CLINICAL CONFERENCE

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Symposium on Coronary Dilator Drugs

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DR. LLOYD HEFNER: This conference on coronary vasodilator drugs is best begun by presentation of a patient, a 59-year old white male semi-retired lumber dealer. He was first admitted to the University Hospital on September 28, 1955, complaining of chest pain. He had been entirely well until 3 months prior to admission, when after carrying a heavy suitcase about 25 yards, he noted an aching pain in the left side of the neck and a sensation of pressure in the substernal area. Movement of the arms, thorax, or neck had no influence on the pain. There was no associated feeling of dyspnea, faintness, weakness, palpitation, or belching. The pain disappeared within 2 min. after he sat down. Since that time, he has had numerous similar attacks varying only in severity and duration. The pains were precipitated usually by exertion or excitement and relieved by rest and by nitroglycerin. Two episodes of pain occurred at night, each following a nightmare. Two attacks of pain stood out as more severe than the rest. Each struck about 30 min. after the noon meal while at rest, and lasted about 20 min., requiring injections for relief. The first of these occurred 1 week after his first attack. At this time nitroglycerin tablets were prescribed and he was advised to restrict physical activity. The second episode appeared 2 weeks later. At this point, he was confined to bed for a period of 1 month, during which time he was free of chest pain. For the 1 month immediately preceding admission he had been up and about, but only to a very limited extent. In spite of the very mild activity that he permitted himself, he continued to have chest pain, averaging about 1 attack every 2 days. He had never experienced orthopnea, exertional dyspnea, palpitation, or peripheral edema.

The past and personal histories were noncontributory. His right arm was amputated 25 years ago after severe trauma. His mother and 1 brother died of "heart attacks" at the ages of 62 and 42, respectively, and 2 other brothers suffered from angina pectoris.

On admission, he appeared to be a pleasant, calm, intelligent man, who was able to lie comfortably flat in bed. He was not obese. The blood pressure was 130/88, temperature normal, pulse rate 80; respirations 18 per minute. There were no xanthelasmata, no sign of congestive heart failure, cardiac enlargement, murmurs, arrhythmia, or gallop rhythm. The apical impulse was not at all remarkable. There was a mild sclerotic change (grade 2) in the arterioles of the fundi. Except for the absence of the right arm, the remainder of physical examination was normal.

Laboratory studies were all within normal limits. These included glucose tolerance test, complete blood count, sedimentation rate, blood urea nitrogen, cholesterol, and roentgenogram of the chest. The electrocardiographic and kinetocardiographic findings will be presented later.

The patient had 2 attacks of chest pain while he was undergoing his initial examination but thereafter had chest pain only following exer-

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tion. For the first 2 days, exercise under supervision was performed. He was never allowed to continue exercise after pain developed. Thereafter, he walked for 10 min. every hour during the day limited only by the appearance of pain. Increasing exercise tolerance was noted on no additional therapy, so that eventually he was unable to induce angina by walking. He was then started on nitroglycerin ointment, in an initial dose of 1 inch applied to the chest every 4 hours during the day. This dose was gradually increased, until at the time of discharge he was applying 2½ inches of nitroglycerin ointment every 4 hours during the day. On this regimen, he had no further attacks of chest pain.

Are there any questions? Dr. Friedman, I will project a slide of the electrocardiographic findings before and after exercise. Would you discuss them and also the use of exercise tests.

DR. BEN FRIEDMAN: The only striking abnormality in the control record is the inversion of the T wave in lead V_4, and the somewhat flattened T wave in aV_L. Following exercise one notes depression of the S-T segment in lead V_4, accompanied by deepening of the S wave, a slight change in a downward direction of the slope of the S-T segment and inversion in the direction of the T wave. These changes have been regarded by many individuals as definitely positive and diagnostic of coronary insufficiency. The criteria for a positive exercise test vary according to the interpreter. No criteria devised thus far will pick up every patient with coronary disease and at the same time exclude all false positive reactions. As the requirements for a positive test are relaxed to be made more sensitive they become perforce less specific.

The major changes that develop in the electrocardiogram during an attack of angina pectoris, whether induced or spontaneous, consist in depressions in the S-T segment, flattening or inversion of the T wave, and, rarely, in the development of Q waves, various degrees of intraventricular block, and transient ventricular tachycardia. Recent studies have emphasized the significance of changes in the configuration of the S-T segment in a downward sloping direction. A negative exercise test does not exclude the diagnosis of coronary insufficiency.

The factors that produce the abnormal electric activity in the heart are not necessarily the same as those that cause the pain. One may develop independently of the other, and when they occur together very often the electric changes may appear 5 or 10 min. after conclusion of the exercise and subsidence of the pain. The degree of stress sufficient to produce angina pectoris varies enormously from patient to patient. Some subjects experience pain and develop electrocardiographic changes on walking a short distance on level ground. Others have discomfort only after climbing 6 flights of stairs half an hour after a meal, while carrying some ice cubes in each hand. To elicit a positive test it is often necessary to reproduce as far as possible those conditions that prevail at the time the individual has a spontaneous attack. The best end point is pain, unless the development of dyspnea or fatigue terminates the exercise.

Finally, the exercise tests carry some risk; they should not be performed as a diagnostic test if the diagnosis is apparent without them, as is the case in the patient presented here this morning. Fortunately, the diagnosis of angina can be made in the majority of cases by a painstaking history. In a few instances the pain may be bizarre, the history atypical, and there may be a confusing variety of pains from which it is difficult to pick out angina pectoris. In those situations the exercise tests are of inestimable value and, indeed, the diagnosis often cannot be made without them. The point I wish to emphasize is that exercise tests should supplement and not replace the more enlightening although more time-consuming methods, namely the history and physical examination.

DR. HEFNER: Thank you Dr. Friedman. Are there any questions or comments concerning the electrocardiogram in angina pectoris?

DR. T. JOSEPH REEVES: Dr. Friedman, will you comment on the effects of digitalis on the electrocardiogram?

DR. FRIEDMAN: Digitalis, even in normal individuals, followed by exercise, can produce changes that are identical to those observed during exercise in a patient with angina pectoris.

DR. HEFNER: Dr. Eddleman, will you begin the discussion of coronary vasodilator drugs?

DR. E. E. EDDLEMAN, JR.: The beneficial

effect of nitrites in the treatment of angina pectoris has been attributed to increased coronary blood flow, which has been shown to occur both in systole and in diastole. The pharmacologic action of the nitrites is more complex than just a dilator effect on the coronary vessels. It has been well recognized that nitrites do dilate veins and arterioles. The facial flush is probably due to dilation of the arterioles. In addition, relatively large arteries are dilated, as indicated by the temporal pounding that one often sees clinically.

Studies on changes in cardiac output produced by the nitrite drugs have given variable results. Some have reported an increase and others a decrease; the consensus is that the stroke volume diminishes but the minute volume of cardiac output is not appreciably altered as long as the patient is in the supine position. There is a fall in blood pressure in the upright posture and the cardiac output may similarly decrease in that position. There are other cardiovascular effects of the nitrites that are of interest.

1. The heart's size decreases, the stroke volume diminishes, the minute volume being maintained by the increase in the heart rate.

2. Pulmonary artery pressure increases and in some instances in the experimental animals, it has risen to levels comparable to systemic pressure. This is associated with blanching of the lungs. Therefore, the action of the nitrite on the pulmonary vessels produces constriction rather than dilatation.

3. The cardiac pulsations are increased after the nitrites. This is manifested by an overactive precordium that can easily be detected with the kinetocardiogram or slit kymogram.

In summary, even though there is more than 1 pharmacologic action of the nitrites, they are undoubtedly our most potent coronary dilators.

DR. HEFNER: Thank you, Dr. Eddleman. Are there any comments?

DR. S. RICHARDSON HILL: Would you comment, Dr. Eddleman, on the use of nitroglycerin in patients with myocardial infarction?

DR. EDDLEMAN: I think the question of the use of nitrites in the presence of myocardial infarction is still unsettled at the present time. The objection has been that a possible fall in blood pressure may lead to extension or to the occurrence of an additional myocardial infarction. Since in the supine position the blood pressure is not significantly affected by small doses, I think that there is some rationale for the use of nitroglycerin in patients with myocardial infarction; however, I do believe that they should be used with caution.

DR. HEFNER: Are there any further comments? Dr. Reeves, will you continue the discussion of the coronary vasodilator drugs and give us some of the clinical applications of these medicines.

DR. REEVES: As Dr. Eddleman has indicated, the most effective coronary vasodilator drug thus far found is nitroglycerin. This is a reflection of the balance between the effect of the vasodilator on cardiac work against its action on coronary flow. Aminophylline and papaverine in appropriate dosage may result in an absolute increase in coronary blood flow that may equal or actually exceed that induced by nitroglycerin. However, these drugs, particularly aminophylline, have a direct effect on the myocardium to increase cardiac output and to increase cardiac work. Consequently, the balance between work and coronary flow is altered in a less favorable way than is the case with nitroglycerin. As pain of angina pectoris itself is characteristically of very brief duration, it is at times very difficult to tell whether or not a particular agent has actually resulted in abbreviation of the duration of that episode. Of considerably greater importance in the clinical usage of the coronary vasodilator drugs is the prevention of pain, and in the enhancement of the exercise tolerance of a given individual with angina pectoris. The brief duration of action of nitroglycerin has led to agents possessing more prolonged effects. Various drugs have been used, including aminophylline, papaverine, the analogues of papaverine and the various long-acting or slowly absorbed nitrite or nitrate preparation. Dr. Russek and his co-workers studied the effect of various preparations on exercise tolerance, as measured by pain response and by prevention of the abnormal changes in the electrocardiogram. With this procedure they were unable to demonstrate a protective action for aminophylline[1] and for

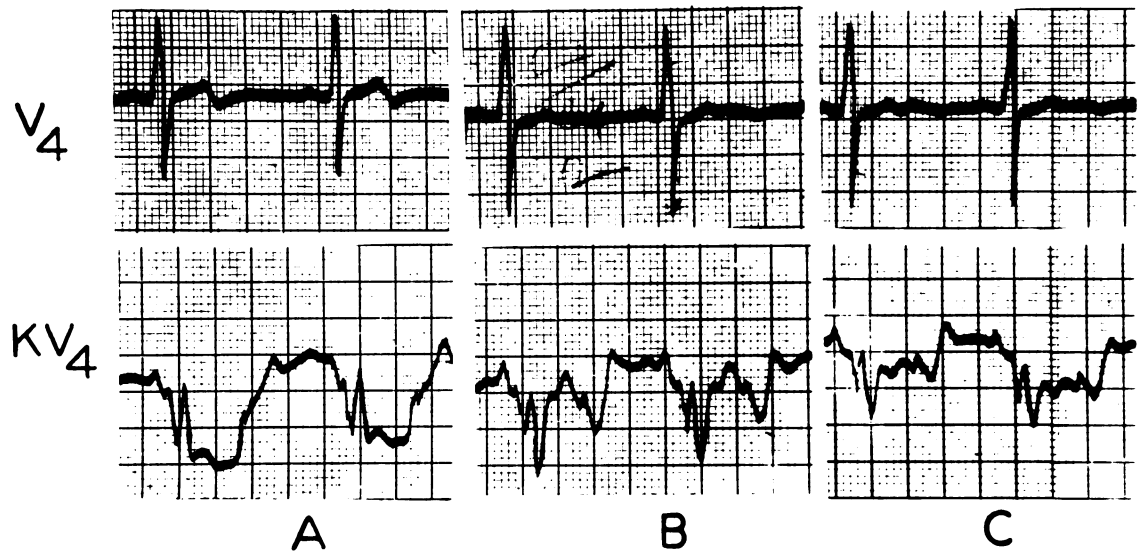

FIG. 1. Simultaneous electrocardiogram and kinetocardiogram at the apex. Tracing *A* is a resting control, showing the normal systolic retraction of the chest wall. Tracing *B* was obtained on the same patient a few minutes later, after he had exercised sufficient to produce slight anginal pain. Note the systolic bulge, most marked in late systole. Tracing *C* was made 30 min. after tracing *B*, during which time the patient had rested. The bulge has partially but not entirely disappeared.

papaverine in doses ordinarily employed. They did note a significant protective effect with pentaerythrol tetranitrate (Peritrate) administered with the stomach empty. This fact possibly explains some of the contradictory findings that have been reported. Other clinical studies in which this factor has not been completely controlled have indicated that Peritrate itself will not significantly reduce the incidence of pain in patients with angina pectoris. Nitroglyn, a preparation of nitroglycerin in sustained-release form, has been studied in a similar fashion by Dr. Russek and his group. They were unable to demonstrate any significant protection afforded by this drug, presumably due to failure of absorption at rapid enough rates. Papaverine, when given in adequate dosage may afford significant protection, but being on the narcotic list and rather expensive it has not been employed widely.

DR. BERRY: What is the duration of the protective action of sublingual nitroglycerin?

DR. REEVES: Objectively, as far as one can tell by protection afforded in exercise tolerance tests, utilizing the electrocardiogram, the duration of action does not extend beyond 30 to 45 min., the average being between 15 and 30 min. On the other hand, many patients are convinced that the duration of protection is between 2 and 3 hours.

DR. HEFNER: At this point it will be appropriate to discuss the kinetocardiographic tracings obtained on the patient presented earlier. The kinetocardiograph is an instrument that measures movements of the chest wall. Figure 1 shows a simultaneous electrocardiogram and kinetocardiogram. Tracing *A* was made while he was resting, and shows the normal systolic retraction of the chest wall beginning early in systole, and maintained throughout systole, and the outward motion occurring at the end of systole, with relaxation of the heart. Tracing *B* was obtained on the same patient a few minutes later, after he had performed a standardized exercise for 1 minute. There is the expected change in the electrocardiographic lead, which is V_4. There is a striking change in the kinetocardiographic tracing, which is also taken in the V_4 position, namely, an outward bulge of the precordium, most marked in late systole. This is an abnormal bulge and has not been found following exercise in normal subjects. Tracing *C* was made 30 min. after tracing *B*, during which time the patient had rested. It is

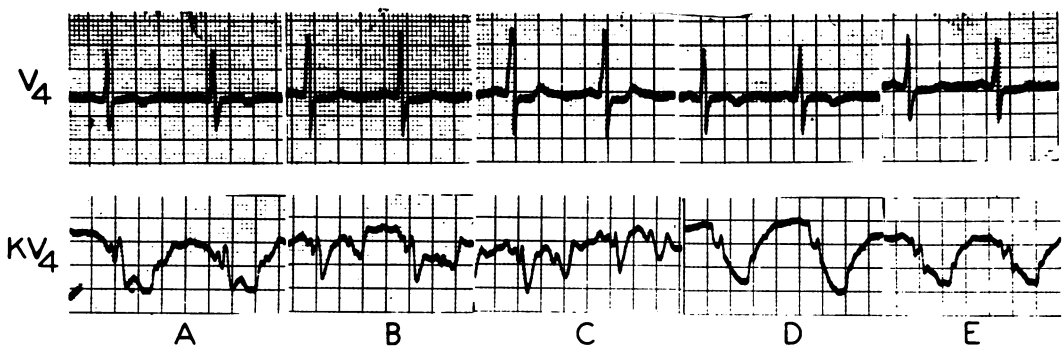

FIG. 2. Simultaneous electrocardiogram and kinetocardiogram at apex. Tracing *A* is a resting control. Tracing *B* was made after 1 minute of exercise. The patient had no pain but the systolic bulge has appeared. Tracing *C* was made a few minutes later; after 10 sec. additional exercise had produced anginal pain. The bulge is still obvious. Tracing *D* was made after 30 min. rest, and is again normal. Tracing *E* was made after the patient was given 1/100 gr. of nitroglycerin sublingually, following which he again performed the same exercise that produced both pain and a systolic bulge in tracings *B* and *C*. No pain and no bulge appeared.

obvious that the bulge has partially but not entirely disappeared.

Figure 2 again demonstrates a simultaneous electrocardiogram and kinetocardiogram at the V_4 position. This figure is designed to show the effects of oral nitroglycerin. Tracing *A* was made as a control with the patient at rest, and again one sees the normal retraction of the V_4 precordium throughout systole. Tracing *B* was made immediately after 1 minute of the standard exercise, and again the systolic bulge appeared. At this time the patient had no pain, but 3 min. later, after about 10 sec. of additional exercise, he developed typical anginal pain and the bulge was still obvious. Tracing *D* was made after the patient had rested about 30 min. and again shows a normal tracing in the kinetocardiogram in the V_4 position. Tracing *E* was made after the subject was given 1/100 gr. of nitroglycerin sublingually, following which he again performed the same exercise that produced both the pain and the systolic bulge in tracing *C*. As you can see, after premedication with sublingual nitroglycerin, he had no pain and the systolic bulge did not develop.

Figure 3 is designed to demonstrate the effectiveness as well as the duration of action of nitroglycerin ointment. Tracing *A* is the control tracing with the patient at rest. Tracing *B* was made after 1 min. of standard exercise. A tremendous systolic bulge is obvious in the kinetocardiogram. The patient, however, experienced no anginal pain at this time. The patient was then given an application of 2 inches of nitroglycerin ointment to the chest, and at intervals over the succeeding 3½ hours other tracings were made, each immediately after the same standard exercise. Tracing *C* was recorded one half hour after the application of the nitroglycerin ointment. There was no pain but, as you can see, the systolic bulge was still present, although with not as great amplitude as in tracing *B*. Tracing *D* was made 1 hour following the application of the nitroglycerin ointment. One can hardly say there was a bulge but there was certainly failure of systolic retraction as compared to the normal tracing *A*. Tracing *E* was taken at 2 hours. There was no pain and no systolic bulge was demonstrated. Tracing *F* was made 2½ hours after the application of the nitrol. Again, the tracings were normal and the patient had no pain. Tracing *G* recorded at 3 hours showed again no bulge and the patient had no pain. Tracing *H* was made at 3½ hours after the application of the nitrol ointment. At this time the patient had mild anginal pain. The reappearance of the bulge is apparent.

Are there any questions?

Dr. Harrison, will you conclude the discussion, and please discuss these tracings, too?

DR. TINSLEY R. HARRISON: There is 1 point that should be emphasized. This man had been taking practically no physical exercise. He had

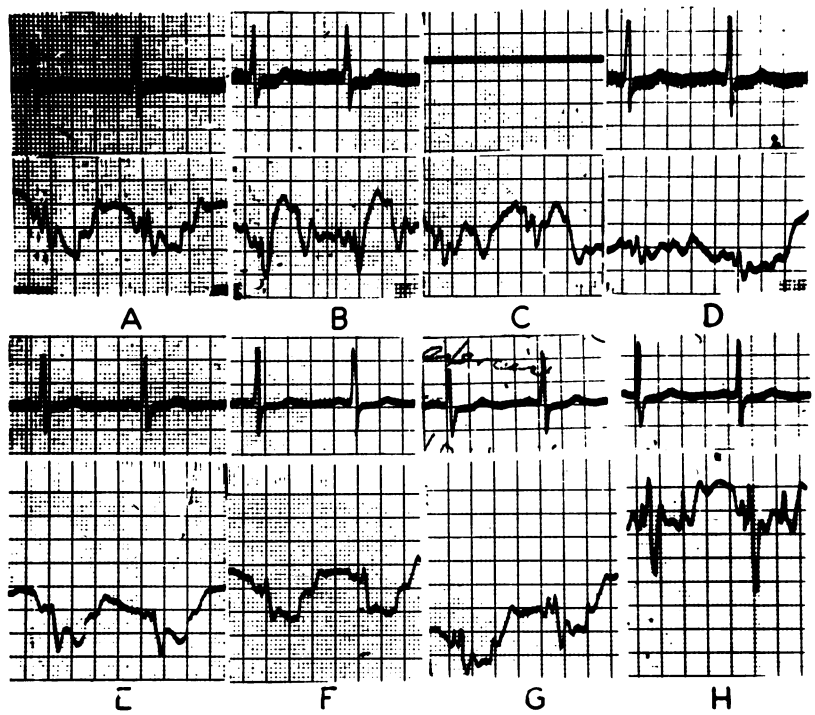

FIG. 3. Simultaneous electrocardiogram and kinetocardiogram at the apex. Tracing *A* is the resting control. Tracing *B* was made after 1 minute of a standardized exercise. A tremendous systolic bulge is present, but the patient had no pain. The patient was then given an application of 2 inches of 2 per cent nitroglycerin ointment to the chest, and the succeeding tracings were made at intervals thereafter, each immediately after the same standardized exercise. Tracing *C* was recorded ½ hour after the application of the ointment. The exercise produced no pain but the bulge is still present, though less marked. Tracing *D* was made 1 hour after the ointment. The presence of a bulge is questionable. Tracing *E*, 2 hours after the ointment, demonstrates no bulge, and the patient had no pain. Tracing *F*, 2½ hours and *G* 3 hours after the ointment, reveal normal tracings, and the patient had no pain. Tracing *H* at 3½ hours after the ointment shows that the bulge is beginning to reappear. The patient had mild anginal pain at this time.

been having pain at home and during the past few days in the hospital, on very slight effort—walking a couple of hundred feet or less. On no therapy other than being encouraged to walk every hour, the severity and frequency of pain diminished sharply, and the amount of exercise required to induce it increased markedly. This is analogous to the individual who has his pain on the first hole of the golf course, and plays the remaining 18 holes with no further discomfort. The evidence that mild physical exercise, not sufficient to induce pain, is not harmful but is positively beneficial, is in my opinion becoming stronger each year. If a patient repeatedly undertakes subthreshold exercise, it is not long before the amount of exercise required to induce the pain is increased. This is not true in every patient, but it is true in a large percentage of them. I have been interested in coronary dilator drugs for about 30 years, and all of them, in my experience, have been disappointing except the nitrites. The long-acting nitrites such as erythrol tetranitrite, pentaerythrol tetranitrate (Peritrate), have occasionally seemed to have a striking effect, but much more commonly the results have been disappointing.

Some years ago, having read a paper in one of the Scandinavian journals describing the use of nitroglycerin ointment locally for intermittent claudication, we tried it on a patient who happened to have both intermittent claudication and angina pectoris. Before medication, this patient developed leg pain and chest pain about the same time, with walking. Rather to our surprise, after application of nitrol ointment the patient had no improvement in the leg pain on walking, but his chest pain disap-

peared. This was the beginning of my interest in the use of this ointment. We have now tried it in more than 20 patients, who have been well controlled, and in most of them one could demonstrate benefit. Thus, during a period beginning about 30 to 60 min. after application of the ointment and extending up to 2 to 4 hours the amount of effort required to induce chest pain has usually been definitely increased. Of the various long-acting nitrites, this is the only one that in my experience has been effective in a large percentage of patients.

More than 20 years ago Wiggers and Tennant showed that when one ligated a coronary artery of a dog, within a matter of a few beats there was a bulge in the ischemic area,[2] which, of course, is due to failure of contraction of that part. It has long been known that people who have had a myocardial infarction may show a ventricular aneurysm at autopsy, and under certain circumstances a ventricular aneurysm may be detected during life. Dr. Myron Prinzmetal pointed out to me, when he was here last year, that in the studies he and his colleagues had made on the dog's heart they could find 2 different types of bulges, which he called the "late systolic bulge" and the "early systolic bulge." In his dogs it appears that moderate degrees of ischemia tended to cause the late systolic bulge. Our experience in human subjects has been similar. We have had a number of other patients who exhibited a precordial bulge during anginal attacks. This is by no means true in every patient with angina pectoris. We assume that if the bulge is downward or posterior we cannot detect it at present but if it happens to involve the septal region or the apex, we often detect it. From a physiologic standpoint, the demonstration that a person may have a temporary ventricular aneurysm, if you want to call it that, is of interest. Most of the people with anginal attacks who have shown a bulge have shown it during the early part of ejection, i.e., the bulge starts in midsystole. Individuals who have had ventricular aneurysms after myocardial infarctions have shown the bulge very early in systole, beginning within .02 to .04 sec. after the onset of the ventricular complex in the electrocardiogram. In other words, if all the muscle is destroyed, the slightest rise in pressure in the ventricle produces this bulge. If the muscle is still living but nevertheless is ischemic a greater rise in intraventricular pressure is required to produce the bulge. At times it has been possible to localize the infarct by simple palpation. Studies such as this one seem to indicate that under certain conditions the nitrite group of drugs helps not only the pain but also the physiologic mechanism of the disease. I do not see how one can escape such a conclusion when one sees evidence such as Dr. Hefner has presented.

That brings us to the question of the role of nitrites in the treatment of coronary artery disease. I may say in answer to Dr. Hill's question about the use of nitroglycerin in myocardial infarction, that I do not believe anyone really knows. We have very cautiously given it to a large number of patients, and all I can say with certainty is that we have never seen harm from it. The initial dose has usually been 1/400 gr. every 2 hours. The blood pressure is observed carefully and if a significant decline occurs, which is rare so long as the patient remains recumbent, dosage is decreased. Otherwise, dosage is gradually increased to about 1/200 gr. every hour. In a few instances favorable electrocardiographic changes have been demonstrated. In the majority of cases there has been no obvious objective change, and we cannot say with certainty that the patient was benefited. We can say, I think, that no patient has been hurt.

Insofar as the use of nitroglycerin in angina pectoris is concerned, we have a different situation. I think there is no question whatever about the benefit of the combination of subthreshold exercise, plus repeated use of coronary vasodilator drugs—nitroglycerin for quick effect, and the nitrol ointment for a prolonged effect. We have enough objective data to indicate that this is a method of treatment that helps the disease as well as the symptoms.

REFERENCES

[1] Russek, H. I., Zohman, B. L., Drumm, A. E., Weingarten, W., and Dorset, V. J.: Long-acting coronary vasodilator drugs: Metamine, Paveril, Nitroglyn and Peritrate. Circulation **12**:169, 1955.

[2] Tennant, R., and Wiggins, J.: Effect of coronary occlusion on myocardial contraction. Am. J. Physiol. **112**: 351, 1955.