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REVIEW

Nitroglycerin—the first one hundred years: new facts about an old drug

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One hundred years ago William Murrell published a series of papers in the Lancet in which he described his own experiences (and those of 'his friends and others') with 'nitro-glycerine' (Murrell 1879). Using a sphygmograph he found that six or seven minutes after an oral dose the pulse pressure, heart rate and the rate of rise of systolic pressure increased and the dicrotic notch became more prominent. He wrote that 'from a consideration of the physiological action of the drug and more especially from the similarity existing between its general action and that of nitrite of amyl, I concluded that it would probably prove of service in the treatment of angina pectoris, and I am happy to say that this anticipation has been realized'. This is a remarkable statement and surely Murrell, had he understood the term, could have claimed to have been one of the first 'clinical pharmacologists'. It was because of the 'physiological' effects of the drug in normal individuals that led him to prescribe it for angina and although it is unlikely that his explanation, and that of Lauder Brunton before him, for the clinical efficacy of amyl nitrite and nitroglycerin is the correct one (reduction in ventricular afterload) it is certainly the reason for the recent proven efficacy of nitroglycerin in the treatment of cardiac failure secondary to acute myocardial infarction.

There is no doubt as to the effectiveness of nitroglycerin in angina pectoris (Aronow 1972) and it is not the purpose of this review to provide a comprehensive account of the pharmacology of this remarkable compound. Instead, an attempt will be made to summarize some of the main experimental and clinical findings that have been published over the past five years and especially to discuss the recent evidence for new uses for the drug—namely to reduce myocardial ischaemic damage and to alleviate cardiac failure in acute myocardial infarction. For a discussion of the literature before 1975 the reader is referred to the reviews by Charlier (1971) and by Parratt (1974, 1975).

Nitroglycerin as an antianginal agent—mechanisms of action

For over half a century the explanation given for the effectiveness of nitroglycerin in angina was coronary vasodilatation. This arose from Francois-Franck's finding that nitrites dilate coronary vessels in isolated hearts; even today it is a view widely held. The most important clinical evidence that this view is untenable came from the studies of Ganz & Markus (1972). They compared the effects of nitroglycerin administered intravenously (systemic administration) with those when the drug was injected directly into the myocardial circulation following coronary artery catheterization for angiography. Coronary sinus outflow was measured in these patients using a thermodilution technique. Anginal pain induced by pacing was relieved by systemically administered nitroglycerin but not by locally administered nitroglycerin, despite the fact that intracoronary administration increased total coronary flow; the systemic administration of nitroglycerin *decreased* coronary blood flow, probably because of reduced myocardial oxygen demands. Ganz & Marcus concluded that 'the effects of nitroglycerin on the coronary vascular bed play little, if any, role' in the relief of anginal pain. They did however concede the possibility, since proven, that nitroglycerin-induced dilatation of large coronary vessels might be important in that group of patients with 'variant' or Prinzmetal's angina, in which arterial smooth muscle spasm plays a prominent role.

The above study shifted the emphasis from the coronary to the peripheral circulation as the basic mechanism by which nitroglycerin alleviates pain in angina pectoris. It follows that a reduction in myocardial oxygen demand and not an increase in myocardial oxygen supply is the primary explanation for the efficacy of the drug. This was in fact the original explanation for the usefulness of amyl nitrite (a 'diminution in arterial tension'; Brunton 1867). However arteriolar dilators are not effective antianginal agents, probably because, concomitant with the fall in arterial pressure, there is a reduction in coronary perfusion. Nitroglycerin, like amyl nitrite, has its predominant vascular effect on venous smooth muscle and reduces the haemodynamic consequences of angina. These changes, well described by Parker (1972) include abnormally elevated pul-

monary arterial, pulmonary wedge and left ventricular end-diastolic pressures. The latter can increase during exercise to 40 mmHg in patients with angina (the normal range for non-anginal patients during exercise is 8–10 mmHg). Since the abnormally increased filling pressure (and volume) which results, at least in part, from decreased ventricular compliance (or 'give'), is not accompanied by parallel increases in cardiac output, depressed left ventricular function is indicated; angina is therefore a form of acute, readily reversible, left ventricular failure. A further consequence of the elevated filling pressure is a reduction in the flow of blood to the inner (endocardial) regions of the left ventricular wall which normally occurs only during diastole. This flow reduction is known as the 'diastolic crunch' and is due to a reduction in the perfusion pressure gradient across the ventricular wall (Marshall & Parratt 1974). Yet another consequence of the elevated left ventricular filling pressure during angina is an increased myocardial wall tension (or stress). This is a major determinant of myocardial oxygen consumption. Anginal pain thus occurs because the increased myocardial oxygen demands of physical exertion are not matched by a corresponding and proportionate increase in coronary blood flow. This imbalance arises because of a restriction to flow (caused by atherosclerosis or, less commonly, arterial spasm) in the major coronary arteries. This, in turn, leads to ventricular failure, characterized by increased filling pressures, a subsequent increase in wall tension (and oxygen demands) and reduced endocardial perfusion.

How does nitroglycerin alleviate these symptoms? Certainly, from the clinical studies of Ganz & Marcus described above, by a peripheral action. This is unlikely to be on the arteriolar segment of the vascular bed, since arteriolar dilators such as hydrallazine and nitroprusside are not effective antianginal drugs. There is however much evidence for a dilator action on veins; this results in an increase in venous capacitance (venous pooling). Some of the aspects of the pharmacology of nitroglycerin that bear on its antianginal action will now be discussed.

(a) *Nitroglycerin as a venodilator*

Experimental studies have clearly shown that venous return is decreased after the administration of nitroglycerin (Holtermann & Lochner 1972; Cyong et al 1976). This is predominantly due to venous pooling since there is no evidence that fluid is sequestrated outside vascular channels; there is no effect on total circulating blood volume (Ferrer et al 1966) and no significant effect on transcapillary exchange (Ablad & Mellander 1963). It is interesting to observe that Lauder Brunton was himself very near to explaining the mechanism of action of amyl nitrite in this way. He drew attention to the similarity between relief of anginal pain by bleeding ('small bleeding of three or four ounces by venesection were always effective'; Brunton 1867) and by amyl nitrite; this in fact induces a form of 'pharmacological venesection', the patient bleeding into his own veins.

The sites of nitroglycerin-induced venous pooling have not yet been clearly elucidated, especially in man. There is however some evidence from clinical studies that pooling can occur in the pulmonary bed (Ferrer et al 1966) and in forearm skin and muscle (Mason & Braunwald 1965; Campion et al 1970). In cats, skin and muscle (Johnsson & Oberg 1968) and the splanchnic vascular bed (Chen et al 1979) are important sites.

In an important recent study comparing the haemodynamic effects of nitroglycerin with those of another effective antianginal agent, molsidomin (Holtz et al 1978) it has been shown, using the newly developed technique of induction angiometry to register luminal vessel diameter, that both drugs increase venous capacitance and hence decrease left ventricular end-diastolic pressure (LVEDP) and myocardial oxygen consumption. Molsidomin was much less active than nitroglycerin in this respect but the increase in capacitance was much more prolonged (more than 4 h compared to less than 2 min). Studies in vitro have also clearly shown that nitroglycerin has a preferential dilator effect on venous smooth muscle (Mackenzie & Parratt 1977). This is in contrast to agents such as papaverine and diazoxide which inhibit arterial and venous smooth muscle contractions to the same extent.

Although most of the evidence still points to venodilatation as the predominant mechanism whereby nitroglycerin relieves anginal pain, there are two other pharmacological actions of the drug which may contribute to its efficacy in angina. These are a direct cardiac stimulant action and a unique dilator effect on large coronary arteries and collateral vessels.

(b) *Nitroglycerin as a cardiac stimulant*

There now seems little doubt that nitroglycerin has moderate positive inotropic activity. In vivo this is shown by an increased or unchanged LV dP/dt_{max} with a reduced left ventricular filling pressure (Wiener et al 1969; Holtz et al 1978), by an increased

$_{L}$VdP/dt when systemic arterial pressure and $_{L}$VEDP are held constant (Raff et al 1970; Strauer & Scherpe 1978) and by an increase in the ejection fraction and the rate of circumferential shortening (Greenberg et al 1975). In isolated ventricular muscle preparations positive inotropic effects have been demonstrated in some species (cat, guinea-pig and man; Strauer 1973; Korth 1975). Since these effects, both in vivo and in vitro, are prevented by propranolol (and, in animal preparations, by pretreatment with reserpine; Korth 1975; Wiener et al 1969) it appears that myocardial noradrenaline release is, at least, partly responsible.

(c) *Nitroglycerin as a coronary vasodilator; unique action on large coronary vessels*

The transience, variability and generally unimpressive nature of the coronary blood flow response to nitroglycerin suggests that an increase in total coronary blood flow is not a major explanation for the undisputed antianginal effect of the drug (see Parratt 1974). There is however good evidence for a redistribution of blood flow, without necessarily an increase in total coronary flow, such that the inner (endocardial) layers of the left ventricular wall are better perfused. This is especially so when the systemic arterial pressure does not fall (Paradise et al 1976) and in myocardial ischaemia. This redistribution means an increase in the LV endocardial/LV epicardial blood flow ratio.

There are several possible explanations for this effect (Parratt 1974). The most likely is an increase in the perfusion gradient to the endocardium as a direct result of the reduction in wall stress and in LVEDP (Marshall & Parratt 1974; Parratt 1975). This has nothing to do with a direct coronary vasodilator action of the drug but is the result of venodilatation. Ganz & Marcus (1972) have clearly shown that intracoronary administration of nitroglycerin does not relieve anginal pain (despite an increase in total coronary blood flow) whereas intravenous nitroglycerin does (despite a *reduction* in total coronary blood flow). A reduced filling pressure, and the consequent relief of the 'diastolic crunch', would adequately explain the impressive results from Winbury's group (Winbury 1971) of increases in the LV endo/epi flow ratio and endocardial tissue oxygen tension. There is recent direct evidence for this view. Gross & Warltier (1977) found that, in isolated and intact dog hearts, only intravenously administered nitroglycerin enhanced endocardial perfusion; this was accompanied by a reduction in filling pressure. Nitroglycerin administered directly into the coronary artery did not alter LVEDP and, in fact, tended to *decrease* endocardial perfusion by inducing a coronary steal (see Parratt 1975).

Another possible explanation for this beneficial blood flow redistribution across the left ventricular wall is that nitroglycerin has a unique preferential dilator effect on large coronary arteries, such as those penetrating at right angles through the wall from the superficial epicardial vessels. This is the view advanced by Winbury (e.g. Winbury et al 1969). There is now increasing evidence for this possibility from studies on isolated coronary arteries and from high resolution coronary angiograms in patients with coronary artery disease. In vitro studies by Schnaar & Sparks (1972) have shown that nitroglycerin (in contrast to adenosine) preferentially relaxes large coronary arteries. This relaxation is associated with a blockade of the slow Ca^{2+} inward current by nitroglycerin and adenosine on large and small arteries respectively (Harder et al 1979). Recent clinical studies support the view that sublingual nitroglycerin has a preferential dilator effect on normal large coronary arteries and on large collateral vessels in doses less than those required to lower blood pressure or increase heart rate (Feldman et al 1979). Whether such an action of nitroglycerin is in any way related to its efficacy in patients with classical angina is debatable but such an action is clearly relevant to the relief afforded by the drug in patients with 'variant' angina resulting from coronary vasospasm (see below).

The effects of nitroglycerin in a new experimental model for angina

Up to recently suitable experimental methods for the screening of potential antianginal drugs were almost non-existent. A very significant recent advance in this field has been the canine model developed by Szekeres and his colleagues in Hungary (Szekeres 1978; Szekeres et al 1976). In this model a major (left anterior descending) branch of a coronary artery is autoperfused from a systemic artery. Flow is then reduced until ST-segment elevation and lactate production (or reduced extraction) occur, in the area of myocardium supplied by the artery, when the heart rate is increased by electrical pacing. These indices of myocardial ischaemia (ST-segment elevation; alterations in lactate handling) are reduced or abolished following the administration of nitroglycerin, verapamil or the β-adrenoceptor blocking agent pindolol (Szekeres 1978). Nitroglycerin was by far the most active of the drugs investigated in this model and standard coronary vasodilators, like dipyridamole and carbochromen, were ineffective.

Using a similar technique, Nakamura et al (1978) found that nitroglycerin increased the endocardial/epicardial flow ratio in the ischaemic area. In contrast, dipyridamole significantly decreased subendocardial blood flow and decreased the endo/epi blood flow ratio.

Nitroglycerin relieves the coronary spasm of Prinzmetal's variant angina

A return to the concept that nitroglycerin relieves anginal pain by a direct dilator action on the coronary vessels has received recent support from studies in patients with Prinzmetal's 'variant' angina. Classical angina is induced by physical exertion and occurs when the increased myocardial oxygen demands outstrip the myocardial oxygen (blood) supply through severely atherosclerotic vessels. Electrocardiographic ST-segment depression occurs in standard limb leads because the reduction in blood supply is more marked in the subendocardial regions of the left ventricular wall. In contrast, Prinzmetal's angina is characterized by chest pain at rest, by ST-segment elevation (rather than depression) in standard electrocardiographic leads and by ventricular ectopic activity (including tachycardia and fibrillation) and/or atrioventricular block. Pacing-induced angina in these patients does not usually result in abnormal left ventricular filling pressures or in abnormal myocardial lactate handling (Mammohansingh & Parker 1975). Prinzmetal postulated that 'variant angina' is due to coronary artery smooth muscle spasm superimposed on fixed proximal atherosclerotic stenoses. However there is now considerable evidence that some of these patients have spasm of major coronary arteries which appear from angiography to be anatomically normal. Such spasm, occurring in a normal vessel, can be so intense as to completely prevent flow.

The earlier evidence for coronary smooth muscle spasm as a cause of angina, and indeed of infarction, has already been summarized (Parratt 1974); more recent and comprehensive accounts can be found in the reviews by Maseri et al (1978a,b) and by Hillis & Braunwald (1978). Despite being once described as 'an extravagent and improbable hypothesis' the causal role of coronary vasospasm in variant angina is now recognized as a 'proved hypothesis' (Meller et al 1976).

Although the mechanism of coronary vasospasm is controversial (the release of vasoconstrictor substances like thromboxane A_2 and the stimulation of vascular α-adrenoceptors are the most likely explanations) there is little doubt that the spasm is relieved by sublingual or intravenous nitroglycerin, as well as by calcium antagonists such as nifedipine and verapamil (Maseri et al 1978; MacAlpin et al 1973; Hart et al 1974; Hillis & Braunwald 1978). In this situation nitroglycerin has a different mechanism of action from that in classical angina (venodilatation) because, when pain occurs in patients with 'variant' angina, left ventricular filling pressures are usually normal (Mammohansingh & Parker 1975).

Nitroglycerin has also been shown to relieve spasm induced by provocative agents (e.g. ergonovine maleate) in patients with Prinzmetal's angina (Heupler et al 1978) and also the catheter-induced spasm that sometimes occurs during routine coronary angiography (Hillis & Braunwald 1978).

Nitroglycerin reduces the extent and severity of myocardial ischaemic injury

The severity of cellular ischaemic injury can be assessed by measuring the magnitude of the increase in the ST-segment of epicardial electrocardiograms. There is a reasonable correlation between these ST-segment changes and the reductions in myocardial blood flow, tissue PO_2 and cellular creatine phosphokinase (CPK) activity at the same epicardial site (Maroko et al 1971; Hillis & Braunwald 1977). Although an early study (Bleifeld et al 1973) failed to demonstrate a protective effect of nitroglycerin, other studies, in anaesthetized (Chiariello et al 1976), sedated (Hirshfeld et al 1974) and in conscious (Smith et al 1973) dogs all showed that nitroglycerin reduced ST-segment elevation induced by acute coronary artery occlusions. For example, in the conscious dog experiments, nitroglycerin reduced ischaemic injury despite causing a reduction in systemic arterial blood pressure and an increase in heart rate, factors which of themselves would extend the area of ischaemic damage (Maroko et al 1971; Hillis & Braunwald 1977). When these haemodynamic effects of nitroglycerin were prevented by the simultaneous administration of methoxamine, the reduction in ST-segment elevation was even more pronounced (Smith et al 1973).

These beneficial electrocardiographic effects of nitroglycerin have been confirmed by biochemical and morphological indices of myocardial ischaemic damage (Hirshfeld et al 1974). In these studies, in sedated closed-chest dogs, a major coronary artery was occluded for 5 h during which period nitroglycerin was infused together with methoxamine to prevent effects on heart rate and systemic arterial pressure. Coronary perfusion was re-established at

the end of this period and the medication stopped. Twenty-four hours later the dogs were killed; there was gross evidence of transmural infarction in all the control dogs (and marked depletion of myocardial CPK in the infarcted region) but only patchy subendocardial damage, and very little depression of CPK, in the treated animals. Survival was increased in the dogs treated with nitroglycerin and methoxamine. These results indicate that nitroglycerin decreases both myocardial ischaemic injury and the incidence of ventricular fibrillation which results from an abrupt reduction in coronary blood flow (Epstein et al 1975). There is also experimental evidence that nitroglycerin improves myocardial contractile performance at the border zones of ischaemic areas (Theroux et al 1976). However, although there are good reasons for suggesting that nitroglycerin be given early in infarction (Epstein 1973) it should be realized that marked falls in systemic arterial blood pressure and the resultant reflex tachycardia will increase the severity of ischaemic damage, especially if there is pre-existing multivessel coronary occlusive disease (Myers et al 1975).

Nitroglycerin as an antiarrhythmic drug

The finding that survival following infarction is increased by nitroglycerin might be related, in part at least, to suppression of lethal ventricular arrhythmias. This possibility has been examined in anaesthetized dogs (Kent et al 1974). Measurements were made of the ventricular fibrillation threshold, defined as the minimum current required to produce fibrillation when delivered to the ventricle during the vulnerable period. This relates inversely to the tendency of the ventricles to fibrillate spontaneously. Acute myocardial ischaemia, induced by occluding the descending branch of the left coronary artery, markedly decreased the fibrillation threshold. This was partially restored to the non-ischaemic value by infusing nitroglycerin intravenously and completely restored when the nitroglycerin-induced systemic hypotension was prevented by the simultaneous administration of phenylephrine. A nitroglycerin-methoxamine combination also markedly reduced (from 92 to 50%) the incidence of ventricular fibrillation following coronary artery occlusion in dogs (Borer et al 1974). Ventricular fibrillation resulting from the release of a coronary artery occlusion (reperfusion fibrillation) is also significantly reduced by a nitroglycerin-phenylephrine combination (Stockman et al 1979). Clearly nitroglycerin decreases the susceptibility to ventricular fibrillation during both acute myocardial ischaemia and reperfusion and this beneficial effect is enhanced when systemic arterial pressure is maintained.

There is also evidence that nitroglycerin is beneficial in controlling arrhythmias in patients with coronary artery disease (Gey et al 1973) and acute myocardial infarction (Mihalick et al 1974). However, it is not known whether, besides this reduction in ventricular ectopic activity, nitroglycerin in the clinical setting can also reduce the number of deaths due to serious ventricular arrhythmias. Also the mechanism of this protective effect is unknown. There is some controversy as to whether nitroglycerin increases the ventricular fibrillation threshold of the normal, as opposed to the ischaemic, myocardium (Dashkoff et al 1976; Stockman et al 1979) but there is evidence, from guinea-pig isolated papillary muscle studies, that nitroglycerin both increases the duration of the action potential and decreases the rate of rise of depolarization (Korth 1975). Both these actions would contribute to an antiarrhythmic effect of the drug.

The effects of nitroglycerin in experimental chronic myocardial ischaemia

Although the effects of nitroglycerin in acute experimental myocardial ischaemia are somewhat equivocal (Parratt 1974; Most et al 1978) studies in chronic ischaemia are much more consistent. These experimental studies, all performed in dogs, involve placing an ameroid constrictor around a major coronary artery. This device gradually takes up water, swelling as it does so, resulting in a gradual occlusion of the artery and the subsequent development of coronary collateral vessels. It takes about three weeks after coronary artery occlusion for a smooth muscle layer to develop in these vessels and this is probably similar to what happens in patients with coronary artery disease.

When drug effects are examined in dogs with a well-developed collateral circulation created in this way, nitroglycerin invariably increases collateral blood flow, as measured from changes in backflow from the chronically occluded artery (retrograde flow) or in peripheral coronary pressure (Cohen et al 1976; Capurro et al 1977). This is especially so if the arterial pressure is stabilized. There are also increases in myocardial tissue PO_2 (Fam et al 1966) and in myocardial contractile force within the ischaemic region (Cohen et al 1976).

Nitroglycerin in congestive cardiac failure—a new use for an old drug

It was Hering in 1853 who first suggested that nitro-

glycerin might be useful in the treatment of cardiac oedema and failure. Until recently, however, the general view has been that nitroglycerin is contra-indicated in acute myocardial infarction with failure because the decrease in blood pressure and the resultant reflex tachycardia might, by reducing coronary perfusion and increasing myocardial oxygen demands, extend the area of ischaemic tissue injury. This concept is supported by the results of experiments, in animals with experimental coronary artery occlusion, indicating that ischaemic injury is increased by a reduction in blood pressure and by an increase in heart rate (Maroko et al 1971; Redwood et al 1972). However in 1972 Gold et al published a paper describing their experiences with sublingual nitroglycerin in patients with congestive heart failure following acute myocardial infarction. The most consistent finding was a reduction in pulmonary wedge pressure and relief of pulmonary congestion; there were no significant changes in either heart rate or systemic blood pressure and *increases* in cardiac output could be demonsrated in those patients with left ventricular failure. This result, which has been confirmed by subsequent studies (recently reviewed by Massie & Chatterjee 1979) and a similar one using nitroprusside (Franciosa et al 1972), has led to a reassessment of the possible role of peripheral vasodilators in the management of acute myocardial infarction and consequently to a new clinical use for nitroglycerin (Forrester et al 1976; Massie & Chatterjee 1979).

Vasodilators (nitroglycerin, nitroprusside, phentolamine) are often dramatically effective in improving the haemodynamic picture and exercise tolerance in patients with heart failure due to acute myocardial infarction. The clinical response however depends both on the initial haemodynamic situation (e.g. whether or not pulmonary congestion or peripheral hypoperfusion are present) and on the dose of vasodilator administered (Forrester et al 1976). With low doses cardiac output improves, blood pressure changes but slightly and pulmonary congestion (as assessed from measurements of pulmonary capillary wedge pressure) is reduced. With medium doses cardiac output and pulmonary congestion continue to improve and there is a fall in arterial pressure. Larger doses result in profound peripheral vasodilatation, a fall in blood pressure and in cardiac output. It is at this stage that coronary perfusion is impaired and these drugs then become potentially lethal. The most likely explanation for the effectiveness of the arteriolar vasodilators (nitroprusside, phentolamine) in a suitable dosage range is that the abnormally high resistance to ejection (impedance; afterload) present in these patients, decreases when these drugs are administered. The percentage of blood ejected per beat (the ejection fraction) is thus increased and this leads to both an increased stroke volume and a reduced left ventricular volume, with subsequent reductions in left atrial and pulmonary capillary pressures. In the case of phentolamine a direct myocardial stimulation also plays a role (Das & Parratt 1971). It is however more likely that nitroglycerin acts, as in angina, as a venodilator. This would decrease venous return and therefore pulmonary wedge pressure, LVED pressure and volume; cardiac size and hence wall tension would then be reduced, leading to a reduced myocardial oxygen demand.

Gold's original observation has been confirmed in subsequent studies (Epstein et al 1975) and there have been a number of comparisons, often in the same patients, with other vasodilators such as nitroprusside (Armstrong et al 1975; Chiariello et al 1976; Miller et al 1976; Kötter et al 1977) and phentolamine (Miller et al 1976; Kötter et al 1977). All three drugs lower systemic arterial presure and left ventricular filling pressure (i.e. there is 'left ventricular unloading') and there is symptomatic improvement (relief of restlessness, of dyspnoea and of chest discomfort) especially in patients with very high pulmonary wedge pressures (greater than 25 mmHg). The vascular site of action of the drugs varies; phentolamine exerts a peripheral dilator effect on the arterioles and, by effects on presynaptic α-adrenocepors and on myocardial noradrenaline uptake, increases myocardial contractility and heart rate. Nitroglycerin has its principal dilator action on the peripheral venous (capacitance) segment. It is preferred when pulmonary wedge and left ventricular filling pressures are high; recently the combined use of such a venodilator with a cardiac stimulant (e.g. dopamine) has been advocated. Nitroprusside causes similar dilator effects on pre- and post-capillary resistance segments and is to be preferred when arterial pressure is elevated and where pulmonary wedge pressures are normal or reduced. In patients with acute myocardial infarction only nitroglycerin reduces the severity of myocardial ischaemic damage, as assessed from the reduction in ST-segment elevation in praecordial electrocardiograms (Chiariello et al 1976). It seems reasonable to consider the suggestion (Epstein 1973) that 'patients should be advised to self-administer nitroglycerin during the pre-hospital phase of acute myocardial infarction'.

Although nitroglycerin is effective in myocardial infarction patients with accompanying failure, it is less likely to benefit those patients without concomitant left ventricular failure (Epstein et al 1975) where it may lead to pronounced hypotension and tachycardia (Chatterjee et al 1973). It has been suggested, on the basis of animal experiments (Smith et al 1973; Hirshfeld et al 1974; Myers et al 1975) that the beneficial effects of nitroglycerin in decreasing myocardial ischaemic injury (assessed from the reduction in ST-segment elevation in surface map electrocardiograms) are potentiated if the systemic hypotension is counteracted by the simultaneous administration of vasoconstrictor agents such as phenylephrine or methoxamine. There have been two relevant studies in patients with acute myocardial infarction. In one (Borer et al 1975) nitroglycerin was given sublingually and the reduction in ST-segment elevation was indeed more marked when phenylephrine was also given, provided that the patients were not in left ventricular failure. When the patients were in failure the addition of the vasoconstrictor did not further decrease ST-segment elevation. In the study of Come et al (1975), published in the same issue of the New England Medical Journal, intravenous nitroglycerin reduced systemic arterial pressure, LVEDP and ST-segment elevation. This effect was however less marked when phenylephrine was administered in a dose sufficient to restore blood pressure to pre-nitroglycerin levels. The conclusion from this study, performed in patients with grossly elevated left ventricular filling pressures, was that the addition of phenylephrine is *not* beneficial in the treatment of patients with acute myocardial infarction.

Although vasodilators have been shown to be effective in the therapy of both acute and chronic congestive cardiac failure, there are practical problems associated with their use. Nitroprusside and phentolamine have only been given intravenously and the patients require careful monitoring because of the possibility of profound systemic hypotension. Nitroglycerin does not suffer so much from this disadvantage but, when given sublingually, has only a short duration of action (Gold et al 1972). It is however readily absorbed after application to the skin and indeed is an effective antianginal drug when administered by this route. This has led to studies in which the effects of nitroglycerin ointment have been examined in patients with congestive heart failure (Taylor et al 1976) and acute myocardial infarction (Armstrong et al 1976). Both studies demonstrated that this form of therapy is highly effective and safe and has a duration of action of several hours. There were substantial reductions in pulmonary capillary wedge pressure, increases in venous capacitance and, in those patients with congestive heart failure and grossly elevated wedge pressures, increases in the cardiac index. Similar results have also recently been obtained in patients with congestive heart failure in which nitroglycerin ointment was used in combination with orally administered hydrallazine (Mehta et al 1978). It appears that this might prove to be an effective and advantageous method of administration although there are problems associated with the site and area of application, the dose (measured in inches of ointment!) and the variations in cutaneous blood flow (e.g. with temperature).

An old drug in new formulations—sustained release nitroglycerin

One of the disadvantages of nitroglycerin is its short duration of action. Following sublingal administration, peak blood levels occur within 2 min but are barely detectable after 20 min (Armstrong et al 1979). Although attempts have been made to produce compounds resembling nitroglycerin but with a longer duration of action, there is much controversy regarding the efficacy and sustained effects of such 'long-acting' nitrates. More recently sustained-release nitroglycerin preparations have been examined. The microencapsulation procedure allows the drug to be released progressively throughout the gastrointestinal tract; the release of the active drug thus depends predominantly on the mode of pharmaceutical preparation. The efficacy of the oral nitrates has been questioned on the grounds of inadequate absorption and rapid hepatic breakdown but there is now no doubt that nitroglycerin is absorbed from the gastrointestinal tract (Murrell himself administered it in 'half an ounce of water') and there is impressive evidence both for haemodynamic effects (vasodilatation, increased venous volume and cardiac output) and effectiveness in angina (Winsor & Berger 1975) and in acute myocardial infarction with cardiac failure (Strumza et al 1979). In the latter study a reduction in central venous pressure was still apparent after 12 h.

Another effective route of administration, which has already been referred to, is through the skin. In ointment form nitroglycerin provides effective protection in patients with angina for up to 3 h (see Goldstein & Epstein 1973) and haemodynamic changes (e.g. decreases in LVEDP and right atrial pressure) could be demonstrated for at least one hour (Parker et al 1976) and even up to 4 (Armstrong

et al 1976) or 5 h (Taylor et al 1976). Clearly percutaneously absorbed nitroglycerin has potential value in the treatment of cardiac failure, acute myocardial infarction and in the prophylaxis of angina pectoris.

William Murrell suffered from heart disease for several months before his death from cardiac failure in June 1912. There was extreme ventricular hypertrophy and dilatation. One wonders whether his cardiac failure might have responded favourably to the remarkable drug he introduced one hundred years ago for the treatment of angina.

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