we have attempted to discover new and better antiarrhythmic drugs by testing drugs with known neurodepressant effects against experimentally induced arrhythmias. We have found that chlortiazepoxide is effective in the treatment of ventricular arrhythmias induced by either digitalis or coronary occlusion. Chlortiazepoxide in combination with the peripherally-acting antiarrhythmic agent, lidocaine, is able to enhance the effect of lidocaine on arrhythmias evoked by coronary occlusion.

Attacking the "neurophysiologic trigger" with drugs has also been reported by Nixon and colleagues in patients. They suggested that prophylactic use of sleep therapy (i.e., pethidine plus promethazine) reduces mortality from acute myocardial infarction.

Most methods for finding new antiarrhythmic drugs have been based on the idea that drugs must act directly on myocardial cell membranes to exert an antiarrhythmic effect. The failure of studies on isolated tissues to lead to promising new drugs may be due to the fact that the causative factors of arrhythmias occurring in vivo are missing in these preparations. Based on the data cited above plus the data of Lown and colleagues showing that sleep will suppress ventricular premature beats, we feel that consideration of the nervous system may provide the basic understanding for discovering safe and effective new antiarrhythmic drugs.

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References

Propranolol and Oxygen-Hemoglobin Equilibrium

To the Editor:
The article by Lichtman and others (Circulation 49: 881, 1974) entitled "Effect of Propranolol on Oxygen Binding to Hemoglobin in Vitro and in Vivo" was a major step forward in the understanding of the biochemical effects of this drug.

We would disagree, however, with one of the conclusions. The authors state that "Propranolol (10 to 360 mg) administered to human subjects did not affect hemoglobin-oxygen affinity." This was based on measurement of $P_{50}$ in six presumably healthy subjects before propranolol, and four and twenty-four hours after administration of forty milligrams or less. The authors found no significant change in $P_{50}$. They also measured $P_{50}$ in two subjects on large doses (180 and 360 mg per day) of propranolol and found it to be "within one standard deviation of their normal mean."

We have shown that patients with coronary artery disease on chronic oral therapy with propranolol (mean 150 mg per day) for at least three months do have a significantly increased $P_{50}$ on the drug compared to their $P_{50}$ off the drug (Am J Cardiol 33: 170, 1974). This demonstrated shift in oxygen affinity could increase systemic oxygen delivery 20-30%.

Perhaps the differences in our data may be explained by differences in duration of drug ingestion. Most patients in Lichtman's paper were studied after only one dose of the drug. The two patients that were on chronic oral therapy, only had measurements while they were on propranolol. No control $P_{50}$s were done while they were off the drug.

The duration and amount of oral therapy necessary for the in vitro effect of propranolol on $P_{50}$ is incompletely understood. Manchester and others have shown observable effects on $P_{50}$ 2 hours after 40 mg of propranolol given as 10 mg orally q4h (Manchester et al., Circulation 45: suppl II: 11-109, 1972). We have shown that patients on chronic oral therapy with propranolol, when compared to themselves off the drug as controls, do have an increase in $P_{50}$. Studies to elucidate the time course of this effect of the drug are underway.

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To the Editor:

We thank Dr. Sheps and colleagues for calling our attention to their studies and for their comments. Their finding that propranolol results in an increase in $P_{50}$ after at least three months of treatment is of interest but the abstract by Schrumpf et al. to which they refer does not indicate a direct effect of propranolol on the red cell. Propranolol used in higher doses for long periods may lead to changes in cardiac or pulmonary function which might result in an increase in $P_{50}$ indirectly.

At this time four variables are accepted as capable of producing major alterations in the oxygen-hemoglobin equilibrium: red cell temperature, red cell 2,3-diphosphoglycerate (2,3-DPG) concentration, red cell pH and the non-pH related effect of red cell CO$_2$. When $P_{50}$ is measured at standard conditions, all but 2,3-DPG are normalized. $P_{50}$ at standard conditions ($P_{50}$ std), which we assume to have been the variable measured by Schrumpf et al., is usually, therefore, an indirect measure of red cell 2,3-DPG if the red cell contains normal adult hemoglobin. Red cell 2,3-DPG concentration has been correlated most con-
vincingly with blood pH and this correlation appears to be causal; alkalosis results in an elevated 2,3-DPG and acidosis results in a decreased 2,3-DPG. Heart failure has been associated with increased red cell 2,3-DPG; hence, studies of changes in P50 in patients with cardiac disease using propranolol should inquire as to the role of these additional variables.

Also, the net effect of all factors contributing to the oxygen-hemoglobin equilibrium must be measured before estimates can be made of its effect on oxygen delivery. For example, P50 (i.e., red cell 2,3-DPG content) when used by itself may be misleading as an index of the position of the oxygen-hemoglobin dissociation curve particularly if the increase in 2,3-DPG is due to alkalosis, since the net result on oxygen binding to hemoglobin may be nil. From our experience it appears improbable to us that propranolol has a detectable direct effect on the red cell in doses administered to man. Our studies do not exclude the possibility that protracted, high dose propranolol treatment may affect hemoglobin-oxygen affinity indirectly such as by altering cardiac, pulmonary or renal function. We believe, therefore, that it will be important for these additional factors to be considered before any final conclusions can be drawn about the mechanism or the efficacy of long-term propranolol treatment in producing a decrease in oxygen binding to hemoglobin.

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