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 oral 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 longstanding 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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References
2. REDWOOD DR, ROSING DR, GOLDSTEIN RE, BEISER GD, EPSTEIN SE: Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. Circulation 43: 618, 1971
11. LANGE RL, REID MS, TRESCH DD, KEELAN MH, BERNHARD VM, COOLIDGE G: Nonatheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure. Circulation 45: 666, 1972

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 1 131-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 giantlike, analogous to fatal hemoptysis in phthisis. In those who survive, such clots may become calcified, as in Roberts's 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 lipidosis, and in both men and animals with high lipid levels, intimal deposition in systemic arteries, where oxygen tension is
high, is usually striking when there is no lipid in the veins and pulmonary arteries, where hypoxia is marked. Hence intimal permeability due to hypoxia or CO exposure must be one of the minor aggravating factors in etiology of vascular disease, comparable to drinking soft rather than hard water. If Astrup’s hypothesis was valid, lipid deposition should begin in coronary veins, where oxygen tension is lower than in any other vessel, and be least in the systemic arteries. Obviously arterial pressure is the most significant aggravating factor, and low pressure protects veins and pulmonary arteries. But without lipid levels high for any species, there can be no intimal lipid accumulation. In man the normal level is under 180 for cholesterol, 100 for triglyceride. Just as there can be no tuberculosis without the Koch bacillus, there can be no xanthomas of the skin without plasma cholesterol over three or four hundred milligrams per deciliter, no xanthomas of the intima without levels half as high.

WILLIAM DOCK, M.D.

Transfemoral Cardiac Pacing and Phlebitis

To the Editor:

In the January issue of Circulation, Meister et al. expressed concern that phlebitis might complicate prolonged pacing from the transfemoral approach. Hence, prophylactic “mini dose” heparin was utilized to prevent the complication of thrombophlebitis. After reviewing our experience with transfemoral cardiac pacing in 80 consecutive non-anticoagulated patients, we concluded that thrombophlebitis of the catheterized leg is a clear hazard of the procedure.

The 80 patients that were referred for cardiac pacing had an average age of 75 years and included 44 men and 36 women. Temporary transvenous pacing was performed via the transfemoral route with a number 5 bipolar catheter. Critically ill patients had temporary pacemaker insertion in the cardiac catheterization laboratory or in the Intensive Care Unit. In the latter area the procedure was facilitated by the use of a fluoroscopic bed and a portable X-ray machine equipped with an image intensifier.

In the entire group of catheterization, five complications (6.3%) were noted. One episode of femoral phlebitis occurred among the 41 patients in whom a transfemoral catheter was inserted for less than twenty-four hours. Phlebitis occurred in the catheterized leg of this patient after inadvertent femoral artery puncture resulted in a significant hematoma.

In addition, four of 39 patients developed phlebitis when transfemoral pacing catheters were left in position from one to eleven days. Deep calf thromboembolism was evident in one patient three days after removal of a catheter which had been in position for nine days. Femoral thromboembolitis of the catheterized leg occurred in an additional three patients from temporary pacers which had been placed for three to four days. The complication was evident at the time of catheter removal in only one case and was not evident until 13 and 22 days following catheter removal in the remaining two patients (fig. 1).

Previous to our experience, only one case of iliofemoral phlebitis had been reported from transfemoral venous catheterizations of variable lengths of time in a total of 516 patients including the study of Meister et al. It is not known if these patients were followed closely after catheter removal. This rarely reported complication of transfemoral catheterization is of obvious importance because of its potential to result in life threatening pulmonary embolism. In fact, one patient among the 516 previously cited was noted to die from pulmonary embolization 38 days following transfemoral catheter insertion of eight day’s duration. The source of embolus, however, was believed to be from a septic phlebitis of an arm vein.

The low frequency of complications with transfemoral catheterization compares favorably with other transvenous routes for cardiac pacing. Thirteen of the 80 patients in our series had transvenous pacing catheters placed from an arm vein on previous hospital admissions. Four patients (31%) had significant phlebitis of the catheterized arm within two to five days. One of the patients had a right axillary vein thrombosis which was followed by a pulmonary embolism.

We do not believe that the potential to develop phlebitis should significantly detract from the clinical usefulness of the transfemoral approach. Catheters so positioned usually provide stable, continuously effective pacing. In addition, we agree with Meister and co-workers that the potential for phlebitis should be reduced by use of anticoagulants in patients having femoral venous catheterization for extended periods of time.

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Circulation, Volume XLIX, May 1974
Thrombosis and Endothelial Injury
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_Circulation_. 1974;49:1017-1018
doi: 10.1161/01.CIR.49.5.1017
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/49/5/1017.citation

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