III. BIOLOGIC EFFECTS OF EXPOSURE

Nitroglycerin (NG; trinitropropanetriol) is an oily liquid at room temperature that is colorless in pure form and pale yellow or pale brown in commercial form [5]. The chemical formula for NG is C3H5O3(NO2)3 and the molecular weight is 227. It has a bittersweet or burning taste and a slightly sweet smell at temperatures above 50 C [5]. Reported measurements of the vapor pressure of NG at 20 C range from 0.00012 to 0.011 mmHg [5-7]. Local overheating of large or confined quantities of NG may cause an explosion, although small, unconfined quantities will burn without exploding [6]. The two isomeric forms of NG differ in freezing point and in crystalline form. The stable isomer of NG freezes at 12.4-13.2 C [5,6] to form orthorhombic dipyramidal crystals. The labile isomer forms triclinic crystals at 1.9-2.2 C and is converted to the stable isomer after some 1-2 weeks of storage [5]. NG is sensitive to impact, and its sensitivity increases as the temperature increases [6]. Frozen NG is less easily detonated than the liquid form, but it becomes extremely sensitive to impact while it is thawing or when it contains minute bubbles of air.

Ethylene glycol dinitrate (EGDN; dinitroethanediol) is a colorless [6] or yellow [8] liquid at room temperature. The chemical formula for EGDN is C2H4O2(NO2)2 and its molecular weight is 152. It freezes at 22.3 or 22.8 C and measurements of the vapor pressure of EGDN at 20 C range from 0.038 to 0.050 mmHg [5,6]. EGDN is less likely than NG to explode when it burns, but the other burning and explosion characteristics of EGDN are similar to those of NG. EGDN is less sensitive to heat and to impact than NG. Other physical and chemical properties of these compounds are given in

Table XI-1 [5-9]. Numerous synonyms for NG, EGDN, and NG:EGDN mixtures are listed in Table XI-2 [10].

Most of the concentrations of NG and EGDN reported in this chapter were determined by colorimetric analysis of the amount of inorganic nitrite produced after hydrolysis of organic nitroesters. These colorimetric methods cannot differentiate between NG and EGDN or any other nitroester. However, hydrolysis of 1 mole of NG theoretically releases 3 moles of nitrite ion, whereas that of 1 mole of EGDN would free 2 moles of that ion. This means that 1 g of nitrite ion corresponds to 165 g of NG or 1.64 g of EGDN. Calculations by Einert et al [11] indicate that 1 g of nitrite ion is equivalent to 2.56 g of NG or 2.60 g of EGDN under usual laboratory conditions. The amounts of nitroesters calculated from the latter set of equivalents are sufficiently close to the theoretical values and to each other to render immaterial the nitroester chosen for expression of the analytical results. For ease of comparison, concentrations expressed by the authors in ppm have been converted in this document to mg/cu m, using the conversion factor appropriate to the compound stated by the original author or authors.

Extent of Exposure

NG was discovered in 1847 by the Italian scientist Ascanio Sobrero, when he was attempting to produce explosives from sugars and inorganic acids [12]. He synthesized NG by running dehydrated glycerin into a cooled mixture of nitric and sulfuric acids. After Sobrero's discovery, both the Italian and the Russian governments became interested in the potential military uses of NG, but the inherent danger of spontaneous explosion

caused the Italians to abandon experimentation. It was not until Alfred Nobel invented dynamite in 1867 that practical use was found for this compound.

Nobel, who had learned of the explosive properties of NG from Zinin, a Russian scientist, used diatomaceous earth to absorb the NG. The resulting mixture was a dry, less sensitive material that was safer to handle and transport than liquid NG alone [6]. Nobel created "straight" or "active dope" dynamite 2 years later by replacing the diatomaceous earth with a mixture of sodium nitrate and an absorbent, combustible material such as wood pulp. Gelatin dynamites, mixtures of NG and nitrocellulose forming a gel, were invented by Nobel in 1875. Dynamites in this form, which are used primarily to blast hard rock, are less sensitive to initiation than straight dynamite. By 1879, Nobel had established several dynamite plants throughout Europe [12].

EGDN was synthesized by Henry in 1870 but was not used commercially until the 1930's [6]. At first, small amounts of EGDN were added to NG dynamites and gelatins to lower the freezing points of the mixtures to make them safer to use, particularly during the winter months. EGDN is a good explosive in its own right and it has gradually become the major component of dynamite mixtures. This is the only commercial use for EGDN. The EGDN:NG ratio has varied over the years, but currently it is about 8:2 [11] or 9:1 [13].

Although the NG:EGDN dynamites were less likely to explode unexpectedly than straight NG dynamites, the available literature indicates that the effects of exposure to NG:EGDN dynamites on health were apparently more severe than those associated with exposure to dynamites containing NG

mixture. Since the vapor pressure of EGDN is greater than that of NG, the ratio of airborne EGDN to NG is much greater than that of the dynamite mixture itself.

In the United States, NG is manufactured either by the Biazzi process [14], which is a continuous, closed process, or by an open batch process [13]. The raw materials are glycerin and a mixture of concentrated nitric and sulfuric acids [14]. After the glycerin is nitrated, the spent acid is removed and the resulting NG is neutralized and washed. Dynamite is formed by adding "dope," mixtures that have contained sodium nitrate, sulfur, antacids, and carbonaceous combustible material, usually nitrocellulose, to the NG. To make NG:EGDN dynamites and gelatins, NG and EGDN are synthesized together by nitrating a mixture of glycerin and ethylene glycol in the presence of sulfuric acid. "Dope" is then added to the NG:EGDN mixture.

In 1976, about 250 million pounds of dynamite, containing 5-50% NG:EGDN, were produced by US manufacturers (Bureau of Mines, written communication, November 1977). The use of NG:EGDN dynamite, however, is decreasing. At present, only 10% of the blasting agents used in the United States are dynamites containing NG:EGDN.

NG is used in gun powder and rocket propellants in addition to its use in dynamite [15]. Gun powders are also known as smokeless powders [13]. Single-base propellants contain nitrocellulose alone, double-base propellants contain nitrocellulose and small amounts of NG, and triple-base propellants contain nitrocellulose, NG, and other combustible compounds [15]. NG is also used for therapeutic purposes, primarily to alleviate angina pectoris or to treat other circulatory disorders.

NIOSH estimates that about 8,000 persons in the United States are exposed to NG alone or to NG:EGDN mixtures. Occupations with potential exposure to these compounds are listed in Table XI-3 [16].

The effects on the health of workers exposed to NG and EGDN will be stressed in this document. In the workplace, NG and NG:EGDN mixtures are absorbed both by inhalation and directly through the skin. The health effects of exposure to the explosion byproducts of NG or EGDN, ie, the oxides of carbon, hydrogen, and nitrogen are not considered in this document. Regulations for the safe manufacture, handling, and use of NG or EGDN are listed in Chapter V.

Historical Reports

According to Holmes and DiCarlo [12], the physiologic effects of exposure to NG were noted soon after it was first synthesized. Sobrero himself tasted a minute amount of the compound and found that it produced severe headaches. Hering, Davis, and Jeanes began, according to Holmes and Dicarlo [12], in about 1853 to conduct experiments on the effects of NG on humans. They dissolved the compound in alcohol, absorbed the solution on sugar, and administered it orally to themselves and to others. They found that amounts ranging from 1/10 to 1/30 of a drop caused such diverse symptoms as headache, facial pain, stimulation of nerves in the neck, tremors, a sensation of warmth, and extreme thirst. Although the other effects varied, all individuals who ingested the substance developed changes in pulse rate and other cardiovascular effects. Hering proposed using NG in the treatment of a wide variety of ailments, ranging from sunstroke to epilepsy. About 1867, Brunton, a British scientist searching

for a remedy for angina pectoris, found that amyl nitrite relieved chest pains [17]. In 1879, when NG was becoming widely used as the active ingredient in dynamite, Murrell [18] reported that it had effects similar to those of amyl nitrite on the cardiovascular system.

Early literature mentioning NG as a health hazard focused on toxic side effects, overdoses, and accidental poisonings associated primarily with its use as a drug [3]. In 1859, Field [19] reported the use of NG to treat headaches and noted that it relieved them in some patients but caused them in others. Hay [20], a physician studying the mechanism of action of NG, reported in 1883 that two drops of a 1% alcoholic solution of this compound lowered his blood pressure considerably, produced throbbing of his temporal arteries, and caused facial flushing.

The suggestion that NG might be an occupational health hazard first appeared in the US medical literature of the 1890's. In 1890, Darlington [21] described several cases of illness in miners and tunnel workers who handled dynamite and inhaled both unexploded NG and its explosion byproducts. As a physician on an aqueduct project from 1885-1887, Darlington treated 1,300 workers who had complained of headache, nausea, and dizziness when they worked with dynamite. He attributed the headaches and nausea to exposure to NG and the dizziness to exposure to byproducts of explosions and to asphyxiation. The effects were particularly severe when a stick of dynamite burned but did not explode, causing some of the NG in the dynamite to vaporize. Darlington distinguished two levels of effect, which he termed "acute" and "chronic." He said that the symptoms of "acute" illness included loss of consciousness, severe headache, difficulty in breathing, weak pulse, and pallor and occurred after exposure to large

amounts of NG. Almost all workers thus affected recovered after passing through a phase of drowsiness, languor, excessive perspiration, nausea, and vomiting. Symptoms of "chronic" illness included cough, headache, indigestion, and central nervous system (CNS) disturbances. These symptoms occurred after repeated inhalation of smaller amounts of NG or of larger amounts in the presence of ample fresh air. The author also reported that similar but milder symptoms were produced by ingestion of very small quantities of NG or by skin contact with dynamite.

In 1898, Laws [22] described the effects of exposure to NG on the health of workers at a dynamite plant. Since NG was produced in an open system, workers were exposed by both inhalation and skin contact. Laws noted that the most striking and most frequent symptom was "powder headache," of which he said:

> All suffered from it who had anything to do with NG in any way. The head is generally sore; this has to be experienced to be appreciated. The workmen's wives, who do the laundry work, suffer severely every wash day. Not only the underclothing worn by the men, but any clothing, even the bed clothes will cause this feeling. In time they become inured, but all complain of the ironing. Inhaling the steam from the hot clothes makes them very sick [22].

Laws believed that NG affected the vasomotor centers, causing dilation of the left side of the heart and of the entire arterial system [22]. Associated symptoms included flushing, increased pulse rate, palpitations, nausea and vomiting, weakness, prostration, and languor. One worker developed a rash similar to that caused by contact with poison ivy. Laws observed that, after a week of exposure, workers became "accustomed" to NG. Their headaches disappeared, but recurred when they returned to work after 2 or more days' absence. After the workers developed tolerance

to NG and no longer experienced headaches and other acute symptoms during exposure, they often developed a condition that Laws termed "glonoinism." The signs and symptoms included a soft and weak pulse, heart murmurs and palpitations, poor appetite, mental sluggishness, and drowsiness during work.

Laws [22] reported that mixtures of alcohol and NG were "guaranteed to produce a more violent and serious form of intoxication than any other combination known to man." He mentioned that some had become addicted to "Gibbstown punch," the practice of drinking whiskey while rubbing NG into the skin.

The wives of NG dynamite workers often had similar symptoms, although in milder forms [22]. In addition, the wives often experienced heavy menstrual bleeding and had fewer children, often born prematurely. Infants were often cyanotic at birth, were considered to be weaker and less vigorous than others, and were thought to be especially susceptible to disease. Laws noted that infants could become sick when handled by their fathers and indicated that one child had died after being handled. Laws also mentioned that sportsmen who used smokeless powder containing NG experienced headaches similar to those experienced by dynamite workers.

In 1903, Jennings [23], a British military physician, noted that those who ate cordite, a type of dynamite containing 58% NG, and then drank beer would often hallucinate and display aberrant behavior. Jennings indicated that he experienced hammering and ringing sensations in the ears and a "most racking, splitting headache" that lasted 36 hours after he sucked on a small piece of cordite for only 2 minutes.

In 1910, Laws [24] noted that NG workers were "sooner or later troubled with dyspnea and tachycardia on exertion," and that there was an increase in the "area of heart dullness" in workers employed for many years. In this report, Laws indicated that some have a "natural immunity" to the effects of NG but that others become "maniacal" when they have this headache. Since many dynamite workers had large families, despite the tendency of their wives to have fewer successful pregnancies than other women, Laws believed that NG was an aphrodisiac. An extensive description of the symptoms associated with workplace exposure to NG published by Ebright [25] in 1914 is described in Effects on Humans.

The toxic effects of NG and EGDN in animals were studied by Bradbury [26] in 1895. He reported that intragastric administration of NG or EGDN to rabbits caused a rapid decrease in blood pressure and pulse. Haldane et al [27] reported in 1897 that the signs associated with subcutaneous (sc) administration of NG in mice and rabbits were related to the amount of methemoglobin produced.

In 1931, Oltman and Crandall [28] administered NG intravenously (iv) to 23 rabbits as a 10% solution in alcohol diluted with physiologic saline in doses of 40-70 mg/kg in 5-15 seconds. The initial signs of toxicity were immediate respiratory stimulation and slowing of the heart rate. Convulsions appeared within 15-20 seconds after injection and were initially of the tonic type but later became clonic. Between convulsions, the heart rate increased and the respiratory rate decreased. All but two of the animals that died from respiratory depression did so within 20 minutes after NG injection, and the authors stated that recovery was assured if an animal survived 5 hours. The authors noted that the signs

that occurred before death were similar to those associated with sudden asphyxia, such as that produced by a lethal dose of hydrogen cyanide. They concluded that the lethal dose of NG administered iv was about 45 mg/kg in rabbits and suggested that a dose-dependent lethal effect was associated with asphyxia caused by a decrease in blood pressure or by the formation of methemoglobin. Oltman and Crandall were apparently the first to determine the lethal dose of NG in animals.

Effects on Humans

Many reports describing occupational exposure to NG and EGDN in workers in the explosives and pharmaceutical industries have confirmed the clinical effects first noted in the 19th century. Several authors have investigated the effects of exposure to these substances on the cardiovascular system. Effects that have been reported most frequently include headache, dizziness, nausea, palpitation, angina pectoris, and sudden death without any apparent cause. In this document, angina pectoris, precordial pain, stenocardia, or posthiatal distress will be referred to as angina or as chest pain.

In 1914, Ebright [25] published an extensive description of the headaches and other symptoms associated with "acute" exposure to NG and reviewed his findings from examinations of about 20 men who manufactured NG dynamite. Ebright noted that the throbbing headaches usually began in the forehead and moved to the occipital region, where they remained for periods ranging from 1 hour to 4 days. Associated symptoms included depression, restlessness, and sleeplessness. In some cases, headaches were first associated with a sense of exhilaration. The affected workers often

experienced nausea and vomiting, and, in severe instances, diarrhea. Exposures causing these headaches varied from handling large quantities of NG to shaking hands with those who had handled the compound. Headaches were more frequent and more severe in warm weather than in cool weather. The author noted that workers were very susceptible to headaches when first exposed to NG, but that they did not complain of this effect after 3-4 days of exposure. Since tolerance to NG might be lost after a couple of days without exposure, workers often tried to maintain their tolerance by placing some material containing NG underneath their hatbands when they were away from work. Alcohol reportedly enhanced the symptoms associated with exposure to NG and sometimes precipitated severe headaches in workers who had been exposed to NG but had not developed any symptoms.

Ebright [25] examined about 20 dynamite workers to determine whether exposure to NG had effects on health other than the headaches and associated symptoms reported by the workers. Blood pressure was reported to have been within normal limits, and no abnormalities of the heart or radial artery were found. The men's complexions were normal, suggesting that there had not been appreciable methemoglobin formation, and no glucose was found in their urines. At the time of examination, one of the workers had a headache from exposure to NG, but no evidence of flushing of the skin or relaxation of the radial artery was found. The author concluded that examinations of these workers had not revealed any permanent ill effects from exposure to NG. The clinical picture of the specific type of headache caused by exposure to NG has not changed appreciably since Ebright's extensive description. In addition, Ebright [25] like Laws [23], considered NG to be an aphrodisiac.

Since Ebright's work was published, many investigators have studied headaches in workers exposed to NG or to NG:EGDN mixtures, but little information is available which specifically relates the extent of exposure with the development of headaches. In 1966, Hanlon and Fredrick [29] briefly reviewed findings from the 1961 Annual Report of the Bureau of Industrial Hygiene, Detroit Department of Health, indicating that workers who made NG tablets developed headaches and "irritation." Concentrations of airborne NG in the breathing zones of the workers ranged from 0.28 to 1.02 mg/cu m. Tablets were manufactured 2-3 times a week rather than continuously and, according to the authors, the intermittence of exposure prevented the workers from developing tolerance to the vasodilatory effect of NG. Concentrations of NG in the urines of these workers were below 0.2 mg/liter, the limit of sensitivity of the analytical method used. Hanlon and Fredrick indicated that the workers no longer complained of headaches after changes were made in operations that reduced the concentration of airborne NG to 0.09 mg/cu m. Supporting data were not provided, however. Bresler [30], Martimor et al [31], and Heimlich (written communication, September 1977) have also indicated that workers who make NG pharmaceuticals can develop headaches.

In 1946, Schwartz [32] conducted several studies on military personnel who handled dynamite sticks and who had experienced intense, throbbing headaches, vomiting, and occasional tremors of the arms about 3-4 hours after starting work. He measured blood pressures, performed blood and urine studies, recorded ECG's, and observed the retinal vessels of 10 workers who had developed headaches. Dilation of the retinal vessels was

found in all 10 workers, but no other abnormalities except decreases in blood pressure were identified.

To determine whether exposure to NG dynamite caused these symptoms, a dime-sized patch of dynamite was applied to the left scapular area of 15 men who had reported for morning sick call with unrelated complaints [32]. Another 15 men were patch-tested with "C2," a substance similar to trinitrotoluene, in an oily base. Schwartz wanted to control for the possible effects of psychogenic factors, and apparently the subjects were not informed of the identities of these substances. Fourteen of the 15 men treated with dynamite developed severe, throbbing headaches, a feeling of warmth in the face, and nausea within 3 hours of application. One subject reported seeing scintillating bodies in his right visual field. The symptoms increased in severity in some subjects during an unspecified period. None of the 15 subjects treated with C2 developed headaches within the same 3-hour period.

Schwartz [32] believed that headaches induced by NG were similar to those induced by histamine and that both were caused by dilatation of intracerebral rather than of extracerebral blood vessels. After testing many agents that cause vasoconstriction, he concluded that pretreatment with amphetamine sulfate or prostigmine bromide taken orally would minimize or prevent NG-induced headaches in workers who handled dynamite.

The headaches characteristic of exposure to such vasodilating agents as histamine and NG are thought to be produced by distention of the cerebral arteries [33]. The extracranial vessels recover more rapidly from the general vasodilatation than do the intracranial vessels, so that each systole distends the passive intracranial vessels, producing a severe,

throbbing headache. The intensity of the headache diminishes as the vascular tone of the intracranial vessels is restored.

The development of these headaches appears to be the most characteristic symptom of initial exposure to NG or EGDN. Headaches have also been reported in workers who make NG rocket propellants [34-36], who make or handle NG:EGDN dynamite [11,37-46], and who detonate NG:EGDN dynamite [47,48, and Bureau of Mines, written communication, November 1977]. Decreases in systolic, diastolic, and pulse pressures are the initial signs of exposure to NG or EGDN.

In 1966, Trainor and Jones [49] reported a study conducted in Australia of the relationship of headache and changes in blood pressure with concentrations of NG:EGDN vapor from dynamite. The study was initiated when workers complained of headaches. The magazines were ventilated by draft vents in the roof and walls, and additional ventilation could be supplied through the entrance door and three windows. Standard operating procedures provided that the buildings should be opened 1 hour before the workers entered, but this procedure usually was not followed. A preliminary evaluation indicated that concentrations of airborne NG:EGDN in six magazines ranged from 0.10 to 0.53 mg/cu m and averaged 0.36 mg/cu m as NG. The authors measured the blood pressures of eight men who worked in these magazines on a Thursday afternoon during work and on the following Monday before work. Seven of the eight men had headaches of varying severity when at work. Data were not presented, but the authors reported that there were no "significant" differences between the blood pressure measurements made on Thursday during work and those made on Monday before work. These findings suggest, however, that workers can develop headaches

when exposed to NG:EGDN vapor at concentrations as low as 0.10 mg/cu m even in the absence of skin contact.

Using volunteers, Trainor and Jones [49] assessed the effects of exposure to airborne NG:EGDN dynamite on blood pressure and on symptoms such as headache or feelings of dullness in the head. Concentrations of airborne NG:EGDN in the magazine were measured on Monday morning after various quantities of dynamite had been placed on a table the previous Friday afternoon. The effects of exposure were assessed at three different concentrations of airborne nitroester: 2.0, 0.7, and 0.5 mg/cu m expressed as NG. Blood pressure was measured before and after a 25-minute exposure, or after a shorter period if severe symptoms developed. Pulse pressure (systolic minus diastolic pressure) was calculated from the authors' data. Changes in the systolic, diastolic, and pulse pressures after exposure were determined for each subject, and the statistical significance of these changes for each exposure group was determined using a paired t-test. The results are shown in Table III-1.

Four volunteer workmen and the two authors were exposed to vapor from NG:EGDN dynamite at concentrations of 2.0 mg/cu m as NG (range not specified). The maximum allowable concentration in Australia in 1966 was 2 mg/cu m [49]. Three of the six subjects developed headaches 1-3 minutes after entering the magazine. Systolic pressure decreased in five subjects and diastolic pressure decreased in four subjects. Blood pressure readings were the same before and after exposure for the one subject who did not develop a headache.

TABLE III-1

BLOOD PRESSURES IN MEN EXPOSED TO VAPORS FROM NG:EGDN DYNAMITE

Concentration* (mg/cu m)	No.	Exposure (min)	Pressure Measured	Before Exposure (mmHg)		After Exposure (mmHg)		Decrease (mmHg)	
				Mean	SD	Mean	SD	Mean	SD
2.0	6	1-3	Systolic	120.8	7.3	108.3	6.0	12.5**	4.0
			Diastolic	72.2	4.8	70.8	4.6	1.3	5.9
			Pulse	48.7	6.7	37.5	3.6	11.2**	4.0
0.7	10	25	Systolic	121.0	2.3	103.0	4.3	18.0**	3.6
			Diastolic	86.2	3.1	77.2	3.2	9.0**	2.8
			Pulse	34.8	2.1	25.8	2.2	9.0**	2.7
0.5	7	25	Systolic	125.0	7.6	114.0	7.0	11.0**	4.1
			Diastolic	83.6	5.0	77.1	4.9	6.4**	2.6
			Pulse	41.4	4.6	36.9	4.3	4.5	4.4

*As NG
**Statistically significant ($P<0.05$)

Adapted from Trainor and Jones [49]

All 10 volunteer workmen exposed to vapors from NG:EGDN at 0.7 mg/cu m as NG (range 0.65-0.75 mg/cu m) developed sensations of pulsation in the temporal region, headache, or dullness in the head [49]. Systolic pressure decreased in eight workers, and diastolic pressure decreased in seven workers. For one subject, systolic and diastolic pressures were the same before and after exposure, although he did develop a slight headache.

Six of seven subjects exposed to vapors from NG:EGDN at 0.5 mg/cu m

susceptible to the headaches associated with exposure to dynamite, although both his systolic and diastolic pressures decreased by 10 mmHg after exposure. Systolic and diastolic blood pressures were the same before and after exposure for one worker, although he developed a slight sensation of dullness in his head. The average decrease in blood pressure was 11.0 mmHg for systolic pressure, 6.5 mmHg for diastolic pressure, and 4.5 mmHg for pulse pressure.

Although it was not explicitly stated in the report, the experiments involving exposures at airborne concentrations of 0.5 and 0.7 mg/cu m as NG were apparently performed on Mondays, since air concentrations were achieved by leaving dynamite on a table in the magazine over the weekend [49]. By Monday morning, the volunteer workmen had probably lost most of the tolerance to NG:EGDN that they had acquired during the previous week. The responses of those not exposed to NG:EGDN in the workplace might be greater than the responses of dynamite workers. For instance, the blood pressure of one of the authors decreased from 150/90 to 120/70 within 3 minutes of exposure to the dynamite mixture at 2.0 mg/cu m expressed as NG. The author's systolic pressure decreased by 30 mmHg, compared with the group average of 12.5 mmHg, and his diastolic pressure decreased by 20 mmHg, compared with the group average of 1.4 mmHg.

Although such symptoms are difficult to evaluate objectively, the authors [49] concluded that the headaches were "marked," "slight," and "mild" at concentrations of 2.0, 0.7, and 0.5 mg/cu m expressed as NG, respectively. The mean systolic, diastolic, and pulse pressures for each group decreased after exposure at the three concentrations, but the large standard deviations indicated that there was considerable variation in the

response of individuals. Only the mean difference between pulse pressures measured before and after exposure appeared to be dose-related.

This study [49] showed that, in most workers, initial exposure to NG:EGDN vapor from dynamite is consistently associated with headache or similar symptoms and with decreases in systolic, diastolic, and pulse pressures. These signs and symptoms can be considered to be indicative of changes in blood flow associated with vasodilation. The study conclusively shows that exposure to NG:EGDN vapor at an average concentration of 0.5 mg/cu m as NG, even in the absence of direct skin contact, is associated with the development of headache and decreases in blood pressure. From their preliminary study, inhalation of airborne NG:EGDN at concentrations as low as 0.1 mg/cu m as NG may have been associated with the development of headaches.

Decreases in systolic, diastolic, and pulse pressures during initial exposure are suggestive of vasodilation, and increases in diastolic pressure from the levels during initial exposure are indicative of compensatory vasoconstriction. However, other factors, including activity level, use of stimulant beverages such as coffee or tea, and underlying diseases can affect measurments of blood pressure in workers exposed to NG or EGDN.

The monitoring of blood pressure in dynamite workers began in the US in 1937 [50], and scoring procedures similar to those developed by Foulger [51,52] have often been used. Workers were usually removed from exposure if their scores indicated that their blood pressures were not within normal limits, ie, if the extent of compensatory vasoconstriction during exposure to NG or EGDN was not sufficient to maintain normal blood pressure. Some

US dynamite manufacturers are currently measuring the blood pressures of workers exposed to NG:EGDN [13].

Although most of the monitoring data has not been published, a few authors [11,46,53,54] have reported blood pressure measurments in dynamite workers. Einert et al [11] measured the blood pressures before and after work and found that, during each workshift, systolic pressures decreased, diastolic pressures increased, and pulse pressures decreased in dynamite workers. However, Hasegawa et al [53] did not find any significant differences in the systolic, diastolic, or pulse pressures of 29 NG:EGDN dynamite workers compared with those of 8 controls. The results of these studies are discussed in further detail in Epidemiologic Studies.

In 1957, Forssman et al [54] reported findings from medical examinations of 276 workers (174 men and 102 women) employed at three dynamite plants in Sweden. At the first plant, EGDN was mixed with NG only during the winter months; the ratio of EGDN:NG was 1:1 at the other two plants throughout the year. Concentrations of airborne NG:EGDN from various operations were measured at all three plants. The samples were taken at face level as close to the work areas as possible, and the results were expressed in mg/cu m as NG. Using a colorimetric method, airborne concentrations ranged from undetectable in the packing and the washing and drying operations at the first plant to 11 mg/cu m as NG in the "gelatinating" operation at the second plant. Average airborne concentrations were 2.3 mg/cu m as NG at the first plant (10 operations), 3.7 mg/cu m at the second plant (7 operations), 3.4 mg/cu m at the third plant (14 operations), and 3.1 mg/cu m for all three plants combined.

Information on the potential for dermal absorption of NG:EGDN was not provided.

Blood pressure was measured for each of the 276 workers at the beginning of a workweek, after a holiday, and at the end of the week [54]. Twenty-four per cent of the men and 30% of the women were less than 30 years old, 54% of the men and 60% of the women were 30-49 years old, and 22% of the men and 10% of the women were 50 or more years old. Information on duration of employment was not available for the third plant. At the other two, the average length of employment was about 6 years for men and about 5 years for women.

The authors [54] reported average blood pressure readings in each of the three age groups at each of the three plants. Since airborne concentrations of NG:EGDN at the three plants were in the same range, the data for each age group at the three plants were averaged by NIOSH, weighted by the number of workers in each group, so that blood pressure measurements could be compared easily. At the beginning of the week, average blood pressure measurements for the 174 men were 123 mmHg for systolic pressure, 75 mmHg for diastolic pressure, and 47 mmHg for pulse pressure. At the end of the week, average blood pressure measurements for these workers had increased to 129 mmHg for systolic pressure, 79 mmHg for diastolic pressure, and 51 mmHg for pulse pressure. For the 102 women, average blood pressure measurements at the beginning of the week were 145 mmHg for systolic pressure, 77 mmHg for diastolic pressure, and 47 mmHg for pulse pressure. At the end of the week, average blood pressure measurements for these women were 132 mmHg for systolic pressure, 82 mmHg for diastolic pressure, and 55 mmHg for pulse pressure.

Forssman et al [54] stated that initial exposure to NG or to EGDN was associated with rapid decreases in both systolic and diastolic blood pressures. They also believed that long-term exposure to EGDN tended to raise diastolic pressure and reduce systolic pressure but that long-term exposure to NG had no known effects on blood pressure. References were not cited, however. During the week, average diastolic and pulse pressures increased in both men and women, but systolic pressure decreased by an average of 13 mmHg in women, whereas that in men increased by an average of 6 mmHg. The increase in diastolic pressure in both men and women suggests, however, that there is some compensatory vasoconstriction during exposure to these compounds. Information was not provided on the circumstances during which the workers' blood pressures were measured, but if physical activity is required by the job, particularly for the men's jobs, the measurements taken after a week of work probably reflect a combination of the effect of exposure to NG:EGDN and compensatory vasoconstriction as well as differences in level of activity and other factors.

Forssman et al [54] reported that 31 of the 276 dynamite workers (11%) had "light" ECG changes which were associated with increased blood pressure, or "moderate" changes which were associated with organic heart disease, but they did not attribute these changes to exposure to NG:EGDN. The extent or degree of these changes was not specified. Pulse rates and respiratory rates were measured as indicators of physical capacity. Fifteen workers had readings indicative of "reduced capacity", but the authors reported that 14 of these 15 (93%) also had symptoms (not specified) that could have contributed to reductions in physical capacity. They also indicated that the absence records of workers exposed to NG:EGDN

were generally similar to those of workers who were not exposed.

Forssman et al [54] concluded that permanent symptoms of impaired health that could be attributed to exposure to "nitrocompounds" were not found in medical examinations of this group of dynamite workers. With the exception of the blood pressure measurements, the authors reported their conclusions without citing supporting data.

A comparison of pulse pressure measurements in workers employed at an NG:EGDN dynamite plant in Tamaqua, Pennsylvania, was reported by Keogh et al [46] in 1977. The 46 workers, all volunteers, were divided by the authors into four exposure groups based on the jobs they performed when the study was conducted. The cleanup crew was in the heavy exposure group, mixing and packing workers were in the moderate exposure group, locomotive operators and laundry workers were in the minimal exposure group, and nitrocellulose and dope house workers were in the no exposure group. The pulse pressures of workers determined after work on Friday and before work on a Tuesday after a long weekend are shown in Table III-2 [46].

All the workers had been engaged in strenuous physical activity before pulse pressures were determined on Friday, but they had been at rest before the determinations on Tuesday [46]. On Friday after work, average pulse pressures were lower in workers in the minimal, moderate, and heavy exposure groups than in those in the no exposure group. On the following Tuesday, after 3 days without exposure, average pulse pressures of the three exposed groups were somewhat higher than that of the unexposed group. In workers not exposed to NG:EGDN, the average pulse pressure was 6 mmHg higher (20%) on Friday after work than on Tuesday before work, suggesting that physical activity in the absence of exposure to NG:EGDN can cause an

TABLE III-2

PULSE PRESSURES* IN NG:EGDN DYNAMITE WORKERS

Exposure	Workers		Pulse Pressure (mmHg)				Difference Friday-Tuesday
	No.	Av Age	Friday after Exposure (Mean)	(SD)	Tuesday before Exposure (Mean)	(SD)	
Heavy	5	39	28	23	36	10	-8
Moderate	22	36	30	8	35	10	-5
Minimal	4	38	33	12	35	12	-2
None	2	36	39	10	33	14	+6

*Determined while workers were standing

Adapted from Keogh et al [46]

increase in pulse pressure. In contrast, average pulse pressures were lower on Friday after work than on Tuesday before work in those with minimal, moderate, or heavy exposure to NG:EGDN. Measurements of pulse rates would have been useful in determining whether differences in pulse pressures were affected by differences in level of activity. A quantitative index of exposure was not available, but in the three exposure groups, decreases in average pulse pressures at the end of work on Friday below the presumably normal pulse pressures determined on Tuesday before work appear to be related to the estimated intensities of the exposures. These findings suggest that the vasodilating activity of NG:EGDN causes decreases in pulse pressures of exposed workers even during activity that

would normally be associated with increases in pulse pressure.

In another study, Keogh et al [46] attempted to identify an adequate biologic index of exposure to NG:EGDN. Blood pressure, pulse rate, pulse wave changes in the fingertips, heart chamber volume, and concentrations of NG and EGDN in the blood and on the skin surface were measured in volunteer workers after work on Friday and before work on Monday. The analysis of this information, however, is not yet complete.

Kubota [55], in 1975, reviewed findings from studies on workers exposed to NG:EGDN at a dynamite plant in Japan. He indicated that the amount of EGDN absorbed through bare hands was about twice the amount absorbed through rubber gloves. The study design, however, was not presented. Kubota noted that the surface of "sticky" dynamite contained a surface activating agent that accelerated EGDN absorption through the skin, but the agent was not identified. The author listed the methods that he considered to be useful for the early detection of EGDN poisoning, based on a study during 1963 of workers at a Japanese dynamite plant. Postural hypotension, a decrease in blood pressure of more than 10 mmHg upon standing, was found in about 15% (12 of 81) of the workers exposed to NG:EGDN and in about 4% (2 of 50) of the unexposed workers. Of the 22 former dynamite workers with a history of "EGDN poisoning," 32% (7) also had postural hypotension. Kubota also indicated that another useful indicator of early intoxication by NG:EGDN was found in the concentrations of fatty acids in the workers' sera: decreases in those of free fatty acids and of linoleic acid and an increase in that of oleic acid. Liver function disorders were apparently more common in workers with a history of EGDN poisoning but, again, details were not reported. Kubota's findings

suggest that the effects of exposure to NG:EGDN dynamite are not completely reversed when exposure is terminated.

Laws [24] noted in 1910 that some dynamite workers employed for many years developed an enlarged "area of heart dullness." The first reports of what have become known as "Monday morning angina or sudden death" were published in the 1950's [37,56]. In 1952, Symanski [56] described three cases of sudden death without any apparent cause in men who made or filled cartridges with NG:EGDN dynamite in the Saar (West Germany). One worker was 42 and the other two were 50 years old at the time of death. All died suddenly on Monday or Tuesday morning. Distension of the cerebral blood vessels was the only autopsy finding in the two cases examined shortly after death. In the third case, no evidence of heart disease, cerebral hemorrhage, or hypertensive disease was found in an autopsy performed 1 year later on the exhumed body. Symanski [56] concluded that the deaths were associated primarily with exposure to EGDN although he suggested that alcohol ingestion or physical exertion over the weekend may have been contributing factors.

Symanski [56] learned through personal communication that 6-8 dynamite workers from Scotland and 1 from West Germany had died suddenly and that 37 sudden deaths had occurred in dynamite workers in the United States between 1927 and 1936. Apparently these deaths were more frequent in the United States in 1935-1936 than in earlier years [56]. The workers who died had presumably developed tolerance to NG:EGDN, since they had not complained of headaches. The deaths seemed to occur shortly after slight physical exertion, and some of the workers had complained of weakness shortly before death. All 37 dynamite workers in the United States

apparently died suddenly from heart attacks, most of which occurred during summers. Symanski [56] did not learn of any sudden deaths in US dynamite workers that occurred after it had become the practice to circulate fresh air in the breathing zone of workers in the homogenizing and cartridge-filling areas. According to a personal communication from Naoum cited by Symanski [56], this procedure apparently helped to keep the concentration of NG:EGDN in the mixing and cartridge-filling areas below 2 mg/cu m, as measured by a colorimetric method using sulfuric acid.

Symanski's report [56] was the first to mention that sudden deaths had occurred in dynamite workers in the United States, yet further details on the circumstances of these deaths have apparently not been published. In an oral deposition taken in 1975 [50], Foulger said that Symanski's report of 37 sudden deaths in US dynamite workers was only a rumor, although he indicated that an unspecified number of sudden deaths in this group had occurred when they were away from work.

In 1954, Barsotti [37] described symptoms of angina in 14 workers who manufactured NG:EGDN dynamite in Italy. Medical histories and interviews with workers were used to identify workers with symptoms and to characterize these symptoms. Seven of the 14 workers had frequent and severe attacks of angina, and the other 7 had had mild and occasional attacks. These symptoms were more severe in the summer than in the winter months. In most instances, the workers suddenly developed angina on Sunday night or Monday morning, about 48-60 hours after their last workplace exposure to the dynamite mixture. The pain usually began in the chest and spread to the left side of the neck. Associated palpitations and difficulty in breathing were sometimes so severe that the workers were

immobilized. The attacks usually lasted for several minutes; shorter, less severe episodes often continued to occur for several hours and for up to 3-4 days in severe cases. The workers experienced relief from mild attacks immediately after they returned to the same workplace. Angina attacks were equally prevalent in men and women and were reported only in workers over 40 years old.

Barsotti [37] noted that other symptoms, including severe headache, weakness, loss of appetite, hot flashes, palpitations, and intolerance to alcohol, occurred more frequently and were more severe when dynamite workers were exposed during production of dynamite containing NG and EGDN than when they were exposed to dynamite containing NG alone. Medical examinations indicated that bradycardia and hypotension also were more frequent and severe when workers were exposed to the NG:EGDN mixture. There was no evidence of production of methemoglobin or Heinz bodies, and no ECG changes were found regardless of the time of examination.

The types of work engaged in by some of the workers who developed angina were described. Two worked in the nitration operation, one in solidification, two in forming, and two in cartridging [37]. Barsotti indicated that the ventilation in work areas was being increased in an attempt to keep the concentration of airborne NG:EGDN below 2 mg/cu m and that the plants were eliminating EGDN from the dynamite mixture during the summer months. Environmental concentrations of NG:EGDN were not given. The author reported that the frequency and severity of angina attacks and other symptoms in workers progressively declined and then nearly disappeared after ventilation was increased and the use of EGDN was restricted to the cooler months, but supporting data were not provided.

Barsotti [37] believed that exposure to EGDN aggravated the symptoms, such as headache, associated with exposure to NG, and that angina and similar symptoms were associated with exposure to and withdrawal from EGDN alone. He based these inferences on the observation that angina was first reported in dynamite workers after the practice of adding EGDN to the mixture began in the 1930's. Barsotti suggested that angina was a symptom of deficiency in blood flow caused by reflex vasospasms in the heart mediated by the CNS during a period when the worker was not exposed to the vasodilating effect of EGDN.

In 1963, Bille and Sivertssen [57] reported the circumstances of the death of a 34-year-old man who had been employed for 6 years in a Norwegian dynamite plant, where his most recent duty had been to mix NG and EGDN by hand with other substances, such as nitrocellulose. A mixture of 40% NG and 60% EGDN was used in the winter, and the reverse mixture was used in the summer. The authors reported that air samples taken during recent years revealed concentrations of airborne explosives, expressed as NG, of 0.3-1.4 mg/cu m in the winter and 1.4-3.8 mg/cu m in the summer. The authors noted that these concentrations were well below the MAC in Norway at that time (4.7 mg/cu m). The extent of skin exposure was not determined.

The worker, a very heavy smoker, complained of chest pains for 3 weeks in January 1959, but no other signs or symptoms were detected in a medical examination [57]. Later in the same year, during a 60-hour vacation period, he went outside after smoking a few cigarettes and eating breakfast, but returned immediately because he was feeling ill. He developed chest pains and died within 10 minutes of returning to the house.

An autopsy revealed enlarged lungs with the alveoli containing bloody edema fluid [57]. The heart was flabby, blood vessels were dilated, and the coronary arteries were atherosclerotic to varying degrees. The worker's death was considered to have been job-related, although heavy smoking was regarded as a contributory factor. This is one of the few reports describing sudden deaths in workers exposed to NG or EGDN in which information on airborne concentrations of these compounds is included.

In 1963, Carmichael and Lieben [58] investigated six deaths at one dynamite plant, four at a second plant, and three at a third plant. These deaths occurred between 1956 and 1961 in a group of some 125 workers employed in NG:EGDN dynamite mixing or cartridge-filling operations at plants in Pennsylvania. The authors summarized the available occupational, clinical, and autopsy information on these cases and compared the estimated death rates in dynamite workers with expected values for all coronary artery diseases combined and for sudden unexpected death. They also discussed several theories of the toxicity of EGDN and NG.

From 1957 through 1960, 6 deaths occurred among 75 workers employed in the nitrating, mixing, and packing and shoveling operations at one plant. Four of the six workers died suddenly, one a few hours after the initial heart attack and one 8 days after an attack. In all cases, coronary artery disease was considered the cause of death. All but one of the workers in the plant were under 55, and the six workers who died were between 32 and 50 years old. The authors estimated that the expected number of deaths from coronary artery disease (ICD No. 420.1, including coronary artery disease, sclerosis, and myocardial infarction) for the 75 dynamite workers was 0.084/year, based on Pennsylvania statistics for 1957-

60, and 0.1/year, based on statistics for the county in which the plant was located. Thus, the risk of death from coronary artery disease among the 75 dynamite workers was 15-18 times greater than expected in the 4-year period.

Carmichael and Lieben [58] also compared the risk of sudden death from heart disease in these workers with estimates available for men aged 30-62 from the Framingham (Massachusetts) Heart Study [59]. The incidence of sudden death in Framingham men was 10.5/1,000 for a 6-year period. At one of the dynamite plants in Pennsylvania, 5 of 65 men aged 30-62 died suddenly within 4 years. Compared with the Framingham men, these dynamite workers were about 11 times as likely to die suddenly from heart disease. Carmichael and Lieben acknowledged that these estimates were crude but thought that the estimates did give some indication of the extent of the increase in deaths from heart disease in dynamite workers at one plant in Pennsylvania.

Complete information was not available for any of the six workers from the first plant who died suddenly [58]. Autopsy information was given for five workers, and some information about work histories and clinical findings was given for all six workers. Five of the six who died suddenly had packed dynamite into cartridges by hand for periods ranging from 3 to more than 13 years. The five died on a Saturday morning, a Sunday evening, a Monday morning, or a morning after a holiday. Three of the five had not complained of chest pain, one had complained for 10 years, and one had had chest pains shortly before his death. Blood pressure measurements were variable, but they generally showed decreased systolic and diastolic pressures and increased pulse rates after workshifts. ECG recordings were

described for four of the five handpackers. The recordings were considered to be normal for three of the workers; an inverted T wave (V3 and V4 leads) was noted in the recording of the fourth worker, in whom a healed infarct was found at the autopsy. Autopsies of four of the five handpackers showed that all organs except the heart were normal. Sclerosis of the coronary arteries was moderate to severe, and the vessels were often thickened with hyaline or connective tissue. A thrombus was found in the coronary artery of one worker, and an atherosclerotic plaque that almost completely occluded a coronary artery was found in another worker, but no anatomic anomalies or accumulation of lipids that could cause sudden death were found in the other two workers.

The sixth death reported from the first dynamite plant was that of a man in his mid-40's who had been employed in the mix house and who was admitted to the hospital on Sunday evening with severe epigastric pain [58]. Acute myocardial infarction was diagnosed and he died 8 days later. Moderately severe coronary arteriosclerosis, a thrombus of the right coronary artery, and an arteriosclerotic occlusion of the left coronary artery were found at autopsy. The man reportedly drank large amounts of alcohol.

In a small plant in Pennsylvania employing fewer than 25 people, 4 men who had worked as dynamite packers for 1 year or more died suddenly during a period of 5 years [58]. The authors stated that the concentrations of airborne "nitrates" in the areas where cartridges were filled by hand were elevated, but the concentrations were not given. Review of the plant personnel records indicated that many workers had left the plant after less than 2 months' employment, apparently because they had

developed severe headaches. The four workers who died suddenly at this plant were 34-43 years old. Three of these had experienced chest pain before death. One of the workers had worked as a dynamite cartridge-filler for 3 years and had passed a comprehensive physical examination 2 weeks before his death at age 37. The cause of death was diagnosed as acute myocardial infarction secondary to coronary occlusion. The walls of the coronary arteries were thickened, and arteriosclerotic plaques almost completely occluded the lumen in some areas. A previous infarction was indicated by the extensive replacement of myocardial tissue with fibrous tissue.

The authors [58] were able to provide even less complete information on workers from the third plant, where four workers had died suddenly on Monday mornings over a 12-year period. At autopsy, a worker who died at the age of 32 was found to have had severe sclerosis of the coronary arteries. The authors reviewed the medical records from one of the plants (unspecified) and found that many workers had complained of indigestion, chest pain, and shortness of breath, although indications of cardiac ischemia had rarely been found in their ECG's. Blood pressure measurements, apparently made at regular intervals, indicated that there was no consistent rise in diastolic pressure, although pulse pressure measurements had decreased considerably from preemployment measurements in many exposed workers.

Information given by Carmichael and Lieben [58] indicated that there were many similarities between the cases of sudden death in workers at these three dynamite plants. All the workers died suddenly at a relatively early age during a period of up to 48 hours when they were not exposed to

NG or EGDN in the workplace. In most of the autopsies, the walls of the coronary arteries were found to be thickened with fibrous and hyalinized connective tissue, and the lumina were restricted with moderate to severe arteriosclerosis. However, the arteriosclerosis appeared to be limited to the coronary vessels. The cause of death appeared to be acute myocardial infarction, but in only a few cases was there evidence that an occlusion had occurred shortly before death. About half the workers had experienced angina or similar symptoms before death, but at least two of them had not reported having any pain.

The authors [58] were unable to determine the toxic mechanism that caused sudden deaths in dynamite workers, but they suggested two theories. One possibility was that the deaths were associated with a spasm in a coronary artery that occurred when the worker was not exposed to the vasodilatory effects of the dynamite mixture. The other was that death was related to peripheral vasodilatation consequent to reexposure to nitroesters after withdrawal from repeated exposures on workdays. The expansion of the peripheral circulatory bed in conjunction with sclerosis of the coronary arteries would require the heart, through barostatic reflexes, to pump extra blood, a requirement it could not meet because of deficient venous return and insufficient supply of oxygen to its own muscles. If the subsequent peripheral hypoxemia resulted in release of catecholamines from the adrenals and chromaffin tissue, these sympathomimetic amines would tend to further increase demands on the heart without increasing either the venous return or the intramural supply of oxygen. Carmichael and Lieben indicated that they favored the second theory, since they had found little pathologic evidence of coronary

vasospasm in the autopsied workers. It is unlikely, however, that a spasm of a coronary artery would result in findings that could be identified in an autopsy. It is possible that both mechanisms were associated with these sudden deaths.

According to Carmichael and Lieben [58], Hueper [60,61] had suggested that the nutrient arterioles in the heart might have been damaged by repeated dilation and constriction, promoting the deposition of hyaline connective tissue. This tissue could then have resulted in sclerosis that could not be distinguished at autopsy from arteriosclerosis associated with other factors. However, these data do not indicate whether arteriosclerosis was more or less severe in the hearts of the dynamite workers than in those of others, since the coronary arteries from these autopsies were not compared with those from autopsies of unexposed men of similar age.

In conversations with medical personnel from other US explosives manufacturers, Carmichael and Lieben [58] learned that sudden deaths had occurred in US dynamite workers some 20-25 years previously, but that they could not be directly attributed to exposure to either NG or EGDN. Apparently on the basis of these conversations, the authors indicated that there had been a nearly tenfold increase in sudden deaths in workers since EGDN had been introduced into the dynamite manufacturing process. Therefore, they implicated EGDN as the agent responsible for angina and for sudden deaths in dynamite workers. Carmichael and Lieben were the first to describe cases of sudden death in workers employed in the manufacture of NG:EGDN dynamite in the United States.

Yamagawa [62] reported in 1965 that eight workers aged 35-51 who had been employed at a NG:EGDN dynamite plant in Japan for 12-26 years had died suddenly without any apparent cause. Six of the eight died on Sunday or Monday. An unspecified number of workers had angina and numbness in the fingers. Both symptoms disappeared when the workers changed jobs, suggesting that at least some effects of exposure to NG:EGDN are reversible.

Lund et al [63], in 1968, described nine cases of toxic effects in workers after they were withdrawn from exposure to NG. The exposures occurred at an explosives factory in Sweden during 8 years when workers were handling NG directly. Although the workers wore protective clothing and gloves, the authors indicated that some NG might have been absorbed through the skin.

A 35-year-old worker who died had been exposed to NG for 9 years [63]. He had consulted a physician about 5 months before his death about severe attacks of chest pain. These attacks occurred on Sundays, during either the evening or the night, but disappeared shortly after he returned to work on Monday. Physical examination and an ECG recording at that time revealed no abnormalities. At a routine physical examination 1 month later, the patient indicated that the chest pains had not returned. He died 4 months later on a day after a national holiday. Myocardial infarction was the clinical diagnosis of the cause of death, but an autopsy did not reveal any signs of atherosclerosis in the coronary arteries or any other pathologic condition except lung congestion. It was learned later that the worker had experienced chest pains before his death.

Eight cases of nonfatal symptoms associated with withdrawal from exposure to NG were described in this report [63]. Seven of the subjects were men aged 38-55 who had worked with NG for 2-27 years; one of these men had also been exposed to EGDN, but only for 24 hours. The eighth subject was a 45-year-old woman who had worked with NG for 11 years. In most of these cases, the workers suffered from headaches and chest pains that developed 30-65 hours after their last contact with NG, in several cases when the employees returned to work on Monday. Physical examination of these workers did not reveal any pathologic conditions, and ECG recordings contained no abnormalities. None of the workers reported having continued chest pains after they were no longer exposed to NG in the workplace.

Lund et al [63] concluded that withdrawal from exposure to NG was the cause of the chest pains in all these workers, since they could find no other reason for their occurrence. This was the first report to indicate that workers exposed to NG alone as well as to NG:EGDN mixtures could experience angina or die suddenly without any apparent cause. The authors suggested that the symptoms associated with withdrawal from NG were qualitatively similar to those associated with withdrawal from EGDN. They also suggested that angina would probably occur less frequently in dynamite workers exposed to NG alone than in those exposed to NG:EGDN mixtures, since they believed that both the vapor pressure and the toxicity of NG were lower than those of EGDN.

In 1977, the US Army Environmental Hygiene Agency (AEHA) provided NIOSH with information on work practices, engineering controls, and environmental concentrations of NG at 11 installations [35]. This information, apparently collated from industrial hygiene surveys conducted

by the AEHA, is reviewed in Chapter IV. The AEHA also provided some information on the health of workers at two of the installations.

At "Installation H," about 120 workers engaged in the manufacture of double-base rocket propellant were exposed to airborne NG at concentrations ranging from 1.3-2.0 mg/cu m for 4-8 hours a day [35]. Workers were provided with neoprene gloves or cloth gloves with leather palms. The report indicated that workers complained of occasional headaches, but no further details were provided.

The 1977 AEHA report [35] included a summary of an industrial hygiene survey and a review of medical records conducted in 1971 at a plant listed as "Installation K." A 1971 report from the AEHA [36] indicated that Installation K was the Badger Army Ammunition Plant in Baraboo, Wisconsin. Double-base rocket and small arms propellants containing NG were manufactured at this plant, which had operated during World War II and the Korean War and had been reopened in 1966 to make ammunition for the Vietnam War. The plant is no longer in operation.

There was concern, beginning in 1968, that exposure to NG might be affecting the health of some workers. The AEHA was asked to perform this study after the appearance of magazine and newspaper reports of chest pain in workers exposed to NG. A total of 8,836 workers were employed at the Badger plant at the time of the AEHA survey in 1971 [36]. Of these, 266 workers (136 men and 130 women) were employed in areas where there was a potential for exposure to NG.

The AEHA first reviewed the medical records of 40 workers from this plant alleged to have had illnesses or diseases associated with exposure to NG between January 1968 and August 1971 [36]. The AEHA decided that there

was no potential for exposure to NG in the jobs of 7 of the 40 workers. A table in the report indicates that three of these seven people worked in the smokeless powder or the nitrocellulose (nitrocotton) areas where there probably was little or no exposure to NG, but the other four operated transport carts or were supervisors in areas where NG was present.

The AEHA found that 5 of the 40 workers (13%) alleged to have had conditions related to exposure to NG had not reported having heart problems or other illnesses to the plant medical department [36]. Four workers had reported rashes and four others, all employed in the roll and press area, had reported headaches but no other symptoms. The AEHA concluded that 12 of the 40 (30%) had "heart conditions," based on ECG evidence of myocardial infarction or coronary occlusion, or on complaints of angina, burning in the chest, or chest pain. Eight of the 40 workers (20%) were considered to have had "chest pains", which were described as coronary spasms, gas pains, or dull pains in the chest. The criteria used to distinguish "chest pains" from "heart conditions" were not discussed.

Seven of the 40 workers (18%) employed at the plant had died between January 1968 and August 1971 [36]. In 1968, a 49-year-old man who had worked in the paste area died on a Tuesday, and a 40-year-old woman who had worked in the roll and press area died on a Monday. The cause of death was not listed in the plant medical records of either worker. The AEHA classified both of these deaths as "sudden." A 60-year-old man who worked in the roll and press area died on a Thursday and a man (age not specified) who was a supervisor in the rocket area died on a Monday. No cause of death was listed for either worker, but both of them were considered to have had heart conditions when they were first employed at the plant. The

AEHA had stated that there was no potential for chronic exposure to NG for supervisors in the rocket area, although it had indicated that supervisors in rocket manufacturing areas would occasionally handle propellant paste or chips with their bare hands.

The fifth worker, a 50-year-old man who was also a supervisor in the rocket area, died on a Thursday. Again, no cause of death was listed, but he was considered to have had a "heart condition," since "minimal" ECG changes had been found previously in a periodic examination. The sixth worker, a 53-year-old woman employed in the roll and press area, died on a Thursday in 1969. No cause of death was given, although she had been referred to a private physician on the morning of her death. The AEHA indicated that she also had a previous heart condition, since she had complained of "shortness of breath" and "burning in the chest." The seventh worker, a 40-year-old woman employed in the finishing area, died in 1968. The death was attributed to a cause other than cardiovascular disease (not specified). The AEHA concluded that only two of the seven deaths that occurred in workers employed at the Badger plant should be classified as "sudden," but their criteria may have been too stringent.

Concentrations of airborne NG in the Badger plant were measured in August 1971 [36]. The rocket propellant manufactured at that time contained 50% nitrocellulose, 35% NG, 10% diethylphthalate, 2% 2-nitrodiphenylamine, 1.5% lead 2-ethyl hexanoate, 1.3% lead salicylate, and a trace of candelilla wax. The small-arms propellant contained 84% nitrocellulose, 10% NG, and 6% other compounds. A total of 118 samples were taken: 84 breathing-zone samples and 34 area samples. Concentrations of NG were measured by a colorimetric method described by Yagoda and

Goldman [64]. The average and highest concentrations of airborne NG were 0.5 and 1.7 mg/cu m in the NG manufacturing area (8 breathing-zone samples, no area samples), 2.7 and 12.5 mg/cu m in the rocket paste manufacturing area (30 breathing-zone samples, 2 area samples), 1.7 and 9.2 mg/cu m in the rocket roll and press area (31 breathing-zone samples, 26 area samples), and 1.6 and 7.1 mg/cu m in the rocket finish area (14 breathing-zone samples, 7 area samples). The lowest concentrations of NG measured in all four areas were said to have been below the unspecified limit of sensitivity of the analytical method used. These findings suggest that the average concentrations of airborne NG were lowest in the NG manufacturing area (0.5 mg/cu m), higher in the rocket roll and press and the rocket finish areas (1.6-1.7 mg/cu m), and highest in the rocket paste manufacturing area (2.7 mg/cu m).

The AEHA interviewed 83 of the 266 workers (31%) employed in these four areas at the Badger plant in August 1971 [36]. In addition, the plant medical records of these 83 workers from September 1966 to August 1971 were reviewed. Details of the methods used to select workers, conduct interviews, and analyze results were not provided. The results of the survey are shown in Table III-3.

In general, headaches, chest pain, and ECG changes appeared to be more prevalent in workers employed in the rocket paste, roll and press, and finishing areas than in those employed in the NG manufacturing area. Headaches were reported most frequently on hot, humid days, particularly late in the afternoon [36]. A few workers reported having headaches after a weekend away from work, but most of those who reported headaches complained when they returned to work after an absence of a week or more.

TABLE III-3

SIGNS AND SYMPTOMS IN WORKERS WHO MADE ROCKET PROPELLANT CONTAINING NG*

	NG Manufacturing Area				Rocket Paste Manufacturing, Roll and Press, and Finishing			
	Men		Women		Men		Women	
	No.	%	No.	%	No.	%	No.	%
Signs and Symptoms								
Headaches	3	27	-	-	8	22	12	33
Chest Pain	1	9	-	-	0	-	5	14
ECG Changes	0	-	-	-	5	14	5	14
Hypertension**	0	-	-	-	3	8	7	19
Rash	0	-	-	-	7	19	4	11
Number of Workers	11		-		36		36	
Average Concentrations of Airborne NG (mg/cu m)	0.5		0.5		2.7 1.7 1.6		2.7 1.7 1.6	

*Information from interviews in August 1971 and from medical records (September 1966-August 1971) of workers at Badger plant in Baraboo, Wisconsin

**Hypertension diagnosed if systolic pressure was greater than 160 mmHg, diastolic pressure was greater than 90 mmHg, or both. (Three had a history of hypertension, four had hypertension on examination.)

Adapted from a report of the Army Environmental Hygiene Agency [36]

Based on three to five blood pressure readings, the AEHA concluded that there were no consistent changes in blood pressure or pulse rate, although

the data were not included in the report. The AEHA concluded that "withdrawal from chronic NG exposure could precipitate chest pain and in some instances sudden death." The report stated that the findings from this study were not sufficient to show, however, that workplace exposure to NG can cause, or contribute to, the development of coronary artery disease.

The AEHA survey of the health of workers exposed to NG at the Badger plant [36] is difficult to evaluate, since the criteria used to select workers, classify signs and symptoms, and analyze the findings were not explicitly stated. However, this study and that in 1968 by Lund et al [63] suggest that there is an association between chest pain or sudden death and withdrawal from workplace exposure to NG in the absence of EGDN. The plant medical records of seven deceased workers were reviewed, but the AEHA considered that only two of these were cases of "sudden death." One of these two workers who died suddenly was employed in the rocket paste area, where the average concentration of airborne NG was 2.7 mg/cu m and the highest was 12.5 mg/cu m. The other worked in the rocket roll and paste area, where the average concentration of airborne NG was 1.7 mg/cu m and the highest was 7.1 mg/cu m. Both people died during the early part of the week, one on Monday and the other on Tuesday. Only one of the other five deaths occurred during these 2 days. The AEHA study found that sudden deaths have occurred after reexposure following a weekend of no exposure in workers exposed to NG in the range of the current Federal standard of 2 mg/cu m.

In 1972, Lange et al [34] reported on 9 cases of nonatheromatous heart disease in a group of about 200 workers exposed to NG at a munitions plant in Wisconsin. This was probably the Badger Army Ammunitions Plant in

Baraboo. Rocket propellant containing nitrocellulose and 37% NG was produced at the plant. The authors estimated that about 200 workers, about 160 female process workers and 40 male supervisory or maintenance workers, were subject to exposure to NG between 1967 and 1971. Rubber gloves and protective aprons were provided, but apparently there were instances in which NG contacted the skin directly. Although the work areas were ventilated, many workers developed headaches, weakness, dizziness, and nausea soon after beginning the workshift. Lange et al indicated that a "significant" fraction of those hired quit working at the plant during the first few weeks, but that those who continued to work developed tolerance to NG and took measures to maintain this tolerance.

Lange et al [34] described cases of heart disease in eight women and one man between 35 and 54 years of age who had been employed at the plant for 11-48 months. All had experienced angina during the weekend or on Monday morning and two had died suddenly. A 40-year-old woman who had worked with the NG:nitrocellulose mixture for 11 months died early on a Monday morning about 62 hours after her last workplace exposure. A routine ECG, taken 5 days before her death, was normal. Death was preceded by angina, shortness of breath, pallor, excessive perspiration, hypotension, and bradycardia. A clinical diagnosis of coronary occlusion with myocardial infarction was made, but an autopsy was not performed.

The second case was that of a 54-year-old man who died suddenly in November 1971 [34]. He had been employed at the munitions plant for 4 years but had not returned to work after having an acute myocardial infarction 6 months before his death. About 1.5 years earlier, arterial hypertension and a pattern of incomplete left bundle branch block had been

noted, although they had not been found at the time of first employment. The worker experienced diffuse chest pain on a Sunday evening about 6 months before his death. An ECG taken the following Tuesday showed evidence of an acute myocardial infarction in the anterior wall with a left bundle branch block. After recovery, the worker remained asymptomatic but did not return to work. Coronary angiography and cardiac catheterization 1 month before his death indicated that the coronary arteries were normal and that the left ventricle was normal in size and shape. However, ventricular function was altered and left ventricular end-diastolic pressure was elevated (15 mmHg). He died suddenly while unloading a small boat from a trailer. An autopsy was not performed.

A 52-year-old woman who had been employed at the munitions plant for 28 months began to experience angina on Monday mornings that was relieved by returning to work [34]. An ECG taken after one of these episodes indicated that she had had an acute myocardial infarction in the anterior wall. She was unable to tolerate mild physical activity for about a year and subsequently experienced severe exercise intolerance and recurrent episodes of cardiac irregularity. Coronary angiography and cardiac catheterization showed that the coronary arteries were normal except for a slight irregularity in the midportion of the right artery, ventricular function in response to exercise was abnormal, left ventricular end-diastolic pressure was increased, and there was intermittent atrial fibrillation. She was unable to return to work.

A 51-year-old woman employed at the munitions plant for 4 years was evaluated clinically for ischemic heart disease [34]. After working for about 8 months, she began to have nonexertional chest pain on weekends or

on Monday mornings that was relieved by returning to work. At first, chest pains occurred after she had been away from work for extended periods, eg, 5 days, rather than after a weekend. After episodes of severe chest pain on a Sunday and Monday, clinical examination indicated that she had recently had a myocardial infarction in the anterior wall. She had no symptoms during a 3-month convalescent period, but the chest pains recurred on weekends after she had returned to work. For about 2.5 years, she took one to three tablets of NG sublingually on weekends to relieve the chest pains. A physical examination conducted on a day during which she had worked disclosed no abnormalities, but she experienced chest pain in the hospital 48 and 60 hours after leaving work. Coronary angiography conducted while she had chest pain showed severe spasms of the coronary arteries. The area of the arteriospasm was diffuse, irregular, and relatively small, but there was significant obstruction. The chest pain was relieved by NG taken sublingually. Within 4-6 minutes after the patient took NG, the walls of the coronary arteries became smooth and free of irregularities and the lumens had increased in diameter. The resting cardiac output was normal, but the left ventricle was moderately dilated, the left ventricular ejection fraction was slightly reduced, and the left ventricular end-diastolic pressure was elevated (18 mmHg). The patient was discharged and returned to work 2 days later. Clinical examination was apparently normal on the following weekend after about 20 hours of workplace exposure to NG during a 3-day period. On Friday evening after work, reduced digital pulsations that became normal after administration of NG were found by plethysmography. This case is important because it was the first to provide evidence that the chest pain associated with

intermittent withdrawal from exposure to NG in dynamite workers may be related to spasms of the coronary arteries.

Lange et al [34] also described the cases of five other women exposed to NG who experienced nonexertional chest pain on weekends or on Monday mornings. Three of them had ECG evidence of an ischemic episode or a myocardial infarction after an episode of severe chest pain. Most workers no longer experienced chest pain after they terminated employment, although residual effects, including exercise intolerance, impaired left ventricular function, intraventricular conduction defects, and atrial fibrillation, often remained.

The report by Lange et al [34] indicated that at least 9 of approximately 200 workers (5%) exposed to NG at a munitions plant in Wisconsin that operated for 5 years developed nonexertional chest pain that occurred on weekends or on Monday mornings. Epidemiologic data are not available for comparison, but the finding of chest pain indicative of ischemic heart disease in relatively young women without significant arteriosclerosis is quite striking. Barsotti [37] believed that angina and sudden death in dynamite workers were associated with exposure to EGDN but not to NG. However, reports by Lund et al [63], by the AEHA [36], and by Lange et al [34] have shown that these effects can occur in workers exposed to NG alone.

It is important to note that, according to the report by Lange et al [34], sudden death can occur in workers who did not have premonitory symptoms other than angina. An angiographic study of one worker indicated that the chest pain associated with withdrawal from exposure to NG was related to spasms of the coronary arteries. This suggested mechanism is

plausible, but it may not be the only one responsible for chest pain in workers exposed to NG or to NG:EGDN mixtures.

On the basis of these symptoms, Lange et al [34] proposed that the duration of compensatory vasoconstriction is longer than the vasodilatory effect of NG. They suggested that when workers are no longer exposed, compensatory vasoconstriction is not opposed by the vasodilatory effect of NG, and coronary insufficiency or acute myocardial infarction can result. They suggested that the vasoconstrictor response subsides after 96-120 hours. This is a plausible interpretation of the findings of this and other case reports, but it is clear that further research is needed to determine the actual effects of exposure to, and withdrawal from, NG and EGDN.

In 1975, Klock [48] described a case of nonocclusive coronary artery disease in a 38-year-old man employed as an explosives foreman in a mine in the United States. The worker said he consumed 10-20 aspirins and 10-15 cups of coffee and smoked 2 packs of cigarettes a day. There was no family history of heart disease. He had been working with NG:EGDN dynamite sticks and NG gel daily for 10 years and had experienced nausea, chronic headache, and palpitations since he had begun to work with explosives. His daily exposures were interrupted in December 1972. In early January 1973, he had a severe attack of angina with nausea and sweating. Several weeks later, the attacks began to occur once or twice a week, usually on the weekends or on Monday mornings, but always while he was resting. His work was interrupted only briefly and he was able to lift heavy objects and exercise vigorously. The pain was relieved by taking NG sublingually, by entering the powder magazine, and occasionally by exercising.

The results of a clinical examination of the worker a few months after the attacks of angina began were considered to have been normal except for low blood pressure (100/50) and pulse rate (50 beats/minute) [48]. ECG's recorded during rest and during exercise were normal, with no ST segment changes before or after exercise. Selective right and left coronary arteriograms and left ventricular angiograms were obtained. No circulatory abnormalities were found in the left coronary arteriogram, but the worker developed chest pain just before injection of contrast material into the right coronary artery. A spasm of the midportion of the right coronary artery was detected, but it disappeared, along with the pain, after he took NG sublingually. No changes were found in the ECG's taken during arteriography or during the six attacks of angina that occurred within 3 hours after the procedure. Again, NG taken sublingually relieved the angina; clinical chemistry studies performed and ECG's recorded shortly after the attacks were found to be within normal limits, indicating that he had not recently had a myocardial infarction. One year later, after the worker had changed jobs, the attacks were less severe and had decreased in frequency to one or two a month, and he was able to lead an active and unrestricted life.

Klock [48] indicated that this worker was exposed to stick and gel forms of dynamite that contained contained both NG and EGDN. Although the attacks of angina probably were associated mostly with exposure to an NG:EGDN mixture containing a higher proportion of EGDN than of NG, they were relieved by taking NG sublingually. This report indicated that, in a young and otherwise healthy worker withdrawn from exposure to NG or EGDN,

angina can be caused by muscle spasms in coronary arteries that are not occluded by atherosclerotic plaques or thrombi.

In 1967, Morikawa et al [65] published the results of a study in which they used plethysmography to assess the effects of exposure to "ethylene nitrate" (NG:EGDN) on pulse waves in the fingertips of workers at a dynamite plant in Japan. In accordance with government regulations, the dynamite mixture contained less than 40% of the NG:EGDN mixture. About 200 men and women, with an average age of 40, were studied; most had been working at the dynamite plant for at least 10 years. Workers in areas of the factory where exposure to NG or EGDN was possible were examined once a month for 8 months. There was a control group consisting of an unspecified number of workers not exposed to dynamite, but whether it was matched to the exposed group for age, sex, and other variables was not stated.

Concentrations of airborne nitroesters (NG and EGDN) were measured at each of the selected work areas several times during the study [65]. Room air was sampled for nitroesters with a midget impinger and analyzed by a colorimetric method. The mean concentrations of airborne nitroesters, calculated as EGDN, ranged from 0.12 to 0.41 mg/cu m.

The effects of exposure on the pulse waves were graded by the authors as slight, moderate, or severe [65], but their criteria for these grades were not stated. Of 1,271 recordings of pulse waves, 143 (11%) were classified as abnormal. Of these, 117 (82%) were characterized as slightly changed and 26 (18%) as moderately altered. By comparison, no abnormal pulse waves were found in 175 examinations conducted on the control group. When the apparently affected workers were reexamined the next morning before work, the pulse waves had returned to normal.

No correlation was found between airborne concentrations of nitroesters, expressed as EGDN, and the percentage of workers with abnormal pulse waves, although both indices varied from one work area to another [65]. The authors did find that abnormal pulse waves were associated with certain kinds of work. The highest percentages of abnormal pulse waves were found in areas where workers wore surgical rubber gloves without liners or where workers handled unwrapped dynamite, even though those in the latter group wore cotton-lined rubber gloves with a nylon covering. Workers who used similar gloves to handle wrapped dynamite only occasionally had abnormal pulse waves. These data indicated that EGDN can penetrate rubber, nylon, and cotton. This conclusion was supported by the observation of abnormal pulse waves and a decrease in the systolic blood pressure in a nonexposed worker who wore for 3 hours a pair of rubber gloves that had been used just previously in a dynamite workshop.

The authors [65] believed that the abnormal results of plethysmographic examinations were a very sensitive indicator of exposure to nitroesters. However, the usefulness of plethysmography as used by Morikawa et al as a medical surveillance tool is limited at present because criteria for objectively grading the effects of exposure on pulse waves have not been described fully. In addition, the relationship between the degree of change in pulse waves and impairment of health has not yet been established. However, the use of fingertip plethysmography as a means to evaluate the cardiovascular response to nitroesters merits further evaluation.

Foulger [52] attempted to relate the percentage of dynamite workers with abnormal blood pressure measurements with the types of gloves used in

six dynamite plants. The criteria for classifying readings as abnormal were not specified. The percentages of workers with abnormal blood pressure readings were 33% in the first plant, where canvas gloves were changed every 2 hours; 42% in the second plant, where they were changed every 2 hours, and some gloves were discarded after use; 59% in the third, where gloves were changed when "dirty"; 76% in the fourth plant, where rubber-coated canvas gloves were worn and were reused after laundering; 80% in the fifth plant, where the rubber-coated canvas gloves that were used retained NG:EGDN after laundering; and 87% in the sixth plant, where the amount of NG:EGDN remaining in the rubber-coated canvas gloves was sufficient to cause headaches in unexposed persons who wore them. Foulger's findings tend to support the premise that NG:EGDN is retained by the rubber used in protective gloves and is not removed adequately by laundering.

Results from examinations given to workers exposed to NG:EGDN have been reported by many authors [41,42,44,45]. In 1959, Maccherini and Camarri [41] reported that nearly all of 265 dynamite workers complained of having had headaches, palpitations, nausea, and sensations of heat in the face and limbs when they first started work at the plant. These symptoms gradually subsided, disappearing after a few weeks of work. About 15% of the workers continued to experience them occasionally while they were at work. The authors found that 52% of the dynamite workers (137 of 265) but none of the 25 office workers were hypotensive in comparison with a large industrial population not exposed to dynamite. In most instances, systolic and diastolic pressures were reduced, but pulse pressures were within the normal range. The authors indicated that dynamite workers were hypotensive

during working hours only and that hypotension occurred more frequently in those who had direct contact with dynamite than in others at the plant. ECG's recorded during working hours were normal in all but one worker, who had a previous history of cardiac ischemia. Chest X-rays of the 265 dynamite workers and 25 office workers revealed aortic arteriosclerosis with moderate enlargement of the left ventricle in seven dynamite workers and two office workers. Slight leukopenia was found in 27 dynamite workers (10%), and slight normochromic anemia was found in 60 of them (23%), but methemoglobin or Heinz bodies were not found in the red blood cells of either dynamite or office workers.

Of the 70 workers who handled dynamite frequently, 10 (14%) complained of attacks of angina after 40-60 hours away from work [41]. These 10 had been employed at the plant for 8-15 years and were 40-50 years old. A few of the ECG's taken during or shortly after the attacks of angina in these workers showed moderate lengthening of the PR interval. Of the 70 workers, 9 had slight imbalances between plasma albumin and globulin levels and 3 had elevated serum cholesterol levels. Information on concentrations of airborne NG:EGDN or on the extent of skin contact with dynamite was not reported, but the study suggests that, with the exception of blood pressure measurements, clinical signs are less indicative of the effects of NG:EGDN exposure than are symptoms.

Rubino et al [43] reported the effects of exposure to NG:EGDN on 20 dynamite workers (15 men, 5 women, aged 20-53). The workers, employed for an average of 7 years, were engaged in mixing, rinsing, machining, loading cartridges, wrapping, and shipping dynamite. Concentrations of airborne NG:EGDN ranged from 6 to 14 mg/cu m in work areas. Fifteen of the workers

reported headaches, 10 nausea and vomiting, 7 chest pain, 4 heart palpitations, 4 peripheral circulatory disorders and paresthesia (altered sensation), 5 labored breathing related to stress, 2 fainting, 1 cyanosis, and 1 weakness. The authors noted that most of these symptoms were present at the time of examination and interview, and that chest pain, when present, persisted during exposure-free periods. Systolic and diastolic blood pressures increased between Friday evening and Monday morning in six workers and remained unchanged in three of them. The authors found that alterations in ECG's indicative of cardiac ischemia were demonstrably present for six workers, the presence or absence of ECG changes was questionable for nine workers, and that five workers were unaffected.

In 1965, Hanova [44] reported the results of ECG's recorded from 13 NG:EGDN dynamite workers who had experienced angina. Concentrations of airborne NG:EGDN were not given, but the author indicated that they were 2-5 times the admissible concentration (not stated) in Czechoslovakia. ECG's recorded during rest, after exercise, and after oral administration of 0.5 mg of NG, revealed no alterations in the QRS complex or in the PQ and QT intervals. There were, however, changes in the ST segment at rest in 7 of the 13 workers, a depression in 6 and an elevation in 1. Depression of the ST segment became more pronounced after exercise but diminished after administration of NG. There also were alterations in the shape and height of the T wave in several workers. Respiratory arrhythmia was detected in all 13 workers. Hanova concluded that, since ECG changes occurred primarily during the repolarization segments (ST and T), they were probably caused by hypoxia, changes in metabolism, tachycardia, or nervous

conditions. The author also suggested that the occurrence of angina in the employees while not at work was caused by reflex spasms of the coronary arteries.

In 1966, Orlando et al [45] reported the effects of exposure to NG:EGDN on 31 dynamite workers, 25-40 years old, who had blended and mixed dynamite powder for an average of 10 years. ECG's were recorded on Monday morning before work and again during a general examination, but other details of the examination were not reported. Some of the workers had complained of frontal headache, chest pain, or difficulty in breathing, but none of the symptoms was reported to have interfered with normal work activity. Sixteen (52%) of the 31 workers examined had normal ECG's, 9 (29%) had normal tracings with atrioventricular (AV) conduction within what the authors considered the lower limits of normal, and the remaining 6 (19%) had first degree AV blocks. Thus, 15 (48%) of the 31 workers had at least marginal disturbances in AV conduction. The authors presumed that in the workplace, the less volatile NG was less toxic than the highly volatile EGDN, and they therefore concluded that workplace exposure to EGDN could alter AV conduction. The authors believed that chronic exposure to NG:EGDN dynamite could enhance adrenalin-induced arrhythmias of the heart.

Rubino et al [43], Hanova [44], and Orlando et al [45] reported that exposure to NG:EGDN dynamite may be associated with changes in ECG recordings in some workers. Their findings indicate, however, that ECG recordings are not the most sensitive indicators of the effects on health of exposure to NG:EGDN.

In 1967, Bartalini et al [38] reported that, between 1955 and 1965, the severity of symptoms had decreased in NG:EGDN dynamite workers at a

plant in Italy. The dynamite mixture contained 67% EGDN and 33% NG in 1955 and 50% EGDN and 50% NG in 1965; the mean airborne concentrations expressed as EGDN were about 1.7 mg/cu m in 1955 and 1.2 mg/cu m in 1965. Of the 36 workers studied in 1955, 8 had attacks of angina, usually during the afternoons on nonworking days, 12 had Raynaud's phenomenon in the fingers after exposure to cold, and 31 had other symptoms including headache, nausea, vomiting, palpitations, and dizziness, particularly on Mondays during hot, damp weather or when alcohol was consumed. Work practices were improved so that less of the NG:EGDN mixture was absorbed through the skin and workers with symptoms were transferred to jobs in which they were not exposed to NG:EGDN. Preplacement and periodic medical examinations were conducted and the criteria for allowing employees to work in the dynamite area, although not specified, were apparently made more stringent. None of the 65 workers employed in 1965 had attacks of angina, although 7 had Raynaud's phenomena in the fingers and 50 had other symptoms, such as headache or nausea. It appears that reductions in both airborne and dermal exposures to NG:EGDN, the transfer of workers with symptoms, and more stringent evaluation of findings from preplacement and periodic medical examinations contributed to the decrease in the frequency and severity of symptoms in workers at the dynamite plant, although the relative importance of these factors cannot be determined from this study. The authors suggested that Raynaud's phenomenon and the symptoms of transient ischemia in the limbs that usually occurred at night, such as sensations of pricking with pins or needles or heaviness and transitory inability to move the fingers, were related to alterations in arteriolar tone caused by prolonged cutaneous exposure to NG:EGDN.

In 1965, Prerovska and Teisinger [42] described signs and symptoms associated with exposure to NG:EGDN mixtures in workers at a dynamite plant in Czechoslovakia. The authors indicated that concentrations of the airborne mixture were much greater than 5 mg/cu m, but the sampling and analytical methods used were not described. Between 1958 and 1961, four workers, 29-47 years old and employed for 5-7 years, died suddenly after a day away from work; three of them had previous histories of angina. Autopsies of the four workers revealed sclerosis of the coronary arteries and aorta ranging from slight to severe, but none had evidence of a recent infarct. Of the 37 workers who were interviewed at the plant, most of whom were roll-mill operators, nearly all complained of headaches, particularly when returning to work after a weekend. Some had angina, usually on days when they were not at work, some had collapsed, and a few had fainted. Intolerance to alcohol was noted by some workers, and there were a few instances of paresthesia.

Clinical findings were reviewed for 20 workers in whom chronic EGDN intoxication was diagnosed [42]. In all of them, decreases in blood pressure of more than 10 mmHg were found and methemoglobin levels were about 5%. Almost all 20 had serum cholesterol levels of about 220 mg%, which the authors considered to be the upper limit of the normal range. When workers with a diagnosis of chronic EGDN intoxication were transferred to other operations, the frequency of angina attacks decreased in these workers and there were no further instances of collapse or sudden death. The workers who were not transferred continued to have headaches, intolerance to alcohol, and angina, and there were a few instances of collapse. However, the ECG's and concentrations of serum cholesterol

(about 190 mg%) and of other lipids were considered to be within the normal range. According to the plant physician, gastric ulcers seemed to occur more frequently in workers exposed to EGDN than in the general population. It is possible, however, that the development of gastric ulcers is related to hazards to safety in dynamite plants rather than to exposure to NG:EGDN mixtures. Unlike Maccherini and Camarri [41], Prerovska and Teisinger [42] found that serum cholesterol levels were elevated in NG:EGDN dynamite workers. A more rigorous study is needed to determine whether NG or EGDN actually elevates the concentration of cholesterol in the serum in exposed workers.

Lanfranchi and Beraud [40] reported that workers at an NG:EGDN dynamite plant in France had changes in ECG recordings and symptoms similar to those reported by other authors. Four workers had died suddenly without any apparent cause, three on Mondays and one on a Thursday. They also found that one worker, a 26-year-old chemist employed at the plant for 2 years, had attacks of angina at regular intervals and had Raynaud's phenomenon in his arms and legs. These symptoms seemed to be unusually severe for a young man who probably had been exposed only intermittently to NG:EGDN and who had been employed at the plant for a relatively short period.

In 1969, Jacob and Maroun [39] reported a case of peripheral neuropathy in a 49-year-old man who had been handling "organic nitrate" dynamite. Twenty-five years earlier, he had developed severe headaches and nausea while handling dynamite sticks with his bare hands. He was not exposed to dynamite again until 1967, when he developed headaches and nausea, which usually lasted for 2-3 hours. During one episode, he

partially lost his vision either before or during the headache, but his vision returned to normal after a few minutes. Without actually touching the dynamite, he once developed a headache from merely opening the safe in which it was stored. About 2-3 weeks after he had last handled dynamite, he developed pain and swelling in his feet with slight edema at the ankles and small hemorrhages on the skin of the lower leg. The pain and swelling continued, and within a month, numbness had spread to the lower front part of the left leg and more small hemorrhages had appeared on both ankles. A muscle biopsy 3 months later showed that the muscle fibers were normal, but that the media of one small arteriole was necrotic, and that many white blood cells of types indicative of both acute and chronic inflammation were on and around the vessel walls. Treatment with corticosteroids helped to reduce the swelling, but the numbness persisted. The authors concluded that the peripheral neuropathy was related to nerve damage secondary to inflammation of the arteries. This case is probably one of high individual susceptibility. Although sufficient information on which to base conclusions was not reported, the case of Raynaud's phenomenon in the 26-year-old worker reported by Jacob and Maroun [39] may also have been an instance of high individual susceptibility to NG:EGDN. Paresthesia and Raynaud's phenomenon have been reported by a few other authors [38,42,62]. Bartalini et al [38] suggested and the findings of Jacob and Maroun [39] also suggest that nerve damage in the extremities in workers who absorb NG:EGDN through the skin may be secondary to ischemia caused by compensatory vasoconstriction or by vasospasms in the peripheral blood vessels.

In 1959, Planques et al [66] reported a case of skin and nervous allergic reactions induced by dermal exposure to dynamite. A 41-year-old man had worked for 4 months with vibratory pneumatic equipment in a lead mine and had come into contact with numerous compounds including NG:EGDN dynamite. He developed plaques, blisters, and scabs on his hand although no other abnormalitites were found in an examination and complained of severe dysesthesia with a sensation of burning in the fingertips. After 2 months of treatment with lotions containing dyes and antibiotics, the dermatitis disappeared, but the dysesthesia, although somewhat improved, was still present. The dermatitis had first occurred when the worker had handled pneumatic equipment and dynamite, but the authors found that the dysesthesia was not related to vibration. Patch tests were performed on the worker and on an unspecified number of control subjects with four types of dynamite that the affected worker had handled. The tests were negative in the control subjects but highly positive in the worker. To determine the ingredients of dynamite specifically involved, NG, EGDN, and guncotton were applied to the skin on the backs of the worker and the control subjects. NG caused dermatologic reactions and dysesthesia on the hands of the worker but did not affect the control subjects. The authors concluded that NG was responsible for the two types of symptoms developed by the worker and that it acted as both an irritant and a sensitizer

A case of sensitivity to both NG and pentaerythritol tetranitrate (PETN) in a man who took these drugs to alleviate angina was reported by Ryan [67] in 1972. The patient developed an extensive rash and edema in the ankles and wrists that disappeared when treatment with these drugs was discontinued. The rash recurred when he used NG again. The author

concluded that both NG and PETN caused skin sensitization. He speculated that the "trinitrate grouping" in both of these compounds behaved as a hapten that elicited the immunologic response, although evidence supporting this idea was not provided. The possibility that cross-sensitivity also had a role in causing the rash was suggested by the authors as well.

A few reports [21-23,31] suggest that workplace exposure to NG can affect behavior. Darlington [21] indicated in 1890 that some mine and tunnel workers who handled dynamite and were exposed to vapor of NG from unexploded dynamite had disturbances of the CNS, although the types of disturbances were not specified. Laws [22] noted in 1898 that dynamite workers were especially likely to become violent after drinking relatively small amounts of alcohol. Jennings [23] reported in 1903 that those who sucked on dynamite and then drank beer would often hallucinate and display aberrant behavior. In a more recent report, Martimor et al [31], in 1958, described behavioral disorders in a 40-year-old man who made NG-containing pharmaceuticals. He had experienced episodes of mental disorder when he was 7 and 20 years old. He frequently had skin rashes, but no longer had headaches at work after developing tolerance to NG. After 2 years of work, he complained of loss of appetite, insomnia, headaches, nervousness, gastrointestinal pain, vomiting, and weakness so severe that he had to stay in bed. Within a month, he was in a depressed state, his memory was affected, and he was delirious and hallucinating. He eventually committed suicide.

The authors suggested that, although the mental disorders could not be definitely linked to workplace exposure, the pattern of the disease indicated that the patient was particularly susceptible to the effects of

NG. It seems more likely, however, that the headaches caused by exposure to NG could have acted as a nonspecific stress that contributed to an episode of mental disorder in a patient with a previous history of these episodes. This case, then, does not provide evidence that NG acts directly on the CNS to cause mental disorders.

In 1975, Matsushita and Tadokoro [68] reported findings from EEG examinations of nine workers at a NG:EGDN dynamite plant in Japan. The workers were also given physical examinations. The authors indicated that, for several years, concentrations of airborne EGDN in the dynamite workrooms had been below 1.24 mg/cu m. About 3 years before the examinations, four of the workers, men aged 36-49, had been transferred out of dynamite workrooms after they had experienced attacks of angina. The other five workers, four women and one man, aged 22-42, were selected randomly from a group of workers who had been employed in the dynamite area for "many years" and who indicated that they had not experienced angina. There was no group of individuals who had never been exposed to EGDN dynamite.

Findings from the clinical examinations of eight of the nine workers were not unusual. Of the four former dynamite workers, two had no symptoms, one had palpitations and one had altered sensations in the upper limbs. All five of the workers employed in the dynamite area had symptoms, including palpitations (two), headache (two), a heavy feeling in the head (two), fatigue (one), lack of appetite (one), stiffness in the shoulder (one), and backache (one).

The workers were told not to take any medication for at least one week before the EEG examinations [68]. To minimize the effects of acute

EGDN exposure, the authors recorded EEG's in workers who had been away from their jobs for at least 2 days. Recordings were made while the subjects were at rest, while they were asleep, after they had hyperventilated for 3 minutes, and after iv administration of bemegride, an analeptic.

The authors [68] reported that EEG's were "abnormal" in five workers, "slightly abnormal" in two, and "almost normal" in two. There were no apparent differences between EEG's of workers formerly and currently employed in the dynamite area. The authors indicated that the disturbances in the EEG pattern were slight and characterized by fast, diffuse activity.

Matsushita and Tadokoro [68] concluded that seven of the nine workers had abnormal EEG's and that chronic EGDN exposure seemed to influence cerebral activity. The authors did not consider any of the recordings to be normal. These findings are difficult to evaluate because the EEG recordings were not described in sufficient detail and because a control group of individuals who had never been exposed to NG:EGDN dynamite was not included in the study. More rigorous studies with well-defined criteria for the evaluation of EEG's are needed to determine whether exposure to EGDN can affect cerebral activity.

In a 1966 report on the health of workers from the same NG:EGDN dynamite plant in Czechoslovakia studied by Prerovska and Teisinger [42], Styblova [69] found that about a third of the workers had depression and sleep disturbances and that some roll-mill operators also had excessive hunger. Of 85 mine workers exposed to NG:EGDN explosives, the author found that 11 had histories of loss of consciousness for unknown reasons; in 2 workers, these episodes resembled epileptic attacks. The attacks of unconsciousness were first attributed to head injuries, but 10 of the 11

workers continued to have attacks after they were no longer exposed. Fifteen other mine workers also had neurologic symptoms, including tetanus-like spasms in the fingers with altered sensation in the skin around the mouth, dizziness, and weakness in the lower extremities. One of the 15 developed aphasia and slight paralysis on one side, but these symptoms disappeared after 3 days.

Styblova [69] indicated that symptoms such as depression, sleep disturbances, and excessive hunger could be related to the stress of working in a plant where fires and explosions occurred frequently. The author believed, however, that neurologic symptoms were associated with the toxic effects of dynamite on some part of the brain and that these effects may have been potentiated in mine workers by exposure to carbon monoxide after a detonation in the mine. The study is not reported in sufficient detail, however, and the author did not present data to support her hypothesis. This study and other isolated reports of neurologic disturbances in workers exposed to NG or EGDN are merely suggestive. They indicate, however, that further study is warranted to determine whether these compounds may affect the nervous system.

Experimental studies using in vivo and in vitro techniques have investigated the rate of absorption of EGDN through the skin and its metabolic fate. Gross et al [70], in 1960, published the results of a study of the initial rate of percutaneous absorption of EGDN in humans. Six men each had about 100 mg of an explosive mixture containing about 22% EGDN applied to 1 sq cm on the outer sides of their left forearms. An occlusive bandage was placed over the entire preparation for 7 hours, after which time the remaining material was scraped from the skin. By

determining the amount of EGDN remaining on the skin, the authors estimated that an average of 3 mg of EGDN (13.7% of the amount applied) was absorbed by each subject during the 7-hour test period [70]. Evaporation was controlled somewhat, but part of the decrease in the amount of EGDN remaining on the skin may have been the result of evaporation rather than absorption.

In 1966, Williams et al [71] determined the rate of disappearance of EGDN from human blood in vitro. Concentrations of EGDN were measured by gas chromatography with an electron-capture dectector. One-half the EGDN disappeared in 20 hours from a human blood sample that had originally contained 0.18 ppm EGDN, in 10 hours from a sample that had contained 0.08 ppm EGDN, and in about 2 hours from a sample that had contained 0.04 ppm EGDN. Since the rate of disappearance was more rapid when EGDN concentrations were lower, the authors suggested that EGDN concentrations in human urine and blood be measured as soon as possible after the samples are taken.

The authors [71] also measured EGDN concentrations in the blood and urine of two controls and five workers from an unspecified area of the dynamite plant where exposure was reportedly greatest. Blood samples were taken from a peripheral vein a few minutes after work and all blood and urine samples were analyzed within 30 minutes. Blood samples from the five workers contained EGDN at 0.01, 0.04, 0.05, 0.06, and 0.07 ppm (average 0.046 ppm), The corresponding urine samples contained EGDN at 0.03, 0.02, 0.08, 0.04, and 0.02 ppm (average 0.038 ppm). Calculations by NIOSH indicate that the concentrations of EGDN in blood and urine are not well correlated (r=0.07). Blood and urine samples collected 16 hours after work

from the same five workers and from two controls contained no EGDN.

To determine the rate of EGDN disappearance from human skin, 5 mg of EGDN was spread over a 4-sq-cm area of a palm [71]. The rate of disappearance reflects both the rate of absorption through the skin and the rate of evaporation from the surface of the skin. After 3 minutes, the palm was washed with soap and water; 5 mg of skin was removed with a scalpel and found to contain 30 ng of EGDN/mg of skin. After 1 hour, the concentration of EGDN in the skin was 3.5 ng/mg, and after 1.5 hours following a second washing, it was 2 ng/mg. The authors concluded that the usual cleaning methods with soap and water would not remove all the EGDN from the skin. It is also possible that EGDN would be absorbed more rapidly through areas of the skin less thick than the palm.

In a study reported by Sundell et al in 1975 [72] and by Gotell in 1976 [73], blood EGDN concentrations were compared with airborne EGDN concentrations and with various job categories for NG:EGDN dynamite workers. The half-life of EGDN in red blood cells taken from exposed workers and from controls was also investigated. To correlate blood and airborne EGDN concentrations, blood EGDN concentrations were measured by gas chromatography in an unspecified number of volunteers exposed to airborne EGDN at concentrations of 1.2, 6, and 7.8 mg/cu m [73]. The volunteers did not handle EGDN directly, although some airborne EGDN may have been absorbed through the skin. Blood EGDN concentrations, which ranged from 0.9 to 8.0 ng/ml, were highly correlated with airborne EGDN concentrations (R=0.95) in volunteers. Based on this finding, Gotell estimated that a maximum blood EGDN concentration of 2 ng/ml would correspond with an 8-hour TWA exposure to EGDN of 1 mg/cu m. Gotell [73]

also suggested that a maximal blood concentration of NG of 4 ng/ml would correspond to an 8-hour TWA exposure to NG of 2 mg/cu m. The derivation of these estimates was not provided, however.

Concentrations of EGDN in the blood of 333 dynamite workers exposed to airborne EGDN at concentrations ranging from less than 0.5 to 10 mg/cu m were also measured [72]. The procedures used to select workers and to collect blood samples were not discussed. The results are shown in Table III-4.

No significant differences were found between any of the concentrations, suggesting that, for these workers, EGDN absorbed through the skin probably influenced blood EGDN concentrations more than exposure to airborne EGDN did [72]. The association of blood EGDN concentrations with job classification in 278 dynamite workers was also studied. In a review of this study, Gotell [73] indicated that the blood samples were taken at random intervals during the workshift. The results are shown in Table III-5.

The finding that blood EGDN concentrations were 10 times higher in cartridge makers than in other dynamite workers suggests that the amount of EGDN absorbed through the skin by workers who handle dynamite is substantial [72]. This study emphasizes that airborne EGDN concentration is not an accurate indicator of the extent of exposure to EGDN when the compound is handled directly, so that large quantities are absorbed through the skin.

The authors also studied the half-life of EGDN in vitro [72]. Red blood cells were taken from 26 men and 30 women employed in the dynamite

TABLE III-4

CONCENTRATIONS OF EGDN IN WORKPLACE AIR AND IN THE BLOOD OF EXPOSED WORKERS*

Concentrations of Airborne EGDN (mg/cu m)	Number of Workers	Concentrations of Blood EGDN (ng/ml)		
		Mean**	SD	Range
<0.5	192	43	121	<1-920
>0.5-1.0	93	55	123	<1-675
>1.0-2.0	22	99	250	1-1,160
>2.0-10.0	26	88	138	2-450

*Blood samples taken after 3-5 hr of work
**No significant differences found between the means

Adapted from Sundell et al [72]

TABLE III-5

CONCENTRATIONS OF EGDN IN THE BLOOD OF EXPOSED WORKERS*

Job	Number of Workers	Concentrations of Blood EGDN (ng/ml)		
		Mean	SD	Range
Supervisors, Truck Drivers, etc	28	4	4	0.5-16
Nitrifying Workers	24	8	11	0.5-39
Knead-house Workers	44	8	8	1-30
Cartridge makers	182	89	176	1-1,160

*Blood samples taken during the workday

Adapted from Sundell et al [72]

industry for more than 2 years and from 22 men and 28 women who were not exposed to EGDN in the workplace. The details of the procedure were not reported. The half-life of EGDN in vitro was 0.8 hour for male dynamite workers, 0.4 hour for male controls, 0.7 hour for female dynamite workers, and 0.6 hour for female controls. The half-life was signficantly longer in male dynamite workers than in male controls, but it was not significantly different in female dynamite workers and controls. The half-life was also significantly longer in female controls than in male controls. The authors did not suggest why the half-life of EGDN in human red blood cells in vitro might be different in men and women or in dynamite workers and controls, although this finding suggests that prolonged exposure to EGDN may increase the half-life of EGDN. Thus, if dynamite workers and controls were exposed to EGDN at the same concentration, blood EGDN concentrations would be greater in male and possibly in female dynamite workers than in controls.

Although the details of these experiments [72] were not reported, one of the experiments indicated that airborne and blood EGDN concentrations were correlated in the absence of skin contact. However, the finding that workers who handled dynamite, eg, cartridge makers, had greater blood EGDN concentrations than those exposed primarily by inhalation suggests that skin absorption was a major route of exposure to EGDN in the workplace.

In 1977, Blumenthal et al [74] compared NG concentrations in the plasma of one healthy volunteer after sublingual (0.3 mg), oral (2.4 mg and 6.5 mg), and topical (equivalent to 16 mg) administrations with associated changes in pulse rate and mean arterial pressure. The authors used gas chromatography with an electron-capture detector to measure concentrations of plasma NG as low as 0.1 ng/ml. Thus, an apparently satisfactory

analytical method seems to be available to determine concentrations of NG in the blood plasma that are associated with exposure to NG by inhalation as well as by skin absorption and to relate these concentrations to changes in blood flow.

Plasma NG concentrations did not rise above 0.1 ng/ml until approximately 20 minutes after topical application of the NG-containing ointment [74]. A peak concentration of 0.25 ng/ml was reached at about 22 minutes and the concentration was about 0.2 ng/ml 60 minutes after application of the ointment. Mean arterial pressure began to decrease gradually from the preadministration level shortly after the ointment was applied. The effect was maximal after 45 minutes, when mean arterial pressure had decreased by 20%. Sixty minutes after administration, mean arterial pressure was about 10% less than the preadministration level. The change in pulse rate was maximal, a 12% increase over the preadministration level, after 20 minutes, although no consistent effect on pulse rate was noted before 20 minutes had elapsed. During the 20-60 minutes after administration, the pulse rate was increased by an average of about 5%, but returned to normal within 60 minutes.

These preliminary findings [74] indicate that plasma NG concentrations below 0.1 ng/ml, the limit of sensitivity for the assay, are associated with decreases in mean arterial pressure. Since results are available for only one healthy volunteer, further tests are needed before the technique can be considered to be an appropriate assay for the biologic monitoring of exposed workers.

Epidemiologic Studies

A study of deaths from ischemic heart and cerebrovascular diseases in a parish in Sweden in which there was a dynamite plant was reported by Hogstedt and Axelson [75] in 1977. Noraberg, a parish of about 8,000 people, had mining, forestry, agricultural, engineering, and service industries in addition to a plant where NG:EGDN dynamite was manufactured. The parish register of deaths and burials was reviewed to identify deaths that had occurred between January 1955 and October 1975. A total of 408 men aged 36-70 had died during the study period. However, the deaths of 55 men were excluded from the study because the authors believed that these deaths could bias the results. Ten of the 55 excluded men, 7 of them dynamite workers, had died in explosions, 20 had died of diabetes or "primary debilitas," diseases that the authors thought would have caused the workers to have been excluded from dynamite operations, and the underlying cause of death could not be determined for the other 25 men.

From plant employment records beginning in 1921, Hogstedt and Axelson [75] found that 31 of the remaining 353 men (9%) who died had worked in dynamite operations for at least 1 year. Of these, 68% (21) had died of ischemic heart or cerebrovascular disease (ICD No. 410-412, 427-428, and 430-438). In contrast, only 46% of the deaths (148 of 322) in men from the parish who had not worked at the dynamite plant were from ischemic heart or cerebrovascular disease. The difference between the percentages of deaths from these diseases in dynamite workers and in other men is statistically significant ($P<0.05$). Only 3 of the 21 deaths in dynamite workers were from cerebrovascular disease. For dynamite workers and other men who died between the ages of 36 and 50, the percentages of deaths from ischemic

heart or cerebrovascular disease were similar, 25% in dynamite workers (2 of 8 deaths) and 27% in other men (12 of 44 deaths). However, in men who died between the ages of 51 and 70, 83% of the deaths in dynamite workers (19 of 23) but only 49% of the deaths in other men (135 of 278) were from ischemic heart or cerebrovascular disease. Again, the difference between the percentages is statistically significant ($P<0.05$). Of the 21 dynamite workers who died of ischemic heart or cerebrovascular disease, 4 (19%) had worked at the plant for 1-20 years and 17 (81%) had worked there for over 20 years. None of the deaths in men who had worked at the dynamite plant for more than 20 years was from a cause other than ischemic heart or cerebrovascular disease. At the time of their death from ischemic heart or cerebrovascular disease, 3 of the 21 dynamite workers were still employed at the plant but the other 18 had not worked at the plant for months or years. The difference between the percentages of deaths from ischemic heart or cerebrovascular disease in dynamite workers and in other men as well as the clustering of deaths from these causes in men who had worked at the dynamite plant for more than 20 years strongly suggest that those exposed to NG:EGDN in the workplace were more likely to die from diseases of the circulatory system than those who were not exposed. It is important to note that although most of the dynamite workers who died of diseases of the circulatory system had worked at the plant for a long time, they had not worked there for months or years before death.

Studies discussed in Effects on Humans indicate that workers exposed to NG or EGDN can develop chest pains or die suddenly, particularly after a brief period of withdrawal from exposure, eg, a weekend. This study [75] suggests that people who had been dynamite workers for a long time but were

no longer exposed to NG or EGDN in the workplace were also more likely to die from circulatory diseases than those who had never been exposed. It appears, then, that the effects of long-term workplace exposure to NG or EGDN on the circulatory system may not be reversed completely after exposure is discontinued, and that these changes can result in severe effects on the health of former dynamite workers.

Einert et al [11] in a 1963 report of a study of dynamite workers in California, estimated their extents of exposure to NG:EGDN by inhalation and by skin absorption and attempted to relate this to findings obtained from clinical examinations of the workers. The dynamite produced at the plant consisted of up to 80% EGDN and at least 20% NG. Air was sampled with midget impingers charged with ethyl alcohol, and the samples were analyzed using a colorimetric method. Air samples were taken in the breathing zones of workers throughout the plant. Concentrations of NG:EGDN ranged from 0.03 to 4.35 mg/cu m as EGDN, depending on the worksite. Because EGDN has a greater vapor pressure than NG, the exposure to airborne NG was considered by the authors to be negligible compared with that to EGDN. Einert et al considered EGDN exposure levels "low" when the TWA concentration of airborne EGDN was less than 0.25 mg/cu m, "moderate" when TWA concentrations were between 0.25 and 0.75 mg/cu m, and "much" when they were over 0.75 mg/cu m. Exposure tests were conducted to estimate the amount of NG and EGDN that came in contact with employees' hands. Thin cotton gloves that had been cleaned specially and dried were worn by workers during 2- or 4-hour exposures. The used gloves were analyzed for total nitrites. Amounts of NG and EGDN recovered from the gloves varied from less than 0.1 mg to 1.0 mg for 4-hour exposures. Exposures of skin to

EGDN were based on the amount of EGDN recovered from glove linings, and were considered "low" if they were less than 0.25 mg, "moderate" if they were between 0.25 and 0.75 mg, and "much" when they exceeded 0.75 mg in an 8-hour period.

To relate these concentrations of NG and EGDN to medical findings, the authors [11] studied 38 workers exposed to dynamite and 20 unexposed workers with a similar distribution of ages and years of employment. Each worker was interviewed to elicit medical, personal, and occupational histories. Following initial medical examination, the 58 workers were examined before and after each workshift. Blood pressure, pulse rate, and respiration rate were determined, and information was obtained on the actual job performed during the shift, the amount of sleep before work, ingestion of food, coffee, tea, or any medication taken before or during work, and any symptoms experienced by the worker. These examinations were repeated on 8 different days, the first set of data for each man being discarded. A total of 349 paired preshift and postshift examinations was obtained, each representing one workshift or "manshift."

Einert et al [11] included in their analysis all "unusual" findings that occurred in 1% or more of the workshifts. Findings were considered unusual when they were beyond the following "normal" limits: pulse rate 65-84 beats/minute after work; systolic blood pressure of 140 mmHg or more before work; diastolic blood pressure of 64-85 mmHg after work; and pulse pressure of 30-60 mmHg after work. Changes during the workshift of 8 or more beats/minute for pulse rate or of 10 mmHg or more for systolic, diastolic, or pulse pressure were considered to be unusual findings. Complaints of headache, dizziness, or nausea were also classified as

unusual findings. The prevalences of these findings were compared on the basis of exposure during the workshift (fully exposed, intermittently exposed, or unexposed), but also on the basis of age and years of employment, as well as that of other factors, such as smoking history, eating before work, drinking stimulant beverages, such as coffee or tea, before or during work, amount of sleep, and air temperature during the workshift.

Einert et al [11] found that the workers were generally healthy. Using exposure estimates based on job titles, the investigators assumed that 102 of the workshifts measured had no exposure, 61 had intermittent exposure, and 186 had full-time exposure to NG:EGDN dynamite. From these figures, they calculated that the group of exposed workers showed an increase in pulse rate during work, averaging 5.7 beats/minute for fully exposed workers and 1.8 beats/minute for intermittently exposed workers, whereas the mean pulse rate for the group of unexposed workers decreased by 0.4 beats/minute. These findings, however, were considered to be within the normal limits established by the authors. All groups showed decreases in systolic blood pressure (averaging 12.7, 3.9, and 3.7 mmHg for fully exposed, intermittently exposed, and unexposed workers, respectively) and in pulse pressure (13.8, 7.9, and 4.6 mmHg for the same groups). Complaints of headache were reported for only 4.0% of the unexposed workshifts but for 14.7% of the intermittently exposed group and for 49.8% of the group with full-time dynamite exposure.

Subsequent analyses of the data were not based on these preliminary exposure classifications because evaluation of actual exposures showed that only 86 workshifts were free of exposure, while 223 workshifts had varying

degrees of exposure that could be estimated [11]. Exposures could not be evaluated for 40 of the 349 workshifts, but these were added to the group of exposed workshifts. Comparison of these groups showed that several unusual findings occurred more than twice as frequently in the 263 exposed workshifts as in the 86 unexposed shifts. These were: (1) unusually high pulse rate after work (27.8% for all the exposed shifts versus 4.7% for unexposed shifts); (2) unusually low pulse pressure after work (20.6% versus none); (3) complaint of headache (39.2% versus 4.7%); (4) unusual rise in pulse rate during work (39.2% versus 15.1%); (5) unusual drop in systolic blood pressure (48.3% versus 24.4%); (6) unusual rise in diastolic blood pressure (17.2% versus 7.0%); and (7) unusual drop in pulse pressure (56.3% versus 23.2%).

Comparing the unusual findings by age groups for all 349 shifts, the authors [11] found three trends with increasing age. Using age categories of up to 35, 36-45, 46-55, 56 and over, they observed that, with increasing age, there were decreasing percentages of increased pulse rates, increased diastolic blood pressures, and decreased pulse pressures. Subdividing the 349 shifts by years of employment (1-5, 6-15, 16-25, 26 and over), the authors found that the percentage with pulse rates below 65 beats/minute after work increased, and the percentage of workers with unusual increases in pulse rate during work decreased with longer employment. Nonsmokers had lowered postshift pulse rates in a higher percentage of workshifts than the total group (24.0% versus 14.3%), but they also had a higher percentage of unusual increases in pulse rate during work (45.3% versus 33.2%). Workers who did not drink tea or coffee before work had higher percentages than the total workshift population for all unusual findings except high pulse rate

after work. Findings in workers who did not eat before work varied in the opposite direction. Comparison of unusual findings on 2 "hot" days (maximum effective temperatures, 76F and 78F) and 2 "cold" days (maximum effective temperatures, 58 F and 63 F) revealed little difference associated with the ambient temperature in either the exposed or the unexposed group. Although no consistent relationship with dose could be demonstrated, the medical findings were influenced by both airborne and skin contact exposures. All findings except low pulse rate after work tended to increase with the extent of exposure by inhalation. Within any single inhalation exposure category, most of the unusual medical findings tended to increase with increasing exposure to dynamite through the skin of the hands.

To evaluate whether the medical findings could be used as a measure of excessive exposure, the authors [11] attempted to use four of these findings as indicators: pulse rate increases of 8 or more beats/minute, decreases in systolic pressure of 10 mmHg or more, similar decreases in pulse pressure, and complaints of headache. A significant difference ($P<0.05$) between the incidences of these findings in 21 exposed and 18 unexposed workers was found. In 86 unexposed shifts (18 men), the 4 findings never occurred simultaneously, but all four occurred together in 21.6% of 88 shifts (21 men) with "much" exposure through the hands and in 43.7% of 16 shifts with much exposure by inhalation. The authors concluded that these results provided some assurance that their four criteria constituted a reasonable means for detecting exposure to EGDN.

To determine whether the workers needed medication containing NG to maintain tolerance to "organic nitrates" when they were away from work, the

authors [11] compared the percentages of workshifts in which there were complaints of headaches before and after three weekends. Headaches were not reported any more frequently on Monday than on Friday. The authors saw no reason, therefore, to provide medication to continue tolerance to "organic nitrates" on weekends or during vacations.

Einert et al [11] concluded that the amount of skin absorption was an important consideration in evaluating workplace exposures to NG and EGDN. They suggested that a glove test, such as that employed in this study, be used to estimate skin exposures, but they added that refinement of this method was needed. They concluded that requiring the use of plastic gloves with cotton liners and conducting simple clinical tests such as measurements of pulse rate and blood pressure before and after the workshift would be of value in protecting the health of workers exposed to NG:EGDN.

In 1962, Hasegawa et al [53] reported on the concentrations of airborne NG:EGDN dynamite, expressed as EGDN, and its effect on workers at a plant in Japan. Data from medical examinations of 29 workers who had no symptoms, selected "impartially" from about 600 men and women, were presented. The control group consisted of eight clerical workers and four of the authors. The average age was 24.1 years for both the dynamite workers (range 15-37 years) and the control group (range 20-29 years), but the numbers of men and women in each group were not reported. EGDN workers had been employed for an average of 7.0 years (range 0.5-16 years) in various areas, including the powder dynamite packing house, the gelatin dynamite packing house, the extruding house, and the cartridging house. Concentrations of airborne nitroesters in these four areas ranged from 1.37

to 2.43 mg/cu m expressed as EGDN, with the highest concentration being reported in the cartridge house. Neither the number of measurements made nor the sampling method used was disclosed by the authors.

Blood samples were collected from the 29 dynamite workers and their blood pressures were measured after 2 hours of work [53]. Erythrocyte counts, resistance to hemolysis, methemoglobin concentration, catalase activity, oxygen affinity, and the concentration of nitrate in the blood were measured. Blood EGDN concentrations were measured in three workers. For 9 of the dynamite workers, all measurements except blood pressure and erythrocyte count were taken on both Friday and Monday; the other 20 were examined only once. The same measurements were made on the eight clerical workers but not on the four authors.

For the 29 dynamite workers and 8 controls, the means and standard deviations for blood pressure and other measurements were calculated, based on the authors' data [53]. They are shown in Table III-6.

Average systolic, diastolic, and pulse pressure measurements were nearly the same in dynamite workers and controls [53]. The authors also found that there were no statistically significant differences between blood pressure measurements taken on Mondays and those taken on Fridays in nine dynamite workers. Catalase activity, apparently measured in red blood cells, was about 28% less in dynamite workers than in controls, but the difference was not statistically significant. Catalase activity decreased by 3% between Monday and Friday in the nine dynamite workers in whom it was measured. The number of erythrocytes was about 5% less in dynamite workers than in controls, but the differences were not statistically significant.

TABLE III-6

COMPARISON OF BLOOD PRESSURE AND OTHER MEASUREMENTS OF THE BLOOD OF JAPANESE DYNAMITE WORKERS EXPOSED TO NG:EGDN AND OF CONTROLS

Measurements	Dynamite Workers* (No.=29)		Controls (No.=8)	
	Mean	SD	Mean	SD
Blood Pressure (mmHg)				
Systolic	109	2	111	4
Diastolic	68	2	69	3
Pulse	41	2	42	4
Other				
Nitrate (μg/ml)	1.49	0.05	1.22	0.02**
Catalase Activity (%)	74	3.2	101	1.9**
No. Erythrocytes (X 10,000)	424	6.7	450	21
Methemoglobin (%)	3.1	0.34	-	-
Hemolytic Resistance (%)	0.384	0.006	0.373	0.01
Oxygen Affinity (PC 1/2)	15	3	16	0.3

*Exposure concentration=1.37-2.43 mg/cu m
**No.=4 for blood nitrates; No.=12 for catalase activity and oxygen affinity

Adapted from Hasegawa et al [53]

The percentage of methemoglobin decreased by about 1.5% between Friday and Monday in dynamite workers. The authors claimed that methemoglobin values were normal in dynamite workers, but control values were not provided. Oxygen affinity, measured as the partial pressure of oxygen at which 50% of

the hemoglobin is saturated with oxygen (PC 1/2), was about 1 mmHg lower in dynamite workers than in controls, and it decreased between Friday and Monday in dynamite workers. Resistance of red blood cells to hemolysis, expressed as the concentration of a sodium chloride solution at which hemoglobin escapes from 50% of the blood cells suspended in the solution, decreased in dynamite workers from an average of 0.403% on Friday to 0.363% on Monday, but was nearly the same in dynamite workers and controls.

Concentrations of EDGN, measured in the blood of three workers, were 1.0, 1.3, and 1.1 μg/ml [53]. Citing animal studies that indicated that EGDN is rapidly metabolized to nitrates, the authors suggested that blood nitrate concentrations were an adequate indicator of EGDN absorption. In workers under 25 years of age, the average blood nitrate concentration was 3.3 μg/ml (SD=0.11) for those employed less than 5 years, and 1.42 μg/ml (SD=0.17) for those employed more than 5 years. Blood nitrate concentrations averaged 1.49 μg/ml (SD=0.19) in EDGN workers over 25 years of age and employed 5 years or more and 1.22 μg/ml (SD=0.04) in the four authors, all of whom were over 25. Workers employed in the extruding process had the highest blood nitrate concentrations, averaging 1.71 μg/ml. Blood nitrate concentrations decreased an average of 0.43 μg/ml between Friday and Monday in EGDN workers, although the mean blood nitrate concentrations measured on Monday were still greater in EGDN workers (mean=1.30 μg/ml, SD=0.04) than in the controls (mean=1.22 μg/ml, SD=0.02).

The study by Hasegawa et al [53] suggests that exposure to airborne concentrations of 1.37 to 2.43 mg/cu m expressed as EGDN was associated with elevated blood nitrate concentrations in workers. Certain characteristics of the blood in dynamite workers, such as catalase

activity, hemolytic resistance, and number of erythrocytes, differed from control values, although the authors did not discuss any correlation of these findings with impairment of health. Interpretation of these findings is difficult since the number of workers in the study was small, the workers were not chosen randomly, and the selection and matching of controls were inadequate, particularly for a cross-sectional study. The study does suggest, however, that exposure to nitroesters at concentrations of 1.37-2.43 mg/cu m can affect the composition of the blood of workers even though they may not have any symptoms.

Animal Toxicity

The effects of exposure to NG and EGDN by inhalation and dermal absorption have been investigated in experiments on animals. Other routes of exposure have also been used in studies designed to investigate the development of tolerance and to identify metabolic pathways and products resulting from exposure to these compounds. A few investigators have studied the carcinogenic and mutagenic potentials of NG and EGDN in animals.

(a) Inhalation

In 1942, Gross et al [76] evaluated the effects of inhaling EGDN and NG on cats (sex and age not stated) exposed for 8 hours/day, 5 days/week, except Saturdays, Sundays, and holidays, for as long as 1,000 days. A regulated flow of air at 36 C was passed over weighed amounts of each compound in a Petri dish. The air was then cooled to room temperature and passed into the exposure chamber. The concentrations of airborne EGDN and NG in the chambers were measured daily, and the authors reported that the

values were consistent from day to day. One cat each was exposed to EGDN at concentrations of 13, 134, and 140 mg/cu m for 1,000, 1,000, and 273 days. Two cats were exposed to EGDN at a concentration of 170 mg/cu m for 8 hours/day, 5 days/week, one for 102 days and the other for 97 days. Three cats were exposed to NG at approximately 0.005 mg/liter (5 mg/cu m), one cat each for 31, 68, or 156 days. The authors indicated that they could not measure accurately concentrations in the chambers, but they calculated an approximate value of 5 mg/cu m.

The cat exposed to EGDN at a concentration of 13 mg/cu m for 1,000 days showed few effects [76]. Erythrocyte counts decreased during days 30-120 but then returned to the initial values. Heinz bodies were detected occasionally, but the blood was considered to be normal otherwise. Methemoglobin was not detected. The cat was killed 2 months after the exposure ended. No abnormalities were found at necropsy.

Another cat exposed to EGDN at 134 mg/cu m for 1,000 days was found to have anemia, an increased leukocyte count, Heinz bodies, and up to 29% of total hemoglobin converted to methemoglobin. During two interruptions in the experiment totaling 45 days, erythrocytes and hemoglobin values returned to normal. At necropsy, 2 months after the end of the exposure period, the authors found evidence of fatty degeneration of the heart, liver, and kidneys and pigmentation of the liver and spleen.

The cat exposed to EGDN at concentrations of 140 mg/cu m died after 273 days, and the two exposed at 170 mg/cu m died after 102 and 97 days [76]. All three had normoblastic anemia and decreased appetite, and their deaths were preceded by clonic and tonic seizures. Autopsy findings were severe anemia, hemorrages in the internal organs, and marked renal damage.

Exposure to airborne NG at a concentration of about 5 mg/cu m for 31 and 156 days produced slight to moderate anemia in two cats, but neither methemoglobin nor Heinz bodies were detected. One cat exposed for 68 days to NG at 5 mg/cu m showed moderate lymphocytosis.

Absorption of EGDN vapor by test animals was measured in an experiment described by Frimmer et al [77] in 1960. Radioactive 14C-labeled EGDN was evaporated into a chamber in which a fan was used to circulate the air. Concentrations of airborne 14C-EGDN in the chambers ranged from 133 to 428 mg/cu m. (The saturation concentration of EGDN at room temperature and standard pressure is about 400 mg/cu m.) Fifteen Wistar rats and 1 guinea pig were anesthetized with 1.25 g/kg of urethane and connected to the chamber by rubber tubing attached to tracheal cannulae. Potassium hydroxide was used to remove carbon dioxide from the chamber and constant pressure was maintained by adding oxygen. To determine the amount of EGDN absorbed by the animals in 10 minutes, the authors measured EGDN concentrations in the chamber before the animals were attached and again 10 minutes later. The rats absorbed an average of 20% of the EGDN they breathed (range 10-34%), and the guinea pig absorbed 27%.

In 1956, Stein [78] studied the effects of exposure to airborne EGDN on mice, rats, and guinea pigs. Thirty white mice of unspecified age, strain, and sex were exposed to EGDN at a concentration of 800 mg/cu m for 8 hours/day, 6 days/week, for 10 weeks. The mice were observed for a total of 24 weeks, and an unstated number of the animals that died during the experiment were examined for macroscopic and microscopic changes.

During the first 4 weeks of EGDN administration, mice showed progressive signs of lethargy, Heinz body formation, cyanosis, and

exhaustion [78]. By the end of the 7th week of exposure, three mice had died after having spasms. Examination of the surviving mice revealed intensive Heinz body formation, reticulocyte increases, hemolytic phenomena, skin erosion, and thin coats. Three more mice had died by week 10, when exposure was terminated. By this time spasms had become less frequent, but skin damage continued to increase. By the 15th week after initial exposure, half (15) of the animals had died. Only 10 were alive after 20 weeks, and 7 animals were alive at the end of the experiment (24 weeks). Surviving animals showed no external effects of EGDN exposure. Dead animals randomly chosen for dissection during the experiment showed no pathologic changes in the heart, lungs, or brain.

Stein [78] concluded that exposed mice died from hemolytic anemia, Heinz body formation, and hemoglobinemia. Since spasms often occurred just before death, the author speculated that the proximate cause of death was probably cerebral hypoxia caused by circulatory and respiratory paralysis. Ulceration of the skin was attributed to the effects of EGDN on tissue metabolism rather than to direct dermal contact.

In Stein's other experiments [78], mice were exposed to EGDN at a concentration of 300 mg/cu m for 14 days, and rats, mice, and guinea pigs were exposed at concentrations varying from 500 to 1,500 mg/cu m for from 3 weeks to 3 months. The details of these experiments are sketchy, but the animals were observed to be sleepy and to have Heinz body formation, increased reticulocyte counts, and anemia. The severity of these signs increased with the length of exposure.

Stein [78] concluded that mice were more sensitive to the effects of EGDN than rats or guinea pigs. However, all three species were able to

tolerate exposure to EGDN at relatively high concentrations without developing the circulatory changes that have occurred in workers exposed to EGDN from NG:EGDN dynamite. The animals died only after severe blood changes had occurred, including hemolytic anemia, Heinz body formation, and methemoglobinemia. The effects on circulation in man occurred at lower concentrations of EGDN than those associated with blood changes such as methemoglobinemia and Heinz body formation in animals.

(b) Dermal Absorption

Gross et al [76] reported on the effects of absorption of EGDN and NG through the skin of animals in 1942. Seven cats were exposed to NG and an unspecified number to EGDN by application of 4-cm x 6-cm gauze sponges to the shaved skin on the cats' backs. The sponges were saturated with NG or EGDN, but the amount of these substances on the sponges was not reported. An unspecified number of rabbits was also exposed dermally to EGDN, apparently using the same method. The sponges were held in place by occlusive bandages for up to 96 hours in EGDN-exposed animals and for up to 10 days in NG-exposed animals. Blood samples were taken at various times after the exposures ended.

One of the cats exposed to EGDN died of severe methemoglobinemia after less than 5 hours of exposure [76]. The others survived exposures of 96 hours or longer. One survivor, exposed to EGDN for 7 hours, developed anemia after 3 days and then Heinz bodies and methemoglobin appeared in the blood. This animal died 7 days after exposure ended. Another cat, exposed for 70 hours, survived but developed anemia and Heinz bodies and had methemoglobin values of up to 4 g/100 ml. The anemia was most severe 10

days after exposure to EGDN. No blood changes were found in rabbits dermally exposed to NG for 24 hours.

Only one of seven cats dermally exposed to NG died [76]. A sponge saturated with NG was held in place on the cat for 7 days. After a 2-day interval, a fresh sponge was applied to the same cat for 3 days, and the animal died 10 days after the experiment ended. The only findings reported from the autopsy were hemorrhages in the heart muscle. There were no unusual findings in a cat exposed for 5 days, and skin irritation was the only finding in a cat exposed for 9 days. The skin of nearly all the cats was irritated by the NG-soaked sponges. In a cat with an open wound caused by irritation from a sponge, erythrocyte and hemoglobin counts decreased, and Heinz body formation increased, more rapidly than in cats with intact skins that were exposed to NG. The authors concluded that EGDN was absorbed through the skin more rapidly than NG and that EGDN, therefore, caused more severe toxic effects more quickly.

Gross et al [70] reported in 1960 on the rate of dermal absorption by rats of EGDN in a gelatinous mixture and in an "explosive soft paste." The authors also studied the rate of EGDN absorption from human skin; these findings are reported in Effects on Humans. A gelatinous mixture containing 93% EGDN and 7% nitrocellulose was applied to 1 sq cm of depilated skin on the backs of 308 male Wistar rats weighing 200-300 g and was covered with an occlusive bandage. The amounts of EGDN applied ranged from 100 to 600 mg/sq m in 100 mg/sq m increments. The animals were divided into 36 groups, with at least 6 animals in each group receiving similar doses. An unspecified number of depilated control animals were bandaged in the same manner as these animals, but no EGDN was applied.

Each animal was caged alone during the experiment. A similar study was conducted using a soft paste consisting of 22.0% EGDN, 6.0% dinitrotoluene, 5.0% trinitrotoluene, 0.9% nitrocellulose, 1.0% sawdust, 64.9% sodium chloride, and 0.2% iron oxide [70]. Eighty-four male rats, divided into 14 groups of 6, received skin applications of 200, 400, or 800 mg of the paste.

The bandages on the test animals with the two preparations were opened at intervals, starting 12 hours and ending 8 days after application. When a bandage was removed, the remaining gel or paste was completely removed and analyzed for EGDN by a colorimetric method. A separate experiment indicated that not more than 1% of the applied EGDN was released from the bandages by evaporation.

In the rats treated with 100 mg of the gel containing 93% EGDN, half of the EGDN was absorbed after 1 day and all of it was absorbed after 8 days [70]. Larger quantities of EGDN required more time for complete absorption. The initial rate of absorption of EGDN from the gel was approximately 10 mg/sq cm/hour. EGDN was absorbed more slowly from the soft paste containing 22% EGDN, with an initial absorption rate of approximately 6.5 mg/sq cm/hour. The authors pointed out, however, that the difference between the absorption of EGDN from the two preparations was not proportional to the difference in EGDN concentrations. Since the concentration of EGDN was only 22% in the soft paste, compared with 93% in the gel, the authors concluded that EGDN was absorbed more rapidly from the soft paste form. However, because of the consistency of the soft paste and the lower concentration of EGDN in it, application of amounts equivalent to those in the gel was not feasible.

In the experiment with the gel, many animals died from the toxic effects of EGDN during the first days, when absorption was most rapid [70]. Mortality increased with higher doses. Within 12 hours after application, 1 of 41 (2%) rats receiving 100 mg/kg died; none of 36 died at 200 mg/kg, 8 of 45 (18%) died at 300 mg/kg, 17 of 78 (22%) died at 400 mg/kg, 9 of 47 (19%) died at 500 mg/kg, and 18 of 61 (30%) died at 600 mg/kg. Heinz bodies and methemoglobin concentrations of up to 30% of the total blood pigments were found in the blood of one of the rats that died from the toxic effects of an unspecified concentration of EGDN. None of the rats treated with soft paste containing EGDN and none of the control rats died during the experiment, although both groups had poor appetites and lost weight. Gross et al concluded that, under the same experimental conditions, 3-4 times less EGDN was absorbed through human skin than through rat skin.

Gross et al [79] also reported in 1960 on the amount and rate of dermal absorption by rats of NG from two different formulations. Wistar rats weighing an average of 243 g were treated with the same "gel and soft paste" mixtures used in the previous study, but with NG replacing EGDN. The gel (93% nitroglycerin) and soft paste (22% NG) preparations were applied to 1 sq cm of depilated skin on the back of each rat and were covered with a dressing as described in the preceding study [70]. The gel preparation was applied in amounts of 100, 200, 400, and 800 mg, and the soft paste was applied in amounts of 100, 200, and 400 mg; both preparations were applied to 24 rats at each concentration. The dressings were left in place for 4 days over the gel preparation and for 8 days over the soft paste preparation. The amounts of NG left in the residues at the

ends of these periods were determined by weight for the gel formulation and by the colorimetric method of Bandelin and Pankratz [80], following extraction with alcohol, for the soft paste formulation.

Because similar results were obtained from gravimetric and spectrophotometric determinations of NG lost from the gel form, mean values determined by each method [79] were calculated for six rats. The authors reported that 56.8 ± 7.4 mg and 86.8 ± 13 mg of NG were absorbed from the 100- and the 800-mg compresses of NG gel, respectively, during the 4-day experimental period. The rate of absorption of NG was reported to have been 0.85 mg/sq cm/hour and was independent of the amount applied to the skin. This rate of absorption was about 1/12 that found in the earlier study [70] for EGDN (10 mg/sq cm/hour).

The initial rate of absorption of NG from the soft paste containing 22% of that ester was 0.63 mg/sq cm/hour, or 75% of the rate of absorption from gel containing 93% NG (0.85 mg/sq cm/hour) [79]. None of the rats died from the action of either NG-containing substance applied to the skin.

(c) Tolerance

Bogaert and De Schaepdryver [81] studied the development of tolerance to NG in dogs in 1968. Dogs weighing 6-12 kg were anesthetized with pentobarbital (30 mg/kg) and were then given increasing iv doses of NG (0.1-100 μg/kg) while their arterial blood pressures were continuously monitored. Before the anesthetic was administered, six dogs were each given a total of 1 mg/kg of NG during 3 days by sc injection, and six dogs were each given 1 mg/kg of NG by sc injection 20 times/day for 4 days. Fifteen control dogs received the iv injections without pretreatment with NG.

The blood pressure responses in pretreated dogs given iv doses of 3 or more μg/kg of NG were significantly less than those in controls ($P<0.05$) [81]. In dogs pretreated with 20 mg/kg/day of NG for 4 days, the dose needed to produce a 25 mmHg decrease in blood pressure (ED 25-mmHg) was 242.7 μg/kg (SE=27.9), while for six controls it was 12.2 μg/kg (SE=3). The results indicated that dogs apparently developed tolerance to NG, although no explanation was provided for the mechanism of action.

To determine whether short-term exposure to NG had a lasting effect on tolerance, the ED 25-mmHg was determined 7 days after the initial blood pressure measurement for three dogs that had been pretreated with 20 mg/kg of NG for 4 days [81]. Tolerance to NG was less marked: the mean ED 25-mm Hg at this stage was 74.1 μg/kg.

Bogaert and De Schaepdryver [81] also investigated the possibility that cross-tolerance to NC was produced by exposure to another nitroester. Two dogs were given 3 mg of PETN orally 4 times/day for 1 week, and three dogs were given 80 mg of the long-acting PETN orally 2 times/day for 10 days. Following PETN pretreatment, the dogs were anesthetized and given 0.1-100 μg/kg iv injections of NG while their blood pressures were monitored. The pretreated dogs responded to NG no differently than did those that were not pretreated, indicating that cross-tolerance between NG and PETN had not developed.

Bogaert [82] also reported on the development of tolerance to NG in rabbits. In one experiment, 28 rabbits were divided into 4 groups of unequal size; 3 of these were given various doses of NG. Ten control rabbits were not pretreated. Five rabbits were given sc injections of 1 mg/kg of NG every 30 minutes, 12 hours/day for 3-5 days, ending 12-16 hours

before the experimental regimen was begun. Eight rabbits received similar pretreatment ending 3 hours before the final test began, and five rabbits were pretreated with NG only on the day on which the final test began.

The rabbits were anesthetized with urethane, apparently before the final pretreatment dose, and arterial blood pressures were recorded [82]. Various doses of NG and bradykinin (a vasodilator) were then administered iv separately, and the decreases in blood pressure were recorded. To quantify the tolerance produced by pretreatment with NG, the authors calculated the doses of NG and bradykinin needed to produce a decrease of 25 mmHg in blood pressure (ED 25-mmHg) from dose-response curves. Tolerance was judged by comparing the ratio of the ED 25-mmHg for NG in the pretreated animals to that in the controls with the similar ratio for bradykinin in the various groups. A high ratio indicated that tolerance had developed.

Rabbits pretreated with NG for 3-5 days required larger doses of NG to cause a 25 mmHg decrease in blood pressure than did rabbits that received no pretreatment or pretreatment only on the final day [82]. The effect was most noticeable in rabbits that received sc injections of NG up to 3 hours before it was administered iv. The ratio of the ED 25-mmHg for NG to that for bradykinin in this group (424, SE=100) was significantly higher ($P<0.05$) than it was in the controls (42, SE=13).

Bogaert [82] also examined the response to NG of vascular smooth muscle from rabbits. Doses were identical to the pretreatment regimens in the previous experiment, but 41 rabbits were used. After the dosage schedule was completed, portions of the rabbits' aortas were removed, and contractions of the aortic strips against a 4-g load were induced by

exposing the strips to l-noradrenaline at a concentration of 30 ng/ml. When maximum contraction at this dose was reached, increasing amounts of NG were added to the tissue bath. Tolerance was determined by calculating the dose of NG needed to produce a 50% relaxation from the maximally induced contraction (RD50). In rabbits pretreated for 3-5 days, greater amounts of NG were required to produce 50% relaxation. The average ED50 for rabbits pretreated until 3 hours before their aortas were removed was 776 ng/ml (SE=317), compared with 0.50 ng/ml (SE = 0.26) of muscle bath solution for controls. The author added that tolerance disappeared rapidly, although supporting data were not presented. Bogaert concluded that continued exposure to NG produced tolerance by altering the sensitivity of the smooth muscle to NG. The fact that this effect was obtained in isolated smooth muscle indicates that tolerance may result from a local component as well as from the adaptive changes mentioned previously in Effects on Humans.

Needleman and Johnson [83] have proposed that tolerance to organic nitrates in vascular smooth muscle is related to a change in the interaction of this class of compounds with its specific vascular receptor rather than to increased biotransformation or increased sympathetic compensatory mechanisms. In in vivo and in vitro studies, they found that tolerance to NG was reversed by treatment with D-1,4-dithiothreitol, a reducing disulfide. Needleman and Johnson suggested that NG and other nitroesters can oxidize a critical sulfhydryl group in the receptor, lowering its affinity for organic nitrates. The authors indicated that, after tolerance was induced, the preferred receptor conformation might favor the disulfide form. Changes in the affinity of the receptors 24-48

hours after organic nitrate tolerance has been induced should be studied further, however.

(d) Metabolism

Many investigators have studied the transformation of lipid-soluble NG and EGDN to water-soluble metabolites that are excreted rapidly by the kidney. Using in vitro techniques, Heppel and Hilmoe [84] found that NG reacted spontaneously with reduced glutathione to form inorganic nitrite and oxidized glutathione and that the reaction could be catalyzed by one enzyme found primarily in the soluble fraction of the liver. Since reduced glutathione did not react spontaneously with inorganic nitrite, the authors proposed reduction of NG by reduced glutathione must have preceded hydrolysis. Because simple hydrolysis of the ester, as by strong alkali, will yield nitrite ions, hydrolysis and oxidation of GSH may be simultaneous, the electrons liberated by the formation of a disulfide simply adding to the nitro groups of nitrite ions.

Di Carlo et al [85] studied the absorption and excretion of NG using a radioactively labeled compound. A single dose of 14C-NG was administered to rats through a stomach tube. Absorption was rapid; within 30 minutes of administration, about 6.4% of the radioactivity appeared in the blood, 2.9% in the urine, and 2.4% in carbon dioxide in expired air. The rates of elimination in urine and exhaled air were very similar; in 4 hours, about 20% of the administered radioactivity had appeared in each of them. 1,2-dinitroglycerin, 1,3-dinitroglycerin, 1-mononitroglycerin, 2-mononitroglycerin, glycerol, unidentified acids, and other products were detected in urine. Of these, glycerol was the major component followed by the acids, the two mononitroglycerins and the two dinitroglycerins. The intact

compound was not found in the urine, indicating that all the NG had been metabolized.

Needleman and Krantz [86] reported on the pharmacologic activity of 1,2-dinitroglycerin and 1,3-dinitroglycerin formed when NG reacts with reduced glutathione. They found that NG was about four times as effective as the dinitroglycerins in increasing coronary blood flow in isolated rabbit hearts and about eight times as effective in lowering systolic blood pressure in dogs. Thus, the pharmacologic activity of NG in rabbits and dogs is related primarily to the concentration of the intact compound.

Using in vivo and in vitro techniques, Clark and Litchfield [87] studied the metabolism of EGDN and ethylene glycol mononitrate (EGMN). In rat blood, EGDN was metabolized to EGMN, inorganic nitrite, and inorganic nitrate. Inorganic nitrite was then oxidized to the nitrate form. EGDN was metabolized in erythrocytes and in whole blood, but not in plasma, and the transformation was complete in 3 hours. In contrast, EGMN breakdown proceeded very slowly; only 4% of the compound was transformed within 4 hours.

In the in vivo studies, EGDN (65 mg/kg) and EGMN (46 mg/kg) were injected sc into rats. Blood samples taken at intervals of 0.5-96 hours were analyzed for EGDN, EGMN, inorganic nitrite, and inorganic nitrate [87]. Urine collected for 24 hours was pooled and analyzed for metabolites. Control values for inorganic nitrite and nitrate in blood and urine were obtained from untreated animals. In rats injected sc with EGDN, peak blood concentrations were reached at 30 minutes for EGDN, at 1-2 hours for inorganic nitrite, at 3 hours for EGMN, and at 3.5 hours for inorganic nitrate. No EGDN was found in blood after 8 hours and none of the other

three substances was found after 12 hours. Blood pressure decreased immediately after sc injection of EGDN and reached 50% of its original value after 30 minutes. There was a secondary fall at 2-3 hours followed by a steady rise. Preinjection levels were reached at 12 hours, and there were no changes thereafter. The initial decrease in blood pressure coincided with an increase in blood EGDN concentrations and the second decrease coincided with maximum concentrations of inorganic nitrite and EGMN in the blood. When blood pressure had returned to normal, there no longer were significant concentrations of EGDN, EGMN, inorganic nitrite, or inorganic nitrate in the blood. The metabolism of EGDN injected sc into rabbits was similar to that in rats.

In rats injected sc with EGMN, blood pressure decreased to its lowest value of 30% of the original value in 2 hours and returned to normal levels at 8 hours [87]. Inorganic nitrate was the major metabolite in the urine for both EGDN and EGMN, and excretion was complete after 24 hours. These findings indicate that although EGDN can be metabolized in erythrocytes, some other organ, such as the liver, is responsible for the rapid in vivo metabolism of EGMN. The authors injected rats sc with various concentrations of sodium nitrite and found that blood pressure decreased only slightly until blood nitrite concentrations reached 3 μg/ml. Since blood nitrite concentrations did not rise above 1.5 μg/ml and since inorganic nitrate is generally considered to be pharmacologically inert, the authors concluded that EGMN causes vasodilation, although it is less potent than EGDN. Like NG, EGDN and EGMN appear to be denitrated by reduced glutathione in a reaction catalyzed by an enzyme found primarily in the soluble fraction of the liver. Both NG and EGDN are metabolized

principally in the liver, where concentrations of reduced glutathione and the enzyme that catalyzes the reaction are optimal, but they can be metabolized in other tissues such as the blood. The suggestion has been made that nitroesters may be metabolized also by direct hydrolysis. This may be a minor route for transformation of the polynitroesters but may be a major route for the mononitroesters [88]. For both NG and EGDN, the pharmacologic activity is related most closely to the concentration of parent compound, although their metabolites, with the exception of inorganic nitrate, also have some pharmacologic activity.

Reviews published by Nickerson in 1970 [89], by Litchfield in 1971 [88] and 1974 [90], by DiCarlo in 1975 [91], and by Needleman in 1976 [92] contain more detailed information on the metabolism of various nitroesters.

The effects of NG, EGDN, and their metabolites on the intake and metabolism of alcohol in rats and mice were reported by Komura and Yoshitake [93] in 1971 and by Komura [94] in 1974. In mice, preference for drinking a 10% ethanol solution decreased by 48% in those injected ip with NG (2 g/kg) [93]. The effect of pretreatment with EGDN on the rate of alcohol disappearance was also assessed. Three hours after ip injection, blood alcohol concentrations were about 2.2% in mice treated with EGDN (0.2 g/kg) and 0.5% in control mice injected with water. Activity of alcohol dehydrogenase (ADH), an enzyme in the liver that catalyzes the oxidation of alcohol, decreased by 56% in mice injected ip with EGDN (0.2 g/kg) and by 28% in those injected ip with NG (0.2 g/kg).

In similar experiments, Komura [94] found that alcohol preference was decreased in rats injected ip with NG, EGDN, EGMN, or propylene glycol dinitrate, but not with their metabolites. Komura suggested that decreases

in alcohol preference in mice after administration of EGDN and NG and the delay in the disappearance of alcohol from the blood of EGDN-treated mice were related to decreases in the rate of metabolism of alcohol caused by decreases in ADH activity in the liver.

(e) Carcinogenicity

A study of the potential carcinogenicity of NG in rats was reported by Takayama [95] in 1975. Eight-week-old Sprague-Dawley rats, 50 males and 48 females, were given NG as a 0.03% solution in drinking water for 10 months. The same animals were then given plain tap water for 8 months. A control group of 53 male and 49 female rats was given tap water for the full 18 months. After the 10 months of continuous administration and the 8-month withdrawal period, five males and five females were randomly selected from the surviving animals for necropsy, followed by biochemical and hematologic examinations. All survivors at 18 months were necropsied and examined microscopically. Five surviving males and five females randomly selected from each group were also examined for biochemical and cellular compositions of the blood.

At the end of the dosing period, rats in the control and NG groups had similar survival rates, and no behavioral or physical abnormalities were observed in either group [95]. Mammary tumors were found in 8 of 44 (18%) of the female rats treated with NG and in 5 of 45 (11%) of the female rats in the control group. The difference is not statistically significant. All the mammary tumors were found to be fibroadenomas by microscopic examination. An adenoma of the pituitary gland was found in one of the female rats in the control group. The author concluded that NG was not carcinogenic under the experimental conditions.

In 1975, Suzuki et al [96] reported the results from a study of the potential carcinogenicity of NG administered to mice in drinking water. NG was dissolved in tap water to make 330, 40, and 10 mg/liter solutions. Four-week-old C57BL/6Jms mice, 169 males and 144 females, were exposed to NG at these 3 concentrations in their drinking water. About 100 mice were in each dosage group, and the control group consisted of 60 male and 63 female mice.

The group drinking water containing NG at the highest concentration was given tap water only for drinking during weeks 52-80 [96]. This alteration in their regimen gave to the mice of this group a time-weighted average concentration during the 80-week period of 214.5 mg/liter of NG in their drinking water. The other two groups received NG in their drinking water for 80 weeks. Necropsies were performed on all mice that had not died by the end of the experiment and on as many of those that died during the experiment as possible.

In macroscopic examination of 376 mice, 221 tumors were found [96]. There were 160 tumors in the 260 mice treated with NG and 61 tumors in the control group of 112 mice. With one exception, the percentages of tumors found were similar in the three groups exposed to NG and in the control group. However, tumors of the hypophysis were identified macroscopically in 5 of 34 female mice (15%) exposed to NG at the highest concentration; no tumors at this site were found by macroscopic examination in any other group.

The heart, liver, kidneys, spleen, and bone marrow of each animal, other organs with macroscopic changes, and any palpable nodules were examined microscopically [96]. A total of 163 tumors (69 in males, 94 in

females) were identified by microscopic analysis; 53 were in the high-dosage group, 57 in the mid-dosage group, 53 in the low-dosage group, and 52 in the control group. Enlargements of the pituitary gland, reported as adenomas (benign tumors), were found microscopically in 10 female mice exposed to NG; in 6 of 34 in the high-dosage group (18%), in 3 of 39 in the mid-dosage group (8%), and in 1 of 40 in the low-dosage group (3%) that were examined microscopically. One adenoma of the pituitary gland was found in the 50 females (2%) and none in the 32 males in the control group. No other differences between animals in the control groups and those administered NG were noted.

The authors [96] concluded that NG did not show any carcinogenic effect under the experimental conditions. Apparently the tumors of the pituitary gland found in female mice exposed to NG were benign, but their development suggests that prolonged exposure to this nitroester could affect the human pituitary gland. Takayama [95] did not find adenomas of the pituitary gland in male or female rats exposed to NG. However, the finding by Suzuki et al [96] of a high incidence of apparently benign tumors in the pituitary glands of female mice indicates that the potential carcinogenicity of NG merits further study. No reports have been found in the literature concerning the carcinogenic potential of EGDN.

(f) Mutagenicity

In 1972, Kononova et al [97] reported from the USSR on the potential mutagenicity of purified NG and EGDN on extracellular bacteriophage T4B of Escherichia coli, as indicated by the frequency of mutations. The actions of 10 other organic nitro compounds on this phage were studied also. Cultivation and inoculation of the bacteria and phage were performed by the

Adams method. The phage was exposed to 0.084M solutions of NG and EGDN in 0.2M carbonate buffer (pH 9.0) at 27 C. Survival of the phage and alterations of its UV absorption spectrum were measured, the latter effect being used as an index of mutagenic activity.

Survival of the bacteriophage was found to decrease with longer exposures to both EGDN and NG [97]. However, the survival rate of bacteria treated with EGDN was at least 96% below that of bacteria treated with NG. In untreated bacteria, the frequency of mutation was about 0.1/1,000 organisms. The frequency ranged from 0.42 to 0.55/1,000 bacteria in those treated with EGDN and from 0.05 to 0.07/1,000 bacteria in those treated with NG. Kononova et al concluded that EGDN had some mutagenic activity but that NG did not. More studies are needed to determine whether EGDN and NG are mutagenic.

Correlation of Exposure and Effect

At present, workers who make or use dynamite are potentially exposed to NG:EGDN mixtures. Those who make or use double- or triple-base propellants for rockets or guns and those who make pharmaceuticals are exposed to NG but not to EGDN. Adverse health effects, nearly all of which are associated with changes in the circulatory system, have been reported in all three groups of workers.

In most of the reports, the signs and symptoms noted in dynamite workers exposed to NG or to NG:EGDN were discussed. Dynamite workers were exposed to NG alone before the 1930's and to both NG and EGDN after the 1930's, when EGDN began to be added to the mixture to make it safer to manufacture and use. The ratio of EGDN:NG in dynamite has been increased

in many plants from about 1:1 in the 1930's to about 8:2 or 9:1 at present [13]. Vapor pressure measurements vary for EGDN (0.038-0.050 mmHg) and even more for NG (0.00012-0.011 mmHg) [5-7]. From a dynamite mixture containing 50% EGDN and 50% NG, the concentration of airborne EGDN from the mixture would be 3 to 400 times greater than that of airborne NG. Therefore, dynamite workers employed before the 1930's were exposed to NG alone and those employed after that time were exposed primarily to EGDN. Estimates of the concentrations of airborne NG or EGDN to which workers were exposed were provided by some investigators, but estimates of the extent of absorption through the skin of workers who came into direct skin contact with dynamite have not been reported. Studies reported by Sundell et al [72] and by Gotell [73] indicated, however, that workers who had direct skin contact with dynamite absorbed more NG and EGDN through the skin than through the lungs.

There is a characteristic progression in the signs and symptoms associated with exposure to NG:EGDN and to NG alone. When first exposed, most workers developed intense, throbbing headaches. Ebright [25] indicated that these headaches usually began in the forehead and moved to the occipital region. Other symptoms associated with initial exposure include facial flushing, nausea, vomiting, palpitations, weakness, prostration, languor [22], a sense of exhilaration before developing a headache, diarrhea, depression, restlessness, sleeplessness [25], copious sweating [40], impaired vision, abdominal pain [47], tremors in the arms, sensations of heat on the face and limbs [41], cough, difficulty in breathing, pallor, and loss of consciousness [21]. The symptoms reported most frequently by workers during initial exposure to NG or EGDN are

headache, dizziness, and nausea [11,22,25]. A throbbing headache is generally considered to be the first and the most sensitive and specific symptom associated with initial exposure to these compounds. Some workers never develop headaches, but for a group of workers as a whole, initial exposure to NG or to EGDN is consistently associated with the development of headaches. In addition to causing discomfort, these headaches may cause affected workers to lose some of their ability to follow the stringent safety precautions necessary to prevent explosions. Headaches have been reported in workers who make dynamite [11,22,25,38,40,41,45,46,49,68], in workers who use dynamite [21,47,48, and Bureau of Mines, written communication, November 1977], in workers who make rocket propellants [34-36], and in workers who make pharmaceuticals containing NG [29,30].

Trainor and Jones [49] found that six of seven workers developed "mild" headaches when they were exposed to NG:EGDN vapor at a mean concentration of 0.5 mg/cu m (range, 0.40-0.67 mg/cu m) for 25 minutes or less. Since the workers did not handle dynamite directly during the experiment, their headaches resulted only from exposure by inhalation of NG:EGDN vapor. Trainor and Jones [49] also noted that workers in storage magazines complained of headaches when exposed to NG:EGDN vapor at concentrations in the range of 0.10-0.53 mg/cu m. Hanlon and Fredrick [29] stated that pharmaceutical workers did not develop headaches when exposed to airborne NG at concentrations below 0.09 mg/cu m, but supporting data were not presented. These findings indicate that at least some workers will develop headaches when exposed to NG:EGDN vapor at concentrations above 0.1 mg/cu m.

The most important signs associated with initial exposure to NG or EGDN are decreases in diastolic, systolic, and pulse pressures [11,46,57]. In general, diastolic pressure decreases less than systolic or pulse pressure [11,49]. Findings reported by Trainor and Jones [49] indicate that there is a dose-response relationship between pulse pressure and concentrations of NG:EGDN vapor; as the airborne concentrations increase, the pulse pressures of exposed workers decrease. In men exposed to NG:EGDN vapor for 25 minutes, average decreases in pulse pressure from preexposure levels were 9.2 mmHg in 10 men exposed at 0.7 mg/cu m and 4.5 mmHg in 7 men exposed at 0.5 mg/cu m. If the dose-response relationship between exposure to NG:EGDN vapor and the decrease in pulse pressure were linear, then pulse pressure would not be expected to decrease during a 25-minute exposure to NG:EGDN at 0.3 mg/cu m. The utility of the pulse pressure as an indicator of exposure is limited, however, because many other factors also affect its magnitude.

The signs and symptoms of initial exposure to NG or EGDN are indicative of a rapid and substantial shift in blood volume from the central to the peripheral circulatory system initiated by dilation of the blood vessels. After 2-4 days of workplace exposure to NG or EGDN, most workers do not have these signs or symptoms, ie, they have become tolerant to the vasodilatory activity of NG or EGDN [22,25]. Since the half-life of EGDN in blood, measured in vitro, was longer in dynamite workers than in unexposed controls [72], the development of tolerance to these compounds does not appear to be related to an increase in the rate of biotransformation in the blood. The development of tolerance is probably related to an increase in sympathetic compensatory activity, but it may be

related to a decrease in the sensitivity of the vascular receptors to these compounds [83], to an increased ability of the liver to metabolize the nitroesters [98], or to a combination of these factors. Since tolerance is lost during periods without exposure, some workers have tried to maintain their tolerance to these compounds when away from work [22,25,34] by procedures such as placing NG or EGDN underneath their hatbands [25] or sucking chips of explosive material from time to time.

Blood pressure is affected by many factors other than workplace exposure to NG or EGDN, including stress, level of activity, diet, and underlying disease. Changes in blood pressures therefore are difficult to assign categorically to any one cause. Many investigators have found that measurements of blood pressure in dynamite workers were within normal limits [25,52-54]. These findings reflect the development of tolerance in exposed workers, but in most instances they also reflect differences in activity levels before, during, and after exposure and the removal from exposure of workers who were less able to develop tolerance, either by self-selection or by the employer.

Laws [22] noted in 1910 that workers employed in dynamite plants for a few years can develop an enlarged area of "heart dullness" as well as labored breathing and tachycardia on exertion. Angina pectoris has been reported in workers who made NG:EGDN dynamite [38,43-45], in a worker who used NG:EGDN dynamite [48], in workers who made NG dynamite [63], and in workers who made rocket propellants containing NG alone [34-36]. In affected workers, angina usually occurred during brief periods away from work, eg, a weekend or early in workshifts following periods away from work. Reexposure to NG or EGDN, by returning to work, wearing contaminated

clothing, or taking NG sublingually, usually relieved the pain. Angina pectoris is believed to result from a transient imbalance between myocardial needs for oxygen and the supply of oxygen in the coronary blood flow, and attacks in people not exposed to NG:EGDN were usually precipitated by exertion and relieved by rest. It was noted by Robbins [99] that people who have attacks of angina "almost invariably have atherosclerosis of the coronary arteries, usually moderately severe." In workers exposed to NG or EGDN, however, attacks of angina often occurred on a Sunday night or a Monday morning and were usually not related to exertion [34]. Coronary arteriograms from one worker exposed to NG:EGDN [48] and from two workers exposed to NG alone [34] were considered normal, ie, blood supply to their hearts was not restricted by atherosclerotic plaques or thromboses. In two instances [34,48], the workers experienced chest pains while the arteriograms were being taken. In both cases, spasms of the coronary arteries were revealed by the arteriogram, and the spasms, along with the pain, were relieved when they took NG sublingually. Lange et al [34] found that attacks of angina in affected workers generally decreased in frequency and severity after they terminated employment. Although most former dynamite workers no longer experienced chest pains, evidence of heart damage often persisted, including exercise intolerance, impaired left ventricular function, intraventricular conduction defects, and atrial fibrillation [34].

Sudden deaths without any apparent cause have occurred in NG:EGDN dynamite workers [40,49,57,58], in a NG dynamite worker [63], and in workers who made rocket propellants containing NG [34-36]. These deaths were first attributed to exposure to EGDN, but it is now apparent that

workers exposed to NG alone also can die suddenly. Like the attacks of precordial pain (angina), the sudden deaths that were reported occurred most frequently during brief periods away from work, and in particular, on Sunday nights or Monday mornings. In most cases, the worker had no premonitory signs or symptoms other than a history of angina during brief periods away from work. Some of the workers who died suddenly had never reported having attacks of angina, however [58]. Atherosclerotic plaques or thromboses were occasionally found in the coronary arteries of workers who were autopsied, but their coronary arteries were not occluded to the same extent as those of unexposed people who died suddenly [56,58,99]. Little information is available on the extent of exposure to NG or EGDN for workers who developed angina or died suddenly. Bille and Sivertssen [57] reported on the death of a 34-year-old man employed at a dynamite plant for 6 years who had been exposed to NG:EGDN at concentrations ranging from 0.3 to 1.4 mg/cu m. Information provided by the Army Environmental Hygiene Agency (AEHA) [36] and by Lange et al [34] suggested that at least two workers exposed to NG at average concentrations in the range of 1.7 to 2.7 mg/cu m died suddenly. It should be noted, however, that these workers may have also absorbed considerable amounts of NG or EGDN through the skin.

The study by Lange et al [34] indicated that, in former dynamite workers, symptoms of heart disease, such as chest pain, had disappeared but that some signs of heart disease had remained. Until recently, however, no information was available on the health of former dynamite workers who had not been exposed to NG or to EGDN for long periods. By reviewing death certificates from a county in Sweden, Hogstedt and Axelson [75] found that dynamite workers were more likely to die from heart disease than were other

men in the same county. Twenty-one deaths from cardiovascular diseases occurred in men who had been employed at the dynamite plant. Three of the deaths occurred in workers who had been actively employed, but the other 18 occurred in men who had not worked at the plant for months or years. It appears, then, that the effects of long-term workplace exposure to NG or EGDN may not be completely reversed after exposure is terminated and that these changes can have severe consequences on the health of former workers.

Some authors have reported that workers who handle dynamite can develop numbness in the fingers, paresthesia, or Raynauds's phemonena [38-40,42,62,68]. The cause of these symptoms is not known, but the suggestion by Jacob and Maroun [39] that they may be related to nerve damage that is secondary to peripheral stagnation of blood flow due to the vasodilatory action of nitroesters is reasonable.

It is generally recognized that workers exposed to NG or EGDN have less tolerance for alcohol [22,25,42]. Animal studies [93,94] indicate that exposure to NG or EGDN decreases the activity of alcohol dehydrogenase, an enzyme in the liver that catalyzes the metabolism of alcohols. This suggests that the rate of alcohol metabolism may be decreased in exposed workers.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

In 1898, Laws [22] noted that the wives of dynamite workers often experienced heavy menstrual bleeding and had fewer children than did other women. He added that often the children of dynamite workers were born prematurely, were cyanotic, or were not as strong as other children. Additionally, however, Laws, in 1910 [24], and Ebright, in 1914 [25],

suggested that NG was an aphrodisiac, since it appeared to them that most dynamite workers had large families. Other than these two impressions of historical interest, observations of the effects of exposure to NG or EGDN on reproduction in humans have not been reported and no study of the effects of exposure to NG or EGDN on reproduction in animals has been found.

The potential carcinogenicity of NG administered in the drinking water was recently evaluated in rats [95] and in mice [96]. No differences in tumor site or incidence were found in rats [95], but the study by Suzuki et al [96] suggested that female mice given NG in their drinking water had an excessive incidence of adenomas of the pituitary gland. Apparently these tumors were benign, but their development suggests that exposure to NG could affect the pituitary gland. No case reports or epidemiologic studies on cancer in workers exposed to NG or EGDN were found.

A study [97] of the potential mutagenicity of NG and EGDN in phage from E. coli cannot be adequately evaluated, since the study was not reported in sufficient detail. More information is clearly needed to determine whether NG or EGDN can affect reproduction, increase the mutation rate, or increase the risk of developing cancer in exposed workers.

A summary of the effects on humans of exposure to NG, EGDN, or NG:EGDN mixtures is presented in Table III-7.

TABLE III-7

EFFECTS OF WORKPLACE EXPOSURE TO
NG OR TO NG:EGDN MIXTURES

Concentration (mg/cu m)	Compound	Effect	Reference
0.3 -12.5*	NG	Headache	29,35,36
0.3 -12.5*	"	Blood pressure changes, rash, chest pain, EEG changes	36
0.1 - 14*	NG:EGDN	Headache	11,43,49, 54
0.12- 0.41*	"	Pulse wave changes in fingertips	65
0.3 - 4.35*	"	Pulse rate changes	11
0.3 -14*	"	Blood pressure changes	11,43,54
<1.24*	"	EEG changes	68
<1.24-14*	"	Palpitations	38,43,68
<1.25->5*	"	Chest pain	38,42,68
1.2 -14*	"	Nausea, altered sensation in extremities	38,42,43, 68
1.7 ->5*	"	Alcohol intolerance	38,42
1.7 -14*	"	Dizziness and fainting	38,43

*Also absorbed through the skin