MEDICAL GRAND ROUNDS

NITROGLYCERIN EXPLOSIONS, TOLERANCE, AND MYTHS

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Nitroglycerin and other nitrates have been the subject of controversy ever since their discovery. Most physicians have very strong opinions concerning nitrates and their effectiveness, but these opinions are as many times based on myths as on realities. Every aspect of nitroglycerin has been controversial, even its history.

Nitroglycerin was synthesized by an Italian in 1846 or 1847. Adam Schneeweiss says it was Sabrero in 1846.[1] R. Berlin stated that it was Sombrero in 1847.[2] Bruce Fye stated that it was Sobrero in 1846.[3] U. Thadani said it was Sobrers in 1846.[31] Using consensus standards techniques, three of four sources said the second letter of his name was "o" not "a", three of four sources did not have an "m" in his name, and three of four sources said his name ended in "o" not "s", and three of four sources said 1846; therefore, it was apparently Sobrero in 1846. In 1859 Guthrie discovered amyl nitrite. And, according to Berlin, Guthrie used it in the treatment of angina pectoris. However, no other reference was found to Guthrie using amyl nitrite in angina pectoris.[2] According to Berlin, Brunton wrote the first comprehensive report in 1869;[2] however, it was actually in 1867 in Lancet.[4,5] Brunton later wrote a textbook recounting the studies and reports.[6] William Murrell reported the drug's use in normal subjects and patients with angina pectoris in 1867 in a serialized set of articles; Murrell described one patient with severe angina pectoris who returned to an almost normal life style after being treated with cod liver oil and nitroglycerin.[7] This is the traditional history that is written in most textbooks. However, there is another version.

Anyone interested in a more complete history should read the excellent review by Bruce Fye; a brief summary of the article follows.[3] To understand the confusion in the history of nitroglycerin, it is important to understand that in the 1800's there were three major schools of thought -- the allopathic, the homeopathic, and the osteopathic. Constantin Hering was trained at the Universities of Leipzig and Wurzburg and received a regular medical degree (allopathic) in 1826. While preparing a treatise refuting homeopathy, he read the works of Samuel Hahnemann and converted to the homeopathic school and emigrated to Philadelphia to work with Hahnemann. Hahnemann had declared in 1798 that "Nothing remains for us but experiment on the human body";[3,8] it was the belief of the homeopathic school that drugs should be proved. To be proved, a drug should be taken by the physician and his colleagues and family. Once proved then believing in simile, it should be given to patients with similar conditions. Hering described the development of headaches and palpitations when administering nitroglycerin (which they called glonoine); thus, it was used to treat headaches and palpitations.[3,4] When reports of glonoine appeared in an allopathic journal in 1849, Hering is said to have gloated about regular physicians using glonoine. Hering provided William Jackson, a student at Jefferson Medical College (allopathic), with glonoine; Jackson used the drug on both himself and on animals and reported the heart rate and pressure effects of the drug. Hering did report the side effects of tightness of the chest and pressure in the chest; though, despite simile, there is no report in the homeopathic literature about its use in angina. It is interesting to note that most homeopathic physicians felt that angina was extremely rare and most physicians would not see it more than once in a lifetime. Hering wrote a major work on glonoine in 1851 in a German homeopathic publication. In 1858 Alfred Field, an allopath, described the

effects of sublingual nitroglycerin. Field also described the relief of severe epigastric pain which extended to the top of the chest in a 68-year-old women; he attributed this to an antispasmotic action of the drug. Many physicians and investigators used the drug for various purposes and experiments over the next twenty years. Sydney Ringer, the noted pharmacologist, brought a number of homeopathic agents from the homeopathic pharmacopeia into allopathic medicine. One of Ringer's students was Murrell. Thus, the history of exactly how nitroglycerin was developed is a little murky.

The debate over nitroglycerin has continued over the decades. A noted address in 1905 by H. P. Loomis stated about nitroglycerin that "It is difficult to explain why certain drugs have come into such general use unless it is a question of fashion as in other things, nor are we right in assuming that their popularity assures their value, much less their permanency. The study of the physiological action of drugs, first upon animals and then upon man, furnishes of course the only scientific and reliable method we have, of predicting future usefulness in the treatment of disease; still it is before the result of clinical experience alone that a drug must take or lose its place in the world's pharmacopeia."[3,9] Hence, the feelings and controversies about nitroglycerin are not new.

MECHANISMS OF ACTION

Cellular Mechanisms

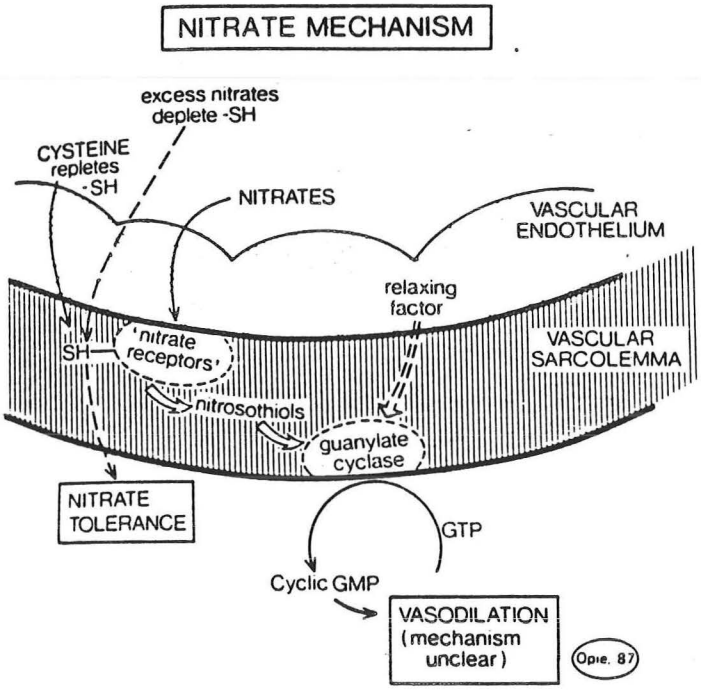

Figure 1. Hypothesis of mechanism of action of nitrates. Nitrates pass through the vascular endothelium and enter the nitrate receptor in the vascular sarcolemma. The nitrates form nitric acid. The nitric acid interacts with the sulfhydryl groups to form nitrosothiols and depletes the sulfhydryl groups. The nitrosothiols stimulate guanylate cyclase to convert GTP to cyclic GMP causing vasodilation by some mechanism.[10]

Brunton noted that amyl nitrite dropped arterial pressure, and Murrell noted that nitroglycerin had similar properties when he compared the drugs in the same normal individuals.[5,7] Thus the vasodilator properties were noted from the very beginning. The mechanism by which this vasodilation occurs has been debated over the years. Most authorities believe that there is a specific nitrate receptor that contains sulfhydryl groups. This receptor then stimulates the production of cyclic guanosine monophosphate (cGMP). Cyclic GMP then causes relaxation of vascular smooth muscle.[1,4,10-18]

It is believed that nitrates pass through the endothelium. The endothelium does not have to be intact as with other vasodilators, but it still has an effect in disrupted cells. The hypothesis is that there are nitrate receptors; though these receptors have not been isolated and identified. These receptors appear to be within the sarcolemma. Nitrates may then be converted into nitric acid. The nitric acid may then interact with the sulfhydryl groups to form nitrosothiols. By forming nitrosothiols the sulfhydryls are depleted. The sulfhydryls may be repleted by cysteine. The nitrosothiols then may activate guanylate cyclase to convert GTP to cyclic GMP, and the cyclic GMP then can cause vasodilation by some mechanism that is not defined. The cyclic GMP could be exerting its influence by decreasing calcium entry into the muscle, increasing calcium entry into the sarcoplasmic reticulum, or by interfering with the actin-myosin interaction. This whole process has not been proven.[1,4,10-18]

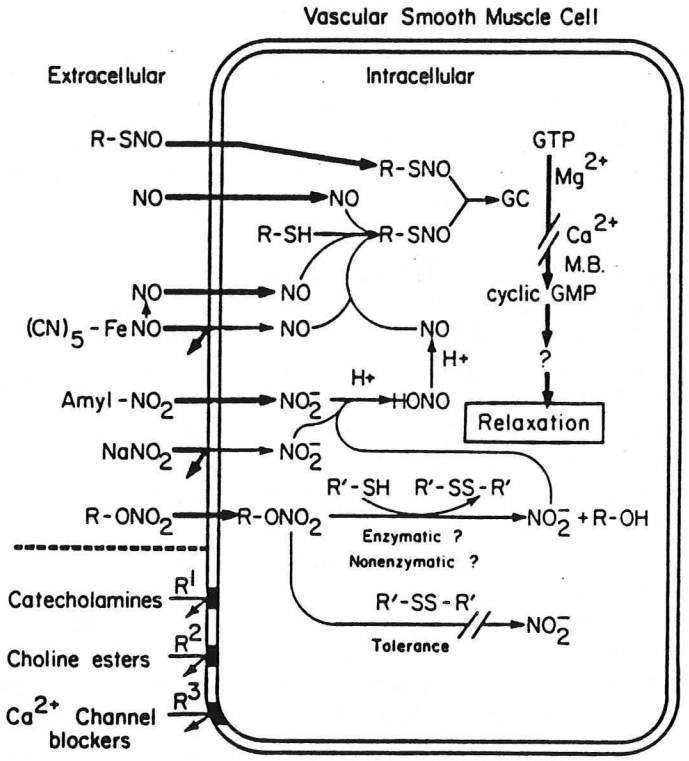

Figure 2. Schematic diagram of proposed mechanisms by which nitrogen oxide-containing vasodilators relax vascular smooth muscle. Abbreviations: R-SNO, S-nitrosothiol; NO, nitric oxide; HONO, nitrous acid; $(CN)_5$-FeNO, nitroprusside; R-ONO_2, organic nitrate; R-OH denitrated organic nitrate; R-SH low or high molecular weight thiol; R'-SH, thiol that is distinct from R-SH; GC, guanylate cyclase; M.B., methylene blue; R^1, R^2, R^3, extracellular specific receptors.[13]

Ignarro and co-workers[13] have postulated a mechanism by which all of the various forms of nitrogen oxide containing vasodilators might work (Figure 2). Organic nitrates and nitroglycerin react with thiols to free the nitrite radical, which then combines with H^+ to form nitrous acid. Nitrous acid reacts with H^+ to form nitric acid, which then breaks into water and nitric oxide. Nitric oxide then can react with a different thiol to form nitrosothiols, which stimulate guanylate cyclase. Amyl nitrite and sodium nitrite can enter the cascade by freeing the nitrite radical. Nitroprusside can just give rise to free nitric oxide.[13]

However, these are not the only theories of how nitrates might be working. There are interactions between nitrates and prostaglandins; nitrates appear to stimulate the synthesis of vasodilating prostaglandins. The prostaglandins may stimulate cyclic AMP.[4,16,19-22] The anti-platelet effects of nitroglycerin and other nitrates appears to inhibit release of thromboxane A_2 and cause release of prostacyclin.[21-25] Other proposed mechanisms have included inhibition of ATPase activity in arteries,[26] uncoupling of oxidative phosphorylation,[27] hyperpolarization of the smooth muscle cell,[28] and interactions with specific nitrate receptors.[29,30] The most likely mechanisms appear to be the presence of receptors that then allow stimulation of cyclic GMP and the antiplatelet activities causing alterations in thromboxane A_2 and prostacyclin. Both of the mechanisms could be playing a role and might be an explanation for the contradictory results seen clinically. This possibility will be discussed later.

Hemodynamic Mechanisms

The vasodilator properties of nitroglycerin were noted early. Jackson and Hering may have noted the changes; however, Brunton first described the drop in arterial pressure with amyl nitrite.[5] Murrell did comparative tracings on the pulse between amyl nitrite and nitroglycerin and showed that they had similar effects.[7] The vasodilator characteristics have been well defined in isolated vessel strips as well as intact animals and man. The dominant site of action in intact animals and in normal human subjects has been venodilation. There is also dilation of arterioles and large arteries. However, the major effect is venodilation causing a reduction in preload. The reduction in preload shrinks chamber size so that end diastolic and end systolic volumes decrease, thereby reducing myocardial work. The arteriolar dilation also reduces afterload, which also reduces myocardial work; but in normals the preload change is the more important change.[1,4,31-33]

The reason for a greater venous than arterial effect appears to be twofold. There appears to be a difference in responsiveness of arteries and veins in isolated preparations or strips of vessels. The veins dilate at very low doses of organic nitrates and do not dilate further at increasing doses (Figure 3). Conductance arteries seem to dilate in a linear relationship to dose starting at very low doses. Resistance arterioles do not dilate until higher doses of organic nitrates are obtained. This difference in responsiveness has been demonstrated in a number of studies. In intact vessels there are neurohumoral changes that tend to counteract the effects of vasodilators. Due to the vasodilation, there is reflex sympathetic stimulation that increases contractility and heart rate. These reflex sympathetic changes tend to minimize the fall in cardiac output that would normally occur with decreased preload, though it is somewhat variable. These

neurohumoral changes appear to affect arteries more than veins. However, these can not explain all of the differences. For example, why are organic nitrates more of venous dilators, while nitroprusside--which is believed to act by the same pathways as organic nitrates--more of an arterial vasodilator?[1,4,31-35]

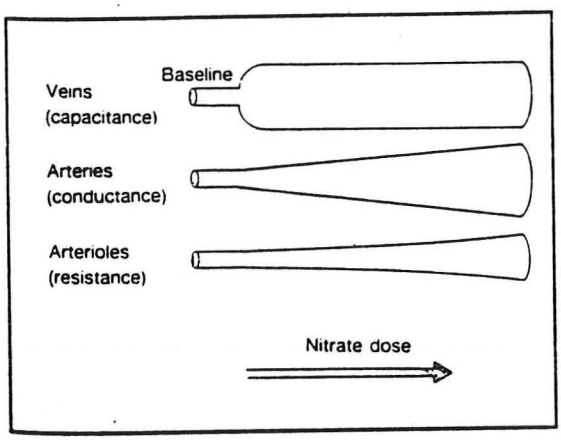

Figure 3. Effects of nitrates on the peripheral circulation. With low doses of glyceryl trinitrate, venodilation is maximal; further increases in nitrate plasma concentrations result in relatively little additional increment in venodilatation. Conversely, arterial and arteriolar vasodilatation is seen at moderate to high concentrations of nitrates. With very large doses the nitrates have a considerable dilating effect on the arteriolar or resistance vessels.[33-34]

Mechanisms of Action in Coronary Artery Disease

Brunton[5] and Murrell[7] both felt that the mode of action of nitrates in angina pectoris was to lower the arterial pressure, thereby reducing the amount of work that the heart had to do. Sir Thomas Lewis in 1933 first proposed that nitroglycerin was dilating coronary arteries, not lowering blood pressure. Thus started the controversy over whether nitrates affected myocardial oxygen supply or myocardial oxygen demand.[36] In patients with coronary artery disease there is a balance between myocardial oxygen supply and demand (Table I). Myocardial oxygen supply can be acutely altered by either changing coronary artery flow or by changing the AV O_2 difference. Since the AV O_2 difference is near maximal at rest in man, the only thing that changes on the supply side of the equation is coronary flow. A number of different things can be changed on the demand side of the equation. Nitrates decrease preload and, to a lesser extent, afterload. This shrinks heart size. Therefore, wall stress is decreased; thereby decreasing myocardial oxygen demand. Afterload reduction lowers the pressure that the heart is working against. Thus, myocardial oxygen demand is reduced. Due to sympathetic reflex changes, heart rate and contractility are increased.[1,4,31-34,37-43]

The question of the effect of organic nitrates on coronary flow in patients with ischemic heart disease has been a matter of great debate. Normal coronaries can be dilated, and there is evidence of increased flow in normal coronaries. Animal models of coronary artery disease have raised

Table I Myocardial Oxygen Supply - Demand Balance
Effects of Organic Nitrates

Supply	NTG Effect	Demand	NTG Effect
Coronary blood flow	↑	Heart rate	↑
Coronary AV O_2	-	Developed pressure	↓
		Contractility	↑
		Ventricular volume	↓
		Duration of systole	-
		Basal metabolism	-

questions. The possibility of a coronary steal syndrome has long been discussed and does hold in some models where there is circumferential restriction of the coronary artery. In animal models, constrictors around a coronary artery cannot dilate. Since only the normal vessel can dilate and with the fall in blood pressure caused by the nitrates, the flow to the area distal to the constrictor may have decreased blood flow. In other words blood preferentially goes to the normal area, not the ischemic area -- a "steal" is formed. In man the "steal" question has been repeatedly raised. Freudenberg et al[44] has shown that in 75% of patients with coronary artery disease the plaque is not circumferential but is eccentric leaving some normal vessel wall that is capable of dilation. Brown et al[45] have confirmed this in vivo and have shown that even tight coronary lesions can be dilated. Brown et al have shown that coronary flow can almost double through a tight lesion. The lesion dilates to the same degree as the vessel. Gage et al[46] have shown in 12 patients that the area of stenosis decreases with exercise to 71% of the resting area; sublingual nitroglycerin increased the area to 112% of control. Pre-treatment with nitroglycerin blocked the constriction that occurred with exercise. However, one study revealed that even though the coronaries were dilated, myocardial blood flow did not increase. The majority of studies, however, have suggested that there is an increase in blood flow to ischemic areas by increasing collateral flow and dilating eccentric stenoses of the coronary artery as well as epicardial vessels. The decrease in left ventricular end diastolic volume has a corresponding decrease in left ventricular end diastolic pressure. A decrease in left ventricular end diastolic pressure will increase subendocardial blood flow. Nitrates also can inhibit coronary spasm and vasoconstriction that occur with alterations in vasomotor tone. Thus, the evidence for a salutary effect on flow has been shown in man with coronary artery stenoses.[1,4,38-39,42,44-57]

The effect of nitrates on the demand side of the equation is well accepted. There is no disagreement that preload is reduced. The lower preload decreases end diastolic volume. A lower end diastolic volume decreases wall stress, which is a major determinant of myocardial oxygen consumption. The lower end diastolic volume causes a decrease in stroke volume via the Starling mechanism. There is reflex sympathetic stimulation which tends to increase heart rate and contractility. The increase in heart rate and the increase in contractility tends to minimize the fall in cardiac output. Cardiac output may fall or stay the same. The reduction in afterload may be offset partially by increased arterial tone, particularly if there is a fall in cardiac output. Arterial pressure tends to fall, due both to decreases in cardiac output and to decreased arterial compliance and reduced systemic vascular resistance.[1,4,31-34,37-43]

PROBLEMS WITH ANGINA PECTORIS TRIALS

Studies in patients with angina pectoris are always very difficult. Relief of pain, though that is a major goal of angina therapy, is very difficult to prove. Diaries of patients reporting the number of episodes of pain and the number of nitroglycerin tablets taken have been used for some time. The problem with these types of studies is several fold. Reporting is very subjective; and if the investigator wants the patient to be better, the patient will often state that he or she is better. With time, patients often adjust their lifestyle to avoid angina. Thus, many times the patient will get better by diary reporting. Recently, the advent of surgery and angioplasty has removed patients who are having a lot of angina. In fact, in most recent trials the number of angina attacks are less than once per week. It becomes statistically very difficult to prove a reduction in angina attacks when a patient only has angina once every other week. In the recent FDA trial with nitroglycerin patches, the majority of patients never had a spontaneous episode of angina during the trial. Thus, the ability to prove reduction in angina attacks has been difficult, so other techniques have been utilized. Exercise testing has been one of the surrogates.

Exercise testing, though more objective than patient diaries, also has a number of problems when trying to prove efficacy of antianginal drugs. The time until angina on a treadmill or bicycle will vary with time of day, how long it has been since the last meal, the temperature of the room, the humidity of the room, as well as psychological effects.[58] The effects become important when you are trying to measure small differences in exercise capacity. There is also a training effect that can become very important. In fact, in the recent FDA trial, the training effect was much greater than the effect of the drug. By doing three Bruce exercise test protocols a day once a week, there was a 35% increase exercise time to angina in the placebo group. Hence, exercise testing has some limitations when trying to study angina pectoris.

The use of Holter monitors to record the number of minutes per day of ischemia, as well as the number of episodes of ischemia, is another way of studying patients with ischemic heart disease. Silent ischemia episodes can be used to measure effectiveness. However, the relationship between silent ischemia and events is not well known. There is no evidence that reducing the number of silent ischemia episodes or duration correlates with pain relief or survival. Thus, many are reluctant to use Holter monitors as a surrogate for determining efficacy in angina pectoris.

The type of protocol used also presents a problem. Obviously, open label studies and studies without a placebo control immediately raise suspicion as to their credibility. However, even placebo controlled randomized double blinded studies have major problems. To measure the effect of a monotherapy other antianginal drugs need to be withdrawn. Obviously some drugs have a long half-life, requiring long periods of time off the drugs. This is further aggravated by a carry-over effect that is not dependent upon the blood level of an antianginal drug. When an effective drug is withdrawn, there is still improvement for days after the blood level of the drug is zero. Part of this carry-over effect may be psychological, in that the patient has been treated with an effective drug, so the patient is happier and not as depressed. Hence, the patient will still show improvement even on exercise tests. There

may also be some other long term effects of antianginal therapy that we do not understand. Another problem with the studies is the placebo problem. Most patients will get better even by exercise testing if they feel that the therapy is effective. If the physician convinces the patient that they will be better, most patients will do better. With paste and patches, the larger the patches, then the patient thinks that he or she is getting more medications; and this will cause a placebo effect. Increasing the number or size of pills will also make the patient think he or she is doing better. Hence, the trial should be a double dummy trial; a double dummy trial is one in which the size and number of doses are always the same. If two different sizes of patches are to be compared, then both sizes must be applied each time. Another major problem is the fact that all antianginals give the patients effects that they can tell. Nitrates and nifedipine will cause vasodilator effects for the first few doses after changing from placebo. Beta blockers, verapamil, and diltiazem cause noticeable changes in heart rate. Hence, it is extremely difficult to mask the active drug from the patient. Hence, there can still be a placebo-like effect from the active drug. Other problems include that many studies have inadequate dosages of drugs and too few patients. To be statistically sound, studies should have at least 24 patients and preferably more than 50 patients. There are only three published trials with 24 or more patients that are double blinded placebo controlled trials. Only one trial had more than 50 patients. Two unpublished trials have had more than 50 patients. This includes all types of nitrates. Hence, scientific information about nitrate usage in angina is very minimal.

Another problem that occurs in antianginal trials is the design of the groups to be compared. The most commonly used type of trial is the crossover type of trial. After a washout and placebo run in period, the patients are randomized to either placebo or active drug for a period of time. The patients then enter another washout period, and then the groups are switched in a blinded manner. The patients who got placebo in the first period get active drug in the second and vice versa. This sounds like a good design, but there is a crossover phenomena that is poorly understood. Almost all trials that have had positive results have a much greater difference in the first crossover period than in the second. In the first crossover period the placebo group does a little better than placebo in the washout period, while active drug does significantly better. During the second crossover period, the placebo is much better than the washout placebo, and the active drug also is better, but the difference between placebo and active drug is not usually statistically significant. To truly prove effect, not only should the trial as a whole show statistical significance, but both crossover periods should also be significant in of themselves. None of the trials that has reported this comparison is statistically significant. The reason for this crossover problem is not well understood. Some of it may be carry-over of active drug. The active drug may stabilize the patient in a way not known that is long term. We are all familiar with a bad hypertensive patient, who may stop their medications and still not be hypertensive several days later, even though the drug has been cleared. This type of carry-over appears to occur in angina for reasons that we do not understand. A second type of carry-over phenomena is psychological. A patient on active drug may feel better and be better psychologically, so that when they go on placebo they do not feel as bad, therefore, doing better. The patient on placebo may also carry-over depressed feelings - because the medication was not working - and therefore not do as well on active drug. Therefore, these types of studies are fraught with problems.

Statisticians have been pushing for a randomized parallel design. Patients are randomized to long periods of placebo or active drug. This type of study is free from the crossover effect. The problem with this kind of study is that it takes large numbers of patients - because you are comparing patients, not the effect in the same patient. This type of design should be better, but other things can cause variance. For example, the patients may get better or worse during the study independent of the drug or placebo. There is a seasonal variation in myocardial infarction and unstable angina. If the study begins in the late summer and extends until winter, the incidence of myocardial infarction and unstable angina will be increasing during the study. If the study itself trains the patients, then this will cause problems. Most patients in studies improve even if they get placebo. This is because the study gives them support and reassurance. Angina patients even lose their fear of angina. Having exercised a few patients over 100 times over three years, we noticed that after the first few times the patients would not want a nitroglycerin tablet when we precipitated chest pain. The patients tend to become more active outside of the study, and their spouses would state that they are greatly improved. Thus, this parallel design also has major problems when trying to study angina.

Thus, designing angina studies is difficult at best. To do good angina studies is very costly. Since organic nitrates have been around for so many years, their patents have long since run out. Drug companies, therefore, are not very interested in investing large sums of money on drugs that are generic. In fact, most clinical studies done have been done with patches, since they are new. In fact, more angina patients have been studied on patches than on all other forms of nitrates combined. These problems should be kept in mind as we review some of the efficacy data on nitrates.

CLINICAL STUDIES IN ANGINA PECTORIS

There are three goals of nitrate therapy. The first is to relieve pain. The second goal is to prevent an attack by giving a drug just prior to doing an activity that would cause pain. The third goal is to give chronic prophylaxis to prevent attacks.[31]

There are many studies that have shown effectiveness of nitrates at terminating pain. The duration of pain has been shortened by giving sublingual nitroglycerin, sublingual isosorbide dinitrate, nitroglycerin spray, or buccal nitroglycerin. Oral and transdermal forms have not been shown to be effective, due to their slow onset of action. It is widely accepted that nitroglycerin tablets relieve pain, though thorough studies have not been performed.[1,4,31,59-61]

The second goal has also been shown. Angina attacks have been prevented by administering an acute dose of sublingual nitroglycerin,[59-60,62-64] nitroglycerin spray,[65] or isosorbide dinitrate[63,65a-67] just prior to therapy. The first doses of any nitrate can prevent such attacks. Nitroglycerin patches, paste, and oral nitrates of all kinds have been shown to increase exercise tolerance when an acute dose is given at the appropriate time before the stress is encountered. Repeated studies have shown that a single acute dose at the proper time before stress can prolong exercise tolerance. This has been done with both upright and supine exercise in order to show that it is not just the hypotensive effect of nitroglycerin in the

upright position that is responsible for the antianginal effect. Thus, the first dose of any nitrate is effective at preventing angina and improving exercise tolerance. Though recent studies have shown that every form of nitrate can provide immediate prophylaxis, older studies were sometimes negative, usually due to very low doses being administered.[1,4,31,59-60,62-67]

The third goal is where the problem arises. It is much more difficult to prove that a chronically administered nitrate can reduce the episodes of angina. The chronic studies will be discussed by drug.

Isosorbide dinitrate

Isosorbide dinitrate has been studied in many different trials. However, most trials are open label, without placebo controls and with inadequate numbers of patients. The few trials that are double blind placebo controlled are shown in Table II.

Table II
Placebo Controlled Trials with Chronic Isosorbide Dinitrate Therapy

	No. Pts.	Dose	Angina Frequency	Exercise time
Goldbarg[68]	21	10 mg po QID	No change	No change
Aronow[60]	20	5 mg sl QID	No change	
Livesley[69]	18	20 mg po TID	No change	No change
Danahy[70]	19	29 mg po QID		Increased at 1,3,5 hr
Lee[71]	28	40 mgSR po TID	Decreased	Increased at 2,6 hr
Blasini[72]	11	40/60 mg po TID	No change	
Rudolph[73]	13	20 mg po TID	No change	
Thadani[31,74]	12	15-120 mg po QID		Increased at 1,2 hr; but not at 4,8 hr
Schneider[75]	11	40 mg po QID	Decreased	Increased

Thadani U, Whitsett T, Hamilton SF: Nitrate Therapy for myocardial ischemic syndrome: Current perspectives including tolerance. ***Curr Prob Card*** 13:746; 1988.[31]

As can be seen, most of the early studies were negative studies. Most of these studies were with low doses of isosorbide dinitrate and had few patients.[60,68-69,72-73] The first trial that showed that isosorbide dinitrate had an effect on exercise capacity chronically was the study by Danahy and Aronow[70] in 1977. This study is frequently quoted as the study that proves that isosorbide dinitrate is effective chronically. However, when one reads the methodology, the isosorbide dinitrate was held for 16 or 40 hours before giving the dose, after which exercise tests were performed. So this study is not a chronic study, as the drug was washed out prior to the testing. So this study should be considered a first dose study and not a chronic study.

The study by Lee[71] used a sustained release form of isosorbide dinitrate. The patients were given 40 mg sustained release forms of isosorbide dinitrate for one month then had exercise tests two hours and six hours after each dose. They also showed that the patients had less ST depression after a month

of therapy. Thus, this is a well conceived trial that appears to have shown that high doses of sustained release isosorbide dinitrate was effective with exercise testing.

The most helpful paper was one by Thadani et al[31,74] in 1982. This was a blinded study that carefully studied 12 patients in a multiple crossover design at several doses of isosorbide dinitrate ranging from 15 mg every six hours to 120 mg every six hours. This study is summarized in Figure 4. Thadani et al gave acute single doses of placebo or isosorbide dinitrate ranging in doses of 15 mg, 30 mg, 60 mg, or 120 mg. They showed that this acute dose had a hypotensive effect that lasted over eight hours. The higher the dose, the larger the drop in blood pressure. Blood levels correlated with the dose. The acute dose of isosorbide caused an increase in exercise capacity that lasted over eight hours. Each increased dose caused a greater increase in exercise capacity. The first dose of isosorbide dinitrate caused long lasting improvements in exercise capacity, and there was a dose dependent

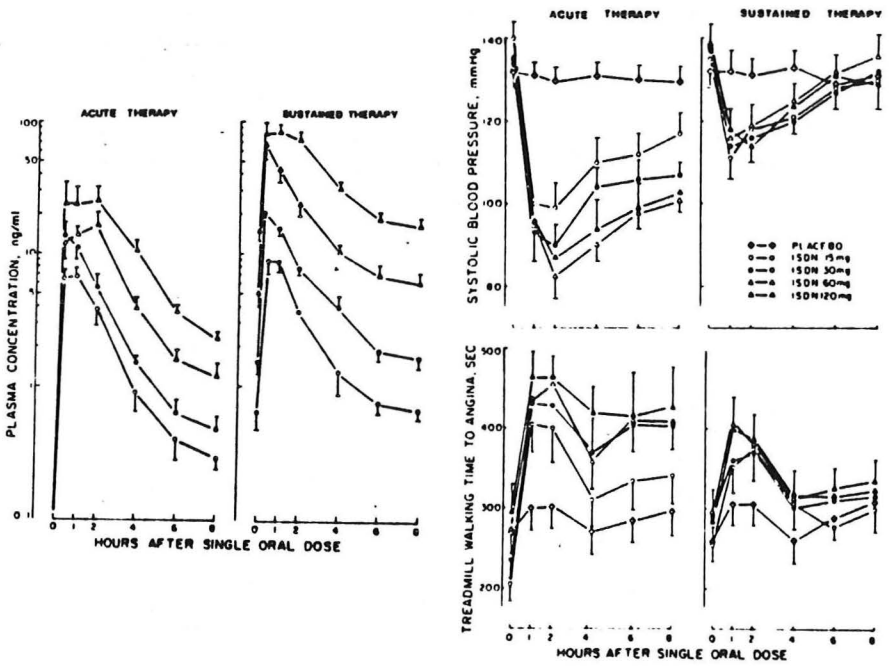

Figure 4. Plasma concentrations and duration of effects of isosorbide dinitrate (ISDN) during acute and during sustained, four-times-a-day therapy in patients with angina pectoris. The 0 hour values during sustained therapy represent values 10 hours after a previous dose taken the night before. Plasma ISDN concentrations were higher during sustained therapy, but peak effects and duration of effects on systolic blood pressure at rest, in the standing position and exercise time to angina were markedly attenuated. (Thadani U, Fung HL, Darke AC, et al: Oral isosorbide dinitrate in angina pectoris: Comparison of duration of action and dose-response relation during acute and sustained therapy. ***Am J Cardiol*** 49:411-419, 1982)[31,74]

linear increase in exercise capacity. However, with sustained therapy there was no longer a dose dependent drop in blood pressure or increase in exercise capacity. The drop in blood pressure and increase in exercise capacity lasted only two hours. This was not explained by blood levels. With sustained therapy, the blood levels were higher at each dose of medication and had a longer half-life. Thus, there is an attenuation or tolerance that can be seen with isosorbide dinitrate. This issue will be discussed later.

Thus, there are contradictory studies with isosorbide dinitrate chronically. The only chronic therapy trial that looked at different times after dosing found marked attenuation chronically.[31,74] The only other papers looked only at one time. Hence, isosorbide dinitrate has had quite variable data as to its efficacy. Chronic efficacy by exercise testing, except shortly after a dose is administered, remains a question.

Isosorbide-5-mononitrate

In Europe isosorbide-5-mononitrate is used - as it is believed to be effective for a longer period of time, be less likely to develop tolerance, and be nearly 100% bioavailable.[31] Isosorbide dinitrate is broken into the two mononitrates in the body. In patients being treated with isosorbide dinitrate there is a significant blood level of the isosorbide-5-mononitrate. Isosorbide-5-mononitrate has been shown to be effective with the first dose but to have tolerance chronically (Figure 5). This tolerance has been shown with both the once-a-day form and the twice-a-day form.[31,76-77]

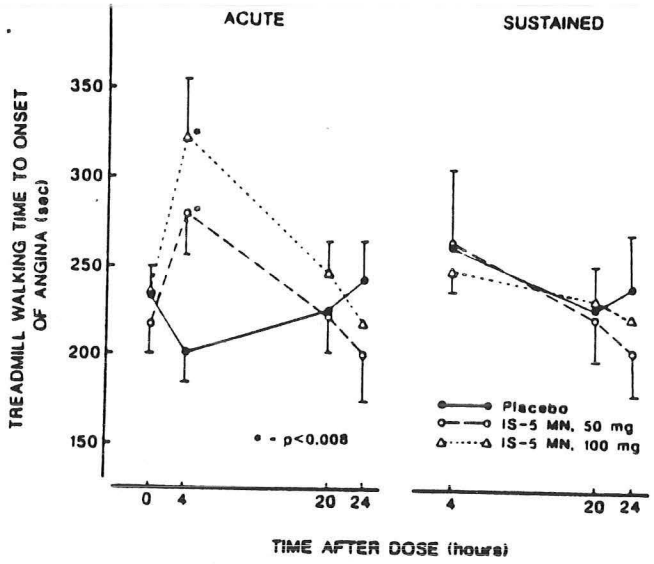

Figure 5. Changes in exercise duration during acute and sustained therapy with slow-release isosorbide-5-mononitrate (IS-5MN) therapy. Compared to placebo (closed circle), an increase in exercise duration was seen at four hours ($p<0.0001$), but not at 20 or 24 hours after the first dose of slow-release IS-5MN 50 mg (open circle) or 100 mg (open triangle). After once-a-day therapy for one week, no effect was seen at four, 20, or 24 hours. (Thadani U, Hamilton SF, Olson E, et al: Duration of effects and tolerance of slow release isosorbide-5-mononitrate for angina pectoris. ***Am J Cardiol*** 59:756-762, 1987)[77]

Pentaerythritol Tetranitrate

There is only one study that showed improvement after four hours following a single oral dose of 40 mg.[78]

Sustained Release Nitroglycerin

Sustained release nitroglycerin that has an effect for five hours was given three times daily for two weeks after a one week washout of other antianginal drugs in 46 patients. This was a double blind crossover trial compared to placebo. Exercise testing was performed one hour after the last dose. It was not stated what the timing of the TID dosage was or whether all tests were done after the morning dose or the afternoon dose or if they were at different times. The study showed a significant improvement in duration of exercise, the double product achieved, the amount of ST depression, the number of angina episodes, and the number of sublingual nitroglycerin tablets taken.[79]

Buccal Nitroglycerin

The buccal form of nitroglycerin has shown that exercise tolerance is improved up to five hours after an acute dose. Buccal nitroglycerin 3 mg was given with a TID regimen, with the last dose given 15 hours before the morning dose. After two weeks, there was an improvement out to five hours after the morning dose of buccal nitroglycerin.[80]

Nitroglycerin Ointment

There is very limited data with nitroglycerin ointment. Most studies have been single dose or open label.[31] After single doses of paste, exercise tolerance has been shown to be increased at three and six hours after an acute single dose. One trial has reported long term benefit after low and high doses of a new preparation of nitroglycerin ointment. This preparation has been shown to be effective after five hours. The paste was applied once a day and covered with a plastic sealed bandage. Exercise capacity was measured six hours after a dose had been applied. They showed improvement at six hours after three weeks of therapy. However, there was a decreased response as compared to the first dose. It is difficult to know if this is a chronic study or a series of acute studies, as the half-life of this compound used in this manner is not known.[81]

Nitroglycerin Patches

Nitroglycerin patches are discussed last because there is more information about patches chronically than all other forms combined. Also, all of the larger studies are with nitroglycerin patches. Acutely there are many studies that show efficacy of nitrates as seen in Table III. With the first patch applied, 10 of 11 double blinded placebo controlled trials showed significant improvement in exercise capacity during the first four hours after applying the patch. The only negative study was a low dose study; these same patients did respond to a higher dose of nitroglycerin patches. Three of four studies that looked at five to eight hours after applying the first patch also showed a significant improvement in exercise capacity. The negative study was the same low dose study where a higher dose showed benefit. There is only one trial that looked at exercise capacity between nine and 16 hours, and it

showed improvement. By 24 hours the situation became muddy. Between 22 and 26 hours seven studies showed no improvement, two studies showed improvement, and one study showed improvement only at high doses of nitroglycerin patches. Chronically only two studies have shown improvement by exercise testing. Hence, there seems to be a problem with nitroglycerin patches after 16 hours. To understand the problem better, a closer look at some of these studies is needed.

Table III
Placebo Controlled Trials with Transdermal Nitroglycerin Patch Therapy

	No. Pts.	Dose	Increase in Exercise Tolerance First Dose After Washout				Chronic	
Time After Patch Applied		-----	1-4h	5-8h	9-16h	22-26h	1-4h	24h
Thompson[82]	8	14.5	↑			↑		
Naafs[83]	10	5			↑			
Crean[84]	10	5					Neg	
Reichek[85]	7	9.4	Neg	Neg		Neg		
	8	22,25	↑	↑		Neg		
Parker[86]	11	5,10,15	↑	↑		Neg	Neg	Neg
	6	15,30,45	↑	↑		Neg,↑		
Schneider[87]	12	2.5,5,10					↑	
James[88]	12	5	↑			Neg		
Sullivan[89]	16	10					Neg	Neg
Scardi[90]	15	10,20	↑			↑		
Kohli[91]	14	5,10,15				Neg		
Thadani[92]	14	5-10	↑			Neg		
Muiesan[93]	52	10					↑	
Cowan[94]	12	10	↑				Neg	
Luke[95]	12	10	↑				Neg	
Thadani[31]	60	5-40	↑			Neg		

Thadani U, Whitsett T, Hamilton SF: Nitrate therapy for myocardial ischemic syndrome: Current perspectives including tolerance. ***Curr Prob Card*** 13:746, 1988.[31]

The first study was by Thompson[82] in eight patients with an average dose of 14.5 mg/24 hour. This study showed a continued improvement in exercise capacity over 26 hours. However, the effect at 26 hours was less improvement than at two hours. Reichek[85] in 1984 reported on seven patients in several different protocols. The patients were continued on other non-nitrate antianginals. Most patients were taking beta blocking agents and calcium channel blocking agents. A low dose study was performed with the average dose of nitroglycerin patches being 9.4 mg/24 hours. This study was negative at four, eight, and 24 hours. With eight patients a higher dose study was performed, with doses averaging 22 and 25 mg/24 hours. This study revealed that there was a significant improvement in exercise capacity at four and eight hours, but not at 24 hours. This was widely quoted as meaning that patches did not deliver drug for 24 hours. Blood level studies have shown that patches can deliver stable blood levels for at least 24 hours. The problem is the development of tolerance or attenuation. Parker[86] also reported a study that was positive for improving exercise tolerance at two and four hours after several different doses of nitrates. Except for 45 mg/24

hours, these studies did not show improvement at 24 hours. Even the 45 mg/24 hours dose showed an attenuation of effect. Thus, there was a hint of a problem with tolerance. However, all of these studies had small patient numbers, were not double dummy, or lacked adequate washout periods. It was easy to attack these studies, for these and many other reasons.

A multi-center study from Italy by Muiesan et al[93] was the first to really open the door to what was going on with nitroglycerin. Muiesan studied 57 patients; five dropped out during the study. This study featured a discontinuation of all antianginal drugs for two weeks, followed by a one week placebo period. The patients then entered a double blind placebo controlled crossover trial at 10 mg/24 hours nitroglycerin patches. After one week, the patients were studied four hours after administering the new patch. This study showed a significant reduction in angina attacks, a significant reduction in nitroglycerin tablet usage, and a significant improvement in exercise capacity. The study showed an improvement in exercise duration, the maximum work load achieved, and the total work time. The study also showed an increase in the time it took for 1 mm ST segment depression to occur. Thus, this was a very positive study. Since this study had 52 patients who completed the study, subgroup analysis was performed as shown in Table IV.[93]

Table IV
Reduction in frequency of anginal attacks according to exercise duration

Group	Change in exercise testing	No. Pts.	Reduction in angina attacks	p
I	Decrease	2	-42%	<0.008
	No change	11		
II	1% to 15% increase	10	-48%	NS
III	16% to 30% increase	15	-62%	<0.001
	>30% increase	14		

Muiesan G, Agabiti-Rosei E, Muiesan L, et al: A multi-center trial of transdermal nitroglycerin in exercise-induced angina: Individual antianginal response after repeated administration. ***Am Heart J*** 112:233-238, 1986.[93]

About one quarter of the patients developed complete tolerance to nitroglycerin patches by exercise testing criteria. About a fifth of the patients developed marked but not complete tolerance by exercise testing. More than half of the patients did not develop significant tolerance, and their exercise capacity was significantly improved. It is fascinating to note that the group that had complete tolerance (Group I) still had a significant reduction in angina frequency of 42%. This finding is similar to several other reports. Even though there is tolerance to exercise testing in several studies, angina frequency is still reduced. This presents us with a perplexing problem at trying to understand what is happening. This will be discussed in more detail later.[93]

The FDA and three major drug companies making patches have recently completed a very large (more than 500 patients) parallel design trial comparing many different doses of nitroglycerin patches from 15 mg/24 hours to 105 mg/24 hours. This trial has been publicly presented but is not in print at this time. In this trial there was a significant improvement of 35% in exercise capacity, however this increase was identical in the placebo arm and in each of the drug arms. Hence, this study confirmed the finding of tolerance. The study showed significant improvement in active drug over placebo only in the first dose studies, not in the chronic studies. No identifiable subgroup could be found that had an improvement in exercise capacity. However, in spite of this, there was a significant reduction in angina in those patients who had more than seven angina attacks per week. Also, it should be pointed out that more than half of the patients in this trial never had a single episode of spontaneous angina at any stage of the trial.

So, there appears to be tolerance to improvement in exercise test capacity in a number of trials; but pain relief persists in spite of this exercise tolerance. This phenomena appears to be a problem for all nitrates. Any nitrate that is given around-the-clock can cause tolerance, but not necessarily in all patients.

UNSTABLE ANGINA

Intravenous nitroglycerin has been a mainstay of therapy in unstable angina for some time.[1,4,31] The use of nitroglycerin in combination with beta adrenergic blocking agents, calcium channel blockers, aspirin, heparin and/or thrombolytic agents has been tried.[1,4,31] Of these drugs, aspirin has been shown to reduce both morbidity and mortality in patients with unstable angina.[96-97] There is a lot of evidence that nitroglycerin reduces ischemia in patients with unstable angina.[98-107] However, there is no evidence that morbidity or mortality is effected by treatment with nitrates, because there have been no trials. Some believe that they are protective, but there is no adequate control. Patients are often given multiple drugs and interventions, and it is very difficult to determine the effectiveness of one drug when a whole cocktail of drugs has been given. In a study by Kaplan et al[99] patients treated with beta adrenergic blocking agents, isosorbide dinitrate, or nitroglycerin paste who still had pain were given intravenous nitroglycerin; and the number of attacks was reduced from 3.5±0.4 to 0.3±0.1 episodes per day. The development of attenuation is difficult to determine, as many patients with unstable angina cool off with bed rest only. The fact that the starting dose of nitroglycerin did not have to be increased does not prove that there is no attenuation of effect. The need to increase the intravenous nitroglycerin to keep pain controlled was seen in half to two-thirds of the patients. Thus, there is probably some attenuation of effect. The only trial that did not allow upward titration of nitrates was one by Curfman et al.[106] In this trial, only 31% of patients treated with intravenous nitroglycerin remained pain free. This suggests that there is significant attenuation of effect. It is not possible to determine the exact percentage, because there is no control and an unstable condition.

SILENT ISCHEMIA

There have been many trials using nitrates in the treatment of silent ischemia. Shell, in a single blinded pilot study in eight patients, reported that transdermal nitroglycerin reduced the number of episodes of silent ischemia per 24 hours from 5.3 ± 3.3 episodes to 0.8 ± 1.2 episodes. The mean duration per 24 hours was reduced from 95.8 ± 87.0 minutes to 17 ± 27.1 minutes.[108-110] In an unpublished, double-blinded placebo controlled trial, Shell has told me that there was about a 60% reduction in episodes and duration of silent ischemia. Pepine and co-workers have shown that intravenous nitroglycerin can improve ejection fraction and decrease wall motion abnormalities significantly.[111] Pepine and co-workers have reported that hourly sublingual nitroglycerin tablets reduced the number of episodes from 3.5 with placebo to 0.5 per 24 hours with nitroglycerin.[112-113] Von Arnim and Erath have shown in a double blinded crossover trial that silent ischemia was reduced from 2.4 episodes per day to about 0.8 episodes per day, both with isosorbide mononitrate 20 mg TID and 50 mg sustained release.[114] Schneeweiss and Marmor placed eight men on nitroglycerin patches who were on standard therapy; all eight were on calcium antagonists, and six were also on beta blockers. Standard therapy was continued, and a nitroglycerin patch 20 to 30 mg/day was added. The number of silent ischemia episodes was reduced from 9.25 ± 5.52 to 2.4 ± 2.0 episodes. The maximum ST segment depression was reduced from 3.1 ± 0.7 to 0.9 ± 0.7 mm.[115] Thus, it appears that nitrate therapy can reduce the number, duration, and severity of episodes of silent ischemia. There is only one study that was entirely negative for reducing silent ischemia. There is little evidence of attenuation or tolerance in these trials. However, there have not been adequate attempts to find attenuation; and more work is needed.

ACUTE MYOCARDIAL INFARCTION

The role of acute and chronic nitrates in myocardial infarction has been extensively investigated, both in animal models and patients. Though the use of nitrates was condemned for many years in acute myocardial infarction, recent evidence has shown benefit of nitrates. Reduction in pain of patients with acute myocardial infarction has been reported.[98] There has been good evidence in animal models that nitrates can reduce infarct size and arrhythmias.[116-120] A recent study by Jugdutt and Warnica[121] has shown good evidence that the same is true in man. They randomized 310 consecutive patients admitted with acute myocardial infarctions to nitroglycerin or to the control group. Patients were randomized if they had ECG findings suggestive of an acute myocardial infarction, pain less than 12 hours before randomization, and did not have any exclusion criteria. Exclusion criteria were cardiogenic shock, systolic blood pressure <100 mmHg, heart rate >120, age> 75, heart rate <55, heart block, blood pressure >200/120, and right ventricular infarction. If the patients were randomized to nitroglycerin, they were given sufficient nitroglycerin to lower their blood pressure by 10% if normotensive or by 30% if hypertensive; however, their systolic pressure was not taken below 80 mmHg. There was significant reduction in infarct size as measured by creatine kinase in all patients and in both anterior and inferior infarctions. There was significant reductions in creatine kinase in patients treated within four hours of onset of symptoms as well as patients treated after four hours from onset of symptoms. With serial 2-D echocardiography there was significant improvement in ventricular function.

On ECHO LV asynergy was 40% less, and LV ejection fraction was 22% more. The Killip class was significantly improved with intravenous nitroglycerin. Most impressive were the infarction related complications as shown in Table V.[121]

Table V
Effects of Nitroglycerin on Complications of Infarction

Complication	Control (%)	NTG (%)	p value
Infarct expansion syndrome	15%	2%	<0.0005
LV thrombus	22%	5%	<0.0005
Cardiogenic shock	15%	5%	<0.005
Infarct extension	22%	11%	<0.025
Mortality			
In-hospital	26%	14%	<0.01
3 months	28%	16%	<0.025
12 months	31%	21%	<0.05

Jugdutt BI, Warnica JW: Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. ***Circulation*** 78:906-919; 1988.[121]

This study strongly suggests that intravenous nitroglycerin is of benefit in most patients with an acute myocardial infarction, both in ventricular function as well as mortality. This had been suggested in several other studies; but this is the first study with good, strong evidence favoring the benefit of intravenous nitroglycerin. Meta-analysis by Yusuf et al[122] of this study and several previous randomized trials supports the concept that intravenous nitroglycerin reduces mortality by an estimated 49%.

Long term administration of nitrates after hospital discharge may also be of benefit. Elliott Rapaport[123] has reported that the administration of chronic nitrates after hospital discharge might influence survival. This was a retrospective analysis of 139 patients discharged from San Francisco General Hospital. Of those discharged after recovery from an acute myocardial infarction, 49 patients received long-acting nitrates - mainly due to angina or CHF - and 90 patients did not receive long-acting nitrates. The mortality rate for those receiving long-acting nitrates was 10% versus 26% for those not receiving nitrates. This difference was statistically significant and the life table calculations were highly significant. However, this was retrospective analysis; and there is no good evidence that the groups were truly comparable. There is need for a randomized study to look at these points. The other important question is the relationship between nitroglycerin and other agents that can improve infarct size and affect acute and long-term mortality such as beta adrenergic blocking agents, thrombolytic agents, and aspirin. It appears that each of these may have a role to play. It remains to be proven that combinations of these agents can provide additive improvements in infarct size, ventricular function, or mortality. However, it clearly gives us alternatives in high risk patients where there is anxiety over the use of thombolytic agents and/or beta adrenergic blocking agents.

ISCHEMIC CONGESTIVE HEART FAILURE

The use of nitrates in congestive heart failure has been advocated for many years. There appears to be benefits of nitrates both in the short and long term. It has been felt by most that the effect of nitrates on congestive heart failure is on venodilation, sequestering blood in the venous pool and lowering preload.[31,124-127] It is widely believed that there is arterial and pulmonary artery vasoconstriction. This certainly seems to be the acute effect of nitrates. However, this does not explain the long term effects. Packer[128] states that the effect is actually on systemic and pulmonary resistance vessels; this allows increased flow and results in increased venous return. Cohn and the Veterans cooperative group[129] have shown that patients with congestive heart failure live longer on nitrates; they have also shown that this increase in survival is the same whether or not they have coronary artery disease. This is in contrast with other authors.[31] Long term the use of isosorbide dinitrate in doses of 40 mg QID has been shown to improve exercise capacity both by itself and in combination with hydralazine.[130-132] Nitroglycerin paste, isosorbide-5-mononitrate, and nitroglycerin patches have all been shown to be effective in congestive heart failure.[133-135] However, in some patients there has been the rapid development of tolerance within 24 hours.[136-138] There seems to be considerable controversy over the question of tolerance with nitrate therapy in congestive heart failure.

Elkayam et al[139] has published a very interesting paper on the incidence of early tolerance to continuous intravenous infusion of nitroglycerin. They studied 31 patients with coronary artery disease and congestive heart failure who responded to intravenous nitroglycerin by dropping their pulmonary artery wedge pressure by 10 mmHG or 30%. Sixteen patients were randomized to placebo, and 15 patients were randomized to IV nitroglycerin. All patients receiving nitroglycerin dropped their pulmonary artery wedge pressure, and the entire group of patients had significant lowering of pressure through eight hours. They found that the group as a whole developed tolerance, and that by 12 hours there was no difference between placebo and active drug. When the patients receiving nitroglycerin were examined, it was found that eight patients continued to have significant reductions in pressures for all 24 hours, and seven had the very early onset of complete tolerance. The only difference between long term responders and those who developed tolerance was the initial systemic vascular resistance. Those who continued to have a response had a baseline systemic vascular resistance of 2195±765 dyne-sec cm^{-5} versus 1517±355 dyne-sec cm^{-5} for those who developed rapid tolerance. It is potentially possible that this higher systemic vascular resistance group had more of an arterial effect of nitroglycerin that may not attenuate to the same extent as those who had primarily a venous effect.

OTHER USES CITED IN THE LAST TWO YEARS

There are many other uses of nitrates that have been described. Some are probably not effective, such as their use for headaches or palpitations.[3] Other uses may have some benefit, such as use in portal hypertension,[140] pulmonary hypertension in interstitial lung fibrosis,[141] microsurgery of the middle ear,[142] following coronary artery bypass grafting,[143] perioperative hypertension during surgery,[144] aid in insertion of venous catheters in neonates,[145] impotence,[146] pulmonary hypertension,[147] skin necrosis following extravasation of parenteral nutrition,[148] keeping peripheral intravenous

infusions open,[149] acute aortic regurgitation,[150] and chronic mitral regurgitation.[151] There is even an interesting article that carried the title "Effect of intranasal introglycerine on circulatory responses to laryngoscopy & endotracheal intubation".[152]

PROBLEMS WITH NITRATE THERAPY

Individual Variation

One problem with trying to evaluate the effects of nitrates and some of the problems associated with their use is the fact that there is marked individual variation. When oral or transdermal types of nitrates are used there are marked variations in peak blood levels. For example, in two studies where blood levels were measured, there was a 5-fold and 11-fold variation in peak blood levels from the same dose of isosorbide dinitrate.[65a,74] With all preparations save intravenous infusions, there are large differences in bioavailability from one person to the next.[1,4,31] Nitrates that are taken orally have considerable first pass metabolism in the liver. There appears to be marked individual differences in the extent of first pass metabolism. When nitrates are given through the skin, skin organisms can break down some of the nitrates. Even sublingual nitroglycerin has a wide variation in absorption, particularly when the mouth is dry. Thus, it is very difficult to predict the blood level that can be achieved when any form of nitrate is given. Therefore, one must titrate to the desired response. Often the endpoint of that titration is not easy to measure or evaluate, making it very difficult to properly use the drug.[1,4,31]

Placebo Effect

Some skeptics may feel that nitrates do not work at all. Since even in blinded studies patients might be able to tell an effect of the first dose, maybe the venodilation that is seen and is beneficial might be a reflex change to the headache caused by the nitrates. As discussed earlier, most authorities believe that nitrates have an acute effect. One paper that supports that nitrates are more than placebo is one by Martines.[153] The study was a double blind randomized trial in 24 patients with angina. All patients were given placebo for two weeks in a double dummy style. The patients were then randomized to 5 mg/24 hour or 10 mg/24 hour patches continuously for three weeks. The 10 mg patch had a significantly greater increase in exercise capacity than the 5 mg patch. While many patients can tell the difference between placebo and nitroglycerin, very few patients can tell the difference between two different doses of the same medication. The fact that you could show difference between two doses of the same medication in a double dummy style is strong evidence that the drug has more than a placebo effect.

Nitrate Tolerance

Tolerance to nitrates is quite variable. On one hand there is little evidence of any attenuation or tolerance in the symptomatic treatment of angina. No matter how nitrates are given, most of the studies have reported marked decreases in the incidence of angina pectoris and in nitrate tablet usage for pain, as has been previously described. Also, there is little evidence of tolerance using silent ischemia as a marker. Most studies of unstable angina suggest that tolerance occurs in half to two-thirds of the

patients, but it is not complete tolerance. Treatment of congestive heart failure shows marked tolerance, with at least half the patients developing complete tolerance in a few hours to a fixed dose of nitroglycerin. Exercise testing of patients with angina also reveals a high incidence of tolerance usually within 12 to 16 hours. But this tolerance is quite variable. One study has many patients with tolerance, and the next study has a low incidence of tolerance. Thus tolerance seems to be quite variable. Potential mechanisms of this tolerance include chemical tolerance, hemodynamic tolerance, and different responses to nitrates.

The cellular basis for nitrate tolerance has been extensively researched; but, as with everything else, with nitrates controversy remains and studies are contradictory. The most widely held theory is that the sulfhydryl containing compounds that degrade the nitrates in to free nitrite radicles are depleted with two molecules, with SH groups, forming a single molecule with an SS bond. The molecules are then recycled by NAD(P)H acting as a hydrogen donor. This repletion takes a nitrate free or low nitrate interval. This reaction also can be reversed with something that can act as a hydrogen donor. N-acetylcysteine can act as a donor, and there have been a large number of studies - including some from this program - that has demonstrated this.[12,154-157] It was shown by May, Popma, Black, Schaefer, Lee, Levine, and Hillis that N-acetylcysteine could reverse the tolerance in human coronary arteries.[154] It has also been shown in unstable angina.[155-156] However, Fung showed evidence in a rat model that the effect of N-acetylcysteine was on extracellular S-nitrosothiol formation rather on the intracellular thiol repletion.[158] Recently, there have been several papers showing that N-acetylcysteine cannot reverse nitrate tolerance in animal models.[159-161] Parker et al[162] has recently shown that N-acetylcysteine cannot improve exercise tolerance and hemodynamics in angina patients who have nitrate tolerance. Thus, the effect of N-acetylcysteine in potentiating some of the nitroglycerin effects is controversial, and the best studies suggest it is by some mechanism other than interacting with the sulfhydryl compounds. Methionine, which can also interact with the sulfhydryl groups, has also been shown to have hemodynamic effects that appear to be reversal of nitrate tolerance, but it is too early to accept this based on what is now known about N-acetylcysteine.[163] The exact site of where tolerance occurs is not known; Henry et al[164] have shown good evidence that chemical tolerance probably occurs at multiple sites in the nitrate cascade. There is also evidence that tolerance is correlated to reduced cGMP response and an alteration in cGMP turnover.[165-166]

Another possible mechanism of tolerance is that of hemodynamic changes. When any vasodilator is given, there are reflex changes in heart rate and contractility that are sympathetically mediated.[4,31-32] There is also evidence that salt and water retention may play a role; in one study chronic nitroglycerin was shown to cause a reduction in hematocrit, suggesting plasma volume expansion.[4,167] With nitroprusside there are associated increases in plasma renin activity and catecholamine levels.[168-169] These have not been adequately studied with nitrates. Thus one component of the nitrate tolerance may be neurohumoral in nature. At present there are not adequate studies to see if neurohumoral changes are responsible for some of the nitrate tolerance.

The reason for different results from different studies on the effects of nitrates is not clear. There is increasing evidence that part of the reason for different results is that different vascular beds respond differently to

nitrates. In a number of animal models there is evidence that tolerance mainly occurs in the venous capacitance vessels not in the arteriolar resistance vessels. Initially the major response to nitrates is venodilation with reflex arterial vasoconstriction due to the decreased cardiac output. However, as venous tolerance occurs, nitrates seem to effect the arterial resistance vessels more. The arterial resistance vessels tend to have far less tolerance than the venous capacitance vessels.[170-173] This may make a difference in how different patients respond.

The difference in responsiveness of different beds could explain some of the results in congestive heart failure. Elkayam et al[151] showed that the patients who had higher systemic vascular resistance did not develop tolerance, while those with lower systemic vascular resistance did develop tolerance. It is conceivable that patients with congestive heart failure and lower systemic vascular resistance may get most of their benefit from venodilation and venous pooling of blood, which is the effect that seems to rapidly develop tolerance. On the other hand, those patients with high systemic vascular resistance may obtain their major effect from arteriolar vasodilation which is much less likely to develop tolerance.

Patients with stable angina pectoris have also had variable results. When patients exercise, there are two major effects of nitrates on the development of angina. Venodilation is the major factor at work on the demand side of the equation. Chronically, tolerance may well develop to the venodilation; therefore, there may no longer be a reduction in myocardial oxygen demand. If coronary flow does not increase, then there would be no benefit of nitrates on exercise performance in angina pectoris. However, spontaneous episodes of angina and silent ischemia episodes are frequently not related to effort but to changes in arterial vasomotor tone. This increased arterial vasomotor tone may not develop tolerance, and the patient may have a reduction in the spontaneous episodes of angina and silent ischemia, but the patient may show tolerance to exercise testing. The studies in which an improvement in exercise capacity was noted tended to be European. The patients had more spontaneous angina than in American studies. The average number of angina episodes per week in many European studies was over seven, while in the American studies the number of episodes was usually once per week or less. Patients having daily angina could have more arterial vasomotor tone and therefore could show improvement in exercise capacity. Most of the patients in the European studies would have coronary artery bypass grafting or angioplasty in the United States. There could be a real difference in the mechanisms of angina in the two different groups of patients. Another major difference between the two groups is smoking. In Europe, many patients with angina continue to smoke. In the United States, patients who volunteer for these types of studies usually have quit smoking. There is evidence for increased arterial vascular tone in people actively smoking. Nitrates could be causing arterial vasodilation in the patients with increased vasomotor tone. Another potential hypothesis that could explain some of the results is that the platelet effects of nitrates play a major role. If nitrates are acting primarily through platelet effects, then one could expect to see tolerance to exercise testing but not to spontaneous episodes of angina or silent ischemia. This is because there is probably little platelet mediated vasoconstriction during exercise in most patients, where platelet mediated vasoconstriction might be occurring in spontaneous angina and silent ischemia. These hypotheses could be partial explanation for some of the

results; however, there are so many different aspects of the nitrate question in dispute that it is hard to make a strong hypothesis.

Therefore, tolerance to nitrates is a real phenomena. Most likely it is a combination of many different types of changes combined to marked individual variation. Because of these factors, it is hard to predict who will and will not develop tolerance. The importance of tolerance must also be questioned. If there is tolerance by exercise testing in an angina patient, but the spontaneous angina and silent ischemia is markedly reduced, which is more important to the patient? Likewise, if there is tolerance in patients with congestive heart failure but exercise capacity and survival is improved, which is more important to the patient? Adequate studies have not been done to see if those patients with tolerance could be managed better in terms of symptoms and survival with some other regimen.

Cross Tolerance

There is cross tolerance between nitrates and those agents acting to stimulate cyclic GMP. Among the long acting nitrates, there are several studies which demonstrate both in man and animals that when tolerance develops against one product tolerance occurs to any long acting nitrate.[174-180] Hence, the practice used by some of giving isosorbide dinitrate during the day and nitroglycerin paste at night does not avoid tolerance. In normal doses of nitrates, sublingual nitroglycerin is still effective, probably due to the rapid rise in blood level and the much higher blood level achieved with sublingual nitroglycerin.[71,80,86,181] Zimrin et al[182] have reported that tolerance to sublingual nitroglycerin can develop when high dose chronic therapy is used. Thus, cross tolerance between nitrate products can occur. Switching compounds will not avoid tolerance.

Miscellaneous Myths

1. Myth - The nitroglycerin on the skin might explode.

   Truth - There is not enough nitroglycerin in a patch or paste to cause an explosion; however, the pastes, adhesives, and backings are made of hydrocarbons, plastics, cloth, paper and aluminum foil. If one were to defibrillate a patch or paste with 15,000 volts and 45 amps (360 joules), the results would be quite colorful.

2. Myth - Higher doses will prevent tolerance.

   Truth - Higher doses will accelerate tolerance; the highest dose in most patients for isosorbide dinitrate is probably 30 mg a dose, for nitroglycerin paste is about 2 inches, and for patches is 15 mg or 30 mg/24 hours. There is no evidence that higher doses of these agents provide any further improvement in any parameter chronically.

3. Myth - Using patches twice a day or isosorbide dinitrate or paste every two hours will prevent tolerance.

   Truth - More frequent dosing will not prevent tolerance; it may accelerate tolerance.

4. Myth - Cutting a patch in half and saving the other half until the next day will save money and be as effective.

   Truth - Nitrates are volatile; cutting a patch in half will allow the nitrates to evaporate and the two halves will lose potency faster.

5. Myth - If you use intermittent therapy, you can take the patch off and cover it and use it the next day.

   Truth - There are primers in the adhesive of most patches; once activated they will lose potency and not be as effective.

PREVENTION OF TOLERANCE

Pulse versus Continuous Dosing

It has been hypothesized that pulse dosing may be better than continuous dosing for nitrates. The argument is that pulse dosing will allow the nitrate levels to fall between doses, and the sharp rise with the next dose will have more of a reaction on the vessels; therefore, less tolerance will develop. In angina there is no evidence that this is the case. All nitrates that were given around the clock developed tolerance in some patients as described earlier. Pulse dosing with isosorbide four times daily provided four 2-hour times when exercise capacity was increased.[74] Nitroglycerin patches had a measurable effect for four to eight hours in the studies where it was adequately investigated.[82-95] In comparison trials between nitrates when both products were used in the same patients, no difference was found between one product or the other. Two comparison studies have been published comparing isosorbide dinitrate to nitroglycerin patches, and no differences were found.[183-184] No difference was seen between buccal nitroglycerin and isosorbide dinitrate.[185] There is a need for good comparative studies to be done to see if one product has advantages over another in a variety of clinical situations. Until more studies have been performed with good comparisons, it is pure speculation as to which is best.

Nitrate Free Interval

Tolerance may be prevented in those who develop tolerance by giving the patient a nitrate free interval. Several studies have shown that the tolerance can be overcome by having an 8-12 hour period off nitrates each day.[186-195] In each of these studies, having nitrate free intervals increased the exercise capacity in chronic therapy over those patients with continuous therapy. The study by Nabel et al[186] has shown that continuous therapy reduced the number of episodes per day of ischemia on Holter monitoring but intermittent therapy did not reduce the number of episodes significantly. Thus, the interrelationship of the exercise testing data and the silent ischemia data remains confusing at best. Thus, intermittent therapy may improve exercise testing performance long term but may increase the symptoms and the number of episodes of ischemia. Those patients who develop tolerance to the effects of nitrates with congestive heart failure may benefit from intermittent therapy.[31] To prevent tolerance to exercise testing with isosorbide dinitrate, patients should be treated with an eccentric TID or BID regimen.[194] Parker et al[194] have shown that treating patients with 30 mg

isosorbide dinitrate at 0700 and 1200 hours or with the same doses at 0700, 1200, and 1700 hours will not cause tolerance to exercise testing; while giving the doses at 0700, 1200, 1700 and 2300 hours would cause the development of tolerance. This is shown in Figure 6.

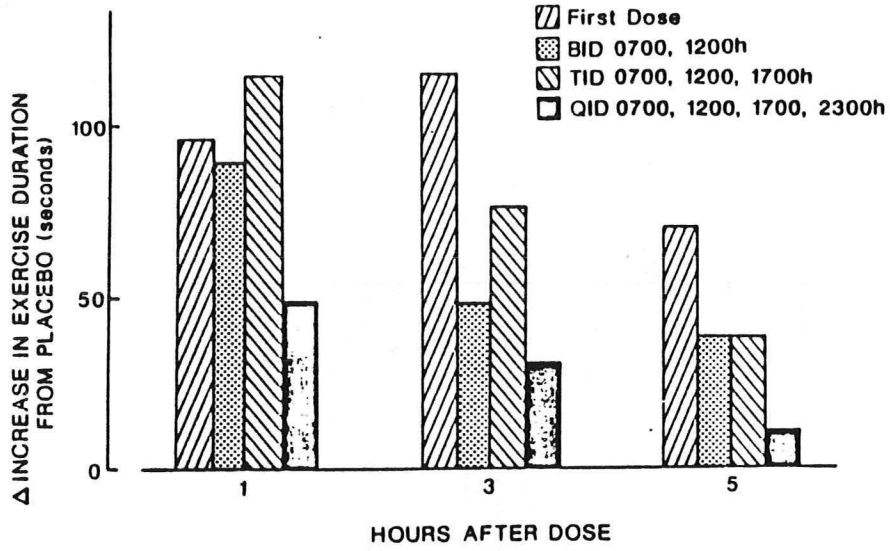

Figure 6. Duration of effects after the first dose of 30 mg of isosorbide dinitrate and after the same dose after one week of twice-a-day therapy (BID), three-times-a-day therapy (TID), and four-times-a-day therapy (QID) given at the times indicated in the legends. Data show a marked attenuation of effects after QID therapy compared with the first dose effect. However, some attenuation also was present even after BID and TID therapy. (Parker JO, Farrell B, Lahey KA, et al: Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. ***N Engl J Med*** 316:1440-1444; 1987.)[194]

Similarly, the same phenomena has been shown with intermittent administration of transdermal nitroglycerin as shown in Figure 7.[195]

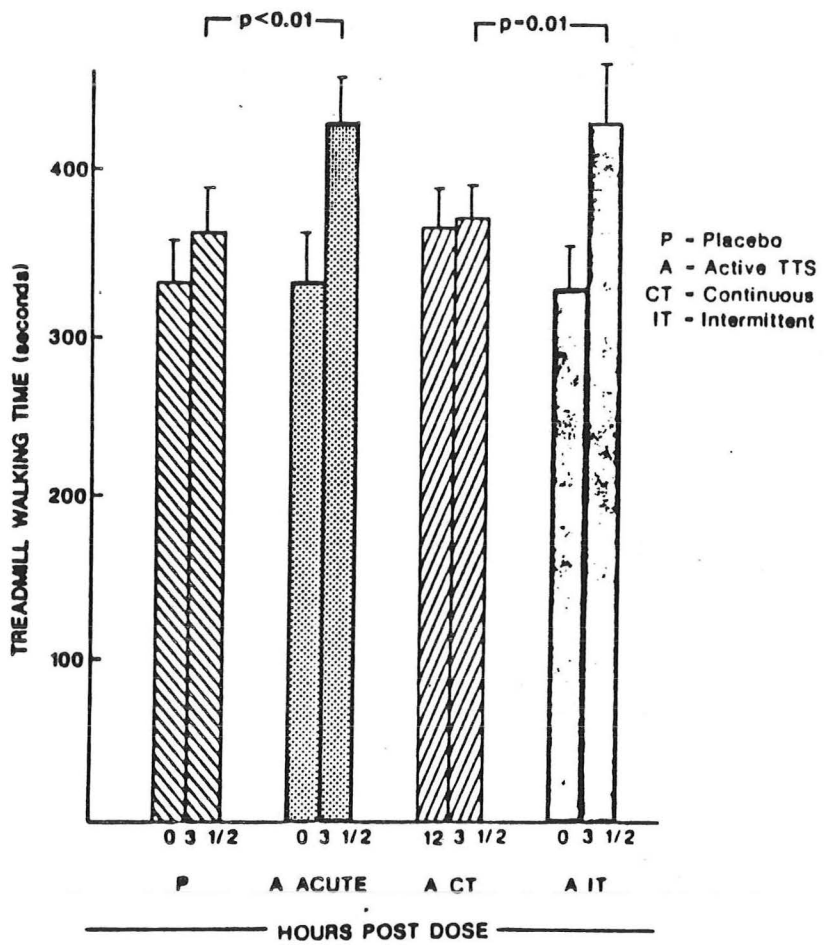

Figure 7. Treadmill walking time after the first dose (acute, dotted bars) and after one week of intermittent therapy (IT, filled bars) with active (A) transdermal nitroglycerin patch applied for only 12 hours each day produced a significant increase in exercise time at 3.5 hours post dose. No improvement in exercise duration occurred when the active patch was applied twice a day 12 hours apart continuously (CT, back striped bars) for one week. Placebo patches P, striped bars) had no effect on exercise time. (Cowan C, Bourke J, Reid DS, et al: Tolerance to glyceryl trinitrate patches: prevention with intermittent dosing. ***Br Med J*** 294:544-545; 1987.)[195]

Combination Therapy

Combination therapy has been strongly suggested as a means of counteracting some of the effects of nitrates in angina pectoris.[4,31,196-199] The use of beta adrenergic blocking agents, verapamil, or diltiazem to reduce heart rate and contractility is an effective way of reducing myocardial oxygen demand. Nitrates may then help block increases in arterial tone that occur spontaneously. Thus the two drugs have a synergistic effect. Tolins et al[199]

have shown that nitrates can improve exercise capacity more than propranolol alone, thus showing a synergistic effect. Schneeweiss and Marmor have shown that nitroglycerin patches added to beta blockers and calcium channel blockers caused a further significant reduction in frequency and duration of silent ischemia.[200]

RECOMMENDATIONS

Stable Angina Pectoris

1. Do not use nitrates as monotherapy.
2. Combine nitrates with a beta adrenergic blocking agent, verapamil, or diltiazem.
3. If the patient has rare angina, then use intermittent dosing.
4. If the patient has daily angina, then use continuous dosing and switch to intermittent dosing if continuous fails. If that fails, switch to nifedipine or add nifedipine as a third drug.

Unstable Angina Pectoris

1. Use intravenous nitroglycerin acutely in combination with other effective antianginal drugs and aspirin and/or heparin.
2. Once controlled, treat as stable angina pectoris.

Acute Myocardial Infarction

1. Consider the use of nitrates acutely and long term after infarction.

Congestive Heart Failure

1. Use of nitrates in combination with diuretics and after load reducing agents may be of benefit particularly in those patients who can not use ACE inhibitors.
2. If the patient has a high vascular resistance (>1800 dyne-sec-cm^{-5}) or seems to be peripherally clamped down, then give the nitrates continuously.
3. If the patient has a more normal vascular resistance(<1800 dyne-sec-cm^{-5}), then use intermittent therapy with nitrates.

These recommendations are based on the current state of knowledge which is poor. Further research into all aspects of nitroglycerin therapy is needed. Of particular need, is good comparative studies to see if one regimen is better than another.

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