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16. ABSTRACT 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 obstacles to progress in cardiovascular disease research, key technical or measurement system obstacle, for research, and findings related to noise and suggestions for further research. <i>see p. 215</i>		
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NOISE, GENERAL STRESS RESPONSES,
AND CARDIOVASCULAR DISEASE PROCESSES:
REVIEW AND REASSESSMENT OF
HYPOTHESIZED RELATIONSHIPS.

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June 1980

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— 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

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

*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 realizable 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

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:

*Net after the action of repair processes.

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

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 arrhythmias (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:

*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).

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:

	<u>Under 40 years</u>	<u>Over 40 years</u>
Systolic	3 mm Hg	6 mm Hg
and/or		
Diastolic	2.5 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:

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.

o 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

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.

- 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 arrhythmias³⁷⁶ 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 Taggart³⁶⁵ 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.