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FIREFIGHTERS OCCUPATIONAL EXPOSURE TO CARBON MONOXIDE

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FIREFIGHTERS OCCUPATIONAL EXPOSURE TO CARBON MONOXIDE

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DEDICATED TO THOSE WHO SERVE AND HAVE SERVED THEIR FELLOW MAN - THE PROFESSIONAL FIREFIGHTER

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

FIREFIGHTERS OCCUPATIONAL EXPOSURE TO CARBON MONOXIDE

CHAPTER I

INTRODUCTION

Carbon monoxide (CO), as a component of the ambient air, has existed for as long as the earth has been alive, a period of time estimated by most authorities to be approximately 4.5 billion years (1). Since many of the geologic ages prior to the Pleistocene, when man first appeared, were those during which there was a tremendous vegetative and animal growth as well as volcanic activity, relatively high concentrations of atmospheric CO from natural sources already existed before man started to make his contribution.

Maugh (2) has reported that in excess of 3.5 billion tons of CO per year are produced in the Northern Hemisphere from natural sources, primarily from the oxidation of methane produced in swamps and paddies and the degradation of chlorophyll from rotting plants. This is considerably in excess of both the 530 million tons of CO estimated to be normally present in the troposphere (2, 3) and the 270 million tons of CO which are released annually by man-made sources (2). It is

therefore obvious that man contributes a minimal amount of the total CO quantity.

If it is accepted that the earliest evidence of the existence of a homonid creature, Australopithecus boisei, dates back some 2.6 million years to the Great Rift Valley in Africa, an area of great volcanic activity, then surely near-man and early man was exposed to CO in substantial amounts even prior to the discovery of fire (4). Since then, man as a result of his intellectual capabilities has produced the automobile, numerous manufacturing processes and an almost insatiable requirement for energy. Thus, man by his own activities and complex social requirements has more than doubled the amount of atmospheric CO to which he has been exposed (2, 3).

Nature in its own mysterious and wonderful way has apparently provided means to remove CO from the ambient atmosphere. Inman and associates (5, 6) have reported that biological soil systems are an active and efficient natural sink for CO. Their research indicates that soil systems, in a geographical area the size of the continental United States, can remove approximately 570 million tons of CO per year, an amount more than six times the estimated annual production of CO attributed to man's activities in the United States and over twice the world wide production.

Even though natural mechanisms to remove a significant amount of CO from the ambient atmosphere apparently exist,

nevertheless, there is reason for concern. The industrialization process triggered a migration of people to the humid middle latitudes more suitable for the establishment of population and industrial centers (7). As urbanization has increased more and more soil systems have been destroyed as active CO absorbers. Moreover, the emission of man-made CO has also increased.

Today, CO resulting from the combustion of carboniferous compounds must be considered as a pollutant which, without doubt, is the most cosmopolitan and potentially dangerous of the myriad of toxic substances to which man is exposed. If it is accepted that CO has become an atmospheric pollutant as a result of man's gregarious rush into industrialization then the physiological effects of the agent in confined spaces must be considered. Since on a global basis man's contribution is minimal it is the non-dispersed local source that creates physiological hazards. Indeed this hazard is primarily the confined space. Confined spaces can range from geographical areas such as the Los Angeles Basin, cities such as New York and London, various work areas, and automotive vehicles, to the alveoli of the lung itself.

The effects of CO, as an air pollutant, on human health have been pondered for years (8-24) and much has been written about the amount of this gas discharged into the fragile atmosphere of space ship earth and of its potential effects on life. However, it was not until 1961 when Hechter (12)

compared air pollution with daily mortality and concluded that there was a possible correlation between daily highs and mortality and postulated that this was seasonal in nature. In 1969, Cohen and associates (21) studied the effects of CO pollution in the Los Angeles Basin on case fatality rates of patients with myocardial infarction admitted to 35 Los Angeles hospitals. Their findings indicate that there was an increased myocardial infarction-case-fatality-rate in areas of high levels of CO pollution.

It remained for Hexter (24) in 1971, through a complicated mathematical model using complex regression analyses, to indicate significance ($P < 0.002$) between CO levels in the Los Angeles Basin and mortality. A similar statistical evaluation revealed no association between oxidant levels and mortality.

In 1965 the President's Science Advisory Committee (25) reported that air pollution, under certain atmospheric conditions, caused significant increases in deaths and in the same document lamented the fact that CO, although extensively studied, remained an enigma and called for more detailed studies on its chronic effects on exposed populations.

Interestingly, the work that led up to and ultimately proved that CO as an air pollutant significantly affects overall mortality was done in California (12, 13, 15, 16, 21, 23 24). Quite anachronistically Schimmel (26) in 1972, again through the use of an elaborate mathematical model, compared air pollution in New York City with excess mortality. For

some unexplained reason neither this work (26) nor any of its references considered CO as a parameter nor did they refer to the work done in California. The data used in addition to death certificate data were SO_2 levels and Smoke Shade measures. The closing statement in this article recognized the need for further studies and stated that data on additional pollutants should be included.

The Community Health and Environmental Surveillance System (CHESS) of the Environmental Protection Agency has as its main purposes the evaluation of existing environmental standards, the obtaining of health intelligence for new standards and the documentation of the health benefits of air pollution controls. This program has been in effect since 1968 and has included 33 neighborhoods in six geographical areas of the United States. The health indicators that have been used are: chronic respiratory disease in adults, acute lower respiratory disease in children, acute upper respiratory disease in families, daily asthma frequency, acute irritation symptoms during air pollution episodes, pulmonary function of school children, tissue residues of cumulative pollutants in humans and in two areas the daily aggravation of symptoms in subjects with preexisting heart and lung diseases. The CHESS area sets were selected to evaluate air quality standards for particulates, sulfur oxides, nitrogen oxides and photochemical oxidants. Carbon monoxide was not included because the

"...effects of short term carbon monoxide exposures are more precisely studied in controlled exposure chambers..." (27). This is confusing because the effects of atmospheric pollutants, and more specifically CO, on mortality were proven significant by Hexter in 1971 (24). Ambient atmospheric pollutants usually do not cause acute episodes of death or illness. Exposure to these agents is continuous and involves lower concentrations than an occupational exposure to similar agents. The major exceptions to this are the rare acute episides such as those occurring at Donora, Pennsylvania, and London where large numbers of people died in a short period of time. Because of the possible chronic and cumulative effects of CO it would seem that the CHESS program should have included one of the most important pollutants in its study.

Most exposures to CO, other than the low levels involved with air pollution, are occupational and under regulated and controllable situations (9, 18, 19, 20, 25, 27, 28, 29, 30). The most significant exception to this has been the firefighter who by the nature of his occupation has been exposed to CO under the most violent and stressful conditions. Since his exposure would be better described as daily sub-acute episodes rather than chronic low-level, the amounts of CO as well as those of other toxic substances involved in an uncontrolled fire have been largely unmeasured or for that matter, unmeasurable.

In an era of unparalleled concern over the safety of the occupational environment and for the protection of the health of the worker, it is ironic that combat firefighters, one of the largest, most essential and stressed occupational groups has been virtually overlooked. Consequently, it is considered imperative that the physiological effects of their daily exposure to airborne pollutants, such as CO, be elucidated in order that meaningful protection and control might be instigated.

CHAPTER II

LITERATURE REVIEW

Hemoglobin is a protein composed of four sub-units containing one heme moiety each. A heme moiety is a complex capable of binding reversibly one molecule of oxygen (O_2). Since the hemoglobin molecule contains four sub-units it actually reacts with four molecules of O_2.

$$Hb_4 + O_2 \rightleftharpoons Hb_4O_2$$

$$Hb_4O_2 + O_2 \rightleftharpoons Hb_4O_4$$

$$Hb_4O_4 + O_2 \rightleftharpoons Hb_4O_6$$

$$Hb_4O_6 + O_2 \rightleftharpoons Hb_4O_8$$

This saturation of the hemoglobin molecule occurs in four separate steps with the affinity constant increasing from step one to step four. The reactions are allosteric and result from intra-molecular forces acting as intermediate equilibria occur. This reversible oxygenation-deoxygenation of the hemoglobin molecule is extremely rapid, usually requiring less than 0.01 seconds (31). On the other hand CO is taken up by hemoglobin almost as well as O_2 but is released at a much

slower rate. Bartlett (17) reported the half life of CO *in vivo* to be 1.5 to 4 hours.

The effects of CO and its interaction with hemoglobin were first set forth by Douglas and the Haldanes (32). It is still an accepted fact that CO combines with hemoglobin with an affinity approximately 210 times greater than O_2 (33, 34, 35). This phenomenon produces a situation where even small exposures become significant when considering such tissues of the body as the myocardium that require the maximum amount of oxygen. In the case of a person engaged in activity requiring the expenditure of large amounts of energy and with increased stress, the myocardium requires virtually 100 per cent of the available O_2 (31, 36, 37). Any circumstance that places an additional burden on the O_2 transport system in conjunction with a decreased O_2 availability can result in tissue anoxia. It is well documented that a heavy smoker has a significant amount of his hemoglobin constantly bound as COHb and therefore unavailable for O_2 transport (38-41).

In addition to hemoglobin, myoglobin is an O_2 transport mechanism present in the tissues and is equally as capable of binding CO. Oxygen stored as oxymyoglobin is consumed during the early stages of physical exertion before circulation can provide an additional supply. In the event that a significant amount of the hemoglobin has been rendered inoperative for O_2 transport by CO, and myoglobin is also inoperative or

reduced in efficiency, then the resulting tissue anoxia probably will result in damage.

Jones and associates in 1971 (42) exposed rats, guinea pigs, monkeys and dogs to 61, 115 and 240 mg/m^3 of CO continuously for 90 days. At the end of the study no detectable pathological or biochemical changes were noted in the animals. The only change noted was increased hemoglobin values in all four species from pre-exposure values. In a companion study where all four types of animals were exposed repeatedly to 127 mg/m^3 CO, 8 hours per day, 5 days a week for 6 consecutive weeks no adverse toxic signs were produced. Theodore and associates (43) exposed monkeys, baboons, dogs, rats and mice continuously for 168 days to 460 mg/m^3 CO and reported no apparent physiological effects on the animals. No detectable pathological changes were observed in the central nervous system. The only change noted was some cardiac hypertrophy in the rats but the larger species failed to show any cardiovascular changes. The investigators failed to produce any operative decrement in Rhesus monkeys chronically exposed to 440 mg/m^3 CO and no performance decrements in human subjects exposed to 60 and 300 mg/m^3 for 3 hours. They guardedly concluded that mammalian species apparently were able to tolerate CO well under their test conditions and postulated that adaptive processes must occur early in the exposure and that resulting compensatory changes could over-ride the initial effects of CO. Eckhardt and associates (44) conducted a

similar experiment where Cynomolgus monkeys were exposed for 22 hours per day, 7 days a week for 2 years, to an average of 23.8 and 78.6 mg/m^3 CO. Nine monkeys served as the test group and nine as the control with the only dose related difference being an increase in COHb levels in the exposed animals. These elevated COHb levels did not lead to any compensatory increases in hemoglobin, cardiac fibrosis or brain pathology. They concluded that this 2-year exposure to CO at the levels used did not result in any biologically significant changes in the Cynomolgus monkey (44). These findings as well as those of Theodore (43) seem to contradict the findings of Shulte (45), Halperin and associates (46) and others (47, 48, 49, 50, 51) who found varying physiological effects and performance decrements. The latter being detectable at as low as 5 per cent COHb.

Possibly the best review of the literature concerning this specific subject was done by Rockwell (52) in 1967. He cautioned against accepting the results without critical evaluation because the experiments were usually conducted under highly selective conditions. The author reviewed the literature and concluded that there is performance decrement at increased levels of COHb. There is however an apparently valid study where non-smoking subjects were exposed intermittently to varied concentrations of CO (48). The investigator reported that individual hematological responses to the exposures varied widely but that significant hemoglobin and hematocrit elevations

continued in the exposed subjects for as long as 2 months after exposure. He also presented data that indicated persons occupationally exposed to automobile exhaust emissions as well as smokers tend to have a higher hematocrit than non-smokers. The presumption is that CO hypoxia in varying degrees stimulates increased erythrocyte production (48).

That there are effects of CO inhalation in human subjects was demonstrated by Stewart and associates (49, 50) who exposed healthy male volunteers to concentrations of CO ranging from 1 to 42,720 mg/m^3 for periods of time from 45 seconds to 24 hours. By using the predictive equation, log (Δ% COHb/liter) = 1.036 log (ppm CO inhaled) - 4.4793, they were able to accurately predict the COHb values. Physiological symptoms, other than abrupt increases in COHb saturation, were a slight sagging of the ST Segment of Lead II, mild frontal headaches, changes in the visual evoked response and impairment of manual coordination. The authors indicated that these responses were noted only after the COHb levels reached 15 per cent saturation or greater.

Much research has been done on the effects of exposure to the concentrations of CO found in cigarette smoke and the evidence has accumulated that this exposure to the agent has been more of a hazard to life than had been previously realized (13, 15, 16, 22, 23, 29, 38, 40, 41, 51, 52, 53, 54). A non-smoker, in a confined space with smokers, is at risk since cigarette sidestream smoke contains four to six times more CO

than mainstream smoke (55). Even cigar and pipe smoke contains larger amounts of CO than had been anticipated (55). A person who smokes from 10 to 20 cigarettes per day maintains a constant COHb saturation of from 5 to 10 per cent (17, 38, 40, 41). A COHb saturation of 5 per cent renders 0.1 per cent of the body's hemoglobin inoperative for oxygen conveyance. Furthermore, this loss of O_2 carrying capacity is as acute as if bleeding from trauma had occurred (18).

The body stores of CO are not restricted to the hemoglobin in the circulating blood. Coburn (39, 56) reported on the presence of extravascular stores of CO bound to myoglobin as well as cytochromes (a_3 and P_{450}), catalase and some of the perioxidases. This same research suggested that the myocardial myoglobin of heavy smokers, those who carry COHb levels of 10 per cent or greater, may be 30 per cent saturated with CO. The potential significance of this is that myoglobin is the mechanism of O_2 transport in the tissues, therefore the major source of oxygen for the myocardial tissue.

In an average 63 kg human, myocardial tissue comprises approximately 0.5 per cent of the total mass of the body and consumes O_2 at the rate of 9.7 ml/100 gm/minute. The kidneys comprise the same percentage of the total body mass but consume oxygen at the rate of 6 ml/100 gm/minute. Blood flows to the myocardium at the rate of 84 ml/100 gm/minute and to

the kidneys at 420 ml/100 gm/minute. The myocardium exhibits an arteriovenous oxygen difference of 114 ml/liter as compared to 62 ml/liter for the brain and 14 ml/liter for the kidneys (31, 36, 37, 57). Based on these comparisons, it is evident that the myocardium demands the largest amount of O_2 and exhibits the greatest arteriovenous O_2 difference. The myocardium consumes 11.6 per cent of the O_2 consumed by the total body.

The most common site for myocardial infarctions and the one most prone to myocardial ischemia is the subendocardial region of the left ventricle. This is attributed to the fact that there is little or no blood flow to this region during systole. Since the myocardium extracts such large amounts of O_2 from the blood (9.7 ml/100 gm/minute) consumption can be increased only by increasing the coronary blood flow. This is accomplished in two ways: neural, stimulated by adrenergic factors; and chemical, stimulated by asphyxia and hypoxia. The one factor common to both of these is myocardial fiber hypoxia. If a significant amount of the hemoglobin is bound to CO and the myoglobin is also operating at a reduced efficiency, it is reasonable to assume that the compensatory mechanisms are not sufficiently sensitive to prevent damage to myocardial fibers or that there is simply not enough available O_2 to prevent the damage regardless of the amount of blood flow through the coronary system. This damage is usually reported on autopsy as focal myocardial necrosis.

In a survey of 351 accidental and 182 suicidal deaths from the files of the Armed Forces Institute of Pathology* covering the years 1940 to 1950, Finck (58) reported that petechiae were noted on autopsy in the hearts of 21 per cent of the accidental victims and 13 per cent of the suicidal deaths. Focal myocardial necrosis was reported in three out of 37 persons who survived CO poisoning from 34 hours to 10 days. The survival time for the 37 cases ranged from 15 minutes to 9.5 months. It is interesting to note that the three cases of reported focal myocardial necrosis were the only cases with detailed microscopic remarks concerning the myocardium or heart.

In August of 1972, another computer assisted review of approximately two million autopsies accessioned at the Armed Forces Institute of Pathology was accomplished by this investigator. Seventy cases were selected where the report specifically included detailed microscopic diagnoses pertaining to the heart or myocardium of persons dying from CO poisoning. After the 13 aircraft accident victims were deleted, the 57 remaining files were screened for extensive microscopic reporting. Detailed microscopic evaluation was sketchy up until approximately 1960 when more detail was put into each autopsy. The majority of the cases were the results

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*Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D.C., 20380.

of massive, usually suicidal, excursions with the agent where death was so rapid that very little damage was reported other than autolysis and similar actions in the post mortem body. Other microscopic myocardial diagnoses reported were usually chronic and long standing disease entities such as atherosclerosis. These cases were selected to be presented here because of their uniqueness and their relationship to the thesis of this investigation.

Case 1. AFIP 1132361 - A 25-year-old white male in excellent health with the cause of death listed as "Chronic Carbon Monoxide Poisoning, Accidental." This man was exposed for approximately 18 hours to CO from coal gas with a CO content of from 4 to 6 per cent. Later investigations estimated that the victim had been breathing an atmosphere of approximately 360 mg/m^3 CO for this period and probably had received a lower level chronic exposure for much longer. The victim did not smoke. After his removal from the CO atmosphere the victim survived for approximately 18 hours. His COHb saturation on admission was 9 per cent. Upon autopsy the following observations were made:

> The myocardium was markedly soft and flabby. Along the courses of all the major coronary vessels there was hemorrhage into the adipose tissue in some instances extending for a distance of almost one cm from the vessel. ... Further examination of the myocardium revealed an area of hemorrhage approximately 2.5 x 5 cm in the posterior wall of the left ventricle which on cross section extended deep into the muscle. The myocardium in scattered areas appeared pale and somewhat yellowish while in others it was somewhat more nearly normal color. Dissection of the coronary vessels

> and cross sectional studies revealed no evidence of obstruction or atherosclerosis. ... Microscopic examination: Sections reveal a striking degree of hemorrhage about many of the vessels, both arterial and venous as well as capillaries. In some the vessels walls appear to have undergone almost a dissolution of a patchy character. There is marked segmentation and fragmentation of myocardial fibrils with hemorrhage into the myocardium. The hemorrhage has a tendency to be arranged in rather linear bands. In some places there are small local collections of segmented neutrophils. There is also some interstitial edema. The myocardial nuclei vary somewhat in both size and staining reaction and an occasional fiber appears to actually be in the early stage of necrosis.

The second victim of this episode, the wife, did not expire but evidenced classical signs of CO poisoning. She was resuscitated shortly after being removed from the area and subsequently recovered. The efforts being made to save her husband's life precluded any diagnostic workup on the wife.

The source of CO for this case was an unvented water heater of the European demand type with a pilot light. The wife of the victim had been complaining to her mother that she was having difficulty in sleeping and had been suffering from headaches, not relieved by aspirin, the day before the episode. Both the victim and his wife had complained of headaches and nausea for several days before the death of the husband.

Case 2. AFIP 1252493 - A 24-year-old Negro female in good health with the cause of death listed as "Acute Carbon Monoxide Intoxication (Accidental)." This woman had been

exposed for at least 12 hours and possibly longer as she had complained of "not feeling well" for at least 36 hours prior to the apparent fatal exposure. Carboxyhemoglobin saturation of venous blood on autopsy was 47 per cent and the following observations were included in the autopsy protocol:

> Heart, Myocardium, Micro: Sections of the myocardium of both right and left ventricles show a focal myocarditis with small clusters of neutrophils in the interstitial tissue. The blood vessels in the myocardium are moderately dilated. The left descending coronary artery shows a slight degree of focal intimal thickening. On the adjacent pericardium there are several focal collections of lymphocytes. ... Epicardium, Micro: A section of epicardium in the posterior portion of the heart near the intraventricular septum shows a fibrinous pericarditis that is focal. Fibrinoid material is present in the epicardium together with small clusters of meutrophils.

All internal organs were reported to have a reddish-pink discoloration attributed to COHb. The apparent source of exposure was from an unvented gas oven in the kitchen.

The victim's 4.5-year-old daughter was admitted for observation following the discovery of her mother's body. She was frightened, drowsy, did not respond well to her surroundings and exhibited a tachycardia of 160 beats per minute. Her hospital course was uneventful and she appeared to recover quickly although it was suggested that she be examined periodically for long term effects of CO poisoning to the central nervous system.

Case 3. AFIP 1338516 - A 22-year-old white male in previously excellent health who was found dead in a bed next

to an unvented butane heater with the valve on. There was no noticeable odor of gas in the closed room. The cause of death was listed as "Carbon Monoxide Intoxication, Circumstances Unknown." The blood was 55 per cent saturated with COHb. The victim was last seen approximately 72 hours before being discovered. On autopsy the following remarks were made:

> Heart: ... The coronary arteries are traced and a small amount of arteriosclerosis is present. There are petechiae under the epicardium over the complete left ventricle. On sectioning the myocardium, petechiae are present in the intraventricular septum. Microscopic - Heart: Slides of the heart show small focal hemorrhages.

Anderson and associates (59) reported on seven cases of CO poisoning, two fatal and five nonfatal, where definite electrocardiographic changes were noted. One of the fatal cases was a 33-year-old white male of undetermined health status admitted unconscious after being found in a tightly closed home with an unvented natural gas heater. Both the heater and pilot light were burning. The COHb saturation of the blood 2 hours after admission was 10 per cent. The patient recovered full consciousness after 48 hours and was discharged. On the fifth day after the exposure he suffered intense chest pain and died less than 1 hour later. On autopsy the following pathology was found in the heart:

> A mural thrombus measuring 2.5 x 2 cm was found near the apex of the left ventricle. A terminal branch of the left anterior descending coronary artery was occluded by a thrombembolus for a distance of 4 cm. At microscopy there was no evidence of acute myocardial infarction in the area of the heart supplied by the occluded vessel. Focal degeneration of the myocardium was present throughout the heart but mainly the left

ventricle. Individual muscle fibers were swollen and necrotic and aggregates of inflammatory cells were present in several areas of the myocardium.

Pathological lesions in the heart attributed to CO poisoning were first described by Klebs in 1865 (60) who reported diffuse and punctiform hemorrhages as well as necrotic foci throughout the heart and particularly in the intraventricular septum and papillary muscles. Anderson and associates (59), in addition to describing seven cases of CO poisoning with myocardial involvement, provide an excellent set of references attesting to the fact that, in the human heart, CO exerts a definite and deleterious effect on the myocardial tissue. Diffusely distributed focal myocardial injury and necrosis are common histologic findings as are leukocytic infiltration and punctate hemorrhages. These pathological findings are indicators of severe damage or of the beginning of a series of serious consequences, depending on the individual and the amount of exposure.

Among the cases reviewed above the first (AFIP 1132371) is an example of chronic exposure to relatively low levels for a period of time culminating in an exposure that resulted in coma and eventually death from extensive myocardial damage rather than hypoxemia as one would expect. The wife, who apparently had the same amount of exposure, did not suffer the ultimate consequence as did her husband. The second case (AFIP - 1252493) was an episode resulting in a COHb level of 47 per cent which is usually considered lethal

(14); however, the myocardial tissue showed conclusive evidence of the beginning of a process that ultimately would have led to deterioration of the tissue had death not resulted earlier from hypoxemia. The daughter was exposed for the same length of time and evidenced only minimal signs of CO poisoning. These two cases illustrate individual susceptibility and response to CO. The third case (AFIP - 1338516) died with a COHb of 55 per cent. Again death from hypoxemia was the primary cause, however the heart evidenced the beginnings of major damage. The case reported by Anderson and associates (59) was an exposure to an unknown level of CO that resulted in a COHb level of 10 per cent 2 hours after admission. This man succumbed 5 days later from massive myocardial damage caused, not by a classical myocardial infarction but from damage resulting from the toxic effects of CO on the myocardial tissue.

These cases were presented as illustrative of the effects of differing exposures to CO under similar and varying sets of circumstances and to point out the individual susceptibility and response to the agent.

Electrocardiographic diagnosis of acute myocardial infarction provides the earliest and most rapid, non-physical indicator of myocardial damage. Most physicians generally feel that the electrocardiogram is the single most reliable diagnostic tool for determining myocardial damage despite the

fact that from 25 to 30 per cent of acute mycardial infarctions are not diagnosed--a fact that has been substantiated in repeated post-mortem studies (61).

The need for another diagnostic tool to assist in detecting damage and one that is relatively organ specific is met fairly well by the various enzyme analyses available in most clinical laboratories. These assays are being used more and more by physicians to clarify diagnoses.

There are at least nine different enzyme assays available in most laboratories for the diagnosis of myocardial damage. Only four will be discussed in this paper, total lactic dehydrogenase, heat stable and heat labile isoenzymes of lactic dehydrogenase, hydroxybutyric dehydrogenase and creatine phosphokinase. Lactic dehydrogenase with isoenzymes and hydroxybutyric dehydrogenase were selected because their serum levels rise slowly after myocardial damage but tend to remain above normal for as long as 16 days. Serum creatine phosphokinase elevates to a much higher level after damage and remains above normal for approximately 5 days but adds diagnostic credibility when done in conjunction with the other enzyme assays selected (61, 62).

Lactic dehydrogenase (LDH) is an enzyme that catalyzes the reversible conversion of lactic acid to pyruvic acid and is found in varying concentrations in all tissues of the body. An increase in LDH levels indicates tissue injury and is often non-specific. Serial determinations can be used to indicate

the approximate time of the injury so that correlations can be made. In cases of myocardial infarction the LDH level is noted to rise within the first 12 to 24 hours and to remain elevated for up to 14 days. The discovery that LDH has a series of identifiable isoenzymes has added a new dimension to the determination of specific tissue damage (61, 62, 64).

Isoenzymes of lactic dehydrogenase were first demonstrated in 1952 (63) and in 1957 it was observed that sera and most tissue homogenates contained up to five such protein fractions (61, 63, 64). Each of the five commonly encountered LDH isoenzymes is thought to represent a genetically controlled tetramer containing varying combinations of two different monomers.

One method for analyzing for LDH isoenzymes is to separate them into two categories, heat labile (LDH_5) and heat stable (LDH_1). The heat labile isoenzymes are found primarily in those tissues exhibiting a high degree of glycolosis and anaerobic metabolism such as liver and skeletal muscle. The heat stable isoenzymes occur primarily in tissues that exhibit high levels of aerobic metabolism, such as the myocardium. The basis for this differentiation is the ability of LDH_1 to survive incubation at 65 degrees centigrade, whereas LDH_5 is inactivated by an incubation at 57 degrees centigrade. LDH_2, LDH_3 and LDH_4 have heat stabilities intermediate between LDH_1 and LDH_5. By this method the total LDH as well as the stable and labile isoenzymes can be determined

colorimetrically. These data are indicative of myocardial versus other tissue damage (61, 63, 64, 65). Lactic dehydrogenase isoenzymes, with heat inactivation, have been supported as a valid alternative to electrophoretic separation by Coodley (61). In a report by Auvinen and Konttinen (65) the more simple heat inactivation method appeared to give more accurate confirmation of myocardial damage than the more complicated electrophoretic separations.

α-Hydroxybutyric dehydrogenase (HBD) activity provides a measure of the concentration of the heat stable LDH_1 isoenzymes and indicates the contribution of the heart to elevated LDH levels. The HBD assay is based on the fact that two isoenzymes, LDH_1 and LDH_2, can utilize the next higher homologue α-ketobutyric acid almost as readily as pyruvate but the isoenzymes LDH_3, LDH_4 and LDH_5 are unable to use this alternate substrate (61, 63, 66). Hydroxybutyric dehydrogenase catalyzes the reduction of α-ketobutyric acid to α-hydroxybutyric acid in the presence of NADH and should give results comparable to the heat stable isoenzyme assay.

Creatine phosphokinase (CPK) is an enzyme which reversibly catalyzes the phosphorylation of creatine with ATP to form adenosine diphosphate and creatine phosphate. It has been reported that myocardial damage produces an increase in serum CPK levels while liver damage produces little or no change (61). Since the enzyme is found so abundantly throughout the musculature of the body, its prime clinical use is in

ascertaining that damage has occurred. One study has suggested that CPK might be a more sensitive indicator of myocardial ischemia than the other enzymes and may be potentially more useful in diagnosing subendocardial infarctions (61, 62).

Figure 1 illustrates the comparative curves of the enzymes discussed and provides graphic evidence of their possible relative values as indicators of measurable damage resulting from repeated sub-acute exposures to CO.

There are many occupations whose work environments have resulted in exposures to CO in varying concentrations, even just living in some areas of the world results in significant exposure (12-24). The occupation that apparently suffers greater exposures to CO, under physical and emotional conditions unequalled anywhere, has been the firefighter. The fire service has very little if any control over the conditions under which it must work and devices to control exposures such as air masks and portective clothing have been less than adequate (67, 68, 69). Almost without exception professional fire fighters have been subjected to increased insurance rates. The literature that is available pertinent to the subject addresses itself primarily to mortality with very little mention of morbility (67, 70, 71).

Since 1969 members of the fire service have had the highest death and injury rate of any occupational group including miners and quarry workers (72). One publication

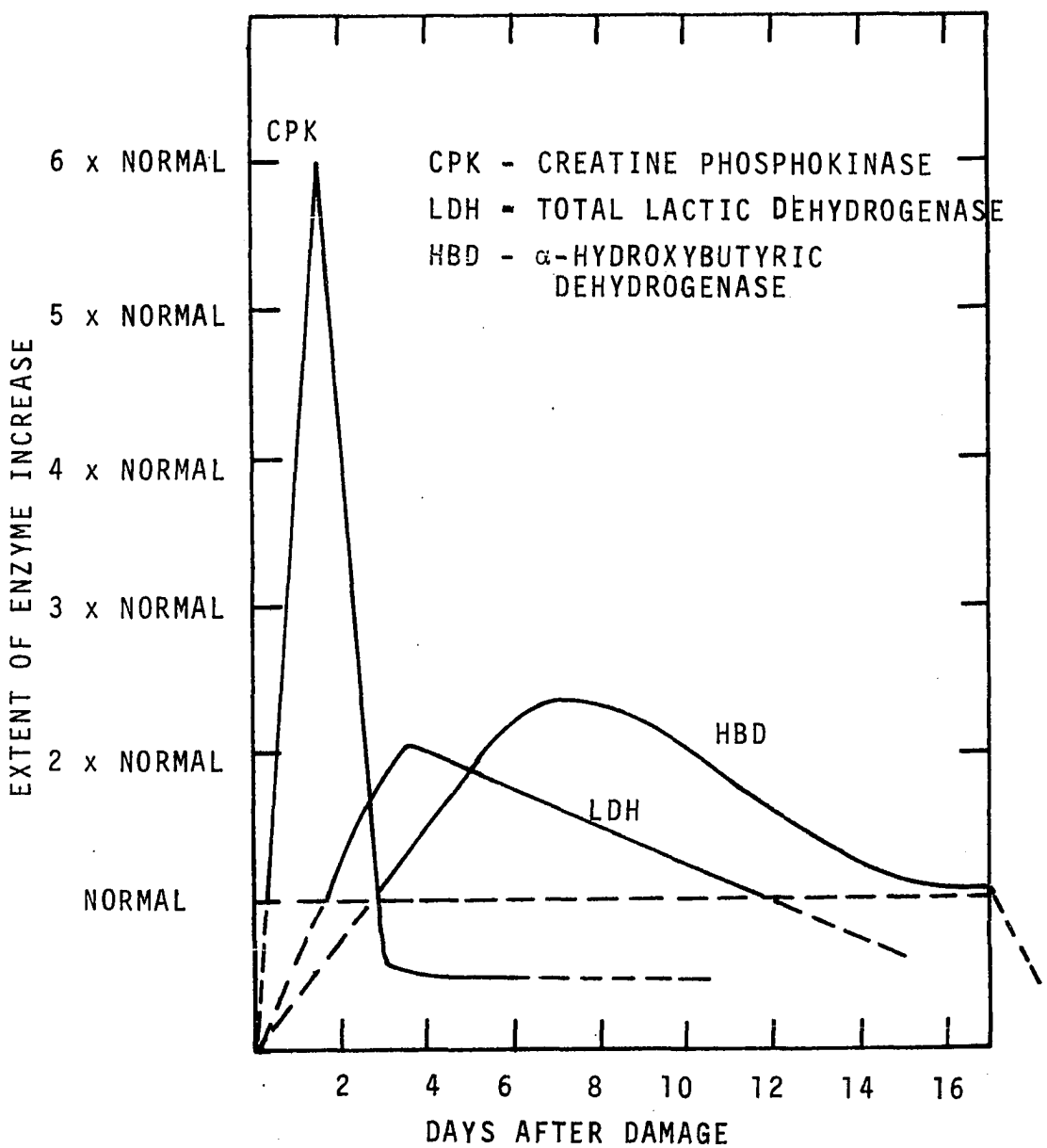

Figure 1. The variation of the enzymes CPK, LDH, and HBD as a function of days after damage.

in 1970 reported 233 fire service deaths from occupational diseases with 96 being from heart and cardiovascular diseases, 126 from lung and respiratory diseases and 11 from other non-specified occupational diseases (72). Moreover, of the 463 fire fighters who left the fire service because of occupational diseases 310 had cardiovascular conditions, 80 had lung diseases and the remainder had non-specified job related diseases (72).

The existence of an increased incidence in cardiopulmonary related diseases in fire fighters has been postulated for years by many physicians closely associated with various Fire Departments (67, 71) and has led one cardiologist to coin an appropriate name for the conditions, "Smoke Eaters Heart Disease" (73). More epidemiological and clinical studies need to be done along these lines since the literature contains a most definite paucity of work pertaining to the fire service as an occupation.

CHAPTER III

PURPOSE AND SCOPE

The major emphasis in this study was to determine if an occupational group exposed repeatedly to sub-acute episodes of CO inhalation as well as other toxic gases had a significantly higher residual COHb level than members of a non-exposed control group. The second portion of the study was to investigate possible repeated minimal myocardial damage as a result of the occupational exposure. Accompanying this was a tentative effort to develop a physiological monitor sensitive enough to detect subtle shifts in baseline values of selected indicator enzymes including lactic dehydrogenase (LDH) with heat stable and heat labile fractions, creatine phosphokinase (CPK) and alpha hydroxybutyric dehydrogenase (α HBD) levels in serum. If such a monitor could be developed then regular clinical examination could detect early evidences of myocardial damage and prevent serious heart disease and possibly death.

The test population was a random selection from members of the Oklahoma City, Oklahoma, Fire Department who were paired with non-firefighter controls as to age,

weight, height, race, smoking habits, and family history of cardiovascular disease.

All subjects were treated in exactly the same way and blood specimens were taken at 28-day intervals throughout the 5-month duration of the study.

Paired t-tests were done on a Monroe 1665 programmable calculator. Regression and correlation analyses were done on a WANG* Series 700 computer.

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*WANG Laboratories, Inc., Tewksbury, MA 01876.

CHAPTER IV

EQUIPMENT AND PROCEDURES

Analytical Procedures

Carboxyhemoglobin and reduced hemoglobin saturations were determined by utilizing the IL-182 CO-Oximeter*. This procedure involved the combination of a sensitive and accurate absorption spectrophotometer with an analog computer. Three precision interference filters were used as monochromators to measure the absorbance of oxyhemoglobin (HBO), COHB and reduced hemoglobin at selected wavelengths. A change of absorbance at 568 nanometers (nm) compared to the absorbance at 548 nm indicated the relative concentration of COHB while a change in absorbance at 578 nm compared to 548 nm indicated the concentration of HBO. COHb and reduced hemoglobin were calculated by solving the following simultaneous equations and the results presented in digital form:

(1) $A_1 = a_1Hbr\ BCHBr + a_1HbO_2\ bc\ HBO_2 + a_1HBCObc\ HBCO$

(2) $A_2 = a_2Hbr\ BCHBr + a_1HbO_2\ bc\ HBO_2 + a_2HBCObc\ HBCO$

(3) $A_3 = a_3Hbr\ BCHBr + a_1HbO_2\ bc\ HBO_2 + a_3HBCObc\ HBCO$

*Instrumentation Laboratory, Inc., 133 Hartwell Ave., Lexington, MA, 02173.

"A" represents the absorbance (log I_0/I) measured at a given wavelength, "a" is the absorptivity of each species at that wavelength and "b" is the sample path length. 1 - 548 nm, 2 - 569 nm, and 3 = 578 nm.

Total lactic dehydrogenase with isoenzymes LDH_1 and LDH_5 was determined by utilizing Sigma Chemical* procedure No. 500 for the colorimetric determination of LDH at 475 nm. Lactic dehydrogenase catalyses the reversible conversion of lactic acid to pyruvic acid with the rate of reaction being proportional to the amount of lactic dehydrogenase. The amount of pyruvate remaining after the incubation is inversely proportional to the amount of lactic dehydrogenase present in the reaction. In this procedure pyruvic acid reacts with 2, 4-Dinitrophenylhydrazine to form a hydrazone which has a high absorptivity over the 400-550 nm range.

Hydroxybutyric dehydrogenase (α-HBD) activities were determined by Sigma Chemical procedure No. 495 for the colorimetric determination of Hydroxybutyric dehydrogenase in serum at 440 nm. Hydroxybutyric dehydrogenase catalyzes the reversible reduction of α-ketobutyric acid to α-hydroxybutyric acid. In this procedure the α-ketobutyric acid remaining after incubation is determined by forming a hydrazone which is colored in alkaline solution. This provides a colorimetric measure of the original α-hydroxybutyric dehydrogenase activity.

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*Sigma Chemical Co., P.O. Box 14508, St. Louis, MO 63178.

Creatine phosphokinase (CPK) was determined colorimetrically using Sigma Chemical procedure No. 520 for the determination of CPK at 520 nm. In this procedure creatine phosphokinase catalyzes the reversible reaction in which phosphocreatine is dephosphorylated to creatine. A color complex is then formed by reacting the creatine with α-napthol and diacetyl for an indirect measure of the activity of the enzyme.

Carboxyhemoglobin and hemoglobin analyses were performed on whole blood drawn in a heparinized* 10 ml disposable syringe. Air was expelled and the syringe capped immediately after the specimen was taken. COHb and hemoglobin determinations were usually done within one hour.

The serum was obtained from blood placed in a scrupulously clean tube and allowed to clot. Enzyme assays were performed on the same day the blood was drawn.

Specimens were taken at 28-day intervals during the 5-month duration of the study. All determinations were done in duplicate.

Population Selection

The pairing of the two populations was accomplished by extensive interview to assure the most exact pairing possible. All test subjects were chosen from the randomly

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*Aqueous Soidum Heparin 10,000 units/ml, Riker Laboratory, Inc., Northridge, CA 91342.

selected pool and paired on the basis of matching as many criteria as possible for the interview and index schedules (see appendix). Control subjects were drawn from local military reserve units. This resulted in a virtually identical pairing as to age, weight, height, smoking habits, sex, race and family history of cardiac or pulmonary disease. Effort was made to exclude any control subjects who might have been engaged in an occupation or hobby that would have offered significant exposures of CO. Similarly, test subjects were screened closely for second jobs or hobbies that would have offered additional exposure to the agent. Tables 1 and 2 indicate the closeness of the pairing which took over four months to complete.

TABLE 1

TEST POPULATION PAIRING DATA

Test Subject	Cigs per Day	Age Start Smoke	Age	Pack[a] Years	Years in Fire Svc	Body Area m^2	Family[b] History
1	40+	18	49	62	26	1.8	+
2	10-20	20	42	16.5	21	2.0	-
3	0	0	40	0	15	2.0	-
4	0	0	37	0	10	2.3	-
5	0	0	37	0	9	2.1	+
6	0	0	35	0	3	2.1	+
7	40+	11	35	48	6	1.9	+
8	10-20	16	34	13.5	2	2.2	+
9	10-20	23	34	8.25	10	2.1	-
10	21-39	17	33	24	5.5	1.9	-
11	0	00	33	0	6	2.0	-
12	10-20	19	33	10.5	3	1.9	-
13	40+	15	33	36	2	1.9	+
14	21-39	16	32	24	2	1.9	-
15	0	00	30	0	6	2.0	-
16	10-20	20	30	7.5	5	2.1	-
17	0	0	29	0	6	2.0	-
18	40+	20	29	38	7	1.9	-
19	10-20	18	29	8.25	8	1.9	-
20	10-20	14	29	11.2	7	1.9	-
21	1-9	20	28	4.5	5	1.9	+
22	10-20	16	28	9	5.5	1.9	-
23	0	0	28	0	2	2.1	-
24	21-39	17	27	15	2	2.1	-
25	10-20	21	26	3.75	1	1.9	-
26	10-20	16	25	6.75	3	1.9	-
27	40+	18	25	14	0.25	1.8	-

[a]Number of cigarettes smoked per year/years smoked.

[b]See appendix for questionnaire.

TABLE 2

CONTROL POPULATION PAIRING DATA

Test Subject	Cigs per Day	Age Start Smoke	Age	Pack[a] Years	Years in Fire Svc	Body Area m^2	Family[b] History
1	40+	14	48	68	0	1.8	+
2	10-20	18	41	17.25	0	1.9	-
3	0	0	40	0	0	2.0	-
4	0	0	38	0	0	2.2	-
5	0	0	37	0	0	2.0	+
6	0	0	36	0	0	2.1	+
7	40+	14	35	42	0	1.9	+
8	10-20	18	34	12	0	2.2	+
9	10-20	20	34	10.5	0	2.0	-
10	21-39	18	34	24	0	2.0	-
11	0	0	33	0	0	2.0	-
12	10-20	19	33	10.5	0	1.9	-
13	40+	16	33	34	0	1.9	+
14	21-39	17	31	21	0	1.9	-
15	0	0	30	0	0	2.0	-
16	10-20	19	30	8.25	0	2.0	-
17	0	0	29	0	0	2.0	-
18	40+	20	29	38	0	1.9	-
19	10-20	18	29	8.25	0	1.9	-
20	10-20	16	29	9.75	0	1.9	-
21	1-9	19	28	4.75	0	1.9	+
22	10-20	16	28	9	0	1.9	-
23	0	0	27	0	0	2.1	-
24	21-39	13	27	21	0	2.0	-
25	10-20	18	26	6.0	0	1.9	-
26	10-20	17	25	6.0	0	1.9	-
27	40+	13	25	24	0	1.8	-

[a]Number of cigarettes smoked per year/years smoked.

[b]See appendix for questionnaire.

CHAPTER V

OBSERVATIONS AND DISCUSSION

Observations

Hemoglobin

Hemoglobin values in the test population ranged from 14.4 to 17.2 grams per 100 ml of blood with a mean of 15.5 Table 3 presents the five month mean values for each person in the test group. Hemoglobin values in the control group ranged from 11.9 to 17.3 grams with a mean of 15.6. Table 4 presents the five month mean values for the control group.

Paired t-tests were used to test for significance between the individual five month mean values of both the test and control populations. Individual probabilities obtained from the paired t-test are presented in Table 5. No significance was found when the test and control populations, each as a single group, were subjected to the paired t-test. A plot of the regression analyses of hemoglobin against smoking habits is presented as a graphic illustration of the homogeneity of the two populations in Figure 2. This homogeneity is strengthened when the two mean values, 15.5 and 15.6 grams, are considered. These values compare almost

TABLE 3

TEST GROUP DATA - FIVE MONTH MEAN VALUES

Pair	COHB[a]	HB[b]	Total[c] LDH	Stable[d] LDH	Labile[e] LDH	CPK[f]	HBD[g]
1	11.12	14.4	262	198	28	17	72
2	9.88	15.4	330	137	8	6	82
3	2.76	15.7	284	122	56	7	82
4	4.52	15.5	324	146	49	0	81
5	2.5	17.2	268	114	78	2.0	73
6	4.5	14.6	362	184	68	10	81
7	8.3	16.7	264	126	0	0	74
8	10.7	14.7	562	370	52	39.0	117
9	4.3	14.9	242	156	12	7.0	72
10	13.9	15.8	260	173	0	12	96
11	6.9	15.1	272	182	53	15.0	77
12	11.4	17.2	246	126	60	0	75
13	12.55	14.1	336	138	58	17	87
14	8.4	15.9	213	110	42	0	71
15	7.3	15.5	238	142	58	12	72
16	9.1	16.5	212	120	0	5	84
17	5.9	16.0	226	126	16	5	73
18	13.1	16.1	306	134	0	17	73
19	9.4	16.2	270	134	42	3	96
20	7.2	14.5	268	146	0	0	73
21	12.1	16.3	324	112	22	7	78
22	8.8	16.5	346	160	80	9	78
23	6.1	15.3	240	170	0	0	76
24	13.5	15.4	224	154	46	0	73
25	8.1	16.3	278	173	52	0	78
26	6.4	13.5	318	106	0	0	72
27	12.5	14.4	214	134	30	15	74

[a] Carboxyhemoglobin (grams per 100 ml blood).

[b] Hemoglobin (grams per 100 ml blood).

[c] Total lactic dehydrogenase (units: See appendix).

[d] Heat stable Lactic dehydrogenase (units: See appendix).

[e] Heat labile lactic dehydrogenase (units: See appendix).

[f] Creatine phosphokinase (units: See appendix).

[g] α-Hydroxybutyric dehydrogenase (units: See appendix).

TABLE 4

CONTROL GROUP DATA - FIVE MONTH MEAN VALUES

Pair	COHB[a]	HB[b]	Total[c] LDH	Stable[d] LDH	Labile[e] LDH	CPK[f]	HBD[g]
1	11.12	15.3	236	154	45	4	78
2	8.62	14.9	173	100	16	1	72
3	2.12	11.9	171	85	22	1	75
4	1.8	15.0	310	124	85	7	72
5	1.0	15.6	166	75	10	0	72
6	3.3	16.2	190	118	74	0	73
7	7.3	15.6	178	76	70	3	74
8	8.5	15.3	163	86	33	5	74
9	3.9	15.0	168	106	55	3	72
10	8.8	16.8	189	96	88	5	81
11	4.0	15.0	184	89	24	0	72
12	7.5	15.9	198	80	10	0	75
13	11.7	15.4	242	46	45	0	90
14	7.3	17.3	202	132	64	0	76
15	0.9	15.2	157	86	60	4	63
16	7.4	15.9	252	78	44	4	65
17	3.2	17.1	202	64	74	5	82
18	10.8	16.1	200	103	58	0	71
19	8.3	15.9	192	102	72	1	61
20	7.4	15.4	164	61	82	0	82
21	7.5	16.6	207	128	62	4	64
22	4.5	16.8	236	118	96	0	71
23	2.0	16.1	216	90	103	0	78
24	7.6	17.1	232	93	89	0	77
25	2.1	15.0	176	87	72	0	71
26	7.5	12.9	257	115	52	4	70
27	5.9	15.0	134	70	44	0	71

[a] Carboxyhemoglobin (grams per 100 ml blood).

[b] Hemoglobin (grams per 100 ml blood).

[c] Total lactic dehydrogenase (units: See appendix).

[d] Heat stable lactic dehydrogenase (units: See appendix).

[e] Heat labile lactic dehydrogenase (units: See appendix).

[f] Creatine phosphokinase (units: See appendix).

[g] α-Hydroxybutyric dehydrogenase (units: See appendix).

TABLE 5

PROBABILITIES DETERMINED BY PAIRED T-TEST
(FIVE MONTHS OF DATA)

Test Cont. Pair	COHb[a]	Hb[b]	LDH(T)[c]	LDH(S)[d]	LDH(L)[e]	CPK[f]	HBD[g]
1	NS[h]	-0.01	0.3	0.05	-0.4[i]	0.01	-0.2
2	0.05	0.2	0.001	0.3	-0.3	0.2	0.05
3	0.2	0.001	0.001	0.1	0.1	0.05	0.1
4	0.001	0.05	0.4	0.3	-0.001	-0.02	0.05
5	0.001	0.02	0.001	0.001	0.001	0.4	NS
6	0.2	-0.02	0.001	0.01	-0.5	0.001	0.2
7	0.02	0.01	0.03	0.01	-0.2	-0.2	NS
8	0.02	-0.5	0.001	0.001	NS	0.001	0.01
9	0.1	-0.4	0.05	0.02	-0.05	0.2	NS
10	0.001	-0.1	0.01	0.02	-0.001	0.1	0.1
11	0.01	NS	0.01	0.001	0.2	0.001	0.3
12	0.01	0.01	0.02	0.1	0.01	NS	--0.4
13	0.5	-0.1	0.05	0.01	0.3	0.001	NS
14	0.2	-0.02	NS	-0.2	-0.2	NS	-0.2
15	0.001	0.02	0.001	0.001	NS	0.02	0.1
16	0.2	0.2	-0.4	0.1	-0.05	NS	0.01
17	0.01	-0.1	NS	0.01	-0.05	NS	-0.3
18	0.01	NS	0.1	0.2	-0.2	0.001	NS
19	0.02	0.4	0.01	0.001	-0.02	0.2	0.001
20	NS	NS	0.05	0.02	-0.01	NS	-0.1
21	0.01	-0.2	0.1	-0.5	-0.2	0.3	0.5
22	0.01	NS	0.02	0.2	-0.3	0.01	0.2
23	0.05	-0.05	NS	0.01	-0.01	NS	-NS
24	0.01	-0.1	-NS	0.01	-0.05	NS	-NS
25	0.001	0.1	0.001	0.01	-0.5	NS	0.4
26	-0.1	0.3	0.2	-0.5	-0.1	-0.1	NS
27	0.01	-0.3	0.01	0.01	-NS	0.001	0.5

[a] Carboxyhemoglobin (grams per 100 ml blood).
[b] Hemoglobin (grams per 100 ml blood).
[c] Total lactic dehydrogenase (units: See appendix).
[d] Heat stable lactic dehydrogenase (units: See appendix).
[e] Heat labile lactic dehydrogenase (units: See appendix).
[f] Creatine phosphokinase (units: See appendix).
[g] α-Hydroxybutyric dehydrogenase (units: See appendix).
[h] No significance.
[i] Negative t-value.

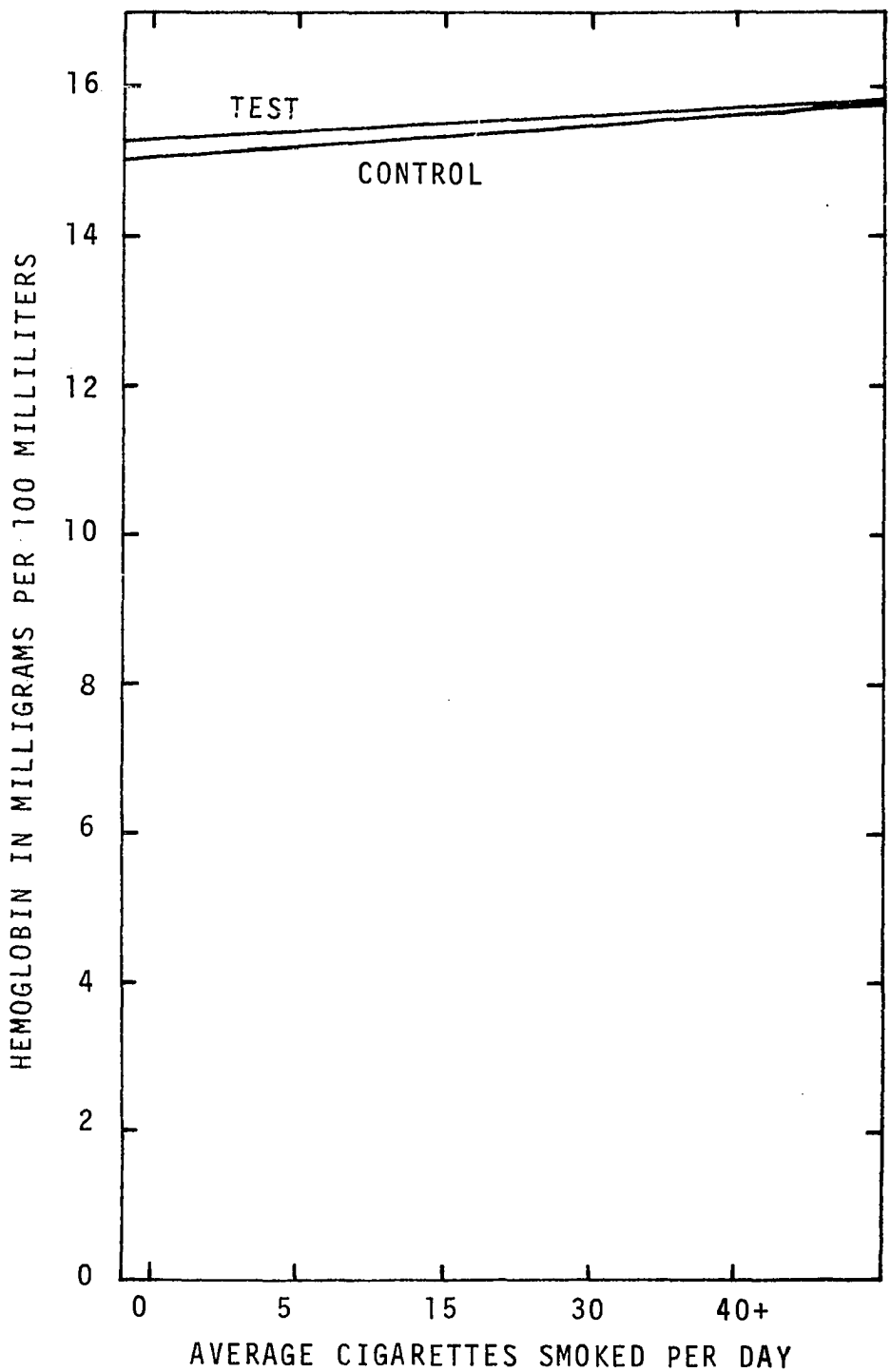

Figure 2. The comparison of hemoglobin levels in the test and control groups with their smoking habits.

exactly with the 15 gram population mean value established for males (31, 36, 37).

There was no indication of any compensation, acclimatization or adaptation to CO as suggested by Killick (34, 35) and Ramsey (48). Had this occurred, the hemoglobin values for the test group would have been significantly different from the controls.

Carboxyhemoglobin

Carboxyhemoglobin values in the test population ranged from 2.5 to 13.5 per cent saturation with a mean of 8.6 Table 3 presents the five month mean values for each person in the test group. COHb values in the control population ranged from 0.9 to 11.7 per cent saturation with a mean of 6.0. Table 4 presents the five month mean values for each person in the control group.

Paired t-tests were used as a test for significance between the individual five month mean values of both the test and control populations. The results of these tests are presented in Table 5. When the level of significance was set at the 5 per cent level, 66.66 per cent of the pairs were in the significant range. A paired t-test using the five month mean values of both the test and control populations as groups gave a probability of $p < 0.001$, a highly significant difference.

Regression analyses comparing COHb saturations against such variables as age, length of time in the fire service, and smoking habits were done. All regressions were indicative of the previously described significant difference between the COHb levels of the test and control populations. The results presented in Figure 3 more clearly define this and also reinforce the relationship between COHb levels and smoking habits. These results are not necessarily linear, however, when the mean COHb levels of smokers versus non-smokers in both groups are compared the results strengthen the significance of the observed differences.

The mean COHb value for test group non-smokers is 5.0 per cent as compared to 2.3 for the non-smoking controls. This value for the non-smokers is within the 0.0 to 2.5 per cent range found by Lawther (29) but is much higher than the mean of 0.8 per cent described by Lawther and reaffirmed by the 1972 Surgeon General's Report and its references (41). The most recent study (still in progress) by Stewart and Peterson (79) has demonstrated that COHb levels range from 0.48 to 2.18 per cent for non-smokers and from 1.95 to 6.99 per cent for smokers. The only report in the literature, other than Lawther (29), dealing with a selected group such as fire fighters was that of Gordon (74) where the fire fighter was used as his own control. The COHb level of the fire fighter increased when he was actively engaged on the firegrounds and returned, after several hours, to five per

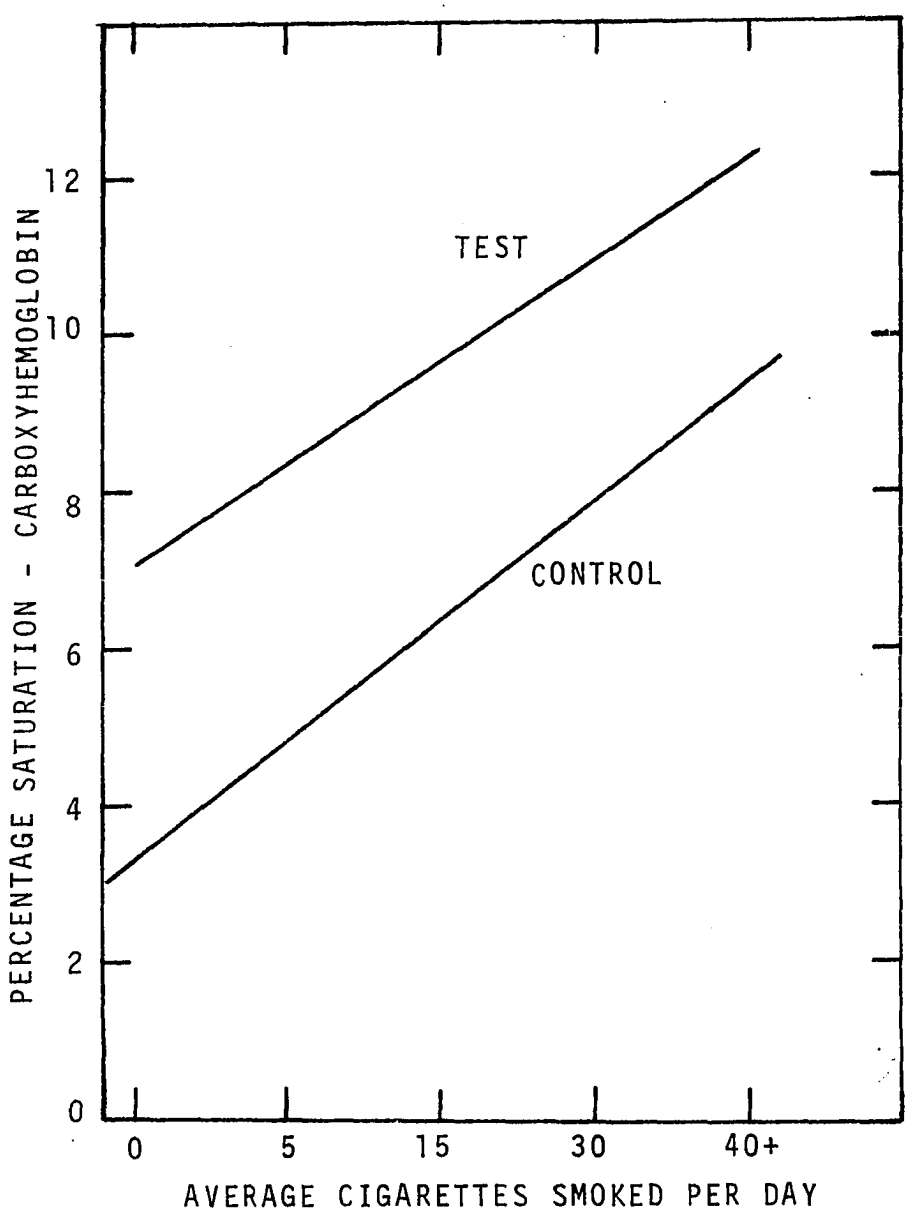

Figure 3. The comparison of carboxyhemoglobin levels in the test and control groups with their smoking habits.

cent COHb or less. In Gordon's study five per cent COHb or less was considered baseline rather than accepted population normals. Bridge (55) found that a non-smoker, in a confined space with a smoker, was also at risk since cigarette side-stream smoke contains four to six times more CO than main-stream smoke. Unfortunately this study did not involve biological measurements so the actual COHb enhancement is unknown. Cohen and associates (75) found significantly high COHb levels in both smoking and non-smoking border inspectors which were correlated with high ambient CO levels. Ramsey (76) studied the occupational exposure of parking garage attendants who attained COHb levels of 10 per cent following a daily exposure to CO that averaged slightly under 72 mg/m^3. It was concluded in this study that the occupational exposure was more instrumental in producing the COHb levels than the smoking habits. Contrasting studies conducted by Breysse (77) and Buchwald (78) concluded that smoking among workers made a significant contribution to their COHb levels when their occupational exposure was 60 mg/m^3 or less. It is logical to assume that, based on all of these studies, an occupational exposure to CO would have the same effects as an exposure from a smoker.

The 5.0 percent COHb saturation for the test group non-smokers compares well with Lawther (29) who found the COHb levels in non-smoking firemen to range from 0.4 to 8.8

with a mean of 3.2. The Surgeon General (41) considers the COHb levels in smokers to average 4 per cent. It is also most significant to note that the current recommended time weighted average (TWA) for an occupational exposure to CO (30) is predicated on an exposure of 42 mg/m^3 CO for an eight hour period to achieve no greater than a 5 per cent COHb saturation. Therefore it would seem that the non-smoking fire fighter, by virtue of his occupation, has already achieved the maximum allowable COHb concentration and any additional exposure could be considered detrimental to his health.

Lactic Dehydrogenase and Isoenzymes

Total Lactic Dehydrogenase (LDH), Heat Stable Lactic Dehydrogenase (LDH-S) and Heat Labile Lactic Dehydrogenase (LDH-L) values for both populations are presented in Tables 3 and 4. The range of values for LDH as established by the procedure (44) is:

Normal	100 - 350 units*
Borderline	350 - 500 units
Elevated	> 500 units

Only one test subject was outside the range of normal (562 units) and no controls were outside the normal range. The mean value for the test group was 285 units as compared to 200 for the controls.

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*One unit will reduce 4.8×10^{-4} micromoles of pyruvate per minute at 25 degrees Centigrade.

The range of values for the isoenzymes as established by the procedure is:

	Heat Stable	Heat Labile
Normal	0 - 140 units*	0 - 105 units
Borderline	140 - 200 units	105 - 150 units
Elevated	> 200 units	> 150 units

Thirteen members of the test group exceeded the normal range of the LDH-S with one falling in the elevated range (370 units). No test subjects exceeded the normal range for LDH-L. Only one control subject exceeded the normal LDH-S range (154 units) and no controls were outside the range of normal for the LDH-L determination. The mean population value for the test group LDH-S was 152 units as compared to 95 for the controls. The mean for the LDH-L was 34 for the test population and 55 for the controls.

Paired t-tests were done on each of the individual paired LDH determinations. The probabilities obtained are presented in Table 5. A paired t-test using five month mean values for both the test and control population as groups gave the following probabilities:

LDH - $p < 0.001$

LDH-S - $p < 0.001$

LDH-L - $p < 0.02$ (-)

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*One unit will reduce 4.8×10^{-4} micromoles of pyruvate per minute at 25 degrees Centigrade.

Regression analyses comparing LDH, LDH-S and LDH-L with such variables as age, length of time in the fire service and smoking habits were inconclusive, however, a difference in the two populations was evident. Considering the care taken in the pairing of subjects, this difference can best be described as occupationally related. Figure 4 illustrates this difference for LDH-S.

Coodley (61), while stating positively that the isoenzyme determination is invaluable in assisting the physician to diagnose specific organ damage, warns that the isoenzymes aid in localizing organ damage but provide no insight into etiology. Since the LDH, LDH-S and LDH-L values were virtually all within the limits of normal and those outside the normal range were borderline, the results presented here must be evaluated in this light. The face that there was a definite, measurable and statistically significant difference between the test and control populations, normal values notwithstanding, has raised the strong presumption that the difference must have been occupational. There is no diagnostic suggestion of any specific organ damage but the preponderance of the evidence available would seem to indicate that the occupational factor/exposure is a prime suspect to consider in evaluating this difference.

The inversion of the test and control mean values for LDH-L would appear to indicate that fighting fires improves

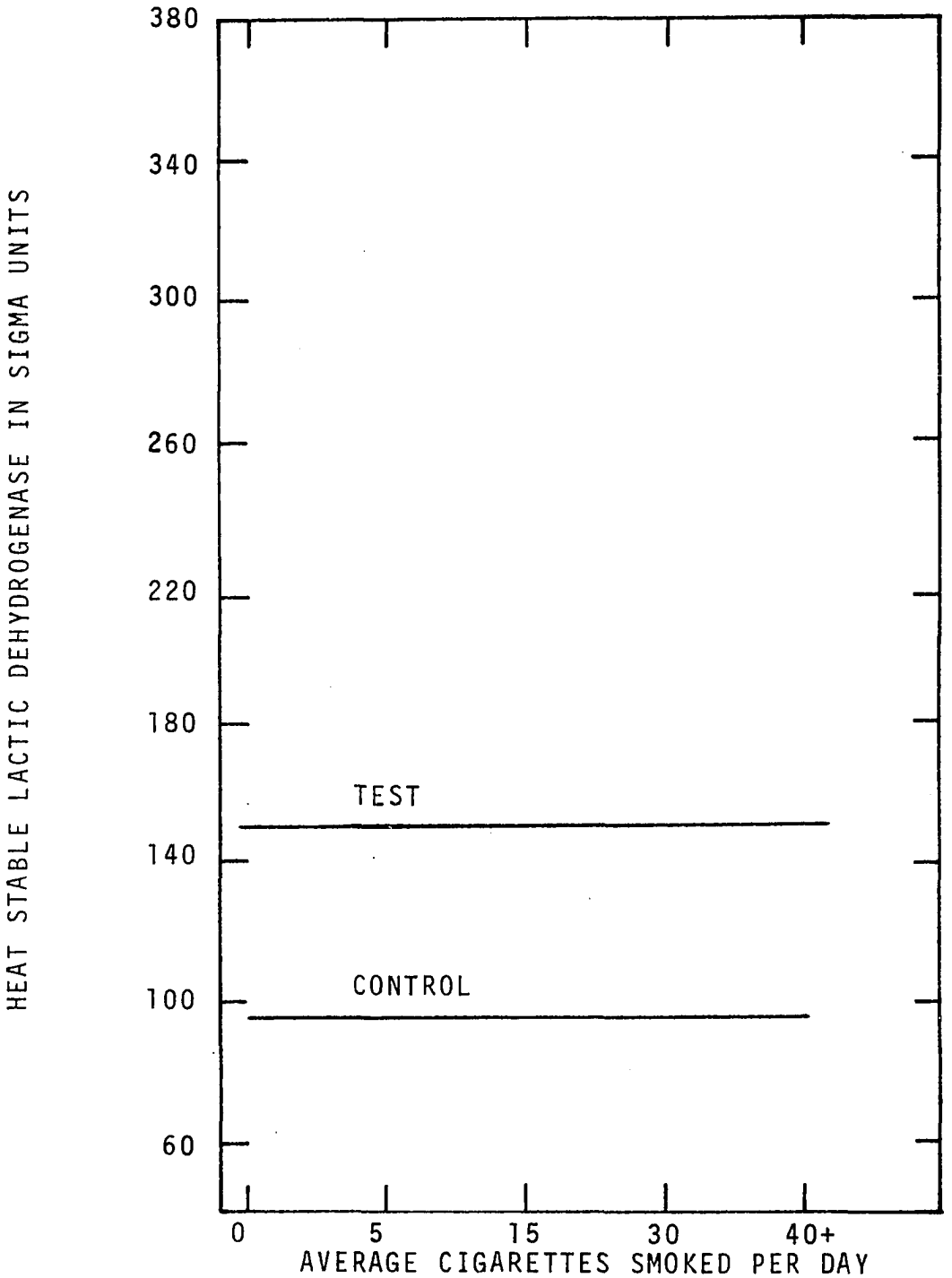

Figure 4. The comparison of stable lactic dehydrogenase activities in the test and control groups with their smoking habits.

the health of the individual. Inspection of the data reveals a range of values from 0 - 80 units for the test population as compared to 7 - 103 for the controls. Although all determinations were set in duplicate and were repeated if any disparity appeared, it was possible that this was a procedural artifact rather than a biologically significant occurrence. Since the sensitivity of the procedure at low values has been reported to be erratic (61, 64, 65) the predominance of these values in the test results leads to the belief that the observed inversion was procedural. However, it is possible that the increase in the LDH-S/LDH ratio as evidenced in the test data could reduce the LDH-L/LDH ratio. This phenomenon was not observed in the control data.

Hydroxybutyric Dehydrogenase

Serum α-hydroxybutyric dehydrogenase (HBD) levels for both the test and control groups are presented in Tables 3 and 4. The range of values of HBD as established by the procedure (66) is:

Normal	55 - 125	units*
Borderline	125 - 145	units
Elevated	> 145	units

No subjects, either test or control, were outside the range of normal. The mean for the test population was 79 units as compared to 74 for the controls.

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*One unit will reduce one millimicromole of α-ketobutyric acid per minute at 25 degrees Centigrade.

Paried t-tests were used as the test for significance between the individual five month means of both the test and control populations. The results of these tests are presented in Table 5.

Regression analyses comparing HBD against such variables as age, length of time in the fire service, and smoking habits produced no correlation but the indication of a difference between the test and control populations was again strong.

A paired t-test using the five month mean values of the test and control populations again confirmed this difference and established the probability at $p < 0.02$ despite the closeness of the two means.

The HBD assay is highly specific for cardiac disease since it measures only those isoenzymes specific to the myocardium. Other conditions known to elevate HBD levels are hepatitis, megaloblastic anemia and renal infarction; all conditions which would be clinically apparent (61-64). The HBD assay is highly specific and the level of enzyme in serum remains elevated longer (Figure 1) after a slower elevation. The correlation coefficient (r) between LDH-S and HBD was 0.6 for the test group and 0.2 for the control which reinforces the apparent difference between the two populations. This recurring difference was, most probably, related to the occupational differences between the test and control groups since the occupation was the major variable not removed by the pairing.

Creatine Phosphokinase

Serum creatine phosphokinase (CPK) levels for both populations are presented in Tables 3 and 4. The range of values for CPK as established by the procedure (62) is:

Normal	0 - 12	units*
Borderline	12 - 20	units
Elevated	> 20	units

Four test subjects were borderline and one was elevated to 39 units with no controls being outside the normal range. The mean value for the test group was 8 units as compared to 2 for the controls.

Paired t-tests were used to test for significance between the individual five month mean values of both the test and control populations. The results of these tests are presented in Table 5.

Regression analyses comparing CPK against such variables as age, length of time in the fire service and smoking habits were done. All regressions, although showing virtually no correlation, were again indicative of a definite difference between the two populations.

A paired t-test using the five month means of both the test and control populations gave a probability of $p < 0.01$. This significance is difficult to interpret in view of the normalcy of the results; however, the procedure

*One unit will phosphorylate one millimicromole of creatine per minute at 25 degrees Centigrade.

(62) presented several references in which the range of values was defended and several conditions that have been reported to result in elevated CPK levels, including myocardial infarction and muscular exercise, were presented. Coodley (61) confirmed these causes but also suggested that CPK might be a more sensitive indicator of myocardial ischemia and subendocardial infarction than the other enzymes. Since the heart and skeletal muscle are the richest sources of CPK in the body, this difference must be considered real realizing that firefighting is a strenuous occupation and that exercise has been reported to increase CPK levels.

Discussion

The most significant findings of this project were the obvious significant differences between the test and control populations. Without doubt, in the populations tested, members of the fire service had significantly higher COHb, LDH, LDH-S, CPK and HBD levels. The hemoglobin determination indicated that, for this group, there was no difference in hemoglobin thereby substantiating the homogeneity of the populations and strengthening the pairing.

LDH and its isoenzymes may be elevated in anemia, pulmonary disease, liver disease, muscle disease, renal disease and hemolysis of serum. The HBD and CPK determinations add greater specificity in diagnosis and produce a lower number of false positives. The CPK is highly specific for

myocardial necrosis if complicating factors such as muscle damage, brain damage and hypothyroidism are first ruled out. CPK presents an earlier and more dramatic amplitude of change (Figure 1). The HBD assay is more specific for myocardial damage than LDH and LDH-S because it measures only those isoenzymes of LDH found in myocardial cells. The two determinations would then appear to improve the diagnostic credibility of the enzyme battery selected for this project.

Although there was no suggestion of specific organ disease nor any clinical heart disease among any of the study groups, there was some factor at work to create the levels of significance found between four of the five components of the enzyme battery, all of which are myocardial related. Because of the closeness of the pairing, with occupation being the major difference between the groups, the presumption is strong that, for this group of men, the occupation is the main contributing factor to explain the enzymatic differences.

Enzymatic shifts following exposure to CO have been reported in the literature. Lassiter (80) provided evidence that rats exposed to CO at 600 mg/m^3 for four and five hours sustained myocardial damage manifested as an increase in plasma LDH_1. Gordon (74) found that firefighters, when fighting fires, exhibited increased LDH and CPK values as compared to firefighters who were not actively engaged on the fireground. The elevated enzyme levels appeared to be related to

the duration of the fire and the COHb levels. It is a recognized fact that exposure to high concentrations of CO could result in cardiac damage and numerous investigators have reported damage ranging from subtle EKG changes to visible myocardial necrosis (24, 38, 53, 59, 81-89).

With few exceptions the enzymatic values obtained in this study were within or close to the normal range. The difference is that ranges of normals are designed to accomodate individual rather than group variability. Taking into account the normal ranges the paired individual values obtained in this study were inconclusive, however, when taken as group values the differences become highly significant. The same rationale holds for the enzymatic battery versus individual determinations. Taken alone, any one of the determinations would have left considerable doubt as to the effects of chronic occupational exposure to CO and the other components of the fire-smoke complex. Taken as a battery, the results leave little room to doubt that such an occupational effect could exist in this study group.

The consequences of increased COHb levels have been generally considered transitory in nature and result in few, if any, chronic effects. Recently Lassiter (80) and the National Institute of Occupational Safety and Health (NIOSH) (30) have indicated that the potential exists for myocardial damage as a result of exposures, ambient or occupational, to CO. Ayers (54) determined that when the COHb level approached

8.7 per cent the myocardium produced lactate. The production of lactate in the myocardium is indicative of tissue hypoxia which can lead to decreased cellular function and ultimately to cell death. Ayers in the same study determined that coronary blood flow was increased only in persons free from coronary artery disease. Adams and associates (90) studied the effects of low concentrations of COHb on coronary blood flow, myocardial oxygen consumption, and cardiac function in conscious dogs. They found that the myocardium compensates for the CO induced hypoxia but that this compensation was probably not adequate.

Astrand (91) stresses that in the case of low level exposures to CO such as smoking the required level of O_2 unloading from increased COHb levels may demand O_2 tensions so low that cells distant from capillaries may be exposed to hypoxic conditions. This creates a definite handicap for a smoker, or for an occupationally exposed individual, during exercise or heavy work. All other factors being equal, a reduction in the O_2 transporting capacity is associated with a corresponding reduction in physical performance capacity during heavy or maximal work. Since the O_2 transporting capacity declines with increasing altitude (34, 35) or with a decrease in available O_2, and the maximal aerobic power depends partly on the maximal cardiac output and partly on the O_2 carrying capacity of the blood, the aerobic power must therefore decline with increasing COHb levels.

In an individual with a COHb saturation of from 5 to 10 per cent there is a corresponding decrease in the O_2 carrying capacity of the blood. During strenuous physical exertion involving large groups of muscles for more than a few minutes this represents a definite potential for tissue damage. The smoker, however, can not compensate for the CO content of the blood during maximal work (91). A five to ten per cent reduction in maximal aerobic power due to smoking or occupation might well play a significant role in myocardial damage during or subsequent to very heavy work.

This inability to compensate for COHb becomes most critical when a worker, such as a firefighter, is exposed to levels of CO far exceeding those of the smoker and those recommended by NIOSH (30). The firefighter must enter areas where the temperatures may range from 500 to 1500 degrees Fahrenheit and the CO levels, as well as other toxic and potentially hazardous materials, are unmeasured (67). The protective clothing, including air masks, required for this entry weigh in the range of 60 pounds dry weight and over 75 pounds when soaked with water. In addition to this the firefighter must struggle against a hose charged with from 100 to 250 psi of water through a most hostile environment. There have been no measurements of actual work involved and energy expended, but from personal observation and numerous discussions with fire fighters, fire fighting seems to be one of the most strenuous occupations. It is a documented fact that

fire fighting is also the most hazardous occupation (72).

The question must inevitably arise as to why the length of time in the fire service or age were not good indicators of the observed occupational effects. Figure 5 presents a simplified graphic illustration of the career progression of a combat fire fighter as it relates to the amount of exposure he receives. As can readily be seen the exposure is bi-modal with the first high levels of exposure and maximum work efforts being upon entry into the service and the second equally significant exposure coming some 15 years later following a lag phase during which he remains generally outside the fire itself. The age of the individuals at each flow point can vary greatly since the maximum age for entry into employment is 32. Here we have a situation where the man, when he reaches Captain, is moving into the cardiovascular hazardous years (41) and must again enter the fire as he did as a rookie fire fighter. The design of this study was not such that subjects in each category could be identified. It was simply a computer assisted random selection of 36 men from the Oklahoma City Fire Department of whom 27 completed the five month study period with their controls. The initial design limits were set at 36 pairs because of financial constraints. During the course of the investigation nine men were dropped from the study for various reasons including death, discharge and resignation. The effects of stress,

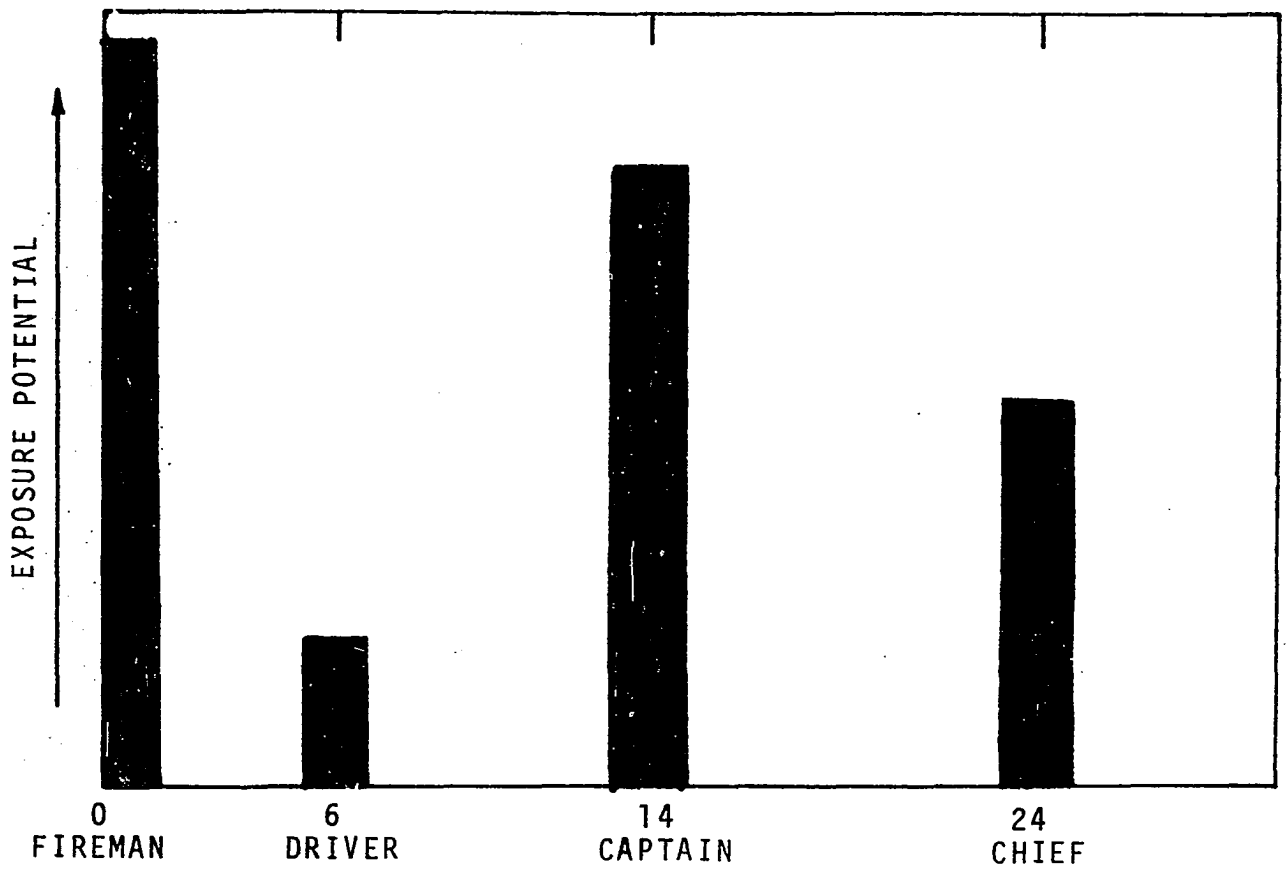

Figure 5. Years in fire service with approximate promotion flow points and exposure potential.

dietary habits, and physical exertion were considered but the paucity of data pertaining to these parameters and the fire service mitigated against using them.

All this notwithstanding, for this group of men there was a definite, measureable and highly significant difference between the test and control populations which can best be described as resulting from their occupational exposure on the firegrounds.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Thirty-six men were selected at random from the Oklahoma City Fire Department and interviewed extensively relative to their occupation and health status. These men were paired as closely as possible with members of local military reserve units.

Every 28 days blood was drawn from each test and control subject and analyzed for hemoglobin, carboxyhemoglobin, total lactic dehydrogenase, heat stable lactic dehydrogenase isoenzymes, heat labile isoenzymes, creatine phosphokinase and α-hydroxybutyric dehydrogenase.

At the end of the study period each group of individual values was tested for significance and definite significant trends appeared. The five month mean values taken as a group were tested for significance and demonstrated highly statistically significant differences with the exception of hemoglobin.

Regression analyses comparing the various determinations with parameters such as age, length of time in the fire service and smoking habits were generally inconclusive except

for COHb which predictably increased with increased smoking. Despite this there was a definite indication of differences between the populations which could best be attributed to the occupation of the test group.

It was concluded from this study that in the population studied:

1. The non-smoking fire fighter has already achieved the maximum allowable COHb saturation under NIOSH guidelines.
2. The test group, as a whole, exceeded the COHb content that would be achieved if they labored at heavy work for 1440 minutes in an atmosphere of 42 mg/m^3 CO.
3. As a group, the test population exhibited changes in enzymes that suggest myocardial damage resulting from repeated, chronic, sub-acute exposures to CO.
4. There was no demonstrable difference in the hemoglobin values of the test and control groups.
5. For this group of fire fighters and their controls, the observed differences could best be attributed to occupation.
6. The enzyme battery selected appeared to provide a sensitive physiological measure for minimal myocardial damage resulting from repeated, chronic, sub-acute exposures to CO.
7. The significance of the observed differences between the populations demands further studies to better understand and define the role of CO as it related to the health of the fire fighter.

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APPENDIX

TEST POPULATION

INTERVIEW AND PHYSICAL PROFILE DATA CARD

1. (SSAN) ___ ___ ___--___ ___--___ ___ ___ ___
2. Race Codes--(1) White, (2) Black, (3) Am Indian, (4) Other
3. Marital Status--(1) Single, (2) Married, (3) Sep, (4) Div, (5) Widowed
4. Fire Company Assigned
5. Occupation/Trade other than Fire Service, CO Significant, (1) Yes, (2) No
6. Hobby/Recreation other than Fire Service, CO Significant, (1) Yes, (2) No
7. Age to last birthday in years _____
8. Age on entry to Fire Service in years to last birthday _____
9. Length in Fire Service to nearest year _____
10. Length in Oklahoma City Fire Service in years _____
11. History of smoke inhalation:
    Have you ever been overcome by smoke? (1) Yes, (2) No
    How many times_____, Hospitalized, (1) Yes, (2) No
12. Headaches after fighting a fire
    (1) Yes, (2) No, (3) Frequently, (4) Seldom, (5) Occasionally

13. Height in centimeters _____ ( )

14. Weight in kilograms _____ ( )

15. Smoking habits: (0) Never Smoked, (1) Smoked but stopped, (2) Cigarettes only, (3) 1-9/day, (4) 10-20/day, (5) 21-39/day, (6) 40 plus/day, (7) cigars and pipe only, (8) cigars, pipe and cigarettes. Inhale: (9) Yes, (10) No

16. Age to nearest year when started smoking _____

CONTROL POPULATION

INTERVIEW AND PHYSICAL PROFILE DATA CARD

1. (SSAN) ___ ___ ___--___ ___--___ ___ ___ ___

2. Race Codes -- (1) White, (2) Black, (3) Am Indian,
   (4) Other

3. Marital Status -- (1) Single, (2) Married, (3) Sep.,
   (4) Div., (5) Widowed

4. Occupation/Trade other than USN/USMC_____

5. Hobby/Recreation _____

6. Age (to last birthday) in years _____

7. Height _____

8. Weight _____

9. Smoking habits:

   (0) Never smoked
   (1) Smoked but stopped
   (2) Cigarettes only

   _____Number per day of cigarettes smoked:
   (3) 1 to 9 per day
   (4) 10 to 20 per day
   (5) 21 to 39 per day
   (6) 40 plus per day

   (7) Cigars and pipe only
   (8) Cigars, pipe and cigarettes

   Inhale:
   (9) Yes
   (10) No

10. Age to nearest year when you started smoking _____

NAME: _____

ADDRESS: _____

_____

TELEPHONE: _____

HEALTH QUESTIONNAIRE

Social Security Account Number: __ __ __ - __ __ - __ __ __ __

This information will be held as confidential material until a control/test pair has been found for you. No copies of this will be made and this will be destroyed at the end of the test.

1.	Do you need glases to read?	Yes	No
2.	Do you need glases to see things at a distance?	Yes	No
3.	Has your eyesight often blacked out completely?	Yes	No
4.	Do your eyes continually blink or water?	Yes	No
5.	Do you often have bad pains in your eyes?	Yes	No
6.	Are your eyes often red or inflamed:	Yes	No
7.	Are you hard of hearing?	Yes	No
8.	Have you ever had a bad running ear?	Yes	No
9.	Do you have constant noises in your ears?	Yes	No
10.	Do you have to clear your throat frequently?	Yes	No
11.	Do you often feel a choking lump in your throat?	Yes	No
12.	Are you often troubled with bad spells of sneezing?	Yes	No
13.	Is your nose continually stuffed up?	Yes	No
14.	Do you suffer from a constantly running nose?	Yes	No
15.	Have you at times had bad nose bleeds?	Yes	No

16. Do you often catch severe colds? Yes No

17. Do you frequently suffer from heavy chest colds? Yes No

18. When you catch a cold, do you always have to go to bed? Yes No

19. Do frequent colds keep you miserable all winter? Yes No

20. Do you get hay fever? Yes No

21. Do you suffer from asthma? Yes No

22. Are you troubled by constant coughing? Yes No

23. Have you ever coughed up blood? Yes No

24. Do you sometimes have severe soaking sweats at night? Yes No

25. Have you ever had a chronic chest condition? Yes No

26. Have you ever had T.B. (Tuberculosis)? Yes No

27. Did you ever live with anyone who had T.B.? Yes No

28. Has a doctor ever said your blood pressure was too high? Yes No

29. Has a doctor ever said your blood pressure was too low? Yes No

30. Do you have pains in the heart or chest? Yes No

31. Are you often bothered by thumping of the heart? Yes No

32. Does your heart often race like mad? Yes No

33. Do you often have difficulty in breathing? Yes No

34. Do you get out of breath long before anyone else? Yes No

35. Do you sometimes get out of breath just sitting still? Yes No

36. Are your ankles often badly swollen? Yes No

37. Do cold hands or feet trouble you even in hot weather? Yes No

38. Do you suffer from frequent cramps in your legs? Yes No

39. Has a doctor ever said you had heart trouble? Yes No

40. Does heart trouble run in your family? Yes No

41. Have you lost more than half your teeth? Yes No

42. Are you troubled by bleeding gums? Yes No

43. Have you often had severe toothaches? Yes No

44. Is your tongue usually badly coated? Yes No

45. Is your appetite always poor? Yes No

46. Do you usually eat sweets or other food between meals? Yes No

47. Do you always gulp your food in a hurry? Yes No

48. Do you often suffer from an upset stomach? Yes No

49. Do you usually feel bloated after eating? Yes No

50. Do you usually belch a lot after eating? Yes No

51. Are you often sick to your stomach? Yes No

52. Do you suffer from indigestion? Yes No

53. Do severe pains in the stomach often double you up? Yes No

54. Do you suffer from constant stomach trouble? Yes No

55. Does stomach trouble run in your family? Yes No

56. Has a doctor ever said you had stomach ulcers? Yes No

57. Do you suffer from frequent loose bowel movements? Yes No

58. Have you ever had severe bloody diarrhea? Yes No

59. Were you ever troubled with intestinal worms? Yes No

60. Do you constantly suffer from bad constipation? Yes No

61. Have you ever had piles (rectal hemorrhoids)? Yes No

62. Have you ever had jaundice (yellow eyes and skin)? Yes No

63. Have you ever had serious liver or gall bladder trouble? Yes No

64. Are your joints often painfully swollen? Yes No

65. Do your muscles and joints constantly feel stiff? Yes No

66. Do you usually have severe pains in the arms or legs? Yes No

67. Are you crippled with severe rheumatism (arthritis)? Yes No

68. Does rheumatism (arthritis) run in your family? Yes No

69. Do weak or painful feet make your life miserable? Yes No

70. Do pains in the back make it hard for you to keep up with your work? Yes No

71. Are you troubled with a serious bodily disability or deformity? Yes No

72. Do you suffer badly from frequent severe headaches? Yes No

73. Does pressure or pain in the head often make life miserable? Yes No

74. Are headaches common in your family? Yes No

75. Do you have hot or cold spells? Yes No

76. Do you often have spells of severe dizziness? Yes No

77. Do you frequently feel faint? Yes No

78. Have you fainted more than twice in your life? Yes No

79. Do you have constant numbness or tingling in any part of your body? Yes No

80. Was any part of your body ever paralyzed? Yes No

81. Were you ever knocked unconscious? Yes No

82. Have you at times had a twitching of the face, head or shoulders? Yes No

83. Did you ever have a fit or convulsion (epilepsy)? Yes No

84. Has anyone in your family ever had fits or convulsions (epilepsy)? Yes No

85. Do you often get spells of complete exhaustion or fatigue? Yes No

86. Does working tire you out completely? Yes No

87. Do you usually get up tired and exhaused in the morning? Yes No

88. Does every little effort wear you out? Yes No

89. Are you constantly too tired and exhausted even to eat? Yes No

90. Do you suffer from severe nervous exhaustion? Yes No

91. Dees nervous exhaustion run in your family? Yes No

92. Are you frequently ill? Yes No

93. Are you frequently confined to bed by illness? Yes No

94. Are you always in poor health? Yes No

95. Are you considered a sickly person? Yes No

96. Do you come from a sickly family? Yes No

97. Do severe pains and aches make it impossible for you to do your work? Yes No

98. Do you wear yourself out worrying about your health? Yes No

99. Are you always ill and unhappy? Yes No

100. Are you constantly made miserable by poor health? Yes No

101. Did you ever have scarlet fever? Yes No

102.	As a child, did you have rheumatic fever, growing pains or twitching of the limbs?	Yes	No
103.	Did you ever have malaria?	Yes	No
104.	Were you ever treated for severe anemia (thin blood)?	Yes	No
105.	Were you ever treated for "bad blood" (venereal disease)?	Yes	No
106.	Do you have diabetes (sugar disease):	Yes	No
107.	Did a doctor every say you had a goiter (in your neck)?	Yes	No
108.	Did a doctor ever treat you for tumor or cancer?	Yes	No
109.	Do you suffer from any chronic disease?	Yes	No
110.	Are you definitely <u>under</u> weight?	Yes	No
111.	Are you definitely <u>over</u> weight?	Yes	No
112.	Did a doctor ever say you had varicose veins (swollen veins) in your legs?	Yes	No
113.	Did you ever have a serious operation?	Yes	No
114.	Did you ever have a serious injury?	Yes	No
115.	Do you often have small accidents or injuries?	Yes	No
116.	Do you usually have great difficulty in falling asleep or staying asleep?	Yes	No
117.	Do you find it impossible to take a regular rest period each day?	Yes	No
118.	Do you find it impossible to take regular daily exercise?	Yes	No
119.	Do you smoke more than 20 cigarettes a day?	Yes	No
120.	Do you drink more than six cups of coffee of tea a day?	Yes	No
121.	Do you usually take two or more alcoholic drinks a day?	Yes	No

DEFINITION OF ENZYME UNITS

Lactic Dehydrogenase (LDH): One unit will reduce 4.8×10^{-4} micromoles of pyruvate per minute at 25 degrees Centigrade.

Hydroxybutyric Dehydrogenase (HBD): One unit will reduce one millimicromole of α-ketobutyric acid per minute at 25 degrees Centigrade.

Creatine Phosphokinase (CPK): One unit will phosphorylate one milli cromole of creatine per minute at 25 degrees Centigrade.