lingual long-acting nitrates more prolonged than that achieved by nitroglycerin. It is likely that the duration of action of the sublingual nitrates is not as long as would be ideal, merely more prolonged than that achieved by nitroglycerin; a 1-2½ hour duration of action seems most likely. Evidence that oral "long-acting" nitrates have a prolonged duration of action is, we agree, lacking. Although the information that nitroglycerin ointment may be superior is potentially exciting, its preliminary nature deserves reconfirmation before its acceptance to the exclusion of the sublingual mode of administration.

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References

The authors reply:

Dr. Cohn's thoughtful letter raises some interesting and important points. We agree that the complexities of evaluating antianginal agents and the resultant lack of precise information are a major reason for continuing uncertainty concerning the relative therapeutic merits of the various nitrate esters. Rather than resolving conflicting opinions, we hoped that our editorial would clarify certain therapeutic concepts and focus attention upon important gaps in factual information that is presently available.

Dr. Cohn is certainly entitled to his doubts concerning the role of exercise testing. Nevertheless, exercise evaluation remains uniquely related to therapeutic choice simply because it represents a systematic way of studying symptomatic response. We have emphasized previously that testing techniques must be selected carefully to optimize their discriminative potential. In our hands, exercise testing has readily documented the efficacy of several modes of therapy for angina — including isosorbide dinitrate. We do not mean to detract from the importance of physiologic and pharmacodynamic investigations of the nitrates. Indeed, these studies provide information that is essential in arriving at an integrated concept of nitrate therapy for angina. However, we anticipate that the findings of these more basic studies would ultimately receive confirmation in studies related immediately to the therapeutic goal, i.e., relief of ischemia and its symptomatic sequelae.

Dr. Cohn has very astutely identified the central dilemma involved in comparing nitrate esters: What dose should be selected for each drug? Clearly, it is not satisfactory to presume that a single, arbitrarily chosen dose will be representative of the actions of all possible doses of each agent. Yet this arbitrary choice beclouds comparative studies purported to demonstrate the advantages of sublingual "long-acting" nitrates. To document unequivocal superiority of a "long-acting" nitrate, one must show that pretoxic doses can achieve greater efficacy and/or duration of action than any pretoxic dose of the rival nitrate.

The repeated testing needed to support such a claim is arduous and (since one is dealing with the borderlines of toxicity) potentially hazardous. Nonetheless, if definitive supporting evidence cannot be produced, unqualified claims of superiority should be muted.

An alternative to arbitrary dosage choice can be achieved by a technique matching physiologic action of nitrates. Such a technique has been used by us and, in a slightly different context, by Dr. Cohn and associates. We thought it of some interest that doses of sublingual nitroglycerin and sublingual isosorbide dinitrate producing equal physiologic change and equal increment of exercise capacity showed equally rapid disappearance of clinical benefit. As Dr. Cohn points out, however, the nature of matching is, itself, an arbitrary choice. What if our criteria for matching had been entirely different? Would we have achieved the same result? Moreover, what if large doses of sublingual isosorbide dinitrate were better tolerated than matched (or less-than-matched) doses of nitroglycerin? Wouldn't this supersede the therapeutic implications of our previous study. Obviously, we are no more capable of finally resolving the nitrate controversy than we are of resolving the religious and political questions mentioned in Dr. Cohn's letter. We assert that we looked for evidence of a longer action for sublingual isosorbide dinitrate (within a commonly employed dosage range) and failed to find such evidence. We remain open-minded about the possibility that future testing using different techniques may document improvement in ischemic symptoms resulting from sublingual isosorbide dinitrate that cannot be achieved by any pretoxic dose of sublingual nitroglycerin. We might add that the same open-minded attitude should logically be extended to oral nitrate esters. Studies of these agents also suffer because of the difficulties involved in studying many different doses. Impressive claims of prolonged hemodynamic efficacy have been advanced regarding agents such as oral nitroglycerin. Perhaps more complete testing with a wide range of doses will succeed in identifying a practical and uniformly effective regimen for oral nitrates. We should not solidify our current skepticism into rigid orthodoxy.
Our ignorance about the clinical actions of nitrates includes a lack of knowledge about individual variability of response. Dr. Cohn as well as other clinical observers have suggested that sublingual isosorbide dinitrate may be particularly long lasting in certain subgroups of patients. While this remains an intriguing possibility, studies have not been undertaken to determine whether some patients repeatedly respond in a more prolonged fashion. Such studies are necessary to discriminate between mere statistical fluctuation and true difference in biologic response. Moreover, it is unclear that differences in response, if real, are very important, since no patient in our study was improved two hours after sublingual isosorbide dinitrate.

To circumvent the myriad of unknowns mentioned above, we turned to an entirely different mode of nitrate therapy, nitroglycerin ointment, and found it highly effective in improving exercise capacity for at least three hours after treatment. As Dr. Cohn points out, these results must be regarded as preliminary. We explored responses to doses yielding a narrow range of physiologic change one hour after application. Furthermore, we did not attempt comparative studies in these patients receiving nitroglycerin ointment. It is possible that the observed actions might be duplicated or exceeded by appropriately chosen doses of sublingual or other nitrates. Nevertheless, documentation of clinical benefit with other nitrates equaling or exceeding that seen after nitroglycerin ointment has not been published. Dr. Cohn indicates that even the most ardent advocates of sublingual nitrates do not claim to have achieved significant benefit for more than 2½ hours. It remains possible that oral agents may match the prolonged and consistent efficacy of nitroglycerin ointment, but such evidence is, at present, not available.

In this age of "miracle drugs" it is perhaps somewhat embarrassing that a homely remedy such as nitroglycerin ointment seems more lasting than nitrates with more impressive structural formulas. The tortoise appears to have beaten the hare! Nitroglycerin ointment, however, may not be the "ultimate" long-acting nitrate. It seems logical that current technology can improve substantially on the transcutaneous route of administering nitrates — perhaps physical or chemical alterations can make this approach easier to use and even more beneficial than it currently is.

Although our own limited experience with nitroglycerin ointment and other studies of nitrate therapy have not revealed evidence of significant adverse effects due to prolonged use, we urge that lack of nitrate tolerance or dependence in clinical medicine should not be taken for granted. The high doses and prolonged exposure available with cutaneous nitrate administration may cause angina patients to share the ill effects that apparently appear in industrial workers with cutaneous exposure to nitroglycerin. In the past, angina patients may have been protected from possible ill effects of prolonged nitrate exposure only by the inability of standard treatment modes to produce sustained nitrate action.

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Thrombosis and Endothelial Injury

To the Editor:

It is unfortunate that Roberts (Circulation 48: 1161, 1973) did not emphasize that the thromboses he discussed were very late complications of arterial plaque formation, having the same relation to etiology that bronchial hemorrhage has in tuberculosis. Also Astrup (Circulation 48: 1167, 1973) did not note that injury to the endothelium by hypoxia or carbon monoxide was only a minor aggravating factor in arterial disease.

Thrombosis in arteries follows ulceration or stagnation beyond marked obstruction. Ehrrhardt et al. (Lancet 1: 387, 1973) reported that 1131-tagged fibrinogen was found in postmortem thrombi in coronary arteries distal to the point of obstruction, after intravenous injection at the clinical onset of myocardial infarction. Here the clots were agonial, analogous to fatal hemoptyis in phthisis. In those who survive, such clots may become canalized, as in Roberts' figures 4 and 5.

Astrup has shown that endothelium can be damaged by hypoxia or by low levels of CO in the inspired air. This raises the blood cholesterol levels in rabbits fed cholesterol and accelerates deposition of intimal lipid. Animals and men living at high altitudes are not prone to intimal lipoidosis, and in both men and animals with high lipid levels, intimal deposition in systemic arteries, where oxygen tension is
Treatment of Angina Pectoris: The authors reply:
ROBERT E. GOLDSTEIN and STEPHEN E. EPSTEIN

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