*, 1964; Shanks, 1964). Propranolol, in contrast to its predecessor pronethalol, achieves effective beta-adrenergic blockade at about one-tenth the dose required with pronethalol. Moreover, no carcinogenic effects or central nervous system disturbances, previously reported with the administration of pronethalol, have been noted. Although propranolol has been used extensively in the treatment of a number of clinical disorders, including arrhythmias (Schamroth, 1966; Bath, 1966; Harris, 1966; Turner, 1966; Harrison, Griffin, and Fiene, 1965), angina pectoris (Hamer, Melen-dez, and Sowton, 1964; Grant *et al.*, 1966; Gillam and Prichard, 1965), idiopathic hypertrophic sub-aortic stenosis (Cherian *et al.*, 1966), phæochromocytoma (Prichard and Ross, 1966; Robertson, 1965), acute myocardial infarction (Snow, 1965), systemic

hypertension (Prichard and Gillam, 1964), and Parkinsonism (Vas, 1966), there are few reports on the hæmodynamic effects of propranolol in men studied by cardiac catheterization. This paper reports cardiac catheterization findings in eight patients to whom propranolol was administered.

SUBJECTS AND METHODS

Eight patients, 3 to 31 years of age, underwent right heart catheterization. Three had minimal to moderate degrees of muscular outflow obstruction from the right ventricle, one had a small ventricular septal defect, one had a small ventricular defect that had been closed two years previously, and one had a ventricular septal defect and valvular pulmonary stenosis. The two remaining patients had been under consideration for some while as possibly suffering from ventricular septal defect; in both, hydrogen curves had seemed to exclude a left-to-right shunt, but right heart catheterization was performed for confirmation. Details of the 8 patients are given in Table I.

Five patients received premedication consisting of 1 mg./kg. of meperidine and 4 mg./kg. of secobarbital sodium. Three patients received no premedication. Resting pressures were obtained with a P-23db Statham strain gauge energized by an Electronics for Medicine carrier amplifier and were recorded photographically.

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TABLE I
SUMMARY OF THE PATIENTS STUDIED

Case No.	Age (yr.)	Sex	Diagnosis	BSA (m. ²)	Height (cm.)	Weight (kg.)
1	7	M	Small ventricular septal defect	0.89	123	22.9
2	15	M	? Minor ventricular septal defect	1.58	164	54.0
3	15	M	Mild infundibular pulmonary stenosis	1.82	173	68.0
4	13	M	Mild infundibular pulmonary stenosis	1.64	171	54.5
5	31	F	? Minor ventricular septal defect	1.82	146	92.0
6	11	M	Ventricular septal defect (closed surgically)	1.24	143	38.1
7	5	M	Moderate infundibular pulmonary stenosis	0.71	108	17.0
8	3	M	Ventricular septal defect; valvular pulmonary stenosis	0.64	99	14.4

Mean pressures were obtained electronically. Cardiac outputs were estimated by the Fick method. Oxygen contents were determined by the method of Van Slyke and Neill (1924) and expired gas was analysed by the Scholander technique (1947). In some cases indicator dilution curves employing indocyanine dye were used for determination of cardiac output during hypoxia.

In three subjects the effects of propranolol on the response to 10 or 13 per cent oxygen administration were determined. Two carried out supine bicycle exercise before and after propranolol. In three subjects the effects of propranolol on the response to isoprenaline were determined. In one subject the effects of tolazoline were recorded after propranolol administration.

Following control observations on the responses to hypoxia, exercise, or isoprenaline, propranolol* was administered in a dose of 0.066 to 0.103 mg./kg., diluted in 5 ml. saline, and administered over a 2- to 5-minute period into the pulmonary artery. Repeat studies were then obtained 15 to 30 minutes after the administration of propranolol.

RESULTS

The results are set out in Table II. The administration of propranolol resulted in an average decrease of 16 per cent in heart rate and 13 per cent in cardiac output. Pulmonary arterial pressure increased an average of 7 mm. Hg (44%). Total pulmonary resistance increased from an average value of 343 dynes sec. cm.⁻⁵ m.² to 588 dynes sec. cm.⁻⁵ m.² (Fig. 1) and arterio-venous oxygen difference widened from 4.67 vol. per cent to 5.63. Changes in brachial arterial pressure and stroke volume were variable; however, in 3 patients there was an increase in total systemic resistance ranging from 371 dynes sec. cm.⁻⁵ m.² to 1025. Maximal changes were achieved within 15 to 30 minutes. Further, a square wave response to the Valsalva manoeuvre was noted following the administration of propranolol (Fig. 2).

Effect of Propranolol on Response to Hypoxia (Cases 1, 2, and 3). Following propranolol the responses to 10 or 13 per cent oxygen were modified with a slower heart rate and less increase in cardiac output. As the increase in mean pulmonary arterial pressure was similar to that observed with hypoxia before administration of propranolol, total pulmonary resistance was higher in view of the lower cardiac output. Similarly, total systemic resistance was higher. Fig. 3 shows an example of such a response.

Effect of Propranolol on Infundibular Pulmonary Stenosis and Response to Isoprenaline. In Cases 3 and 4 with mild infundibular obstruction, propranolol eliminated the minimal resting gradient, and blocked

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FIG. 1.—Total pulmonary resistance (TPR) is plotted before and after propranolol. Note that in all cases TPR was higher after beta-blockade with propranolol.

FIG. 2.—Valsalva manoeuvre before and after propranolol. Duration of Valsalva denoted by shift in baseline. Note "square-wave" effect after beta-blockade.

TABLE II
CATHETERIZATION DATA IN THE 8 PATIENTS STUDIED, BEFORE AND AFTER ADMINISTRATION OF
PROPRANOLOL

Case No.		Heart rate	Right atrium	Brachial artery	Wedge	Pulmonary artery	Rt. vent. outflow	Rt. vent. body	Gradient	Pulm. A-V O ₂ diff. (vol. %)	O ₂ consumption (ml./min.)	Cardiac output (l./min.)	Stroke volume (ml.)	System. art. O ₂ sat.	Mixed venous O ₂ sat.	Total syst. resist. (dynes sec. cm. ⁻⁵ m. ²)	Total pulm. resist.
1.	Before	C	72	7	97	8	13	—	—	3.89	155*	3.98	55	92.8	72.9	1736	232
	After	H	144	—	96	—	58	—	—	2.47	155*	6.27	44	45.0	32.0	1088	658
	0.087 mg./kg. H	C	66	9	93	—	29	—	—	4.03	155*	3.85	58	89.5	67.7	1721	536
2.	Before	C	84	4	103	6	17	—	—	3.58	255	7.12	85	89.7	73.1	1827	300
	After	E	142	—	130	—	16	—	—	10.19	1310	12.85	90	89.4	42.2	1279	158
	0.093 mg./kg. E	C	114	—	92	—	16	—	—	4.25	255*	6.00	53	83.3	63.6	1936	337
3.	Before	C	60	3	112	5	23	35/4-7	—	4.08	280	6.86	114	95.0	73.0	2352	376
	After	I†	133	—	—	—	18	24/0-4	—	3.47	280*	8.07	74	93.0	75.0	—	328
	0.074 mg./kg. I†	C	57	—	—	—	22	—	—	—	—	—	—	—	—	—	—
4.	Before	C	80	2	88	6	19	34/0-6	—	5.03	280	5.56	70	93.3	71.0	2072	448
	After	I†	120	—	90	—	16	32/0-6	—	4.10	330	8.05	67	95.6	77.7	1464	261
	0.092 mg./kg. I†	C	60	2	92	—	24	—	—	6.61	280	4.23	70	95.3	65.3	2848	744
5.	Before	C	108	—	97	8	14	—	—	4.17	263	6.31	60	96.8	76.2	2232	322
	After	E	130	—	95	11	19	—	—	9.22	763	8.28	64	92.8	47.7	1672	333
	0.076 mg./kg. E	C	70	2	108	10	19	—	—	6.36	307	4.83	69	95.7	64.1	3264	573
6.	Before	C	55	6	80	—	20	—	—	4.91	207*	4.21	77	95.3	66.8	1888	472
	After	H	88	—	65	—	42	—	—	3.88	201	5.18	59	77.4	54.6	1248	800
	0.066 mg./kg. H	C	53	—	77	—	31	—	—	4.88	207*	4.24	80	91.8	63.6	1800	720
7.	Before	C	84	—	76	6	14	19/0-7	—	4.79	135*	2.82	34	94.8	68.0	1530	282
	After	I†	138	—	—	—	13	20/0-7	—	96	—	—	—	—	—	—	—
	0.103 mg./kg. I†	C	72	8	—	—	21	31/11	—	5.47	135*	2.47	34	—	65.1	—	483
8.	Before	C	115	3	96/75	—	—	—	—	6.34	115*	1.82	16	87.1	60.5	—	—
	After	C	100	4	98/65	—	—	—	—	7.24	115*	1.59	16	85.1	58.2	—	—
	0.104 mg./kg.																

*—Estimated †—4 µg./min. (left ventricular body 166/3 mm. Hg; aorta 166/118 mm. Hg) ‡—2 µg./min. §—Tight VPS by angiocardigram.

Before and after = before and after propranolol. C = control, H = hypoxia, E = exercise, I = isoprenaline, T = tolazoline. A pressures are mean values in dynes sec. cm.⁻⁵ m.²

the development of any gradient with the administration of isoprenaline (Fig. 4). In Case 7 which had moderate infundibular obstruction, propranolol reduced the degree of outflow obstruction resulting from the administration of isoprenaline. Of interest was that propranolol reduced the resting gradient from 27 to 14 mm. Hg by virtue of an increase in pulmonary arterial pressure, rather than a reduction in right ventricular pressure, thereby creating a

partial masking of the infundibular stenosis (Vogel and Blount, 1965).

Further, propranolol modified the chronotropic effect of isoprenaline in all 3 subjects, and in 2 the pulmonary arterial vasodilating effect of isoprenaline was partially blocked (Fig. 5).

Effect of Propranolol on Response to Exercise. In Cases 2 and 5 propranolol significantly modified the

FIG. 3.—(Case 6). Cardiac output (Q), mean pulmonary arterial (PA) pressure, and the heart rate are plotted under influence of 13 per cent oxygen under control conditions and after propranolol. Note that increase in PA pressure with 13 per cent oxygen was not blocked by beta-blockade, though the heart rate was less and cardiac output actually fell. Moreover, tolazoline blocked the effect of both propranolol and 13 per cent oxygen on PA pressure, decreasing PA pressure to control levels. However, the usual tachycardia following tolazoline was blocked by propranolol.

reponses to exercise. Heart rate was slower in response to a similar degree of exercise, and cardiac output was also lower as evidenced by a greater widening of the arterio-venous oxygen difference. Mean pulmonary arterial pressure was higher with exercise following propranolol, and consequently total pulmonary resistance was significantly higher (Fig. 6). Stroke volume was not significantly changed.

DISCUSSION

Although propranolol was first described less than two years ago in 1964 (Black *et al.*; Shanks), this drug is now on the open market in the United Kingdom and is being investigated in the United States. However, few reports of its haemodynamic effects in man have been published.

In most studies propranolol has resulted in a decrease in cardiac output and heart rate (Tsolakas, Davies, and Oram, 1965; Sowton and Hamer, 1966; Taylor, 1965; Epstein *et al.*, 1965; Stavropoulos, Davies, and Gazetopoulos, 1965), though some have reported no change in heart rate or cardiac output (McKenna *et al.*, 1965). Stroke volume has been decreased (Sowton and Hamer, 1966; Taylor, 1965), or unchanged (Stavropoulos *et al.*, 1965). Systemic blood pressure has been either unchanged (Sowton and Hamer, 1966; McKenna *et al.*, 1965)

or decreased (Stavropoulos *et al.*, 1965). Although most reports have noted little or no change in pulmonary arterial pressure and pulmonary resistance (McKenna *et al.*, 1965; Stavropoulos *et al.*, 1965), one recent paper noted an increase in resting pulmonary arterial pressure following propranolol, which was accentuated with exercise (Taylor, 1965).

Our results were consistent with previous reports, showing a reduction in cardiac output and heart rate, and a widening of the arterio-venous oxygen difference, with little change in systemic pressure. Although most reports have indicated no change in pulmonary arterial pressures, we noted an increase in all patients except one, which is in agreement with a recent report by Taylor (1965). In addition, there was a consistent increase in total pulmonary resistance (Fig. 1) which was further increased with exercise or hypoxia as compared to control studies. Moreover, propranolol limited the increase in heart rate and cardiac output resulting from exposure to acute hypoxia.

The modification of the response to exercise was similar to that previously reported, in that heart rate and cardiac output was less with a given level of exercise. The reduction of infundibular pulmonary stenosis by propranolol was of considerable interest and suggested that beta blockade might be useful in the treatment of such conditions. This is further supported by the clinical observations of less cyanosis with exercise following beta-blockade in patients with tetralogy of Fallot (Honey, Chamberlain, and Howard, 1964; Singh and Gotsman, 1966).

Although there has been considerable controversy concerning the role of the sympathetic nervous system in the regulation of the pulmonary circulation, the results in our patients suggest an active role. Thus, in six of seven patients, there was an increase in pulmonary arterial pressure and total pulmonary resistance following the administration of propranolol, suggesting that beta-adrenergic blockade in some manner allowed those factors governing vasoconstriction to predominate. What system was modified by propranolol, or what constitutes the so-called beta-receptor, is not clear.

However, studies by Murad and his associates (1962) have shown that the administration of catecholamines results in an increase in cyclic 3' 5' AMP, presumably mediated by adenylic cyclase, and Bartelstone, Nasmyth, and Telford (1964) have shown the importance of 3' 5' AMP in mediating the effect of norepinephrine on blood vessels. Further, studies by Levine and Vogel (1965) showed that the effects of administered cyclic 3' 5' AMP were not modified by the previous administration of propranolol. This suggests that, if one way in which catecholamines exert their

FIG. 4.—(Case 4). This shows the effect of isoprenaline on infundibular pulmonary obstruction and complete blockade of isoprenaline effects by propranolol.

effects is via production of cyclic 3' 5' AMP, then adenylic cyclase may well represent the "beta-receptor" which is competed for by propranolol. Recent studies have shown that blockade of isoprenaline by propranolol is a competitive inhibition (Nakano and Kusakari, 1965).

Our studies further illustrate that the effect of reduced alveolar oxygen tension in eliciting pulmonary vaso-constriction is mediated at a level

distant to beta receptors, not being blocked by propranolol, and, further, that tolazoline exerts its vasodilating activity at or beyond the site of action of hypoxia.

The modification of the Valsalva response is of interest. O'Neill and Cudkowicz (1965) showed that administration of norepinephrine could convert a normal Valsalva response into a square wave response. Presumably this resulted from intense

FIG. 5.—(Case 4). This shows modification of isoprenaline effect on cardiac output (CO), mean pulmonary arterial (PA) pressure, and heart rate by propranolol.

FIG. 6.—(Case 5). This shows modification of responses to exercise of mean pulmonary arterial (PA) pressure, cardiac output (CO), and heart rate by propranolol. With the same oxygen consumption, note that PA pressure is higher in association with a lower cardiac output and heart rate following propranolol.

stimulation of the so-called alpha receptors. Possibly the square wave response following the administration of propranolol is on the same basis by virtue of an inhibition of the beta receptors, thus allowing the alpha receptors and vaso-constrictive action to operate unopposed. Support for increased alpha activity following beta-blockade is forthcoming from reports that have shown an accentuated rise in systemic blood pressure with epinephrine following beta-blockade (Kako *et al.*, 1964).

The use of propranolol is not without hazard, as three deaths have been reported following its use (Schamroth, 1966; Wolfson *et al.*, 1966; Vogel, 1965). Moreover, a number of patients have developed acute pulmonary oedema or have had worsening of heart failure (Bath, 1966; Turner, 1966). The drug is contraindicated, therefore, in patients with overt or incipient heart failure (Vogel, 1965). Further, it may be hazardous in the presence of pulmonary hypertension, particularly acute pulmonary hypertension, in view of the limited capacity of the right ventricle to sustain a pressure load (Vogel *et al.*, 1966; Overy *et al.*, 1966). If failure occurs with propranolol, epinephrine may be effective in reversing the failure (Vogel *et al.*, 1966). Further, increased airway obstruction has been noted following the administration of propranolol. Consequently its use in people with airway obstruction may be hazardous, though aminophylline is successful in reversing such induced bronchoconstriction (McNeill and Ingram, 1966).

SUMMARY

Propranolol, a potent beta adrenergic receptor

blocker, 0.066 to 0.103 mg./kg., was administered to eight subjects during right heart catheterization. In six there was an increase in pulmonary arterial pressure and total pulmonary resistance. With hypoxia, exercise, or isoprenaline, total pulmonary resistance was greater than before propranolol. Heart rate and cardiac output were decreased after propranolol with variable changes in systemic arterial pressure and stroke volume. A "square-wave" response to the Valsalva manoeuvre was noted after propranolol. In two subjects mild infundibular pulmonary obstruction was abolished. The results suggest that after propranolol the pulmonary vascular bed functions on a different pressure-flow curve as a result of unopposed pulmonary arterial vasoconstriction.

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REFERENCES

- Bartelstone, J. H., Nasmyth, P. A., and Telford, J. M. (1964). A possible role for adenosine 3', 5'-phosphate (3', 5'-AMP) in controlling the vascular response to noradrenaline. *J. Physiol. (Lond.)*, **171**, 48P.
- Bath, J. C. J. L. (1966). Treatment of cardiac arrhythmias in unanesthetized patients. Role of adrenergic beta receptor blockade. *Amer. J. Cardiol.*, **18**, 415.
- Black, J. W., Crowther, A. F., Shanks, R. G., Smith, L. H., and Dornhorst, A. C. (1964). A new adrenergic beta-receptor antagonist. *Lancet*, **1**, 1080.
- Cherian, G., Brockington, I. F., Shah, P. M., Oakley, C. M., and Goodwin, J. F. (1966). Beta-adrenergic blockade in hypertrophic obstructive cardiomyopathy. *Brit. med. J.*, **1**, 895.

- Epstein, S. E., Robinson, B. F., Kahler, R. L., and Braunwald, E. (1965). Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. *J. clin. Invest.*, **44**, 1745.
- Gillam, P. M. S., and Prichard, B. N. C. (1965). Use of propranolol in angina pectoris. *Brit. med. J.*, **2**, 337.
- Grant, R. H. E., Keelan, P., Kernohan, R. J., Leonard, J. C., Nancekivell, L., and Sinclair, K. (1966). Multicenter trial of propranolol in angina pectoris. *Amer. J. Cardiol.*, **18**, 361.
- Hamer, J., Melendez, L., and Sowton, E. (1964). Propranolol for angina. *Brit. med. J.*, **2**, 1136.
- Harris, A. (1966). Long term treatment of paroxysmal cardiac arrhythmias with propranolol (Inderal). *Amer. J. Cardiol.*, **18**, 431.
- Harrison, D. C., Griffin, J. R., and Fiene, T. J. (1965). Effects of beta-adrenergic blockade with propranolol in patients with atrial arrhythmias. *New Engl. J. Med.*, **273**, 410.
- Honey, M., Chamberlain, D. A., and Howard, J. (1964). The effect of beta-sympathetic blockade on arterial oxygen saturation in Fallot's tetralogy. *Circulation*, **30**, 501.
- Kako, K., Kräyenbühl, H. P., Lüthy, E., and Hegglin, R. (1964). Cardiovascular effects of catecholamines in dogs before and after beta-adrenergic blockade. *Nauyn-Schmiedeberg's Arch. exp. Path. Pharmacol.*, **246**, 297.
- Levine, R. A., and Vogel, J. A. (1965). Cardiovascular and metabolic effects of adenosine 3', 5'-monophosphate *in vivo*. *Nature (Lond.)*, **207**, 987.
- McKenna, D. H., Corliss, R. J., Sialer, S., and Rowe, G. G. (1965). Systemic and coronary hemodynamic effects of propranolol. *Clin. Res.*, **13**, 401.
- McNeill, R. S., and Ingram, C. G. (1966). The effect of propranolol on ventilatory function. *Amer. J. Cardiol.*, **18**, 473.
- Murad, F., Chi, Y.-M., Rall, T. W., and Sutherland, E. W. (1962). Adenyl cyclase. *J. biol. Chem.*, **237**, 1233.
- Nakano, J., and Kusakari, T. (1965). Competitive antagonism between isoproterenol and a new beta-receptor adrenergic blocking agent, propranolol. *Proc. Soc. exp. Biol. (N.Y.)*, **119**, 350.
- O'Neill, A., and Cudkowicz, L. (1965). Effect of 1-nor-epinephrine on right atrial pressure and the "square wave response" to the Valsalva maneuver. *Amer. Heart J.*, **69**, 220.
- Overy, H. R., Vogel, J. H. K., Grover, R. F., and Blount, S. G., Jr. (1966). Coronary vascular development in response to increased right ventricular pressure loads. *Circulat. Res.*, **18**, 634.
- Prichard, B. N. C., and Gillam, P. M. S. (1964). Use of propranolol (Inderal) in treatment of hypertension. *Brit. med. J.*, **2**, 725.
- , and Ross, E. J. (1966). Use of propranolol in conjunction with alpha receptor blocking drugs in pheochromocytoma. *Amer. J. Cardiol.*, **18**, 394.
- Robertson, A. I. G. (1965). Pre- and post-operative care of patients with pheochromocytomas. *Postgrad. med. J.*, **41**, 481.
- Schamroth, L. (1966). Immediate effects of intravenous propranolol on various cardiac arrhythmias. *Amer. J. Cardiol.*, **18**, 438.
- Scholander, P. F. (1947). Analyser for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J. biol. Chem.*, **167**, 235.
- Shanks, R. G. (1964). The pharmacology of a new β -adrenergic receptor antagonist. *Pharmacologist*, **6**, 166.
- Singh, S. P., and Gotsman, M. S. (1966). Pronethalol for cyanotic attacks. *Brit. Heart J.*, **28**, 98.
- Snow, P. J. D. (1965). Effect of propranolol in myocardial infarction. *Lancet*, **2**, 551.
- Sowton, E., and Hamer, J. (1966). Hemodynamic changes after beta adrenergic blockade. *Amer. J. Cardiol.*, **18**, 317.
- Stavropoulos, S., Davies, D. H., and Gazetopoulos, N. (1965). Hemodynamic studies with propranolol in normal subjects and patients with congenital and acquired cardiac lesions. *Symposium on Propranolol*. Buxton, Derbyshire (unpublished).
- Taylor, S. H. (1965). The circulatory effects of beta-sympathetic blockade at rest and during exercise in normal subjects and hypertensive patients. *Symposium on Propranolol*. Buxton, Derbyshire (unpublished).
- Tsolakas, T. C., Davies, J. P. H., and Oram, S. (1965). Effect of a beta-adrenergic-blocking agent on the pulmonary circulation in mitral stenosis. *Lancet*, **2**, 416.
- Turner, J. R. B. (1966). Propranolol (Inderal) in the treatment of digitalis-induced and digitalis-resistant tachycardias. *Amer. J. Cardiol.*, **18**, 450.
- Van Slyke, D. D., and Neill, J. M. (1924). The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. biol. Chem.*, **61**, 523.
- Vas, C. J. (1966). Propranolol in parkinsonian tremor. *Lancet*, **1**, 182.
- Vogel, J. H. K. (1965). Propranolol therapy of cardiac arrhythmias. *New Engl. J. Med.*, **273**, 1052.
- , and Blount, S. G., Jr. (1965). Masked infundibular pulmonary obstruction in ventricular septal defect with pulmonary hypertension. *Circulation*, **31**, 876.
- , Overy, H., Brammell, H., Page, H., and Paton, B. (1966). Effects of isomers of propranolol on the pressure loaded ventricle. *Clin. Res.*, **14**, 129.
- Wolfson, S., Heinle, R. A., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R. (1966). Propranolol and angina pectoris. *Amer. J. Cardiol.*, **18**, 345.