An important advantage of a standard administration scheme of S.K. is that the laboratory control is greatly simplified and is not even essential. This burden of control, and the lack of good assay systems, have in the past been major problems in fibrinolytic therapy. The required facilities for plasminogen determinations and other assays are not necessarily present in smaller hospitals and the accuracy of laboratory assessments only occasionally performed may be questioned.

Using intense and prolonged S.K. administration, properly conducted according to the criteria mentioned above, pulsative blood flow was restored in 12 of the 15 treated cases. In nine cases where the pulsative flow was restored, arteriographic series were taken before and after the S.K. administration. In all of them clearing of the main artery was found.

It was hoped that rapid restoration of blood-flow would prevent irreversible tissue necrosis. However, in some cases, though pulsative blood flow was restored, amputation of at least some part of the involved extremity was necessary. Therefore any modification of S.K. treatment which restores the blood-flow more rapidly could be of crucial importance. This might be a further reason for presenting a standard administration scheme for S.K., rather than a scheme varying according to the patient, where the necessary laboratory controls would delay the start of S.K. administration.

We are aware that this new administration scheme may result in very widespread use of this material in hospitals. At present, however, only a high incidence of thrombolysis *in vivo* by streptokinase administration has been proved. Comparative studies of the mortality rate, limb amputation rate, and the incidence of recurrence with S.K. therapy and other forms of treatment of recent peripheral arterial occlusions are not available at this time. This information should be available before the widespread use of S.K. can be justified.

Summary

The feasibility and efficiency of a standard administration scheme have been explored, using experience gained from previous experiments and clinical trials with streptokinase (S.K.) as a thrombolytic agent in man. With a set initial dose of 1,250,000 U. S.K. administered intra-arterially or intravenously in less than 30 minutes and a maintenance dose of 100,000 U. S.K./hour for three days, restoration of arterial blood-flow was obtained in 12 of 15 arterial occlusions.

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Exercise Performance and Electrocardiographic Changes as Indices of Effect of Long-acting Nitrates in Angina Pectoris

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Evaluations of anti-anginal drugs are usually based on electrocardiographic changes observed after a standard exercise test. Since there is little correlation between angina and electrocardiographic evidence of myocardial ischaemia (Katz, 1935 ; Russek *et al.*, 1955), the conclusion is often drawn that anginal pain is a poor criterion of the effect of a drug in improving myocardial ischaemia (Russek, 1955 ; Sandler *et al.*, 1963). This is obviously true for drugs acting on pathways of pain transmission. Alcohol, sedatives, tranquilizers, and monoamine oxidase inhibitors may favourably influence angina without electrocardiographic improvement (Russek *et al.*, 1950, 1955). On the other hand, the validity of the electrocardiographic method in identifying effective agents, such as glyceryl trinitrate, is based on the observation that such drugs increase the exercise tolerance (Sandler *et al.*, 1963, Russek and Howard, 1964). Angina and electrocardiographic changes may both reflect ischaemia in a minute area of the myocardium. The choice of method for evaluating less potent long-acting nitrates depends, therefore, on which method is most sensitive and

reproducible when applied to a population with angina pectoris.

Most patients with coronary insufficiency believe that they are able to state quite exactly the onset of pain, and often develop pain in their daily life after the same amount of exercise. Whether this reflects coronary insufficiency at identical work loads or is due rather to a psychological reaction to the situation when pain is known to occur has not been settled. By using a Master two-step technique (Sandler *et al.*, 1963) the patients may count the number of circuits accomplished. In the present study exercise was therefore performed on a bicycle ergometer. The ordinary controlled double-blind technique was modified in so far that the patients were told that the drugs had different potency and were likely to delay the onset of pain differently. This was done in order to minimize the placebo effect. The order of administration was of course kept secret. On three consecutive days one hour before exercise a placebo tablet or one of two long-acting nitrates (pentaerythritol tetranitrate and methylpropylpropandiolinitrate) was administered according to a permutation scheme (Kiil, 1960). Methylpropylpropandiolinitrate is synthesized by Apotekernes Laboratorium for Specialpraeparater, Oslo, and marketed as Nitral.

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Method and Material

Twenty-four patients with precordial pain that radiated to one or both arms under strenuous activity were selected for this study. All had had a stable weekly consumption of glyceryl trinitrate for several months before the study. Two patients were excluded because of lack of co-operation and four others became heavily dyspnoeic during the exercise test. The study group was therefore composed of 18 patients—16 men and two women aged 46 to 66 years (average age 55 years). Angina pectoris had been present for one to eight years (average 3.5 years). Six patients had been hospitalized seven to 16 months previously because of well-authenticated myocardial infarction, and five of these showed electrocardiographic changes of an old infarction. The resting electrocardiogram was normal in seven of the 12 patients constituting the angina pectoris group without previous infarction. None of the patients included in this study had overt signs of heart insufficiency and they all tolerated the exercise tests without becoming severely dyspnoeic.

The exercise studies were performed in the morning on three consecutive days three to four hours after the previous meal. Tablets containing 8 mg. methylpropylpropandioldinitrate, 30 mg. pentaerythritol tetranitrate, or a placebo tablet were swallowed 60 minutes before exercise, so that the drugs were given in all permutations to the six patients with previous myocardial infarction. This scheme was also followed for the 12 patients in the angina pectoris group without previous myocardial infarction. The drugs were called A, B, C and their identity was not revealed to the leader of the exercise tests (A. M. A.) until the results for all patients were collected. All exercise tests were performed on an Elema bicycle ergometer and none of the patients had any difficulty in keeping the frequency of pedalling constant. A work load of 300–800 kpm./min. was chosen after a preliminary trial and kept constant for each patient throughout the study. Exercise time was measured with a stop-watch until the patient reported initial anginal pain, and the exercise was then stopped. Before and immediately after each test 12-lead electrocardiograms were obtained.

Results

Electrocardiographic changes when precordial pain was present were most consistent in chest leads, especially V₄ and V₅ (see Table). STV₅ changes measured to the nearest half-millimeter are shown in the last column of the Table. Only two of the six patients with previous infarction developed ST-

changes. The single patient who developed ST-changes after all tests was the only one belonging to this group with a normal resting electrocardiogram. Five of the 12 patients without previous infarction showed ST-changes. The magnitude of the ST-depressions did not vary significantly with treatment. T-inversions occurred in three patients without previous infarction equally under all medications.

The exercise time was not significantly shorter in patients with previous infarction and there was also no difference in response to treatment between patients with or without previous infarction. Both groups are therefore treated as one in the following discussion. The exercise time did not vary significantly throughout the study.

Using Student's t-test for individual differences, the exercise times after treatment with pentaerythritol tetranitrate and placebo were not altered. Comparison of these responses obtained one or two days apart showed a correlation coefficient of 0.84. The relationship between the responses is apparent from Fig. 1.

FIG. 1.—Plot of exercise time until onset of pain after treatment with 30 mg. pentaerythritol tetranitrate (P.E.T.N.) and placebo. Solid line: line of equal response.

FIG. 2.—Plot of exercise time until onset of pain after treatment with 8 mg. methylpropylpropandioldinitrate (M.P.D.N.) and placebo. Solid line: line of equal response. Stippled line: regression line.

A slightly higher correlation (0.91) was obtained when the exercise times after the administration of methylpropylpropandioldinitrate and placebo were compared. In Fig. 2 the stippled line is fitted by the method of least squares. It runs parallel ($b=0.97$) to the solid line of equal response. The exercise time was on average 21.8 seconds longer after treatment with methylpropylpropandioldinitrate. This difference was found to be significant ($P<0.02$) and corresponds to an increase in exercise time of 18%.

Sequence of Administration of Drugs, Work Performances, and ST-changes									
Diagnosis	Sex	Order of Treatment*	Work Load (kpm./min.)	Exercise Time (sec.)			STV ₅ Changes (mm.)		
				Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Angina pectoris with previous infarction	M	ABC	300	103	115	149	0	0	0
" "	M	BCA	500	185	213	165	2	2	1.5
" "	M	CAB	300	33	32	29	0	0	0
" "	F	ACB	300	46	48	32	1	0	0
" "	F	BAC	300	138	142	135	0	0	0
" "	M	CBA	300	127	74	94	0	0	0
Angina pectoris	M	ABC	500	199	239	292	0.5	2	2
" "	M	BCA	300	250	338	282	0	0	0
" "	M	CAB	500	128	81	67	1	1	1
" "	M	ACB	300	44	62	43	0	0	0
" "	M	BAC	300	307	238	269	0	0	0
" "	M	CBA	500	57	90	103	0	0	0
" "	M	ABC	500	79	110	132	0.5	1	1
" "	M	BCA	500	108	113	132	1	0.5	0
" "	M	CAB	300	150	123	113	0	0	0
" "	M	ACB	800	88	86	91	0	0	0
" "	M	BAC	300	31	60	101	0	0	0
" "	M	CAB	300	132	150	104	1	1	1
Means of daily exercise times:				122.5	128.4	129.6			
Means of exercise time after medications A, B, C:				117.5	120.7	142.5			

* Treatments: A = 30 mg. pentaerythritol tetranitrate one hour before exercise; B = placebo tablet one hour before exercise; C = 8 mg. methylpropylpropandioldinitrate one hour before exercise.

Since the figures might suggest that the material is not normally distributed, Wilcoxon's non-parametric ranking test was also used, and confirmed that the exercise time was significantly longer after the administration of methylpropylpropandioldinitrate than after placebo ($P < 0.05$). This was also found when the response after methylpropylpropandioldinitrate was compared with individual mean responses of the two other drugs.

Discussion

ST-changes are recorded in 50–60% of patients with a definite history of angina pectoris and with normal resting electrocardiograms after a standard exercise test (Davis *et al.*, 1953; Gazes *et al.*, 1964). In the present study, where all post-exercise recordings were obtained during precordial pain, STV_s changes occurred in seven out of 18 patients, whereas nine patients showed ST-changes when all leads were taken into account. Though ST-changes were observed in only two of six patients with previous myocardial infarction, it might be argued that patients with precordial pain without electrocardiographic changes did not suffer from coronary insufficiency. Exclusion of these patients does not, however, render the effect of methylpropylpropandioldinitrate and pentaerythritolpropandioldinitrate more favourable.

The electrocardiographic response varied with treatment in five patients, and in four of these the smallest ST-changes occurred after pentaerythritol-propandioldinitrate (see Table). Selection of these patients for further study might well confirm that pentaerythritol-propandioldinitrate has a beneficial influence on ST-changes, as previously found by Russek and Funk (1962). However, the criterion of benefit should be relief of anginal pain and not decrease in degree of electrocardiographic abnormality or the extent of coronary dilatation. We found no relationship between exercise time and electrocardiographic changes, and it is doubtful if ST-changes reflect myocardial blood supply either absolute or relative to metabolic demand:

1. The characteristics of the input capacitors of the clinical electrocardiographs prevent a discrimination between ST-segment shifts and base-line shifts. The latter may occur, for instance, during tachycardias and make the interpretation "extremely complicated" (Schaefer and Haas, 1962).

2. Severe acute disturbances of myocardial blood flow and electrical activity in dogs may be induced without changes of the epicardial electrocardiogram (Sayen *et al.*, 1961).

3. The large variability between local myocardial flow, measured by hydrogen polarography (Aukland *et al.*, 1964), and ST-changes would invalidate any attempts to quantitate ischaemia even by intramyocardial recordings (Aukland, unpublished studies).

Though anginal pain is considered unreliable as a quantitative measure of coronary insufficiency (Russek, 1955), detailed studies have been lacking. Sandler *et al.* (1963) used a Master two-step test and found that their patients with and without placebo treatment accomplished on average 44.7 and 43.9 circuits respectively until pain or dyspnoea prevented further exercise. From their data we calculated a correlation coefficient of 0.89, which corresponds well with those obtained in the present study (0.91–0.83) by comparing the performances on different days.

In a bicycle ergometer test, where the work load is adjustable so that pain develops suddenly after a few minutes' exercise,

initial pain should be the end point. One should not depend on the decision of the patient when to stop exerting himself, since this is likely to reduce the sensitivity of the test and increase the hazard. Patients with severe dyspnoea should be excluded, since onset of dyspnoea is gradual and reflects myocardial insufficiency only in a very indirect way.

Mathisen and Holen (1962) showed in a long-term study that methylpropylpropandioldinitrate had a better glyceryl trinitrate sparing effect than placebo, whereas recent studies have shown that pentaerythritol tetranitrate is without effect (Oram and Sowton, 1961; Cole *et al.*, 1963). The effect of long-acting nitro-esters must be considerable compared with glyceryl trinitrate in order further to reduce a low and regular consumption of glyceryl trinitrate. Sandler *et al.* (1963) found that 1 mg. glyceryl trinitrate administered sublingually immediately before a Master two-step test increased the number of circuits accomplished from 43.9 to 63.7 (mean response of 15 patients). This corresponds to an increase in work performance of 45%, whereas 8 mg. methylpropylpropandioldinitrate in the present study increased the work performance by 18%. Though these studies are not strictly comparable, they suggest that methylpropylpropandioldinitrate has an effect which is definitely lower than that of glyceryl trinitrate, but that methylpropylpropandioldinitrate is a useful adjunct in the treatment of angina pectoris.

Summary

Eighteen patients with typical angina pectoris with or without electrocardiographic abnormality performed exercise on a bicycle ergometer after receiving long-acting nitrates (pentaerythritol tetranitrate and methylpropylpropandioldinitrate) or placebo tablets according to a permutation scheme. Exercise time until onset of pain was found to be highly reproducible and the technique sensitive enough to measure an increase in exercise time of 18% after methylpropylpropandioldinitrate, whereas pentaerythritol tetranitrate had no significant effect. Nine of the 18 patients, including four of six with previous myocardial infarction, did not develop ST-changes and there was no relationship between degree of ST-changes and exercise time. This study suggests that exercise time is a better criterion than electrocardiographic changes in the quantitative evaluation of anti-anginal drugs.

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