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NOISE, GENERAL STRESS RESPONSES, AND CARDIOVASCULAR DISEASE PROCESSES: REVIEW AND REASSESSMENT OF HYPOTHESIZED RELATIONSHIPS

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This Report contains a limited survey on the existing literature indicating cardiovascular effects of high noise exposure and places that literature and places that literature in perspective based on the available knowledge of general cardiovascular effects of stressful stimuli. The authors also discuss conceptual abstacles to progress in cardiovascular disease research, key technical or measurement system obstacle, for research, and findings related to noise and suggestions for further research.

see p. 215

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

APR 20 1982

Dear Colleague:

Enclosed for your reference is a copy of EPA's Noise General Stress Responses, and Cardiovascular Disease Processes: Review and Reassessment of Hypothesized Relationships. This report contains a limited survey on the existing literature on cardiovascular effects of high noise exposure in perspective to the available knowledge of general cardiovascular effects of stressful stimuli.

Topics include the short term responses to stressful stimuli, the relationship between short term stress responses and chronic disease processes. The authors illustrate the clinical mechanisms of cardiovascular disease, postulate statistical models for disease analysis and cite other pertinent epidemiological observations.

We have been very limited in the number of copies we could print. Please share this report with your staff, and feel free to reproduce this document as needed. We hope that the information contained in the report will assist researchers who wish to pursue noise effects research following the phase-out of noise programs at EPA.

Sincerely yours,

John M. Ropes, Director
Office of Noise Abatement
and Control

Enclosure

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NOISE, GENERAL STRESS RESPONSES, AND CARDIOVASCULAR DISEASE PROCESSES: REVIEW AND REASSESSMENT OF HYPOTHESIZED RELATIONSHIPS

I. INTRODUCTION

In earlier work in the context of hearings on permissible occupational exposure limits for noise,[1] we reviewed the available data on possible cardiovascular effects of noise and integrated the material into a general framework. Considerable additional data has become available in the four years since then. In this report, we shall reappraise the earlier framework in the light of the new data and attempt to expand it in the light of contemporary concepts of stress responses and cardiovascular disease processes. By placing the noise work in the more general context of stressor/cardiovascular disease relationships, we hope to identify:
to identify:

(1) avenues of research for noise workers which are likely to clarify hypothesized relationships between noise stress and cardiovascular disease, and

(2) any special advantages and disadvantages there may be for workers concerned with general stress/cardiovascular disease relationships to ask scientifically interesting questions using noise as a model stressor.

1.1 Scientific Interest and Potential Social Importance of the Problem

For many years, it has been suspected that physiological responses to a wide variety of psychosocial "stressors" may contribute to cardiovascular disease processes. Beginning with the pioneering work of Cannon[2] and Selye,[3] researchers have found that both physical and psychological stimuli, acting through central neural mechanisms, can evoke numerous short-term changes in hormone levels,[3-8] serum lipid levels,[10-14] platelet functions,[15-19] blood pressure,[19-22] and other parameters.[23-24] Such responses present the analyst with a large array of possible mechanisms whereby an irritating stimulus might influence either:

- the chronic, cumulative disease processes of atherosclerosis and long-term increases in blood pressure, or

- the sequence of short-term events which precipitate the clinical manifestations of disease such as myocardial infarction and stroke.

Epidemiological studies conducted in recent years,[25-32] though by no means presenting a clear and uniform picture of causation,[33-34] generally reinforce the suspicion that neurogenic factors may make important contributions to cardiovascular pathology.[34-36]

A number of considerations make noise an interesting and potentially socially important agent for study as a candidate stressor:

(1) *Large numbers of people are exposed to high levels of noise on their jobs and in selected community situations.*

Estimates made in 1976 indicate that of approximately 13 million workers in major manufacturing industries and electric utilities (Standard Industrial Classification codes 20-37 and 49), about 4 million were routinely exposed to noise levels in excess of 90dBA (eight-hour Leq basis), and an additional two million were exposed at levels between 85 and 90 dBA.*[37]

A recent attitudinal survey of a representative sample of U.S. workers provides evidence that the noise exposures encountered by many people on the job have subjective importance to them.[38] When asked, "Does your job ever expose you to too much noise?" nearly thirty percent of all workers gave a positive response. When the positive respondents were asked to rate how much of a problem the noise was for them on the following four-point scale:

(1) No problem at all
(2) Slight problem

*These levels are sufficient to cause appreciable permanent hearing damage if exposure is continued for several years.

(3) Sizeable problem
(4) Great problem,

17.4% of all those interviewed reported a "sizeable" or "great" problem from workplace noise, and an additional 6.5% reported a "slight" problem. As might be expected, the frequency of reported noise problems was higher in blue-collar occupations.* Other attitudinal surveys have indicated that large numbers of people consider noise in their community to be a significant problem.[39] Such data cannot, of course, be used to derive any absolute measure of either noise exposure or noise stress. They do, however, suggest that daily noise exposures are significant irritants for an appreciable number of people.

(2) *Noise levels are easily and objectively measurable (relative to other physical and psychosocial stressors), and are often amenable to direct control by societal action.*

Reduction of traditional cardiovascular risk factors and many other psychosocial stressors depends primarily upon bringing about changes in individual lifestyles. Benefits achieved by reducing stressors through collective action would supplement whatever benefits are achievable by educational efforts to bring about individual lifestyle changes.

Additionally, the fact that noise is a physical agent subject to external control means that it may present opportunities for epidemiological research into mechanisms of stress response which would be more difficult with other stressors. Noise exposures can be reliably manipulated either by engineering controls on noise sources or by ear protectors. Existing social efforts to reduce noise exposures which are considered particularly serious threats to hearing or community peace represent opportunities to conduct controlled intervention trials. In 1976, over 1500 citations were issued by the Occupational Safety and Health Administration to require firms to reduce worker exposure to below the current

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*For all "craftsmen," "operatives," and "laborers" combined, 46.3% reported that they were sometimes exposed to too much noise and 24.5% reported that noise was a sizeable or great problem.[38]

occupational standard of 90 dBA for eight hours.*[40] Ongoing efforts to reduce community noise exposures from aircraft and other sources present additional "experiments of nature" which could be observed.

(3) *Although past work on noise suggests that it is generally plausible that, under some circumstances, noise may contribute to some cardiovascular disease processes, great uncertainties remain about the nature and magnitude of such effects.*

Many of the same short-term changes induced by other stressors have been reported to occur in response to noise at least under several experimental conditions.** A few studies report long-term increases in blood pressure in chronically noise-exposed animals. Additionally, a number of cross-sectional epidemiological studies recently reviewed by Welch[64] have reported an increased prevalence of hypertension among workers exposed to relatively high noise levels.

The present picture is very far from complete, however. The available experimental findings in the areas cited above contain many examples of experiments which have failed to demonstrate appreciable effects attributable to noise.*** It is very possible that the nature and magnitude of stress responses induced by noise can be greatly influenced by a host of situational,[47, 48, 59] personality,[47] and individual physiological factors[43] which at present are incompletely delineated.

Second, and probably more important, there is currently little information on the quantitative relationships between the magnitude of short-term physiological variations induced by stressors and the magnitudes of

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*It should be noted that these noise citations represented a significant part of the overall OSHA enforcement effort for health hazards. There were over twice as many citations for noise exposure as for all chemical and dust air contaminants combined.

**Positive findings have been reported for selected hormones,[41-48,386] blood pressure,[41,49,50,386] platelet aggregation,[51-52] and serum cholesterol.[43,54-56]

***For example, findings have often been negative for hormone levels,[57-59] and short-term blood pressure effects.[60-62]

(1) any increased rate of progress in atherosclerosis or blood pressure elevation, and (2) any increased short-term risk of myocardial infarction or stroke. It will be a major theme of this work that research into the quantification of such relationships is of prime importance to the design and assessment of the benefits of intervention efforts to reduce cardiovascular damage both from physical stressors such as noise, and also from other types of psychosocial stressors which act on groups of people. For example, if it were known that specific types of variations in parameters measurable in the short-term were good indicators of long-term stress effects on cardiovascular pathology, corporate medical departments or HMO's serving defined industrial and community groups could monitor those short-term parameters to detect groups at high risk or potentially dangerous trends over time. Follow-up efforts could then attempt to discover and reduce the sources of increased stress in the group, using the short-term parameters to assess the success of various attempted interventions.

1.2 Difficulties in Present Research Approaches on Cardiovascular Disease

If, as claimed above, there is relatively little useful information quantifying relationships between short-term variations in physiological parameters which are responsive to stimuli and chronic disease processes, one may well ask why this is so. After all, there have been major long-term research programs designed to discover the antecedents of cardiovascular diseases precisely for the purpose of designing appropriate interventions to reduce factors associated with disease risk. If past efforts have not yielded data of the types considered desirable, is it because such information is intrinsically very difficult to obtain, or did the conceptual framework of the research simply not call for measurements and analyses of the kinds which would have yielded the desired information?

Our tentative impression is that research in this area may well be able to benefit from novel approaches for defining its problems. Most current epidemiological studies or heart disease risk use multiple regression

analysis based on a single postulated mathematical model* to relate the levels of various risk factors measured at a single time point to observed heart disease morbidity and mortality in subsequent years. Although the model generally used is convenient for statistical analysis, there was little discussion in the paper which first developed the model[63] (or, as far as we can determine, subsequently) of an underlying biological rationale. The model does not incorporate specific hypotheses about the underlying pathological processes involved in various cardiovascular diseases or the specific ways in which particular risk factors contribute to those processes. Implicitly, all risk factors are treated as if they operated in the same way (or analogous ways) to increase a single underlying disease-producing mechanism.

Existing knowledge may already be sufficient to begin to posit mathematical descriptions of the risk of clinical cardiovascular disease manifestations which are likely to be more realistic reflections of actual pathological processes. At the minimum, risk functions for disease manifestations such as myocardial infarction and stroke should be separated into components which represent (1) the accumulated stock of atherosclerotic lesions, estimated by some weighted function of the levels and variability of various risk factors which have prevailed over the individual's past lifetime, and (2) the probability of the appropriate precipitating events, estimated by a different weighted function of <u>current</u> levels and variability of various risk factors. Data for deriving the first component may come from a variety of sources, including the apparent contributions of risk factors to disease manifestations such as angina (which do not depend on the dramatic precipitating events of heart attacks and strokes), angiographic findings, human autopsy studies, and animal studies. Data for deriving the second component may come from studies of heart attack and stroke risk among patients whose atherosclerotic disease has

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*The logistic model which is generally used has the form:

$$R = \frac{1}{1 + e^{-(B_0 + B_1X_1 + \ldots + B_kX_k)}},$$

where R is the risk (probability) of developing one or any clinical manifestation of cardiovascular disease, the "X's" are measured levels of particular risk factors, and the "B's" are constants.

been assessed by angiography, and possibly from comparisons of the degree to which specific risk factors influence event-requiring and non-event-requiring disease manifestations.*

The cardiovascular system and its neuroendocrine controls represent one of the most outstanding examples of a complex, interacting dynamic system. It seems likely that the best ultimate hope for understanding the chronic processes by which the system goes awry must lie in the development of sophisticated system-dynamic models incorporating the large amount of information obtainable about relationships among the system's many components. In this project, we cannot even begin the process of constructing such a quantitative model. As we review the system in subsequent sections, however, we can note some information relevant for model building and some opportunities for research to produce additional relevant information.

1.3 Organization of the Report

Section 2 immediately below gives an overview of possible relationships to be described in the remainder of the report. Section 3 then discusses relationships between various stimuli and short-term variations in physiological parameters which are potentially relevant to cardiovascular disease processes. Then Section 4 examines available data relating stimuli and short-term variations in physiological parameters to the chronic processes of atherosclerosis and hypertension. Data relating stimuli and short-term physiological variations to actual manifestations of disease (e.g., myocardial infarction) are explored in Section 5. Finally, Section 6 brings together the various research opportunities noted in earlier sections into a series of suggestions for researchers and funding agencies.

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*For example, it has already been noted that while cigarette smoking clearly increases the risk of myocardial infarction, cigarettes appear to have relatively little effect on the risk of angina. This has been interpreted to mean that cigarettes are relatively unimportant in atherogenesis, and make their primary contributions to cardiovascular disease risk by increasing the probability of precipitating events.[150] The relatively weak contribution of cigarettes to atherogenesis is supported by a recently published multination autopsy study.[151]

2. AN OVERVIEW OF HYPOTHESIZED RELATIONSHIPS BETWEEN STIMULI, GENERAL STRESS RESPONSES, AND CARDIOVASCULAR DISEASE PROCESSES

In this section we shall sketch the broad outlines of a system of hypothesized relationships between environmental stimuli and cardiovascular disease manifestations. We should emphasize at the outset that there is nothing particularly novel about the schema presented here and in the subsequent chapters. Different parts of the picture have been assembled from seminal papers, literature reviews and textbooks in various disciplines.

Figure 2.1 shows the relationships between our major categories of variables. More detailed articulation of relationships between individual parameters is presented in Chapters 3-5. Category I, "Determinants of Stress Responses," basically includes all relevant environmental factors and their processing by the brain above the level of the hypothalamus. Major components of Category I are environmental stimuli (e.g., noise), situational factors which modify the effects of the stimuli on the organism (e.g., task demands which are interfered with by noise), and constitutional or personality factors (e.g., "Behavior Pattern A") which represent different styles of response, or habits of coping with stimuli.

The next row down in Figure 2.1, labelled "Stress Responses," is divided into short-term hormonal (Category II) and non-hormonal (Category III) physiological changes which occur in response to stimuli.* Labelling these short-term changes "stress responses" may be troublesome to some observers, because to do so attaches a negative connotation to them which, at least at this stage of analysis, is not entirely justified. These responses are not, on their face, pathological. They undoubtedly represent

*Major "hormonal" responses include changes in the secretion and/or metabolic handling or norepinephrine, epinephrine, ACTH, aldosterone and other mineralocorticoids, cortisol and other glucocorticoids, antidiuretic hormone, growth hormone, thyroid stimulating hormone and thyroid hormone, and renin. Other major physiological responses (mediated in part by direct sympathetic stimulation and in part by the hormonal changes) include increases in platelet adhesiveness, circulating platelet aggregates, serum free fatty acids, plasma glucose, serum cholesterol, triglycerides, cardiac oxygen demand, and blood pressures. These effects will be discussed in Section 3 below.

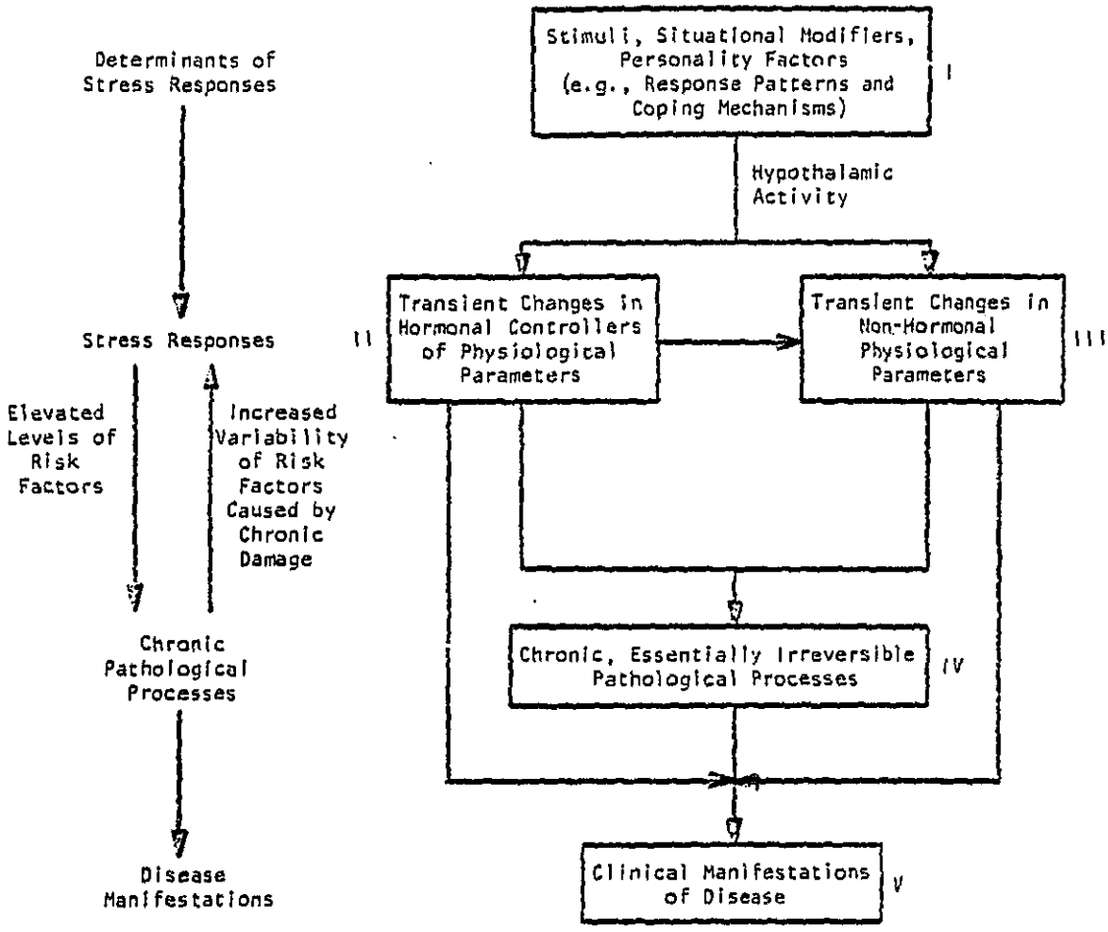

FIGURE 2.1 Overview of General Relationships

age-old patterns of biological adaptation, evolved to enable mammals to cope with threats or other kinds of increased short-term demands for the environment. The fact that these response patterns are the products of evolution does not mean, however, that they are without cost to the organism. It merely implies that under the conditions where the responses generally occurred in nature, the short-term benefits outweighed the short- and long-term costs, if any. Indeed the very fact that these changes are transient, returning to basal levels at various times after the inducing stimuli are removed, implies that it would in some way be disadvantageous for the organism to maintain them indefinitely.*

Possible long-term costs in the form of chronic, essentially irreversible pathological processes, atherosclerosis and long-term increase in blood pressure are represented in Figure 2.1 as Category IV. The rate at which these processes occur depends in some way on the amount of time which the organism spends with various elevated levels of particular relevant variables ("risk factors") in Category III. As the cumulative pathological processes progress, there may be a vicious circle (positive feedback) effect if some control mechanism which restrains the variability of short-term parameters is impaired or if the system is made more responsive to perturbations in some other way. For example, the Folkow model of hypertension[108] postulates a vicious circle in which short-term rises in blood pressure first give rise to hypertrophy of the media of small arteries. The hypertrophic arterioles, with thicker walls and narrower lumens, then prove to be more reactive--giving rise to a greater increase in blood pressure per unit of sympathetic stimulation and smooth muscle shortening than before the initial damage. Thus, initial blood pressure variability gives rise to greater blood pressure variability and eventually becomes

*For example, one of the short-term responses is an increase in the adhesiveness of platelets (mediated by increased circulating norepinephrine levels). It is likely to be very beneficial to the organism to have stickier platelets at times when it is threatened because in case of injury there would be faster clotting and less loss of blood. On the other hand, if there were not some disadvantage to higher levels of platelet adhesiveness, then natural selective pressures would have favored organisms with a higher basal level of platelet adhesiveness who were prepared for a wound at all times, whether or not a specific threat had been detected.

independent of further outside stimulation.

Finally, the accumulated changes from the chronic pathological processes (Category IV) combine with some extreme fluctuation of short-term parameters (Categories II and III) to produce clinical manifestations of disease (Category V).

Figures 2.2 and 2.3 show these hypothesized relationships in greater detail. Figure 2.2 illustrates the interplay of some short-term responses with chronic pathologies (Categories II through IV) and Figure 2.3 shows some known or likely pathways to clinical disease manifestations (Categories II through V). Details of these figures will be discussed in various parts of Sections 3, 4 and 5 below.

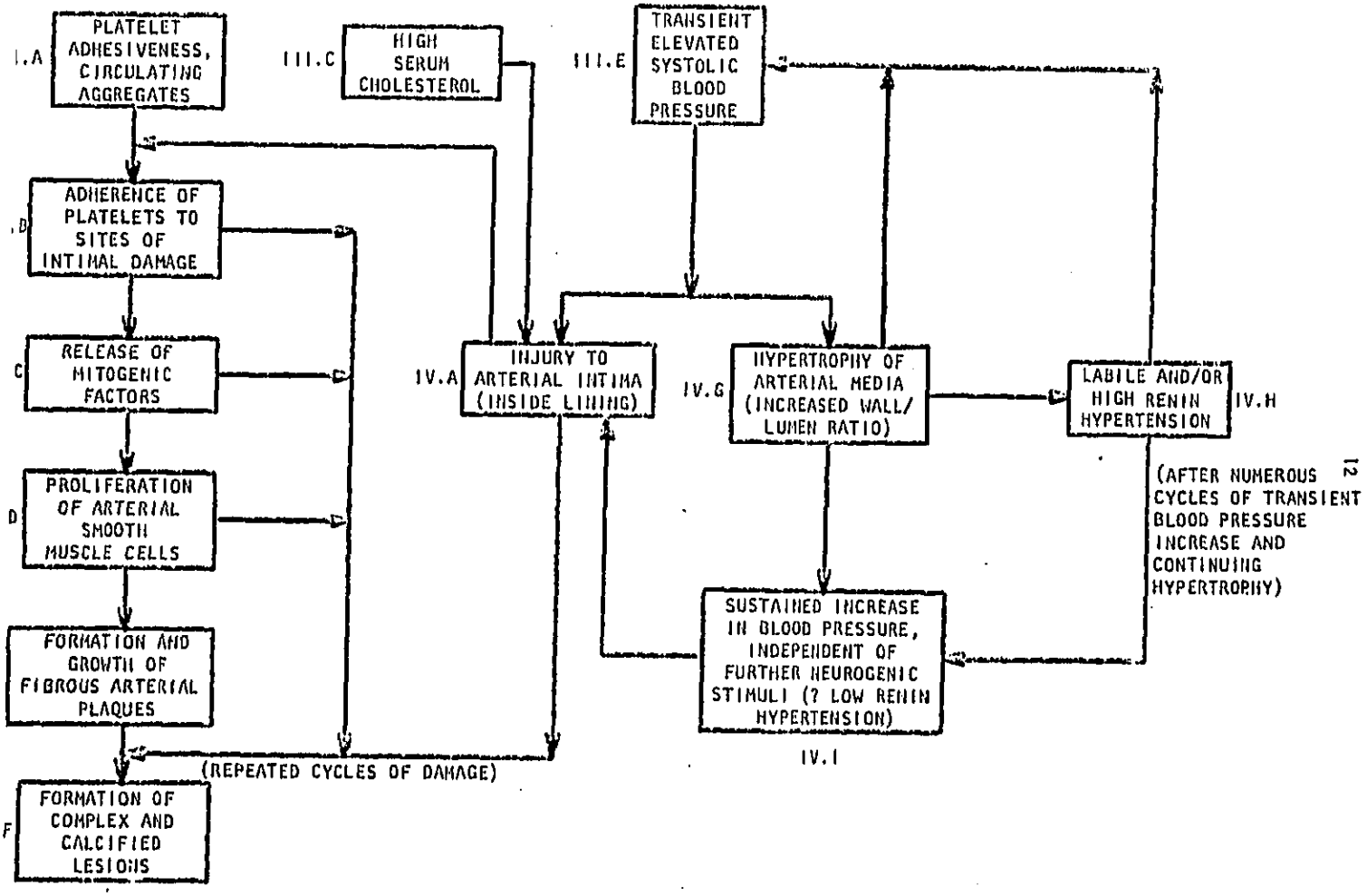

FIGURE 2.2 Mechanisms of Chronic Atherosclerosis and Blood Pressure Increase

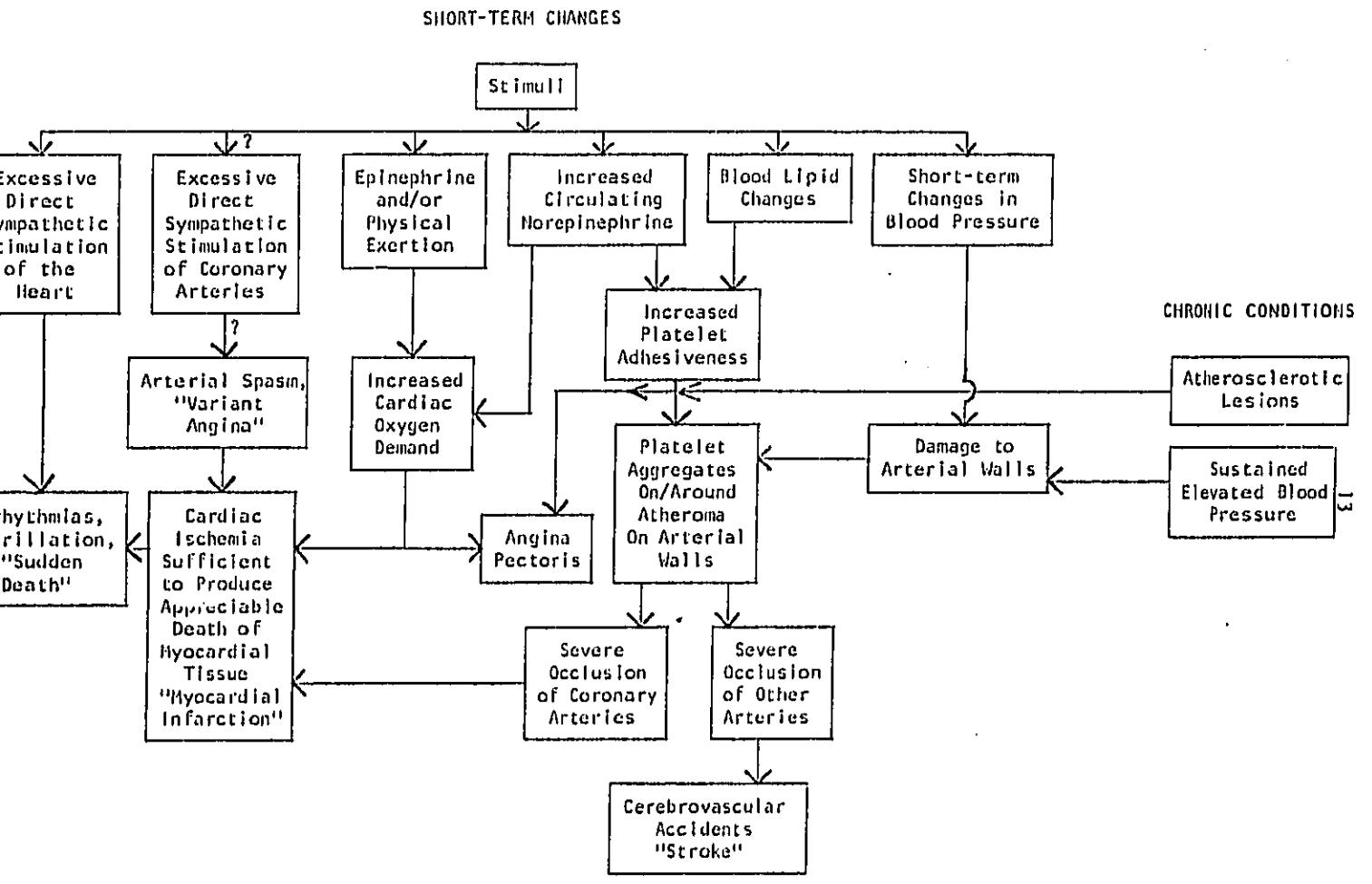

FIGURE 2.3 Possible Contributions of Transient and Chronic Factors to Clinical Manifestations of Cardiovascular Disease

3. SHORT-TERM RESPONSES TO STIMULI

This section is divided into three parts. First, 3.1 surveys the major features of the physiological systems which respond in the short term to environmental stimuli. Section 3.2 then uses this background to discuss observations of short term responses to noise in the context of some observations of responses to a variety of other stimuli. Finally, Section 3.3 sets forth some suggestions for avenues of research to improve understanding of these dynamic systems.

3.1 Discussion of Basic Mechanisms

The short term changes which occur in response to different kinds of physical and psychosocial stimuli are complex and diverse. The discussion here will omit much even of that portion of the complexity which is known. (In particular, many feedback processes which damp and compensate for short term responses of other kinds will often be alluded to only briefly.) Our emphasis reflects some initial judgements about the specific types of responses which we think may be most directly involved in cardiovascular disease processes.

In viewing the complex interacting system of short term responses, it is helpful to have in mind an overall unifying theme which integrates the separate responses into a coherent, understandable pattern. Mason[69] in 1968 synthesized the previous literature and his own extensive experiments with monkeys exposed to a 72-hour avoidance ordeal by dividing hormone responses into two general subgroups:

- a "catabolic"[2] subgroup, including epinephrine, norepinephrine, corticosteroids, growth hormone, and thyroxine prepares the organism for possible exertion by mobilizing available energy resources:

  > "In addition to the hyperglycemia known to Cannon, epinephrine promotes the release of short chain free fatty acids, which are now believed to have primary importance as fuel for increased energy metabolism.[70-71] Although norepinephrine has little hyperglycemic effect, it has a strong free fatty acid releasing effect, perhaps even greater than that of epinephrine.[72]

The 17-hydroxycorticosteroids, and particularly cortisol, promote hyperglycemia, probably because of increased gluconeogenesis in the liver.[73] Cortisol also increases free fatty acid release, apparently having both permissive and potentiating effects upon the free fatty acid release induced by epinephrine.[74] The importance of cortisol in supporting muscular work capacity has been well documented by Ingle.[75] Some interesting recent evidence has also been presented by Grossfield to indicate that high concentrations of cortisol increase the capacity of cells to produce energy anaerobically. The capacity for anaerobic energy metabolism is believed to be a critical factor in unusually strenuous muscular work.[76]

Growth hormone accelerates triglyceride breakdown and induces fatty acid release.[77-79] It appears, in fact, that there is a synergism between growth hormone and corticosteroids in fatty acid release.[79]

Thyroxine also has some prominent effects which should be useful in providing increased amounts of utilizable energy, such as the increase of rates of oxidation and the potentiation of some of the major catabolic effects of epinephrine, including the release of free fatty acids.[80-81]*

- an "anabolic" subgroup, including insulin, estrogens, testosterone, and androgens, which facilitate the rebuilding of energy stores and protein synthesis in muscle and other tissues.

Given this division, Mason found that there was an understandable dynamic pattern in the hormone responses of monkeys to his 72-hour avoidance stress period.** (Figure 3.1) Levels of the catabolic hormone subgroup generally rose during the period of avoidance stimulation and then returned to basal levels at varying rates after the stimulus. On the other hand, the levels of hormones within the anabolic subgroup generally were depressed during the avoidance period, but rebounded to levels over their baselines for a brief period after the avoidance period was over.

There was one significant departure from this easily interpretable pattern. Urinary norepinephrine excretion, while being modestly elevated

*Quote from Mason.[69]

**During these experiments, monkeys were required to press a hand lever every twenty seconds to avoid mild shocks to the feet.

during the avoidance period, rose to peak levels only during the recovery period. It is possible to develop ad hoc rationalizations for this,* but for our purposes it is primarily important to note this pattern because of possible implications for the design and interpretation of experiments using brief (several hours or less) periods of stimulation and measurement.

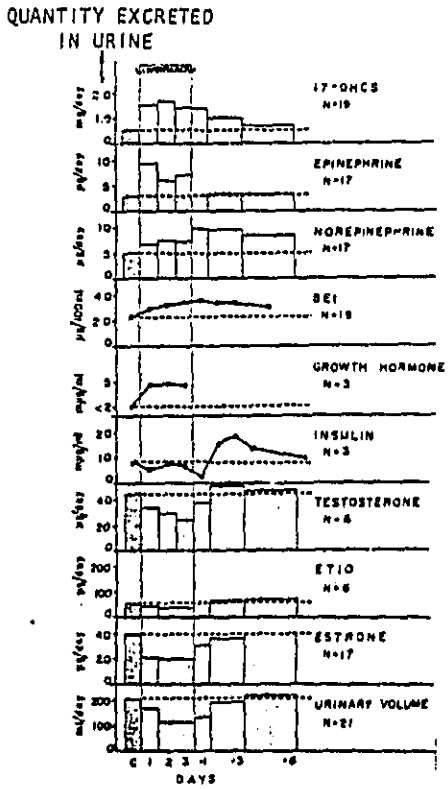

FIGURE 3.1 Pattern of multiple hormonal responses to 72-hour avoidance sessions in the monkey.[69]**

*For example, norepinephrine's effect increasing the adhesiveness of platelets might be needed for a few days after a hypothetical injury to reduce bleeding in case a wound were to be reopened.

**17-OHCS = 17-hydroxycorticosteroids
BEI = thyroid (plasma butanol-extractable iodine)
ETIO = etiocholanone fetosteroid (an androgen metabolite)

In our subsequent discussion, we will focus primarily on changes in the catabolic subgroup of hormones and their physiological sequellae (in addition to non-hormonal changes induced by direct sympathetic nervous stimulation). In general we have far less information about the effects of environment stimuli by way of the anabolic group of hormones, and little indication that changes in the anabolic group may have long term consequences for cardiovascular disease.* Given this caveat, we will now briefly review the responses of various organs to sympathetic nervous stimulation and the "catabolic" hormone subgroup.

3.1.1 Hypothalamic and Other Sympathetic Nervous Control of Endocrine Responses

Many of the hormonal responses discussed above are controlled directly or indirectly by the hypothalamus. There are several other sites in the brain and spinal cord which are also likely to be important in sympathetic nervous system activation. The hypothalamus, however, has been called the preeminent neuro-endocrine transducer of the body, converting neural impulses into endocrine stimulation. The afferent fiber bundles projecting to the hypothalamus come from the pre-frontal cerebral cortex, from limbic structure, and from the diffuse thalamic system. Its major projections are to be the brainstem, spinal cord, thalamus, and pituitary gland. The hypothalamus is a major correlational area which Thompson[82] characterizes as "one of the few places inside the CNS in which electrical stimulation will yield an integrated pattern of emotional behavior." Various nuclei in the hypothalamus, when stimulated, can produce such behaviors as eating, drinking, attack, flight, and alert posture.[83]

More subtle, but at least as important, is the physiological control exerted by the release of various hormones either directly by the hypothalamus or indirectly by control of other glands or organs. The hypothalamus directly releases growth hormone releasing factor, thyroid stimulating hormone releasing factor, and adrenocorticotropin releasing factor. The

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*Shreds of evidence which do come to mind, however, are changes in cardiovascular risk which appear to occur in women about the time of menopause, and possible increases in cardiovascular risk among women taking birth control pills.

latter "releasing factors" in turn stimulate the anterior pituitary gland to release the corresponding hormones. The posterior pituitary is actually neural tissue and is an outgrowth of the hypothalamus. The important hormone released from this structure, antidiuretic hormone, is synthesized in hypothalamic cells and travels down nerve fibers in the connecting stalk, and is released into nearby capillaries when the appropriate hypothalamic nerve centers are stimulated.

Finally, it should be emphasized that nearly all of the controls on physiological responses which the hypothalamus and other sympathetic nervous system centers exert through humoral mechanisms (e.g., circulating hormones) are supplemented with controls through direct sympathetic nervous innervation of important target tissues. Kidney responses, blood vessel responses, and lipid mobilization responses may all be more powerfully influenced by catecholamines released locally from sympathetic neural synapses than from catecholamines circulating in the blood.

The adrenal gland is also divided into two separate entities, the cortex and the medulla. In response to ACTH secretion from the pituitary, the cortex secretes mineralocorticoids and glucorticoids, the most important of which are, respectively, aldosterone and cortisol. Aldosterone stimulates sodium reabsorption by the distal tubules of the kidney, and cortosol affects metabolism and enhances vascular reactivity.

The adrenal medulla secretes epinephrine and norepinephrine in response to direct neural signals from the hypothalamus.[86] Norepinephrine has a unique place in this schema. It is both the neurotransmitter* of the sympathetic nervous system and a major hormone carried to target organs by the circulatory system.

The thyroid gland also has direct sympathetic innervation.[91] Additionally, circulating NE can cause secretion of thyroid hormones, thyroxine and triiodothyronine. The result of thyroid stimulation is a general bodily increase in metabolic activity manifested by increases in oxygen

*A neurotransmitter is a chemical which passes from one neuron to another, communicating the signal to fire.

consumption and heat production.[87] (There are some organs which are not responsive to this manner to thyroid hormones; among them are the brain and anterior pituitary.)

3.1.2 Kidney Responses

Stimulation of the kidneys by the sympathetic nervous system increases constriction of the renal arterioles, which decreases blood flow and, therefore, pressure in the glomerular capillaries.[88] This in turn reduces sodium loss by lowering the total amount of protein-free plasma filtered. Increased retention of sodium automatically means fluid retention since water is passively reabsorbed and follows sodium reabsorption. Sympathetic stimulation also increases renin release by the kidney.[86] Renin, in turn, catalyzes the production of angiotensin from the liver protein angiotensinogen, and is the rate limiting step in this reaction. Angiotensin, then, strongly stimulates the adrenal cortex to produce aldosterone, which feeds back to the kidneys and stimulates sodium reabsorption further, increasing fluid retention and, therefore, blood pressure.

3.1.3 Blood Vessel Responses

The overall response of the vascular system to stressful stimuli is to reroute the major portion of the blood supply to skeletal muscles and heart and cause vasoconstriction to digestive organs, kidneys, and peripheral vascular beds such as the finger tips.[89] This may take place in part because of an immediate increase in circulating levels of norepinephrine and epinephrine, and the interaction of norepinephrine and cortisol, a hormone which enhances vascular reactivity to the catecholamines. However, vasoconstriction, while it insures adequate blood supply to heart and muscles needed in a "flight or fight" situation, raises blood pressure by increasing peripheral resistance. Both increased blood pressure and vascular resistance subjects the vessels involved to risk of damage from increased sheer forces.[90]

3.1.4 Blood Lipid and Platelet Responses

As has already been mentioned, growth hormone,[77-79] catecholamines[70-72] and cortisol[74] all participate in the mobilization of free fatty acids from adipose tissue into the blood stream. Data cited by Taggart and Carruthers[92] is said to indicate that norepinephrine is a more potent inducer of FFA release then epinephrine, and that the elevated free fatty acid levels induced by norepinephrine last longer than those induced by epinephrine.[93] The obese and the less physically fit are also said to exhibit more sustained serum FFA elevations in response to norepinephrine.[94-95] The data in Figure 3.2 indicate that peak levels of free fatty acids appear to coincide with the peak levels of catecholamines induced by an acute stimulus, whereas peak levels of triglyceride occur somewhat later.

Serum cholesterol did not appear to respond within the period of observation in this experiment. Serum cholesterol does appear to be elevated in response to stimuli lasting days or weeks. Cholesterol increases were found in the now classic 1958 study by Friedman, et al.[96] of tax accountants in heavy work periods around April 15 and January, as compared to periods of lighter pressure, and also in studies in medical students during final examinations, as compared to other times of more normal pressures.[97-98] The mechanism by which cholesterol levels are raised in such situations is unclear. Glass[35] cites evidence[99] that cortisol is involved, but Rahe, et al.[100-101] report relatively small and inconsistent correlations between cortisol and cholesterol levels in their extensive observations.

The adhesiveness of platelets is increased by catecholamines, as measured by both in vitro and in vivo experiments.[102-104] Free fatty acids also appear to have the potential to cause similar effects.[105-106] However, findings by Gordon[107] suggest that free fatty acids are not the primary determinants of platelet aggregating properties in the course of at least some stress responses in vivo. In this experiment, blood was drawn from patients who were to undergo cardiac catheterization at various times before, during and after the procedure. As can be seen from the results

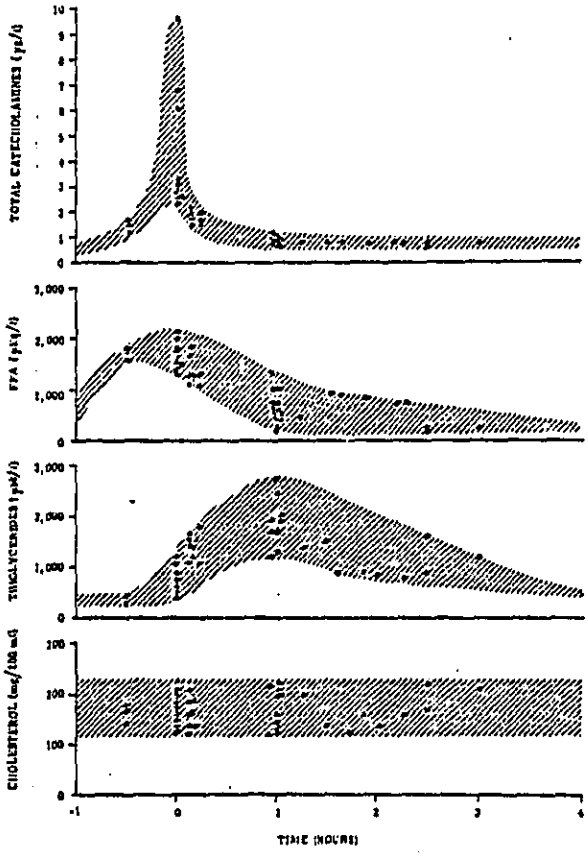

FIG. 3-2. Plasma catecholamine, free fatty acid, triglyceride, and cholesterol concentrations in racing car drivers. Time 0 indicates the end of their event.

From Taggart and Carruthers, Ref. 9.

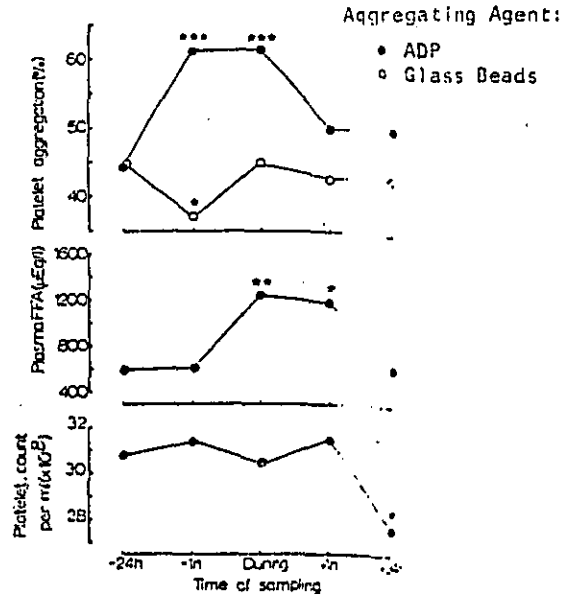

FIGURE 3.3 Platelet aggregation responses, plasma FFA levels, and platelet counts in patients undergoing diagnostic procedures. Each point represents the group mean value. The -24 hr values have been compared with all subsequent values in turn, and levels of significance are shown. *$p<0.05$; **$p<0.01$; ***$p<0.001$ From Gordon, Ref. 107.

(Figure 3.3) the platelet aggregating activity in response to adenosine diphosphate first rose in anticipation of the catheterization procedure, before the rise in free fatty acid levels, and then fell substantially, by the first hour after the procedure at a time when the plasma free fatty acids were still elevated.

3.2 Observations of Short-Term Responses to Noise and Other Stimuli

In this section, we will assemble available evidence on the short-term responses to noise exposure, and attempt to place it in the perspective of increases in the same variables observed in response to other psychosocial stimuli. The purpose here is not to present an exhaustive compilation of the literature on all short-term responses to noise and other stimuli as modified by all of the situational and personality/constitutional factors which might modify the responses. Rather, we shall review here some of the findings with noise that we judge to be relatively noteworthy in the context of the portion of the general stress research literature which we have reviewed.

3.2.1 Adrenal Medulla Responses, Elevation of Serum Lipids, and Platelet Aggregation

Catecholamine Responses

The catecholamines, and in particular norepinephrine, appear to have a very prominent place in current theories of psychosocial stress and disease processes. For example, Glass,[35] after citing the platelet aggregating properties of catecholamines and possible direct contributions by this route to myocardial infarction, goes on to say:

> Since the catecholamines elevate blood pressure, they can potentiate bleeding in arterial atheromata induced by enhanced mechanical strain in the vessel wall. Moreover, epinephrine and norepinephrine may lead to a narrowing of the capillaries nourishing the blood vessels and associated coronary plaques. Such narrowing eventually interferes with nourishment of the plaques which leads to further arterial damage, and even an infarction.

> It would thus appear that the catecholamines may have a special significance in the development of coronary disease. It follows that any psychological agent which increases circulating catecholamines may be potential pathogen for cardiovascular function. Several studies document the relationship between psychological stressors and catecholamines.[109] Consider, for example, a study by Nestel, Verghese, and Lovell[110] which shows that subjects with angina pectoris responded to a test of intellectual ability with a greater average increase in secretion of vanilmandelic acid (VMA), a metabolite of norepinephrine, compared to patients with CHD but no anginal pain. The authors suggest that the effect may have been due to the way in which their subjects responded to the test rather than to the disease.
>
> Friedman, Byers, Diamant, and Rosenman[111] report that under competitive conditions the plasma norepinephrine concentration of coronary-prone subjects rose an average of 30%, while that of noncoronary-prone subjects remained unchanged. There were no differences between the two groups under resting conditions, and epinephrine concentrations were virtually the same in both groups under resting as well as competitive conditions. This result suggests that norepinephrine, in particular, may be influenced by efforts to cope with psychological stressors.
>
> Earlier research[112, 113] indicates that active coping with a stressor leads to the increased specific discharge of norepinephrine, and we have already cited studies showing a linkage between norepinephrine and aggressiveness (.e.g, Funkenstein et al.[114]). More recent work suggests that norepinephrine levels in blood and urine remain elevated in subjects engaged in active efforts to escape or avoid stressors[115-117], whereas substantial depletions in brain norepinephrine occur when subjects react to uncontrollable stressors with helplessness or giving-up responses.[118] It is not surprising that concomitant increases in epinephrine levels have also been observed following a reduction in coping activity.[119]

Plasma catecholamine levels can fluctuate very dramatically within a short time in response to changes in sympathetic nervous system activity. Plasma norepinephrine has a half-life of less than two minutes, and has been reported to double within five minutes of a change from reclining to sitting posture.[120] Basal plasma catecholamine excretion appears to be fairly reproducible on separate measurements of the same individual, but different individuals vary widely in this parameter, and there is an appreciable increase with advancing age.[124] (See Figure 3.4.)

As a more stable and accessible measure of sympathetic nervous system

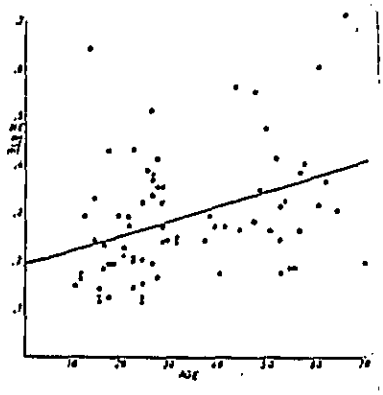

FIGURE 3.4 Relation of Basal Plasma NE levels and Age. The basal plasma NE levels are significantly related (L.R. = 0.33, $p < 0.01$) to age 74 in normal controls. Mean age is 32.7 ± 1.9 (SEM) years and mean NE level is 0.292 ± 0.016 (SEM) ng/ml.

FROM: Reference 124.

activity, most stress researchers have followed catecholamine excretion in the urine. Although 98% of plasma catecholamines are eventually excreted in the form of metabolites,[121] it has been the hope that urinary concentrations of unmetabolized norepinephrine and epinephrine represent a time-weighted index of plasma concentrations. Plasma and urinary epinephrine levels, but not norepinephrine levels, appear to undergo pronounced diurnal changes.[122, 123]

Table 3.1 presents in primarily qualitative form the findings of various investigators who have measured catecholamine responses to stressful stimuli and situations including noise. Table 3.2A presents a more quantitative view of the results of experiments involving relatively high noise exposures (over 85 dB) for which it has been possible to compute observed changes in urinary norepinephrine output in terms of nanograms/minute. For comparison, Table 3.2B lists some observations of alterations in norepinephrine (or in one case, total catecholamine) excretion on this same basis in response to other psychosocial stimuli.

In our view, the single most important positive result is in the recent work of Ising.[41, 386] The methodology used was to compare catecholamine excretion and blood pressures over normal eight-hour workdays on days in which the workers did and did not wear ear protectors. This represents a relatively simple and replicable way to obtain clean comparisons of physiological parameters under differing noise exposure conditions while leaving other stimuli relatively unaffected in real-life settings. If this methodology were to be extended to other workplace and non-workplace noise exposure situations in a systematic way, it should be possible to determine whether, and how much, noise induces particular stress responses as a function of noise level and other characteristics, situational variables, and individual worker constitutional and psychological variables.

As can be seen in Tables 3.2A and 3.2B, the 30% average increase in norepinephrine output observed by Ising in the workers exposed to the highest noise levels is somewhat larger than the increases observed by Levi[65] in female office clerks induced to work harder by a piece-rate system of compensation, or the nonsignificant 15% increase in 24-hour norepinephrine observed by Dutton[68] in comparing work and non-work days in paramedics who reported heavy workload and excessive responsibility. On the other hand, Levi[66] observed a 34% increase during a 90-minute viewing of a horror film and Bellet[67] observed a 47% increase in total catecholamines (epinephrine and norepinephrine) in young normal subjects during two hours of automobile driving. One aspect which distinguishes the Ising result from these other situations is that apparently the brewery workers studied had a very high urinary output of norepinephrine even under the "low stimulus" hearing protector condition, compared with other results shown in Tables 3.2A and 3.2B. Depending on the exact shape of the dose-response curves for norepinephrine's platelet-aggregating and other effects, such elevations from an apprently already-high base may be indicative of increased risk.

TABLE 3.1

RELATIONSHIPS BETWEEN NOISE EXPOSURE AND CATECHOLAMINE SECRETION

Reference Number	Citation	Summary Conclusions
1,386	Ising, H. and Melchert, H.U., "Endocrine and cardiovascular effects of noise," Mimeo, presented at Freiburg Conf. (1978) Ising, H. et al.,"Study on the quantification of risk for the heart and circulatory system associated with noise workers" (final report, 1979).	30 workers in noisy departments in three breweries (86-102 dBA) were observed on different days with and without hearing protectors. Of the 30, 18 workers were observed for periods of one day with and without hearing protectors and 12 workers were similarly observed for periods of 5 days. When data from the total group was separated into subgroups with relatively high (95-102 dBA) noise exposure levels the following average increases were observed on days without hearing protectors, compared to days on which the hearing protectors were worn:

	Number of Workers	Increases in: Systolic blood pressure mm Hg (%)	Diastolic blood pressure mm Hg (%)	Norepinephrine mcg/8hr (%)
86-94 dBA	14	3.9 (3.1%)	1.0 (1.2%)	-.3 (-1%)
95-102 dBA	16	8.9 (7.2%)	3.4 (3.9%)	7.5 (30%)

The size of the blood pressure changes induced by noise appeared to be larger for workers with relatively low levels of magnesium ion in their red blood cells. Subdividing the workers into groups with relatively low magnesium (1.2-1.49 mg/g total solids) and high magnesium (1.5-2.1 mg/g total solids) reveals the following differences in systolic pressure change/diastolic pressure change:

	Lower blood sediment magnesium (1.2-1.49 mg/g Total Solids)		Higher blood sediment magnesium (1.5-2.1 mg/g Total Solids)	
	No. Workers	Blood pressure changes	No. Workers	Blood pressure changes
86-94 dBA	7	+4.9/+2	6	+1.7/-2.7
95-102 dBA	7	+11.0/+2.7	7	+5.0/+1.0

Reference Number	Citation	Summary Conclusions
387	Ising, H. et al. Zur Gesundheitsgefahrdung durch Verkerrslarm (1980).	57 younger male adult subjects worked at soldering electric circuits on two successive days with and without exposure to traffic noise at 85 dBA. Changes under noise exposure appeared to be somewhat different in subgroup 1, (see below) which was exposed to noise on the second day after the task had already been learned, than for subgroup 2, which experienced the noise exposure in combination with the demands of learning the task on day 1:

	Subgroup 1 (Noise on 2nd Day)	Subgroup 2 (Noise on 1st Day)	Total Group
Systolic blood pressure	+1 mm Hg	+5 mm Hg	+3 mm Hg
Diastolic blood pressure	0 mm Hg	+3 mm Hg	+2 mm Hg
Epinephrine	+21%	+38%	+33%
Norepinephrine	+18%	+3%	+7%
Renin	-23%	-12%	-16%

It is also noteworthy that subgroup 2 showed a much more pronounced epinephrine than norepinephrine response. For both groups there was a significant decline in plasma renin activity.

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erence iber	Citation	Summary Conclusions
42	Tsaneva, N. et al., "The catecholamines as a criterion for the functional state in different activities," Agressologie 16 179 (1975)	Urinary epinephrine and norepinephrine levels were measured in interpreters doing foreign translations and exposed to various levels of sound for an unspecified period of time. Appreciable increases in both catecholamines were observed at relatively low noise exposure levels in this system: Exposure / Epinephrine (mcg/ml) / Norepinephrine (mcg/ml urine) "silence" / 34 / 244 60 dB / 42 / 358 70 dB / 73 / 354 85 dB / 194 / 506 The norepinephrine increase was similar to one observed in typists typing at three pages per hour, compared to the same typists at rest. Typists typing at six pages per hour showed a noradrenaline level of 909 mcg/ml urine.
43	Ortiz, et al. (1974) "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium."	Marked elevations of catecholamine excretion and more modest, but statistically significant increases in systolic and diastolic blood pressure, and serum cholesterol in the majority of a group of aircraft turbine testers after 3 hours of normal exposure in their work to noise which "varies between 105 and 115 dB (sic)" in intensity. No changes observed in urinary 17 OHCS exretion. *CAVEAT:* Other potential noxious agents in the workplace not discussed or controlled. Comparison of different 3-hour periods on the same day means that results may be confounded with diurnal changes.
44	Arguelles, A. E., et al. (1970), "Endocrine and metabolic effects of noise in normal, hypertensive and psychotic subjects."	Increased excretion of epinephrine and norepinephrine in urine after 3-hour exposure to 90 dB (2000 Hz). Plasma cholesterol and cortisol not significantly affected. Systolic and diastolic blood pressure increased among 11 hypertensives. *CAVEAT:* Possible confounding with effects of diurnal changes.

ference umber	Citation	Summary Conclusions
45	Carlson, L. A., et al. (1972), "Stressor-induced changes in plasma lipids and urinary excretion of catecholamines, and their modification by nicotinic acid."	Monotonous but attention-demanding psycho-motor performance (sorting small ball-bearings) under unfavorable environmental conditions (97-104 dB (c)) (noise, flickering light), shortage of time and criticism ... evoked moderate distress, accompanied and/or followed by increases in heart rate, blood pressure, urinary excretion of adrenaline and noradrenaline, and levels of free fatty acids and triglycerides in arterial plasma. *CAVEAT:* Contribution of noise to the observed effects is obviously confounded with the contributions of several other stressors.
46	Slob, A., et al. (1973), "The effects of acute noise exposure on the excretion of corticosteriods, adrenalin and noradrenalin in man."	Noise exposure (1/3 octave noise band, middle range, frequency 4000 Hz. at 80 dB) appeared to cause a significantly different adrenaline excretion, insofar that among those exposed to noise no drop in excretion occurred in the afternoon. A similar effect, be it to a somewhat lesser degree, was noticed with regard to noradrenaline excretion ... These results appear to be in good agreement with (positive) findings reported in the literature, provided that ... the influence of two simultaneously occurring stressors is taken into account: (1) exposure to noise, and (2) the fact that the subjects were confronted with an unfamiliar laboratory situation. No effect was observed on urinary OHCS excretion. *CAVEAT:* Small, brief study. Noradrenaline effect not statistically significant.
59	Frankenhauser, M. and Lundberg, U., "The influence of Cognitive set on performance and arousal under different noise loads" Motivation and Emotion 1 139 (1977).	Three groups of 12 subjects each performed a mental arithmetic task while exposed to continuous white noise in two 75 minute experimental sessions. In Session I, each group was exposed to a different noise level (56, 72.5, or 85 dB (A)) whereas in Session II, all had the medium (72.5 dB (A)) intensity. Although performance on the arithmetic task was affected by noise level, no significant differences in urinary epinephrine or norepinephrine excretion rates were observed.

ference umber	Citation	Summary Conclusions
47	Lundberg, U. and Frankenhauser, M., "Adjustment to Noise Stress," Reports from the Department of Psychology, the University of Stockholm, No. 484, November 1976.	Same design as in the experiment discussed above, except that subjects all received the medium intensity noise (72.5 dB (A)) in Session I and either low, medium or high intensity noise in Session II. With this design significant differences were observed in urinary norepinephrine, epinephrine, and cortisol excretion, but no difference was noted in performance of the arithmetic task. In other experiments control over noise exposure and particular personality factors were found to significantly modify adrenaline and cortisol excretion.
48	Frankenhauser, M. and Lundberg, U., "Immediate and delayed effects of noise on performance and arousal," Biol. Psychol. 2 127 (1974).	Fourteen male university students were exposed to intermittent, aperiodic noise of 65-85 db(A) while performing mental arithmetic. Measures of performance, subjective stress, catecholamine excretion and heart rate obtained during and/or after noise exposure were compared with corresponding data from a "noise-free" session. Performance was not impaired by noise, but the physiological and subjective measures reflected noise-induced changes in arousal level. The time pattern differed between variables, so that the increase in subjective arousal was most pronounced during noise exposure, and that of adrenaline excretion after noise exposure. Sessions lasted 80 minutes each.
58	Carlestam, G., et al., "Stress and disease in response to exposure to noise--a review," (1973).	No significant increase in catecholamine levels in 22 young female IBM operators exposed to their normal working noise at 76, 82, 88 and 94 dB for one day each. *CAVEAT:* Authors cite "generally positive attitudes of these subjects to the job per se and to the experiment" and conclude that "noise may be a potential stressor under some circumstances and in some individuals, but need not generally be so."

TABLE 3.2

CHANGES IN URINARY NOREPINEPHRINE EXCRETION INDUCED BY NOISE AND OTHER STIMULI

A. SELECTED EXPERIMENTS INCLUDING HIGH (≥ 85dB) NOISE EXPOSURE

REFERENCE	STIMULUS AND CONDITIONS	SUBJECTS	NOREPINEPHRINE EXCRETION IN LOW STIMULUS CONDITION (NANOGRAMS/MIN.)	NOREPINEPHRINE EXCRETION IN HIGH STIMULUS CONDITION (NANOGRAMS/MIN.)	% CHANGE
ng[41, 386]	8 hours of normal work in a noisy department of a brewery with and without ear protectors.	14 workers exposed to 86-94 dBA.	53.9	53.3	-1% (ns)*
		16 workers exposed to 95-102 dBA.	51.7	67.4	+30%
ng[387]	7 1/2 hours of soldering work on days with and without exposure to 85 dBA traffic noise.	Noise given on first day when the task was unfamiliar.			+3% (ns)*
		Noise given on second day when the task was familiar.			+18%
:lz[43]	3 hours of work testing aircraft turbines, at 105-115 dB, compared with 3 hours at rest on same day.	Group I: 13 "responders"	18.5	45.7	+147%
				40.2	+1% (ns)*
		Group II: 5 "non-responders"	39.7		
		18 total subjects	24.4	44.2	+81%

; = nonsignificant ($p > .05$)

'age 2 of A. SELECTED EXPERIMENTS INCLUDING HIGH (≥ 85dB) NOISE EXPOSURE

REFERENCE	STIMULUS AND CONDITIONS	SUBJECTS	NOREPINEPHRINE EXCRETION IN LOW STIMULUS CONDITION (NANOGRAMS/MIN.)	NOREPINEPHRINE EXCRETION IN HIGH STIMULUS CONDITION (NANOGRAMS/MIN.)	% CHANGE
rguelles[44]	3 hours of exposure to 90 dB of 2000 Hz tone while resting and reading, compared with 3 similar hours at rest on the same day.	5 normal controls	18.2	25.0	+38%
		12 subjects with myocardial infarction more than 3 months previously	20.5	37.7	+84%
		11 hypertensive patients (diastolic pressures 100-130 mg hg)	17.0	30.0	+76%
ankenhauser and ndberg[59]	75 minute exposure to 85 db(A) noise plus mental arithmetic, compared to a similar period on the following day of mental arithmetic with 72.5 dB(A).	12 male university students	(Day 2) 30.92	(Day 1) 27.61	-11% (ns)*
	Same 72.5 dB(A) noise exposure on both days.		(Day 2) 32.88	(Day 1) 30.70	-7% (ns)*
ndberg and ankenhauser[47]	Same design as above except that 72.5 dB(A) condition presented on the first day and 85 dB(A) on second day.		(Day 1) Not Given	(Day 2) 4 mg/min. more than Day 1	+? (∿15%)
	Same 72.5 dB(A) noise exposure on both days.		(Day 1) Not Given	(Day 2) 2 mg/min. less than Day 1	-? (∿7%)

* = nonsignificant ($p > .05$)

ge 3 of A. SELECTED EXPERIMENTS INCLUDING HIGH (≥ 85 dB) NOISE EXPOSURE

REFERENCE	STIMULUS AND CONDITIONS	SUBJECTS	NOREPINEPHRINE EXCRETION IN LOW STIMULUS CONDITION (NANOGRAMS/MIN.)	NOREPINEPHRINE EXCRETION IN HIGH STIMULUS CONDITION (NANOGRAMS/MIN.)	% CHANGE
rlson[45]	2 hour exposure to 97-104 dB(C) noise, combined with an attention-demanding task, flickering light and criticism, compared with 2 hours of rest prior to exposure.	11 subjects not otherwise treated.	23.8	33.1	+39%
		11 subjects treated for one week with nicotine (3 g/day)	29.0	42.0	+45%
vidsson[64]	One hour exposure to 85 dB(A) traffic noise and an arithmetic task, compared to one hour of the arithmetic task alone (this low stimulus condition was begun 30 minutes after the combined exposure)	100 male students	33.6	34.2	+1% (ns)*
rlstam[58]	Normal work of "IBM operators" (key-punch?) for 6 hours/day on four successive days with increasing noise levels (76,82,88 and 94 dB(A)). Data for 88 and 94 dBA days compared with data for 82 and 76 dBA days.	11 young female workers	23.8	22.6	-5% (ns)*
	Same design as above, except noise levels presented in decreasing order.	11 young female workers (other than those used above).	13.3	15.2	+15% (nd)**

34

ıs = nonsignificant ($p > .05$)

ınd = statistical test not done

CHANGES IN URINARY NOREPINEPHRINE INDUCED BY NOISE AND OTHER STIMULI

B. SELECTED EXPERIMENTS WITH PSYCHOSOCIAL STIMULI OTHER THAN HIGH NOISE

REFERENCE	STIMULUS AND CONDITIONS	SUBJECTS	NOREPINEPHRINE EXCRETION IN LOW STIMULUS CONDITION (NANOGRAMS/MIN.)	NOREPINEPHRINE EXCRETION IN HIGH STIMULUS CONDITION (NANOGRAMS/MIN.)	% CHANGE
Levi[65]	Piece wages (pay according to output) compared to monthly salary for individual work (2 workdays observation in each condition).	12 healthy female office clerks (ages 18-31)	20.97	23.53	+12%
Levi[66]	90 minutes of film viewing, compared with 90 minutes of relaxation prior to film.	20 healthy female office clerks			
	Natural scenery films		14.83	10.83	-27%
	"Paths of Glory" (tragic and agitating)		15.21	16.43	+8% (ns)*
	"Charley's Aunt" (comedy)		16.48	18.03	+9%
	"The Devil's Mask" (gruesome ghost story)		14.61	19.57	+34%

ns = nonsignificant ($P > .05$)

age 2 of 8. SELECTED EXPERIMENTS WITH PSYCHOSOCIAL STIMULI OTHER THAN HIGH NOISE

REFERENCE	STIMULUS AND CONDITIONS	SUBJECTS	NOREPINEPHRINE EXCRETION IN LOW STIMULUS CONDITION (NANOGRAMS/MIN.)	NOREPINEPHRINE EXCRETION IN HIGH STIMULUS CONDITION (NANOGRAMS/MIN.)	% CHANGE
ellet[67]	2 hours of automobile driving, compared with 2 hours of rest (sitting).	17 young (19-25 yrs.) normal subjects	23.83**	35.42**	+47%**
		19 patients with coronary artery disease (38-72 yrs., 8 with angina only and 11 with previous myocardial infarction, with or without angina)	37.33**	59.58**	+60%**
utton[68]	24-hour urine collection for a work day, compared to an off-day with normal activities.	67 paramedics, subject to heavy workload, self-reported excessive responsibility on days monitored	∿34***	∿40***	+15% (ns)*
		56 firefighters, subject to relatively light workload (few minor fires) on days monitored	∿39***	∿38***	-4% (ns)*

36

is = nonsignificant ($p > .05$)

Results in these experiments refer to total catecholamines (norepinephrine + epinephrine). About 80% of normal total urinary catecholamine levels is norepinephrine.

**Data showing the absolute levels of output are approximate--they were reconstructed from bar graphs.

As can be see in Table 3.2, larger percentage changes in norepinephrine levels than reported by Ising were found by Ortiz (three hours of work testing aircraft turbines at 105-115 dB),[43] Arguelles (three hours of 90 dB of 2000 Hz tone while at rest),[44] and Carlson (two hours of exposure to 97-105 dB(C).[45] The effects reported in the Ortiz and Carlson experiments, however, are confounded with possible effects of other stimuli because in both cases, the comparisons were made between a period of work under other adverse conditions and a period of rest. The laboratory experiment of Arguelles with a tone exposure is of considerable interest because (1) the norepinephrine response was observed at a relatively low noise level, and (2) it appears that the two groups of subjects with cardiovascular disease were more responsive to the noise than the normal controls.

The rest of the experiments reported in Tables 3.2 and 3.2A present an irregular picture of occasional slight positive findings, and many negative or insignificant changes in norepinephrine excretion in response to noise exposure. In general, these studies were carried out in laboratory settings at somewhat lower noise levels and shorter durations of exposure than the studies cited earlier. The work of Frankenhauser and Lundberg reveals small increases in norepinephrine excretion in response to 85 dB(A) noise exposure for 75 minutes in some experimental designs,[47,48] but not others.[59] Their finding that noradrenaline excretion may be raised somewhat after the end of the stimulus period[48] may be a partial explanation for Arvidsonn's[64] negative finding with one hour of 85 dB(A) traffic noise exposure, compared to control periods begun 30 minutes later. The most extensive and realistic study producing an essentially negative result is that of Carlstam.[58] Groups of eleven female IBM operators exposed on four successive days to increasing levels of their normal office noise showed no tendency to higher norepinephrine excretion on the higher two days (88 and 94 dBA) as compared to the lower two days (76 and 82 dBA). There is some suggestion of a trend to decreasing noradrenaline excretion when another group of eleven workers were presented with the same noise exposures in decreasing order for four days. If, instead of the comparison shown in Table 3.2A, one were to compare the highest day (94 dBA) with the average of the three others, the result would be:

	Low Stimulus Condition (76,82,88 dB(A)) (ng NE/min.)	High Stimulus Condition (94 dB(A)) (ng NE/min.)	% Change
Noise levels presented in increasing order	22.9	24.3	+6%
Noise levels presented in decreasing order	13.5	16.4	+21%

The validity of this comparison is questionable, however, because the raw data seem to indicate a puzzling day-of-the-week effect. Norepinephrine seems to be elevated on the first and last days (Tuesday and Friday) of stimulus presentation over the intermediate days. This does not compromise the Tuesday-Wednesday vs. Thursday-Friday comparisons shown in Table 3.2A, but it becomes a confounding factor when a beginning- or end-day is compared with the three other days.

In summary, the available data indicate that norepinephrine excretion is likely to be somewhat elevated in all-day exposures to very loud (over 90-95 dBA) noise. More work is needed to define the magnitude of the increase among different population groups with different kinds of noise exposures (including lower exposures), possible changes in excretion patterns in post-work hours, and possible long-term changes in excretion with exposures repeated every day over prolonged periods.

Serum Lipid and Platelet Responses

Available data indicate that serum free fatty acid levels are relatively sensitive to changes in plasma catecholamine concentrations. Taggart and Carruthers,[125] in their racing car driver experiment, found a very strong correlation between plasma catecholamines and free fatty acids until a maximum was reached at about 2 mcg/liter of plasma catecholamines (Figure 3.5).

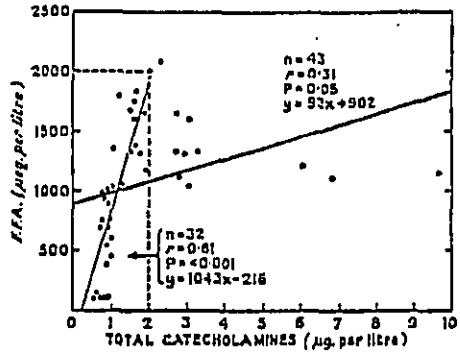

FIGURE 3.5 Relationship of plasma/free fatty acid levels and catecholamine analyzed for catecholamine values below 2 mcg/liter (within interrupted lines) and for all values.

From: Reference 125.

An experiment by Nordoy[126] finds significant increases in serum free fatty acids in response to intravenous infusion of a dose of noreadrenaline which appears to leave many other physiological parameters relatively unaffected immediately (Table 3.3). The only other significant increase found in this experiment was in platelet numbers. The slowed pulse rate may have tended to counteract norepinephrine's peripheral vasoconstrictive effects here to produce little net change in systemic blood pressures.

Table 3.4 reviews some experiments where serum lipid and plate aggregation responses to noise exposure have been assessed. As might be expected from the discussion above, free fatty acids appear to be elevated in short-term experiments where norepinephrine elevations have also been observed.[43,45] The magnitude of the changes observed appears to be somewhat less than the 32% elevation* observed by Taggart and Carruthers in response to public speaking (Figure 3.6) and much less than that observed in the racing drivers (see Figure 3.2, p. 26 above).

*From 622 to 822 meq/liter.

TABLE 3.3

DIFFERENCES IN PHYSIOLOGICAL PARAMETERS BEFORE AND AFTER INFUSION OF NORADRENALINE 0.1 µg/kg/min. I.V. FOR 30 MINUTES IN 5 HEALTHY MALE SUBJECTS

Test	Before	After
Serum free fatty acids (micromoles/ml)	-7*	-10*
Total cholesterol (mg/dl)	162 ± 28	160 ± 28
Cholesterol ester (%)	68 ± 10	69 ± 10
Triglycerides (µM/ml)	0.29 ± 0.04	0.30 ± 0.07
Total lipid-P (µM/ml)	0.94 ± 0.20	1.07 ± 0.11
Lysolechithin/lecithin	0.28 ± 0.13	0.33 ± 0.26
Pulse rate	76 ± 4	56 ± 4**
Blood pressure: systolic (mm Hg)	131 ± 18	132 ± 17
Blood pressure: diastolic (mm Hg)	88 ± 8	90 ± 11
Hematocrit	43 ± 1.8	44 ± 0.4
Platelets (x $10^3/mm^3$)	191 ± 103	238 ± 100**
Recalcification time (sec.)	194 ± 16	205 ± 17
Ac. part. thrombopl. time (sec.)	44.2 ± 1.7	43.5 ± 2.0

*Data approximate -- reconstructed from a figure. Difference is reported to be statistically significant.

**Significance of difference $p < 0.05$.

From: Nordoy, Reference 126.

TABLE 3.4

RELATIONSHIPS BETWEEN NOISE EXPOSURE AND SERUM LIPID LEVELS, AND PLATELET AGGREGATION

eference Number	Citation	Summary Conclusions
43	Ortiz, et al. (1974) "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium."	(See Table 3.1 above for other findings). 3 hours of turbine testing work at 105-115 dB.
		Before / After / % Change
		FFA (microequil./l): 640 / 711 / +11%
		Triglycerides (mg/100 ml): 146 / 173 / +18%
		Cholesterol (mg/100 ml): 251.2 / 273.9 / +14%
44	Arguelles, A. E., et al. (1970), "Endocrine and metabolic effects of noise in normal, hypertensive and psychotic subjects."	(See Table 3.1 above for other findings.) 3 hours exposure to 90 dB tone at rest.
		Plasma Cholesterol Levels (mcg %)
		Before / After / % Change
		Cardiac infarction patients: 263 / 275 / +5% (ns)
		Hypertensive patients: 264 / 270 / +2% (ns)
45	Carlson, L. A., et al. (1972), "Stressor-induced changes in plasma lipids and urinary excretion of catecholamines, and their modification by nicotinic acid."	(See Table 3.1 above for other findings). 2 hours work at an attention-demanding task under 97-104 dB (C) noise exposure, flickering light, and criticism.
		Before / After / % Change
		FFA (microequil./l): 710 / 829 / +17%
		Triblycerides (mmol/l): 1.78 / 1.88 / +6% (ns)
		Cholesterol (mg/100 ml): 271 / 278 / +3% (ns)

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eference Number	Citation	Summary Conclusions
55	Cantrell, R. W. "Prolonged exposure to intermittent noise: audiometric, biochemical, motor, psychological, and sleep effects." Mimeo. Presented before the American Laryngological, Rhinological and Otological Society, Inc., Palm Beach, Fla., April 24, 1974.	After a baseline measurement period of 15 days, 20 men were exposed to brief tonal pulses at 80 dB for ten days followed by 85 dB for ten days and then 90 dB for ten days. Significant increases in both serum cholesterol (from about 175 mg/100 ml to about 208 mg/100 ml - + 19%) and serum cortisol (from about 12.3 mcg/100 ml to about 18.1 mcg/100 ml - + 47%) observed, in comparison with the first day of confinement. *CAVEAT*: Little difference observed between periods of exposure at different intensity or between the exposure period and a subsequent 15-day no-exposure period prior to the end of confinement. Observed differences may be attributable to experimental confinement or may be slow to return to basal levels.
54	Geber, W. F. et al. Physiological responses of the Albino rat to chronic noise stress. Arch. Environ. Health 12 751 (1966).	Rats exposed to a mixture of bells, buzzers, horns, gongs at 73-93 dB for six minutes of each hour for three weeks. Serum cholesterol increased 31% after one day and 48% by the end of three weeks, compared to either animal-house controls or initial hour of exposure.
130	Friedman, M. et al. Plasma lipid responses of rats and rabbits to an auditory stimulus. Am. J. Physiol. 212 1174 (1967).	White noise of 102 dB, interrupted by random burst of 114 dB on average every 3 minutes for ten weeks caused significantly larger serum cholesterol concentrations (averaging about 35% greater) and greater arherosclerosis in rabbits fed a high cholesterol-oil diet, but not in rabbits fed a stock diet.
51	Haas, B., et al. (1973). Platelet adhesiveness during exposure to noise.	Experiment in rats demonstrating a large increase in platelet adhesiveness in response to "a standardized noise of 113 dB (sic)" for three days. Also a less directly relevant finding of increased platelet adhesiveness (compared to normal controls) in clinic patients with several types of hearing loss not obviously related to noise.

ference umber	Citation	Summary Conclusions
52	Deryagina, G. P. et al. Effect of acoustic stimulation on lipid metabolism, indices of the blood coagulation system and development of experimental atherosclerosis. (Russian) Fiziol. Zh. SSSR 62 1171 (1976).	Reported increases in free fatty acids, platelet adhesiveness and atherosclerotic changes due to 14 or 28 days of 94 - 96 dB noise 4.5 hr/day in rabbits fed 500 mg/day cholesterol. Some other experiments in the same paper report contrary results.

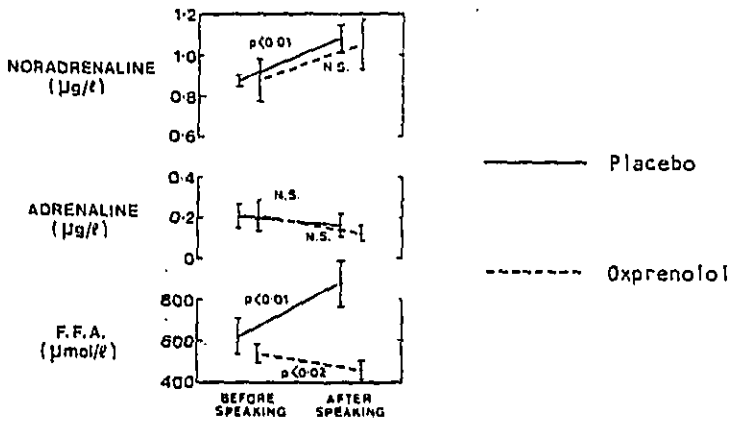

FIGURE 3.6 Elevation of circulating free fatty acids (FFA) in response to the emotional challenge of speaking before an audience.

From: Taggart and Carruthers, Reference 92.

Also parallel with the findings in racing drivers, it seems that cholesterol levels are rarely elevated appreciably in experiments lasting a few hours or less. An apparent exception to this is the findings of Ortiz,[43] who observed the effects of extremely high noise levels. Of potentially major importance, however, is the finding of Cantrell[55] that serum cholesterol levels were appreciably increased in men exposed to tonal pulses of 80-90 dB for a few weeks. The 19% difference observed between the exposure and pre-exposure condition is comparable in magnitude to differences observed in subjects fed high and low saturated fat diets,[128] and with differences reported by Friedman et al.[129] between small groups of subjects exhibiting extremes of Type A and Type B behavior patterns. It is also comparable to the difference observed in tax accountants at times of maximum vs. minimum occupational stress[96] (minimum stress average = 210 mg/100 ml; maximum stress average = 252 mg/100 ml; change = +20%), and is somewhat greater than the difference observed in Johns Hopkins medical students at final exam time vs. other times[98] (other times average = 205 mg/100 ml; final exam time average = 226 mg/100 ml; change = +11%).

The findings of Geber[54] and Friedman[130] in rabbits and rats further suggest that chronic exposures to noise may modify serum cholesterol levels. Because of the relatively strong relationship between serum cholesterol and heart disease risk observed in epidemiological studies,[131] these findings warrant further follow-up.

There are no human studies available assessing possible relationships between noise exposure and platelet aggregation properties. Such effects have been observed in rats and rabbits,[51,52] and may be expected wherever noise appreciably elevates norepinephrine levels. Haft and others have observed changes in platelet aggregation in response to the stress of medical students presenting a case at grand rounds,[18] in anticipation of minor surgery,[15] and elsewhere.[17]

3.2.2 Responses of Pituitary/Adrenal Cortical and Other Hormones, and Blood Pressures

Available observations of pituitary/adrenal cortical and other hormones under conditions of noise exposure are summarized in Table 3.5. The only positive finding of potential importance with regard to plasma cortisol is in the Cantrell experiment with several weeks of exposure to tonal pulses.[55] With the exception of the early experiment of Arguelles[133] and some work in rats,[135] the overwhelming weight of the literature shows negative or at best very transient positive findings despite considerable careful work[57] and conditions which produced positive results in the adrenal medullary hormones.[43,44,46] Because of Cantrell's result, and because of the interactive effects between adrenal cortical hormones and the catecholamines in raising blood pressure, it may be important to include these hormones in future long-term studies. However, there is little in available data to suggest that noise-induced short-term adrenal cortical responses are a potential mechanism of adverse effects.

The findings by Favio[127] for lutenizing hormone and growth hormone are very preliminary, but warrant some further exploration.

TABLE 3.5

RELATIONSHIPS BETWEEN NOISE EXPOSURE AND SHORT-TERM CHANGES IN PITUITARY/ADRENAL CORTICAL AND OTHER HORMONES

Reference Number	Citation	Summary Conclusions
133	Arguelles, A. E. et al. Pituitary-Adrenal stimulation by sound of different frequencies. J. Clin. Endocrin. 22 846 (1962).	Substantial elevations claimed in 17-OHCS levels in plasma in response to one-hour exposure of men at various single frequencies (125-10,000 Hz) at either 63 or 93 dB. Effect apparently greatest (50% increase) at 10,000 Hz. Caveat: lack of clear distinction between effects at greatly different noise levels makes results difficult to interpret.
127	Favio, A. et al. Radioimmunoassay measurements of serum cortisol, thyroxine, growth hormone and luteinizing hormone with simultaneous electroencephalographic changes during continuous noise in man. J. Nucl. Biol. Med. 119 (1973).	Five normal men subjected to 90 dBA continuous industrial noise or 50 dBA background noise for three hours at similar times on different days. Blood samples collected from catheter every fifteen minutes. Authors note transient increase (about 35%) in serum cortisol at 15 min. point, irregular increases in growth hormone throughout experimental period. Averaging data from all time points, luteinizing hormone appears to be appreciably (55%) increased, with lesser average increases in growth hormone (35%) and cortisol (20%) levels during the 90 dBA noise as compared with 50 dBA noise. Statistical analysis by t-test not performed, but luteinizing hormone difference is clearly significant by a sign test.
55	Cantrell, R. W. "Prolonged exposure to intermittent noise: audiometric, biochemical, motor, psychological, and sleep effects. Mimeo. Presented before the American Laryngological, Rhinological and Otological Society, Inc. Miami Beach, Fla., April 24, 1974.	After a baseline measurement period of 15 days, 20 men were exposed to brief tonal pulses at 80 dB for ten days followed by 85 dB for ten days and then 90 dB for ten days. Significant increases in both serum cholesterol (from about 175 mg/100ml to about 208 mg/100 ml - + 19%) and serum cortisol (from about 12.3 mcg/100ml to about 18.1 mcg/100 ml - + 47%) observed, in comparison with the first day of confinement. *CAVEAT*: Little difference observed between periods of exposure at different intensity or between the exposure period and a subsequent 15-day no-exposure period prior to the end of confinement. Observed differences may be attributable to experimental confinement or may be slow to return to basal levels.
131	Guha, D. et al. Effects of sound stimulus on gastric secretion and plasma corticosterone level in rats. Res. Commun. Chem. Pathol. Pharmacol. 13 272 (1976).	Plasma corticosterone levels of rats were significantly elevated during 1 - 2 hr exposures to 4000 Hz tone at 80 dB, as compared to pre-exposure levels.

Reference Number	Citation	Summary Conclusions
132	Nealis, P. M. and Bowman, R. E. "Behavioral and corticosteroid responses of rhesus monkeys to noise-induced stress." (Unpublished)	Continuous, variable, or impulse noise presented to monkeys at 100 dBA for five hours caused significant increase at the 1-hour time point, which disappeared at 3- and 5-hour time points.
141	Hanson, J. D. et al. The effects of control over high intensity noise on plasma cortisol levels in rhesus monkeys (Behav. Biol. 16 333 (1976).	Monkeys exposed to four 13-minute noise periods separated with 2-minute periods of quiet under conditions where they did or did not have the ability to turn off the noise at the end of the period. Cortisol levels elevated in the monkeys without control, but not in those with control.
57	Brandenberger, G., et al. Failure of noise exposure to modify temporal patterns of plasma cortisol in man. Europ. J. Appl. Physiol. 36 239 (1977).	Healthy men subjected to pink noise of either 96 dBA for 120 min (5 subjects), 99 dBA for 60 min (2 subjects), or 105 dBA and 45 dBA alternating every 10 sec. for 30 min (2 subjects). Plasma cortisol values measured in blood samples collected every 10 min. by catheter for a total of 7 hours surrounding the noise treatment, and compared with control days with no unusual noise exposure. No hint of cortisol elevation in this very careful study. For three other negative studies, see Ortiz,[43] Arguelles,[44] and Slob,[46] summarized in Table 3.1.

Short-Term Blood Pressure Responses, Peripheral Vasoconstriction, and Plasma Renin Activity

The non-auditory effect of noise which occurs most reproducibly at low levels of exposure is vasoconstruction of digital skin blood vessels, measured as a change in finger pulse amplitude. Some results from the classic studies of Lehmann and Tamm[134] are reproduced below as Figure 3.7.

It can be seen that substantial increases in peripheral resistance ("peripherer Widerstand") are usually accompanied by reductions in stroke volume ("Schlagvolumen") with the net result that changes in systolic and diastolic blood pressure ("systol. Druck", "diastol. Druck") are held to modest levels. With respect to this phenomenon, the question has always been asked whether, in the absence of systemic increases in blood pressure, the peripheral vasoconstriction is of any pathological significance. To the best of our knowledge, there is no evidence at present bearing on this question. In the context of current theory of the mechanisms of long-term blood pressure increases in chronic hypertension (Section 4.2), it is not implausible that chronically repeated vasoconstrictive responses could contribute to hypertrophy of the arterial media and thus to the disease. However, in the absence of information or theory on how transient systemic high blood pressures cause medial hypertrophy, little other evaluation of this possibility can be done. Suffice it to say that there is a large literature[136-140] documenting peripheral resistance effects down to quite low levels of noise exposure (on the order of 70 dB(A)) which we will not review in detail.

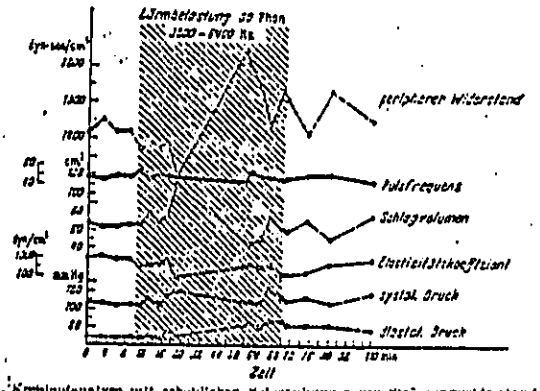

Abb. 7. Kreislaufanalyse mit erheblichen Schwankungen von Strömungswiderstand und Schlagvolumen

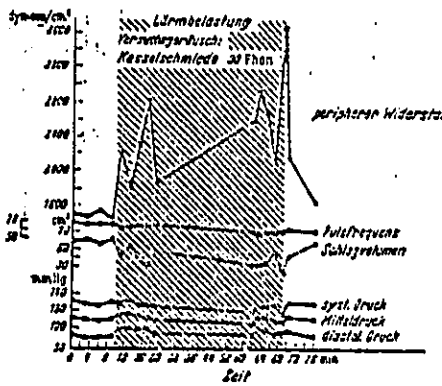

Abb. 7. Kreislaufverhalten eines Industriearbeiters bei Beschallung mit dem Arbeitsgeräusch

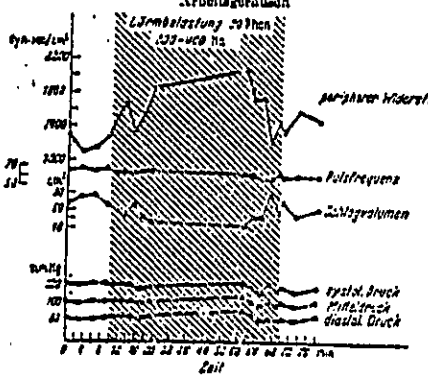

Abb. 8. Kreislaufverhalten eines Industriearbeiters bei Beschallung mit einem weißen Geräusch

FIGURE 3.7 Circulatory Response to Noise Exposure
From: Lehmann and Tamm, Reference 134.

It has been known for quite some time that emotional states and intense physical stimuli such as the "cold pressor test"* [142] can bring about increases in systemic blood pressure. In a 1949 review, Smirk reports that transient increases of 10 or 20 mm Hg can be commonly observed and that rises of 50 mm Hg sometimes occur. [144] Such changes form a background, but not a completely comparable point of comparison for blood pressure responses to noise exposures lasting over the course of a working day.

Table 3.6 reviews the results of some experiments in which blood pressure was measured in the course of noise exposures. It is clear from the work of Turek [145] (using very loud noise presented in a situation where the subject must exert active efforts to protect against even louder noise bursts as a "standardized stress test") that under sufficiently extreme circumstances, noise can reliably induce substantial short-term increases in blood pressure in normal individuals. The experiments of Ortiz [43] (3-hour exposures to 105-115 dB) and Ising [41,386] (8-hour exposures to 86-102 dB(A)) extend this conclusion to successively lower noise levels and longer periods of observation. The experiment of Carlson, [45] on the other hand, (2-hour exposure to a complex stimulus including 97-104 dB(C) noise) did not detect analogous effects beyond the first fifteen minutes of observation.

Part of the discrepancy in observations may arise from differing degrees of sensitivity of the individuals making up each group. The observations of Ising, reproduced as Figure 3.8, suggest that there may be wide differences in individual responsiveness.

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*In the cold pressor test, a hand is immersed in ice water for 60 seconds. Blood pressure in the opposite arm is measured during the last 10 to 15 seconds of immersion and compared with a blood pressure measurement taken 30 seconds before immersion. In a recent epidemiological study [143], the increase of diastolic pressure in this test was 15 mm Hg.

To the surprise of the researchers, this criterion proved to be the single most powerful predictor of subsequent heart disease risk over 20 years of follow-up. Men with cold pressor rises over 20 mm Hg showed a risk of all forms of CHD of 2.4 times the risk of those with rises under 20 mm Hg. [143]

TABLE 3.6

RELATIONSHIPS BETWEEN NOISE EXPOSURE AND SHORT-TERM BLOOD PRESSURE CHANGES

Reference Number	Citation	Summary Conclusions
145	Turek, J. V. Blood pressure response to a new standardized stress test. Neth. J. Med. 20 104 (1977).	14 normotensive subjects (age 22-66) were subjected to 104-108 dB noise from multivibrators and were required to move a non-insulated ring-shaped handpiece around a randomly bent steel rod. Whenever the handpiece touched the rod, it would trigger a burst of 114-124 dB noise in one ear. Blood pressures measured every two minutes for a ten minute period.

Time (min.)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Pre-stress	125.5	82.2
	Change from pre-stress blood pressures	
2	+15.5	+9.6
4	+13.4	+8.8
6	+10.0	+10.1
8	+11.8	+7.8
10	+11.1	+10.7
Ave changes 2 - 10	+12.4	+9.4

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ference umber	Citation	Summary Conclusions
50	Schulte, W. et al. "Der Einfluss von experimentellem Verkehrslarm auf vegetative Funktionen von Normotonikern und Hypertonikern nach Stress" (the influence of experimental traffic noise on autonomous functions of normotensives and hypertensives after stress. Basic. Res. Cardiol. 72 575 (1977).	12 normotensives and 12 hypertensives were exposed to a five minute period of mental arithmetic combined with 81 dB traffic noise followed on two different days either by continuation of the noise for fifteen minutes or fifteen minutes of quiet. In the subjects exposed to quiet, both systolic and diastolic pressure rapidly fell to pre-stress levels. With continued exposure to the noise, blood pressures were maintained at somewhat higher levels: Normotensives / Hypertensives Continued noise exposure: 125/86 / 147/99 Cessation of noise: 117/77 / 138/90 Difference attributable to noise: +8/+9 / +9/+9 (Data based on averages of three separate measurements per person, at five minute intervals.)

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ference umber	Citation	Summary Conclusions
,386	Ising, H. and Melchert, H. U., "Endocrine and cardiovascular effects of noise," Mimeo, presented at Freiburg Conf. (1978) Ising, H. et al.,"Study on the quantification of risk for the heart and circulatory system associated with noise workers" (final report, 1979).	30 workers in noisy departments in three breweries (86-102 dBA) were observed on different days with and without hearing protectors. Of the 30, 18 workers were observed for periods of one day with and without hearing protectors and 12 workers were similarly observed for periods of 5 days. When data from the total group was separated into subgroups with relatively high (95-102 dBA) noise exposure levels the following average increases were observed on days without hearing protectors, compared to days on which the hearing protectors were worn:

		Increases in		
	Number of Workers	Systolic blood pressure mm Hg (%)	Diastolic blood pressure mm Hg (%)	Norepinephrine mcg/8hr (%)
86-94 dBA	14	3.9 (3.1%)	1.0 (1.2%)	-.3 (-1%)
95-102 dBA	16	8.9 (7.2%)	3.4 (3.9%)	7.5 (30%)

The size of the blood pressure changes induced by noise appeared to be larger for workers with relatively low levels of magnesium ion in their red blood cells. Subdividing the workers into groups with relatively low magnesium (1.2-1.49 mg/g total solids) and high magnesium (1.5-2.1 mg/g total solids) reveals the following differences in systolic pressure change/diastolic pressure change:

	Lower blood sediment magnesium (1.2-1.49 mg/g Total Solids)		Higher blood sediment magnesium (1.5-2.1 mg/g Total Solids)	
	No. Workers	Blood pressure changes	No. Workers	Blood pressure changes
86-94 dBA	7	+4.9/+2	6	+1.7/-2.7
95-102 dBA	7	+11.0/+2.7	7	+5.0/+1.0

Table 3.6
Page 4

Reference Number	Citation	Summary Conclusions
387	Ising, H. et al. Zur Gesundheitsgefahrdung durch Verkerrslarm.	57 younger male adult subjects worked at soldering electric circuits on two successive days with and without exposure to traffic noise at 85 dBA. Changes under noise exposure appeared to be somewhat different in subgroup 1, (see below) which was exposed to noise on the second day after the task had already been learned, than for subgroup 2, which experienced the noise exposure in combination with the demands of learning the task on day 1:

	Subgroup 1 (Noise on 2nd Day)	Subgroup 2 (Noise on 1st Day)	Total Group
Systolic blood pressure	+1 mm Hg	+5 mm Hg	+3 mm Hg
Diastolic blood pressure	0 mm Hg	+3 mm Hg	+2 mm Hg
Epinephrine	+21%	+38%	+33%
Norepinephrine	+18%	+3%	+7%
Renin	-23%	-12%	-16%

It is also noteworthy that subgroup 2 showed a much more pronounced epinephrine than norepinephrine response. For both groups there was a significant decline in plasma renin activity.

Table 3.6
Page 5

Reference Number	Citation	Summary Conclusions
43	Ortiz, et al. (1974) "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium."	(See Table 3.1 above for other findings). 3 hours of work testing aircraft turbines at 105-115 dB. 13-Subject group which did show a catecholamine response: Before exposure: 120/74 After exposure: 132/85 Change: +12/+11 5-Subject group which did not show a catecholamine response. Before exposure: 128/79 After exposure: 151/90 Change: +23/+11 Total group of 18 subjects Before exposure: 122/75 After exposure: 137/86 Change: +15/+11

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ference umber	Citation	Summary Conclusions
44	Arguelles, A. E., et al. (1970), "Endocrine and metabolic effects of noise in normal, hypertensive and psychotic subjects."	(See Table 3.1 above for other findings). 3 hr exposure to 90 dB 2000 Hz tone. Data approximate--pressures reported to nearest 5 or 10 mm Hg. Of 5 normotensive individuals (110/75-130/80), no change in either systolic or diastolic pressure was recorded, and in the fifth case the recorded change was 0/-5 mm Hg. Of 11 hypertensives studied, the average change was +10/+10 mm Hg (statistically significant at at p = .01/p = .01). Three subjects who responded with systolic pressure elevations of +30 mm Hg appeared to have somewhat higher pressures in the baseline condition (average 167/112) than 5 patients who showed no elevation of systolic pressures (average 156/103). (No statistical test done on this trend in the data).
45	Carlson, L. A., et al. (1972), "Stressor-induced changes in plasma lipids and urinary excretion of catecholamines, and their modification by nicotinic acid."	(See Table 3.1 above for other findings). 2 hrs work under high noise (97-104 dB(C)), flickering light, and criticism. Transient increases observed at the 15 minute time point of +12/+9 mm Hg, as compared to the pre-stimulus period (statistically significant at p = .001/p = .01) but no significant changes were observed over the entire two-hour work period: Group not treated with nicotine / Group treated with nicotine Pre-stimulus Period: 158.8/98.7 / 143.4/93.6 Stimulus Period: 153.8/99.1 / 144.4/95.9 Change: -5.0/+0.4 / +1.0/+2.3

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ference lumber	Citation	Summary Conclusions
146	Mosskov, J. I. and Ettema, J. H. Extra-auditory effects in short-term exposure to aircraft and traffic noise. Int. Arch. Occup. Environ. Health 40 165 (1977).	12 male students exposed for 15 min. to aircraft noise (84-91 dB(A)) or traffic noise (leq 83.5 dB(A)) in the presence or absence of a mental load from a binary choice test. Significant increases of diastolic pressure but generally negative changes in systolic pressure were observed. Magnitude of observed changes in diastolic pressure was somewhat less under the presence of the mental load. Changes with vs. without noise (mm Hg) Without mental load / With mental load Aircraft noise: -5/+5 / -2/+3 Traffic noise: -2/+8 / -6/+4
147	Mosskov, J. I. and Ettema, J. H. Extra-auditory effects in short-term exposure to noise from a textile factory. Int. Arch. Occup. Environ. Health 40 174 (1977).	Same design as above, but 15 min exposure was to textile factory noise at 98 dB(A). Without mental load / With mental load Textile noise: -3/+6 / 0/+3

ference mber	Citation	Summary Conclusions
48	Hosskov, J. I. and Ettema, J. H. Extra-auditory effects in long-term exposure to aircraft and traffic noise. Int. Arch. Occup. Environ. Health 40 174 (1977).	Same design as above, except exposures lasted for 3 hrs. For this experiment, however, aircraft noise is described as 20 "fly-overs" per hour, periods of 20-30 sec; peak value: 89-100 dB(A) and traffic noise is listed at Leq = 73.2 dB(A). Change relative to rest period (without mental load): 1 hr. 2 hr. 3 hr. Aircraft noise -2/+4 -3/+5 -2/+6 Traffic noise -5/+5 -4/+9 -4/+9 The trend toward increasing diastolic pressures among the three time periods achieved statistical significance ($p < .05$) for traffic noise and was marginally significant ($p < .10$) for aircraft noise.
62	Cartwright, L. B. and Thompson, R. N. The effects of broadband noise on the cardiovascular system in normal resting adults. Am. Ind. Hyg. Ass. J. 653 (1975).	No statistically significant changes observed in response to 91 dBA broadband noise for one hour in a group of twenty subjects. Statistical analysis indicated that observations differed from those which would have been hypothetically produced given a 6 mm Hg or greater change in blood pressure at the 97.5% confidence level.
60	Etholm, B., and Egenberg, K. E. (1964). The influence of noise on circulatory functions.	These two papers have not yet been reviewed. They are cited as indicating no observed effect of noise on blood pressure up to intensities of 100 dB.
61	Klein, K., and Grubl, M. (1970) Hemodynamic reactions to acoustic stimuli.	

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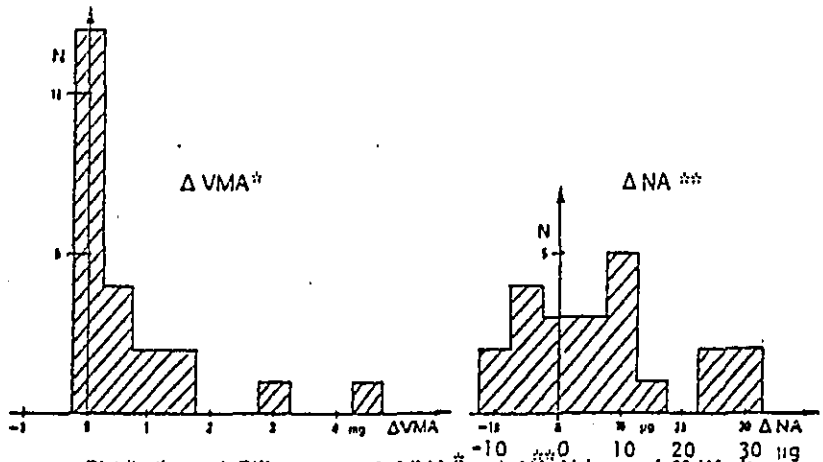
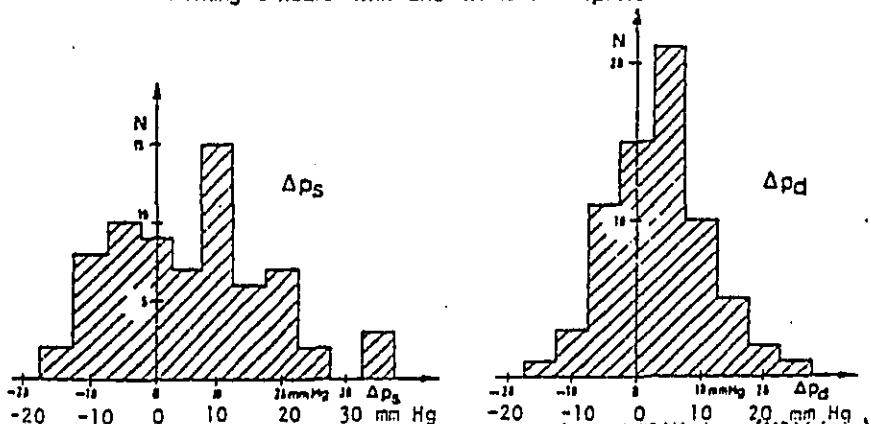
ference uaber	Citation	Summary Conclusions
53	Vander, A. J. et al. Effects of Noise on Plasma Renin Activity in Rats. Proc. Soc. Exp. Biol. Med. 156 24 (1977).	30 minute exposures of rats to broadband noise increased plasma renin activity about 50% at 115 dB. No effects were observed with broadband noise at 90 or 100 dB or with 2000 Hz noise at 90-115 dB. Rats on low salt diet for 4-6 days showed plasma renin responses at lower levels; plasma renin activity increased about 50% at 100 dB and about 25% at 90 dB in such animals.
	Simpson, G. C. et al. The Effects of Noise Stress on Blood Glucose Level and Skilled Performance. Ergonomics 17 481-7 (1974).	15 minutes of 80 dBA white noise increased the rate of fall of blood glucose compared to 50 dBA white noise. Experiment conducted in humans, 30 minutes after administration of 18 gm glucose. Noise had no effect in the absence of pre-loading with glucose.



Distribution of Differences of VMA* and NA-Values of 22 Workers working 8 hours with and without earprotectors



Distribution of Bloodpressure-Differences Δp_S and Δp_d of 22 Workers (140 Values) working 8 hours with and without earprotectors

FIGURE 3.8 Individual Differences in Response

From: Ising, Reference 41.

*VMA = Vanilmandelic acid, a metabolite of epinephrine and norepinephrine.

**NA = norepinephrine.

As noted in the summary presentation of Ising's data in Table 3.6, some of the individual differences in blood pressure responses to noise appear to be associated with erythrocyte magnesium levels. The half of the group with lower levels of blood sediment magnesium showed more than twice as large an increase in systolic blood pressures as the half of the group with blood sediment magnesium concentrations above the median.

On reviewing the literature, there seems to be an appreciable body of evidence that magnesium ion plays a role in the regulation of vascular tone and reactivity to neural stimulation.[388] At a basic biochemical level, it may be relevant that magnesium is a cofactor for all enzymes which synthesize or use adenosine triphosphate (ATP).[389] Given this, it is not unreasonable to suspect on theoretical grounds that there should be some interactions with the physiological processes which are involved in mobilizing energy resources for short-term action. Magnesium also is likely to be important as a competitor for transport of calcium ions, which is a critical cofactor for contraction of smooth muscles.[388, 394] Magnesium deficiency states are associated with generally greater irritability[389-91] and greater myocardial damage in response to cold stress in animals.[390] Both in animals and in humans, there are reports that magnesium deficiency is associated with greater sensitivity to noise in particular.[388, 392] The possible interactions between responsiveness to noise and blood cell magnesium levels in the low normal range is a subject which should be pursued in further work. Recent suggestions from epidemiological observations that dietary and water sources of magnesium may have a protective effect against sudden coronary death,[393-394] and clinical data suggesting antiarrhythmic properties for magnesium ion[395-97] lend support to the possibility that bodily magnesium status within the normal range of concentrations found commonly in human populations may be an important determinant of cardiovascular responsiveness.

Individual differences are also suggested by the apprently different behavior of the catecholamine-responsive and catecholamine-non-responsive subgroups defined in the Ortiz experiment. The observation that the older, catecholamine-non-responsive subgroup had apparently larger increases in systolic blood pressure suggests that other factors than catecholamine

release may be important in producing noise-stimulated systemic pressure rises.

The case for individual differences in responsiveness is further reinforced by the observations of Arguelles[44] (exposure for three hours to a single frequency at 90 dB). As shown in Table 3.6, five normal individuals did not respond and there was a considerable diversity in the response of the hypertensive subjects, with the high-responders (over 30 mmg Hg rise in systolic pressure) tending to have more serious hypertension as indicated by their baseline pressures. As mentioned earlier, much work on mechanisms of hypertension indicates that hypertensive and pre-hypertensive groups should contain individuals with relatively large vascular responses to stimuli. Vander's observations[53] in rats (that differences in dietary salt affect the level at which noise brings about increases in plasma renin activity) show another mechanism potentially producing individual differences.

Of the remaining experiments, that of Schulte[50] indicates an apparent effect using an unusual experimental design, suggesting that a low noise level may delay the decline in blood pressure following a combined noise and mental arithmetic. The 15-minute and 3-hour experiments of Mosskov and Etema[146] consistently find increases in diastolic pressure, but decreases or no change in systolic pressure in response to a wide range of noise exposures. Cartwright[62] reports no significant differences from one-hour exposures to 91 dBA in an experiment which is likely to have detected a difference of 6 mm Hg, had it been present. From inspection of the Cartwright data (Figure 3.9), there is some suggestion of very small effects in the direction found by Mosskov and Etema--increases in diastolic pressure, with, if anything, negative changes in systolic pressure.

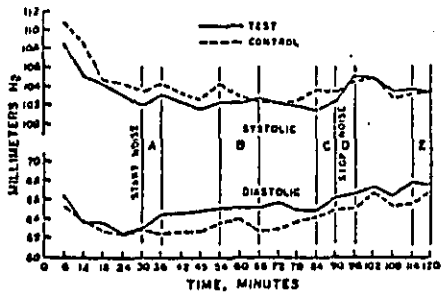


FIGURE 3.9 Mean systolic and corresponding mean diastolic blood pressures based on raw data for all subjects during all experimental runs (20 control, 20 test).

From: Cartwright, Reference 62.

It is also clear from the Cartwright observations, however, that care must be taken in experiments involving comparisons of serial blood pressure measurements on the same day. Cartwright finds that two hours of chair rest in his normal subjects produces the following statistically significant changes ($p = .001$):

(1) a relative bradycardia (slowing of the heart)
(2) a decrease in systolic blood pressure
(3) an increase in diastolic blood pressure.

Additional human and animal studies involving longer-term exposures to noise will be reviewed in Section 4.2 below.

We have not assembled a large body of data with which the pressure increases observed in the positive experiments can be directly compared. One recent, and very extensive, study[149] in an occupational population at high risk for development of hypertension (air traffic controllers) can provide some rough benchmarks, however. Table 3.9 shows a comparison of blood pressure parameters on days when individual air traffic controllers had relatively high workloads (in the upper quartile of all workload values measured on the same day) with days on which the same individuals had relatively low workloads (in the lower quartile of all workload values measured

TABLE 3.9

COMPARISON OF MEN WITH THEMSELVES WHEN THEY HAD VERY HIGH WORKLOAD ON ONE DAY AND VERY LOW ON ANOTHER DAY
(N = 123)

Method A: Work compared to population values. Men in the highest quartile of normalized workload on day 1 and in the lowest quartile on day 2.

	High Workload	Low Workload	Difference	t	p
Average Systolic (mm Hg)	131.85	127.51	4.34	3.73	.0005
Average Diastolic (mm Hg)	88.73	85.80	2.93	4.32	.0005
Maximum Systolic	147.59	141.88	5.71	3.29	.005
Maximum Diastolic	99.30	96.45	2.85	3.13	.005

From: Rose et al., Reference 149.

on the same day). The observed differences of about +4 mm Hg in average systolic pressure and +3 mm Hg in average diastolic pressure are somewhat less than Ising measured when comparing workers with and without ear protectors on different days. Another comparison from the air traffic controller study, showing differences of about 4 mm Hg in both systolic and diastolic pressures in response to days which differ at least 20% in workload, is reproduced in Table 3.10.

More work is indicated using the method of Ising[41] to locate (1) conditions of noise exposure which produce significant increases in blood pressure, and (2) susceptible population groups among which such increases may occur. Such information would allow sharper definition of epidemiological studies of long-term blood pressure changes. At present, one can ask, "What is the relationship between noise exposure (at specified levels and durations) to chronic hypertension and cardiovascular morbidity?" With better information defining short-term responses, one could ask, "What is the effect of noise exposures under circumstances and in population groups where it is known to produce particular short-term responses of defined strength?"

TABLE 3.10

COMPARISON OF MEN WITH THEMSELVES WHEN THEY HAD VERY HIGH WORKLOAD ON ONE DAY AND VERY LOW ON ANOTHER DAY
(N = 161)

Method B: (Ipsative) Work compared to man's own average for five field studies. High day exceeds 10% of own average workload by 10%, low day falls below own average workload by 10%.

Day Average Minus Grand Average for All BP Studies	High Workload	Low Workload	Difference	t	p
Systolic BP (mm Hg)	+2.09	-2.32	4.41	4.01	.001
Diastolic BP (mm Hg)	+1.76	-2.41	4.17	6.69	.001
Maximum Systolic	2.64	-1.66	4.30	2.90	.01
Maximum Diastolic	1.16	-1.52	3.13	4.00	.001

From: Rose et al., Reference 149.

3.3 Avenues of Research Needed for the Understanding of the Dynamic System of Short-Term Responses to Stressful Stimuli

3.3.1 The Need for Quantitative Systems Modelling

The presentation of the system of relationships between sympathetic stimulation and changes in hormonal and non-hormonal variables in Section 3.1 above was at a very qualitative level. Basically, it could be characterized as a "shin-bone-is-connected-to-the-knee-bone" outline of a system. In Section 3.2, we assembled some more quantitative information on responses to noise and other psychosocial stimuli, but the overall thrust of the experiments was to examine whether, rather than how much, particular stimuli affected physiological parameters in defined situations. This level of description of the system can support a general conclusion of plausibility; that under some circumstances, some excessive level of sympathetic stimulation is likely to be able to push physiological parameters to dangerous levels -- at least in people who for other reasons are already close to the limits of normal function or who are more responsive than others to the stimulation.

In a social policy perspective, arguments at this qualitative level can sensibly be used as supplemental reasons to support efforts to control sources of stimulation which appear excessive on other grounds. In the case of noise, controls on occupational exposures which produce appreciable hearing impairment, and on community exposures which disrupt daily and nightly activities to the degree that community groups are moved to seek governmental redress, can reasonably be pursued with somewhat greater vigor in recognition of the general possibility of long-term damage mediated by stress responses. Similarly, efforts to reduce psychosocial stimuli which produce obvious tension and disruption of personal satisfaction may be somewhat aided by general recognition of the risk that long-term damage may occur.

However, in order for the control of stress responses per se to become a major motivating factor for significantly altering societal resource allocation, or making other major changes,* it is helpful to develop a capability for assessing the magnitude of likely benefits of such changes. What levels of sympathetic stimulation produce what degree of increased risk from cardiovascular disease processes? Are there levels and modes of sympathetic stimulation (e.g., from moderate exercise) for which the compensating biological benefits by mechanisms not shown in Figure 2.2 may be judged to exceed the biological costs? At the minimum, in order to set priorities sensibly, it is necessary to have some way of estimating the relative degree of reduction in stress responses and associated risk which may be produced by alternative interventions. Is it better to reduce a set of workers' average exposure from 87 dBA to 81 dBA, or to change the workplace organization so that individual workers have control over their pace of work and can rest whenever they notice themselves becoming bothered by conditions? Is it possible to develop simple tests which would detect those most susceptible to excessive responsiveness to their work situation, which could guide efforts to place people in locations where excessive responses were minimized?

The research questions outlined in Section 3.3.2 below are designed to both build fundamental understanding of quantitative relationships among the different components of stress responses and to locate the real-life situations where particular stress responses may be most markedly reduced by available interventions. Later in the report, we will suggest research questions to elucidate relationships between stress responses and chronic disease processes (outlined in Section 4.3) and between stress responses, chronic disease processes, and clinical manifestations of disease (outlined in Section 5.3).

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*E.g., changes in working conditions (reducing shift work, piece-rate systems of compensation, continual deadline pressures) and other modifications in lifestyles.

3.3.2 Outline of Suggested Research Questions for Elucidating Relationships between Stimuli and Stress Responses

A. What are the dynamic interactions in the short term of the various elements of the system, as observed in controlled laboratory conditions (animal and human experiments)?

1. What are the time and dose-response relationships of all major system elements* to exogenously-supplied hormones (a) infused singly, and (b) infused in various combinations? As larger quantities of various hormones are supplied in shorter time periods, is there evidence of "thresholds" in the system (places where the responses of the system change abruptly)?

2. Is the urinary excretion of specific hormones and their metabolites simply and directly dependent on the time-weighted average of plasma concentrations of those hormones? How should urinary excretion be expressed to best reflect plasma concentrations (for example, for norepinephrine, various authors use:

   (a) $\frac{\text{weight NE excreted}}{\text{unit of time}}$

   (b) $\frac{\text{weight NE excreted}}{\text{unit of time and body weight}}$

   (c) $\frac{\text{weight NE excreted}}{\text{weight creatinine excreted}}$).

3. What statistical models best describe the variability with time of the individual parameters? In other words, if one wished to estimate the fraction of time spent at particular elevated levels of specific parameters thought to produce damage, would it be more accurate to use a normal distribution (arithmetic mean and standard deviation), a log-normal distribution (geometric mean and geometric standard deviation) or some other statistical model?

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*E.g., plasma and urinary catecholamines, adrenocorticol hormones, platelet aggregation properties, blood pressure, serum lipids, etc.

4. Given the quantitative relationships between major system elements developed from the single and multiple infusion experiments, which of the quantitative responses to specific stressful stimuli (e.g., noise) can be "explained" in terms of systemic concentrations of specific hormones, and which must be explained in part by direct sympathetic neural influences, local hormone releases, or as-yet-undetermined physiological processes?
5. How do the relationships developed in (1) and (4) above change with:
   (a) chronic repetition of the stressful stimulus
   (b) quantitative and qualitative changes in the stimulus (e.g., response to different noise levels, response to continuous vs. irregular varying noise)
   (c) changes in situational variables (e.g., control)
   (d) how and how much do different individuals differ in their patterns of response?
      -- differences between individuals with different styles of coping with stress (e.g., Type A vs. Type B)
      -- differences between people of different ages
      -- differences associated with specific pathological conditions (e.g., angina, past myocardial infarction, high and low renin hypertension)
      -- physiological differences between people

B. What dynamic variations in critical parameters (potentially related to disease processes) can be measured or inferred for humans exposed to naturally-presented stimuli in the course of every-day activities? (Less invasive procedures needed for such experiments. Fewer parameters can be measured, and others must be inferred. Therefore, good models are needed from laboratory work in "A" above which specify the relationships between potentially pathology-related parameters and those parameters which can be relatively easily and reliably measured in field situations.)

1. Conduct a broad ranging survey of short term responses to noise in various industrial and community situations. Central organizing question: What types and levels of noise stimulus evoke various amounts of change in relevant short term variables in various kinds of people? Using the Ising model methodology (comparing catecholamine excretion and blood pressure responses with and without hearing protectors, conditions and people where noise appears to produce the largest short term changes.* (Provisional "high risk" groups--specifically explore red cell magnesium as an important modifying variable).

2. For the high response groups and stimuli located by (1), study more intensively the changes associated with the stimulus:
   (a) expand the variables monitored to include some which may be more directly related to disease processes, but which require more invasive procedures (e.g., plasma hormone responses, platelet aggregation, plasma lipid responses, and ECG monitoring to detect arrhythmias.**.
   (b) expand the time over which the effects of the stimulus are monitored. Examine excretion of catecholamines in the several hours between the end of work and sleep, as a function of noise exposure during the day, and examine the effect of an entire two-week period of hearing protector use, as compared to two weeks of no use.***
   (c) sample the responses within shorter blocks of time (e.g., shorter time periods of urine collection) to get a better gauge of the frequency of potentially dangerous temporary elevations of relevant parameters.

3. Observe the effects of long-lasting reductions in noise levels

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*The same survey should reveal groups with high current past noise exposures and chronically elevated blood pressure levels, and, if blood samples were collected, of chronically elevated serum cholesterol.

**See discussion in Section 5.1.2 below.

***See pages 15-16 above for evidence that norepinephrine excretion may be greatest in the several days <u>following</u> prolonged stressful episode.

about by engineering controls:

(a) compare the long-term levels of blood pressure, serum cholesterol, catecholamine excretion, etc., measured before and after the permanent reduction in stimulus levels.

(b) repeat the studies of short-term responses on days with and without ear protectors, to ascertain the change in the variability of risk factors which has been produced by the intervention.

4. RELATIONSHIPS BETWEEN SHORT-TERM STRESS RESPONSES AND CHRONIC DISEASE PROCESSES

In the previous section we have seen the influence of noise and various other day-to-day stimuli in producing short term alterations in various physiological parameters. The notion that such short-term changes may somehow be related to chronic pathological processes will strike many observers as unlikely on its face. Before examining the specifics of possible mechanisms of atherosclerosis and hypertension, it may be helpful to examine a particular paradigm (organizing pattern of intellectual analysis)* in traditional physiology and toxicology which is likely to be a source of discomfort in this case, and the reasons why we think it sensible for people to make some modifications in this basic paradigm when integrating information on cardiovascular disease processes.

A major theme, if not the central organizing principle of traditional physiology and toxicology, is the concept of the homeostatic system. Biological processes are seen as part of a complex interacting web, exquisitely designed so that modest perturbations in any parameter will automatically give rise to adaptive negative feedback processes to restore optimal functioning. In this view, so long as an external stimulus does not push one or more parameters beyond a specified limit ("threshold") adaptive processes will repair any damage which may have been temporarily produced and completely restore the system to the functional state prior to the stimulus.

This paradigm has enjoyed great success in guiding the design and interpretation of a wide range of experimental findings on acute responses to toxic chemicals, heat, cold, and other agents where the mechanism of damage does, in fact, consist of grossly overwhelming a particular set of bodily defenses. However, the homeostasis/threshold paradigm has been less successful (and sometimes very misleading) when applied to situations such as cancer and mutations where subtle but irreversible

---

*The word "paradigm" is used here in the sense of Kuhn's Structure of Scientific Revolutions.[152]

damage can result from one or a small number of events on a microscopic scale governed by stochastic processes.

In the cases of atherosclerosis and chronic increase in blood pressure, we have processes which have conspicuous differences from both the homeostasis/threshold model, and the stochastic molecular biological model. These major cardiovascular disease processes appear to consist of chronic accumulations of incompletely repaired or misrepaired small-scale damage events. Such chronic accumulation of individually insignificant damage events does not fit within the framework of massive short-term breakdown of adaptive mechanisms suggested by an unmodified version of the homeostatis/threshold model. On the other hand, because the events underlying atherosclerosis and long term blood pressure increase must take place in enormous numbers, rather than the few critical events required for the molecular biological diseases, stochastic models based on small numbers of "hits" are also clearly inappropriate.

Homeostatic processes clearly play a prominant role in the day-to-day and year-to-year regulation of cardiovascular functioning, and the overt clinical manifestations of disease may occur only when relevant parameters are pushed to major departures from normal values--i.e., beyond specific thresholds. However, the causes of the underlying disease must be sought within the range of day-to-day fluctuations which are frequently encountered among apparently healthy people in developed countries. It is not unlikely that there are thresholds in the processes which give rise to the small-scale damage events of chronic cardiovascular disease processes (e.g., perhaps the arterial endothelium in a particular region only suffers appreciable damage from sheer stress when systolic blood pressure is temporarily elevated above 180 mm Hg). However, whatever thresholds exist must be low enough to produce a sufficient accumulation of net damage* to account for the observation that atherosclerosis and long term blood pressure increases with age occur in very large numbers of "normal" people exposed to the usual environments of our civilization.

---

*net after the action of repair processes

Cardiovascular disease processes are not the only examples of chronic cumulative pathological processes which require the development of a distinct kind of intellectual framework or paradigm. Other prominent cases include chronic obstructive lung disease (which proceeds by the destruction of individual alveolar septa in response to smoking and environmental air pollutants) and chronic loss of hearing acuity (which proceeds by destruction of terminal neural elements in the organs of corti in response to noise). We suspect that the ultimate understanding of each of these systems' long term deterioration in response to adverse environmental conditions will require detailed systems-analytic mathematical modelling of the biological mechanisms which lead to the small increments of damage on a day-to-day basis in response to day-to-day stimuli.

4.1 Stress Responses and Atherosclerosis

4.1.1 Postulated Mechanisms of Atherosclerosis - Qualitative Overview

Figures 4.1 and 4.2 show the anatomy of normal arteries.

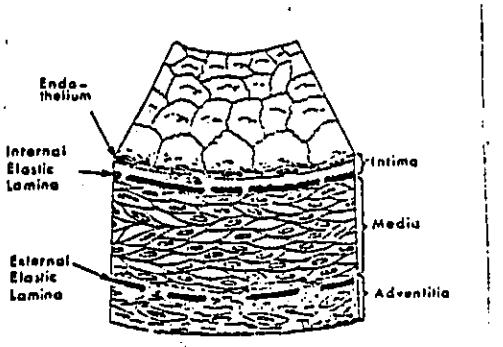


Figure 4.1 STRUCTURE OF NORMAL MUSCULAR ARTERY

(From Ross and Glomset, Ref. 153)

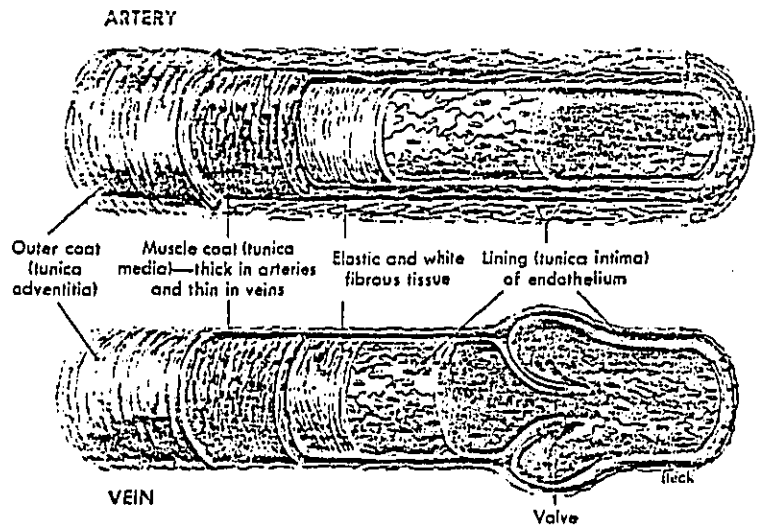


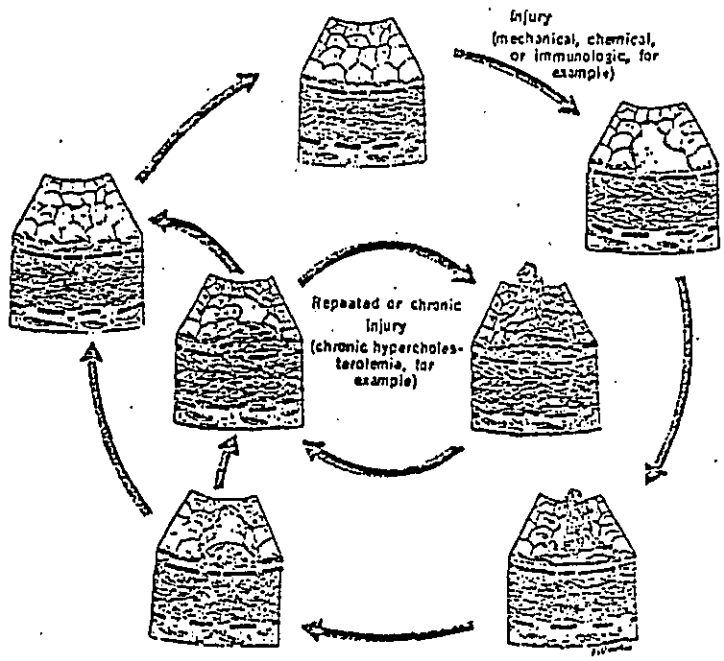
Figure 4.2

Schematic drawings of an artery and vein showing comparative thicknesses of the three coats: outer coat (tunica adventitia), muscle coat (tunica media), and lining of endothelium (tunica intima). Note that the muscle and outer coats are much thinner in veins than in arteries and that veins have valves.

(From Anthony and Kolthoff, Ref. 154)

The principal initial changes in atherosclerosis take place in and on the intima of the aorta coronary and other major arteries.[156] By contrast, the principal initial site of vascular changes associated with chronic increases in blood pressure appears to be the media and intima in smaller arterial branches (arterioles) which immediately precede capillaries.[159] Atherosclerotic lesions initially involve changes in limited focal areas, whereas the medial and intimal thickening seen in the progresss of hypertension is more generalized and diffuse.

Contemporary theory of the mechanism by which atherosclerotic lesions are produced has been articulated in a series of experimental and review papers by Ross, Harker and Glomset.[153, 155-8] The basic schema is illustrated in Figure 4.3.



. In the response to injury hypothesis, two different cyclic events may occur. The outer, or regression cycle, may represent common single occurrences in all individuals in which endothelial injury leads to desquamation, platelet adherence, aggregation, and release, followed by intimal smooth muscle proliferation and connective tissue formation. If the injury is a single event, the lesions may go on to heal and regression occur. The inner or progression cycle demonstrates the possible consequences of repeated or chronic endothelial injury as may occur in chronic hyperlipidemia. In this instance, lipid deposition as well as continued smooth muscle proliferation may occur after recurrent sequences of proliferation and regression, and these may lead to complicated lesions that calcify. Such lesions could go on to produce clinical sequelae such as thrombosis and infarction.

Figure 4.3

(Figure 4.3 - from Ross and Harker, Ref. 155)

The normal arterial intima has a tightly-interlocked single layer of endothelial cells which form an effective barrier against the passage of larger plasma proteins, such as low-density lipoproteins. In young humans and other primates there are only a few scattered smooth muscle cells in the intima below the endothelial cell layer. Under the influence

of any of a number of a different kinds of mechanisms,* endothelial cells can be injured and lost from the monolayer, exposing the underlying intimal smooth muscle cells and the elastic lamina to the action of blood components. Platelets then stick to the sites of injury (and to each other) and release a complex mixture of clotting factors and other constituents including component(s) which stimulate the migration and division of smooth muscle cells. In the absence of further injury, endothelial cells bordering the lesion eventually grow, divide, reestablish the barrier between the blood and smooth muscle cells, and the local accumulation of intimal smooth muscle cells is reduced by an as-yet undefined mechanism.** Repeated cycles of injury, however, lead to the continued proliferation of smooth muscle cells, the secretion of fibrous material (collagen, elastic fibers, and proteoglycans) by the smooth muscle cells, and the accumulation of lipid (primarily cholesterol and cholesteryl ester).

A number of different kinds of lesions are considered to be part of this process. The simplest one, "fatty streak" is made up of a relatively small number of intimal smooth muscle cells containing and surrounded by lipid and does not project appreciably into the arterial lumen. Fatty streak may not be part of the atherogenic sequence at all in the sense of being a precursor of more serious lesions. "Fibrous plaques," by contrast, are considered to be the characteristic lesion of progressive atherosclerotic disease. As described by Ross and Glomset[153], the fibrous plaque

> "consists principally of an accumulation of intimal lipid-laden smooth muscle cells, the lipid being primarily cholestrerol and cholesteryl ester. The cells are also surrounded by lipid and by collagen, elastic fibers and proteoglycans. Together the cells and the extracellular matrix components form a fibrous cap that covers a large, deeper deposit of free extracellular lipid inter-mixed with cell debris."

---

*The different mechanisms which seem to be as effective in producing intimal injury and eventual atherosclerotic lesions in primate studies include mechanical processes (a balloon catheter or sheer stress from high blood pressure[172]), chemical damage (chronic homocystinemia), immunological reactions[153] and a reaction of unspecified nature to chronic high levels of serum lipids.[153]

**Conceivably the layers of smooth muscle cells present in the months immediately after injury migh either disperse to other locations in the intima, or return to the media, or die. The fact that in older animals there are evidently many more intimal smooth muscle cells than in younger animals suggests that some dispersion within the intima may occur.

With the advance of atherosclerotic disease, "complicated lesions" appear. These are thought to be derived from fibrous plaques, but they include the additional features of ulceration, hemorrhage, areas of cell death, platelet aggregates, and in some cases, calcification.

4.1.2 Prospects for Quantitative Dynamic Modelling of Atherogenic Processes

Obtaining information for the development of quantitative dynamic models of atherogenic processes poses both major intellectual and practical challenges. The intellectual challenges arise from the complexity of both the processes and the resulting distribution of lesions in the vasculature. What summary measures would adequately represent the progress of the pathology?

--as summarized above, there are several different kinds of lesions

--the different lesions begin to appear in appreciable numbers at different ages in different parts of the arterial tree, and spread at different rates after initial appearance in different locations.*

---

*For example, in an international study[160] of autopsy material, Vihert finds for the descending thoracic aorta:

> "The total extent of atherosclerotic lesions in men and women increased slightly from 15 to 40 years of age within a range of 15-20% of the arterial surface. After 40 years of age there was a steady increase, amounting to 7-10% of the arterial surface per 5-year period. . . .
>
> Fatty streak differed from all the other lesions. Up to 20-24 years of age it occupied 15-17% of the surface and remained at this level until the age of 40-45 years. From 45 years it decreased gradually to 2-5% per 10-year period. . . .
>
> The area occupied by fibrous plaque hardly increased from 2-3% until 39 years of age. Then there was a swift increase, a little greater in men than in women, up to age 75-79. . . .
>
> The extent of complicated lesions remained at about .5% up to 50-54 years of age and then began to increase quite rapidly, although at no age did it exceed 5% of the intimal surface."

On the other hand,

> "Atherosclerosis in the abdominal aorta developed somewhat differently. The total amount of atherosclerosis began to increase from the age of 20, i.e., there was no period of relative stability such as was found in the thoracic aorta up to 40-45 years of age. . . .

--Both the arterial surface area covered by lesions and the degree of narrowing of the arteries are probably important in characterizing the amount of atherosclerotic damage within any given arterial segment.

Even if one were able to readily ascertain all such aspects of arterial disease in individual people, how should one integrate them into an overall index of "atherosclerosis" for purposes of predicting increased liability to various manifestations of cardiovascular disease (e.g. angina, myocardial infarction, stroke)?

In addition to this theoretical challenge, there are substantial practical difficulties in measuring the effects of various factors on atherosclerosis. There are not yet easy and safe ways of ascertaining either the standing stock of atherosclerotic lesions or the processes of lesion formation and growth in humans. Autopsy studies allow for detailed characterization of atherosclerosis,

---

*(footnote continued from previous page)
The increase in area occupied by fibrous plaque in the abdominal aorta began roughly 5 years earlier than in the thoracic aorta and followed a considerably more rapid course, with an increment of 15-20% in each 5-year period. The changes increased with particular intensity between 39 and 59 years of age and in those 20 years the area occupied by fibrous plaque increased 4-fold in women and 4 1/2-fold in men."

Considering the aorta as a whole, the total extent of atherosclerotic lesions

". . . increased rather in arithmetical progression by 18-20% per decade of the intimal surface; 34 years, 5%; 44 years, 5 and 17.5 = 22.5%; 54 years, 22.5 and 20 = 42.5%."

Thereafter the spread of intimal area occupied by lesions was much slower.

For further comparison, the observations of Vanecek[161] in the same international autopsy study present a differnt picture in the coronary arteries:

"In contrast to the findings for the aorta, the extent of fatty streak did not exceed 3-4% of the intimal surface.

In the left anterior descending coronary artery in men under 30 and in the other two arteries in those under 35, the area of fibrous plaque was of the order of 1-4%. Later in life the area began to increase at a much faster rate, particularly in the left anterior descending and right coronary arteries, which showed a 5-year increase of about 8% during the periods between 35 and 55 years. The area taken up by fibrous plaque attained its maximum by about 65 years and showed very little change thereafter. The greatest age-standardized value was observed in the right coronary artery and the smallest in the left circumflex artery, while in the average coronary fibrous plaques occupied 35% of the intimal surface.

but (1) can only be done once on a single individual and (2) cannot be done on a sample of people representative of the living population.*

The increased use of angiography in recent years has provided some opportunities for study of the progress of atherosclerotic disease which did not previously exist in patients for whom this procedure is indicated. Use of this technique in cross-sectional studies has already provided further support for the association of Type A behavior pattern with atherosclerosis.[34] It seems likely that longitudinal studies, involving serial angiographic determinations in the same patients over periods of several months, can provide quantitative insights into the contributions of various risk factors to the dynamics of lesion progression and regression in people who are already in an advanced stage of the disease. At least one study of this kind has recently appeared. As was suggested earlier in the introduction, such information should eventually have an important bearing on the interpretation of epidemiological studies of clinical manifestations of heart disease. Knowing (1) what factors contribute in what degree to atherosclerosis progression, and (2) the relationship between a given degree of atherosclerosis, risk factor levels, and short-term risk of heart attack and stroke, it should be possible to dissociate the contributions of individual risk factors to the chronic disease processes from contributions to the short-term sequence of events which precipitate overt clinical manifestations of disease.

On the other hand, angiographic studies have important limitations for determining the possible pathogenic influences of stress responses on early stages of atherosclerotic disease. Members of healthy working populations, such as those which experience the bulk of occupational noise exposures, will not undergo repeated angiography with any great frequency, and in any case, angiography may not be capable of efficiently quantifying the modest reductions in arterial lumen size which are present in early stages of disease. A more promising approach would seem to be to return to the schema of Ross and Harker (Figure 4.3, page 76 above) to survey possible avenues for research on the ways in which stimuli and stress responses may influence the course of lesion generation and development.

*Nonetheless, human autopsy information from individuals who died during the Western Collaborative Group Study was able to qualitatively indicate that men with Type A behavior pattern had a generally greater degree of atherosclerotic lesion development than Type B men, even for those who died of non-coronary causes.[162] Autopsy studies have also reinformced the aualitative conclusions that hypertensives have more artherosclerosis than non-hypertensives, and that men with sedentary jobs have more atherosclerosis than men with non-sedentary jobs.[163, 164]

Four different kinds of events depicted in Figure 4.3 afford conceivable experimental handles for the measurement of atherosclerotic lesion progression:

--the initial injury to the intima, and loss of endothelial cells

--adhesion of platelets to the sites of injury, and release of platelet constituents

--migration and multiplication of smooth muscle cells

--synthesis and secretion of extracellular fibrous material and accumulation of lipid

Intimal Injury

Intimal injury has primarily been quantified in the past in animal experiments by detailed examination of arterial segments and direct ascertainment of the percentage of the endothelium lost. The fact that gross amounts of injury are seen in response to hyperlipidemia or homocystine infusion (5-10% of the entire endothelium missing) suggests that an appreciable amount of endothelial cell debris products may be being released into the blood on a continuous basis in response to daily rates of injury. One possible approach to quantifying intimal injury might be to monitor serum concentrations of some product of endothelial cell destruction. For example, many cell types have unique antigens on their surfaces which allow them to be distinguished by specific antibody reagents. Endothelial cell debris would undoubtedly be rapidly scavenged in vivo but it is possible that a sensitive and specific radio-immuno assay could be developed to measure the release of such material into the blood in response to (a) different mean levels of traditional risk factors such as blood pressure and serum cholesterol and (b) short term changes in blood pressure, etc. induced by environmental stimuli.

Another approach for the quantification of intimal injury has recently been suggested for use in guinea pigs in a preliminary report by Herd, et al.[165] Removal of endothelium is known to affect the permeability of the arterial wall

to solutes, particularly to macromolecules. Herd's group infused animals for 2-6 hours with a mixture of labelled materials of different molecular sizes* to constant plasma levels, rapidly froze aortas in vivo, and assessed the ratio of tissue/plasma concentrations for each material. As expected, the large molecular weight dextran showed a much lower ratio of tissue to plasma concentration (.15) than sodium (.44) or the intermediate-weight inulin (.31). Increased permeability of the endothelium subsequent to injury would be indicated by a lessening of the difference between the dextran ratio and the salt ratio. It is not apparent how sensitive an index of injury this would be, but it is conceivable that quite small amounts of desquamation could alter permeability characteristics in this system in a major way. This procedure cannot, of course, be directly applied to human systems** but in experimental animals it will afford a rapid measurement method for investigation of dose response relationships between chronic or short term elevations of risk factors and the initial events of atherosclerotic lesion development.

Intimal injury is a major postulated route of action by both traditional and stress-related riskfactors on atherosclerotic processes. Blood pressure, serum cholesterol, and stress-induced blood pressure variations are all likely to exert their influences at least in part through this mechanism. Development of rapid and reliable means to quantify this step in the process will be a major advance in gathering the data necessary to model the dynamic response of atherosclerotic progression to changes in risk factors.

Platelet Adhesion and Release of Constituents

This step is also both an important postulated route of influence by stress responses on the atherosclerotic process, and a potentially important point for potential measurement of the process in response to changes in risk factors. It is clear that increased catecholamine concentrations lead to increases in various measures of platelet adhesiveness assessed in vitro,[192-3,197] and give rise acutely to intravascular platelet aggregates which can cause

* $^{22}NaCl$, ^{3}H-Inulin (M.W. 5,200) and ^{14}C-dextran (M.W. 16,000)

**It is not inconceivable that other, less destructive assays based on intimal permeability changes could be developed for use in humans. For example, if some rapidly methbolized material were to penetrate arterial walls and then be re-released from them with a specific time course, it is possible that such re-release kinetics could be used as an assay of the amount of material when penetrated during infusion, and hence of arterial permeability characteristics.

areas of focal myocardial necrosis in vivo.[104,168-70] However, there is as yet only sketchy information on the relationship of platelet adhesiveness properties and other factors to platelet-dependent steps in the chronic atherosclerotic disease process.

Table 4.1, from Ross and Harker[155] shows data from pigtail monkeys (macaca nemestrina) maintained on either normal diets or high cholesterol/saturated fat diets for 9-18 months. On average, about 5% of the endothelial surface was missing in the hyperlipidemic animals at the times of sacrifice, and this was associated with a reduction of somewhat over 25% in platelet survival time.

TABLE 4.1

Platelet kinetics in normal and hyperlipidemic monkeys. Cell loss in the aortic endothelium is expressed as the percentage of surface lost.

Diet	No. of animals	Plasma lipids		Endothelial cell loss (% of surface)	Platelet		
		Cholesterol (mg/dl)	Triglyceride (mg/dl)		Count (No./ml)	Survival (days)	Turnover (platelets $(ml)^{-1}$ day^{-1})
Normal	8	88 ± 5.3*	30 ± 9.4	0	383,000 ± 62,000	8.0 ± 0.34	61,000 ± 11,000
Hyperlipidemic	6	223 ± 22	28 ± 14	5.0 ± 1.2	396,000 ± 70,000	5.8 ± 0.54	86,000 ± 13,000
P		< 0.01	> 0.75	> 0.001	> 0.75	< 0.01	< 0.05

*The variation is ± 1 S.D.

From Ross and Harker. Ref. 155.

In another experiment in which intimal injury was produced in baboons by continuous infusion of homocystine, a loss of 10% of the intimal endothelium was associated with a 50% decrease in platelet survival.[158]

Recent experiments in human patients with severe coronary artery disease (over 50% narrowing found by angiography) indicate that quantitatively significant platelet consumption is a regular occurence in atherosclerotic processes.[171] When simultaneous blood samples were drawn from the coronary sinus and aorta in such patients (during cardiac catheterization performed for other clinical purposes) it was found that platelet numbers were significantly lower in the coronary venous blood than in aortic blood (mean 168 ± 20 vs 234 ± 37 X $1000/mm^3$, $P < .05$). This was taken to indicate major platelet absorption in the diseased coronary vasculature. The difference in platelet numbers between coronary venous and aortic blood was abolished when the same patients were given aspirin, and was not seen at all in a group of four patients without severe coronary disease.

Platelet adhesion to sites of injury is evidently a fairly rapid process, beginning within minutes of acute injury by balloon catheter and persisting for at lease 48 hours[153]. It is possible, therefore, that if some accurate and non-destructive way could be developed to assess the number of platelets which were adhering to arterial walls on a daily basis, one might be able to determine the sensitivity of the initial events of atherosclerotic lesion production to dynamic physiological changes induced by environmental stimuli. Ideally, it would be desirable to monitor the concentration of some blood component which was specifically released by platelets following adherence to arterial walls.* The mitogenic factor responsible for inducing division of smooth muscle cells would be a good choice for this if it is sufficiently long-lived in blood to be easily and accurately measurable. Failing that, it may be that other constituents of platelet granules (e.g., ADP, specific enzymes) might be used as an index of intimal damage.

Because platelet adherence to sites of arterial damage seems to be a fairly rapid process relative to the slow rate of endothelial healing responses,** one might think that platelet adhesion would not be a rate-limiting step in the atherosclerotic process and that it would not be easy to interfere with atherogenesis by modifying platelet adhesive properties. Nonetheless it has been reported that in primate systems both anti-platelet antiserum and dipyridamole (an inhibitor of platelet function) can prevent formation of atherosclerotic lesions[153]. It is possible that until the developing lesion is covered by endothelial cells, there are repeated cycles of platelet adhesion, release of mitogenic factors, and adhesion of new platelets. Platelet adhesive properties could contribute to the frequency with which these cycles are repeated for any given area of lost endothelium.

Smooth Muscle Cell Migration and Proliferation

These processes appear to be primarily accessible to experimental study by autopsy experiments in which intimal areas are quantitatively examined for smooth muscle cell numbers at various times after a known stimus or series

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* We suspect that simple platelet survival studies may not be sensitive enough to detect changes in platelet consumption attributable to normal rates of atherosclerotic damage.

** By contrast with the very rapid platelet response after balloon catheter injury, migration of smooth muscle cells from the media is observed at about 5-7 days, and lesions reach maximum size in about 3 months. Lesions substantially regress due to endothelial overgrowth by about six months in the absence of hyperlipidemia.[155]

of stimuli. There is no immediately apparent way of assessing these parameters by non-destructive techniques in man or animals.

Synthesis and Secretion of Extracellular Fibrous Material and the Accumulation of Lipid

It is currently believed that the major carrier of cholesterol for deposition in atherosclerotic lesions is a class of proteins known as low-density lipoproteins. Recent data suggests that low density lipoprotein cholesterol is the significant component of total serum cholesterol which makes a positive contribution to cardiovascular disease risk. It seems possible that the predictive power of the low-density lipoprotein cholesterol concentration might be further enhanced if measurements of turnover of such material were multiplied by absolute concentration levels to form an index of total cholesterol flux. Whether the total flux defined in this way is a reliable indicator of the day-to-day rate of deposition of lipid in the vaculature would need to be determined by validating experiments in animal systems. However, this might be a good way to measure the progress of intermediate stages of atherosclerotic disease (stages which might not be primarily limited by the rate of initial intimal injury and desquamation).

Analogous monitoring of the flux of molecular building blocks for the fibrous components of atherosclerotic plaques might provide additional handles for experimental measurements of the response of the daily progress of atherosclerotic lesion development to variations in risk factors affected by environmental stimuli.

4.1.3 Suggested Questions for Further Research on Relationships Between Noise, General Stress Reponses and Atherosclerotic Processes

There is a small amount of direct experimental evidence in two rabbit experiments that noise exposures exacerbate the development of atherosclerotic lesions in rabbits fed high-cholesterol diets.[130,52] These initial results can and should be pursued.

In addition to increasing intimal injury from serum cholesterol, the other two major likely routes of action of noise and other stressors on

atherosclerotic processes are (1) increased intimal injury by way of transient or long term increases in blood pressure, and (2) increased platelet adhesion to sites of intimal injury (or to other platelets already bound to arterial walls) leading to increased release of factors which stimulate the migration and mitosis of smooth muscle cells. Section 3.3.2 above (p. 70) outlined some research questions helpful in building an understanding of the system of dynamic short-term responses of numerous relevant parameters to stimuli. The addition of short-term assays for the progress of atherosclerotic lesions, such as those suggested in the previous section, would allow a bridging of the gap in knowledge between the short term responses and chronic disease processes. Given the development of one or more assays for intimal injury or platelet adhesion and factor release, the following questions would lead to a better understanding of the degree of atherosclerotic risk from environmental stimuli:

A. What are the time-and dose-response relationships between single stress-responsive parameters and measures of intimal injury and platelet adhesion/factor release? (Animal and some human experiments in controlled laboratory settings.)

   1. Responses to catecholamine infusion

   2. Responses to cholesterol increases (from diet)

   3. Responses to transient blood pressure increases induced by some mechanism which does not disturb other parameters (e.g., infusion of exogenous renin?)

B. What are the time- and dose-response relationships to increases in combinations of stress-responsive parameters (animal and some human experiments in controlled laboratory settings).

   1. Responses to multiple infusion

   2. Responses to the combination of increases in parameters induced by graded exposures to noise and/or other stimuli

C. For the high response groups of humans and stimuli located in field studies (see B-1 on page 70 above) can measures of intimal injury, platelet adhesion/factor release and low-density-lipoprotein flux be shown to be altered in expected ways based on the laboratory model experiments?

4.2 Stress Responses and Chronic Hypertension

Like atherosclerosis, the processes which underlie chronic increases in blood pressure must be pervasive features of the aging process in developed societies. However, as is indicated by Figure 4.4, these processes are not rigidly programmed to occur regardless of environmental influences. Although genetic factors clearly are of major importance in producing differential predispositions toward specific blood-pressure-raising processes,* a wide variety of human groups can be found, coming from all races and levels of general economic affluence, which do not appear to manifest an inexorable increase in blood pressure with advancing age.

In one sense atherosclerosis and chronic blood pressure increase present directly opposite problems for further research. In the case of atherosclerosis, the theory of Ross and Glomset provides a straightforward and widely accepted schema for the underlying pathological process. The prime limiting factor in using this schema to understand the contributions of various etiological factors to the process and the efficacy of control measures is the enormous difficulty in ascertaining the standing stock and rate of change in atherosclerotic lesions in individual living humans. By contrast, systolic and diastolic arterial blood pressures are more easily and widely measured than almost any other medical parameter. Given further the predictive power of blood pressure measurements for the later development of overtly life-threatening manifestations of cardiovascular disease, it is clear that arterial blood pressures must be regarded as eminently useful indices of some chronic pathological process(es)

*For example, in rat models of hypertension, factors such as chronic noise exposure,[174] high salt intake,[175] and chronic conflict,[176] have been found to raise blood pressure in some strains but not others.

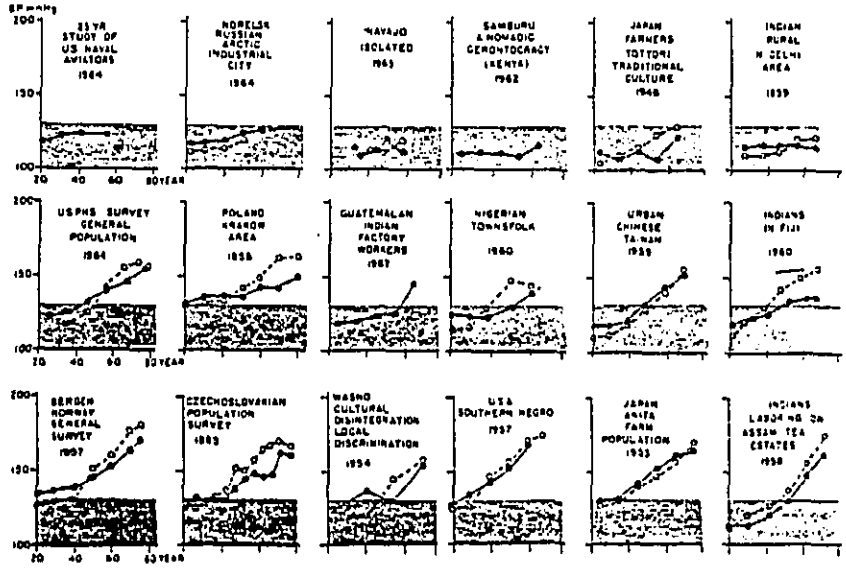

Figure 4.4

Mean systolic blood pressure change with age can be found in all races. In general, blood pressure is lower when the culture is stable, traditional forms are honored, and group members are adapted to their roles by early experience and secure in them. Open circles: females. Closed circles: males (Henry, J.P. and Cassel, J.C., reference 173).

which are relevant to human morbidity and mortality. For this reason, blood pressure has been the subject of a vast amount of clinical epidemiological, as well as experimental, study. However, reflected in the current scientific literature is a profound dissatisfaction with the results of this effort.* Although blood pressures must still be regarded as potentially very useful indicators, unfortunately there is at present no scientific consensus on just what underlying irreversible or poorly reversible changes are indicated by blood pressure increases. While further progress in understanding the causes and prevention options for atherosclerosis seems most likely to be helped by the development of practical clinical assays for a defined process, similar progress for hypertension seems more likely to be assisted by the development of an accurate system for interpreting available clinical observations in terms of underlying pathological processes sensitive to specific environmental (e.g., noise, salt) and internal (e.g., genetic) factors.

In this section we shall first briefly examine the current status of theories of hypertension, and point out some new opportunities from trends in recent research to clarify the contributions of environmental factors. Second, we shall present some features of the overall pattern of blood pressure change in contemporary society in general, and in one high risk occupational group in particular. Then, in the third section below we will examine the specific data available from animal and human epidemiological studies on the blood-pressure increasing effects of noise exposure. Finally, in section four we

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*For example, Leonard Syme, a distinguished epidemiologist in the field, recently characterized the state of the art in the following words:[182]
"In brief, epidemiologic studies of blood pressure have been underway for more than 25 years, and the results of this research can only be described as modest. The basic epidemiologic and demogrphic description of blood pressure distributions in human populations remains unclear, and psychosocial studies of hypertension have not yielded consistent hypotheses pointing the way to future research. And yet, there is no doubt that blood pressures vary among and between population groups, and there seems little doubt that variations in lifestyle are associated with these differences. It is puzzling that we have failed to discern systematic and patterned relationships among these variables."
Some of the frustration is illustrated by the equivocal nature of epidemiological evidence on the risks of salt. Despite the clear role of high salt intake in producing hypertension in some animal strains,[179] evidence from cross-cultural comparisons,[178] and the demonstrated benefits of diuretic drugs in controlling hypertension,[203] no association could be detected between sodium excretion and blood pressure for individuals in the Framingham population,[179] or in some other studies[180-1]. (Such studies may be complicated by possible temporary imbalances between intake and excretion.)

shall outline a set of suggestions for future experimental and epidemiological work relevant both to the fundamental scientific questions of hypertension etiology and to the specific contributions of noise and other environmental agents.

4.2.1 Postulated Mechanisms of Long-Term Blood Pressure Increases

The current lack of agreement on a single coherent theory of "essential"* hypertension has not resulted from any deficiency of suggested mechanisms. Table 4.2 provides a highly condensed overview of major competing and complementary theories for the technically-oriented reader. The theories are organized into four broad groups by the general location of the underlying "ratchet" processes which are thought to initiate and maintain the high pressure state:

1) the sympathetic nervous system and peripheral arterioles
2) the kidney and its control of extracellular fluid and salt
3) the veins and
4) the aorta and other large arteries

Despite the fact that the different theories see changes in different anatomical locations as keys to hypertension, many of the theories are fairly similar in the nature of the processes which are seen happening at key location. In many cases the poorly-reversible "ratchet" process is a series of changes which stiffen and/or narrow specific blood vessels. Such changes generally involve proliferation of smooth muscle cells, and the accompanying deposition of extracellular polymeric material, such as collagen and mucopolysaccharides, in addition to the changes in larger arties typical of atherosclerosis.[192,239]

As is apparent from the brief outline in Table 4.2, the large number and diverse character of blood pressure control processes has spawned a variety of speculations that changes in particular parameters contribute to the pathogenesis of hypertension. In general these speculations are plausible on their face and

*In a small percentage of hypertensive people, high blood pressure can be attributed to kidney disease or specific tumors secreting vasoactive substances. "Essential" hypertension excludes high blood pressure resulting from these known causes.

tentatively supported by observations that appropriate changes in the parameter in question are observed either in a subgroup of hypertensive people or in some animal models of hypertension. However, also in general, there is uncertainty about the direction of causation for changes in the individual parameters associated with hypertension. It is often difficult to choose between the possibilities that:

1) the abnormality in question caused blood pressure to rise
2) rising blood pressure caused the abnormality
3) some other process caused both the abnormality in question and the increase in blood pressure

Precisely because blood pressure is affected by many separate but interrelated control processes, changes in blood pressure from whatever cause automatically set in motion numerous secondary adjustments over various time-spans. At least in the short run, these adjustments will tend to damp the original change in blood pressure, but over long periods both any residual blood pressure change and the secondary adjustments may give rise to changes in still other parameters.

The consensus which appears to be emerging from the profusion of possible blood-pressure-raising mechanisms is that no single underlying process will ultimately be found to be responsible for increasing blood pressure in all, or perhaps even most, patients presently considered to have essential hypertension.[217,227] Increasingly, authors have used observations of specific parameters to sort patients into a number of "types" of hypertensives which are thought to represent either:[225, 228-33]

a) different stages in the development of hypertension or
b) fundamentally different diseases, driven by different progressive pathological processes, but having in common the presence of high blood pressure as one outcome.

There is a pervasive refrain in the recent literature to the effect that people with hypertension are a diverse group, with differing patterns of abnormality in relevant physiological processes.

Table 4.2

Suggested Mechanisms Producing
Long Term Increases in Blood Pressure

Major Proponent, Reference	Suggested Mechanism in Brief	Major Evidence
1. Theory focused on sympathetic nervous system responses to environmental stimuli, and structural changes in peripheral arterioles.		
Folkow, B. and Hallbach, M.[108,159,205] Esler, M.[223] Champlin, J.[225] Kaplan[226]	Transient neurohumorally-induced increases in blood pressure in response to environmental stimulation causes slowly-reversible structural changes in arterioles (principally, thickening of arterial media and a consequent reduction in the size of the lumen). The increase in wall/lumen ratio not only raises basal resistance to flow but greatly amplifies the increase in resistance which occurs when sympathetic stimulation causes arterial smooth muscle to contract, thus leading to a vicious circle. No prominent theory yet exists which proposes a mechanism for the "triggering" increase in sympathetic responsiveness to environmental stimuli, but irreversible changes in neural function (e.g., resulting from death of neurons, which do not replicate) can easily be imagined.	Raised resistance to flow at maximal dilation and vascular hyperactivity have been observed both in hypertensive people and in the Okamoto strain of spontaneously hypertensive rats (SHR), characterized by high renin levels. Both young (prehypertensive) and older SHR rats have also been found to show much larger acute increases in blood pressure to sudden environmental stimulation (including exposure to loud noise)[205] than normotensive controls or rats with renovascular hypertension. "In man, early phases of essential hypertension often resemble a mild defense reaction"*[207-8] and hyperactivity to emotionally disturbing stimuli has been reported.[209-11] When the hypothalamic defense area is exposed to often repeated stimuli, the transient pressure rises can gradually lead to a more persistent pressure elevation,[212] also occurring in animals exposed to prolonged environmental stress."[173,206, 213-5] Recent observations on patients classified as "high renin" hypertensives indicates enhanced sympathetic nervous activity (this group has high plasma norepinephrine concentrations,[218-2,223] large reductions in blood pressure in response to drugs which block adrenergic receptors,[203-223] and tends to exhibit

*The resemblance referred to is hemodynamic--relatively increased cardiac output and heart rate. In established hypertension this pattern is generally replaced by one of normal cardiac output and increased peripheral resistance.

Table 4.2
(cont'd)
Suggested Mechanisms Producing
Long Term Increases in Blood Pressure

Major Proponent, Reference	Suggested Mechanism in Brief	Major Evidence
		more supressed hostility[223] relative to other hypertensive patients.) By contrast, sympathetic nervous activity seems to be supressed in "low renin" hypertensives,[224] and the blood pressure-lowering effect of diuretics is greatest in that group.[222]
2. Theories focused on kidney abnormalities, extracellular fluid and salt.		
Bianchi, G. et.al.[183]	A genetically-determined abnormally low glomerular filtration fraction is compensated for early in life by unusually high renal plasma flow. Later in life, due to senescence of the renal vasculature, the high rate of blood flow through the kidney cannot be maintained, and arterial pressure must be increased to achieve adequate filtration. Thought to yield "low renin" type of hypertension.	In a large survey of renal function in normotensive offspring of hypertensive parents, a subgroup was found with very high renal plasma flow and low filtration fraction. Such a subgroup was not apparent in a parallel survey of normotensive offspring of normotensive parents.[183] This abnormality also seems to be present in the Milan strain of hypertensive rats, "MHS."[184-5] (This strain is not salt-sensitive or unusually susceptible to neurogenic stimuli.[187]) The hypertension-producing defect can be transferred by kidney transplantation.
Brown, J.J. et.al.[188]	The major conclusion of Guyton's system-dynamic model of circulatory function[189-190] is that in the long run, arterial pressure can only rise if the relationship between pressure and urinary output of sodium and water is altered. This relationship may be reset as a result of generally increased arterial resistance in the kidney,* leading to increased glomerular filtration fraction and increased pressure in peritubular capillaries, leading to increased sodium resorption.	(1) "Normal pressure-natriuresis results mainly from reduction of tubular sodium reabsorption," (2) "Increased hydrostatic pressure in the peritubular capillaries reduces sodium resorption," (3) "Increased arterial pressure is transmitted beyond the glomerulus into the peritubular capillaries in some circumstances."[188]

*Possibly produced by transient pressure rises as in the Folkow mechanism (see below).

Table 4.2
(cont'd)

Suggested Mechanisms Producing
Long Term Increases In Blood Pressure

Major Proponent, Reference	Suggested Mechanism in Brief	Major Evidence
Freis, E.D.[178]	Chronic intake of salt over a critical low level (about 1 to 3 g per day) leads to a chronic state of expanded extracellular fluid volume, higher cardiac output, and higher blood pressure than would otherwise be the case (e.g., in unacculturated peoples). In this state, (1) the pressor response to short-term neurogenic stimuli is increased, and (2) short-term pressor responses start from a higher non-stressed "baseline." Both effects increase the structural damage to arteries expected from short-term stimuli due to the Folkow mechanism (see above).	"(1) epidemiological studies in unacculturated peoples showing that the prevalence of hypertension is inversely correlated with salt intake; (2) hemodynamic studies suggesting that the development of chronic experimental hypertension is a homeostatic response to a maintained increase in extracellular fluid volume (ECF); (3) evidence that the ECF of "salt eaters" is expanded in comparison to that of "no-salt eaters" and (4) investigations in hypertensive patients receiving either diets greatly restricted in salt or continuous diuretic therapy which correlate with the fall in blood pressure with a reduction in ECF.[178]
3. Theory focused on changes in venous function.		
Ulrych, M.[104,195,197] Takeshita, A. and Mark, A.L.[196]	Stiffening (decreased distensibility) of veins with age leads to (1) redistribution of venous blood from peripheral to cardiopulmonary circulation, (2) increased cardiac output which directly tends to increase arterial blood pressure, and (3) increased sodium retention by the kidney due to an increased glomerular filtration fraction (see above, Brown mechanism). Renin release is suppressed in this form of hypertension by the stretching of cardiopulmonary mechanoreceptors.[198] Factors producing the stiffening of veins are not clear, but may include changes in prostaglandin synthetase with age observed in a rat model,[200] increased ion-binding cellular and extracellular matrix[201] or venous smooth muscle hypertrophy.[202]	Contrary to what one would expect in simple renal models of hypertension (e.g., Bianchi, Brown/Guyton mechanisms above) blood volume is normal or below normal in essential hypertension.[199] Increased venous constriction would account for this. Direct measurements of venous distensibility in borderline hypertension, and the inverse relationship between plasma renin activity and albumin leakage from circulating blood to extracellular fluid ("Labelled Albumin Disappearance Rate") support the concept.

Table 4.2
(cont'd)

Suggested Mechanisms Producing

Long Term Increases in Blood Pressure

Major Proponent, Reference	Suggested Mechanism in Brief	Major Evidence
4. Theory focused on changes in the aorta and other large arteries.		
Swales, J.D.[191]	"Loss of elasticity of the aortic wall produces a widened pulse pressure and a high incidence of systolic hypertension." Normally, the aorta and to some extent other arteries perform a damping function upon the spikes of pressure generated by the left ventricle during systole. The elastic aortic wall distends and exerts a significant pressure upon the distal part of the arterial tree during diastole.[194] Increased rigidity is caused by several processes: (1) the elastic fibres of the media uncoil and fracture, (2) collagenous matrix increase, (3) calcium is deposited in the media.	Progressive increase in the rigidity of the aorta and peripheral arteries is observed with age,[192,193,194] high resting blood pressures are associated with reduced compliance.[216]

The intellectual basis for this trend toward typologies of hypertension warrants elaboration. An individual's blood pressure at any point in time can be thought of as the dynamic result of many different physiological processes pulling the system in one direction or another. A good analogy might be a tug-of-war contest in which the participants are thought of as individual participants on either the pressure-raising or pressure-lowering sides. Different "types" of hypertensive people could be thought of as having different alignments of participants (processes) on each side. Over time, blood pressure could increase either as a result of participants on the high pressure side getting stronger, or participants on the low pressure side getting weaker or changing sides.

This general framework implies that great improvements may be possible in the "signal to noise ratio" for epidemiological studies attempting to detect the influence of specific environmental factors in raising blood pressure. Environmental factors are likely to act unevenly on different types of processes producing hypertension. Indeed, in fortunate cases it can be expected that a particular agent will act exclusively through one process to raise blood pressure. Because of this,

1) There should be a different distribution of "types" of hypertension among people exposed to different causative agents.*

2) People at all levels of blood pressure in populations exposed to particular causative agents should show an unusual relationship between indices of specific blood pressure raising processes and blood pressure. As illustrated in Figure 4.5, the index of a process which is worsened by the agent in question should be unusually elevated relative to blood pressure. By contrast, the index of a process which is not worsened by the agent in question should show reductions relative to blood pressure in the exposed population. (This is because blood pressures are essentially pulled up away from their normal positions relative to the latter type of index.)

In view of the current rapid rate of change in etiological theories

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* For example, one might expect more "high renin"[228-9] or "hyperadrenergic"[225] hypertensives in populations exposed to a potential source of chronic sympathetic stimulation (e.g., air traffic controllers and/or workers exposed to high noise.

of hypertension, it would be premature at this point to attempt to specify either which typological systems will ultimately prove to have the greatest discriminating power for the first type of investigation above, or which specific clinical indices of blood-pressure raising processes will prove most useful in the second type of investigation. However, among typologies, the currently-prominent high-renin, normal-renin, low-renin, primary aldosteronism system with its well-developed clinical protocol[229] and apparent importance for prognosis[228] and drug therapy,[220.222] is an obvious initial choice. Among clinical indices of blood pressure-raising processes, Table 4.3 lists some which may be worth considering, depending on further refinements in the state of knowledge in this field.

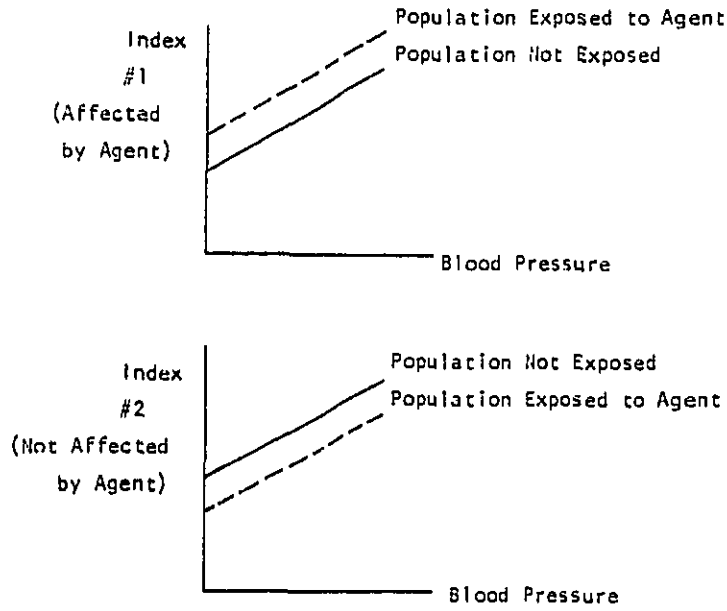

Figure 4.5

Expected Change in Relationships Between Blood Pressure and Indices of Processes Affecting Blood Pressure, for Processes Which Are (Upper Graph) and Are Not (Lower Graph) Affected by a Particular Environmental Agent

Table 4.3

Processes Which Tend to Raise Blood Pressure
and Associated Clinical Indices

Process Contributing to Elevated Blood Pressure	Possible Clinical Index (potentially useful for the type of epidemiological investigation illustrated in Figure 4.5)
General overactivity of the sympathetic nervous system	Plasma renin levels in relation to sodium excretion[228]
	Basal plasma norepinephrine levels[219]
	Urinary norepinephrine excretion (normalized to creatinine excretion)[237]
	Blood-pressure lowering effect of ganglionic blockade with drugs[222-3]
	Blood-pressure lowering effect of saralasin[235] (angiotension inhibitor)
Arteriolar thickening (peripheral)	Peripheral resistance in relation to cardiac output at rest
	Increase in peripheral resistance in response to a standardized sympathetic stimulus[207,210-1]
	Reduction in peripheral resistance in response to blockade of beta and alpha receptors with drugs[220]
Stiffening of aorta and other large arteries	Pulse pressure[191] (systolic pressure minus diastolic pressure)
	Change in arterial compliance with pressure[216]
Stiffening of veins	Venous distensibility measurements[196]
	Increased ratio of central/peripheral blood volume[198]
	Labelled albumin disappearance rate (LADR)[197]
	Reduced blood volume and extracellular fluid per body weight[204,183]

Table 4.3
(cont'd)
Processes Which Tend to Raise Blood Pressure
and Associated Clinical Indices

Process Contributing to Elevated Blood Pressure	Possible Clinical Index (potentially useful for the type of epidemiological investigation illustrated in Figure 4.5)
Kidney dysfunction of the Bianchi[183] type (see Table 4.2, p.94)	Low glomerular filtration fraction[183]
	Increased kidney blood flow per pressure[183,236]
Kidney dysfunction of the Brown[188] type	Blood-pressure lowering effect of diuretics, salt restriction[203,222]
	Increased sodium excretion on sodium loading (in the absence of primary aldosteronism)[234]
Simple renal insufficiency due to loss of tissue/glomeruli[236] (Guyton[190] type)	Increased pressure response to salt/volume loading
	Increased blood volume and extracellular fluid per body weight

4.2.2 Patterns of Blood Pressure Change With Age in the General Population and in a High-Risk Occupational Group: Observations and Implications for Public Health Prevention Policy

Historically, hypertension has been mainly viewed as an individual medical problem--to be dealt with using the same basic set of procedures which practicing physicians have applied for conditions as diverse as cancer, chicken pox, and pregnancy. In general, the approach is to:

1) detect an abnormality, or pattern of abnormalities in the patient

2) from the abnormality, relevant history and other facts, categorize ("diagnose") the patient as having one or more recognized illness or other condition, or as having no definable illness, and

3) based on the diagnosis, expected prognosis in the absence of treatment, and the expected risks and benefits of specific therapeutic options for the individual patient, prescribe appropriate treatment.

Because the physician's principal ultimate need for diagnostic information is to determine in individual cases whether the benefits of specific treatments are likely to be worth the trouble, costs, and risks of side effects to the patient, it is entirely appropriate that the medical profession has chosen to designate specific numerical values of systolic and diastolic blood pressure to help make operational distinctions between patients who are "hypertensive," "normotensive" or possibly "borderline," with corresponding implications for treatment.

Useful as such distinctions may be as benchmarks in medical practice, there is a danger that their use in epidemiological studies to form simple summary measures of the frequency of high blood pressure in various groups may cause researchers to miss features of their data which have important implications both for scientific questions of hypertension etiology, and public policy questions of the health benefits of instituting specific prevention measures to reduce the rate of blood pressure increase in groups at risk. In brief, it is scientifically relevant to ask whether a particular agent increases blood

pressure more or less uniformly in a population, or whether specific subgroups are more affected by the agent than others. This can only be done if the entire blood pressure distribution in the population at risk is examined. Further, it appears from available data that cardiovascular disease risk increases continuously across all blood pressure levels (both below and above standard medical dividing lines for classifying people as "hypertensive").* Therefore in assessing the public health benefits of prevention measures, it is also important to estimate how the entire distribution of blood pressures in a target population will be altered by the specific prevention measure.

In this section we shall lay the background for examining the results of epidemiological studies on the relationship between noise exposure and blood pressure by setting forth basic data on the current pattern of blood pressure change with age in the U.S., with some supplementary data from Canadian and British studies. Then, to illustrate the kinds of information which can be obtained from examining the entire distribution of blood pressure in a high-risk group, we shall present some comparisons between blood pressure distributions of Air Traffic Controllers from a recent longitudinal study, and standard reference populations. The results provide lessons for the design of epidemiological studies and public policy for control of putative blood-pressure raising factors.

Figures 4.6 and 4.7 show the distributions of systolic and diastolic blood pressures found in a single casual measurement for males in the most recent available survey of a large representative sample of the U.S. population.[240] As can be seen, despite the fact that some underlying distortions must result from the use of antihypertensive drugs by a small percentage of the population, the observations appear to be well-described as simple

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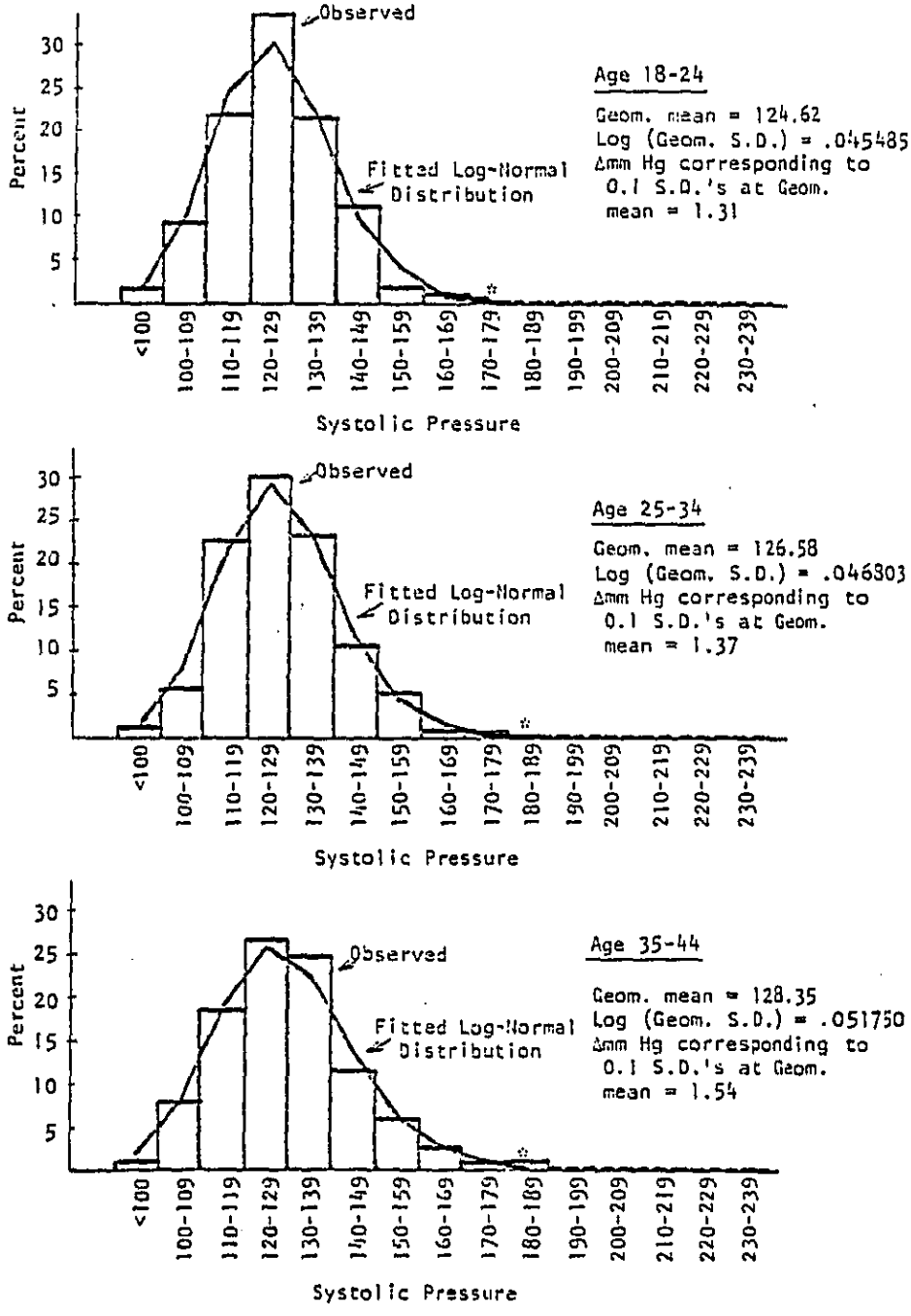
* These data will be discussed in more depth in Section 5 below.

FIGURE 4.6

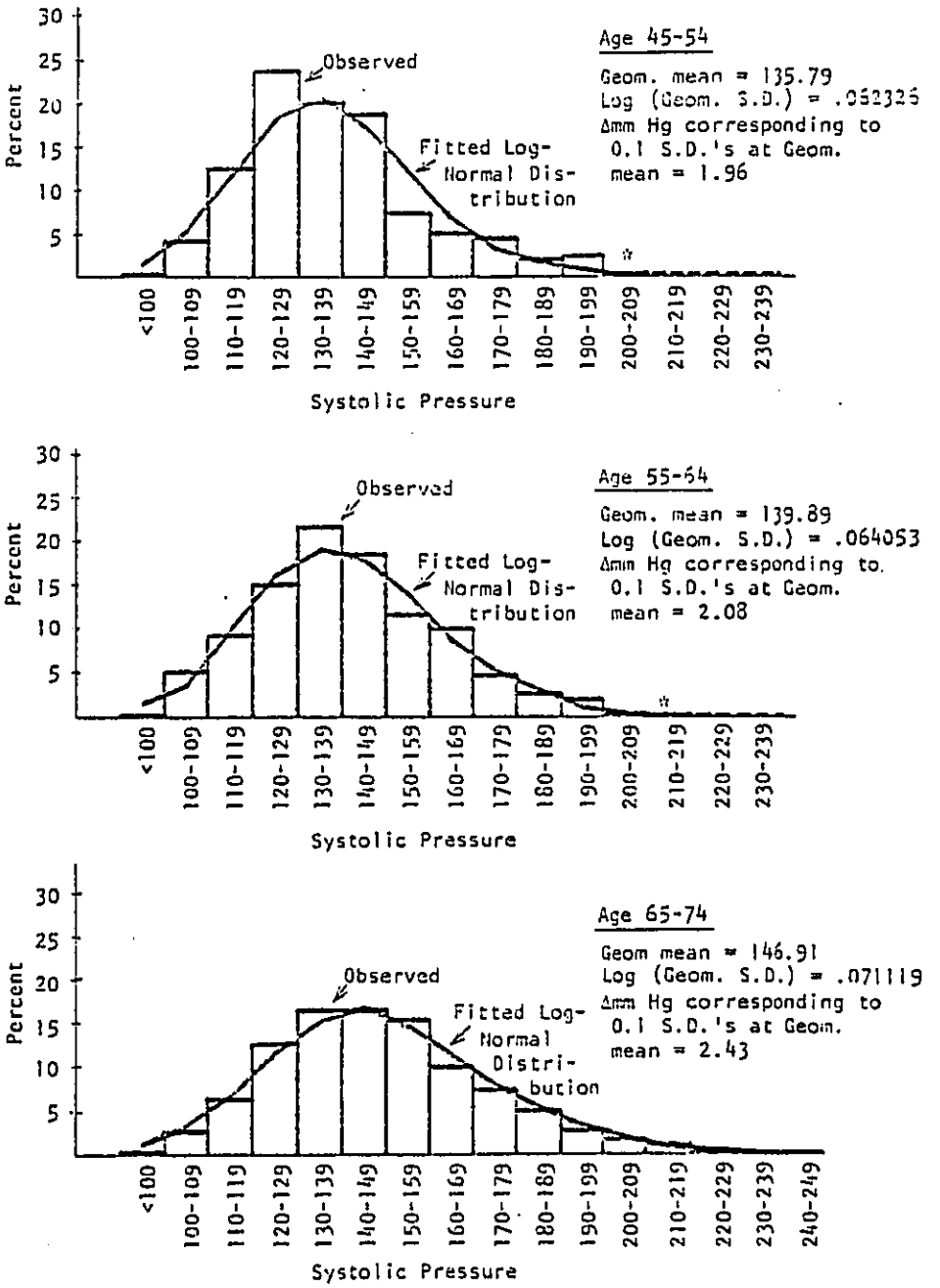
SYSTOLIC BLOOD PRESSURES OF U.S. MEN
HANES Observed Data[240] vs.
Predictions of Log-Normal Distributions



*Last boxes include all higher pressures.

FIGURE 4.6 (cont.)

SYSTOLIC BLOOD PRESSURES OF U.S. MEN
HANES Observed Data[240] vs.
Predictions of Log-Normal Distributions



*Last boxes include all higher pressures.

FIGURE 4.7

DIASTOLIC PRESSURES OF U.S. MEN
HANES Observed Data[240] vs.
Predictions of Log-Normal Distributions

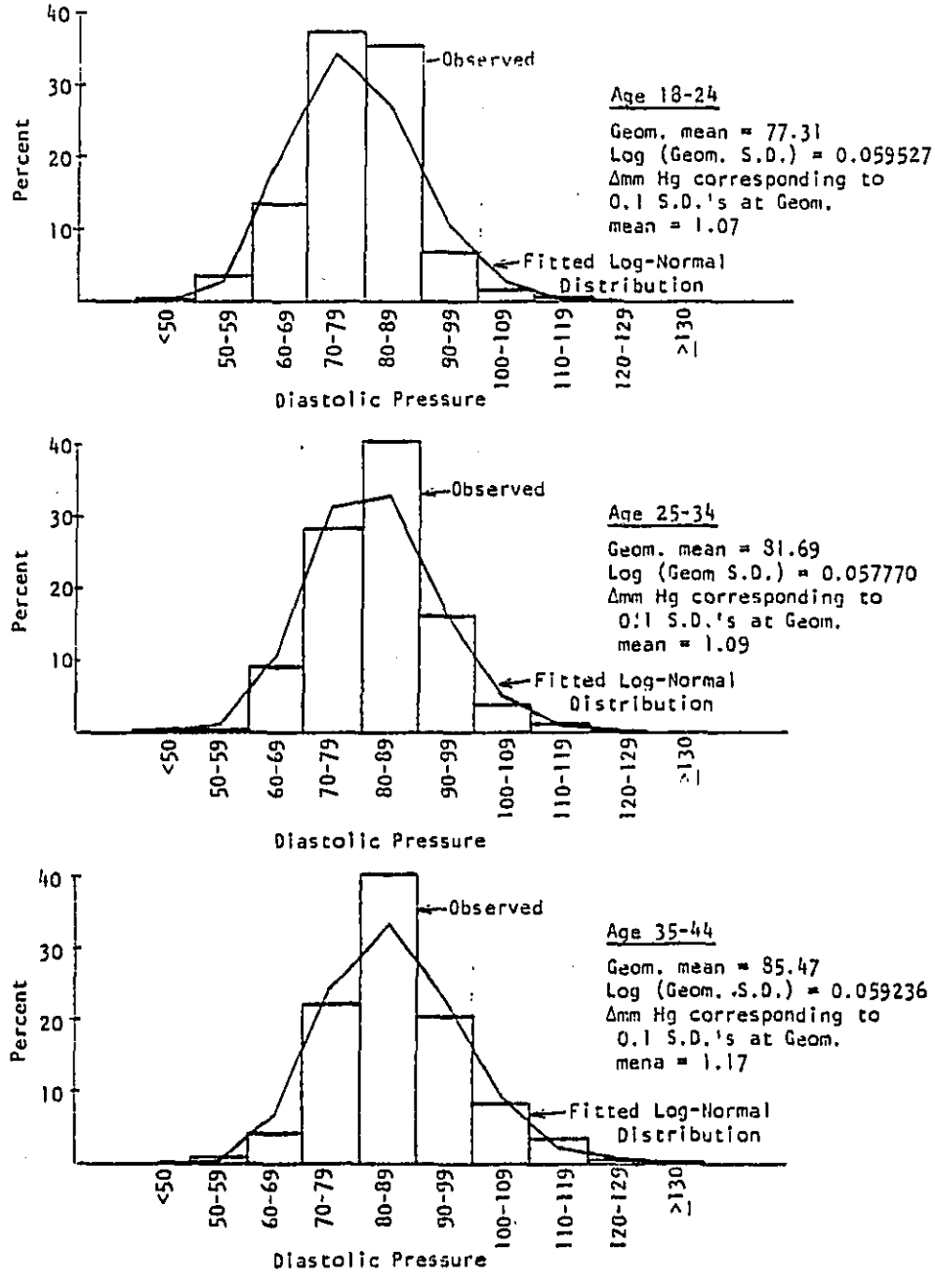
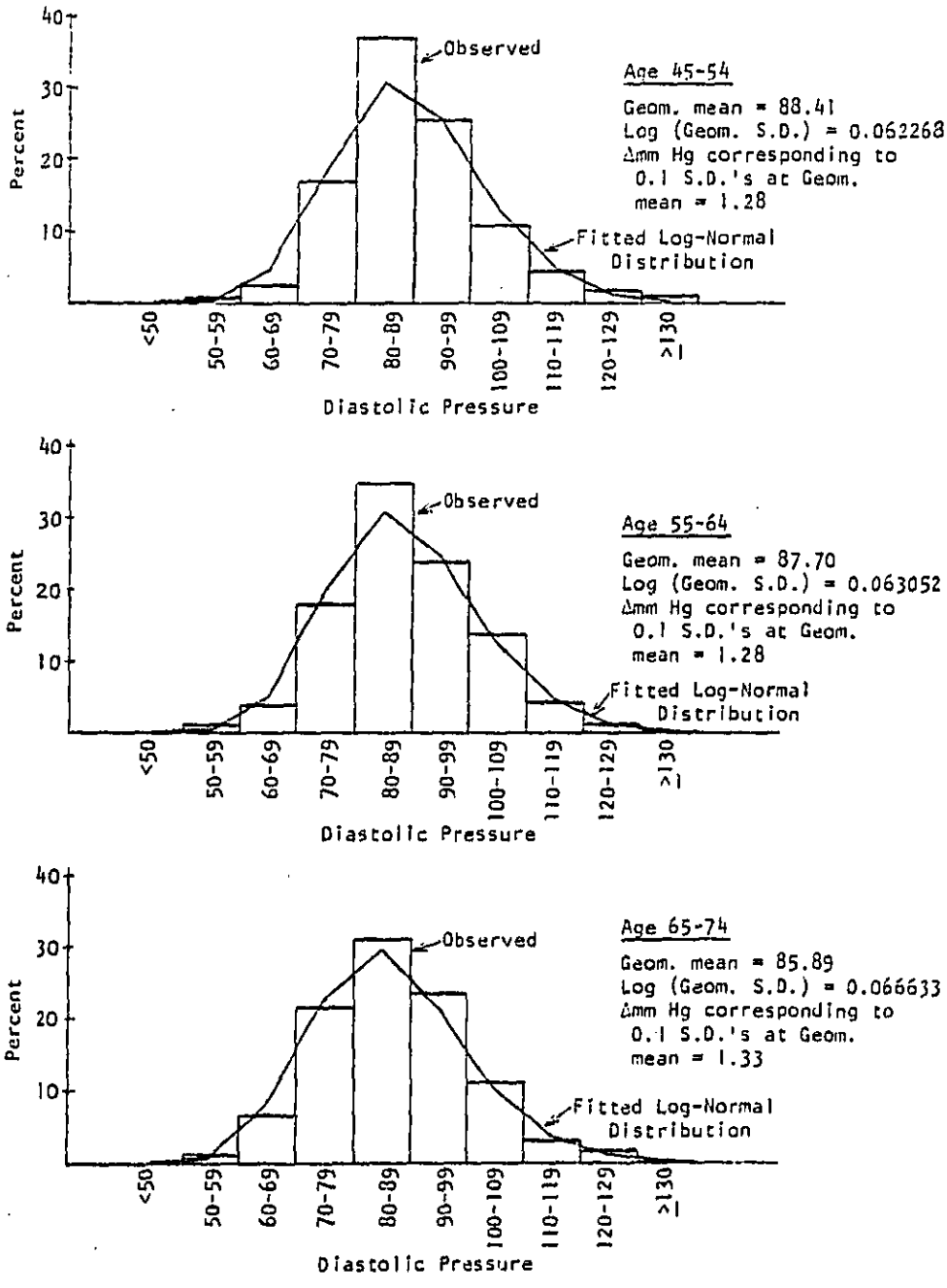


FIGURE 4.7 (cont.)

DIASTOLIC PRESSURES OF U.S. MEN
HANES Observed Data[240] vs.
Predictions of Log-Normal Distributions



unimodal log-normal distributions.*

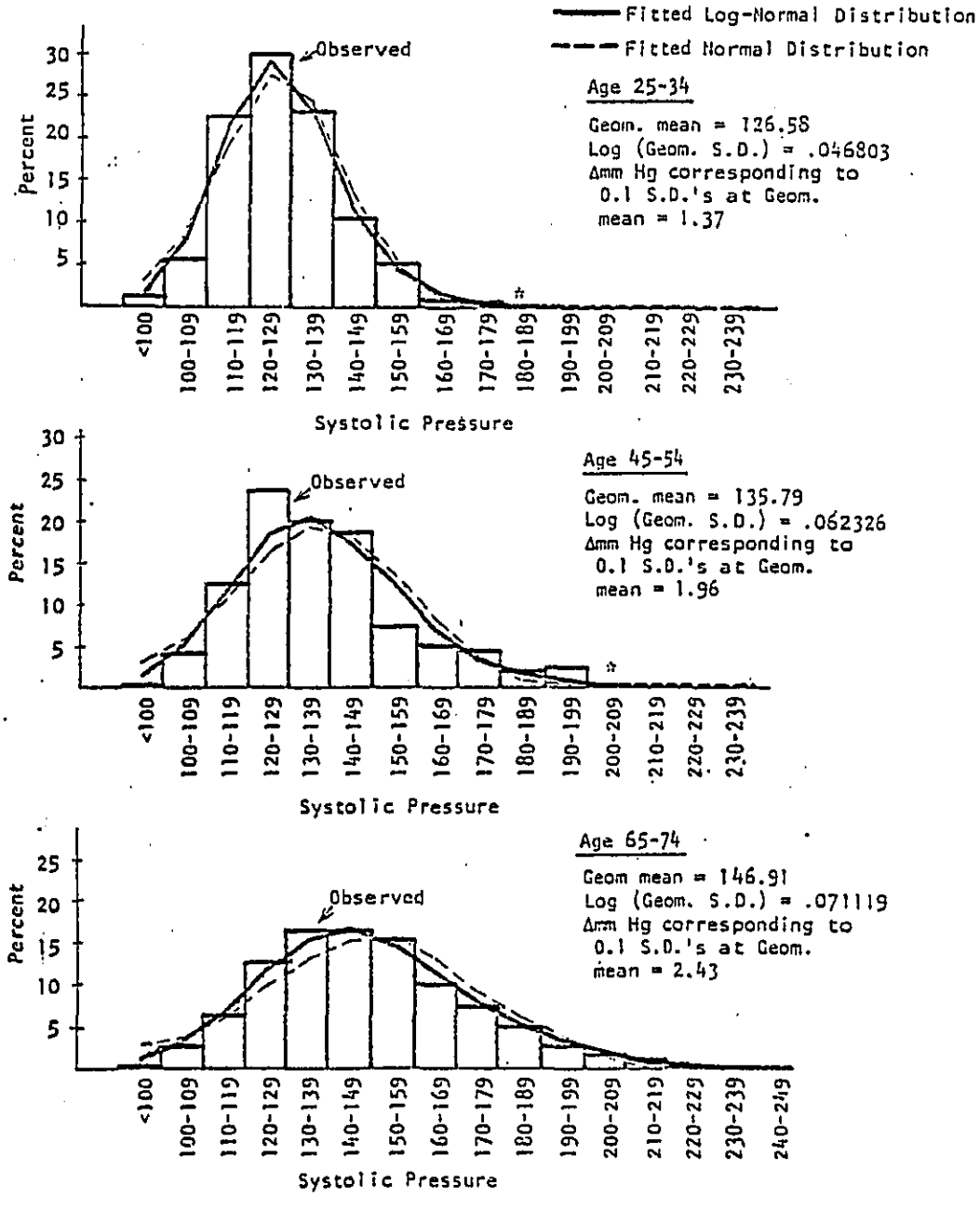
Comparisons of fitted normal distributions vs. fitted log-normal distributions for systolic blood pressure from the HANES study are shown in Figure 4.8 for males of three age groups. Log-normal distributions consistantly show somewhat closer fits to the observed data, both for systolic and diastolic blood pressures (the latter, not shown).

There is no obvious reason, from these data, to make qualitative distinctions between people over 160 mmHg systolic and or 90 mmHg diastolic (frequently used criteria for "hypertension," if maintained consistently) and people who fall below these values. Moreover, if one examines the rates of increase of individual people's blood pressures in long term longitudinal studies (see Figure 4.9) one finds that there is a broad, continuous distribution in the population. There is no suggestion in the data that a discrete "abnormal" subset of the population should be qualitatively distinguished from the remainder.

If one closely examines the geometric means and standard deviations for the various age groups shown in Figures 4.6 and 4.7, one can see that the pattern of change in blood pressure distributions with age appears to be different for systolic and diastolic blood pressures. Systolic blood pressures appear to increase more rapidly in later decades than in earlier decades, and the systolic pressure distributions show a marked spread (increase in standard deviation) with age. By contrast, diastolic blood pressures increase relatively rapidly in early decades until reaching an apparent maximum in the 45-54 age group. There is a relatively modest tendency for the distribution of diastolic pressures to spread with age. As can be seen in Figures 4.10 through 4.13 differential patterns of change between systolic and diastolic blood pressure can be observed in both males and females and at all percentiles in the blood pressure population

*Recently, Makuch, et.al.[238] have provided a theoretical explanation of why distributions of blood pressure among people of a given narrow age range should be log-normal, given basic assumptions that (1) blood pressure increases accumulate over time in many small steps (or "risk cycles" in their terminology) and (2) the blood pressure increase which results from each step is proportional to the aggregate blood pressure increase produced in previous steps.

SYSTOLIC BLOOD PRESSURES OF U.S. MEN
HANES Observed Data[240] vs.
Predictions of Log-Normal and Normal Distributions



*Last boxes include all higher pressures.

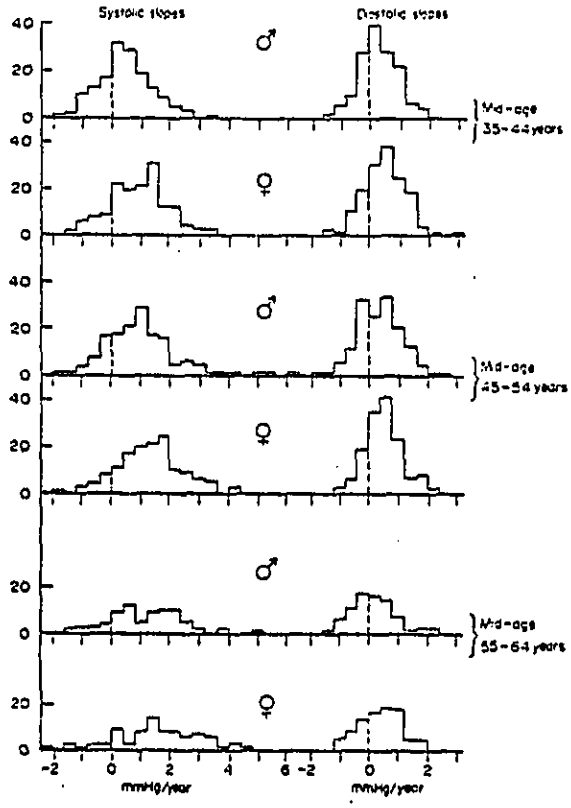


FIGURE 4.9 Distributions of rate of increase of systolic and diastolic pressures (mm Hg/year) for individuals followed 15½-17½ years; Rhondda Fach and Vale of Glamorgan

SOURCE: Reference 241

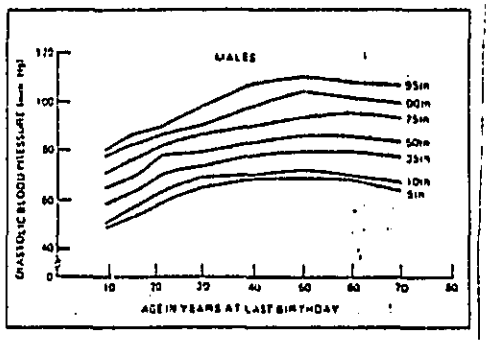


FIGURE 4.10 Selected percentiles in the distribution of diastolic blood pressure of males 6-74 years, by age: U.S., 1971-1974.

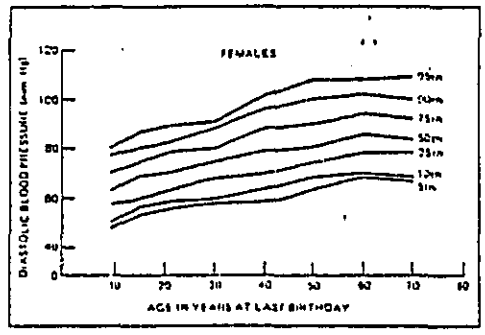


FIGURE 4.11 Selected percentiles in the distribution of diastolic blood pressure of females 6-74 years, by age: U.S., 1971-1974.

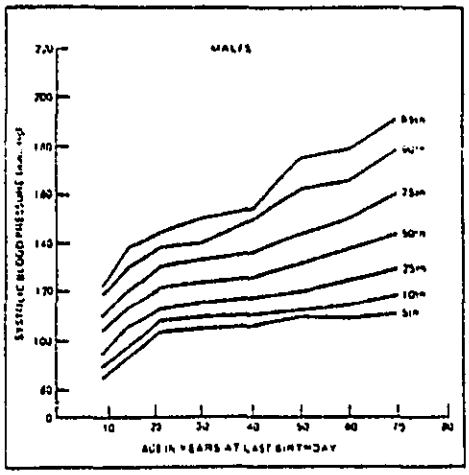


FIGURE 4.12 Selected percentiles in the distribution of systolic blood pressure of males 6-74 years, by age: U.S., 1971-1974.

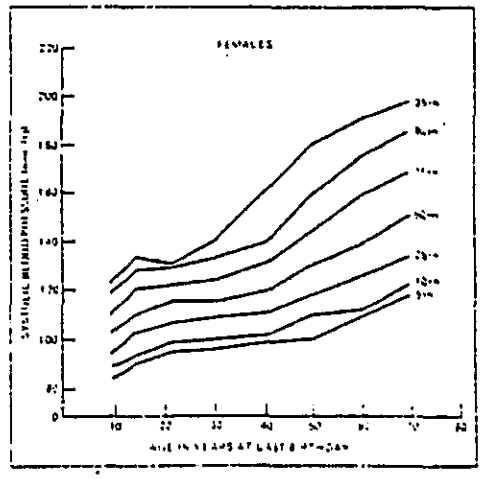


FIGURE 4.13 Selected percentiles in the distribution of systolic blood pressure of females 6-74 years, by age: U.S., 1971-1974.

SOURCE: Reference 240.

distribution. The fact that such differences can be seen in portions of the population which remain far below clinical criteria for treatment as hypertensives suggests that these differences are not likely to have been produced by differential effects of medical treatment. The general pattern of early adult increase in diastolic blood pressure and late adult increase in systolic blood pressure has also been observed in a longitudinal study of a Canadian population.[241] The reason for this differential pattern is not entirely clear. However, among the various blood-pressure raising mechanisms listed in Table 4.2 the loss of distensibility of the aorta and large arteries is hypothesized to produce a differential increase of systolic pressure. The timing of the increase is reminiscent of the information on the timing of the major increase in atherosclerotic changes in the thoracic aorta, quoted on p. 80 above. It is intriguing to speculate that pulse pressure (systolic pressure less diastolic pressure) is likely to be a usable indicator of atherosclerotic changes in this particular portion of the vasculature.

Figures 4.14 and 4.15 illustrate another way of presenting data on population distributions of blood pressure.* This mode of presentation is particularly helpful for comparisons between the blood pressure distributions of different populations. Each point on an individual line represents a statement that the percentage of the population indicated on the y-axis has blood pressures greater than or equal to the pressure indicated on the x-axis. The divisions of the x-axis represent the $\log_{10}$ of blood pressure. Given this, the y-axis is constructed such that a perfectly log-normal distribution of blood pressures in a population will yield a straight line. The slope of the line is related to the standard deviation of the distribution--a steeper slope indicates a smaller standard deviation and a narrower, sharper population distribution curve if plotted in the form of Figures 4.6-4.8. For rapid interpretation of differences between the distributions found in different population, the following rules should be kept in mind:

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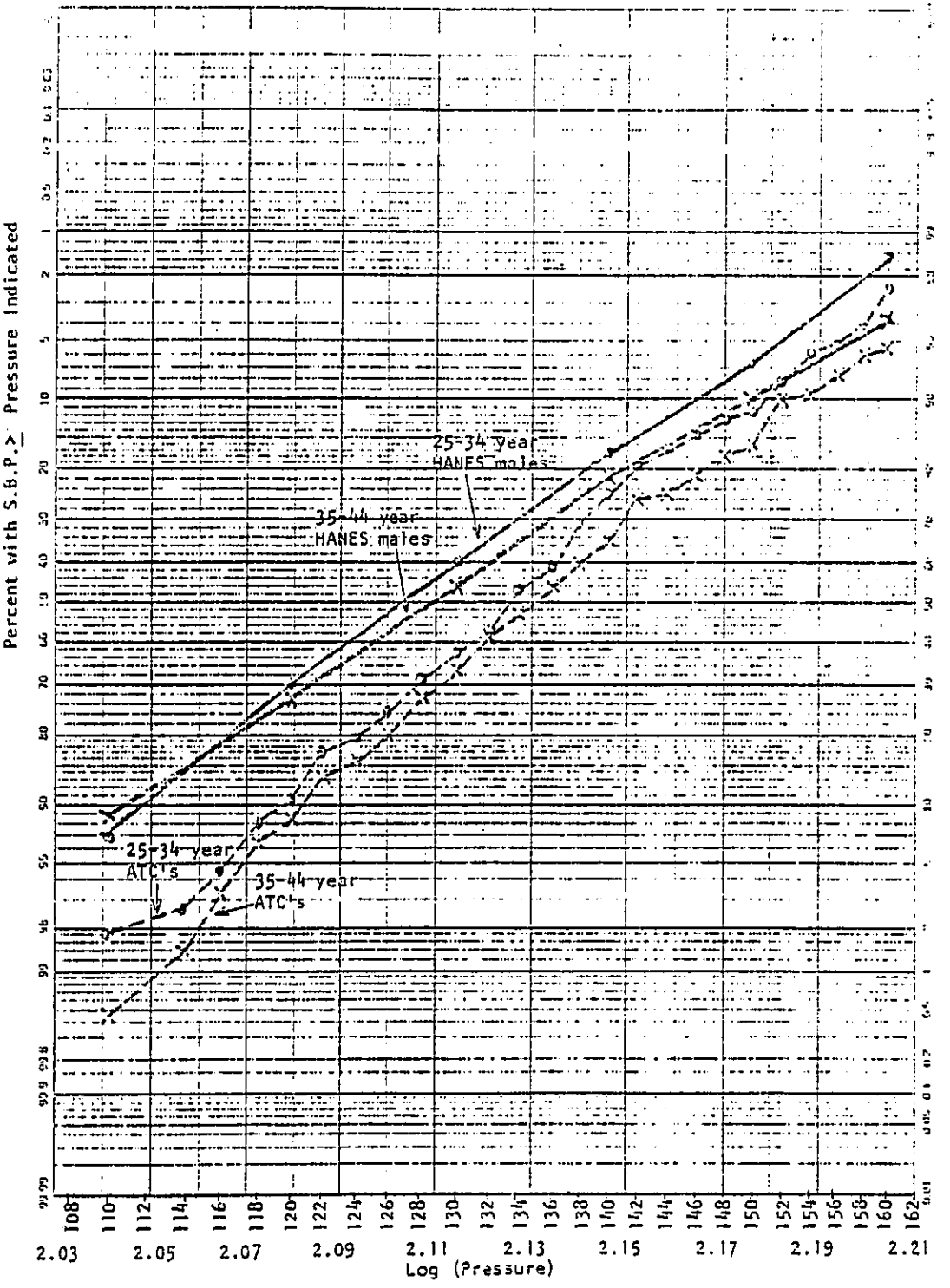
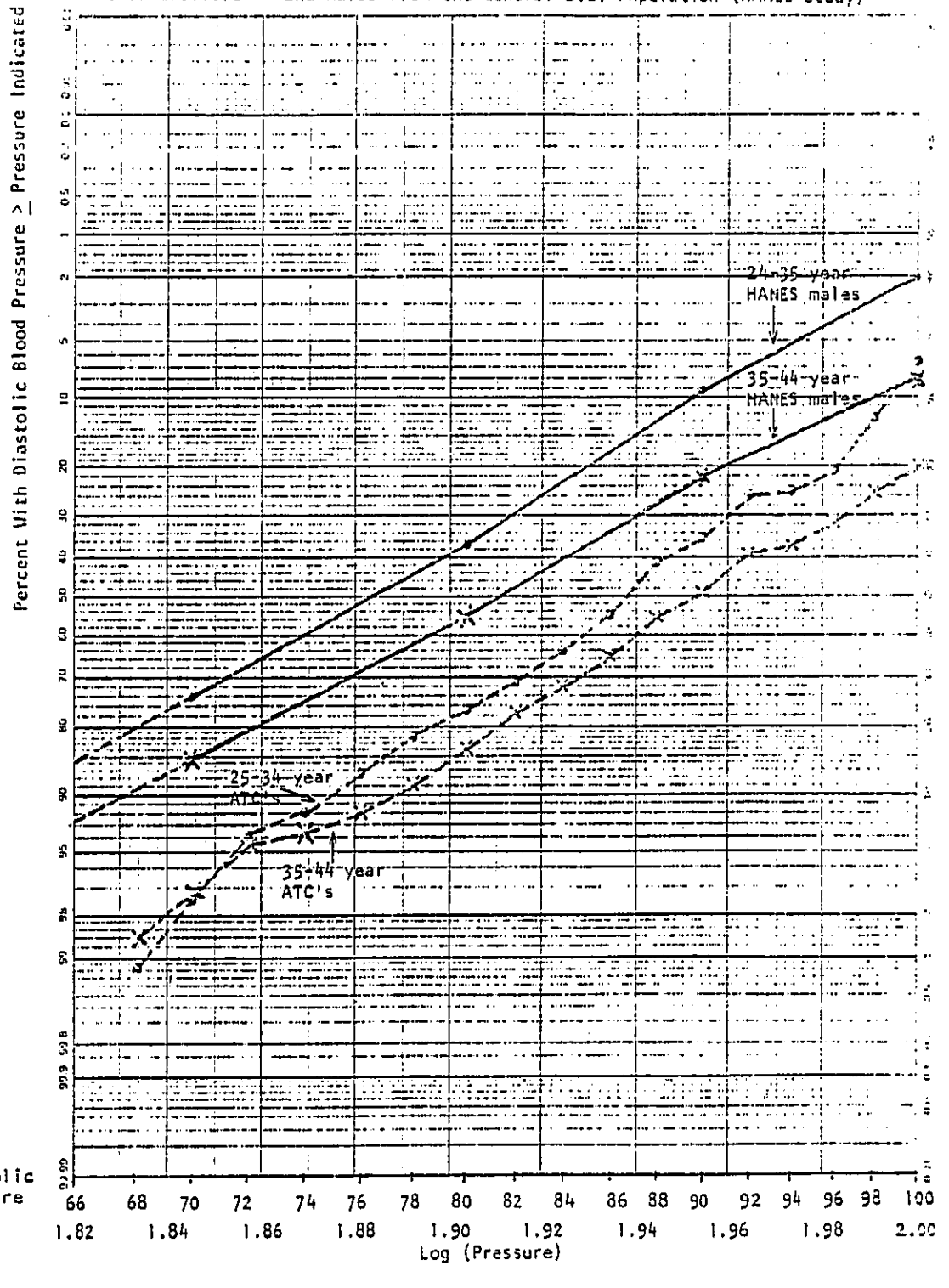
*Data shown in Figures 4.14 and 4.15 on the blood pressures of air traffic controllers at an initial examination in a multi-year longitudinal study by Rose et.al. [149] were generously supplied by M.W. Hurst and L. Anderson of the Department of Psychosomatic Medicine of the Boston University School of Medicine. They are based on observations of 113 controllers in the 25-34 year age group and 221 controllers in the 35-44 year age group.

FIGURE 4.14
SYSTOLIC PRESSURE DISTRIBUTIONS
Air Traffic Controllers[149] and Males from the General U.S. Population (HANES Study)[240]



ystolic
ressure

FIGURE 4.15
DIASTOLIC PRESSURE DISTRIBUTIONS
Air Traffic Controllers[149] and Males from the General U.S. Population (HANES Study)[250]



1) An environmental agent which raises blood pressure by an equal percentage for all members of an exposed population should produce a line parallel to the general population curve but shifted to the right by the amount of the increase.

2) An environmental agent which raises blood pressure in only a subset of the exposed population will shift the line for the exposed population to the right in ways which depend on the distribution of blood pressures of the subset in the absence of exposure to the agent. If, in the absence of exposure to the agent, the sensitive subset tends to have either (a) about equal blood pressures or (b) higher blood pressures than the rest of the population, the right (high pressure) part of the line will tend to be moved to the right more than the left (low pressure) part. If, however, the agent tends to raise blood pressures more among people with low pressures than those with high pressures, the left (low pressure) side of the line will show more of a shift relative to the line for the general population.

3) The mmHg shift for a specific percentile of the population can be found by (a) locating the desired percentile on the y-axis, (b) reading the pressures of the general and exposed groups on the x-axis at the points where the horizontal line for the percentile of interest crosses the population distribution lines of the two populations. (Thus, in Figure 4.14 at the 80th percentile, the 25-34 year HANES population shows a systolic pressure of slightly over 116 mmHG, while the 25-34 year Air Traffic Controllers show a systolic pressure of 124 mmHg.)

It is clear from the data presented in Figures 4.14 and 4.15 that at all percentiles of the population distributions, the air traffic controller population appears to have higher systolic and diastolic pressures than would be expected from the general population data in the HANES survey. The absolute magnitudes of the differences at specific percentiles are shown in Table 4.4. For systolic pressures, the differences appear to be somewhat more pronounced at the low-pressure end of the population distribution, whereas for diastolic pressures the differences appear more or less uniform at 8-11 mmHg for all percentiles of the

populations. These results have the following important implications:

(1) Whatever processes cause the differences in blood pressure between air traffic controllers and the general population, they do not appear likely to be confined to a small minority of the controllers or to controllers which would have had higher-than-average blood pressures in the absence of exposure.

(2) Because ordinary medical treatment for hypertension will only be used for controllers whose blood pressures persistently exceed levels considered indicative of "hypertension," the excess heart disease and stroke risk for the remainder of the population which does not exceed these levels is effectively beyond the realm of secondary medical prevention efforts. Primary prevention efforts, seeking to reduce the action of whatever factors are leading to chronic blood pressure elevation in the controller population, has potential benefits beyond those which are realizeable with the best currently utilized medical care practices for treating "hypertension."

4.2.3 Observations of Blood Pressure in Relation to Chronic Noise Exposure

Like nearly all other aspects of the etiology of hypertension, the possible role of chronic noise exposures in contributing to long term increases in blood pressure is controversial.[241-3] The currently available data can be briefly summarized under three broad headings; animal studies, comparisons of hypertension frequency between human groups with differing noise exposure, and comparisons of hypertension frequency between human groups with differing degrees of hearing impairment.

Animal Studies

More than three decades have now passed since the original observations of Medoff and Bonglovanni[244] that rats chronically exposed to loud air blasts for five to ten minutes per day* developed hypertension more frequently than

*Accompanied, in the case of this original study, by convulsions known as "audiogenic seizures."

Table 4.4

Differences Between Blood Pressures of the General U.S. Population[240] and a Sample of Air Traffic Controllers* at Various Percentiles of Population Distribution

Percentile of blood pressure distribution	25 - 34 Year Ages			35 - 44 Year Ages		
	ATC's*	HANES study Males	Difference (mm Hg)	ATC's*	HANES study Males	Difference (mm. Hg)
SYSTOLIC PRESSURES						
90th	119**	112**	8**	121	111	10
80th	124	116	8	126	117	9
70th	128	120	8	129	121	8
60th	131	123	8	132	125	7
50th	134	127	8	135	129	7
40th	137	130	7	139	132	6
30th	138	134	4	141	136	6
20th	142	138	4	147	141	5
10th	151	146	5	154	150	4
DIASTOLIC PRESSURES						
90th	75	64	11	77	68	10
80th	79	68	11	81	72	9
70th	83	71	12	84	76	9
60th	85	74	11	87	79	8
50th	87	77	10	92	82	10
40th	89	79	10	95	84	11
30th	91	82	9	96	87	9
20th	96	85	11	100	91	9
10th	99	90	10	103	98	5

*Data for 113 air traffic controllers in the 25-34 year age group and 221 controllers in the 35-44 year age group generously supplied by M.W. Hurst and L. Anderson of the Department of Psychosomatic Medicine of the Boston University School of Medicine. (Report of Contract DOT-FA 73-WA-3211, U.S. Department of Transportation, Federal Aviation Administration, 1978; and Rose, R.M., Jenkins, C.D., and Hurst, M.W., "Health Changes in Air Traffic Controllers: A Prospective Study. I. Background and Description," Psychosom. Med., 40: 143-165, 1978.)

**Data presented are rounded to the nearest mmHg. Differences in the final column shown may not correspond exactly to differences between the first two columns because of this.

controls. Subsequently, many investigators have succeeded in producing similar chronic blood pressure elevations in response to irregular loud noises (e.g., see Figure 4.16), either alone, or in combination with other stimuli.[174,244-251] Four important hints relevant to future studies of possible mechanisms seem to have emerged from this work:

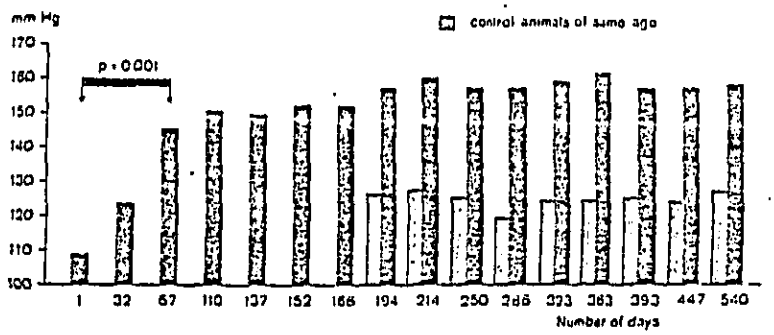
1) Animal strains appear to differ markedly in their susceptibility to the blood-pressure increasing effects of periodic noise exposure[174]-- thus a significant genetic component in responsiveness seems indicated.

2) Chemical sympathectomy with 6-Hydroxydopamine appears to prevent the effect, suggesting that the sympathetic nervous system plays some critical role in the process.[248]

3) Water excretion after saline loading appears to be markedly reduced in rats with audiogenic hypertension (see Figure 4.17)[174] suggesting that alterations in kidney function may also play a role in the process.

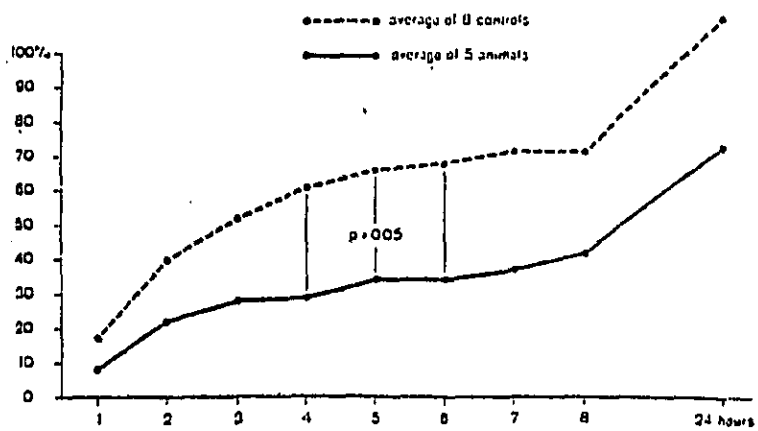
4) Ising et.al.[241] have observed a marked increase in the collagen content in the myocardium of the left ventricle of rats exposed to random noise bursts during their active hours for 28 weeks. If this kind of increase in collagen content were to occur in other parts of the circulatory system, many of the processes listed in Table 4.2 could be enhanced.

Recently there have been two additional significant developments for future research in this area. First, the basic phenomenon of markedly increased blood pressure has been reproduced by Peterson in a primate system, using a 24 hour pattern and intensity of noise stimulation designed to closely mimic the exposures of a worker with a noisy job.[251] Second, Borg and Moller[252] have failed to observe any alteration in the pattern of chronic increase in blood pressure in response to a loud noise stimulus in the strain of rats which, one would suppose, might be most susceptible to such effects; the Okamoto strain of spontaneously hypertensive rats (see Table 4.2, p.94) with known short term



Development of audiogenic hypertension during long-term acoustic stimulation. All pressure values are average results from 20 rats 10 ♂ & 10 ♀.

Figure 4.16
Source: Rothlin, E., ref. 174



Renal function of audiogenic hypertensive rats. Per cent water excretion during 24 h after loading the animals with 30 cc/kg 0.9 % NaCl-solution by stomach tube.

Figure 4.17
Source: Rothlin, E., ref. 174

hyperresponsiveness to brief noise stimuli. One can, of course, speculate that rats of this strain experience so much sympathetic stimulation from their experiences under control (quiet) conditions that their hypertension is not markedly worsened by the additional noise stimulus.* However, although the Okamoto strain did not experience an exacerbation of their tendency to develop hypertension, Borg and Moller did observe that they suffered markedly worse hearing impairment in response to noise than their genetically normotensive counterparts.[253] This result casts a new light on recent studies (discussed below) of blood pressures in worker groups with different degrees of hearing impairment.

Human Studies

Particularly in the Eastern European literature, there have been many reports of cross-sectional studies of the frequency of hypertension in worker groups with differing noise exposures[255-269] or differing degrees of hearing impairment taken to indicate previous noise exposure.[270-277] Welch has recently reviewed these in detail and submitted them, where possible, to statistical testing.[254] He finds, in brief, "A remarkably uniform tendency from one study to the next for an elevation of blood pressure and an increase in the prevalence of hypertension with long-term employment under industrial noise." Welch is critical of the use of hearing impairment as a proxy for noise exposure, contending that the segment of an exposed population which responds to noise with increased blood pressure may be different from the segment which responds with severe hearing impairment. In view of the recent findings of Borg and Moller cited above,[253] there may well be reason for concern on this point.

We shall not provide here an exhaustive review of the individual merits and demerits of the various studies making up this literature. It is not the purpose of this report to attempt to resolve the issue of whether chronic noise exposure does or does not contribute to hypertension. Suffice it to say that there are a number of sets of observations (such as those reproduced in Tables 4.5-4.7) which though individually not performed with sufficiently

*By six months of age, two to three months after the beginning of the experiment, both exposed and non-exposed animals had systolic blood pressures over 200 mmHg.

Age Groups	No. of Persons Examined	Normotensive		Borderline		Hypertensive	
		No.	%	No.	%	No.	%
15	51	51	100	0	0	0	0
20-29	129	125	97.0	3	2.9	0	0
30-39	85	81	44.2	4	4.6	1	1.2
40-49	82	70	85.6	6	12.9	4	4.9
50-59	59	56	94.5	4	6.8	[illegible]	[illegible]
Total	410	383	93.0	17	4.6	10	2.4

Table 4.5: Distribution of the Control Group by Age and Blood Pressure Level

Age Groups	No. of Workers Examined	Normotensive		Borderline		Hypertensive	
		No.	%	No.	%	No.	%
-19	146	146	100	0	0	0	0
20-29	202	196	97.0	4	2.0	2	1.0
30-39	193	151	78.1	26	13.6	14	7.3
40-49	149	97	65.1	34	22.8	18	12.1
50-59	133	59	44.3	33	25.6	38	27.1
Total	821	649	79.1	102	12.4	70	8.5

Table 4.6: Distribution of 821 Weavers by Age and Blood Pressure Level

Hypertension Criteria:

"Normotensive"--systolic<140 and diastolic <90

"Borderline"--140/ ≤90 or < 140/90

"Hypertensive"--systolic <140 or diastolic< 90

Source: Parvizpoor, ref. 255

Table 1. Number of participants according to age and sex in areas with less (L) and much (M) aircraft noise

aircraft noise	total 35–64 yrs	men 35–44	men 45–54	men 55–64	women 35–44	women 45–54	women 55–64
B = 20–40	L 3595	633	523	307	810	654	468
B = 40–60	M 2233	440	381	215	454	452	291

Table 2. Percentage of participants with cardiovascular troubles in areas with less (L) and much (M) aircraft noise

cardiovascular troubles[a]	total 35–64 yrs	men 35–44	men 45–54	men 55–64	women 35–44	women 45–54	women 55–64	significance
angina pectoris	L 2.8 % M 3.0	1.0 % 1.1	1.7 % 3.7	3.9 % 3.7	1.7 % 1.8	4.3 % 3.1	6.0 % 6.5	N.S.
medical treatment for heart trouble	L 1.8 M 2.5	1.2 1.8	2.9 2.9	5.9 5.6	0.6 2.0	0.5 1.1	2.6 3.4	$p < 0.05$
medical treatment for hypertension	L 7.3 M 10.7	1.9 3.2	5.4 5.5	8.1 13.5	5.6 8.4	11.3 16.4	16.2 22.0	$P < 0.001$
taking cardiovascular drugs	L 5.5 M 7.5	1.4 1.8	4.8 4.5	9.8 7.9	2.0 4.2	6.9 12.4	14.7 17.5	$p < 0.01$
pathological heart shape	L 1.6 M 2.5	0.4 1.4	1.0 1.0	2.5 3.3	0.0 0.9	2.0 2.7	6.2 7.5	$p < 0.05$
pathological E.C.G.	L 4.4 M 5.1	1.8 2.0	3.8 2.9	8.5 9.3	2.3 3.3	4.4 5.5	10.5 11.7	N.S.
high blood pressure	L 3.9 M 6.7	1.3 3.2	3.1 3.9	6.5 11.2	1.9 2.0	4.6 10.0	10.0 14.4	$p < 0.001$

[a] for definitions see text

Table 4.7

"High Blood Pressure" Criterion:

Systolic >175 mmHg and/or Diastolic >100 mmHg

Source: Knipschild, ref. 256

unambiguous methodology to be entirely persuasive,* collectively provide a reasonable qualitative basis for the suspicion that under some circumstances chronic noise exposure may contribute to some chronic processes which increase blood pressure. Rather in this section, we shall attempt to bring together the results of diverse observations in the literature to answer two types of questions:

1) If it exists, how important is the blood pressure raising effect of noise likely to be in the context of overall cardiovascular disease (and therefore what priority is warranted for scarce research resources)? Based on the available observations with all their imperfections, how large have the indicated increases in blood pressure tended to be--and as a consequence about how much of an increase in overall cardiovascular disease morbidity should one expect?**

2) In what circumstances of age, sex, magnitude of noise exposure, etc., have the most pronounced effects been observed, and therefore where might they be easiest to detect in clean replicate studies?

The major difficulties which must be faced in attempting to create any kind of overview of the disparate findings of various researchers in the area are:

1) In no case have the data been reported in sufficient detail to plot the population distributions of noise-exposed and control groups as was done for air traffic controllers in Figures 4.14 and 4.15. Under the influence of the standard medical diagnostic

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* The available reports vary greatly in quality and frequently are not reported in enough detail to allow a thorough critique. Potentially confounding factors other than age and sex have often not been discussed and explicitly controlled. At a minimum it would be helpful in future studies for investigators to control for the known effects on blood pressure of relative weight, ambient temperature, and time of day when blood pressures are recorded. Systematic analysis of possible effects of workplace exposures other than noise would, of course, also be desirable.

** The computation of expected excess cardiovascular morbidity will be performed in Section 5 of this report.

view, investigators have overwhelmingly chosen to present their data in the form of the percentage of the exposed and control groups which satisfy medical criteria for defining "hypertensives" and/or "borderline hypertensives." Occasionally mean blood pressures of exposed and control populations are also reported.

2) The specific criteria used by different investigators for defining "hypertension" vary widely, in some cases are not reported at all, and in some cases were not even standardized (i.e., they were based in the latter cases on the diagnoses of individual physicians using their own criteria).

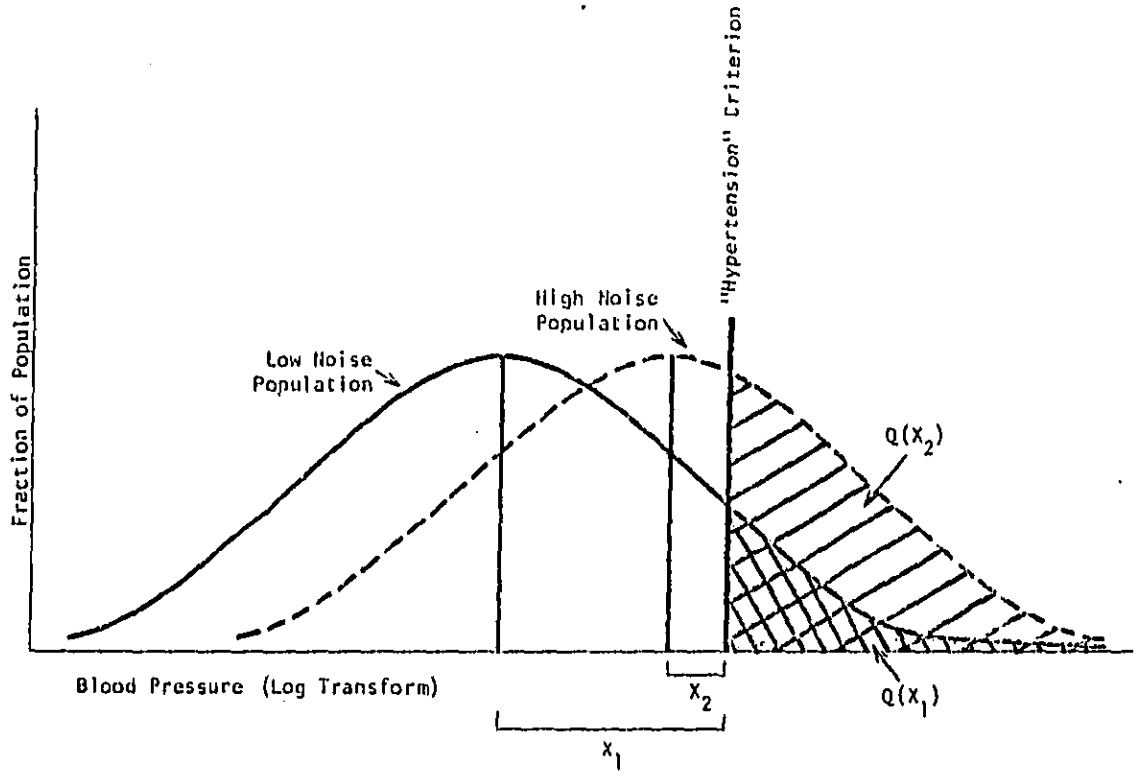
Given these difficulties, any attempt to synthesize a common picture from the data must necessarily be tentative and somewhat speculative. However, if we are careful to test the sensitivity of any results to alternative ways of viewing the information, some preliminary synthesis can be made.

Our basic approach is illustrated in Figure 4.18. In reporting the percentage of people who have blood pressures which exceed a given cutoff for classification as "hypertensives" the different investigators are basically providing us with the areas under the population distribution curves beyond the cutoff--$Q(X_1)$ for the low noise population and $Q(X_2)$ for the high noise population. In order to extract from this information something which is comparable with other experiments, we must devise a summary measure for the change in population distribution curves which would be expected to be the same regardless of the particular "hypertension" criterion chosen by the individual investigator. As shown in Figure 4.18, if one assumes that the effect of noise has been to simply shift the entire population distribution curve to higher pressures (to the right), such a measure is " ΔX"--the difference between "X_1", the number of standard deviation units which separate the normal population mean and the hypertension criterion and X_2, the analogous parameter for the exposed population. " ΔX" represents a prediction of how much the means of the exposed and control populations differ, assuming that the exposure does not change the standard deviation of the population distribution.

Of course, there is excellent reason to suspect that the simple model

Figure 4.18

SCHEMA FOR SUMMARIZING THE RESULTS OF DIVERSE HYPERTENSION EXPERIMENTS



$\Delta X = X_1 - X_2$ (in standard deviation units)

$Q(X_1)$ = Percent of low noise population which exceeds hypertension criterion

$Q(X_2)$ = Percent of high noise population which exceeds hypertension criterion

of change in the population distribution outlined above might be wrong. For example, it is quite possible that the blood-pressure increasing effect of noise might only act on a fraction of the exposed population, thus changing the standard deviation of the population distribution as well as the mean.* In view of this possibility, we shall present parallel results based on a second model of noise-induced blood pressure change (called by us "Model B"). For Model B, ΔX shifts are computed assuming that only 30% of the exposed population experiences a noise-induced increase in blood pressure. Values for the size of the susceptible sub-population much less than 30% would have required exclusion of an appreciable fraction of the data from the analysis, and even the 30% figure appears to be too low based on some of the data. For example, in the Parvizpoor data reproduced in Figures 4.5-6, if we add up all of those people who exceed the "borderline" criterion for 40-49 and 50-59 year age groups we obtain:

Age Range	Control Group % of Population ≥"Borderline"	Exposed Group % of Population ≥"Borderline"	Apparent Minimum** % of Population Shifted
40-49	19.4%	34.9%	15.5%
50-59	15.5%	55.7%	40.2%

Limitations in the sample sizes for these age groups clearly give rise to considerable statistical uncertainty in the calculated percentage of the

*Welch[254] is particularly insistant on this point, based in part on observations in a few of the cited papers that the incidence of very low blood pressures (hypotension) is larger than expected in noise exposed groups, especially in younger age ranges. He postulates that the response to chronic noise exposure in a population may be bimodal, with some people moving to lower blood pressures in early years of exposure. Such a bimodal pattern does not appear to have precedent either in animal models, available data on age-related changes in blood pressure of general Western populations (e.g., Figures 4.6-4.9), or current hypertension theory.

**"Exposed" - "Control." This is an apparent minimum estimate of the size of the sensitive subpopulation (neglecting statistical uncertainty) because some of the sensitive subpopulation would be expected to be above the "borderline" criterion in the absence of exposures, or to remain below the "borderline" criterion even in the presence of exposure.

population which has been moved across the line designating "borderline" hypertensives. However, based on these and other results it is difficult to believe that the size of the sensitive population is much less than about 25-30%.

Basic observations from selected individual reports and calculated "ΔX shifts" using the basic "A" model of change illustrated in Figure 4.18 are presented in Appendix A. Appendix A contains data from the eleven reports which meet the following criteria:

- -a noise-exposed population is compared with an allegedly comparable sample of people with no known unusual noise exposure* (e.g., excluding reports of comparisons which only involve different durations of noise exposure)
- -noise-exposure is assessed directly, and not inferred using a hearing loss criterion for selection
- -some finite (non-zero) proportion of "hypertensives" is found in the control group

In Appendix A, the central section of each page gives the hypertension criteria used by the author, age and sex groups, and the percentages of hypertensives (or average blood pressures) observed in the various study groups. The right-hand section of each page gives the ΔX shifts computed by comparing specific exposed populations to designated comparison groups.** To illustrate the relationships between different hypertension cutoffs and individual observed percentages of hypertensives (Q(X)), at a specific value for ΔX, Table 4.8 shows the ratio of "hypertensives" in exposed and comparison populations which would correspond to a ΔX of .3 standard deviation units, when the hypertension criterion is

---

*Or, where measurements are available, no exposure over 85 dBA.

**Individual "X" values for the ΔX shifts where computed using an iterative approximation procedure.

Table 4.8

X, Q(X) AND RISK RATIOS

X (STANDARD DEVIATIONS ABOVE MEAN)	Q(X) % OF POPULATION EXCEEDING X STANDARD DEVIATIONS ABOVE MEAN	RISK RATIO CORRESPONDING TO A SHIFT IN X OF .3 STANDARD DEVIATION UNITS $\frac{[Q(X)]}{[Q(X-.3)]}$
-1.0	84.134	
-0.9	81.594	
-0.8	78.814	
-0.7	75.804	
-0.6	72.575	72.575/61.791 = 1.174
-0.5	69.146	
-0.4	65.542	
-0.3	61.791	61.791/50 = 1.235
-0.2	57.926	
-0.1	53.983	
0	50	50/38.209 = 1.309
.1	46.017	
.2	42.074	
.3	38.209	38.209/27.425 = 1.393
.4	34.458	
.5	30.854	
.6	27.425	27.425/18.406 = 1.490
.7	24.196	
.8	21.186	
.9	18.406	18.406/11.507 = 1.600
1.0	15.866	
1.1	13.567	
1.2	11.507	11.507/6.681 = 1.722
1.3	9.680	
1.4	8.076	
1.5	6.681	6.681/3.593 = 1.859
1.6	5.480	
1.7	4.457	
1.8	3.593	3.593/1.786 = 2.012
1.9	2.872	
2.0	2.275	
2.1	1.786	1.786/.820 = 2.178
2.2	1.390	
2.3	1.072	
2.4	.820	
2.5	.621	

placed at various positions.

Tables 4.9-4.14 which follow present the ΔX shifts observed in the various studies, arrayed by a number of variables which might be expected to influence the magnitude of the blood pressure difference found--age, sex, baseline percentage hypertensives in the ("quiet") comparison group, rough noise exposure level, and the absolute severity of the hypertension criterion. In each case, parallel tables are presented using both the "A" model of change illustrated in Figure 4.18 (Tables 4.9A, 4.10A, etc.) and the "B" model of change in which all blood pressure increase is attributed to a sensitive subpopulation which constitutes 30% of the total population (Tables 4.9B, 4.10B, etc.).

The basic observations are presented by age group in Table 4.9A and 4.9B. Comparing the ΔX shifts in the two tables it may be noted that the values computed under the "B" model are much larger than corresponding values computed under the "A" model. This is because the distance which the mean of a 30% sensitive subpopulation must move to account for a given increase in the percentage of hypertensives is much larger than the movement needed if the entire population can change positions.

In order to isolate the possible effects of age as much as possible from confounding differences between the various studies, Table 4.10 shows a series of comparisons (based on the data from Table 4.9) of the ΔX shifts observed within individual studies between groups of various ages. Beyond the youngest (20-29 yr.) age group, the data do not seem to indicate a consistent trend toward more pronounced shifts in older age groups. If anything, from these data one might expect to be able to detect noise-induced blood pressure increases most readily among people in their thirties. The fact that, as we saw earlier, the pattern of blood pressure increase in the population seems to change from primarily diastolic increase to primarily systolic increase between younger and older adults may be relevant here, but as in all of the comparisons to be presented, the ΔX shift data are not sufficiently convincing to warrant any very strong statements about epidemiological design. Nonetheless, it can be said that there does not appear to be good reason to confine future studies to very old age groups.

Table 4.9A

"ΔX" SHIFTS IN POPULATIONS OBSERVED IN RESPONSE TO NOISE

(ALL FIGURES IN STANDARD DEVIATION UNITS)

ARRANGED BY AGE GROUP

MODEL A (FIG. 4.18)

STUDY	COMPARISON	AGE GROUP				
		20-29		30-39	40-49	50-59
Andriukin[257]	a) Weighted avg. of factories 2-4 (103-120 dB) compared with "little noise"	.37		.33	.37	.06
	b) Factory 1 (93 dB) compared with "little noise"	-.14		0	.09	-.14
Andrukovitch[258]	87-102 dB female winding and weaving workers, compared with general population	20-24	25-29	30-39	40-49	
		.32	.25	.17	.0-	
Friedlander[259]	Shipyard workers with 70- >85 dB intermittent noise, compared with <70 dB workers		25-34	35-44	45-54	
	Criterion: systolic pressure ≥ 140		-.04	.69	.48	
	Criterion: diastolic pressure ≥ 90		.30	.54	.35	
Gheller[260]	Combined group of high noise (115-125 dB) petroleum workers	Under 40			Over 40	
	a) compared with "quiet" manual laborers	.16			.17	
	b) compared with combined group of "quiet" manual laborers and administrators	.06			.08	
Jirkova[263]	85-115 dB workers, compared with 70 dB workers					
	men, < 10 years employment					
	men, > 10 years employment					
	women					

Table 4.9A, Cont.

STUDY	COMPARISON				
Parvizpoor[255]	96 dBA cotton weaving mill workers, compared with light industry workers without appreciable noice	20-29	30-39	40-49	50-59
	Criterion: ≥140/90	.03	.76	.48	1.16
	Criterion: ≥160/95	ND**	.80	.34	.75
Shatalov and Morov[261]	Weighted average of 95-112 dB groups (with and without) "mental tension") compared with weighted average of "quiet" groups (with and without "mental tension")				
	Men	.10	.53	.24	.26
	Women	ND	.48	.26	.17
Shatalov, Ostapkovitch et al[264]	90-120 workers, compared with workers in quiet jobs, based on change in average	Under 40		Over 40	
	systolic pressures	.61		.71	
	Diastozic pressures	.48		.23	
Sanova[265]	Workers exposed to 87-98 dB compressor noise, compared with workers in quiet jobs, based on change in average systolic pressures	-.09	.59	.35	
Knipschild[256]	Community aircraft noise exposures (more noise; B=40-60, NNI >37 vs. less noise, B=20-40, NNI <37)		35-44	45-54	55-64
	Men		.37	.10	.30
	Women		.02	.40	.22

**ND = not done, numbers too small (< 1% hypertensives)

Table 4.98

"ΔX" SHIFTS IN POPULATIONS OBSERVED IN RESPONSE TO NOISE

(ALL FIGURES IN STANDARD DEVIATION UNITS)

ARRANGED BY AGE GROUP

MODEL B (30% SENSITIVE SUBGROUP)

STUDY	COMPARISON	AGE GROUP				
		20-29		30-39	40-49	50-59
Andriukin[257]	a)Weighted avg. of factories 2-4 (103-120 dB) compared with "little noise"	.79		.76	.94	.20
	b)Factory 1 (93 dB) compared with "little noise"	ND		0	.28	-.55
Andrukovitch[258]	87-102 dB female winding and weaving workers, compared with general population	20-24	25-29	30-39	40-49	
		.71	.58	.67	.25	
Friedlander[259]	Shipyard workers with 70->85 dB intermittent noise, compared with <70 dB workers					
			25-34	35-44	45-54	
	Criterion: systolic pressure > 140		-.14	1.96	1.58	
	Criterion: diastolic pressure ≥ 90		.81	1.59	1.02	
Gheller[260]	Combined group of high noise (115-125 dB) petroleum workers		Under 40		Over 40	
	a) compared with "quiet" manual laborers		.43		.47	
	b) compared with combined group "quiet" manual laborers and administrators		.18		.25	
Jirkova	85-115 dB workers, compared with 70 dB workers					
	men, < 10 years employment		.38		.67	
	men, > 10 years employment		.96		.93	
	women		.69		1.06	

Table 4.98, Cont.

STUDY					
Parvizpoor[255]	96 dBA cotton weaving mill workers, compared with light industry workers without appreciable noise	20-29	30-39	40-49	50-59
	Criterion: ≥140/90	.09	1.73	1.42	.72
	Criterion: ≥160/95	ND**	1.47	.84	1.90
Shatalov and Morov[261]	Weighted average of 95-112 db groups (with and without "mental tension") compared with weighted average of "quiet" groups (with and without "mental tension")				
	Men	.29	1.13	.64	.73
	Women	ND	.93	.68	.50
Shatalov, Ostapkovitch et al[264]	90-120 workers, compared with workers in quiet jobs, based on change in average	Under 40		Over 40	
	systolic pressures	1.89		2.13	
	Diastozic pressures	1.43		.75	
Sanova[265]	Workers exposed to 87-98 dB compressor noise, compared with workers in quiet jobs, based on change in average systolic pressures	-.28	1.81	1.10	
Knipschild[256]	Community aircraft noise exposures (more noise; B=40-60, NNI >37 vs. less noise, B=20-40, NNN <37)		35-44	45-54	55-64
	Men		.80	.29	.75
	Women		.07	.93	.60

**ND = not done, numbers too small (<1% hypertensives)

Table 4.10A

WITHIN - STUDY COMPARISONS OF ΔX SHIFTS FOR DIFFERENT AGE GROUPS

	AGE GROUP COMPARISON MODEL A (FIG. 4.18).							
STUDY #	20-29 vs 30-39		30-39 vs 40-49		40-49 vs 50-59		AGE UNDER 40 vs.	AGE OVER 40
257*	.37	.33	.33	.37	.37	.06	.35	.22
258	.29	.17	.17	.08			.23	.08
259							-.04 .30	.48 .35
260**							.16	.17
263							.14 .40 .30	.27 .41 .40
255	.03	.76	.76 .80	.48 .34	.48 .34	1.16 .75	.41 .80	.82 .55
261	.10	.53	.53 .48	.24 .26	.24 .26	.26 .17	.32 .48	.26 .22
264							.61 .48	.71 .23
265	-.09	.58	.58	.35			.25	.35
AVERAGE SHIFT (S.D UNITS)	.14	.47	.52	.30	.34	.48	.35	.37
SIGN OF DIFFERENCES (OLDER VS YOUNGER)								

* Based only on weighted average of factories 2-4, compared with "little noise."

** Based on comparison with "quiet" manual laborers.

Table 4.10B

WITHIN - STUDY COMPARISONS OF ΔX SHIFTS FOR DIFFERENT AGE GROUPS

AGE GROUP COMPARISON
MODEL B (30% SENSITIVE SUBGROUP)

STUDY #	20-29 vs 30-39		30-39 vs 40-49		40-49 vs 50-59		AGE UNDER 40 vs.	AGE OVER 40
257*	.79	.76	.76	.94	.94	.20	.78	.57
258	.65	.47	.47	.25			.56	.25
259							-.14	1.58
							.81	1.02
260**							.43	.47
263							.38	.67
							.96	.93
							.69	1.06
255	.09	1.73	1.73	1.42	1.42	>2	.91	1.71
			1.47	.84	.84	1.90	1.47	1.37
261	.29	1.13	1.13	.64	.64	.73	.71	.69
			.98	.68	.68	.50	.98	.59
264							1.89	2.13
							1.48	.75
265	-.28	1.81	1.81	1.10				
AVERAGE SHIFT (S.D UNITS)	.31	1.81	1.19	.84	.90	>1.07	.85	.99

* Based only on weighted average of factories 2-4, compared with "little noise.
** Based on comparison with combined group of manual laborers and administrators.

A similar conclusion seems warranted with regard to sex (Table 4.11). The available data do not suggest systematic differences in susceptibility between males and females.

If the effect of noise were to be confined to a minority of the exposed population, there should be a tendency for observed ΔX shifts to be smaller when hypertension criteria are drawn closer to the population mean--i.e., when the "baseline" percentage of hypertensives in the comparison group is relatively large. Data on the ΔX shifts observed in the various studies are arrayed by the percentage of hypertension found in the baseline comparison group in Table 4.12 and plotted in Figure 4.19. With the number of uncontrolled potentially confounding factors present in this gross between-study comparison, it is perhaps not surprising that no clear tencency emerges. Table 4.13, using within-study comparisons of average shifts observed for comparison groups in three broad ranges of "baseline % hypertensives" does appear to show some trend toward smaller ΔX shifts when the comparison groups have more hypertensives, but the magnitude of the effect is so small and the variability of the data so large that little confidence can be placed in this result.

Perhaps the most significant results emerge from Table 14A and 14B, where the data are summarized to the degree possible by noise exposure level. Studies which reported midrange exposure levels over 100dB tended to have somewhat more pronounced blood pressure shifts than those in the lower ranges, but it is clear that appreciable shifts have been observed in more common occupational and community noise exposure situations. The average shifts observed using the "A" model of change for the 85-100dB midrange exposure group correspond to increases of about the following magnitude at the geometric means, based on the population distribution data given in Figures 4.6-7 (pp. 104-6 above):

	Under 40	Over 40
Systolic and/or Diastolic	3 mm Hg 2.5 mm Hg	6 mm Hg 4 mm Hg

Table 4.11A

WITHIN-STUDY COMPARISONS OF ΔX SHIFTS OBSERVED IN MALE VS. FEMALE GROUPS OF COMPARABLE AGES

Model A (Fig. 4.18)

Study	Male vs. Female	
263	.27	.30
	.34	.40
261	.53	.48
	.24	.26
	.26	.17
256	.37	.02
	.10	.40
	.30	.22
Average Shift (S.D. Units)	.30	.28

Table 4.11B

WITHIN-STUDY COMPARISONS OF ΔX SHIFTS OBSERVED IN MALE VS. FEMALE GROUPS OF COMPARABLE AGES

Model B (30% Sensitive Subpopulation)

Study	Male vs. Female	
263	.67	.69
	.80	1.06
261	1.13	.98
	.64	.68
	.73	.50
256	.80	.07
	.29	.93
	.75	.60
Average Shift (S.D. Units)	.73	.69

Table 4.12A

ΔX SHIFTS IN POPULATIONS OBSERVED IN RESPONSE TO NOISE, ARRANGED BY BASELINE % HYPERTENSIVES IN COMPARISON GROUP
MODEL A (FIG. 4.18)

Study	Comparisons	Baseline "% Hypertensives" in Comparison Group: 1 - 4.9%	5 - 15%	>15%
257	Only those baseline % based on weighted average of factories 2-4, compared with "little noise"	1.47% .37	3.10% .33	8.8% .37	19.2% .06
258		1.5% .32	1.6% .25	6.5% .17	23% .08
259	Criterion: systolic >140	13% .69	17% -.04	26% .43
	Criterion: diastolic >90	16% .30	17% .54	19% .35
260		5.5% .16	7.5% .17
263		2% .30	4% .27,.41	7% .14,.40	12% .40
255		1.2% .80	2.8% .03	5.8% .7[illegible]	6.5% .34	8.6% .75	15.5% 1.16	19.4% .4[illegible]
261	Comparison of total group of 95-115dB workers with total quiet group	1.2% .10	1.6% .53	1.7% .48	6.5% .24	9.5% .26	11.0% .26	18.5% .17
256		1.3% .37	1.9% .22	3.1% .10	4.6% [illegible]	6.5% .3[illegible]	10.0% [illegible]

TABLE 4.12B

AX SHIFTS IN POPULATIONS OBSERVED IN RESPONSE TO NOISE, ARRANGED BY BASELINE % HYPERTENSIVES IN COMPARISON GROUP

MODEL B (30% SENSITIVE SUBPOPULATION)

Study	Comparisons	Baseline "% Hypertensives" in Comparison Group: 1 - 4.9%	5 - 15%	>15%
257	Only those baseline % based on weighted average of factories 2-4, compared with "little noise"	1.47% .79 / 3.10% .76	8.8% .94	19.2% .20
258		1.5% .71 / 1.6% .58	6.5% .47	23% .25
259	Criterion: systolic >140		13% 1.96 / 17% -.14	26% 1.53
	Criterion: diastolic >90		16% .81 / 17% 1.59 / 19% 1.02	
260		6.7% .43 / 8.8% .47		
263		2% .69 / 4% .67 / .93 / 7% .38 / .96 / 12% 1.06		
255		1.2% 1.47 / 2.8% .09	5.8% 1.73 / 6.5% .84 / 8.6% 1.90	15.5% >2 / 19.4% 1.42
	Comparison of total group of 95-115dB workers with total quiet group	1.2% .29 / 1.6% 1.13 / 1.7% .98	6.5% .64 / 9.5% .68	11.0% .73 / 18.5% .50
256		1.3% .80 / 1.9% .07 / 3.1% .29	4.6% .93 / 6.5% .75	10.0% .60

FIGURE 4.19

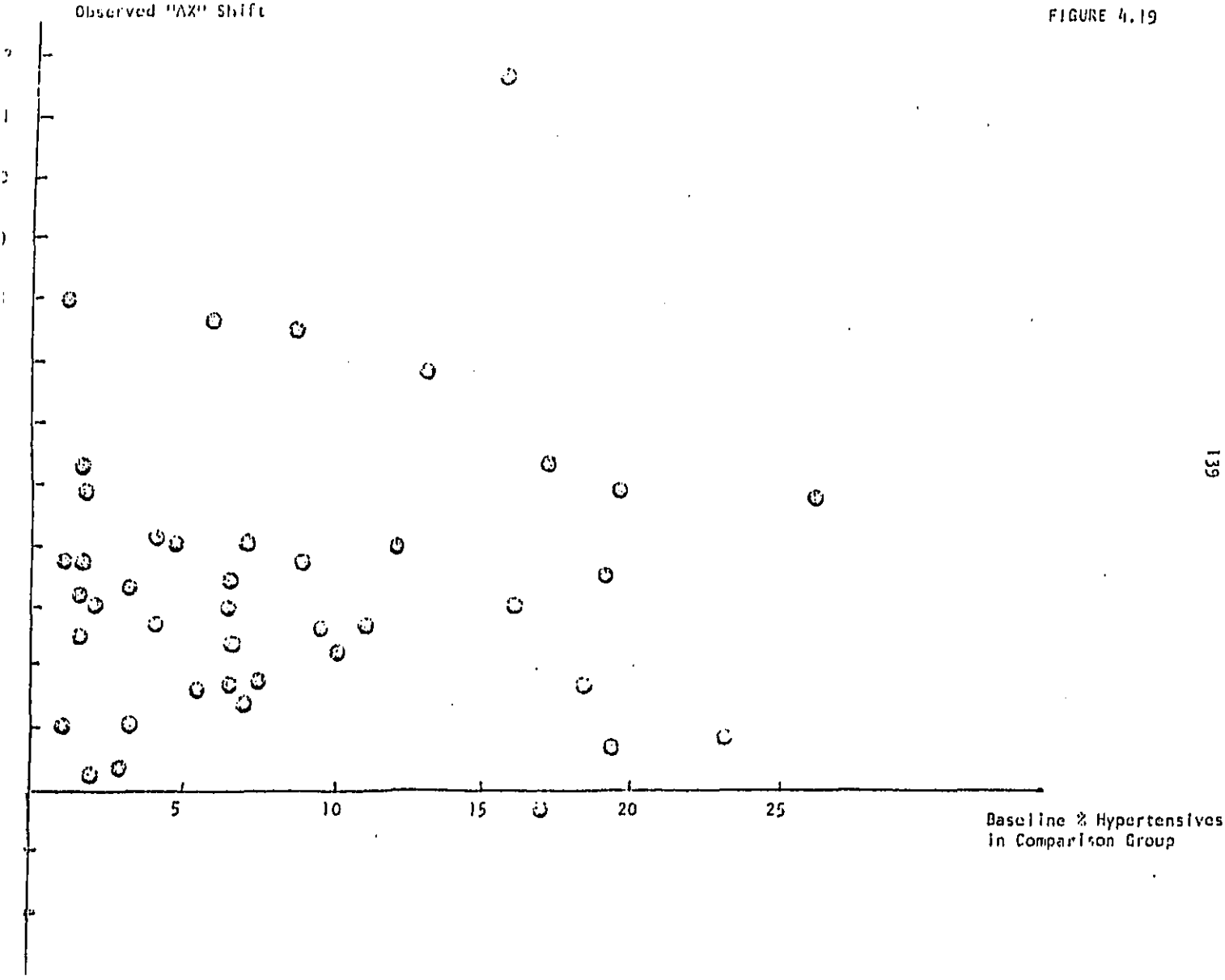

Observed "AX" Shift
5
10
15
20
25
Baseline % Hypertensives
in Comparison Group

Table 4.13A

WITHIN-STUDY COMPARISONS OF ΔX SHIFTS, BY RANGE OF BASELINE
% HYPERTENSIVES IN COMPARISON GROUP
MODEL A (FIG. 4.18)

Study	Baseline "% Hypertensives" 1-4.9% vs. 5-15%		5-15% vs >15%		1-4.9% vs. >15%	
257	.35	.37	.37	.06	.35	.06
258	.29	.17	.17	.08	.29	.08
259 (systolic only)			.69	.22		
263	.33	.31				
255	.42	.49	.49	.82	.42	.82
261	.37	.25	.25	.17	.37	.17
256	.22	.26				
Average	.33	.31	.39	.27.	.36	.23

Table 4.13B

WITHIN-STUDY COMPARISONS OF ΔX SHIFTS, BY RANGE OF BASELINE
% HYPERTENSIVES IN COMPARISON GROUP
MODEL B (30% SENSITIVE SUBPOPULATION)

Study	Baseline "% Hypertensives" 1-4.9% vs. 5-15%		5-15% vs >15%		1-4.9% vs. >15%	
257	.78	.94	.94	.20	.78	.20
258	.65	.47	.47	.25	.65	.25
259 (systolic only)			1.96	.72		
263	.76	.80				
255	.78	1.49	1.49	>1.71	.78	>1.71
261	.80	.68	.68	.50	.80	.50
256	.52	.68				
Average	.72	.84	1.11	>.89	.75	>.67

Table 4.14A

BETWEEN-STUDY COMPARISONS OF AS SHIFTS OF DIFFERENT NOISE LEVELS (COMPARED TO "QUIET" POPULATIONS)

MODEL A (Fig. 4.13)

Study	Comparison and Age Groups	Midrange Exposures <85 dB	Midrange Exposures 85 - 104dB	Midrange Exposures Over 104dB
257	20-29		-.14	.51
	30-39		0	.33
	40-49		.03	.25
	50-59		-.14	.20
	All comparisons with "little noise" group			
258	20-24		.32	
	25-29		.25	
	30-39		.17	
	40-49		.08	
259****	25-34	.13		
	35-44	.57		
	45-54	.42		
260	Comparison with "quiet" manual laborers only (excluding administrators)			
	under 40			.16
	over 40			.17
262				.81
263	Under 40 yrs			
	men <10 yrs empl.		.14*	
	men >10 yrs empl.		.40*	
	women		.10*	
	Over 40 yrs			
	men <10 yrs empl.		.27*	
	men >10 yrs empl.		.41*	
	women		.40*	
255	Average of 20-29 results with 30-39 2140/90 and 40-49 2160/95 50-59 criteria		.03	
			.28	
			.41	
			.96	
251	Men 20-29			.42
	30-39			.83
	40-49			.53
	50-59			.51
	Women 30-39			.48
	40-49			.26
	50-59			.17
264****	Under 40			.55
	Over 40			.47
265	20-29		-.09	
	30-39		.58	
	40-49		.42	
256	Men:			
	35-44	.37		
	45-54	.15		
	55-64	.30		
	Women:			
	35-44	.02		
	45-54	.40		
	55-64	.22		
Grand Averages		.26	.27	.42
Average for groups <40 yrs of age		.13**** (one group)	.23	.47**
Average for groups >40 yrs of age		.25****	.31	.33**

*Midrange exposures = 100dB ("85-115dB")

**One study without breakdown into age groups excluded from under 40 vs. over 40 comparison

***35-44 age groups excluded from computation of "under 40" and "over 40" averages

****Averages of indicated systolic and diastolic shifts

Table 4.148

BETWEEN-STUDY COMPARISONS OF AN SHIFTS BY DIFFERENT NOISE LEVELS (COMPARED TO "QUIET" POPULATIONS)

Study	Comparison and Age Group	Midrange Exposures 70+dB	Midrange Exposures 85 - 100dB	Midrange Exposures Over 110dB
257	20-29			.79
	30-39		0	.76
	40-49		.28	.94
	50-59		-.55	.30
	All comparisons with "little noise" group			
258	20-24		.71	
	25-29		.58	
	30-39		.47	
	40-49		.25	
259	25-34	.34		
	35-44	1.78		
	45-54	1.30		
	(Average of indicated shifts by systolic and diastolic pressure criteria)			
260	Comparison with "quiet" manual laborers only (excluding administrators)			
	under 40			.41
	over 40			.47
262				>2.1
263	Under 40 yrs		.38*	
	men <10 yrs empl.		.96*	
	men >10 yrs empl.		.69*	
	women			
	Over 40 yrs		.67*	
	men <10 yrs empl.		.93*	
	men >10 yrs empl.		1.06*	
	women			
265	Average of 20-29		.09	
	results with 30-39		1.60	
	>140/90 and 40-49		1.13	
	>160/95 50-59		>1.95	
	criteria			
261	Men 20-29			.29
	30-39			1.13
	40-49			.64
	50-59			.73
	Women 30-39			.98
	40-49			.63
	50-59			.50
264	Under 40			1.69
	Over 40			1.44
266	20-29		-.25	
	30-39		1.51	
	40-49		1.10	
256	Men:			
	35-44	.80		
	45-54	.29		
	55-64	.75		
	Women:			
	35-44	.07		
	45-54	.93		
	55-64	.70		
Grand Averages		.76	>.69	>.86
Average for groups <40 yrs of age		(.34)** (one group)	.65	.82**
Average for groups >40 yrs of age		.77***	>.76	.81**

*Midrange exposures = 100+A ("55-110dB")

**One study without breakdown into age groups excluded from under 40 vs. over 40 comparison

***35-44 age groups excluded from computations of "women >30" and "over 40" averages

If, instead, the "Ψ" model of blood pressure change by noise is adopted, the shifts at the geometric mean for the sensitive 30% subgroup of the population would correspond roughly to:

	Under 40	Over 40
Systolic and/or Diastolic	9 mm Hg / 7 mm Hg	16 mm Hg / 10 mm Hg

The derivation of these numbers has clearly included a substantial amount of speculative model-building and extrapolation. They should be regarded as highly preliminary expectations, albeit based on the best data currently available in the literature. The indicated sizes of the blood pressure shifts is not large, although as we shall see in section 5 below, such shifts are by no means negligible in terms of their potential for enhancing cardiovascular disease morbidity. It seems prudent, however, to design future epidemiological studies with sufficient sample sizes and controls that effects of this magnitude will be unambiguously measurable.

4.2.4 Promising Avenues for Future Research

It is almost trite by this time to say that "hypertension" appears to be a diverse collection of diseases, each of which may very well have a multifactoral etiology. Given this as the likely nature of the problem, the watchword of research planning should probably be "diversity." Planners in this area will probably be well advised to resist the natural tendency inherent in the planning process to attempt to sketch a direct linear scenario toward all-or-nothing tests of one or more favored simple hypotheses. Those interested in the possibility that specific environmental agents may contribute to hypertension will probably find it useful to leverage their efforts by collaborating with basic scientific investigators engaged in developing the new typologies for hypertension and exploring physiological variables thought to be related to blood pressure increases. Conversely, the basic scientists

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#Under 40 estimates based on geometric means and standard deviations of HANES[240] study for the 25-34 yr. age group. Over 40 estimates are similarly based on means and standard deviations for the 45-54 yr. age group.

may well find that studies relevant to specific environmental agents may provide a handle for refining typologies and distinguishing which physiological factors really are responsible for long-term increases in blood pressure. A population exposed to a putative blood-pressure raising agent presents opportunities for testing basic scientific hypotheses relevant to hypertension etiology, as well as the central hypothesis that the agent in question does indeed affect blood pressure.

The various types of research projects suggested below have been selected with a view both to the need to get better information on the possible blood-pressure raising effect of noise exposure with reasonably modest expenditure of effort (generally, by adding a noise-exposure measurement or blood-pressure measurement and analysis component to activities ongoing for other reasons), and to the needs to produce information of fundamental scientific interest and investigate the possible roles of other environmental agents in raising blood pressure. Three types of human epidemiological approaches, and two types of experimental animal studies seem to us to have the best promise:

A. Human epidemiological studies

1. Large-scale cross-sectional surveys of blood pressure in relation to workplace and community noise, other workplace exposures, and other factors.

Two invaluable opportunities to assess relationships between blood pressure and workplace noise while controlling for other relevant variables will present themselves early in the 1980's.* First, the planned repetition of the HANES survey of blood pressures in relation to other factors by the National Center for Health Statistics will take place in the context of new enabling legislation** which has given the agency major responsibility for assessing environmental health effects. Addition of an industrial hygienist to the HANES examination team to (1) take a good workplace exposure history from examinees, and (2) where possible, measure selected current and/or past workplace exposures

*The Health Services Research, Health Statistics, and Health Care Technology Act of 1978, PL 95-623.

**Such studies should specifically seek to assess dose-effect relationships between blood pressure and noise type and level, exposure duration, age, sex, and other relevant parameters.

for the examinees could provide relevant and comparable data spanning thousands of people at relatively little incremental cost. Based on people's addresses in relation to airports, etc., possible contributions from community noise exposures could also be assessed. Second, the repetition of the National Institute for Occupational Safety and Health's "National Occupational Hazard Survey" is due to be performed in the early 1990's. This comprehensive survey of workplace exposures would simply need to be supplemented with a blood-pressure sampling program and questionnaire for assessing weight, height, etc., in order to have an excellent chance of both defining the blood pressure increasing effects of noise and systematically uncovering any other workplace agents which may tend to produce hypertension.

2. Cross-sectional correlative studies with physiological variables.

Cross-sectional studies where blood pressure is measured in relation to putative hypertension-producing environmental agents are only the beginning of a process to really define what it is that the agents are doing, and uncover more general rules for predicting and preventing this kind of adverse health effect. Based on samples of people with various pressures exposed to particular environmental agents and non-exposed matched controls, the kinds of correlative studies of putative blood-pressure increasing physiological variables outlined in Figure 4.5 and Table 4.3 (pp. 97-9 above) should be undertaken.

B. Case-control studies, based on emerging hypertension "types"

Many groups of investigators are now regularly categorizing hypertensives under their care into various "types." In general it will be too demanding to incorporate these typing procedures into large scale cross-sectional studies. However, people interested in the role of specific environmental agents in raising blood pressure may well wish to provide an adjunct facility for assisting investigators engaged in such "typing" to ascertain whether patients of different types (and controls) show different frequencies/intensities of exposure to noise and other putative blood-pressure increasing influences.

A finding of an excess of a particular exposure in a particular hypertension "type" would (1) provide clues to the mechanism by which the agent increases pressure, (2) possibly increase the sensitivity of epidemiological studies by lowering the "signal to noise ratio" (see discussion in Section 4.2.1 above), and (3) provide evidence that the typology of hypertension used was successfully separating patients by etiology.

C. Retrospective cohort studies

1. A population with well-defined past noise exposures can be followed up for past and current cardiovascular mortality and morbidity (such as the Baughn/General Motors population which was used to assess hearing impairment in relation to noise exposure, or other populations with good noise exposure and blood pressure measurements in their industrial medical programs--Reynolds may be a company currently under study in this way).

2. A sample of a population with good blood pressure/cardiovascular disease monitoring, such as the Framingham population, can have its past and current noise and other environmental exposures assessed.

D. Animal experiments

The ideal roles of animal experiments in an overall strategy for understanding hypertension etiology are:

(1) to provide insights into mechanisms of hypertension, using experimental methods which, due to their invasive or destructive nature cannot be used in humans, and

(2) to provide system-dynamic models of blood pressure regulation which generate insights into relationships between specific variables to be explored in humans.

In particular, the recent primate work on noise and hypertension may provide useful insights into mechanism if some of the variables listed in Table 4.3 are incorporated into the experimental design. Second, the recent finding of increased collagen deposition by Ising should be replicated and pursued in other anatomical locations.

5. CLINICAL MANIFESTATIONS OF CARDIOVASCULAR DISEASE: PROPOSED MECHANISMS, EPIDEMIOLOGICAL OBSERVATIONS, AND STATISTICAL MODELS

The chronic pathological processes described in the previous section generally go forward insidiously in otherwise apparently healthy people. No telltale symptoms can be perceived by affected individuals. Eventually, however, often suddenly, events occur which bring about obvious abnormalities in physiological function; a stroke, angina, a symptomatic myocardial infarction, or simply sudden death from ventricular fibrillation. In Section 5.1 below we shall outline current theories about the mechanisms which precipitate major types of clinical manifestations of cardiovascular disease, and note a number of ways in which acute stressful stimuli may contribute to the diverse set of precipitating events.

Next, in Section 5.2, we will examine the results of some epidemiological studies which have sought to relate specific risk factors to the incidence of cardiovascular disease manifestations by careful long term prospective observation of defined populations. We shall use the available data to ask two basic types of questions:

(1) Taking the usual analysis of the Framingham study and some others at face value (that is, given the major assumptions that the observed associations of cardiovascular risk with various risk factors reflect causal relationships, and that the mathematical form of the risk relationship is close to the logistic equation used in the analysis of the data) roughly what differences in cardiovascular morbidity would be expected to be associated with chronic increases in specific risk factors of the magnitude observed in the stress literature cited in Sections 3 and 4?

(2) Is it likely that the simple logistic risk functions which have become standard fixtures for analysis of cardiovascular disease observations accurately describe the underlying relationships between risk factors and manifestations of disease?

In brief, our answer to the latter question is "no," based both on theory and on the available data. Theoretically, it seems unlikely that cardiovascular

disease risk can be accurately described by mathematical models which do not include separate representations of the contributions of risk factors to (a) the chronic atherosclerotic process and (b) specific mechanisms acting over short time periods which precipitate specific clinical manifestations of cardiovascular disease. Close examination of data on myocardial infarction risk pooled from five large prospective epidemiological studies[278] (including Framingham) and data on total cardiovascular disease risk from the Western Collaborative Group Study [279] suggests a pattern of deviations from the expectations of the multiple logistic model which may point the way toward the construction of better mathematical descriptions of cardiovascular disease risk.

Finally, in Section 5.3 we shall outline some promising directions for future research into possible contributions by noise and other stimuli to short-term events which precipitate specific manifestations of cardiovascular disease.

5.1 Mechanisms Which Produce Clinical Manifestations of Cardiovascular Disease

Table 5.1 lists and defines major clinical manifestations of cardiovascular diseases. Table 5.2 shows the incidence of each of these conditions observed in men and women in specific age ranges over 18 years of follow-up of the Framingham population. For all of these diverse conditions, reversible symptoms and/or irreversible damage ultimately results from a failure of the circulatory system to deliver oxygen to specific tissues in amounts needed to maintain normal functioning. Where the conditions differ is (a) the location and severity of the oxygen deficit and (b) the kinds of precipitating mechanisms which are thought to be usually involved in producing the oxygen deficit.

In one case, congestive heart failure, the concept of a precipitating event or mechanism (distinct from the chronic cumulative mechanisms which drive underlying cardiovascular disease processes) is probably inappropriate. Congestive heart failure appears to be best thought of as the final culmination of chronic hypertension and other processes, which occurs when the heart simply can no longer cope with the demands to pump adequate amounts of blood through renal, peripheral, and myocardial blood vessels which have been excessively narrowed.

Table 5.1

Definitions of Major Clinical Manifestations of Cardiovascular Disease

Manifestation	Operational Definition Used in the Framingham Study[280]	Medical Dictionary Definition[281]
Myocardial Infarction	Either recent or acute infarctions: (1) "serial changes in the electrocardiograms indicating the evolution of an infarction, including: S-T segment elevation...associated with terminal inversion of T waves and loss of initial QRS potentials (that is, development of 'pathological' Q waves of 0.04 second duration or greater), followed by serial changes indicating reversion towards normal" (2) "an old or remote myocardial infarction was considered to be present when the electrocardiogram showed a stable pattern including a pathologic Q wave or loss of initial QRS potential (R wave) in those leads in which this would not be expected to occur" or (3) "a hospital report showing a rise in the serum glutamic oxalacetic transaminase of at least 60 units along with a history of prolonged ischemic chest pain" or elevation of lactic dehydrogenase or SGOT to defined levels, or (4) an autopsy report showing an acute, new, or recent infarction.	Infarction: "Local arrest or sudden insufficiency of arterial or venous blood supply due to emboli, thrombi, vascular torsion, or pressure that produces a macroscopic area of necrosis; the heart, brain, spleen, kidney, intestine, or lung, and testes are most affected...." Myocardial infarction: "Cardiac infarction, infarction of an area of heart muscle usually as a result of occlusion of a coronary artery.
Angina pectoris	"Brief recurrent chest discomfort of up to 15 minutes duration, precipitated by exertion or emotion and relieved by rest or by nitroglycerine, if two physicians interviewing the subject agreed that this condition was definitely present."	"Severe constricting pain in the chest, often radiating from the precordium to the left shoulder and down the arm, due to ischemia of the heart muscle, usually caused by coronary disease."
Coronary Insufficiency	"...a history of prolonged chest pain accompanied by transient ischemic S-T segment and T-wave abnormality in the electrocardiographic tracing but not accompanied by development of Q-wave abnormality or by serum enzyme changes characteristic of muscle necrosis."	"Inadequate coronary circulation leading to anginal pain."

Table 5.1
(cont'd)

Manifestation	Operational Definition Used in the Framingham Study[280]	Medical Dictionary Definition[281]
Sudden Death from Coronary Heart Disease	"A subject, apparently well, was observed to have died within a few minutes (operationally documented as under one hour) from onset of symptoms, and the cause of death could not reasonably be attributed...to some potentially lethal disease other than coronary heart disease."	
Nonsudden Death from Coronary Heart Disease	Similar to above, but with death occurring more than one hour after onset of symptoms.	
Cerebrovascular Accident	"The diagnosis of overt vascular disease of the brain was based on the occurrence of stroke. Minimal criteria for nonhemorrhagic stroke consisted of sudden onset of a localizing neurologic deficit (such as hemiparesis, aphasia, homonymous hemianopia); for stroke due to intracranial hemorrhage, a change in the state of consciousness, headache, and signs of meningeal irritation in association with a bloody spinal fluid under increased pressure whether with or without other localizing neurological deficits."	"(apoplexy)" "A classical term for cerebral hemorrhage, thrombosis, embolism, or vasospasm usually characterized by some degree of paralysis."
Atherothrombotic Brain Infarction	Specifically, thrombotic brain infarction was defined as the sudden onset of a localizing neurologic deficit...documented by a physician, lasting longer than 24 hours, in the absence of (1) known source of embolism (atrial fibrillation, rheumatic heart disease with mitral stenosis, myocardial infarction within preceding six months, bacterial endocarditis), (2) intracraneal hemorrhage... (3) known hypercoagulable states (for example, erythemia), (4) other disease processes causing focal brain deficits (brain tumor, subdural hematoma, hypoglycemia).	

Table 5.1
(cont'd)

Manifestation	Operational Definition Used in the Framingham Study[280]	Medical Dictionary Definition[281]
Intermittent Claudication	"...a cramping discomfort in the calf clearly provoked by walking but not present on taking the first few steps, with the pain appearing sooner when walking quickly or uphill and being relieved within a few minutes by rest."	A condition caused by ischemia of the leg muscles due to sclerosis with narrowing of the arteries of the legs; it is characterized by attacks of lameness and pain, brought on by walking, chiefly in the calf muscles.
Congestive Heart Failure	Two major criteria or one major and two minor criteria as follows: Major criteria: 1) Paroxysmal nocturnal dyspnea. 2) Distended neck veins (in other than the supine position). 3) Rales. 4) Increasing heart size by x-ray. 5) Acute pulmonary edema described in hospital record. 6) Ventricular S(3) gallop. 7) Increased venous pressure (greater than 16 cm H(2) from right atrium). 8) Circulation time (greater than 24 seconds, arm to tongue). 9) Hepatojugular reflux. 10) Pulmonary edema, visceral congestion, cardiomegaly shown on autopsy. Minor criteria: 1) Bilateral ankle edema. 2) Night cough. 3) Dyspnea on ordinary exertion. 4) Hepatomegaly. 5) Pleural effusion. 6) Decrease in vital capacity by one-third from maximum recorded. 7) Tachycardia (120 beats per minute or more).	Mechanical inadequacy of the heart so that as a pump it fails to maintain the circulation of blood, with the result that congestion and edema develop in the tissues.

Table 5.1
(cont'd)

Manifestation	Operational Definition Used in the Framingham Study[280]	Medical Dictionary Definition[281]
	Arbitrary major or minor criterion: Weight loss (ten pounds or more in five days) while on therapy for congestive heart failure.	

Table 5.2

Incidence of Cardiovascular Disease Manifestations Observed in the Framingham Study[280]

(Number of Events per 10,000 Persons at Risk Per Year)

	MEN			WOMEN		
	Age* 45-54	Age 55-64	Age 65-74	Age 45-54	Age 55-64	Age 65-74
Event**						
Coronary Heart Disease	96	204	197	29	96	144
myocardial infarction	41	89	100	7	18	47
coronary insufficiency	11	11	19	3	13	11
angina pectoris, uncomplicated	28	75	52	16	53	66
coronary heart disease death	20	45	58	3	12	36
(sudden)	(12)	(27)	(23)	(2)	(4)	(13)
(non-sudden)***	(8)	(18)	(25)	(1)	(8)	(23)
Cerebrovascular Accident	20	35	73	9	26	81
atherothrombotic brain infarction	9	22	38	5	17	46
other***	11	13	40	4	9	35
Intermittent Claudication	18	51	59	5	19	40
Congestive Heart Failure	20	41	70	6	30	65
ANY CARDIOVASCULAR DISEASE	127	260	299	41	135	227

*All ages shown refer to ages of people at risk at biennial exams.

**The populations at risk for coronary heart disease and its subdivisions were people free of any manifestation of coronary heart disease at a particular exam. The populations at risk for cerebrovascular accident or atherothrombotic brain infarction were people free of cerebrovascular accident at a particular exam. Populations at risk for intermittent claudication and congestive heart failure were people free of each of those conditions, respectively. Numbers within subcategories of coronary heart disease do not add to total because of the development of multiple manifestations of coronary heart disease between biennial exams, in some people.

***Numbers in these rows calculated by subtraction.

For two of the other events listed in Table 5.1--angina pectoris and intermittent claudication--the "precipitating event" which brings about symptoms appears to be most frequently a simple transient increase in oxygen demand by affected tissues beyond the capacity of the atherosclerotically-narrowed vessels to supply. The symptoms are usually completely reversible when the transient demand is lowered by rest and/or the local supply is increased by vasodilating agents.*

The remaining events in Table 5.1, commonly known as "heart attacks" and "strokes," are precipitated by one or more of the following classes of mechanisms:

(1) Thrombotic events, including[282]
   (a) intravascular platelet aggregation, followed by diffuse deposition of microemboli in small vessels[283-6, 16, 104] or vessels nearly occluded by previous atherosclerosis;[289]
   (b) growth of occlusive thrombi directly from lesions in the arterial wall to the point where they significantly reduce blood flow to a local area[287-8] and
   (c) formation of emboli by rupture or dislodgement of thrombi adhering to arterial or heart walls, followed by deposition of the emboli in major or minor arteries.
(2) Ventricular fibrillation (or other arrythmia) caused in part by unusual inputs from the sympathetic nervous system;[292]
(3) Arterial spasm, producing sufficient temporary ischemia in affected tissue to trigger irreversible damage either by inducing subsequent thrombosis or (in the heart) ventricular fibrillation;[294]
(4) Rupture of arteries or the heart wall, followed by hemmorrhage.[295-7]

Although events involving thrombosis appear to be implicated in the great

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*Some kinds of angina, known as "variant angina" are thought to be precipitated by spasm of coronary arteries (which transiently reduces oxygen supply) rather than transiently excessive demand.[291]

majority of cerebrovascular accidents,* the relative contributions of the four classes of mechanisms to "myocardial infarction" and sudden coronary death are the subjects of intense controversy at present within the scientific community.[299-306] In particular, different investigators have reported widely varying results from autopsy studies on the frequency of major thrombosis in people dying suddenly of coronary disease.[298-9, 296, 301, 307] Even when present, some have postulated that occlusive thrombi in major arteries may sometimes be formed after, rather than before, the heart lesions with which they are associated.[308] The issue is complicated further by the fact that there are plausible reasons to believe that events which start out within each class of mechanism can cause or trigger events belonging to other classes. Thus, abnormal functioning or death of heart muscle due to a blockage of a coronary artery can lead directly to fibrillation,[293] or markedly reduced blood flow or turbulence resulting from a cardiac arrythmia could conceivably lead to thrombosis. In another variation, primary thrombosis has been postulated to cause arterial spasm by the release of the powerful vasoconstrictor, thromoxane A2, from platelets.[282]

Based on current information, it is not clear which mechanisms will ultimately be judged to make what ultimate contributions to myocardial infarction, coronary insufficiency, and sudden coronary disease related death. However, for purposes of our discussion in Section 5.2 below on mathematical models, for heart disease it is helpful to point out here that the most prudent interpretation of available data would lead one to postulate that there may be several independent routes by which major cardiovascular events can be initiated, but that once initiated the severity of individual events may well depend in part on interactions between the risks of events of different types. Mathematically, this might be expressed by

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*A minority of cerebrovascular accidents are caused by hemorrhage, following rupture of cerebral arteries. In the Framingham study, a total of 294 strokes have been observed over 22 years of follow-up. Of these, 59% have been attributed to atherothrombotic brain infarction and an additional 14% have been attributed to emboli which travelled to a cerebral artery from elsewhere. Only 15% of the strokes were attributed to hemorrhage.[297]

having some primary event frequency depend on a summation of the risks of events initiated by the independent mechanisms, but event severity depend in part on an expression containing multiplicative interactions between the different risk mechanisms.

Below we will discuss in more detail two classes of mechanisms (thrombotic events and ventricular arrythmias) which appear both to be appreciably influenced by environmental stimuli and to be of preeminent importance in causing the most serious manifestations of cardiovascular disease.

5.1.1 Thrombotic Events and Environmental Stimuli

A review by Born[310] sets forth the normal role of platelets in limiting loss of fluid from damaged blood vessels:

> Contact with a vascular lesion causes a remarkably rapid change in platelets which makes them adhere and cause other platelets chancing to touch them to adhere also. Thus, the formation of a haemostatic plug involves first *adhesion* of platelets to other tissues, followed very rapidly by the *aggregation* of platelets to each other. Initially the platelets adhere loosely to each other so that the plasma and cells continue to pass out of the vessel. Within a few minutes the platelets become packed much more closely, indeed almost as closely as is theoretically possible[311] so that the plug becomes more effective in its haemostatic function.

Experiments in vitro have yielded insight into the aggregation stage of this process.[310]

> In vitro, human platelets are caused to aggregate by adenosine diphosphate (ADP), adrenaline, 5-hydroxy-tryptamine, thrombin, collagen, and certain fatty acids, as well as by several other agents less immediately relevant to haemostasis. Each agent must have the ability to react initially with some kind of receptor site on the platelet surface membrane. With most, if not with all, this primary reaction apparently induces the formation in and/or release of ADP from platelets and apparently it is this which causes the changes in surface properties of platelets resulting in their aggregation. This conclusion is based on (1) the

demonstration of the release of ADP from platelets by the other agents, (2) the inhibition of aggregation by enzymes which remove ADP from the plasma, and (3) inhibition by specific antagonists of the effect of ADP (for review see Haslam)[312]...

When ADP is added...there is a rapid increase in the optical density of the plasma, amounting to a decrease of a few per cent in light transmission. The optical changes indicate the first and probably the only effect of ADP itself on platelets, namely to change their shape from smooth discs to spheres with pseudopodia of varying lengths protruding from the surface[313]...

First Phase of Aggregation. The optical effect of the shape change is followed by an effect in the opposite direction, i.e., an increase in light transmission which, for the most part, is also much larger. This part of the record is the resultant of several simultaneous processes in which single platelets adhere to each other to form small aggregates and to aggregates already formed and in which small aggregates adhere to each other to form larger ones. So far, there is too little information for the construction of mathematical models of these events. It is known that the stages in which the aggregates are small, i.e., containing less than ten platelets, are passed through very rapidly and that throughout this phase the platelets adhere to each other rather loosely.[311]

Disaggregation. The first phase of aggregation by ADP, just described, is completely reversible and the dispersion of the aggregates is shown by an increase in the optical density of the plasma. Aggregation of human platelets reverses spontaneously when caused by low concentrations of ADP; higher concentrations may induce the second phase of aggregation (see below) which obscures and delays disaggregation.

Potentiating Agents. The effect of ADP is greatly increased by *adrenaline*[314], even in very low concentrations. This potentiation shows itself both as an acceleration of primary aggregation and as a diminution in the ADP concentration required to initiate the second phase of aggregation in which aggregating substances are released from the platelets. These observations are

given clinical significance by the appearance of such concentrations of adrenaline in the plasma of people during stress who seem particularly liable to suffer from thrombotic episodes.

Second Phase of Aggregation and the Release Reaction. The optical method resulted in the discovery that critical concentrations of ADP added to citrated plasma of man[315] or guinea pig[316] at 37°C cause two distinct phases of decrease in optical density. The second phase is associated with the release of ADP from the platelets themselves so that its concentration in the plasma may increase up to seven times.[317] Other substances released at the same time include ATP and 5-hydroxytryptamine as well as platelet factor 3 which accelerates coagulation of plasma.[318] This release reaction can be induced also by thrombin[319] or adrenaline, and the latter diminishes the concentrations of other agents required to initiate the reaction.

The decrease in optical density during this phase of aggregation is caused by the contraction of aggregates already formed rather than by the formation of larger aggregates. There is evidence that this contraction also occurs in vivo where it presumably increases the effectiveness of the platelet plug as a barrier against further blood loss.[319]

The conditions which favor thrombosis have been appreciated for a long time. More than a century ago, Virchow listed three factors as of prime importance: "(1) local injury to the vascular system, (2) stasis of blood flow and (3) alterations in the coagulability of blood."[309]

The tendency of platelets to adhere to sites of injury in the arterial endothelium has been previously discussed in Section 4.1 above as an integral part of the chronic atherosclerotic process. To the degree that direct growth of thrombi on arterial wall lesions is responsible for seriously occluding coronary or brain arteries to produce infarctions, the terminal events in the cardiovascular disease processes can be thought of as simply the extreme tail of the distribution of the events which contribute to the day-to-day progress of atherosclerosis. For this mechanism, the same factors which contribute to primary wall injury in atherosclerosis (e.g., elevated

blood pressure, cholesterol) should contribute to the precipitating events, although transient variability in risk factors may be suspected to be even more important in producing the larger type of events which give rise to clinical manifestations of disease than it may be in causing more common lesions. To the degree, therefore, that stressful stimuli produce large transient elevations in physiological parameters which lead to wall injury, it may be suspected that elevations in the incidence in precipitating events may be relatively important.

The second element of Virchow's triad, stasis of blood flow, needs to be broadened to include other alterations in the normal laminar flow of blood, including turbulence. Ordinarily the particulate components of blood such as platelets tend to travel near the center of the arterial lumen where the flow is relatively swift and contact with the arterial wall is relatively rare. According to a pathology text,[309]

> The roles of stasis and turbulence in promoting thrombosis are clearly documented in many clinical situations. Abnormal dilations of arteries, known as *aneurysms*, frequently are the sites of thromboses. Thrombotic complications are particularly frequent in the leg veins of patients who have cardiac disease or who are confined to bed, both situations being associated with sluggish venous flow...
>
> The coronary arteries provide a dramatic example of the roles of stasis and turbulence. Atherosclerotic disease in these vessels causes roughening of the surface as well as narrowing of the lumen. The flow in these vessels may be reduced to near zero or may even be transiently reversed in early systole. Together, these changes regrettably provide ideal circumstances for thrombosis and its grim consequence, myocardial infarction.

The effects of transient responses to environmental stimuli on this factor in thrombogenesis are probably mixed. Transient elevations of blood pressure may well decrease thrombotic tendencies due to enhanced flow at the same time that thrombosis may be increased due to increased turbulence. Turbulence might well be expected to promote more, but smaller sized platelet aggregates and arterial wall thrombi by causing breakage of loosely held primary aggregates and rapidly dispersing any ADP released during secondary platelet aggregation to the general circulation.

The third element of the triad, alterations in blood coagulability, may present the best opportunities for demonstrating possible contributions of environmental stimuli to thrombotic events which cause ischemia and infarctions. It has been known for some time that infusion of large amounts of catecholamines can cause myocardial necrosis. Early in the 1970's animal studies by Haft and coworkers showed (1) that the necrosis was associated with disseminated platelet aggregates in small vessels of the heart,[104] (2) that the necrosis could be prevented by three unrelated inhibitors of platelet aggregation (aspirin, dipiridamole, and clofibrate),[320-1] and (3) that intravascular platelet aggregation in the heart could be produced by three different forms of stress (immersion in ice-cold water, immersion in hot water, and repeated small electric shocks to the feet.)[322-3] Commenting on their work, the authors conclude:

> These findings suggest that catecholamines secreted endogenously during stress are sufficient to cause platelets to aggregate intravascularly and raise the possiblity that clinical myocardial infarction occurring during severe or prolonged stress may be caused by catecholamine-induced platelet thrombi which occur at, or travel to, and occlude a coronary artery already narrowed by previous atherosclerosis.[322]

Measures of platelet aggregation or aggregability have been reported to be elevated in people with hypertension,[324] diabetes,[325] in smokers shortly after smoking,[282] and to increase with increasing age.[328-9] It is not impossible that part of the excess infarction risk associated with these traditional cardiovascular disease risk factors is mediated by platelet aggregation effects, although these observations could just as easily be due to higher platelet turnover from a greater rate of atherosclerosis in those individuals.* A similar caveat must be attached to observations that platelet aggregation is enhanced in patients who have previously suffered a wide variety of clinical manifestations of cardiovascular disease.[326-33] (In one promising study, platelet aggregation measures were found to be ex-

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*Greater platelet turnover is expected to be associated with greater platelet aggregation and aggregability because younger platelets, making up a higher percentage of platelets in patients with high turnover, are said to be more active in many tests of platelet aggregation.

cessive prior to the occurrence of myocardial infarction).[329] Unfortunately, interpretation of all of these observations is complicated because there are a number of different clinical procedures which are used to assess aspects of platelet aggregation behavior,[326,332-4] and in some cases it appears that these different procedures measure entirely unrelated properties.[325-6] Systematic comparative studies to ascertain which clinical measures are (1) predictive of future risk of infaction and (2) responsive to stressful stimuli should receive priority in future research.

5.1.2 Ventricular Arrhythmias and Environmental Stimuli

In the early 1960's, autopsy studies on people dying suddenly after the onset of coronary symptoms revealed that in an appreciable fraction of cases, no recent major thrombus or infarct could be demonstrated.[337,307] Many of the victims seemed to have "hearts too good to die,"[338] which could reasonably have been expected to sustain life for many years if some subtle short-term functional derangement had been prevented or corrected. Subsequent experience with coronary care units have demonstrated that (1) the mechanism which is immediately responsible for most sudden cardiac deaths is ventricular fibrillation[339] and (2) prompt resuscitation of patients often leads to full recovery and subsequent survival for long periods, depending on the extent of the underlying disease.[340]

In ventricular fibrillation, the normal coordinated pattern of contraction of muscle cells making up the ventricle walls is replaced by a chaotic twitching which is completely ineffective for pumping blood. This is the most extreme and lethal form of a large set of basically electrical abnormalities in heart function known as arrhythmias. We will not present a detailed review of current theories on local alterations in myocardial conduction and other mechanisms which render the heart vulnerable for the induction of ventricular arrhythmias during a specific portion of the cardiac cycle.* What is important for our purposes here is that there is a considerable body of evidence that (1) sympathetic nervous stimulation in

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*For an excellent description of different kinds of arrhythmias and discussion of their physiological bases, see chapters 15-19 of a recent book by Katz, ref. 341.

general, (2) emotional responses to stressful stimuli and (3) responses to brief exposures to loud noises in particular, can trigger dangerous types of ventricular arrythmias in hearts which have been rendered electrically unstable by a variety of other conditions.

(1) Sympathetic nervous stimulation. DeSilva and Lown[292] cite numerous direct experiments in animal systems indicating that

> stimulation of individual loci in the hypothalamus[342-6] diencephalon and mesencephalon[345-9] reticular formation,[346] and quadrigeminal bodies[347] evoked a variety of arrhythmias including ventricular fibrillation.

Similar results have been obtained using animal models of acute myocardial infarction in which a coronary aftery is temporarily occluded by the experimenters. In such models hypothalamic stimulation, stimulation of cardiac sympathetic fibers, or the stellate ganglia greatly enhances the risk of ventricular fibrillation,[350-3] while β-adrenergic blockade[354-6] or surgically cutting the connection between the sympathetic nervous system and the heart[357-9] reduces the risk of ventricular fibrillation.

(2) Emotional responses to stressful stimuli. A number of groups have performed the same kinds of animal experiments referred to above, substituting different forms of putatively stressful stimuli for direct sympathetic stimulation, and have obtained similar results in the induction of arrhythmias. Thus, DeSilva and co-workers produced substantial decreases in the threshold current needed for inducing repetitive extrasystoles* by placing dogs in a "Pavlovian sling" (an apparatus in which the animals had previously experienced an electric shock)[360-1] or by subjecting the dogs to a shock-avoidance schedule.[362] Similarly, the incidence of ventricular fibrillation following coronary artery occlusion was increased by placing pigs in an unfamiliar environment.[363]

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* The threshold current for inducing repetitive systoles is a marker for susceptibility to ventricular fibrillation--generally about two thirds of the current required for fibrillation will induce repetitive extrasystoles.[360]

In addition to these experiments in animal systems, three types of observations in humans indicate relationships between mental/emotional stress and arrhythmias. First, there are experimental studies in patients with pre-existing heart disease. The Lown/Desilva group, using a series of stimuli including mental arithmetic, reading from colored cards, and discussion of emotionally charged experiences, observed significant increases in the frequency of ventricular premature beats in the majority of a set of patients with histories of serious ventricular arrhythmias.[364] Similarly, Taggart and others observed a series of cardiac patients during public speaking and reported:[365]

> Multiple and often multifocal ventricular and supraventricular beats were observed in five of the seven persons with coronary heart disease after they had taken the placebo, but there were no such beats on the recordings following oxprenolol*...(including) one short run of ventricular tachycardia in the trace recorded after placebo.

Second, there are a number of case reports in the medical literature of people who suffer recurrent episodes of ventricular fibrillation in response to emotional stimuli.[366-7] In at least one case, these episodes were controllable by a β-adrenergic blocking drug.[367] Finally, there is the appreciable body of literature on the risk of death or myocardial infarction following bereavement[368-9] or other major "life stress" events,[34,370,379-80] although the specific risk of ventricular fibrillation has not generally been documented in these studies.

(3) Responses to brief exposures to loud noise. There are a number of reports which suggest that, at least under some circumstances, sudden loud noises may trigger or promote serious episodes of ventricular arrhythmia. Information is available from experimental animal models,[293,371-2] and from at least one marginally relevant human case report.[373**] There is also one very tentative but possibly important finding from an epidemiological study of an association between low frequency hearing loss and risk of sudden death.[374]

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* Oxprenolol is a β-adrenergic blocking drug.

** The noise stimulus in this case was originally the ringing of an alarm clock.

In all of the experimental animal studies, noise appears to act synergistically with other factors which promote electrical instability in the heart, including ischemia from concurrent coronary occlusion,[293] a variety of experimentally induced cardiomyopathies,[372] certain widely used drugs,[372] and industrial chemicals.[371] In the experimental coronary occlusion system in dogs, Rosenfeld and co-workers[293] found that exposure to a sudden noise* and/or other stimuli both shortened the "latency" time between experimental occlusion and the induction of the first ventricular premature beat (Table 5.3) and worsened the grade of arrhythmia induced (Figure 5.1). As can be seen in Figure 5.1, the animal exposed to noise

Effects of Stress on Latency in Five Dogs

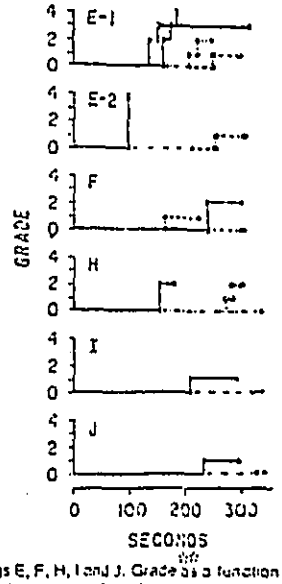
Dog	Occlusion*	Latency (sec)	% Change
E	C	212	...
	S(N)	99	−57
	C	251	...
	S(N)	164	−35
	S(N)	136	...
	C	209	...
F	C	167	...
	S(ES)	241	+3
	C	301	...
H	C	330	...
	S(ES)	151	−50
	C	274	...
I	C	315	...
	S(Env)	204	−35
	C	315	...
J	C	330	...
	S(ES)	230	−30
	C	330	...
Mean ± SEM	...	...	−34 ± 8.5†

* In all five dogs the left circumflex coronary artery was occluded.

† Probability (P) value <0.02, *t* test; *P* <0.05, Wilcoxin rank sum test.

C = control occlusion; Env = strange environment; ES = electric shock; N = noise; S = occlusion under stress; SEM = standard error of the mean.

Table 5.3



Dogs E, F, H, I and J. Grade as a function of time for each occlusion, in each sequence, in which stress was the intervention. Each sequence is shown on a separate set of axes. Grade is indicated on each vertical axis and time on the horizontal axis. The intervention trial (x——x) and each control trial (O——O, ●——●) are shown for each sequence.

Figure 5.1

Source: Rosenfeld, et al., ref. 293

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* The intensity of the noise stimulus was characterized as "sufficient to cause an arousal or a startle response but never sufficient to cause vocalization or evidence of pain."

** Grade 0 = no ventricular premature beat
Grade 1 = one or more isolated premature beats
Grade 2 = two but no more than two premature beats occur in sequence
Grade 3 = three or more premature beats in sequence but no fibrillation
Grade 4 = ventricular fibrillation

reached the highest arrhythmia grade (ventricular fibrillation) on two of three trials. Davidson[372] induced cardiomyopathies by a variety of procedures in rats and after three weeks of various drug treatments, subjected the animals to the sound of a gunshot at 200 dynes/cm^2 (Table 5.4). Electrocardiograms of rats taken immediately after the noise stimulus showed ventricular fibrillation.

Table 5.4

Percent Deaths on Noise Stress (200 dynes/cm^2)
Drug Treatment for 3 Weeks*

Type of Cardiac Damage	None	Amitriptyline (1 mg/kg b.i.d.)	Imipramine (1.2 mg/kg b.i.d.)	Propranolol (1 mg/kg b.i.d.)	Diazepam (3 mg/kg b.i.d.)
None	0	0	0	0	0
Spontaneous	2	80	90	0	0
Isoprenaline	4	90	80	0	0
Cobalt	2	90	80	0	0
Aortic co-arctation	6	70	90	0	0

Several aspects of these findings are noteworthy:

- there were no deaths in animals which had no spontaneous or previously induced heart damage, regardless of drug treatment
- noise induced a small percentage of sudden deaths in all of the groups with cardiac damage in the absence of drug treatment
- noise acted synergistically with the widely-used tricyclic anti-depressants, amitryptyline and imipramine
- sudden deaths were prevented in groups treated with the beta-adrenergic blocking drug, propranolol, and the tranquilizer diazepam (Valium)

These data suggest that some special effort be made to investigate epidemiologically the possibility that sudden, startling noises may trigger ventricular fibrillation and sudden death in people with pre-existing

*Source: Davidson, ref. 372. Generally, data are based on 10 animals per group, with the exception of the groups receiving no drug treatment. The numbers of animals in the no treatment groups are not given.

heart disease with or without exposure to drugs and industrial chemicals which may promote arrhythmias. If further documented, any excessive risk might be efficiently reduced by specific measures to prevent sudden noise exposures, changes in medical practice and/or reduction in exposure of workers at risk to specific chemicals. The unequivocal nature of sudden death as an endpoint for epidemiological studies should allow the design of relatively unambiguous studies in this area.

The Taggart study of the occurrence of arrhythmias during public speaking suggests[365] another potentially productive line of research. The capability to perform electrocardiographic monitoring in people engaged in ordinary day-to-day activities, combined with modern automated data processing methods,[375] opens up many possibilities for researchers to define with precision associations between particular environmental or emotional stimuli, chemical or drug exposures thought to increase cardiovascular risk[376] and the induction of arrythmias. The importance of sudden cardiac death in our society (over four hundred thousand deaths per year, including many in middle age ranges)[339-40] justifies an intensive effort to document and control relevant environmental and occupational risk factors.

5.2 Epidemiological Observations and Quantitative Models of Cardiovascular Disease Risk

There is certain dissonance between the two halves of this section. In 5.2.1 below we present some crude calculations of the quantitative differences in cardiovascular mortality which would be expected to result from specific long term differences in blood pressure and serum cholesterol levels, based on the standard risk relationships derived from the Framingham study.[280] In Section 5.2.2 we assemble some evidence which suggests that the very mathematical models which were the basis for the calculations in 5.2.1 may need substantial modification if they are to accurately describe relationships between risk factors and the incidence of cardiovascular diseases. Given our reservations about the basic form of the risk models and the other major uncertainties posed by such

calculations,* it is fair to ask why we deem it helpful to present them.

We present these calculations because real decisions--in the allocation of priorities for research, in the design of future epidemiological studies, in the investment of regulatory resources, etc.--need to be made whether or not quantitative estimates of these types are available, and they may be made somewhat better in the light of explicit (though highly uncertain) calculations with defined assumptions rather than ill-defined implicit preconceptions. Faced with the data in section 4.2 above suggesting that long term occupational noise exposure may be associated with shifts in average systolic blood pressures on the order of 6 mm Hg in workers over 40, it is reasonable to ask how important one would expect a shift of this magnitude to be, given current data and models of relationships between blood pressure and cardiovascular risk. Would such a change be expected to be more or less important than a long term shift of 33 mg/100 ml in serum cholesterol, as observed in the single available month-long experiment of Cantrell[55] (see in Section 3.2.1, pp. 42-44)? Even the very rough order-of-magnitude answers to such questions which can be produced from available data and assumptions may well be superior to the guesses which decision makers might make in the absence of additional information.

5.2.1 Influence of Blood Pressure and Serum Cholesterol Levels on Cardiovascular Morbidity, Using the Multiple Logistic Model and the Observations of the Framingham Study

Nearly all current analysis of epidemiological data from prospective

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* E.g., are the basic epidemiological associations based on direct causal connections or do elevated levels of traditional risk factors simply serve as proxy indicators of the true causal factors? In the former case, the risk predictions may be valid, in the latter case the predictions would only be valid if changes in the measured risk factor under the influence of an environmental stimulus were paralleled by changes in the underlying causal factor.

studies of relationships between cardiovascular risk factors and disease risks is based on the multiple logistic risk model of Truett et al.[63]:

$$R = \frac{1}{1 + e^{-(B_0+B_1X_1+B_2X_2+\ldots+B_kX_k)}} \qquad (\#1)$$

where R is the risk (probability) of developing one or any clinical manifestation of cardiovascular disease in a defined time period, the "X's" are measured levels of particular risk factors such as serum cholesterol, and the "B's" are constants which define the contributions of unit changes in each risk factor to overall risk. This is mathematically equivalent to:

$$\frac{R}{1-R} = e^{B_0 + B_1X_1+B_2X_2+\ldots+B_kX_k} \qquad (\#2)$$

$$\ln\left(\frac{R}{1-R}\right) = B_0+B_1X_1+B_2X_2+\ldots B_kX_k \qquad (\#3)$$

"$\ln\left(\frac{R}{1-R}\right)$," also known as the logit of R, gives the model its name.[378]

Basic Properties of the Multiple Logistic Risk Model

Two basic properties of this model should be noted at the outset: (1) Equal additive increases in the level of a risk factor basically produce equal multiplicative increases in disease risk. At small values of R, the quantity $\frac{R}{1-R}$ is approximately equal to R. Given this, from equation number 2 the relationship between the risks, R' and R'' at two levels of an individual risk factor X_1' and X_1'' is given by:

$$\frac{R'}{R''} = \frac{e^{B_0+B_1X_1'+\ldots}}{e^{B_0+B_1X_1''+\ldots}} = e^{B_1(X_1' - X_1'')}$$

If X_1 represents systolic blood pressure, this means that we should express the effect of a given increase in blood pressure as a given

percentage increase in risk*, regardless of the baseline level of blood pressure, although the absolute increase in the number of cases will tend to be higher at higher baseline levels of blood pressure and other risk factors. Thus, the model predicts that the percentage increase in risk due to a 6 mm Hg increase in blood pressure should be the same, or a little larger at low systolic blood pressure levels (between 110 and 116, for example) as at high systolic blood pressure levels (between 160 and 166, for example). The model contains no "threshholds" or "safe levels" or "normal levels" below which risk is constant. Thus, if the model is correct, and reflects true direct causal relationships between blood pressure (and other factors) and disease risk, the public health importance of an agent which raises blood pressure in a population cannot be assessed simply based on a count of the number of additional "hypertensives" which are pushed beyond some arbitrary cutoff point. Assessment of the public health significance of such an agent must be based on the number of people who experience blood pressure increases, the amount of the increases, and the baseline cardiovascular disease risk of the population due to other factors.

(2) Increases in more than one risk factor produce synergistic (multiplicative) increases in disease risk.

By the same reasoning as above, if two factors, X_1 and X_2 are raised over the long term in a population, the total increase in $\frac{R}{1-R}$ (or, approximately, R) will be equal to the <u>product</u> of the increases which would be expected from the same increases in X_1 and X_2 separately. According to the model, this should be equally true for all pairs of risk factors, regardless of whether they represent such diverse properties as age, blood pressure, electrocardiographic abnormalities, or glucose intolerance.

Expected Impacts of Specific Increases in Systolic Blood Pressure and Serum Cholesterol

Tables 5.5 and 5.6 list estimated coefficients ("B's" in equations #1-3 above) from logistic regression analyses of various cardiovascular disease

*Or, more precisely, $\frac{R}{1-R}$

risks for males in the Framingham study over 18 years of followup. Table 5.5 lists coefficients for systolic blood pressure as a risk factor for the indicated events and Table 5.6 lists similar coefficients for serum cholesterol. In each table, the first column contains coefficients derived from multivariate regression analyses designed to separately ascertain the contributions to disease risks of six different major risk factors (age, systolic blood pressure, serum cholesterol, cigarettes smoked, left ventricular hypertrophy by electrocardiogram, and glucose intolerance). For purposes of such analysis, all these factors were presumed to be independent of one another, and the resulting multivariate coefficients represent the estimated independent contribution of the factor in question to disease risk after controlling (or holding constant) the contributions of the other factors to disease risk for all men aged 45-75 at a particular biennial exam. By contrast, the coefficients listed in the second through fourth columns in Tables 5.5 and 5.6 represent the results of univariate regression analyses (containing only serum cholesterol or systolic blood pressure, neglecting all other risk factors) of disease risks for men in much narrower age ranges at the time of their last biennial exam. Standard errors for each coefficient are shown in parentheses.

It can be seen that in many cases the age-specific univariate regression coefficients appear to change appreciably between the three different age groups. In most cases, particularly for serum cholesterol, the coefficients indicate much weaker associations between these risk factors and the disease events surveyed in the oldest age group than in the other groups. This is not a new observation[63] but it is helpful to note it here because this should not occur if the multiple logistic risk model were a completely accurate description of true relationships between the differences in cardiovascular risks attributable to age and other risk factors.

Using equation #2 above, each of the coefficients in Tables 5.5 and 5.6 can be used to derive the percentage increase in the risk of a particular event which would be expected to be associated with a given small difference in long term average systolic blood pressure or serum cholesterol for males in the indicated age range. For example, using the multivariate coefficient in Table 5.5 relating systolic blood pressure to cerebrovascular

Table 5.5

Logistic Regression Coefficients for Systolic Blood Pressure
(Framingham Study Males, 18 Years of Followup)

Event***	Multivariate* Coefficients (ages 45-75)	Univariate** coefficients (ages 45-54)	(ages 55-64)	(ages 65-74)
Coronary Heart Disease	.01204 (± .00217)****	.01557 (.00385)	.01738 (.00261)	.00890 (.00464)
myocardial infarction	.00825 (.00327)	.01028 (.00612)	.01183 (.00402)	.01453 (.00599)
coronary insufficiency	.00960 (.00756)	.01315 (.01139)	.01667 (.01075)	.00170 (.01567)
angina pectoris, uncomplicated	.01132 (.00378)	.01522 (.00703)	.01712 (.00411)	-.01553 (.01145)
coronary heart disease death	.01473 (.00423)	.2194 (.00786)	.02079 (.00506)	.01973 (.00735)
(sudden)	.01123 (.00579)	.01052 (.01137)	.01951 (.006607)	.01936 (.01160)
(non-sudden)	not given			
Cerebrovascular Accident	.02103 (.00381)	.02805 (.00709)	.02589 (.00505)	.01429 (.00627)
atherothrombotic brain infarction	.02744 (.00493)	.02703 (.01085)	.3528 (.00597)	.02064 (.00833)
other	not given			
Intermittent Claudication	.00706 (.00426)	.00777 (.00933)	.01509 (.00489)	-.00037 (.00873)
Congestive Heart Failure	.01602 (.00388)	.3965 (.00643)	.02208 (.00501	.01820 (.00637)
ANY CARDIOVASCULAR DISEASE	.01537 (.00194)	.02069 (.00339)	.01994 (.00239)	.01199 (.00391)

Source: Shurtleff, et al., ref. 280

*In each case, the coefficient shown is the coefficient for systolic blood pressure (in mm Hg) in a multiple logistic regression analysis which also contained age, serum cholesterol, cigarettes smoked, left ventricular hypertrophy by electrocardiogram, and glucose intolerance as other risk factors for the indicated event.

**Univariate coefficients result from logistic regression analyses containing only systolic blood pressure as a risk factor, for men in the indicated age ranges at biennial exams.

***For definitions of various events shown see Table 5.1 (pp. 154-156). The populations at risk for coronary heart disease and its subdivisions were people free of any manifestation of coronary heart disease at a particular exam. The populations at risk for cerebrovascular accident or atherothrombotic brain infarction were people free of cerebrovascular accident at a particular exam. Populations at risk for intermittent claudication and congestive heart failure were people free of each of those conditions, respectively.

****Numbers in parentheses are standard errors for the indicated coefficients. Coefficients which are more than about twice their standard error are "significant" at $p < .05$.

TABLE 5.6

Logistic Regression Coefficients for Serum Cholesterol
(Framingham Study Males, 18 Years of Follow-up)

Event***	Multivariate* Coefficients (ages 45-75)	Univariate** coefficients (ages 45-54)	(ages 55-64)	(ages 65-74)
Coronary Heart Disease	.00578 (.00117)****	.00887 (.00168)	.00467 (.00178)	.00166 (.00320)
myocardial infarction	.00541 (.00173)	.00647 (.00261)	.00467 (.00264)	.00571 (.00440)
coronary insufficiency	.00923 (.00309)	.01219 (.00326)	.00482 (.00729)	-.00012 (.01008)
angina pectoris, uncomplicated	.00525 (.00201)	.00801 (.00293)	.00476 (.00286)	.00158 (.00616)
coronary heart disease death	.00611 (.00235)	.01140 (.00307)	.00400 (.00350)	-.01324 (.00591)
(sudden)	.00611 (.00307)	.01140 (.00331)	.00400 (.00471)	-.00351 (.00982)
(non-sudden)	not given			
Cerebrovascular Accident	.00156 (.00245)	.00517 (.00373)	.00222 (.00401)	-.00316 (.00462)
atherothrombotic brain infarction	.00500 (.00300)	.01146 (.00359)	.00129 (.00500)	-.00022 (.00653)
other	not given			
Intermittent Claudication	.00642 (.00215)	.00793 (.00347)	.00807 (.00294)	-.00085 (.00536)
Congestive Heart Failure	.00402 (.00234)	.00172 (.00449)	.00463 (.00348)	.00621 (.00474)
ANY CARDIOVASCULAR DISEASE	.00514 (.00107)	.00766 (.00155)	.00526 (.00162)	.00035 (.00274)

Source: Shurtleff, et al., ref. 280

*In each case, the coefficient shown is the coefficient for serum cholesterol level (expressed in mg/100 ml) in a multiple logistic regression analysis which also contained age, systolic blood pressure, cigarettes smoked, left ventricular hypertrophy by electrocardiogram, and glucose intolerance as other risk factors for the indicated event.

**Univariate coefficients result from logistic regression analyses containing only serum cholesterol as a risk factor, for men in the indicated age ranges at biennial exams.

***For the definitions of the various events shown, see Table 5.1. The populations at risk for coronary heart disease and its subdivisions were people free of any manifestations of coronary heart disease at a particular exam. The populations at risk for cerebrovascular accident or atherothrombotic brain infarction were people free of cerebrovascular accident at a particular exam. Populations at risk for intermittent claudication and congestive heart failure were people free of each of those conditions, respectively.

****Numbers in parentheses are standard errors for the indicated coefficients. Coefficients which are more than about twice their standard errors are "significant at $p < .05$.

accident (.02103), the increase in risk which would be expected to be associated with a 6 mm/Hg difference in systolic blood pressure can be found by:

$$\frac{R'}{R''} = e^{(.02103) \times (6)} = e^{.12618} = 1.134$$

In other words, holding the levels of other risk factors constant, a difference of 6 mm Hg in systolic blood pressure may be expected to be associated with about a 13% difference in cerebrovascular accident (stroke) in males between the ages of 45 and 75. If the overall risk of stroke in males of this age group is about 387 per year for every 100,000 at risk,* then the absolute difference in risk would be expected to be about 52 stroke cases per year per 100,000.

Tables 5.7 and 5.8 present the results of similar calculations for various manifestations of cardiovascular disease for differences of 6 mm Hg in systolic blood pressure and 33 mg/100 ml serum cholesterol, based on the multivariate regression coefficients in Tables 5.5 and 5.6.**

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*Based on the data for the Framingham population in Table 5.2 (p. 154 above) and assuming the following proportions of males in each age range (from 1977 census data for the U.S.)[381]:

Ages	% of total males age 45-74 in U.S.
45-54	41.5
55-64	35.4
65-74	23.1
	100.0

**Parallel calculations (not shown) were also performed with the age-specific univariate regression coefficients and weighted with the proportions of the U.S. male population in the three age groups. These calculations did not yield results which differed appreciably from those shown in Tables 5.7 and 5.8; in no case were there differences in overall risk between the two methods of as much as a factor of two. More uncertainty than this is already represented in the approximate 95% confidence intervals shown in parentheses below each of the estimates in these tables.

TABLE 5.7

Differences in Cardiovascular Disease Risks Expected to be Associated with a 6 mm Hg Difference in Systolic Blood Pressure in Males Ages 45-75*

Event***	Expected Percentage Increase in Risk	Approximate "Baseline" Risk (Cases per 100,000 at Risk per Year)**	Approximate Absolute Magnitude of Excess Risk (Additional Cases Per 100,000 at Risk per Year)
Coronary Heart Disease (Total)	7.5 (4.7-10.3) ****	1576	118 (75-163)
myocardial infarction	5.1 (1.0-9.2)	716	36 (7.4-67)
coronary insufficiency	5.9 (-3.3-16.0)	129	7.6 (-4.2-2)
angina pectoris, uncomplicated	7.0 (2.3-12.0)	502	35 (11-60)
coronary heart disease death	9.2 (3.8-14.9)	376	35 (14-56)
(sudden)	7.0 (-.2-14.7)	199	14 (-4-29)
Cerebrovascular Accident	13.4 (8.4-18.8)	387	52 (32-73)
atherothrombotic brain infarction	17.9 (11.1-25.1)	203	36 (23-51)
Intermittent Claudication	4.3 (-.9-9.8)	392	17 (-3-38)
Congestive Heart Failure	10.1 (5.1-19.3)	390	39 (20-60)
ANY CARDIOVASCULAR DISEASE	9.7 (7.1-12.2)	2138	207 (153-262)

*Based on the multivariate regression coefficients from the Framingham Study, shown in the first column of Table 5.5.

**Based on the Framingham Study data in Table 5.2 (p. 157), weighted by the proportion of the U.S. male population in various age groups (see text).

***For definitions of the various events shown, see Table 5.1 (pp. 154-6).

****Numbers in parentheses are the bounds of an approximate 95% confidence interval, based on the logistic regression coefficient plus or minus twice its standard error.

TABLE 5.8

Differences in Cardiovascular Disease Risks Expected to be Associated with a 33 mg/100 ml Difference in Serum Cholesterol in Males Aged 45-75*

Event***	Expected Percentage Increase in Risk	Approximate "Baseline" Risk (Cases per 100,000 at Risk per Year)**	Approximate Absolute Magnitude of Excess Risk (Additional Cases Per 100,000 at Risk per Year)
Coronary Heart Disease (Total)	21 (12-31)****	1576	331 (189-484)
myocardial infarction	20 (6.6-34)	716	140 (48-244)
coronary insufficiency	36 (11-66)	129	46 (14-85)
angina pectoris, uncomplicated	19 (4.1-36)	502	95 (21-180)
coronary heart disease death	22 (4.8-43)	376	84 (18-162)
(sudden)	22 (-.1-50)	199	44 (0-99)
Cerebrovascular Accident	5 (-10-24)	387	21 (-40-92)
atherothrombotic brain infarction	18 (-14-45)	203	36 (-8-90)
Intermittent Claudication	24 (7.2-42)	392	92 (28-166)
Congestive Heart Failure	14 (-2-33)	390	55 (-8-130)
ANY CARDIOVASCULAR DISEASE	19 (10-27)	2138	395 (223-581)

*Based on the multivariate regression coefficients from the Framingham Study, shown in the first column of Table 5.6.

**Based on the Framingham study data in Table 5.2 (p. 154), weighted by the proportion of the U.S. male population in various age groups (see text).

***For definitions of the various events shown, see Table 5.1 (pp. 151-3).

****Numbers in parentheses are the bounds of an approximate 95% confidence interval, based on the logistic regression coefficient plus or minus twice its standard error).

As would be expected from the logistic coefficients themselves, Table 5.7 shows that the difference in systolic blood pressure would be expected to have its largest percentage impact on stroke, and in particular the sub-category labelled "atherothrombotic brain infarction." In absolute numbers of cases per 100,000 people at risk, myocardial infarctions, uncomplicated angina pectoris, coronary heart disease deaths (both sudden and non-sudden, in people with no previous major symptoms of coronary heart disease), and congestive heart failure all are expected to provide about equal numbers of excess cases as atherothrombotic brain infarctions. The bottom line of the table indicates that overall the 6 mm Hg difference in systolic blood pressure should be associated with about a 10% increase in the risk of suffering at least one of the events listed in the table, or an absolute excess risk of about 200 cases per 100,000 people at risk per year.

Table 5.8 indicates that if an environmental agent or other circumstance were to produce a long term shift in serum cholesterol levels on the order of 33 mg/100 ml, the resulting differences in cardiovascular disease risks would be expected to be generally 2-4 times larger than the differences associated with a 6 mm Hg increase in systolic blood pressure. The only exception to this appears to be the overall risk of cerebrovascular accidents, where it appears likely that the effects of the blood pressure shift would be greater. Overall, the cholesterol shift would be expected to be associated with nearly a 20% increase in the risk of developing at least one of the major manifestations of cardiovascular disease, or with an absolute excess risk of about 400 cases per 100,000 per year.

These findings should not be misread in the process of planning future research on possible cardiovascular risks of noise. Although a 33 mg/100 ml shift in serum cholesterol, were it to occur, might be expected to produce a larger overall cardiovascular disease risk than the 6 mm Hg shift in systolic blood pressure, the body of literature suggesting blood pressure increases with chronic high level occupational noise exposure is vastly more substantial than that which suggests a shift in serum cholesterol levels. The inference which should be drawn is that the very tentative indication of an influence of noise exposure on serum cholesterol should be further pursued <u>together</u> with, not to the exclusion of, suggested effects

on blood pressure. The possible importance of the putative blood pressure effect itself is large enough to warrant further research and regulatory concern, given the millions of workers currently exposed on their jobs to very high noise levels (see exposure estimates, pp. 2-3 above and ref. 37). It should also be remembered that the very tentative, order-of-magnitude assessments of possible cardiovascular risks in this subsection include no allowance for possible noise effects by way of the enhancement of thrombotic tendencies through increased platelet adhesiveness (see Section 5.1.1, pp. 157-62 and Section 3.2.1, pp. 38-45 above) or by the triggering or enhancement of dangerous ventricular arrhythmias (see Section 5.1.2, pp. 162-7 above).

5.2.2 Needs for Better Mathematical Models of Cardiovascular Disease Risks

The multiple logistic risk model has proven to be a very useful tool for first-cut analysis of large volumes of data from long term prospective studies of cardiovascular disease incidence. Treating all putative risk factors impartially, convenient for computerized statistical work, it has allowed investigators to ask (1) which of a large number of clinically measurable parameters can be used to identify individuals with a high risk of developing clinical manifestations of cardiovascular disease, and (2) how strong is the apparent association between specific parameters and disease risk?

These questions, however, do not exhaust the list of interesting, researchable, and potentially useful questions which can be asked with epidemiological observations of cardiovascular disease risk. Moreover, the very properties of the multiple logistic model which make it so desirable for answering questions (1) and (2) above--equal treatment of risk factors, and convenience for computerized linear regression analysis--may well be crippling constraints in asking other important research questions. Prominent among such other questions are:

(A) Given an individual of a particular age and history of past levels of specific risk factors, what portions of the individual's cardiovascular disease risks are essentially fixed as a result of the past

history (embedded in the accumulated stock of atherosclerosis, for example) and what portions could be altered by changing specific risk factors by medical intervention, lifestyle changes, or reduction of adverse environmental exposures?

(B) Is every single relationship between a risk factor and a disease risk really a simple, monotonically increasing function with no threshholds at low levels of the risk factor, and no discontinuities due to unusual* subsegments of the population with very different risks at either high or low risk factor levels? If not, what threshholds do exist? What subpopulations do exist with unusual risk relationships and how can they be best distinguished from the majority?

(C) Do changes in all pairs of risk factors really change every disease risk in a synergistic (multiplicative) way? Aren't there any pairs of risk factors which interact in other ways (e.g., additively or even antagonistically) in changing the risk of a particular cardiovascular disease manifestation. If some pairs of risk factors interact differently than others, how and why does this occur?

One of the oldest traditions in biology is to elucidate relationships between structure and function. So too with mathematical models of disease risk; if they are to assist in the explication of basic biological processes, there should be some coherent rationale by which the structural features of the mathematical model are related to some functional reality about disease mechanisms. A mathematical model should not be simply an arbitrarily chosen convenient tool for summarizing data. Ideally, also:

- It should be at least plausible, both as a description of how changes in individual risk factors change disease risk, and as a description of how simultaneous changes in more than one risk factor combine to change disease risk. Like Watson and Crick's famous double-helical model of DNA structure--which was both compatible with the x-ray data and which illuminated the mechanism of DNA replication--a mathematical representation of a cardiovascular

*I.e., people with specific pathologies, rare genetic conditions, etc.

disease risk should both be compatible with available facts about the phenomenon under study, and it should provide insights into biologically significant mechanisms underlying the observable clinical manifestations of disease.

- It should assist investigators to pose fundamental questions for further research. As Watson and Crick's DNA model immediately raised the issue of how information was coded in the sequence of base pairs in DNA, a good mathematical model of cardiovascular disease risk--with separate representations of biologically meaningful components of the pathological processes (e.g., standing stock and rate of progress of atherosclerosis)--should spur research into whether, how, and why specific risk factors make contributions to specific components of cardiovascular risk.

We cannot hope to prove here that a better mathematical representation of cardiovascular disease risk is possible, much les specify such a representation. In the two subsections below, however, we will (1) offer some tentative analyses of available data which suggest there may be patterned departures from expected relationships under the multiple logistic risk model, and (2) suggest some theoretical starting points for the construction of better cardiovascular risk models.

5.2.1.1 Apparent Departures of Epidemiological Observations from Expectations of the Multiple Logistic Risk Model

Interactions of pairs of dichotomized risk factors, based on data from the Western Collaborative Group Study[382-3]

The Western Collaborative Group Study was an 8-1/2 year prospective cardiovascular morbidity study, patterned after Framingham, but principally designed to ascertain the predictive value of "Type A" vs. "Type B" behavior pattern as an independent risk factor in a group of over 3,000 employed men.* Brand,[394] using dichotomized risk factors (risk factors expressed

*The basic conclusion being that Type A behavior did indeed increase the risk of developing a clinical manifestation of heart disease independent of other risk factors--by about two-fold.[382-3]

as either plus or minus, based on a single cutoff level in each case) compared the overall performance of the multiple logistic risk model with a purely additive model* for the WCGS data. He concluded that the all-multiplicative logistic risk model provided a somewhat better fit to the data than the all-additive model, although neither model could be excluded using traditional statistical criteria based on χ^2 tests of the goodness of fit ($P = .81$ in the case of the multiple logistic risk model vs. $P = .35$ in the case of the all-additive model).

The raw data from Brand's paper is shown in Table 5.9. These data can be used to tentatively examine whether the coronary disease risks produced by specific pairs of risk factors appear to interact additively, multiplicatively, or somewhere in between. Table 5.10 shows the results of arranging these data into simple two-by-two tables for all possible combinations of two risk factors. Thus, for the "-,-" cell in the Age X Blood Pressure table, we combined all of the groups in Table 5.9 which were low in age (40-49 years) and also low in blood pressure (less than 126 mm Hg systolic) to arrive at 47 cases per 1139 men at risk over the study period. Having formed each of the four cells of the table similarly, we used the experience in the "-,-", "-,+", and "+,-" cells to predict the number of cases in the "+,+" cell using both an additive and a multiplicative risk model. First we used the raw numbers in each cell to compute $\frac{R}{1-R}$ for the four cells. If the multiple logistic risk model is correct, and the increases in $\frac{R}{1-R}$ interact multiplicatively, then:

$$\left(\frac{R}{1-R}\right)_{+,+\text{ cell}} = \left(\frac{R}{1-R}\right)_{-,-\text{cell}} \times \frac{\left(\frac{R}{1-R}\right)_{-,+\text{ cell}} \left(\frac{R}{1-R}\right)_{+,-\text{cell}}}{\left(\frac{R}{1-R}\right)_{-,-\text{cell}} \left(\frac{R}{1-R}\right)_{-,-\text{cell}}}$$

$$= \frac{\left(\frac{R}{1-R}\right)_{-,+\text{cell}} \left(\frac{R}{1-R}\right)_{+,-\text{cell}}}{\left(\frac{R}{1-R}\right)_{-,-\text{cell}}}$$

*The all-additive model was formulated as

$R = A_0 + A_1X_1 + B_1X_1 + \ldots$

Table 5.9

Coronary Heart Disease Experience in the Western Collaborative Group Study, for Various Combinations of Dichotomized Risk Factors

Risk Factors					
Serum Cholesterol***	Behavior Pattern****	Systolic Blood Pressure*****	Cigarette Smoking******	"Age-" Risk*	"Age+" Risk**
-	-	-	-	1/232	0/45
-	-	-	+	2/144	0/31
-	-	+	-	7/170	3/47
-	-	+	+	4/103	3/33
-	+	-	-	5/147	0/47
-	+	-	+	6/118	5/53
-	+	+	-	7/135	7/60
-	+	+	+	8/123	9/63
+	-	-	-	3/133	1/30
+	-	-	+	6/126	6/42
+	-	+	-	8/122	5/85
+	-	+	+	19/148	11/67
+	+	-	-	6/109	7/52
+	+	-	+	18/130	7/50
+	+	+	-	15/130	23/103
+	+	+	+	30/172	25/92
				145/2242	112/900

Source: Brand, Ref. 384

*Number of cases of new coronary disease per number at risk, among men between 39-49 years of age.

**Number of cases of new coronary disease per number at risk, among men between 50-59 years of age.

***"-" indicates serum cholesterol levels less than 223.0 mg/100 ml, "+" indicates serum cholesterol levels greater than or equal to this value.

****"-" indicates "Type B" behavior pattern, as determined by an interview procedure "+" indicates "Type A" behavior.

*****"-" indicates systolic blood pressure less than 126 mm Hg, "+" indicates systolic pressures greater than or equal to this value.

******"-" indicates nonsmoker, "+" indicates some cigarettes smoked.

Table 5.10

Crude Tests for Additive vs. Multiplicative Interactions Among Pairs of Dichotomized Risk Factors in the Western Collaborative Group Study

			EXPECTED NUMBER OF CASES (NUMERATOR) IN +/+ CELL UNDER ADDITIVE RISK MODEL*	EXPECTED NUMBER OF CASES (NUMERATOR) IN +/+ CELL UNDER MULTIPLICATIVE RISK MODEL*	TENTATIVE CONCLUSION ###
	SYSTOLIC BLOOD PRESSURE				
	-	+			
AGE	- 47/1139**	98/1103			
	+ 26/353	86/550	65.3	84.6	MULTIPLICATIVE
	BEHAVIOR PATTERN				
	-	+			
AGE	- 50/1178	95/1064			
	+ 29/380	83/520	62.4	80.3	MULTIPLICATIVE
	CIGARETTE SMOKING				
	-	+			
AGE	- 52/1178	93/1064			
	+ 46/469	66/431	58.9	79.3	INTERMEDIATE
	CHOLESTEROL LEVEL				
	-	+			
AGE	- 40/1172	105/1070			
	+ 27/379	85/521	68.0	99.5	INTERMEDIATE
	SYSTOLIC BLOOD PRESSURE				
CHOLESTEROL LEVEL	-	+			
	- 19/817	48/734			
	+ 54/672	136/919	108.3	188.8	INTERMEDIATE
	BEHAVIOR PATTERN				
	-	+			
CHOLESTEROL LEVEL	- 20/805	47/746			
	+ 59/753	131/838	94.3	153.6	INTERMEDIATE
	CIGARETTE SMOKING				
	-	+			
CHOLESTEROL LEVEL	- 30/883	37/668			
	+ 68/764	122/827	89.4	115.3	MULTIPLICATIVE
	SYSTOLIC BLOOD PRESSURE				
	-	+			
CIGARETTE SMOKING	- 23/795	75/852			
	+ 50/694	109/801	101.1	161.0	ADDITIVE
	BEHAVIOR PATTERN				
	-	+			
CIGARETTE SMOKING	- 28/864	70/783			
	+ 51/694	108/801	100.8	151.1	ADDITIVE
	SYSTOLIC BLOOD PRESSURE				
	-	+			
BEHAVIOR PATTERN	- 19/783	60/775			
	+ 54/706	124/878	109.1	191.8	ADDITIVE

*ADDITIVE RISK MODEL: (+/+ cell) = (+/- cell) + (-/+ cell) -(-/-cell)

MULTIPLICATIVE RISK MODEL: $(+/+\text{ cell}) = \frac{(+/-\text{ cell})(-/+\text{ cell})}{(-/-\text{cell})}$

**NUMBERS OF TOTAL CORONARY HEART DISEASE CASES/NUMBERS AT RISK (8-1/2 YEARS FOLLOWUP)

###THESE TENTATIVE CONCLUSIONS ARE NOT INTENDED TO IMPLY STATISTICALLY SIGNIFICANT DIFFERENCES FROM EXPECTATIONS UNDER EITHER THE ADDITIVE OR MULTIPLICATIVE MODELS--THEY SIMPLY NOTE SUGGESTIVE TRENDS IN THE DATA.

If, on the other hand, the increases in $\frac{R}{1-R}$ simply add, then:

$$\left(\frac{R}{1-R}\right)_{+,+\text{cell}} = \left(\frac{R}{1-R}\right)_{-,+\text{ cell}} + \left(\frac{R}{1-R}\right)_{+,-\text{cell}} - \left(\frac{R}{1-R}\right)_{-,-\text{cell}}$$

Having computed each expected $\frac{R}{1-R}$ for the +,+ cell, we found the corresponding R and multiplied by the number of people at risk in the +,+ cell to predict the number of expected cases (i.e., the numerator of the fraction shown in the +,+ cell.) It can be seen that in some cases the data fit quite well with the expectations of the multiplicative model, but in other cases the results are more compatible with additive interactions, or fall between the expectations of the two models. Table 5.11 summarizes the tentative conclusions of Table 5.10 about the interactions between different pairs of risk factors, as additive, multiplicative, or intermediate.

We have done no formal statistical testing of the likelihood that departures from the expectation of the multiplicative model as large as those seen in Table 5.10 would be expected to occur by chance. Such testing would need to be more intricate than a simple χ^2 test for goodness-of-fit because sampling errors in the determination of the "R's" in each cell will propagate in complex ways through the various computations required to calculate the expected number of cases in the +,+ cells. Moreover, because all of the two-by-two tables are based on the same data, they clearly cannot be considered independent of one another. Nonetheless, we feel that particularly for the interactions we have labelled "additive," the departures from expected multiplicative interactions are suggestive enough (and potentially important enough for future model building) to warrant further exploration with other data. Further work should explore finer gradations of risk factor levels, and also attempt more rigorous control of possible confounding effects of other risk factors by matching or other procedures.

Patterned Departures from Expectations of Logistic Models Observed in Data from the "Pooling Project"[57]

The largest single source of epidemiological data which could be used to test whether the interactions between various risk factors depart appreciably from the expectations of the multiple logistic model is a

Table 5.11

Summary of Conclusions of Crude Tests for Additive vs. Multiplicative Interaction of Dichotomized Risk Factors in the WCGs*

	Behavior Pattern	Cigarette Smoking	Cholesterol	Age
Systolic Blood Pressure	ADD.	ADD.	INT.	MULT.
Behavior Pattern		ADD.	INT.	MULT.
Cigarette Smoking			MULT.	INT.
Cholesterol Level				INT.

*MULT. = Multiplicative

INT. = Intermediate

ADD. = Additive

combined set of observations from five different studies* which has recently been compiled under the auspices of the American Heart Association.[131] The resulting data set, collectively known as "Pool 5," contains observations from 8,422 men between 40-59 years of age at entry, followed for a total of 72,011 person-years, during which time 658 "first major coronary events"** occurred.

Unfortunately, the published final report from the pooling project does not express the data in a form which allows direct application of the same techniques used in the previous section. (Also, it appears that the agreement under which the now completed pooling project was conducted does not allow release of the data to outside investigators for further analysis.[385]) Some other types of comparisons of observations with the expectations of the multiple logistic model are possible, however, with the published material. In particular, because the published report contains the results of bivariate logistic regressions including age and one of a set of other risk factors, we can at least get some idea of whether there appear to be any systematic departures from expectations under the logistic model for pairwise combinations of age with other risk factors.

Figure 5.2 is a direct plot of observed incidence of major coronary events (per 1,000 men per 8.6 years of observation) vs. the incidence expected under the pooling project's bivariate logistic fits of the data for combinations of age with systolic blood pressure, serum cholesterol level, smoking, and relative weight. In each case, Figure 5.2 contains five points, corresponding with quintiles of expected risk. The line represents the expectation that (observed risk) = (expected risk).

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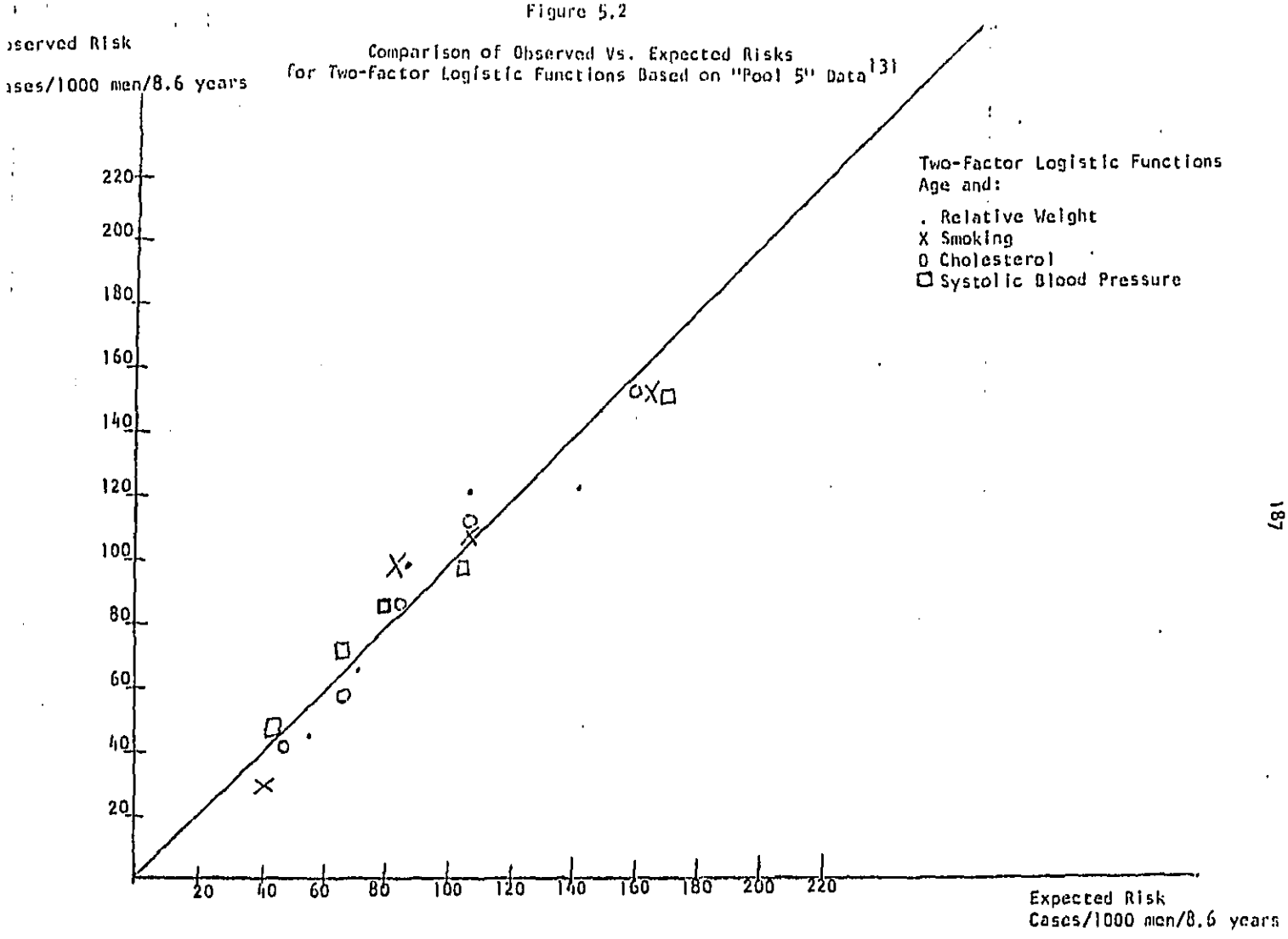
*The Albany Cardiovascular Health Center Study (civil service employees), the Chicago Peoples Gas Co. Study (employees), the Chicago Western Electric Co. Study (employees), the Framingham Heart Disease Epidemiology Study (general community members) and the Tecumseh Health Study (general community members). Three other studies, the Los Angeles Heart Study, the Minnesota Business and Professional Men study and the U.S. Railroad Workers Study, were considered but not ultimately included in the Pool 5 data set.

**"Major Coronary Events" were defined as either fatal or nonfatal myocardial infarction plus sudden coronary heart disease death (death within three hours of the onset of symptoms).

Figure 5.2

Comparison of Observed Vs. Expected Risks
for Two-Factor Logistic Functions Based on "Pool 5" Data[131]



The departures of observed from expected risks in Figure 5.2 are not large; in all cases the observed risks are within about ±25% of expected risks. Nonetheless there is a suspicious tendency for the points in the high- and low-risk ends of the figure to fall below the expected line (7/8 of the points from the highest and lowest quintiles are below the line) while points in the central region of the figure tend to fall above the expected line (4/4 of the points from the middle quintile are above the line).

Re-reading the pioneering paper of Truett et al.,[63] we found that this same kind of anomaly was noticed and pointed out in the earliest application of the multiple logistic model to the Framingham Study data. Table 5.12 shows expected and observed cases for deciles of cardiovascular risk in men and women age 30-62 at entry, based on a seven-factor multiple logistic model (using age, serum cholesterol, systolic blood pressure, relative weight, hrmoglobin concentration, cigarette smoking, and ECG abnormality as risk factors):

Table 5.12

EXPECTED AND OBSERVED NUMBER OF CASES OF CHD AND OBSERVED INCIDENCE IN 12 YR OF FOLLOW-UP AT FRAMINGHAM OF MEN AND WOMEN AGED 30–62 YR AND FREE OF CHD AT ORIGINAL EXAMINATION, BY DECILE OF RISK

Decile of risk	2187 Men		Observed 12-yr incidence (no. of cases per 100)	2559 Women		Observed 12-yr incidence (no. of cases per 100)
	Number of cases			Number of cases		
	Expected	Observed		Expected	Observed	
10	90.5	82	37.5	70.4	54	20.2
9	47.1	44	20.1	24.7	23	8.6
8	32.6	31	14.2	15.0	21	7.9
7	25.0	33	15.1	9.8	14	5.2
6	19.7	22	10.1	6.5	5	1.9
5	15.0	20	9.1	4.4	6	2.2
4	11.5	13	5.9	3.2	2	0.7
3	8.6	10	4.6	2.3	0	0.0
2	6.0	3	1.4	1.7	3	1.1
1	3.4	0	0.0	1.1	1	0.4
Total	259.4	258	11.8	139.1	129	4.8

Source: Truett, et al., Ref. 63

Figures 5.3-5.6 pursue this observation somewhat further based on the "Pool 5" data. For these figures, we have obtained more points for comparison with the expectations of the bivariate logistic models by making some calculations from age-specific univariate logistic regression

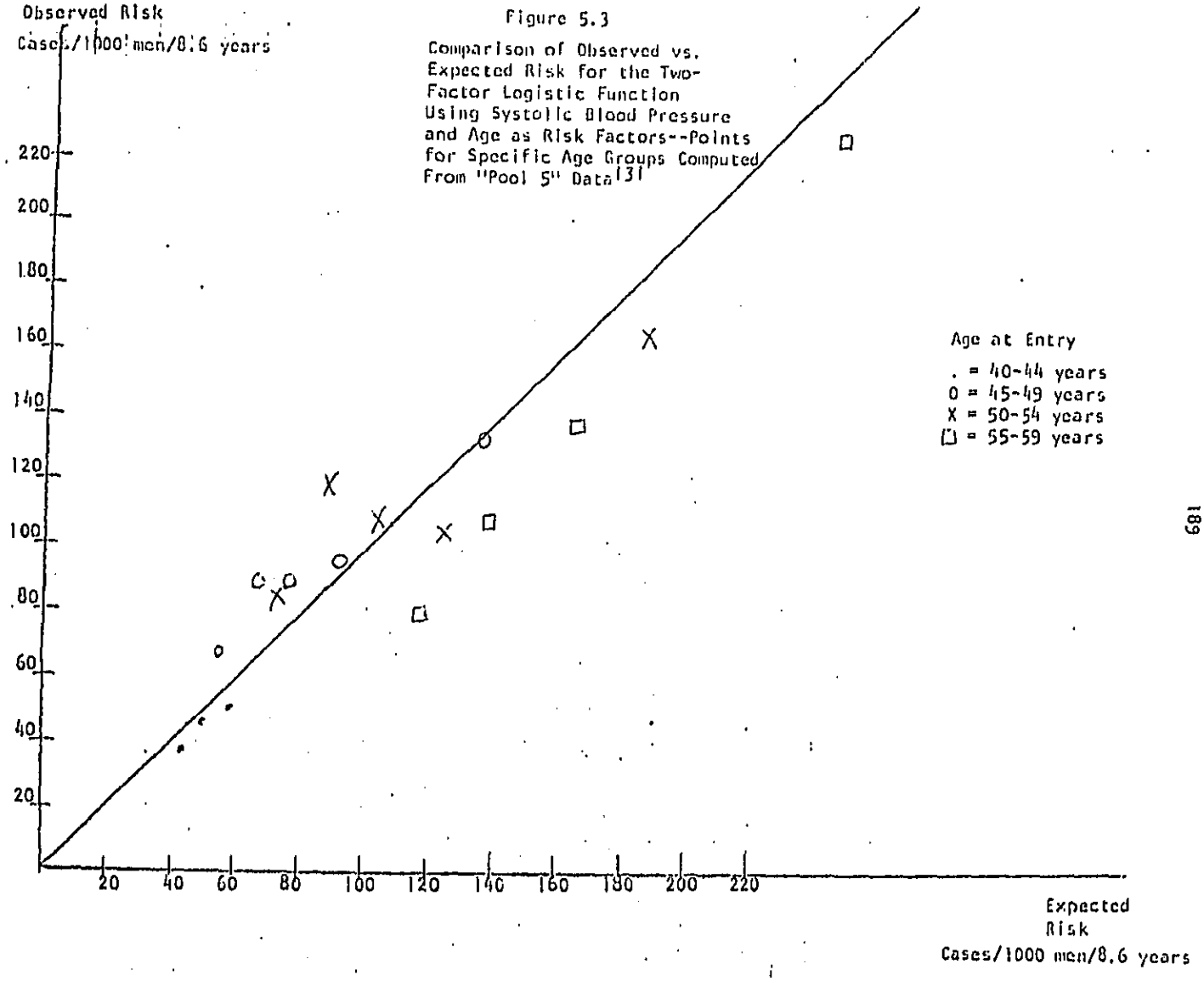


Figure 5.3

Comparison of Observed vs. Expected Risk for the Two-Factor Logistic Function Using Systolic Blood Pressure and Age as Risk Factors--Points for Specific Age Groups Computed From "Pool 5" Data[31]

Figure 5.4

Comparison of Observed vs. Expected Risk for the Two-Factor Logistic Function Using Serum Cholesterol and Age as Risk Factors--Points for Specific Age Groups Computed From "Pool 5" Data[31]

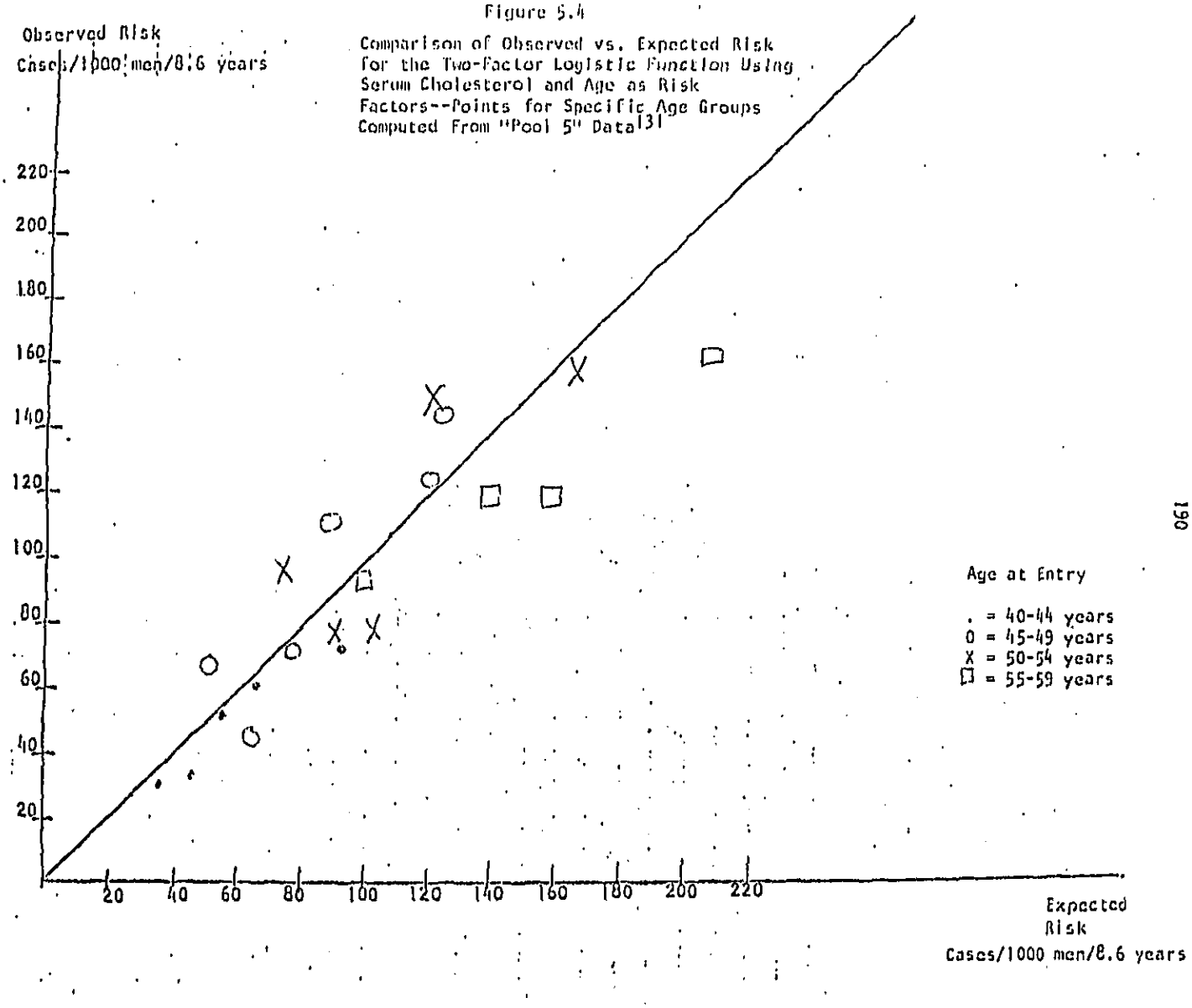


Figure 5.5

Comparison of Observed vs. Expected Risk for the Two-Factor Logistic Function Using Cigarette Smoking and Age as Risk Factors--Points for Specific Age Groups Computed from "Pool 5" Data[31]

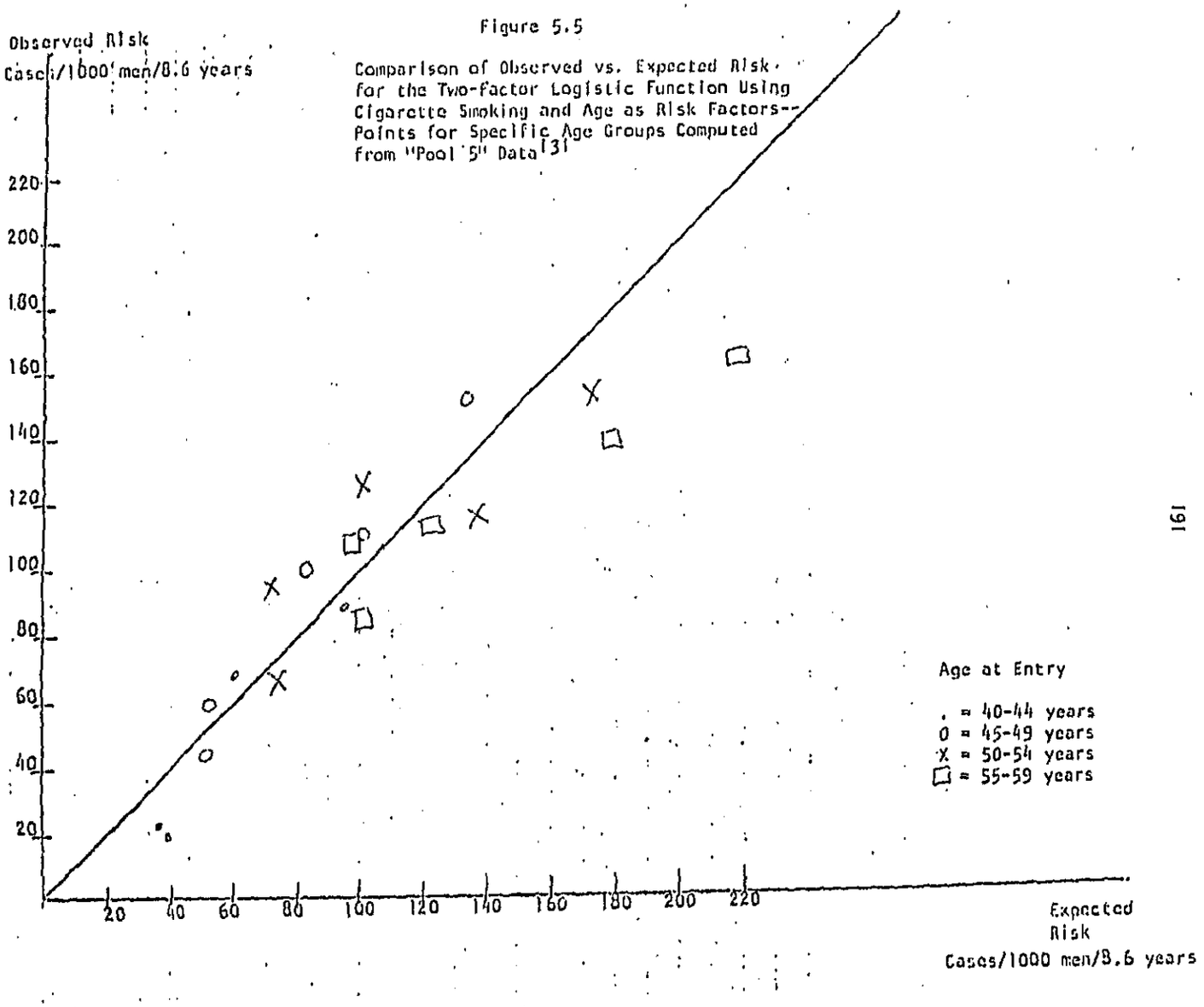
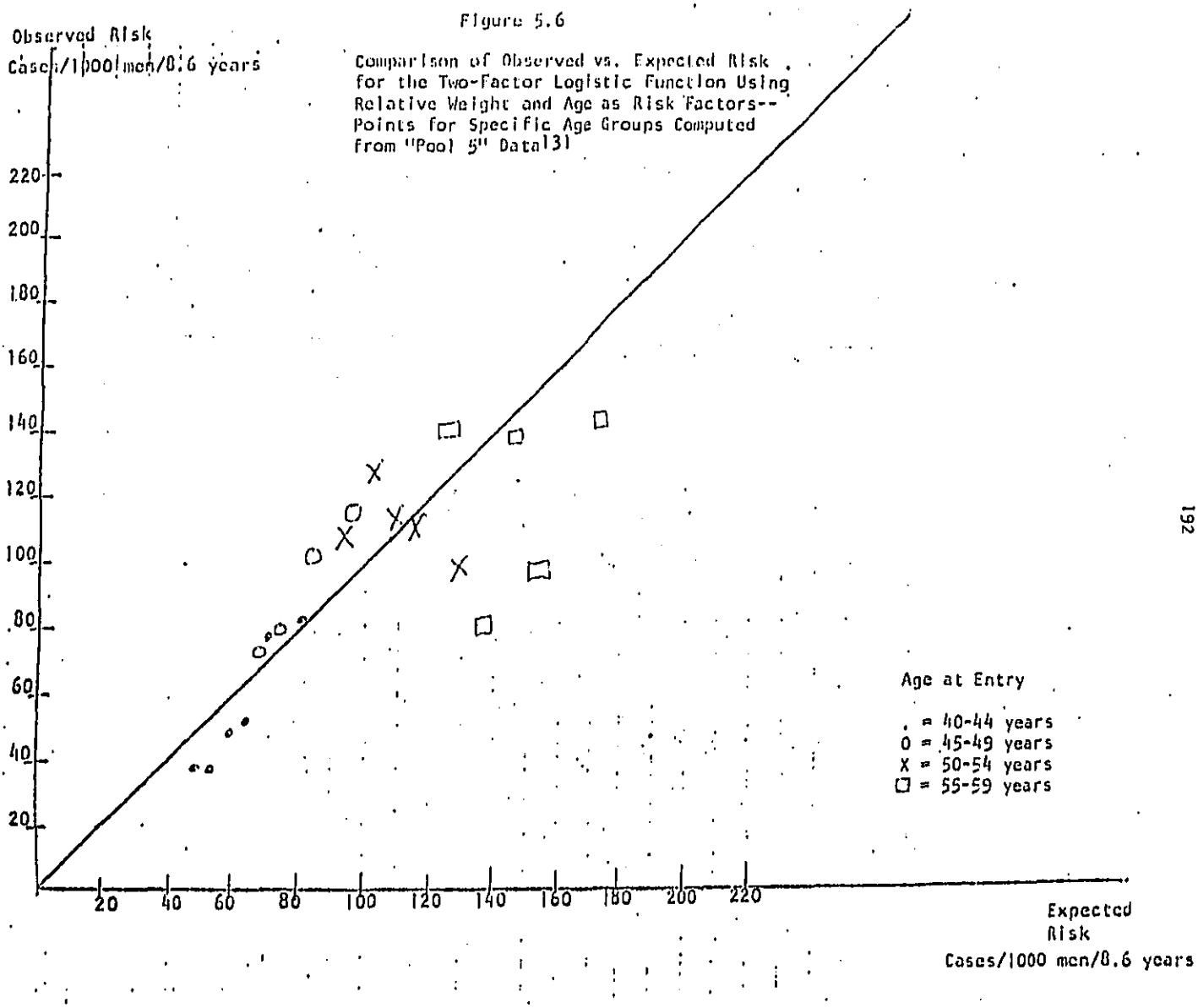


Figure 5.6

Comparison of Observed vs. Expected Risk for the Two-Factor Logistic Function Using Relative Weight and Age as Risk Factors--Points for Specific Age Groups Computed from "Pool 5" Data[3]



coefficients and expected rates of major coronary events within five quintiles of risk factor level for four narrowly-defined ranges of age at entry into the study. From these data it was possible to calculate approximate geometric means for the levels of each risk factor for the men in each quintile of the four age ranges. Using these risk factor levels, together with the middle of the appropriate age range for the various groups, we could then calculate expected risks for each of the 20 (age X risk factor) quintiles using the given bivariate logistic equations. Figures 5.3-5.6 compare each of these expected risks with the corresponding observations for age X systolic blood pressure, age X serum cholesterol, age X cigarette smoking, and age X relative weight. The tendency noted earlier, for observations to exceed expectations in the middle regions of the figures, and to fall below expectations at both extremes, can be clearly seen in these results. The effect appears to be least marked in the case of systolic blood pressure, which, it will be remembered, appeared to show the best synergism with age in the previous section's analysis of WCGS results.

It should be emphasized that these are not large perturbations from the pattern of results expected from the multiple logistic model. Nonetheless, their consistency suggests that there may be more to be learned from close study of existing epidemiological data using models of coronary disease risk constructed to reflect facts and current hypotheses about the biological mechanisms of cardiovascular disease. Like the small perturbations in orbits which led to the discovery of the outer planets, these departures from expected risk patterns may hold a key to fundamental insights into pathological processes and the likely efficacy of alternative measures for prevention.

5.2.2.2 Some Theoretical Starting Points for the Construction of Better Cardiovascular Risk Models

As stated at the outset, we will not attempt here to specify candidate mathematical models to better represent particular cardiovascular disease risks. Such model building must necessarily be an iterative process in which various formulations are generated from basic insights into disease mechanisms, compared with available biological and epidemiological data,

re-cast, and re-compared with the existing and new data. We can, however, suggest some basic theoretical propositions which we hope may be helpful to others in beginning to sort out what are undoubtedly complex relationships between risk factors and disease risks:

- Different kinds of cardiovascular disease risks should be described by mathematical models with different (though, perhaps, related) forms.

It seems impossible to us that conditions as diverse as angina pectoris, stroke, and myocardial infarction can all be described by equations of the same basic form. Their causal mechanisms are different and, as can be seen in Table 5.2 (p. 154), the ways their risks change with age are quite different. Few seem to show the behavior predicted by the multiple logistic model; (i.e., the percentage increase in risk between 45-54 and 55-64 should be about equal to the percentage increase in risk between 55-64 and 65-74).

- A good model of myocardial infarction or other sudden clinical disease manifestations with likely "triggering events" should include separate representations of the contributions of risk factors to (1) chronic cumulative pathological processes* and (2) the sequence of events which precipitates the clinically-observable syndrome.

In other words, at any one time the risk of a particular type of myocardial infarction should be given by:

$$R_{MI(1)} = f(\text{stock of atherosclerotic lesions, probability of precipitating event per unit of atherosclerotic lesion})$$

where

$$\text{stock of atherosclerotic lesions} = F(\text{serum cholesterol and other risk factors, summed in some way over elapsed time since the beginning of lesion generation})$$

*E.g., atherosclerosis, or different aspects of atherosclerosis related to the likelihood of specific kinds of clinical manifestations of disease.

and

probability of precipitating event per unit of atherosclerotic lesion = G(current levels of risk factors and their variability)

- If there is expected to be more than one independent causal route which can produce a particular clinical manifestation of cardiovascular disease, the risk of that event should basically be a summation of the risks of each independent causal route.

Thus, if there are really three independent kinds of events which can initiate a myocardial infarction--say (1) thrombosis, (2) primary arrhythmia from an unusual sympathetic stimulus, or (3) spasm of a coronary artery--then the total risk of myocardial infarction should be given by:

$$R_{MI(any)} = 1 - [1 - R_{MI(1)}] [1-R_{MI(2)}] [1-R_{MI(3)}]$$

or, at small values of all R's, approximately:

$$R_{MI(any)} = R_{MI(1)} + R_{MI(2)} + R_{MI(3)}$$

- If risk factors contribute to successive rate-limiting steps in a particular causal pathway, those contributions should basically interact multiplicatively in affecting the risk from that pathway.

Thus if risk factor A were to increase the rate of primary endothelial injury leading to the initial formation of fibrous plaques, and risk factor B were to increase the rate at which fibrous plaques became complex calcified atherosclerotic lesions with a specific pathological significance, then the total risk from increases in the two factors by this pathway would be approximately the product of the increases due to each factor acting separately.

- Where appropriate, "saturation" phenomena should be built into the representations of chronic or acute processes in recognition of the fact that (1) beyond a certain level, lesion accumulation or the occurrence of a specific event may not be a rate limiting

factor in an overall pathological process or (2) beyond a certain point, a pathological process may be less susceptible to acceleration by a particular risk factor.

As an example of the second point, it seems likely that atherosclerosis occurs first in sections of the arteries which, because of turbulence and other local conditions, are most susceptible to it. After primary atherosclerotic lesions have already covered an appreciable portion of the relevant arterial tree, it probably takes a greater amount of atherogenic input (expressed in time X risk factor levels) to produce a given further increment of atherogenic lesion output or spread. Data on the area covered by fibrous plaque with age suggest diminished rates of spread at older ages (although the interpretation of this is complicated by possible selection bias).

- Individual risk factors should enter the equation more than once (perhaps in different forms) if they are expected to make contributions to a particular cardiovascular disease manifestation by more than one causal mechanism.

Thus, if systolic blood pressure affects both atherogenesis and the production of certain precipitating events, it should appear in portions of the mathematical model which relate to these two processes. If $(\text{blood pressure})^2$ best predicts increased risk in the atherogenesis section and $(\text{blood pressure})^{1/2}$ best predicts increased risk in the precipitating event section, then so be it. It seems unlikely that simple untransformed expressions of variables such as blood pressure and serum cholesterol will provide the best descriptions of the degree of enhancement of underlying pathological processes in all cases.

- Fundamentally different kinds of risk factors should be represented in the model in fundamentally different ways.

It seems to us that there are at least three fundamentally different kinds of parameters which have been treated together as "risk factors." First, there are the primary risk-related parameters like serum cholesterol and systolic blood pressure which are very likely to be direct causal contributors to the atherogenic process, the processes which precipitate

clinical events, or both. Second, there are properties such as ECG abnormalities, which basically indicate that cardiovascular disease has already progressed to a particular stage in the affected individual. They thus capture some aspects of an individual's past history and indicate current, potentially important malfunction, but cannot be said to directly "cause" subsequent disease manifestations. Finally, there is age, which also does not directly cause particular pathological manifestations, but basically indicates the opportunity which has taken place in the past for accumulation of chronic lesions. Age should interact importantly with the risk factors which contribute to atherosclerosis, and may affect precipitating events through otherwise unrepresented mechanisms which increase the variability of other risk factors. In any event, future model builders should give careful thought to the different roles which should be assigned to these three different kinds of parameters in representing cardiovascular disease risks.

5.3 Promising Approaches for Further Research into Relationships Between Responses and Clinical Manifestations of Cardiovascular Disease

Assessing possible relationships between environmental/emotional stimuli, short-term physiological responses, and the events which precipitate clinical manifestations of cardiovascular disease, is an exciting and highly promising area for further research. This area has the immense advantages for researchers and research planners that (1) the phenomena under study occur on a time scale of minutes or hours, rather than months of even decades, and (2) major clinical manifestations of disease usually produce obvious symptoms which cause the victim to be brought to the attention of medical professionals.

- For researchers these properties mean (1) a short turn-around time for feedback of experimental results into theory formation and new experimental design and (2) a large human population which, because of previous and current clinical symptoms, is available to be studied directly (by contrast, experiments investigating the "silent" pre-clinical progression of chronic pathological processes must be conducted primarily in healthy people, in whom severely invasive procedures and intensive repeated follow-up cannot generally be justified or performed.)

- For research planners in agencies concerned with the effects of particular occupational/environmental exposures, these properties mean that (1) health benefits of productive interventions to prevent disease can be expected to become apparent within relatively short times after the intervention measures are implemented and (2) the health benefits appear in the form of reductions in clinical cases of disease--a type of output of obvious value to decision makers (by contrast, the benefits of reducing the rate of asymptomatic progression of atherosclerosis or chronic increase in blood pressure are less readily appreciated though in the long run, perhaps no less important.)

In Section 5.1 above, we explored in some detail two mechanisms which are thought to be important in precipitating the most seriously life-threatening clinical manifestations of cardiovascular disease: thrombosis (important for myocardial infarction and stroke), and ventricular arrhythmias (important for sudden cardiac death, with or without infarction).

In the case of thrombosis, the major research hurdle we identified was the fact that it is uncertain which of several different clinical procedures used to measure aspects of platelet aggregation behavior[326, 332-6] are good predictors of future infarction risks. Results of the Aspirin Myocardial Infarction Study and related studies of the efficacy of aspirin and other anti-platelet drugs in preventing the recurrence of infarction in survivors of previous heart attacks are now in the process of publication. Hopefully future follow-on studies of pharmacological agents which do and do not help to prevent infarctions will illuminate exactly which clinically-measurable aspects of platelet aggregation and/or adhesion are predictive of enhanced risk of myocardial infarction and stroke. Once such information is forthcoming, the effects of noise, other occupational exposures, and emotional stimuli could be assessed with the knowledge that the platelet aggregation/adhesion parameter being measured had a good chance to be causally related to risks of myocardial infarction and stroke. The noise experiments might ideally be performed using the Ising paradigm of comparisons of the same individuals with or without hearing protectors, as described in Section 3.3.

In the case of ventricular arrhythmias, we were surprised to find a not inconsiderable body of direct evidence that (1) sympathetic nervous stimulation

in general, (2) emotional responses to stressful stimuli and (3) responses to brief exposures to loud noises in particular, can trigger life-threatening types of ventricular arrhythmias in hearts which have been rendered electrically unstable by a variety of other pathological conditions. Two kinds of further studies seem indicated on the basis of these findings, and the general importance of sudden cardiac death:*

- In conjunction with the large cross-sectional surveys of noise, other occupational exposures, and blood pressure which were outlined in Section 4.2.4 (pp. 145-6 above), representative samples of workers with documented exposures to noise or other agents suspected of causing arrhythmias[376] should be enrolled into a prospective cohort and followed up periodically for the occurrence of sudden and non-sudden death from coronary disease and other causes. There should at least be a one-time screening for ECG abnormalities and other cardiovascular risk factors upon entry of individuals into the cohort, and if feasible, matching should be performed for risk factors not of primary interest in the study. The unambiguous nature of sudden death as an end-point facilitates the design of high quality epidemiological studies, if sufficient numbers of cases can be accumulated.

- Second, it appears from studies by Tåggart[365] that it may be possible to perform electrocardiographic monitoring of people engaged in ordinary day to day activities, in the presence or absence of specific environmental stimuli. Such studies would be greatly assisted by the use of modern automated data processing methods which have been established to detect and quantify arrhythmias.[375] Again, low cost experiments based on the Ising paradigm of within-individual comparisons on days when hearing protectors are and are not worn, appear likely to yield important insights into which kinds of noise stimuli are dangerous and which kinds of people are at high risk.

We will not recapitulate here the data and reasoning presented in Section 5.2 on needs and opportunities for construction of better mathematical models of cardiovascular disease risks than the standard multiple logistic risk model. Suffice it to say that we believe a creative reanalysis of existing data from long term prospective studies of cardiovascular disease risks is likely to uncover previously unsuspected facts about the interactions of specific risk factors in affecting specific disease risks, among other topics.

N.B. Chapter 6 appears at the beginning of this document.

6. SUMMARY/OVERVIEW OF RESEARCH SUGGESTIONS

This project began as a rather limited effort to (1) survey the existing literature indicating cardiovascular effects of high noise exposure, (2) place that literature in perspective based on the available knowledge of general cardiovascular effects of "stressful" stimuli, and (3) suggest promising avenues for further research. The inquiry mushroomed well beyond the original expectations of size and time required for completion as we realized that in order to sensibly perform the second and third parts of our task as listed above, it would be necessary to include in our work, to the degree possible, an exploration of the needs and opportunities for new directions in cardiovascular disease research in general.

"Cardiovascular disease research in general" comprises so vast a subject area that no one can pretend to have mastered any substantial portion of it in its details. Nonetheless, in attempting to construct overviews of physiological responses to environmental/emotional stimuli (Chapter 3), the chronic cumulative processes of atherosclerosis and long term increases in blood pressure (Chapter 4), and the mechanisms which precipitate clinical manifestations of cardiovascular disease in the short term (Chapter 5), we believe we may have come across some conceptual and technical obstacles which, if removed, might allow more rapid progress in advancing scientific understanding and expanding the range of efforts available to assist in prevention. Before outlining our findings on the needs and opportunities for research into cardiovascular effects of noise, we will highlight some of these more general obstacles to research progress.

6.1 Conceptual Obstacles to Progress in Cardiovascular Disease Research

In a number of fields of cardiovascular disease research, progress may be greatly assisted if investigators fundamentally re-think the way they think about the problems in their disciplines. Most generally, primary biomedical research concerned with the pathological mechanisms underlying cardiovascular diseases must interact much more intimately with epidemiological/statistical/medical intervention research concerned with documenting cardiovascular risk factors and intervening to lower risks by controlling risk factors. There appear to be at least two major

examples where the professional isolation of these two broad groups of researchers may have led large numbers of workers to misperceive basic facts about the cardiovascular disease phenomena under study and ignore likely productive areas for research:

- The multiple logistic risk model, which for practical purposes has been the sole mathematical model used for analysis of the results of long term prospective epidemiological studies such as Framingham, reflects no facts or hypotheses about cardiovascular disease mechanisms or the contributions of various kinds of risk factors to those mechanisms. For purposes of analysis, risk factors as diverse as age, serum cholesterol, and electrocardiographic abnormalities are treated as if they contributed in analogous ways to particular clinical manifestations of cardiovascular disease. The risks of clinical events as diverse as stroke, angina pectoris, and sudden cardiac death are all modelled using equations of identical form. Finally, the equations contain no separate terms or factors which distinguish between the contributions of risk factors to chronic processes such as atherosclerosis, and the contributions to the short-term events which precipitate clinical manifestations such as myocardial infarction and stroke. However well these equations can be made to fit the data by adjusting the coefficients of various risk factors, it seems highly implausible that they can be accurate descriptions of underlying causal relationships. The sole use of such restricted models for analysis of epidemiological data prevents the hard-won numbers from shedding light on alternative hypotheses related to disease mechanisms, and probably introduces errors in the prediction of the efficacy of programs to reduce specific risk factors in reducing cardiovascular disease cases. In Section 5.2.2 (pp. 178-197) we discuss some apparent anomalies in the fit between the multiple logistic risk model and epidemiological data, and suggest some starting points for the construction of better mathematical models.

- Researchers investigating mechanisms of hypertension have very frequently adopted a medical model of the condition they were studying--separating people into a minority of "hypertensives" and a majority of "normals" by one arbitrary diagnostic criterion or another. The fundamental facts from available epidemiological data, (1) that blood pressures typically have continuous unimodal log-normal distributions in populations, and (2) that blood pressures of large portions of the population increase with age, have not been given the weight they deserve in shaping research questions. Investigators have tended to ask "What abnormality about these particular people has made them hypertensive?" (thus focusing only on one tail of the distribution of blood pressures) rather than "What causes long term increases in blood pressure with age in the majority of people?" In the specific case of investigators exploring possible relationships between noise and high blood pressure, this has led nearly always

> to reporting of results in terms of increases in the numbers of "hypertensives" by some defined criterion. Such reporting has obscured important aspects of the results which would have been revealed had investigators realized the need to report findings in terms of the entire distribution of blood pressures in high noise-exposed and control populations.
>
> In Section 4.2.2 (pp. 100-116), we suggest techniques for expressing shifts in population distributions of blood pressure which may be helpful in detecting facts relevant both to mechanisms of blood pressure increase and to the public health significance of those increases. The yield of information from these techniques is illustrated with a reanalysis of data from a recent study of hypertension in Air Traffic Controllers. The important result was obtained that shifts in blood pressure in this population appear to have been at least as great in members of the population toward the low end of the blood pressure distribution as in members of the population with intrinsically greater than average pressures.*

In the first example above, epidemiological/statistical/medical intervention research appears to have suffered for a lack of functional professional interaction with the huge body of research on pathogenic mechanisms of cardiovascular diseases. The second example shows the effects of the reverse problem; research on pathogenic mechanisms may have suffered for lack of appreciation of readily available facts from the epidemiological/statistical literature.

The homeostatic system/threshold paradigm** from traditional toxicology and physiology has been another major conceptual obstacle for researchers in recognizing potential contributions to chronic cardiovascular disease processes from transient physiological responses to "stressful" environmental stimuli. In the homeostatic system/threshold paradigm, biological processes are seen as part of a complex interacting web, exquisitely designed so that modest perturbations in any parameter will automatically give rise to adaptive negative feedback processes to restore optimal functioning. In this view, so long as an external stimulus does not push one or more parameters

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*This kind of observation has important implications for public health policy, if indeed (as the Framingham and other data suggest) increments in blood pressure increase cardiovascular risks continuously over all levels of blood pressure. Because ordinary medical treatment for hypertension will only be used for controllers whose blood pressures persistently exceed levels considered indicative of "hypertension," the excess heart disease and stroke risk for the remainder of the population which does not exceed these levels is effectively beyond the realm of secondary medical prevention efforts. Primary prevention efforts, seeking to reduce the action of whatever factors are leading to chronic blood pressure elevation in the controller population, has potential benefits beyond those which are realizeable with the best currently utilized medical care practices for treating "hypertension."

**The word "paradigm" is used here in the sense of Kuhn's Structure of Scientific Revolutions.[152]

beyond a specified limit ("threshold") adaptive processes will repair any damage which may have been temporarily produced and completely restore the system to the functional state prior to the stimulus.

This paradigm has enjoyed great success in guiding the design and interpretation of a wide range of experimental findings on acute responses to toxic chemicals, heat, cold, and other agents where the mechanism of damage does, in fact, consist of grossly overwhelming a particular set of bodily defenses. However, the homeostasis/threshold paradigm has been less successful (and sometimes very misleading) when applied to situations such as cancer and mutations where subtle but irreversible damage can result from one or a small number of events on a microscopic scale governed by stochastic processes.

In the cases of atherosclerosis and chronic increase in blood pressure, we have processes which have conspicuous differences from both the homeostasis/threshold model, and the stochastic molecular biological model. These major cardiovascular disease processes appear to consist of chronic accumulations of incompletely repaired or misrepaired small-scale damage events. Such chronic accumulation of individually insignificant damage events does not fit within the framework of massive short-term breakdown of adaptive mechanisms suggested by an unmodified version of the homeostasis/threshold model. On the other hand, because the events underlying atherosclerosis and long term blood pressure increase must take place in enormous numbers, rather than the few critical events required for the molecular biological diseases, stochastic models based on small numbers of "hits" are also clearly inappropriate.

Homeostatic processes clearly play a prominent role in the day-to-day and year-to-year regulation of cardiovascular functioning, and the overt clinical manifestations of disease may occur only when relevant parameters are pushed to major departures from normal values--i.e., beyond specific thresholds. However, the causes of the underlying disease must be sought within the range of day-to-day fluctuations which are frequently encountered among apparently healthy people in developed countries. It is not unlikely that there are thresholds in the processes which give rise to the small-scale

damage events of chronic cardiovascular disease processes (e.g., perhaps the arterial endothelium in a particular region only suffers appreciable damage from sheer stress when systolic blood pressure is temporarily elevated above 180 mm Hg). However, whatever thresholds exist must be low enough to produce a sufficient accumulation of net damage* to account for the observation that atherosclerosis and long term blood pressure increases with age occur in very large numbers of "normal" people exposed to the usual environments of our civilization. It certainly must be true, in accordance with the homeostatic system/threshold paradigm, that small frequently-observed swings in physiological parameters responsive to environmental stimuli do not usually cause immediate major damage to vital functions. That does not mean, however, that such swings do not have some long term biological costs, in the form of small cumulative increments of damage which can ultimately result in serious physiological malfunction.

6.2 Key Technical (Measurement System) Obstacles to Progress in Cardiovascular Disease Research

In our survey of cardiovascular disease research, two specific practical measurement problems appeared to be major impediments to systematic exploration of important links in the causal sequences leading to manifestations of cardiovascular disease. First, there is no short term assay system, acceptable for use in normal healthy people, which can be used to assess the daily progress of atherosclerosis. If developed, such an assay system would allow rapid assessment of the roles of both traditional risk factors and environmental agents in accelerating the major chronic cumulative pathological processes underlying cardiovascular diseases. Further, it would allow rapid assessment of the efficacy of a wide range of dietary, pharmacological and psychological** control measures in individuals. As discussed in Section 4.1.2 (pp. 78-85), based on the various steps in the process of generation of atherosclerotic lesions which have been articulated by Ross and Glomset,[153, 155-8] there appear to be a number of promising opportunities for developing measurement systems to assess portions of the atherogenic process. In brief, these include:

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*Net after the action of repair processes.

**E.g., alteration or aspects of "Type A" behavior pattern.

- measurement in blood of debris from injury to arterial epithilium
- measurement in blood of the products released by platelets after adherence to sites of injury on arterial walls
- measurement of transport of lipid to arterial walls, by combining measurements of the concentration of low-density lipoprotein cholesterol with measurements of the turnover of its constituents (another possibility along these lines is that the turnover of building blocks for extracellular fibrous material found in plaques could be measured).

Another major difficulty related to measurement techniques arises not from the absence of a needed assay system but from the presence of several assay systems, all intended to measure platelet adhesion/aggregation properties, but which clearly indicate aspects of platelet behavior very different from one another.[326, 332-6] From available information, it seems very likely that some aspect(s) of platelet aggregation/adhesion properties may play important roles in both atherogenesis and in the sequence(s) of events which precipitate some myocardial and brain infarctions ("heart attacks" and strokes). It should be a high priority for researchers to ascertain which assay(s) of platelet aggregation/adhesion behavior predict (1) long term atherosclerotic progression and (2) short term infarction risks. As discussed in Section 5.3, the results of pharmacological intervention studies to modify infarction risk by modifying platelet behavior may provide the basis for further studies to sort out which platelet aggregation/adhestion properties are in fact of pathological significance. Given such knowledge, those properties could be used to assess cardiovascular risks from environmental/emotional stimuli, and to assess the efficacy of control measures.

6.3 Findings Related to Noise and Suggestions for Further Research

The available information provides substantial grounds to suspect that under some circumstances transient responses to high level noise exposure may contribute to cardiovascular pathology. With respect to chronic processes, evidence is most prevalent (though not entirely conclusive) that high level occupational noise exposures and some community noise exposures may be associated with an increased risk of hypertension (see

Section 4.2.3, pp. 114-144). With respect to the sequences of short term events which acutely precipitate clinical cardiovascular disease manifestations, there are indications that, at least under some circumstances, sympathetic nervous activity in response to emotional stimuli or sudden loud noises may trigger dangerous ventricular arrythmias (including fibrillation) in hearts rendered electrically unstable by a variety of other conditions (see Section 5.1.2, pp. 162-167).

Short Term Responses to Noise

Information on short term changes in blood pressure, catecholamine secretion, platelet aggregation and (over a longer time period) serum cholesterol are summarized in Section 3.2. A promising and generalizable methodology for further research in this area has been pioneered in the recent work of Ising.[41, 386] Ising was able to do relatively well-controlled assessments of short term blood pressure and norepinephrine excretion responses to occupational noise exposures by making measurements in the same workers on days during which they did and did not wear hearing protectors. Based on this methodology, we suggest a broad-ranging survey of short-term responses to noise in various industrial and community situations. The central goal of this survey should be to define in a preliminary way the types and levels of noise exposure, types of people, and other conditions where noise appears to produce the largest short-term changes. The same survey should also serve as a cross-sectional study of chronic blood pressure elevation (and, if blood samples were collected, of chronically elevated serum cholesterol*).

For provisional high risk groups identified by this procedure, we would suggest two sets of further studies:

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*One preliminary finding covered in Section 3.2 was that men exposed continually to tonal pulses over a period of about a month in a confined setting developed elevations in serum cholesterol averaging about 33 mg/100 ml (+19% from baseline levels). It is by no means clear that the cholesterol elevation was produced by the noise in this case, but there is some precedent for cholesterol elevations from long term noise exposure in animal experiments, and other long term stressful situations have been associated with elevations in serum cholesterol in humans (see Section 3.2.1, pp. 44-5).

- Evaluate more intensively the changes associated with the stimulus:

  (a) Expand the variables monitored to include some which may be more directly related to disease processes, but which require more invasive procedures (e.g., plasma hormone responses, platelet aggregation, plasma lipid responses, and ECG monitoring to detect arrhythmias.

  (b) Expand the time over which the effects of the stimulus are monitored. Examine excretion of catecholamines in the several hours between the end of work and sleep, as a function of noise exposure during the day, and examine the effect of an entire two-week period of hearing protector use, as compared to two weeks of no use.

  (c) Sample the responses within shorter blocks of time (e.g., shorter time periods of urine collection) to get a better gauge of the frequency of potentially dangerous temporary elevations of relevant parameters.

- Observe the effects of long-lasting reductions in noise levels brought about by engineering controls:

  (a) Compare the long term levels of blood pressure, serum cholesterol, catecholamine excretion, etc., measured before and after the permanent reduction in stimulus levels.

  (b) Repeat the studies of short term responses on days with and without ear protectors, to ascertain the change in the variability of risk factors which has been produced by the intervention.

Selected studies in animal systems may also be helpful to build more quantitative system-dynamic models of relationships between hormonal and non-hormonal short term variables in response to environmental/emotional stimuli. These are discussed more fully in Section 3.3 (pp. 68-71).

Noise, Atherosclerosis, and Chronic Increases in Blood Pressure

There is only a small amount of evidence from rabbit systems that chronic noise exposure may contribute to atherogenesis, when combined with relevant dietary and other conditions.[130, 52] If, as described earlier in this summary, short term assays are developed which are expected to be good indicators of the daily or hourly progress of atherosclerosis, relationships between short term variations in catecholamine levels, lipid

levels, blood pressure and other parameters could be systematically examined both singly and in combination. Experiments could also be performed in naturalistic stimulus situations in the field using the Ising approach or others (see Section 4.1.3, pp. 85-7 for further details).

Based on our perspective of blood pressures distributed continuously and log-normally in populations, we developed a method to tentatively place the results of different studies of long term noise exposure and the prevalence of hypertension on a comparable basis (using alternative assumptions about the fraction of a noise-exposed population which might experience a shift in blood pressure). Using this techniques (see Section 4.2.3, pp. 100-144), we arranged the results of eleven studies meeting specific criteria (see p. 125) to tentatively indicate any trends in the available data by noise level, age, sex, and the hypertension criterion used in the various studies. Under the assumption that the blood pressure raising effect of long term occupational noise exposure produces a relatively uniform shift in blood pressures (that is, assuming there are no major population subgroups with much more susceptibility to noise-induced blood pressure shift than the average) the data tentatively suggested shifts relative to controls of about the following magnitude for populations reported to have long term noise exposures between about 85-100dB:

	Under 40 years	Over 40 years
Systolic and/or Diastolic	3 mm Hg 2.5 mm Hg	6 mm Hg 4 mm Hg

Treating the same data using an assumption that all of the noise-induced blood pressure shift occurred in a sensitive subgroup, representing 30% of the total exposed populations, the indicated shifts for this sensitive subgroup would be expected to be about:

	Under 40 years	Over 40 years
Systolic and/or Diastolic	9 mm Hg 7 mm Hg	16 mm Hg 10 mm Hg

The derivation of these numbers included a substantial amount of speculative model-building and extrapolation. They should be regarded as highly preliminary expectations, albeit based on the best data currently available in the literature.

Based on our analysis of current research into mechanisms of chronic blood pressure increase, and available opportunities to conduct much improved cross-sectional studies of relationships between noise exposure and blood pressure levels, we developed the following suggestions for further research:

- Human epidemiological studies

  1. Large-scale cross-sectional surveys of blood pressure in relation to workplace and community noise, other workplace exposures, and other factors.

Two invaluable opportunities to assess relationships between blood pressure and workplace noise while controlling for other relevant variables will present themselves early in the 1980's.* First, the planned repetition of the HANES survey of blood pressures in relation to other factors by the National Center for Health Statistics will take place in the context of new enabling legislation** which has given the agency major responsibility for assessing environmental health effects. Addition of an industrial hygienist to the HANES examination team to (1) take a good workplace exposure history from examinees, and (2) where possible, measure selected current and/or past workplace exposures for the examinees, could provide relevant and comparable data spanning thousands of people at relatively

*The Health Services Research, Health Statistics, and Health Care Technology Act of 1978, PL 95-623.

**Such studies should specifically seek to assess dose-effect relationships between blood pressure and noise type and level, exposure duration, age, sex, and other relevant parameters.

little incremental cost. Based on people's addresses in relation to airports, etc., possible contributions from community noise exposures could also be assessed. Second, the repetition of the National Institute for Occupational Safety and Health's "National Occupational Hazard Survey" is due to be performed in the early 1980's. This comprehensive survey of workplace exposures would simply need to be supplemented with a blood pressure sampling program and questionnaire for assessing weight, height, etc., in order to have an excellent chance of both defining the blood pressure increasing effects of noise and systematically uncovering any other workplace agents which may tend to produce hypertension.

2. Cross-sectional correlative studies with physiological variables.

Cross-sectional studies where blood pressure is measured in relation to putative hypertension-producing environmental agents are only the beginning of a process to really define what it is that the agents are doing, and uncover more general rules for predicting and preventing this kind of adverse health effect. Based on samples of people with various pressures exposed to particular environmental agents and non-exposed matched controls, the kinds of correlative studies of putative blood pressure increasing physiological variables outlined in Figure 4.5 and Table 4.3 (pp. 97-99) should be undertaken.

- Case-control studies, based on emerging hypertension "types"

Many groups of investigators are now regularly categorizing hypertensives under their care into various "types." In general, it will be too demanding to incorporate these typing procedures into large scale cross-sectional studies. However, people interested in the role of specific environmental agents in raising blood pressure may well wish to provide an adjunct facility for assisting investigators engaged in such "typing" to ascertain whether patients of different types (and controls) show different frequencies/intensities of exposure to noise and other putative blood pressure increasing influences. A finding of an excess of a particular hypertension "type" would (1) provide clues to the mechanism by which the agent increases

pressure, (2) possibly increase the sensitivity of epidemiological studies by lowering the "signal to noise ratio" (see discussion in Section 4.2.1, pp. 96-7), and (3) provide evidence that the typology of hypertension used was successfully separating patients by etiology.

- Retrospective cohort studies

  1. A population with well-defined past noise exposures can be followed up for past and current acrdiovascular mortality and morbidity (such as the Baughn/General Motors population which was used to assess hearing impairment in relation to noise exposure, or other populations with good noise exposure and blood pressure measurements in their industrial medical programs.

  2. A sample of a population with good blood pressure/cardiovascular disease monitoring, such as the Framingham population, can have its past and current noise and other environmental exposures assessed.

- Animal experiments

The ideal roles of animal experiments in an overall strategy for understanding hypertension etiology are:

1. to provide insights into mechanisms of hypertension, using experimental methods which, due to their invasive or destructive nature cannot be used in humans, and

2. to provide system-dynamic models of blood pressure regulation which generate insights into relationships between specific variables to be explored in humans.

In particular, the recent primate work on noise and hypertension may provide useful insights into mechanism if some of the variables listed in Table 4.3 (pp. 98-9) are incorporated into the experimental design.

Noise, Short Term Physiological Responses, and Clinical Manifestations of Cardiovascular Disease

To assist decision makers and research planners in making judgements about the potential importance of elevations in blood pressure and serum

cholesterol suggested by the data discussed above, we undertook in Section 5.2.1 (pp. 168-78) some very highly preliminary and assumption-laden calculations of the increases in cardiovascular risks which would be expected based on the multiple logistic risk model and risk coefficients derived from the Framingham study. Assuming:

1. long term average elevations of 6 mm Hg in systolic blood pressure, or 33 mg/100 ml serum cholesterol in men between the ages of 45-75,
2. that the associations between systolic pressure, serum cholesterol and clinical cardiovascular disease manifestations found in epidemiological studies reflect direct causal relationships,*
3. that the multiple logistic risk model correctly predicts relationships between changes in risk factors and changes in cardiovascular risks, and
4. that the absolute risk coefficients levels derived from the Framingham study represent values which are close to those which would be found in a representative sample of U.S. males between 45-75,

then the overall risk of developing any clinical manifestation of cardiovascular disease would be expected to be about 10% higher in a population averaging 6 mm Hg increases in systolic blood pressure (for an absolute increased risk of about 200 cases per 100,000 at risk per year). The overall increase in cardiovascular disease risk would be expected to be about 20% in a population with a chronically-maintained average increase in serum cholesterol of 33 mg/100 ml (for an absolute increased risk of about 400 cases per 100,000 at risk per year). More detailed results for individual clinical manifestations of cardiovascular disease can be found in Tables 5.7 and 5.8 (pp. 178-9).

These findings should not be misread in the process of planning future research on possible cardiovascular risks of noise. Although a 33 mg/100

*The uncertainty here is whether the basic epidemiological associations are based on direct causal connections or whether elevated levels of traditional risk factors simply serve as proxy indicators of the true causal factors. In the former case, the risk predictions may be valid, in the latter case the predictions would only be valid if changes in the measured risk factor under the influence of an environmental stimulus were paralleled by changes in the underlying causal factor.

ml shift in serum cholesterol, were it to occur, might be expected to produce a larger overall cardiovascular disease risk than the 6 mm Hg shift in systolic blood pressure, the body of literature suggesting blood pressure increases with chronic high level occupational noise exposure is vastly more substantial than that which suggests a shift in serum cholesterol levels. The inference which should be drawn is that the very tentative indication of an influence of noise exposure on serum cholesterol should be further pursued together with, not to the exclusion of, suggested effects on blood pressure. The possible importance of the putative blood pressure effect itself is large enough to warrant further research and regulatory concern, given the millions of workers currently exposed on their jobs to very high noise levels (see exposure estimates, pp. 3-4 and ref. 37). It should also be remembered that these very tentative, order-of-magnitude assessments of possible cardiovascular risks include no allowance for possible noise effects by way of the enhancement of thrombotic tendencies through increased platelet adhesiveness (see Section 5.1.1, pp. 157-62 and Section 3.2.1, pp. 38-43 or by triggering or enhancement of dangerous ventricular arrhythmias (see Section 5.1.2, pp. 162-7 above).

As discussed earlier, assessment of possible contributions of noise and other environmental/emotional stimuli to cardiovascular risks by way of enhanced platelet aggregation must await further research into which specific platelet aggregation/adhesion measures correctly predict enhanced cardiovascular risks.

In the case of possible cardiac risks by way of arrhythmias (see Section 5.1.2, pp. 162-7), the available data suggest that some special effort be made to investigate epidemiologically the possibility that sudden, startling noises may trigger ventricular fibrillation and sudden death in people with pre-existing heart disease with or without exposure to drugs and industrial chemicals which may promote arrhythmias. We suggest two types of studies for this purpose:

- In conjunction with the large cross-sectional surveys of noise, other occupational exposures, and blood pressure which were outlined in Section 4.2.4 (pp. 145-6 above), representative samples of workers with documented exposures to noise, other agents suspected of causing arrhythmias[376] should be enrolled into a prospective cohort and followed up periodically for the occurrence of sudden and non-sudden death from coronary disease and other causes. There should at least be a one-time screening for ECG abnormalities and other cardiovascular risk factors upon entry of individuals into the cohort, and if feasible, matching should be performed for risk factors not of primary interest in the study. The unambiguous nature of sudden death as an end-point facilitates the design of high quality epidemiological studies, if sufficient numbers of cases can be accumulated.

- Second, it appears from studies by Taggart[365] that it may be possible to perform electrocardiographic monitoring of people engaged in ordinary day to day activities, in the presence or absence of specific environmental stimuli. Such studies would be greatly assisted by the use of modern automated data processing methods which have been established to detect and quantify arrhythmias.[375] Again, low cost experiments based on the Ising paradigm of within-individual comparisons on days when hearing protectors are and are not worn, appear likely to yield important insights into which kinds of noise stimuli are dangerous and which kinds of people are at high risk.

REFERENCES

1. Hattis, D. et al., Some Considerations in Choosing an Occupational Noise Exposure Regulation, EPA 550/9-76-007 (1976).

2. Cannon, W. B., Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches Into the Function of Emotional Excitement, 2nd Ed., Appleton, New York (1929).

3. Selye, H., The Physiology and Pathology of Exposure to Stress, Acta, Inc., Montreal (1950).

4. Mason, J. W., "A review of psychoendocrine research on the pituitary-adrenal cortical system." Psychosom. Med. 30 576 (1968).

5. Mason, J. W., "A review of psychoendocrine research on the sympathetic-adrenal medullary system." Psychosom. Med. 30 631 (1968).

6. Mason, J. W., "A review of psychoendocrine research on the pituitary-thyroid system." Psychosom. Med. 30 (1968).

7. Rose, R. M. and Hurst, M. W., "Plasma cortisol and growth hormone responses to intravenous catheterization." J. Human Stress 1, 22 (1975).

8. Rubin, R. T. et al., "Adrenal cortical activity changes during underwater demolition training." Psychosom. Med. 31, 553 (1969).

9. Levi, L., ed., "Stress and distress in response to psychosocial stimuli." Acta Medica Scandinavia, Suppl. 528 (1972).

10. Friedman, M. et al., "Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress." Circulation 17 852 (1958).

11. Grundy, S. M. and Griffin, A. C., "Effects of periodic mental stress on serum cholesterol levels." Circulation 19 496 (1959).

12. Taggart, P. and Carruthers, M., "Endogenous hyperlipidaemia induced by emotional stress of racing driving." Lancet 1

13. Rahe, R. H. et al., "The three investigators study: Serum uric acid, cholesterol, and cortisol variability during stresses of everyday life." Psychosom. Med. 36 (1974).

14. Pare, W. P. et al., "Cholesterol synthesis and metabolism as a function of unpredictable shock stimulation." Physiol. and Behavior 11 107 (1973).

15. Fleischman, A. I. et al., "Effect of stress due to anticipated minor surgery on in vivo platelet aggregation in humans." J. Human Stress 2 33 (1976).

16. Haft, J. I. and Fani, K., "Stress and the induction of intra-vascular platelet aggregation in the heart." Circulation 48 164 (1973).

17. Gordon, J. L. et al., "Human platelet reactivity during stressful diagnostic procedures." J. Clin. Path 26 958 (1973).

18. Haft, J. I. and Arkel, Y. S., "Effect of emotional stress on platelet aggregation in humans." Chest 70 501-5 (1976).

19. Obirst, P. A. et al., "The relationship among heart rate, carotid dP/dt, and blood pressure in humans as a function of the type of stress." Psychophysiology 15 102 (1978).

20. Manuck, S. B. et al., "Effects of coping on blood pressure responses to threat of aversive stimulation." Psychophysiology 15 544 (1978).

21. Jones, M. T. et al., "Relationship between the cardiovascular and sympathetic responses to the psychological stress of an examination." Clin. Sci. 35 73 (1968).

22. McMurray, G. A. and Jaques, L. B., "Capillary resistance and blood pressure changes associated with pain due to local cooling: cold pressor test." J. Appl. Physiol. 14 813 (1959).

23. Shadid, J. N., "Drop test studies on blood: their prognostic value in thromboembolism." J. Lab. Clin. Med. 56 (1955).

24. Still, J. W., "An attempt to show the links which connect the social-psychological and physiological events which result in coronary (and other) thromboses with some suggestions for breaking the connections." Exercise and Fitness, p. 52, University of Illinois Press (1960). Cited by Dintenfass, L., ref.

25. Rosenman, R. H. et al., "Coronary heart disease in the Western Collaborative Group Study: Final follow-up experience of eight and one half years." J.A.M.A. 233 872-7 (1975).

26. Medalie, J. H. et al., "Angina pectoris among 10,000 men: five year incidence and univariate analysis." Am. J. Med. 55 583 (1973).

27. Floderus, B., "Psychosocial factors in relation to coronary heart disease and associated risk factors." Nord. Hyg. Tidskr., Suppl. 6 (1974).

28. Bruhn, J. G. et al., "Psychological predictors of sudden death in myocardial infarction." J. Psychosom. Res. 18 187 (1974).

29. Parkes, C. M. et al., "Broken heart: A statistical study of increased mortality among widowers." Br. Med. J. 1 740-3 (1969).

30. Rahe, R. H. and Lind, E., "Psychosocial factors and sudden cardiac death: A pilot study." Journal of Psychosomatic Research 15 19-24 (1971).

31. Rahe, R. H. et al., "Recent life changes, myocardial infarction, and abrupt coronary death: Studies in Helsinki." Archives of Internal Medicine 133 221-8 (1974).

32. Theorell, T. and Rahe, R. H., "Life change events, ballistocardiography and coronary death." J. Human Stress 1 18-24 (1975).

33. Haynes, S. G., "The relationship of psychosocial factors to coronary heart disease in the Framingham study. II. Prevalence of coronary heart disease." Am. J. Epidem. 107 38 (1978).

34. Jenkins, C. D., "Recent evidence supporting psychologic and social risk factors for coronary disease." New England J. Med., 294 987, 1033.

35. Glass, D., Behavior Patterns, Stress, and Coronary Disease, John Wiley & Sons, New York (1977).

36. Henry, J. P. and Stephens, P. M., Stress, Health, and the Social Environment--A Sociobiologic Approach to Medicine.

37. Ashford, N. A. et al., Economic/Social Impact of Occupational Noise Exposure Regulations EPA 550/9-77-352, U. S. Environmental Protection Agency, Office of Noise Abatement and Control, Washington, D. C., (September 1976).

38. Survey Research Center, Institute for Social Research, University of Michigan, The 1977 Quality of Employment Survey. Unpublished data supplied in tape form.

39. U. S. Environmental Protection Agency, Office of Noise Abatement and Control, Toward a National Strategy for Noise Control. U. S. Environmental Protection Agency, Washington, D. C. (April 1977).

40. OSHA Management Information System printout, unpublished data.

41. Ising, H. and Melchert, H. U., "Endocrine and Cardiovascular Effects of Noise," Mimeo. presented at Freiburg Conf. (1978).

42. Tsaneva, N. et al., "The Catecholamines as a Criterion for the Functional State in Different Activities," Agressologie 16 179 (1975).

43. Ortiz, G. A. et al., "Modifications of Epinephrine Norepinephrine, Blood Lipid Fractions and the Cardiovascular System Produced by Noise in an Industrial Medium," Hormone Res. 5 57-64 (1974).

44. Arguelles, A. E., Martinez, N. A., Pucciarelli, E. and M. V. Disisto, "Endocrine and Metabolic Effects of Noise in Normal, Hypertensive and Psychotic Subjects," Psysiological Effects of Noise, Plenum Press, New York, N. Y. (1970) pp. 43-55.

45. Carlson, L. A., et al., "Stressor-Induced Changes in Plasma Lipids and Urinary Excretion of Catecholamines, and Their Modification by Nicotinic Acid," Stress and Distress in Response to Psychosocial Stimuli, ed. by Lennart Levi, Acta Medica Scandinavica Supplementum 528 91 (1972).

46. Slob, A., et al., "The Effect of Acute Noise Exposure on the Excretion of Corticosteriods, Adrelin and Noradrenalin in Man," Int Arch Arbeitsmed 31 225-35 (1973).

47. Lundberg, U. and Frankenhaeuser, M. "Adjustment to Noise Stress," Reports from the Department of Psychology, the University of Stockholm, No. 484, (November 1976).

48. Frankenhaeuser, M. and Lundberg, U., "Immediate and Delayed Effects of Noise on Performance and Arousal," Biol. Psychol. 2 127 (1974).

49. Lehmann, G. and J. Tamm, "Uber Veranderungen der Kreislaufdynamik des Ruhenden Meschen Unter Einwirkung von Gerauschen," Internat Zangev Physiol ennshl Arbeitphysiol Bd 16 217-27 (1956).

50. Schulte, W. et al., "Der Einfluss von experimentellem Verkehrlarm auf vegetative Funktionen von Normotonikern und Hypertonikern nach Stress," (the influence of experimental traffic noise on autonomous functions of normotensives and hypertensives after stress), Basic Res. Cardiol. 72 575 (1977).

51. Maas, B., et al., "Platelet Adhesiveness During Exposure to Noise," German Medicine 3 111 (1973).

52. Deryagina, G. P., et al., "Effect of Acoustic Stimulation on Lipid Metabolism Indices of the Blood Coagulation System and Development of Experimental Atherosclerosis in Rabbits," Fiziol. Zh. SSSR 62 1171 (1976).

53. Vander, A. J., et al., "Effects of Noise on Plasma Renin Activity in Rats," Proc. Soc. Exp. Biol. Med. 156 24 (1977).

54. Geber, W. F., et al., "Physiological Responses of the Albino Rat to Chronic Noise Stress," Arch. Environ. Health 12 751 (1966).

55. Cantrell, R. W., "Prolonged Exposure to Intermittent Noise: Audiometric, Biochemical, Motor, Psychological, and Sleep Effects," mimeo. presented before the American Laryngological, Rhinological and Otological Society, Inc. Palm Beach, Fla., April 24, 1974.

56. Friedman, M., et al., "Plasma Lipid Responses of Rats and Rabbits to an Auditory Stimulus," Am. J. Physiol. 212 1174 (1967).

57. Brandenberger, G., et al., "Failure of Noise Exposure to Modify Temporal Patterns of Plasma Cortisol in Man," Europ. J. Appl. Physiol. 36 239 (1977).

58. Carlestam, G., et al., "Stress and Disease in Response to Exposure to Noise," Proceedings of the International Congress on Noise as a Public Health Problem, Dubrovnik, Yugoslavia, May 13-18, 1973. EPA, Office of Noise Abatement and Control, Washington, D. C., pp. 479-86.

59. Frankenhauser, M. and Lundberg, U., "The Influence of Cognitive Set on Performance and Arousal Under Different Noise Loads," Motivation and Emotion 1 139 (1977).

60. Etholm, B. and K. E. Egenberg, "The Influence of Noise on Some Circulatory Functions," Acta Oto-Laryngol 58 208-213 (1964).

61. Klein, K. and M. Grubl, "Uber Hamodynamische Reaktionen unter Akustischen Reizen, (Hemodynamic Reactions to Acoustic Stimuli)," Wien Klin Wschr 81/40 705-709 (1969), and Exc Med 2550 (1970).

62. Cartwright, L. B., and Thompson, R. N., "The Effects of Broadband Noise on the Cardiovascular System in Normal Resting Adults," Am. Ind. Hyg. Ass. J. 653 (1975).

63. Truett, J. et al., "A multivariate analysis of the risk of coronary Heart Disease in Framingham." J. Chron. Dis. 20 511 (1967).

64. Arvidson, O. and Lindvall, T. "subjective annoyance from noise compared with some directly measurable effects." Arch. Environ. Health 159 (July/August 1978).

65. Levi, L., "Conditions of Work and Sympathoadrenomedullary Activity: Experimental Manipulations in a Real Life Setting," Stress and Distress in Response to Psychosocial Stimuli, Lennart Levi, ed. Acta Medica Scand., Suppl. 528, p. 106 (1972).

66. Levi, L., "The Urinary Output of Adrenalin and Noradrenalin during Pleasant and Unpleasant Emotional States--a Preliminary Report," Stress and Distress in Response to Psychosocial Stimuli, Lennart Levi, ed., Acta Medica Scand., Suppl. 528, p. 80 (1972).

67. Bellet, S., et al., "The effect of automobile driving on catecholamine and adrenocortical excretion," Am. J. Cardiol. 24 365 (1969).

68. Dutton, L. M., et al., "Stress levels of ambulance paramedics and fire-fighters," J. Occup. Med. 20 111 (1973).

69. Mason, J. W., "Organization of the multiple endocrine responses to avoidance in the monkey," Psychosomatic Med. 30, 774 (1968).

70. Ellis, S., "The metabolic effects of epinephrine and related amines," Pharmacol Rev 8 485 (1956).

71. Hagen, J. H., and Hagen, P. B., "Actions of Adrenalin and Noradrenalin on Metabolic Systems," Actions of Hormones on Molecular Processes, Litwack, G., and Kritchevsky, D., Eds., Wiley, New York, (1964), p. 268.

72. Schotz, M. C. and Page, I. H., "Effect of norepinephrine and epinephrine on nonesterified fatty acid concentration in plasma," Proc. Soc. Exp. Biol. Med. 101 624 (1959).

73. Renold, A. E., and Ashmore, J. "Metabolic Effects of Adrenal Corticosteroids," Diabetes, Williams, R. H., Ed., Hoeber, New York, (1960), p. 194.

74. Fajans, S. S., "Some metabolic actions of corticosteroids," Metabolism 10 951 (1961).

75. Ingle, D. J., "Metabolic Effects of Adrenal Steroids," A Symposium on Steroid Hormones, Gordon, E. S., Ed., Univ. Wisconsin Press, (1950), p. 150.

76. Grossfield, H., "Action of adrenalcortical steroids on cultured cells," Endocrinology 65 777 (1959).

77. Knobil, E., and Hotchkiss, J., "Growth hormone," Ann. Rev. Physiol. 26 47 (1964).

78. Krahl, M.E., The Action of Insulin on Cells, Acad. Press, New York, (1961).

79. Randle, P. J., "Endocrine control of metabolism," Ann Rev Physiol 25 291 (1963).

80. Hoch, F. L., "Biochemical actions of thyroid hormones," Physiol Rev 42 605 (1962).

81. Tepperman, J. Metabolic and Endocrine Physiology. Yearbook. Medical Publishers, Chicago, (1962).

82. Thompson, R. F. Foundations of Physiological Psychology. New York, Harper and Row, (1967).

83. Perlman, R. L., and Chalfie, M. "Catecholamine release from the adrenal medulla." Clin. Endocrin. Med. 6(3) 551-576 (1977).

84. Wennergren, G., Thoren, P., Lesander, B. "Cardiac receptors activated during the hypothalamic defense reaction." Acta. Physiol. Scand. 101 241-246 (1977).

85. Kvetnansky, R., Palkovits, M., Mitro, A., Torda, T., Mikulaj, L., "Catecholamines in individual hypothalamic nuclei of acutely and repeatedly stressed rats." Neuroendocrinology 23 257-267 (1977).

86. Waldinger, T., Seaton, J.F., Harrison, T.S. "Blood pressure vulnerability to volume contraction: regulation by adrenal cortical hormones." Am. J. Physiol. 233(5) R239-R242 (1977).

87. Bernal., J., Refetoff, S. "The action of thyroid hormone." Clin. Endocrin. 6 227-249 (1977).

88. David, J. O. "The control of renin release." Am. J. Med. 55 33-350 (1973).

89. Vander, A. J., Sherman, J. H., Luciani, D. S. Human Physiology -- The Mechanisms of Body Function, New York, McGraw-Hill Inc., (1975).

90. Ross, R., Glomset, J., Harker, L. "Response to injury and atherogenesis." Am. J. Pathol. 86 675-684 (1977).

91. Melander, A., Westgren, U., Ericson, L. E., Sundler, F. "Influence of the sympathetic nervous system on the secretion and metabolism of thyroid hormone." Endocrinology 101(4) 1228-1237 (1977).

92. Taggart, P. and Carruthers, P. "Behavior patterns and emotional stress in the etiology of heart disease: cardiological and biochemical correlates." In Stress and the Heart, D. Wheatley, ed., New York, Raven Press, (1977).

93. Wenke, M. In Advances in Lipid Research, Vol. 4, edited by R. Paulette and D. Kritchevsky, London, Academic Press, (1966).

94. Dole, V. P. "A relation between non-esterified fatty acids in plasma and the metabolism of glucose." J. Clin. Invest. 35 150 (1956).

95. Johnson, R. H. et al. "Post-exercise ketosis." Lancet 2 1383 (1969).

96. Friedman, J. et al. "Changes in the serum cholesterol and blood clotting time in man subjected to cyclic variation of occupational stress." Circulation 17 852 (1958).

97. Grundy, S. M. et al. "Effects of period mental stress on serum cholesterol levels." Circulation 19 496 (1959).

98. Thomas, D. B., and Murphy, E. A. "Further studies on cholesterol levels in the Johns Hopkins medical students: the effect of stress at examinations." J. Chron. Dis. 8 661 (1958).

99. Netter, G. H. The Ciba Collection of Medical Illustrations: Heart (Vol. 5). Ciba Publications Department, Summit, NJ, (1969).

100. Rahe, R. H. et al. "The three investigators study: Serum uric acid, cholesterol, and cortisol variability during stress of everyday life." Psychosom. Med. 36 258 (1974).

101. Rubin, R.T. et al. "Serum uric acid, cholesterols, and cortisol levels." Arch. Intern. Med. 125 815 (1970).

102. Clayton, S. and Cross, M. J. "The aggregation of blood platelets by catecholamines and by thrombin." J. Physiol. 146 403 (1963).

103. O'Brien, J. I. R. "Some effects of adrenalin and antiadrenalin compounds on platelets in vitro and in vivo." Nature 200 763 (1963).

104. Haft, J. I. et al. "Intravascular platelet aggregation in the heart induced by norepinephrine: microscopic studies." Circulation 46 698 (1972).

105. Hoak, J. C. et al. "Effect of free fatty acids on ADP-induced platelet aggregation." Nature 228 1330 (1970).

106. Conner, W. E. et al. "The role of lipids in thrombosis." Thromb. diasthes. haemorr. Suppl. 21 193 (1966).

107. Gordon, J. L. et al. "Human platelet reactivity during stressful diagnostic procedures." J. Clin. Path. 26 958 (1973).

108. Folkow, B. "Central neurohormonal mechanisms in spontaneously hypertensive rats compared with human essential hypertension." Clin. Science and Molecular Medicine 48 205s (1975).

109. Mason, J.W. "Organization of psychoendocrine mechanisms: a review and reconsideration of research." in N.S. Greenfield and R.A. Sternbach, eds., Handbook of Psychophysiology, New York: Holt, Rinehart and Winston (1972).

110. Nestel, P.J., Verghese, A., and Lovell, R.R. "Catecholamine secretion and sympathetic nervous system responses to emotion in men with and without angina pectoris." Am. Heart J. 73 227-234 (1967).

111. Friedman, M., Byers, S.O., Diamant, J., and Roseman, R.H. "Plasma catecholamine response of coronary-prone subjects (Type A) to a specific challenge." Metabolism 24 205-210 (1975).

112. Elmadjian, F. "Excretion and metabolism of epinephrine and norepinephrine in various emotional states." Proceedings of the 5th Pan American Congress of Endocrinology, Lima, Peru, (November 1963), pp. 341-370.

113. Elmadjian, F., Hope, J.M. and Larson, C.T. "Excretion of epinephrine and norepinephrine under stress." Recent Progress in Hormone Research 14 513-553 (1958).

114. Funkenstein, D.H., King, S.H., and Drollette, M.E. Mastery of stress. Cambridge, MA: Harvard University Press (1957).

115. Frankenhauser, J. "Behavior and circulating catecholamines." Brain Research 31 241-262 (1971).

116. Frankenhauser, J. and Rissler, A. "Effects of punishment on catecholamine release and efficiency of performance." Psychopharmacologia 17 378-390 (1970).

117. Weiss, J.M., Stone, E.A., and Harrell, N. "Coping behavior and brain norepinephrine level in rats." J. of Comparative and Physiological Psychology 72 153-160 (1970).

118. Weiss, J.M., Glazer, H.I., and Pohorecky, L.A. "Coping behavior and neurochemical changes: an alternative explanation for the original 'learned helplessness' experiments." in G. Serban, ed., Psychopathology of Human Adaptation, New York: Plenum Press (1977, in press).

119. Anisman, H. "Time-Dependent variations in aversively motivated behaviors: nonassociative effects of cholinergic and catecholaminergic activity". Psychological Review 82 359-385 (1975).

120. Luke, C.R., Zugler, M.F., and Kopin, I.J. Life Sci. 18 1315-1326.

121. deChamplain, J. "The sympathetic system in hypertension." Clin. Endocrin. Metab. 6(3) 633-644 (1977).

122. Sauerbier, I. and vonMayersbach, H. "Circadian variation of catecholamines in human blood." Horm. Metab. Res. 9 529 (1977).

123. Levi, L. "Psychological and physiological reactions to and psychomotor performance during prolonged and complex stressor exposure." In Stress and Distress in Response to Psychosocial Stimul, Acta. Med. Scand. Suppl. 528 119 (1972).

124. Lake, C.R. et al. "Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man." Life Sciences 18 1315 (1976).

125. Taggart, P. and Carruthers, M. "Endogenous hyperlipidaemia induced by emotional stress of racing driving." Lancet I 363 (1971).

126. Nordoy, A. et al. "The effect of noradrenalin infusion on plasma and platelet lipids and platelet function in man." Thromb. Diasthes. Haemorrh. 33 328 (1975).

127. Favio, A. et al. "Radioimmunoassay measurements of serum cortisol, thyroxine, growth hormone and luteinizing hormone with simultaneous electroencephalographic changes during continuous noise in man." J. Nucl. Biol. Med. 119 (1973).

128. Jackson, R.L. et al. "The role of dietary polyunsaturated fat in lowering blood cholesterol in man." Circulation Res. 42 448 (1978).

129. Friedman, M. et al. "Serum lipids and conjunctival circulation after fat ingestion in men exhibiting Type A behavior pattern." Circulation 29 874 (1964).

130. Friedman, M. "Plasma lipid responses of rats and rabbits to an auditory stimulus." Am. J. Physiol. 212 1174 (1967).

131. The Pooling Project Research Group. "Relationship of blood pressure, serum cholesterol, smoking habit, relative weight, and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project." J. Chron. Dis. 31 201 (1978).

132. Neallis, P.M. and Bowman, R.E. "Behavioral and corticosteroid responses of rhesus monkeys to noise-induced stress." (Unpublished)

133. Arguelles, A.E. et al. "Pituitary-adrenal stimulation by sound of different frequencies." J. Clin. Endocrin. 22 846 (1962).

134. Lehmann, G. and Tamm, J. "Uber Veranderungen der Kreislaufdynamik des ruhenden Menschen unter Einwirkung von Gerauschen". Internat. Z. angew. Physiol. einschl. Arbeitsphysiol. 16 217 (1956).

135. Guha, D. et al. "Effects of sound stimulus on gastric secretion and plasma corticosterone level in rats." Res. Commun. Chem. Pathol. Pharmacol. 13 273 (1976).

136. Froehlich, G.R. "The effects of ear protectors on some autonomic responses to aircraft and impusive noise." AGARD (ADVIS Group Aerospace Res. Dev.) Conference Proceedings 171 C8-1 (1975).

137. Griefahn, B. "Effects of sonic booms on finger pulse amplitudes during sleep." Int. Arch. Occup. Environ. Health 36 57.

138. Guski, R. "Defensive activation toward noise." J. Sound and Vibration 59 107 (1978).

139. Kryter, K.D. et al. Report of Working Group 63. "Non-Auditory Effects of Noise." WAS-NRC Committee on Hearing, Bioacoustics, and Biomechanics, (1971).

140. Jansen, G. "Non-Auditory effects of noise, physiological and psychological reactions in man." In Proceedings of the International Congress on Noise as a Public Health Problem, Dubrovnik, Yugoslavia, May 13-18, 1973. U.S. Environmental Protection Agency, Washington, D.C. 20460.

141. Hanson, J.D. et al. "The effects of control over a stressful stimulus (noise) on plasma cortisol levels." Behav. Biol. 16 333 (1976).

142. Hines, E.A. and Brown, G.E. "A standard test for measuring the variability of the blood pressure: its significance as an index of the pre-hypertension state." Ann. Intern. Med. 7 209 (1933).

143. Keys, A. et al. "Mortality and coronary heart disease among men studied for 23 years." Arch. Inter. Med. 128 201 (1971).

144. Smirk, F.H. "Pathogenesis of essential hypertension." Brit. Med. J. 1 791 (1949).

145. Turek, J.V. "Blood pressure response to a new standardized stress test." Neth. J. Med. 20 104 (1977).

146. Mosskov, J.I. and Ettema, J.H. "Extra-auditory effects in short-term exposure to aircraft and traffic noise." Int. Arch. Occup. Environ. Health 40 165 (1977).

147. Mosskov, J.I. and Etema, J.H. "Extra-auditory effects in short-term exposure to noise from a textile factory." Int. Arch. Occup. Environ. Health 40 174 (1977).

148. Mosskov, J.I. and Ettema, J.H. "Extra-auditory effects in long-term exposure to aircraft and traffic noise." Int. Arch. Occup. Environ. Health 40 174 (1977).

149. Rose, R.M., Jenkins, C.D., and Hurst, M.W. Air Traffic Controller Health Change Study. Report to the Federal Aviation Administration, (August, 1978).

150. Kannel, W.B. "Some lessons in cardiovascular epidemiology from Framingham." Am. J. Cardiol. 37 269 (1976).

151. Lifsic, A.M. "Atherosclerosis in smokers." Bull. World Health Org. 53 631 (1976).

152. Kuhn, The Structure of Scientific Revolutions.

153. Ross, R. and Glomset, J. A. "The Pathogenesis of Atherosclerosis. (First of Two Parts)." New Eng. J. Med. 295 369 (1976).

154. Anthony, C. P. and Kolthoff, N. J. Textbook of Anatomy and Physiology. St. Louis, C. V. Mosley Co., 197-.

155. Ross, R. and Harker, L. "Hyperlipidemia and Atherosclerosis. Chronic Hyperlipidemia Initiates and Maintains Lesions by Endothelial Cell Desquamation and Lipid Accumulation." Science 193 1094 (1976).

156. Ross, R. and Glomset, J. A. "Atherosclerosis and the Arterial Smooth Muscle Cell." Science 180 1332 (1973).

157. Ross, R. et al. "Response to Injury and Atherogenesis." Am. J. Pathol. 83 675 (1977).

158. Ross, R. and Glomset, J. A. "The Pathogenesis of Atherosclerosis (Second of Two Parts)." New Eng. J. Med. 295 420 (1976).

159. Folkow, B. et al. "Importance of Adaptive Changes in Vascular Design for Establishment of Primary Hypertension Studied in Man and in Spontaneously Hypertensive Rats." Circulation Res., Suppl. I to Vol. I 32-33 1-2 (1973).

160. Vihert, A. M. "Atherosclerosis of the aorta in Five Towns." Bull. World Health Organ. 53 501 (1976)

161. Vanecek, R. "Atherosclerosis of the Coronary Arteries in Five Towns." Bull. World Health Organ. 53 509 (1976).

162. Friedman, M. et al. "The Relationship of Behavior Pattern A to the State of the Coronary Vasculatured. A Study of Coronary Vasclature." Am. J. Med. 44 525 (1968).

163. Matova, E. E. and Vihert, A. M. "Atherosclerosis and Hypertension." Bull. World Health Organ. 53 539 (1976).

164. Kagan, A. R. "Atherosclerosis and Myocardial Disease in Relation to Physical Activity of Occupation." Bull. World Health Organ. 53 615 (1976).

165. Herd, J. A. et al. "Solute Penetration of Arterial Walls." Physiology 619 (197-).

166. Haft, J. I, and Fani, K. "Intravascular Platelet Aggregation in the Heart Induced by Stress." Circulation 47 353 (1973).

167. Haft, J. I. and Arkel, Y. S. "Effect of Emotional Stress on Platelet Aggregation in Humans." Chest 70 501 (1976).

168. Haft, J. I. et al. "Protection Against Epinephrine Induced Myocardial Necrosis with Clofibrate." Amer. Heart J. 86 805 (1973).

169. Haft, J. I. et al. "Protection Against Epinephrine-Induced Myocardial Necrosis by Drugs that Inhibit Platelet Aggregation." Am J. Cardiol. 30 838 (1972).

170. Haft, J. I. and Fani, K. "Stress and the Induction of Intravascular Platelet Aggregation in the Heart." Circulation 38 164 (1973).

171. Mehta, J. et al. "Platelet Aggregation Studies in Coronary Artery Disease. Part 4. Effect of Aspirin." Atherosclerosis 31 169 (1978).

172. Hollander, W. et al. "Aggravation of Atherosclerosis by Hypertension in a Subhuman Primate Model with Coarctation of the Aorta." Supp. II, Circulation Res. 38 II-63 (1976).

173. Henry, J.P. and Cassel, J.C., "Psychosocial factors in essential hypertension: recent epidemiologic and animal experimental evidence." Am. J. Epidemiol. 90 171 (1969).

174. Rothlin, E. et al., "Experimental psycho-neurogenic hypertension and its treatment with hydrogenated ergot alkaloids (hydergine)." Acta Physiol. Scand. 154 (Suppl. 312) 27 (1956).

175. Dahl, L.K. et al., "Role of genetic factors in susceptibility to experimental hypertension due to chronic excess salt ingestion." Nature 194 480 (1962).

176. Friedman, R. and Dahl, L.K., "The effect on chronic conflict on the blood pressure of rats with a genetic susceptibility to experimental hypertension." Psychosomatic Medicine 37, 402 (1975).

177. Dahl, L.K., "Salt and hypertension." Am J. Clin. Nutr. 25, 231 (1972).

178. Freis, E.D., "Salt, volume and the prevention of hypertension." Circulation 53 589 (1976).

179. Dawber, T.R. et al., "Environmental factors in hypertension." In Epidemiology of Hypertension, Proceedings of an International Symposium, Stamler, J. et.al., eds., Grune & Stratton, New York, 1967 cited by ref. 178.

180. Miall, W.E., "Follow-up study of arterial pressure in the population of a Welsh mining valley." Br. Med. J. 2 1205 (1959).

181. Langford, H.G. and Watson, R.L., "Electrolytes, environment and blood pressure." Clin. Sci. Mol. Med. 45.

182. Syme, S.L. and Torfs, C.P., "Epidemiologic research in hypertension: a critical appraisal." J. Human Stress 43 (March, 1978).

183. Bianchi, G. et al., "A renal abnormality as a possible cause of 'essential' hypertension." Lancet 1 173 (Jan. 27, 1979).

184. Bianchi, G. et al., "Changes in renin, water balance and sodium balance during development of high blood pressure in genetically hypertensive rats." Circulat. Res. 36 and 37, Suppl 1. I 153 (1975) cited by ref. 187.

185. Bianchi, G. et al., "Kidney function and blood pressure in a genetic type of hypertension." Proc. 6th Int. Congr. Nephrol. Karger, A.G., Basel 1975 cited by ref. 187.

186. Bianchi, G. et al., "Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats (SHR) and normotensive rats (NR)," Clin. Sci. Mol. Med. 47 435 (1974).

187. Hallback, M. et al., "Cardiovascular control in the Milan strain of spontaneously hypertensive rat (MHS) at "rest" and during acute mental 'stress'," Acta. Physiol. Scand. 99 208 (1977).

188. Brown, J.J. et al., "Renal abnormality of essential hypertension," Lancet 2 320 (1974).

189. Chau, N.P. et al., "Essential hypertension: an approach to clinical data by the use of models." Hypertension 1 86 (March-April, 1979).

190. Guyton, A.C. and Coleman, T.G., "Quantitative analysis of the physio-pathology of hypertension," Circ. Res. 24 (Suppl. 1) 1-19 (1969).

191. Swales, J.D., "Pathophysiology of blood pressure in the elderly," Age and Aging 8 104 (1979).

192. Hollander, W., "Role of hypertension in atherosclerosis and cardiovascular disease." Am. J. Cardio. 38 786 (1976).

193. Dustan, M.P., "Atherosclerosis complicating chronic hypertension." Circulation 50 871 (1974) cited by ref. 191.

194. Folkow, B. and Neil, E., Circulation, Oxford University Press, London 1971, p.63, cited by ref. 191.

195. Ulrych, M., "The role of vascular capacitance in the genesis of essential hypertension," Clin. Sci. Mol. Med. 51 203s (1976).

196. Takeshita, A. and Mark, A.L., "Decreased venous distensibility in borderline hypertension," Hypertension 1 202 (May-June, 1979).

197. Ulrych, M. and Ulrych, Z., "Significance of increase in labelled albumin disappearance rate in arterial hypertension," Clin. Sci. Molec. Med. 51 211s (1976).

198. Julius, S. and Esler, M., "Increased central blood volume: a possible pathophysiological factor in mild low-renin essential hypertension," Clin. Sci. Molec. Med. 51 207s (1976)

199. Ulrych, M., "Plasma volume decrease and elevated Evans Blue disappearance rate in essential hypertension," Clin. Sci. Molec. Med. 45 173 (1973) cited by ref. 195.

200. Greenberg, S., "Evidence for alterations in prostaglandin synthesis in veins from genetically hypertensive rats," Circulation 52 Suppl. 2 123 (1975) cited by ref. 195.

201. Friedman, S.M. and Friedman, C.L., "The ionic matrix of vasoconstriction," Circ. Res. 20, 21 (Suppl II.) 11-147 (1967) cited by ref. 195.

202. Greenberg, S. and Wilborn, W.M., "Pressure independent hypertrophy in veins from spontaneously hypertensive rats," Fed. Proc. 37 549 (1978).

203. Sullivan, J.M. et al., "Interrelationships among thiazide diuretics and calcium, magnesium, sodium, and potassium balance in normal and hypertensive man," J. Clin. Pharmacol. 530 (November/December, 1978).

204. Ulrych, M., "Pathogenesis of essential hypertension," Angiology 30 104 (Feb., 1979).

205. Hallback, M. and Folkow, B., "Cardiovascular responses to acute mental 'stress' in spontaneously hypertensive rats," Acta Physiol. Scand. 90 684 (1974).

206. Hudak, W.J. and Buckley, J.P., "Production of hypertensive rats by experimental stress," Pharm. Sci. 50 263 (1961) cited by ref. 205.

207. Kalis, L. et al., "Response to phychological stress in patients with essential hypertension," Amer. Heart J. 53 572 (1957) cited by ref. 205.

208. Julius, S. et al., "Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension," Circulation 44 413 (1971) cited by ref. 205.

209. Kalis, L. et al., "Response to psychological stress in patients with essential hypertension," Amer. Heart J. 53 572 (1957) cited by ref. 205.

210. Nestel, P.J., "Blood-pressure and catecholamine excretion after mental stress in labile hypertension," Lancet 5 692 (1969) cited by ref. 205.

211. Lorimer, A.R. et al., "Blood pressure and catecholamine responses to 'stress' in normotensive and hypertensive subjects," Cardiovasc. Res. 5 169 (1971) cited by ref. 205.

212. Folkow, B. and Rubenstein, E.M., "Cardiovascular effects of acute and chronic stimulations of the hypothalamic defense area in the rat," Acta. Physiol. Scand. 68 48 (1966).

213. Smookler, H.H. and Buckley, J.P., "Relationships between brain catecholamine synthesis, pituitary adrenal function and the production of hypertension during prolonged exposure to environmental stress," Int. J. Neuropharm. 8 33 (1969).

214. Henry, J.P. et al., "The use of psychosocial to induce prolonged hypertension in mice," Psychosom. Med. 29 408 (1967).

215. Herd, A.J. et al., "Arterial hypertension in the squirrel monkey during behavioral experiments," Amer. J. Physiol. 217 24 (1969) cited by ref. 205.

216. Simon, A.C. et al., "Arterial compliance in permanent essential hypertension: preliminary report," Angiology 29 402 (1978).

217. Mendlowitz, M., "Some theories of hypertension: fact and fancy," Hypertension 1 435 (July-August, 1979).

218. Chonabian, A.V. et al., "Studies on the activity of the sympathetic nervous system in essential hypertension," J. Human Stress 22 (September, 1978).

219. Chonabian, A.V. et al., "Relationship of basal plasma noradrenaline to blood pressure, age, sex, plasma renin activity and plasma volume in essential hypertension," Clin. Sci. Molec. Med. 55 93s (1978).

220. Esler, M.D. et al., "Relation of renin status to neurogenic vascular resistance in borderline hypertension," Am. J. Cardiol. 36 708 (1975).

221. Louis, W.J. et al., "Sympathetic activity and essential hypertension," Clin. Sci. Molec. Med. 45 119s (1973).

222. Fagard, R. et al., "Plasma renin concentration and the hypotensive effect of bendrofluazide and of altenolol," Clin. Sci. Molec. Med. 51 215s (1976).

223. Esler, M. et al., "Mild high-renin essential hypertension--neurogenic essential hypertension?" N. Eng. J. Med. 296 405 (1977).

224. Esler, M. et al., "Suppression of sympathetic nervous function in low-renin essential hypertension," Lancet II 115 (1976).

225. deChamplain, J., "The sympathetic system in hypertension," Clinics in Endocrinology and Metabolism 6 633 (1977).

226. Kaplan, N.M., "Stress, the sympathetic nervous system and hypertension," J. Human Stress 29 (September, 1978).

227. Page, I.H., "Some regulatory mechanisms of renovascular and essential arterial hypertension," in Hypertension Genest, J. et.al., eds., McGraw-Hill, New York, 1977, p. 598, cited by ref. 217.

228. Brunner, H.R. et al., "Essential hypertension: renin and aldosterone, heart attack and stroke," N. Eng. J. Med. 286 441 (1972).

229. Grim, C.E. et al., "Diagnosis of secondary forms of hypertension--a comprehensive protocol," J.A.M.A. 237 1331 (1977).

230. Eich, R.R. et al., "Hemodynamics in labile hypertension--a follow-up study," Circulation 34 299 (1966).

231. Adamopoulos, P.N. et al., "Systolic hypertension: nonhomogenous diseases," Am. J. Cardiol. 36 697 (1975).

232. Januszewicz, W. et al., "Metabolic and hormonal studies in patients with essential hypertension," Brit. Heart J. 39 1205 (1977).

233. Julius, S. and Esler, M., "Autonomic nervous cardiovascular regulation in borderline hypertension," Am. J. Cardiol. 36 685 (1975).

234. Friedrich, C.L. et al., "Natriutetic response to saline infusion in normotensive and hypertensive man--the role of renin suppression in exaggerated natriutesis," Circulation 55 779 (1977).

235. Pettinger, W.A. and Mitchell, H.C., "Clinical pharmacology of angiotension antagonists," Fed. Proc. 35 2521 (1976).

236. Epstein, M., "Effects of aging on the kidney," Fed. Proc. 38 168 (Feb., 1979).

237. Weidman, P. et al., "Interrelations among blood pressure, blood volume, plasma renin activity and urinary catecholamines in benign essential hypertension," Am. J. Med. 62 209 (1977).

238. Makuch, R.W. et al., "Justification for the lognormal distribution as a model for blood pressure," J. Chron. Dis. 32 245 (1979).

239. Weller, R.O., "Vascular pathology in hypertension," Age and Aging 8 99 (1979).

240. Roberts, J. and Maurer, K., Blood Pressure Levels of Persons 6-74 Years National Center for Health Statistics, Vital and Health Statistics (Health and Nutrition Examination Survey) DHEW Publication No. 78-1648. Series 11, No. 203. Washington, D.C., (1977)

241. Kryter, K.D., "Extraauditory effects of noise," Effects of Noise on Hearing, Henderson, D. et.al., eds., Raven Press, New York, 1976, p.531.

242. Moller, A.R., "Occupational noise as a health hazard--physiological viewpoints," Scand. J. Work Environ. & Health 3 73 (1977).

243. Miller, J.D., "Effects of noise on people," J. Accoust. Soc. Am. 56 729 (1974).

244. Medoff, H.S. and Bongiovanni, A.M., "Blood pressure in rats subjected to audiogenic stimulation," Am. J. Physiol. 143.

245. Yeakel, E.H. et al., "Blood pressures of rats subjected to auditory stimulation," Am. J. Physiol. 155 118 (1948).

246. Hudak, W.J. and Buckley, J.P., "Production of hypertensive rats by experimental stress," Pharm. Sci. 50 263 (1961).

247. Rosecrans, J.A. et al., "The production of hypertension in male albino rats subjected to experimental stress," Biochem. Pharmacol. 15 1707 (1966).

248. Smookler, H.H. et al., "Hypertensive effects of prolonged auditory, visual and motion stimulation," Fed. Proc. 32 2105 (1973).

249. Smookler, H.H. and Buckley, J.P., "Effects of drugs on animals exposed to chronic environmental stress," Fed. Proc. 29 1980 (1970).

250. Peterson, E.A. et al., "Noise and cardiovascular function in rhesus monkeys," J. Aud. Res. 15 234 (1975).

251. Peterson, E.A., "Noise and cardiovascular function in rhesus monkeys: II," Mimeo, presented at Freiburg conference.

252. Borg, E. and Moller, A.R., "Noise and blood pressure: effect of life-long exposure in the rat," Acta. Physiol. Scand. 103 340 (1978).

253. Borg, E., "Physiological aspects of the effects of sound on man and animals," Acta. Otolaryngol. Suppl. 360 80 (1979).

254. Welch, B. L., Extra-Auditory Health Effects of Industrial Noise--Survey of Foreign Literature Final Report, Wright-Patterson Air Force Base Contract No. 16-88-7 (1978).

255. Parvizpoor, D., "Noise exposure and prevalence of high blood pressure among weavers in Iran." J. Occup. Med. 18 730 (1976).

256. Knipschild, P., "V. Medical effects of aircraft noise: community cardiovascular survey." Int. Arch. Occup. Environ. Hlth. 40 185 (1977).

257. Andriukin, A.A., "Influence of sound stimulation on the development of hypertension--clinical and experimental results. Cor et Vasa 3 285 (1961).

258. Andrukovich, A.I., "Effect of industrial noise in winding and weaving factories on arterial pressure in the operators of the machines." (Russian). Gigiena Truda i Professional'nye Zabolevaniya 9: 39 (1965).

259. Friedlander, B., Grebermann, M., Wathen, G. and Zeidler, W.H., "An analysis of noise and its relationship to blood pressure in an industrial population." Manuscript, Maryland State Department of Health and Mental Hygiene (undated).

260. Gheller, L.I. et al., "The influence of noise on the arterial blood pressure (the aetiology of arterial hypertension)." (Russian). Terapertichkii Arkhiv 35: 83 (1963).

261. Shatalov, N.N. and Murov, M.A., "Effect of intensive noise and neuropsychic tension on arterial blood pressure levels and frequency of hypertensive disease." (Russian). Klin. Med. (Moskova) 48: 70 (1970).

262. Graff, Von Ch. et al., "Noise exposure and essential arterial hypertension in humans." (German). In S. Nitschoff and G. Kriwizkaja (Eds) Larmbelastung, Akustischer Reiz und Neurovegetative Storungen, Leipzig (1968).

263. Jirkova, H. and Kremarova, B. "Studies of the effect of noise on the general state of health of workers in large machine-tool factories: attempt at evaluation." Pracovni Lekarstvi 17: 147 (1965).

264. Shetalov, N.N., "Hearing and arterial pressure in persons affected by intense production noise." Gigiena Truda i Professional'nye Zabolevaniya 13: 2 (1969).

265. Sanova, A.G., "The complex effect of low-frequency noise and infrasound on the bodies of workers." (Russian). Vrachebnoe Delo (10) 133-136 (1975).

266. Cieslewicz, J., "Attempt to evaluate the extra-auditory effects of noise on weaving mill workers in a textile industry factory." (Polish). Medycyna Pracy 22: 447 (1971).

267. Kavoussi, N., "The relationship between the length of exposure to noise and the incidence of hypertension at a silo in Terran." Medicina Lavoro 64: 292.

268. Kaliciniski, A. et al., "Cardiovascular changes in workers exposed to noise." (Polish). Wiadomosci Lekarskie 28: 1 (1974).

269. Kanevskaya, Zh. S. et al., "The effect of pulsed and stable noise on the central nervous system of workers." (Russian). Gigiena Truda i Professional'nye Zabolevaniya: 22 (1977).

270. Meinhart, P. and Renker, U., "Indicators of morbidity in the heart and circulation as a result of excessive exposure to noise." Zeitschrift fur die Gesamte Hygiene und ihre Grenzgebiete 16: 353 (1970). (German).

271. Takala, J. et al., "Noise and blood pressure." Lancet 2 974 (1977).

272. Johnson, A. and Hanson, L., "Prolonged exposure to a stressful stimulus (noise) as a cause of raised blood pressure in man." Lancet 1 86 (1977).

273. Hedstrand, H. et al., "Noise and blood pressure." Lancet 2 1291 (1977).

274. Cohen, A. et al., "Occupational exposures to noise, hearing loss, and blood pressure." Presented at Freiburg conference, (1978).

275. Mannien, O. and Aro, S., "Noise-induced hearing loss and blood pressure." Int. Arch. Occup. Environ. Health 42 251 (1979).

276. Lees, R.E.M. and Roberts, J.H., "Noise-induced hearing loss and blood pressure." Can. Med. Ass. J. 120 1082 (May 5, 1969).

277. Morton, W.E. and Knudsen, J.C., "Correlates of hypertension among young men." Preventive Medicine 4 258 (1975).

278. The Pooling Project Research Group. "Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the pooling project. J. Chron. Dis., 31 201 (1978).

279. Brand, R.J., "An examination of the association between A-B behavior and coronary heart disease incidence." Proceedings of the Forum on Coronary Prone Behavior DHEW Publ. No. (NIH) 78-1451, (1977).

280. Shurtleff, D., et al., "Section 30. Some characteristics related to the incidence of cardiovascular disease and death: Framingham study, 18-year follow-up." in The Framingham Study--An Epidemiological Investigation of Cardiovascular Disease Kannel, W.B. and Gordon, T., eds. DHEW Publ. No. (NIH) 74-599, (1974).

281. Stedman's Medical Dictionary, 23rd ed., William & Wilkins Co., Baltimore, Maryland, (1976).

282. Haft, J.I., "Role of blood platelets in coronary artery disease." Am. J. Cardiol. 43 1197 (June, 1979).

283. Mustard, J.F. and Packham, M.A., "Platelet function and myocardial infarction." Circulation 39-40, Suppl. IV IV-20 (1969).

284. Harem, J.W., "Sudden coronary death: the occurrence of platelet aggregates in the epicardial arteries of man." Atherosclerosis 14 417 (1971).

285. Schneider, M.D. and Kelman, B.J., "A proposed mechanism(s) of transitory ischemic injury to myocardium."

286. Jorgensen, L. et al., "Adenosine diphosphate-induced platelet aggregation and myocardial infarction in swine." Lab Invest. 17 616 (1967).

287. Friedman, M. and Vandenbovenkamp, J.G., "The pathogenesis of a coronary thrombus." Amer. J. Path. 48 19 (1966) cited by ref. 283.

288. Constantinides, P., "Plaque fissures in human coronary thrombosis." J. Atheroscler. Res. 6 1 (1966) cited by ref. 283.

289. Folts, J.D. et al., "Platelet aggregation in partially obstructed vessels and its elimination with aspirin." Circulation 54 365 (1976) cited by ref. 282.

290. Mustard, J.F., "Platelets and thrombosis in acute myocardial infarction." Hospital Practice 115 (January, 1972).

291. Madias, J.E., "The syndrome of variant angina culminating in acute myocardial infarction." Circulation 59 297 (February, 1979).

292. Desilva, R.A. and Lown, B., "Ventricular premature beats, stress, and sudden death." Psychosomatics 19 649 (1978).

293. Rosenfeld, J. et al., "Pharmacologic and behavioral effects on arrythmias that immediately follow abrupt coronary occlusion: a canine model of sudden coronary death. Am. J. Cardiol. 41 1075 (1978).

294. Boyd, G.W., "Stress and disease: the missing link. A vasospastic theory. I. Acute myocardial infarction--a potentially reversible event?" Med. Hypotheses 4 411 (1978).

295. Kagan, A.R., "Atherosclerosis and myocardial lesions in subjects dying from fresh cerebrovascular disease." Bull. World Health Org. 53 597 (1976).

296. Vihert, A.M., "Atherosclerosis of the aorta and coronary arteries in coronary heart disease." Bull. World Health Org. 53 585 (1976).

297. Wolf, P.A. et al., "Epidemiology of stroke." Advances in Neurol. 16 5 (1977).

298. Jorgensen, L. et al., "The pathology of acute coronary death." Acta Anaesthesiol. Scand. (Suppl.) 29 193 (1968).

299. Roberts, W.C., "Coronary arteries in fatal acute myocardial infarction." Circulation 45 215 (1972).

300. Penther, P., "Coronary thrombosis and acute myocardial infarction: cause or consequence?" Am. Heart J. 94 392 (1977) and "Reply" by Baroldi, G., same page.

301. Baroldi, G., "Coronary thrombosis: facts and beliefs." Am. Heart J. 91 683 (1976) cited by ref. 300.

302. Davies, M.J. et al., "Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi." Br. Heart. J. 38 659 (1976) cited by ref. 300.

303. Chapman, I., "The cause and effect relationship between recent coronary artery occlusion and acute myocardial infarction." Am. Heart J. 87 267 (1974) cited by ref. 300.

304. Waldenstrom, A.P. et al., "A possible role of noradrenaline in the development of myocardial infarction." Am. Heart J. 95 43 (1978).

305. Schwartz, C.J. and Gerrity, R.G., "Anatomical pathology of sudden unexpected cardiac death." Circulation, Suppl. III, 51-2 III-18 (1975).

306. Baba, N. et al., "Pathology of atherosclerotic heart disease in sudden death." Circulation, Suppl. III, 51-2 III-53.

307. Spain, D.M. and Bradess, V., "Frequency of coronary thrombus as related to duration of survival from onset of acute fatal episodes of myocardial ischemia." Circulation 22 816 (1960) cited by ref. 284.

308. Erhardt, L. et al., "Incorporation of 125 I-labeled fibrinogen into coronary arterial thrombi in acute myocardial infarction in man." Lancet I 387 (1973) cited by ref. 304.

309. Robbins, S.L. and Angell, M., Basic Pathology, W.B. Saunders Company, Philadelphia, (1971).

310. Born, G.V.R., "Platelet aggregation in the pathogenesis of cerebrovascular disorders," Platelet Aggregation in the Pathogenesis of Cerebrovascular Disorders, Springer-Verlag, New York (1977).

311. Born, G.V.R., Hume, M., "Effects of the numbers and sizes of platelet aggregates on the optical density of plasma. Nature 215, 1027 (1967), cited by ref. 310.

312. Haslam, R.J., "Biochemical aspects of platelet functions. In: Proc. 12th Congr. Int. Soc. Haemat., N.Y. 198 (1968), cited by ref. 310.

313. Macmillan, D.C., Oliver, M.F., "The initial changes in platelet morphology following the addition of adenosine diphosphate, J. Atheroscl. Res. 5, 440 (1965), cited by ref. 310.

314. Ardlie, N.G., Glew, G., Schwartz, C.J., "Influence of catecholamines on nucleotide-induced platelet aggregation, Nature 212, 415 (1966), cited by ref. 310.

315. Macmillan, D.C., "Secondary clumping effect in human citrated platelet-rich plasma produced by adenosine diphosphate and adrenaline, Nature 211, 140 (1966), cited by ref. 310.

316. Constantine, J.W., "Aggregation of guinea-pig platelets by adenosine diphosphate," Nature 210, 162 (1966), cited by ref. 310.

317. Mills, D.C.B., Roberts, C.G.K., "Membrane active drugs and the aggregation of human blood platelets," Nature 214, 35 (1967), cited by ref. 310.

318. Hardisty, R.M., Hutton, R.A., "Platelet aggregation and the availability of platelet factor 3," Brit. J. Haemat. 12, 764 (1966), cited by ref. 310.

319. Grette, K., "Studies on the mechanism of thrombin-catalyzed haemostatic reactions in blood platelets," Acta. physiol. scand. 56, Suppl. 195, 5 (1962), cited by ref. 310.

320. Haft, J.I. et al., "Protection against epinephrine induced myocardial necrosis with chlofibrate," Am. Heart J. 86 (1973).

321. Haft, J.I. et al., "Protection against epinephrine induced myocardial necrosis by drugs that inhibit platelet aggregation," Am. J. Cardiol. 30, 838 (1972).

322. Haft, J.I. and Fani, K., "Intravascular platelet aggregation in the heart induced by stress," Circulation 47 353 (1973).

323. Haft, J.I. and Fani, K., "Stress and the induction of intravascular platelet aggregation in the heart," Circulation 48 164 (1973).

324. Fleischman, A.I. et al., Hypertension and in vivo platelet function in humans," Fed. Proc.

325. Fleischman, A.E. et al., "In vivo platelet function in diabetes mellitus," Thromb. Res. 9, 467 (1976).

326. Wu, K.K. and Hoak, J.C., "A new method for the quantitative detection of platelet aggregates in patients with arterial insufficiency," Lancet ii, 924 (1974).

327. Fleischman, A.I. et al., "In vivo platelet function in acute myocardial infarction, acute cerebrovascular accidents and following surgery," Thromb. Res. 6, 205 (1975).

328. Couch, J.R. and Hassanein, R.S., "Platelet aggregation, stroke, and transient ischemic attack in middle-aged and elderly patients," Neurology 26, 888 (1976).

329. Breddin, K. et al., "Enhanced platelet aggregation as a risk factor for progress and complications of vascular disease. New findings with a platelet aggregation test (PAT III) and on the dependence of different aggregation tests on morphologic platelet changes," in Platelet Aggregation in the Pathogenesis of Cerebrovascular Disorders, Springer-Verlag, New York (1977).

330. Dougherty, J.M. et al., "Platelet activation in acute cerebral ischemia. Serial measurements of platelet function in cerebrovascular disease," Lancet i, 821 (1977).

331. Fleischman, A.I. et al., "Increased in vivo platelet aggregation in patients with coronary heart disease," Clin. Chem. 23, 1138 (1977).

332. Mornstra, G. et al., "Influence of dietary fat on platelet in man," Lancet I, 1155 (1973).

333. Breddin, K. et al., "On the measurement of spontaneous platelet aggregation. The platelet aggregation test III. Methods and first clinical results," Thromb. and Haemostasis 35, 669 (1976).

334. Hutton, R.A. et al., "Platelet aggregation studies during transient hypoglycaemia. A potential method for evaluating platelet function," J. Clin. Pathol. 32, 434 (May, 1979).

335. Fleischman, A.I. and Bierenbaum, M.L., "Comparison of the in vitro platelet aggregation test of Wu and Hoak with the in vivo procedure of Hornstra," Clin. Chem. 22, 1227 (1976).

336. Chung-Hsin Ts'ao, et al., "'Spontaneous' platelet aggregation: its characteristics and relation to aggregation by other agents," Thrombos. Haemostas. 39, 379 (1978).

337. Adelson, L. and Hoffman, W., "Sudden death from coronary disease," J.A.M.A. 176, 129 (1961).

338. Beck, C.S. and Leighninger, D.S., "Should patients with coronary heart disease be treated by surgical operation?" Ohio Med. J. 56, 809 (1960) cited by ref. 337.

339. Lown, B., "Sudden cardiac death: the major challenge confronting contemporary cardiology," Am. J. Cardio. 43, 313 (Feb., 1979).

340. Lown, B., "Sudden cardiac death--1978," Circulation 60, 1593 (Dec., 1979).

341. Katz, A.M., Physiology of the Heart, Raven Press, New York, (1977).

342. Beattie, J. et al., "Physiological and anatomical evidence for the existence of nerve tracts connecting hypothalamic with spinal sympathetic centers,"Proc. Royal Soc. (Series B) 106, 253, (1930) cited by ref. 292.

343. Brow G.R. et al., "Irregularities of the heart under chloroform: their dependence on the sympathetic nervous system, JAMA 95, 715, (1930) cited in ref. 292.

344. Watts, J.W. and Fulton, J.F., "The effects of lesions of they hypothalamus upon the gastrointestinal tract and heart in monkeys, Ann. Surg. 101, 363, (1935) cited by ref. 292.

345. Weinberg, S.J. and Foster, J.M., "Electrocardiographic changes produced by localized hypothalamic stimulation," Ann. Intern. Med 53, 332, (1960) cited by ref. 292.

346. Altar, H.J. et al., "Effect of stimulation of hypothalamus and reticular activating system on production of cardiac arrhythmia," Circ. Res. 12, 14, (1963) cited by ref. 292.

347. Kortweg, G.C.J. et al., "Influences of stimulation of some subcortical areas on the electrocardiogram," J. Neurophysiol 20, 100, (1957) cited by ref. 292.

348. Hockman C.H. et al., "ECG changes resulting from cerebral stimulation II. A spectrum of arrhythmias of sympathetic origin," Am. Heart J. 71, 695, (1966) cited by ref. 292.

349. Hockman, C.H., "ECG changes resulting from cerebral stimulation III. Action of diphenylhydantoin on arrhythmias,"Am. Heart J. 74, 256, (1967) cited by ref. 292.

350. Satinsky, J. et al., "Ventricular fibrillation induced by hypothalamic stimulation during coronary occlusion, abstracted," Circulation 44, suppl 2, (1971) p. 2, cited by ref. 292.

351. Harris, A.S. et al., "The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart," J. Electrocardiol. 4, 34, (1971) cited by ref. 292.

352. Verrier, R.L. et al., "Ventricular vulnerability during sympathetic stimulation. Role of heart rate and blood pressure," Cardiovas. Res. 8, 602, (1974) cited by ref. 292.

353. Kliks, B.R. et al., "Influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion," Am. J. Cardiol. 36, 45, (1975) cited by ref. 292.

354. Rosenfeld, J. et al., "Pharmacologic and behavioral effects on arrhythmias that immediately follow abrupt coronary occlusion: A canine model of sudden coronary death," Am. J. Cardio. 41, 1075, (1978) cited by ref. 292.

355. Corbalan, R. et al., "Differing mechanisms for ventricular vulnerability during coronary artery occlusion and release," Am. Heart J. 92, 223, (1976) cited by ref. 292.

356. Hai, H.A. et al., "Changes in ventricular fibrillation threshold during coronary artery occlusion and release induced by beta-adrenergic blockade, abstracted," Am. J. Cardiol. 37, 140, (1976) cited by ref. 292.

357. Leriche, R. et al., "Ligature de la coronaire gauche et fonction cardiaque chez l'animal intact," C.R. Soc. Biol. (Paris) 107, 545, (1931) cited by ref. 292.

358. Schaal, S.F. et al., "Protective influence of cardiac denervation against arrhythmias of myocardial infarction," Cardiovas. Res. 3, 241, (1969) cited by ref. 292.

359. Ebert, P.A. et al., "Effect of chronic cardiac denervation on arrhythmias after coronary artery ligation," Cardiovasc. Res. 4, 141, (1970) cited by ref. 292.

360. DeSilva, R.A. et al., "Effects of psychological stress and vagal stimulation with morphine in the conscious dog," Am. Heart J. 95, 197, (1978) cited by ref. 292.

361. Lown, B. et al., "Psychologic stress and threshold for repetitive ventricular response," Science 182, 834, (1973) cited by ref. 292.

362. Matta, R.J. et al., "Ventricular electrical instability in the conscious dog: Effects of psychologic stress and beta-adrenergic blockade," Am. J. Cardiol. 34, 692, (1974) cited by ref. 292.

363. Skinner, J.E. et al., "Modification of ventricular fibrillation latency following coronary artery occlusion in the conscious pig: The effects of psychological stress and beta-adrenergic blockade," Circulation 34, 692, (1974) cited by ref. 292.

364. Lown, B. et al., "Role of psychologic stress and autonomic nervous system processes in provocation of ventricular premature complexes," Am. J. Cardiol. 41, 979, (1978).

365. Taggart, P. et al., "Electrocardiogram, plasma catecholamines and lipids, and their modification by oxprenolol when speaking before an audience," Lancet II, 341, (1973).

366. Harvey, P. and Levine, S.A., "Paroxysmal ventricular tachycardia due to emotion. Possible mechanism of death from fright," JAMA 150, 479, (1952).

367. McRae, J.R. et al., "Paroxysmal familial ventricular fibrillation," J. Pediatrics 84, 515, (1974).

368. Parkes, C. M. et al. "Broken heart: Statistical study of increased mortality among widowers," Br. Med. J. 1, 740 (1969).

369. Rees, W. D. and Lutkins, S. G. "Mortality of bereavement, Br. Med. J. 4, 13 (1967).

370. Rahe, R. M. et al. "Recent life changes, myocardial infarction and abrupt coronary death. Studies in Helsinki," Arch. Intern. Med. 133, 221 (1974).

371. Reinhardt, C. F. et al. "Cardiac arrythmias and aerosol 'sniffing,'" Arch. Env. Health 22, 265 (1971).

372. Davidson, W. J. "Psychotropic drugs, stress and cardiomyopathies," In Stress and the Heart, D. Wheatley, ed. Raven Press, New York, (1977).

373. Wellens, H. J. J. et al. "Ventricular fibrillation occurring on arousal from sleep by auditory stimuli," Circulation 46, 661 (1972).

374. Friedman, G. D. et al. "Predictors of sudden cardiac death," Circulation, Suppl. III to Vols. 51 and 52, III-164 (1975).

375. Antman, E., et al. "Continuous monitoring for ventricular arrythmias during exercise tests, " J.A.M.A. 241, 2802 (June 29, 1979).

376. Rosenman, K. D. "Cardiovascular disease and environmental exposure," Brit. J. Indust. Med. 36, 85 (1979).

377. Lown, B. et al. "Ventricular premature beats and coronary risk factors," Am. J. Epidemoil. 108, 228 (1978).

378. Rosenman, R.M. et al., "A study of comparative blood pressure measures in predicting risk of coronary heart disease," Circulation 54, 51 (1976).

379. Theorell, T., and Rahe, R.M., "Life change events, ballistocardiography and coronary death," J. Human Stress 18 *1976).

380. Connolly, J., "Life events before myocardial infarction," J. Human Stress 3 (December, 1976).

381. Bureau of the Census, Statistical Abstract of the United States--1978, 99th edition, U.S. Department of Commerce, GPO, Washington, D.C., pp. 29 and 31 (1978).

382. Brand, R.J. et al., "Multivariate prediction of coronary heart disease in the Western Collaborative Group Study compared to the findings of the Framingham study," Circulation 53 348 (1976).

383. Rosenman, R.H. et al., "Coronary heart disease in the Western Collaborative Group Study--Final follow-up experience of 8-1/2 years." J.A.M.A. 233, 872 (1975).

384. Brand, R.J., "An examination of the association between A-B behavior and coronary heart disease incidence," in Proceedings of the Forum on Coronary Prone Behavior DHEW Publ. No. (NIH) 78-1451 (1977).

385. Moore, Felix E. (Professor of Biostatistics, University of Michigan), personal communication.

386. Ising, H. et al., Study on the Quantification of Risk for the Heart and Circulatory System Associated with Noise Workers, EPA translation TR-79-0857, Office of Noise Abatement and Control (1979).

387. Ising, H. et al. "Zur Gesundheitsgefardung durch Verkehrslarm," Z. Larmbekampfung 27 1 (1980).

388. Altura, B.M., and Altura, B.T. "Magnesium and vascular tone and reactivity," Blood Vessels 15 5 (1978).

389. MacIntyre, I. "An outline of magnesium metabolism in health and disease--a review," J. Chron. Dis. 16 201 (1963).

390. Herous, O., et al. "Long-term effect of suboptimal dietary magnesium on magnesium and calcium contents of organs, and cold tolerance and on lifespan, and its pathological consequences in rats," J. Nutrition 107 1640 (1977).

391. Krasner, B.S. "Cardiac effects of magnesium with special reference to anaesthesia: a review," Canad. Anaesthes. Soc. J. 26 181 (1979).

392. Fehlinger, R., and Littmann, E. "Ergebnisse klinischer paraklinischer und testpsychologischer Untersuchungen beim tetanischen Syndrom, 1.-3.," Mitteilung Deutsches Gesundheitswesen 33 592 (1978) cited by ref. 387.

393. Anderson, T.W. et al. "Ischemic heart disease, water hardness and myocardial magnesium." CMA Journal 113 199 (1975).

394. Altura, B.M. "Sudden-death ischemic heart disease and dietary magnesium intake: Is the target site coronary vascular smooth muscle?" Medical Hypotheses 5 843 (1979).

395. Critelli, par G., et al. "L'action antiarythmique des cations de magnesium," Arch. Mal. Coeur 72 879 (1979).

396. Krasner, B.S., and Girdwood, R. "The use of oral magnesium chloride (slow-releasing) in open-heart surgery with special reference to arrhythmias and recovery times." Abstracts of Scientific Papers, A.S.S. Meeting, Chicago, 589 (1978) cited by ref. 391.

397. Chadda, K.D. et al. "Hypomagnesemia and refractory cardiac arrhythmia in a non-digitalised patient." Am. J. Cardiol. 31 98 (1973) cited by ref. 391.