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Physiological and Pathogenic Effects of Sound

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Foreword

The contents of this supplement are based on research performed from 1974 to 1978 on the physiological and medical effects of noise. This project was supported by The Swedish Work Environment Fund (project no. 74/24 and 77/49) and carried out at the Department of Physiology II at Karolinska Institutet, under the auspices of Professor A. R. Møller. The author Erik Borg was responsible for the design and accomplishment of the experiments. The laboratory work was performed by Agneta Viberg, Ulla Elmér, and Gunilla Jalmarsson. The pathological-anatomical analyses and the diagnoses were made at The Swedish National Veterinary Institute by Assistant Professor Bertil Järplid, Professor Nils-Erik Björklund, and Veterinarian Lena Renström. This presentation is introduced by a review of the literature covering the non-auditory effects of noise.

The following articles based on these experiments have been published, or are in press:

Borg, E. 1977. Tail artery response to sound in the unanesthetized rat. *Acta Physiol Scand 100*, 129.

Borg, E. 1977. Ljudutlöst perifer kärlkontraktion hos råtta. Svensk Otolaryngologisk Förening.

Borg, E. 1977. Jämförelse mellan olika metoder för hörselmätning på råtta. Svensk Otolaryngologisk Förening.

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Møller, A. R. & Borg, E. 1977. Extra-aural effects of noise. EBC Noise Abatement Symposium. Carlsberg Symposium Series.

Borg, E. 1978. Peripheral vasoconstriction in the rat in response to sound. I. Dependence on stimulus duration. *Acta Otolaryngol* (Stockh) *85*, 153.

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Borg, E. 1978. Peripheral vasoconstriction in the rat in response to sound. III. Dependence on pause characteristics in continuous noise. *Acta Otolaryngol* (Stockh) *86*, 155.

Borg, E. & Møller, A. R. 1978. Noise and blood pressure: Effect of lifelong exposure in the rat. *Acta Physiol Scand 103*, 340.

Borg, E. 1979. Physiological aspects of effects of sound on man and animals. *Acta Otolaryngol* (Stockh) *80*, Suppl. *360*.

Borg, E. & Viberg, A. 1980. Role of heating in non-invasive blood pressure measurements in rats. *Acta Physiol Scand 108*, 73.

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Borg, E. & Järplid, B. Life span and organ pathology in rats after life-long noise exposure. Submitted for publication.

Borg, E. & Viberg, A. Validity and reproducibility of indirect blood pressure measurements in the rat. In preparation.

I. Introduction

The occupational environment has gained increased interest during the past decades from the point of view of somatic and physic health and well-being. A wide spectrum of research efforts is being directed to detect, establish, or exclude environmental factors as agents threatening health and causing disease. Due to the numerous individual and environmental factors involved, it is often difficult to establish a correlation between specific agents and organ lesions, and particularly to prove a cause–effect relationship. Symptoms are often observed only after prolonged exposure, or even as delayed reactions following determination of the exposure. Several simultaneous factors, external-environmental and internal-individual, may interact in an additive, potentiating, or inhibiting manner. A certain environment or factor may have a widely different, or opposite effect on different individuals. Examples of such divergences can be taken from everyday medical practice. A pharmaceutical agent may be life-saving for one patient in proper dosage, but it may have deleterious effects on another patient or a healthy test subject. Some differences in response to an exposure have a physiological-biochemical explanation, whereas others mainly express psychological factors. Certain environmental phenomena can be perceived as very annoying without actually being harmful, while others may have *very* insidious effects. The fear of harm may even in itself cause psychic tension and psychosomatic disorders. The real importance of environmental factors, alone or in combination, can be assessed only on the basis of an analysis with different techniques, both in the field and in the laboratory if the occupational environment is to be improved. It is therefore of the greatest importance to pinpoint the true cause–effect relationships and not to be misled by interpretations more apparent than real. Simplified interpretations may be totally misleading.

The acoustic environment has certain special features. Sound is, in contrast to most other environmental factors, continuously present in the human external milieu. Although sound and noise as a physical concept is well defined, environmental "noise" is much less so. Since noise has the subjective quality of interaction with humans, it can be described in several, both physical and psychological, dimensions. Sound can be wanted or unwanted; "unwanted sound" is a traditional definition of environmental "noise". The same sound from a human voice or a musical composition, for example, can be subjectively pleasant or unpleasant depending on the situation. Sound can be disturbing for sleep, distracting for intellectual work, or masking for perception of speech. The noise quality of sound is as much dependent on the context as on the physical properties of the sound itself. In many, perhaps in most, situations it is not possible to decide unequivocally whether a sound is wanted or not. Sound waking somebody in the middle of the night is usually not desired. The sound of a smoke-detector alarm is probably utterly unwanted (= noise) in the sense that one does not want a fire. It is, however, certainly wanted in the sense that one thereby has a chance to escape.

Since the environmental "noise" by the traditional definition only refers to unwanted sound, a significant limitation is introduced by the utilization of this concept. "Sound" and "noise" will not be used synonymously in this presentation; rather "sound" will be used in a general sense and "noise" only when the unwanted character is obvious. In the literature survey, however, it has sometimes been more appropriate to follow the nomenclature of the referenced author, although it has meant departing from the above-mentioned principle.

In comparison with most other physical and chemical factors in the environment, sound has a great capacity to carry information or to interfere with interchange of information. Sound may be neutral and only carry information about its own presence, but it often carries highly significant information about processes in the environment. It can also carry "negative" information, i.e. mask expected or unexpected acoustic information of relevance, or speech. More or less consciously, we judge a traffic situation on the basis of acoustic cues. In work environment, sound often carries information that has to be utilized to initiate reactions and behav-

iors in order to improve adaptation to the work situation and possibly avoid accidents.

In fact, sound may be a threat to health just because it is a source of information, warning for risks, strains or dangers. Sound plays a general role of warning throughout the animal kingdom and facilitates physiological adjustments to cope with demanding situations. One may therefore speculate that there may exist, also in humans, primitive neural mechanisms, reflexively adjusting physiological homeostasis to meet the demands of the situations signalled by the sound. Such adapting reactions have been extensively analysed (Cannon, 1929; Selye, 1971 and others) and include a redistribution of blood, a rise of systemic blood pressure, an increase of muscle tone, in other words, processes controlled to a large extent by autonomic nerves and adrenal hormones. These primitive reactions have evolved under conditions where sound often signalled danger and the reflexive adjustments formed a basis adequate for coping with the threat. In modern society, where there is a progressive increase in the variety and level of sound, the relationship between the incidence and the levels of sound and actual dangers is much looser, and physiological and psychological adaptation is not, to the same extent, as purposeful. Nonetheless, sound may cause physiological adjustments resulting in inappropriate reactions that, if persistent, may lead to a deterioration of health and an increase in morbidity.

II. Literature Survey

In this review, investigations on non-auditory physiological and pathogenic effects by sound with relevance for work environment will be emphasized. Effects of psychomotor behavior and sleep, or the effects on traffic and airport sound will only be touched upon briefly. Literature on the infrasound (sound with a frequency below 20 Hz) and ultrasound (frequency above 20 kHz for humans) will also be largely omitted.

Several review articles on noise pollution have appeared in the last 25 years, some including material on the general physiological and medical effects of sound (Davis et al., 1955; Grandjean, 1960; Nitschkoff & Kriwizkaja, 1968; Welch & Welch, 1970; Finke & Martin, 1974; Miller, 1974; Finke et al., 1975; Cohen, 1977; McLean & Tarnopolsky, 1977).

The present review has the ambition to cover also the rapidly expanding literature over the last few years, and to present a critical examination, comparison and evaluation of existing informations which are often contradictory and incomplete. It is divided in separate sections with different organ systems, and also contains a section about underlying central nerve mechanisms of the physiological effects. Finally, some questions are raised concerning the direction of future research.

A. CARDIOVASCULAR SYSTEM

1. Short-term exposure

a. *Peripheral blood-flow*

In 1875 Mosso showed that sudden sensory stimuli, such as sound, induced a decline in the hand volume which was interpreted as a peripheral vasoconstriction. The sound in Mosso's investigations usually carried information, e.g. foot-steps telling about the immediate arrival of his teacher, Professor Ludwig. Peripheral blood-flow (and other cardiovascular) parameters were extensively studied around the turn of the century, especially in relation to emotional states (reviewed by Robbins in 1919). Robbins further made his own observations on different types of sound acting on both normal subjects and stammerers. He found that peripheral vasoconstriction occurred with a latency of 3 s, and that its size depended on the type of sound, e.g. it increased as a function of sound level. He also found a larger response in stammerers than in normal subjects, and noted that the more unexpected the presentation of the sound, the greater the response.

Substantial work in this field has also been done by Sokolov (1963), Jansen & Rey (1962), Jansen et al. (1964), Jansen (1961, 1974), and Sokolov & Vinogradova (1975). Sokolov recorded pulse volume, both from the forehead and from the finger. On the basis of different reaction patterns in these two organs, he postulated two basic response types; the "orienting reflex" and the defence reaction. Low level sound (below about 70 phon) induced a vasoconstriction in the finger, but a vasodilatation in the forehead, and this pattern was defined as the "orienting reflex" (a terminology first introduced by Pavlov, 1928). High level sound gives rise to a generalized vasoconstriction, the defence reaction. The orienting reflex and the defence reaction differ also in sensitivity to habituation (decline of reaction upon repeated stimulation). The orienting reflex generally habituates more rapidly than the defence reaction (Sokolov, 1963, and e.g. Thompson & Spencer, 1966, for a review). However, opinions differ among authors regarding the sensitivity of these reactions to habituation. According to Lehmann & Tamm (1956) and Jansen and co-workers, habituation is minimal for high level sound. Unger (1964) found great individual differences in rate of habituation. Glass & Singer (1972), on the other hand, found a rapid habituation of the vascular reaction independent of sound level in most subjects. In 5% of the individuals tested, however, habituation was not seen at all. These subjects were suggested to constitute a risk-group in "noise"-environments. Possible reasons for the differences were discussed by McLean & Tarnopolsky (1977) in their review article. They emphasized the likelihood of emotional conditioning counteracting habituation (see Lehmann & Jansen). The differences can also be explained, if it is assumed that Jansen's

subjects were asleep, since it has been shown that habituation of vegetative reactions is slow or absent during sleep (Johnson & Lubin, 1967).

That the size of the vasoconstriction is dependent upon the physical characteristics of the sound was already reported by Robbins in 1919, and later works have subsequently supported and extended his findings. The intensity dependence and the possible existence of a threshold of vasoconstriction has been emphasized by Lehmann (1955). Jansen & Rey (1962) further showed that vasoconstriction increased as a function of bandwidth of the sound. Jansen (1974) made the interesting observation that sound simulating an object approaching the listener (increase in level and frequency) gave a greater vasoconstriction than a steady sound. The dependence on sound frequency has not been investigated in detail for vasoconstriction, but Berlin (1963) found a pronounced frequency-dependence to another peripheral autonomic reaction (psycho-galvanic response) in mice (see also Barr, 1955).

Further examples of factors causing variability of peripheral vasoconstriction are given by Ickes et al. (1979). They found that male subjects with stress-prone personalities (Pattern A), exhibited greater sound-induced peripheral vasoconstrictions than subjects with Pattern B. They also speculated that a similar vasoconstriction may take place in the inner-ear and make males with Pattern A more sensitive to noise-induced hearing-loss than subjects with Pattern B. Differences between "extroverts" and "introverts" are also seen reported in psychological literature (Eysenck, 1980). Matthias & Jansen (1962) furthermore investigated peripheral vasoconstriction in children. From the ages of 8 to 11, most children showed reactions akin to adults, although somewhat smaller. Young children (3 to 6 years of age) showed only a very short-lasting initial vasoconstriction without the prolonged response of the type seen in adults.

In animal experiments, Caraffa-Braga et al. (1973) found an increase in heart rate, a biphasic reaction of systolic blood pressure and a decrease of blood-flow in mesenteric and renal vessels, but an increase of hind limb blood-flow in dogs in response to sound stimulation, lowering of external temperature on confrontation with a cat. Either stimulus was presented only once in order to avoid habituation. These findings and among others those of Turpin & Siddle (1978) emphasize that sudden sounds and emotional situations lead to a redistribution of blood from the skin and internal organs to limb muscles. In rabbits, however, Hultcrantz (1979) found a decrease of renal and muscle blood-flow, but an increase of blood-flow in some parts of the brain, e.g., the inferior colliculi. Regularly repeated sensory stimulation also leads to rapid habituation in animals, supporting the observations of Glass & Singer (1972) in humans. Yukie et al. (1976) showed, for instance, that peripheral autonomic reactions habituated rapidly during repeated stimulations with 5 s intervals (500 Hz, 85 phon, i.e. about 95 dB SPL).

Although vasoconstriction is part of a normal physiological response to a novel stimulus, it may relate to hypertension and coronary heart disease (see below). It may also aggravate peripheral vascular disease, such as "vibration disease". It has been found by Matoba et al. (1975) that subjects suffering from "vibration disease" in the hands have a more prolonged vasoconstriction to acoustic stimuli than do normal subjects.

In summary, during exposure to a novel sound environment a redistribution of blood from skin and certain inner organs to muscles occurs. The adjustments depend on the features and timing of the sound, and are sensitive to habituation.

b. *Heart rate*

This cardiovascular parameter is perhaps the easiest to record, and consequently the one most widely used for study of non-auditory responses to sound. Phasic changes in heart rate are usually seen at the onset of an unexpected sound. The size and direction of this change is not unequivocally described. According to Sokolov (1963) and Graham & Slaby (1973) low level stimuli give a deceleration (orienting reflex) and high level stimuli an acceleration (defence reaction). The change is usually small in humans, less than 5 beats per minute. Berg & Beebe-Center (1941), in analysing heart rate reactions to gunshots, found either a pure increase or a biphasic acceleration–deceleration. Habituation was observed if the shots were less than 5 min apart, but dishabituation occurred after a change of interval or after an interposed sound of a different type. Biphasic reactions were also described by Baust & Marbaise (1971), whereas Gerber et al. (1977) claim that the normal heart rate reaction to sound consists of a pure decrease, a deceleration. The latter authors discussed the differences and pointed out the importance of baseline heart rate

for the type of reaction obtained ("law of initial value", Wilder, 1950, cit. by Gerber et al., 1977). The level of arousal (Baust & Marbaise, 1971), age and sound level are other factors of importance. It was especially pointed out by Lobstein et al. (1978) that high background sound activity increases the accelerative component of the heart rate reaction. Gerber et al. (1977) used tones with levels up to 80 dB SPL, whereas gunshots produce much higher levels. Furthermore, it can be assumed that the background levels in Gerber's experiments were much lower, since their study aimed to the development of a new audiological test technique. The results of Graham & Slaby (1973) further emphasize the role of the acoustic features for the type of heart rate response. They obtained different response patterns to white noise and a 1000 Hz pure tone of the same level (total level 85 dB SPL), as well as different patterns of habituation.

Cloete (1979) differentiated between stress-sensitive (low body boundary subjects) and stress-resistant (high body boundary subjects) with respect to heart rate reactions to 85 dB (A) noise. The stress-sensitive subjects showed a significantly larger reaction which habituated at a slower rate than in the stress-resistant subjects. There was no difference between the groups with respect to skin conductance changes. The reaction observed by Cloete was a pure increase of heart rate. This agrees with Sokolov's (1963) findings that the heart rate increase of the defense reaction is insensitive to habituation. However, Turpin & Siddle (1978) obtained a biphasic (acceleration–deceleration) response at 110 dB SPL white noise which habituated after first having turned into pure acceleration. Turpin & Siddle also recorded a long-lasting cardiac acceleration reaching a maximum about 35 s after the stimulus. This response, which was seen at 110 dB, also habituated. Preterm neonates, in contrast to term neonates, did not habituate to repeated 2.5 s stimuli (rattle, buzzer at 90 dB SPL) over 10 trials (Field et al., 1979). Gerber (1979) concludes that age and prestimulus heart rate have the largest influence on heart rate in 1 to 3 months' infants.

Soltysik et al. (1961) gave a rather detailed review of the older literature on the influence of sound and other "neutral" stimuli on heart rate in animals, and a discussion of the relation between heart rate response and the orienting reflex (see also Robinson & Gantt, 1947; Turpin & Siddle, 1978). Furthermore, they made extensive observations on the heart rate of dogs exposed intermittently to a sound (buzzer) with different levels (0–80 dB) and different temporal patterns. Initially, the response was a typical acceleration–deceleration which largely habituated within 10 presentations. At the end of the sound presentation, extended between 10 s and several minutes, a drop in the heart rate was observed in most, but not all, cases. It was not mentioned whether the aberrant reactions were obtained randomly or if stable individual differences existed. A qualitative difference in the heart rate reaction pattern between different individuals has also been described by Kneis (1978) in guinea-pigs. Most animals reacted with a drop in heart rate during exposure, whereas a few showed a biphasic acceleration–deceleration pattern. Hallbäck & Folkow (1974) usually encountered a rise of heart rate during a continuous "neurogenic" stimulation (sound, light and vibration). About 40% of the normotensive animals showed a decrease in heart rate interpreted as a vagal response, while 90% of the spontaneously hypertensive rats showed an increase of heart rate. These differences in cardiac response between individuals, strains and species are in accord with the variability seen in studies on human subjects and also to the observations on blood pressure reactions in animals by Williams (1979). The complexity of the cardiac reaction is further emphasized by the result presented in an abstract by Bilsing (1978), in which she describes how the direction of the heart rate reaction to a light-flash depended on the properties of an acoustic background environment. In a further analysis of interaction between different stimuli, she found that white noise potentiated a heart rate deceleration elicited by species-specific cries in guinea-pigs (Bilsing & Schneider, 1979). Presented alone, white noise increased the heart rate acceleration during exploratory behavior, suggesting a general facilitation of the orienting reflex and a rise of sensory-motor activity.

The heart rate reaction to sound is most likely mediated by vagal as well as sympathetic nerves (Berg & Beebe-Center, 1941; Ames & Arehart, 1972; Hallbäck & Folkow, 1974). Usually, the heart rate response is phasic. A late component occurring about 30–40 s after short sound stimuli has, however, been found by Turpin & Siddle (1978) (110 dB SPL white noise) and slowly changing basic heart rate conditions over several weeks have been

found by Peterson et al. (1975, 1978) (112 dB (A) wide-band noise). The phasic nature of the heart rate change is, however, not surprising with regard to the crucial role played by heart rate in the reflexive regulation of blood pressure and peripheral blood flow.

c. *Blood pressure*

Since blood pressure has a close relationship to cardiovascular pathology, it has been regarded as the most important parameter to observe in the analysis of non-auditory effects in the acoustic environment. Although many experiments have been performed contradictory observations predominate, particularly with respect to humans.

Lehmann (1955) and Lehmann & Tamm (1956) have published some of the most cited articles in this field. Their observations were drawn from experiments performed mainly with a non-invasive, ballistocardiographic technique using octave-band noise up to 90 phon. They obtained a minimal effect on the systolic blood pressure, but a slight rise of the diastolic pressure. A clearcut decline of total peripheral resistance and an increase of stroke volume was, however, observed. A habituation can be seen in most of their illustrated recordings of 60-min sequences. A delayed rise in peripheral resistance was noted in several cases.

Steinmann et al. (1955) found an immediate rise in the systolic blood pressure of 5–20 mmHg during exposure to high-frequency, metallic sounds, level not specified. They particularly emphasized that the effect was dependent in a qualitative way, on the type of sound used, and on the emotional value of the stimulus. Classical music usually produced a drop in systolic pressure, whereas oriental music caused a rise in pressure. This difference was interpreted to show that the emotional reaction to the oriental music was stronger than it was to the more familiar European music. Etholm & Egenberg (1964), on the other hand, could not find any reactions to 90 dB white noise during 20 min. They recorded heart rate, stroke volume and cardiac output with intra-arterial catheters. Their findings are not necessarily contradictory to the findings of Steinmann et al., but rather emphasize the importance of the informative and associative aspects of sound. Although Etholm & Egenberg used a direct technique for recording cardiovascular functions, they may have run into a different type of methodological problem. Intra-arterial catheterization is a stressful procedure and the reactions to the superimposed sound stimulus may consequently have been concealed. In addition, all of their 10 subjects suffered from cardiac or pulmonary diseases, conditions likely to upset the control mechanisms for cardiovascular homeostasis, and also depress the sound-induced reactions.

Several investigations have been performed in Russia and other countries in Eastern Europe and are, with few exceptions, published in Russian. Cartwright & Thompson (1975) reviewed some of this work. In contrast to the studies cited above, a decline of the systolic pressure was observed during exposures to 75 or 101 dB wide-band noise. The influence on the diastolic pressure varied. Subsequently, Cartwright & Thompson made a careful analysis of the effect of 91 dB (A) broad-band noise on subjects sitting and in a state of physical and mental rest. During one hour's exposure, the blood pressure changed: systolic pressure decreased and diastolic pressure increased somewhat. Heart rate decreased from 80 to 72 beats/min. None of these changes differed from those obtained in the control session, although the data sampling was made with relatively long intervals of 2 min and therefore minor phasic changes could not be excluded. The authors pointed out that a normal cardiovascular adaptation during an experimental session had not been adequately considered in previous works.

It was already pointed out by Steinmann et al. (1955) that the blood pressure response to sound was significantly influenced by the "emotional" (associative) aspects of the signal. This idea is also in accordance with the observations by Mosso (1875) and by Hyde & Scalapino (1918). More recently, Peeke & Zeiner (1970), in a study using rats, arrived at a similar conclusion by comparing neutral sound and sound with emotional content. They showed that tape-recorded distress calls (1.5–3.5 kHz 100 dB 3.6 s) gave more pronounced and more slowly habituating behavioral reactions than pure tones (1.5 kHz 100 dB, 3.6 s). Associative processes have to be considered in studies of traffic, airports and industries. The acoustic features of such milieus are well known to most experimental subjects and refer to situations demanding attention or action. Schulte et al. (1977) obtained a significant rise in systolic blood pressure in normotensive subjects as well as in those with labile hypertension

during exposure to traffic noise 81(±3) dB (A), if the exposure coincided with or followed a mental task. Pure tones (2.0 kHz 90 dB during 30 min), however, gave a rise of systolic and diastolic blood pressure only in subjects with labile hypertension, but not in normotensive ones (Argüelles et al., 1970). Mosskov & Ettema (1977*a*, *b*, and *c*) found a slight drop of systolic pressure in 12 male normotensive students and a small rise of diastolic pressure (less than 10 mmHg). They utilized a sound (83.5 dB (A), L_{eq}) similar to the one used by Schulte et al. (1977) and found a slightly greater alteration of blood pressure if the subjects participated in a mental test situation during sound exposure. The drop in blood pressure seen by Mosskov & Ettema also contrasts with the findings of Ortiz et al. (1974). In their study, Ortiz et al. exposed 18 subjects to turbine noise recorded from their usual place of work at the testing bands for aircraft turbines (105 or 115 dB). A rise of systolic and diastolic pressure was encountered (from 128/79 to 151/90) and changes in adrenaline and 11-OH corticoid levels were seen. The difference between the findings of Mosskov & Ettema and of Ortiz et al. may be explained by the difference in noise level or the more advanced age of Ortiz's subjects. In addition, Ortiz et al. used subjects who may have been conditioned to the exposure sound. It is relevant to recall the findings of Bolme & Novotny (1969) in dogs. They found that a combination of sound and a physical work-load in a conditioning paradigm had a markedly augmenting effect on the acoustic influence on the blood pressure reactions and delayed the habituation.

The observations in rats made by Williams & Eichelman (1971) and Williams et al. (1979) may be relevant to the interpretation of the variation between the above-mentioned studies. They found that the blood pressure reactions in rats subjected to electric foot shocks appeared related to the behavioral responses available in the experimental situation.

When foot shocks are delivered to two rats together in the same enclosure the behavior is characterized by species-specific threat and attack postures, and the systolic blood pressure is decreased from pre-shock levels when measured immediately after the shock session. In contrast, when the same foot shocks are delivered to a single rat in the enclosure, the behavior is different, consisting primarily of disorganized escape attempts, and the post-shock systolic blood pressure shows an increase from pre-shock levels (Williams et al., 1979).

The subjects in Ortiz's study were exposed to a sound that usually demanded action from them. In the experimental situation, they were not able to cope with the command and accordingly responded with an increase of blood pressure. A less pronounced reaction is to be expected when the exposure sound is artificial or less relevant to the subjects.

In summary, most studies indicate that non-informative sound and sound below the pain threshold do not systematically alter blood pressure in humans. On the other hand, in studies where association or conditioning situations have been tested or where such factors were not excluded, an alteration of blood pressure was usually seen. This alteration, a rise of diastolic pressure and either a rise or a decrease of systolic pressure, is determined more by the situation of which the sound carries information than by the sound itself. The problem of coping with the situation also has to be considered.

In animals, the actions of short sound exposures have been extensively studied, alone or in combination with other sensory stimuli, such as flashing light and vibration. Most studies supply evidence for physiological alterations during sound exposure. In several of these experiments the sound levels used are so high that they are only rarely encountered in human occupational environments and never in experiments on humans. In dogs, Corbeille & Baldes (1929) found an increasing or decreasing influence of short sound bursts of pure tones (256–8000 Hz, 2 s to 5 min) on blood pressure. A rapid habituation was observed. In further experiments on dogs, Bolme & Novotny (1969) showed that a pure tone (250–600 Hz, unspecified level) caused a small rise of systolic blood pressure. This reaction habituated during a repeated stimulation of two to four days when the sound was presented in a non-conditioned paradigm. This means that the sound was not associated with any other stimulus, such as pain or a physical work-load. On the other hand, if the sound was used as a conditioned stimulus for an electric shock or a load of physical exercise, a rise of the systolic blood pressure was obtained (and an increase of muscular blood flow and heart rate), which did not habituate for a long time.

Hallbäck & Folkow (1974) exposed rats of two different strains to sound, or a combination of

sound and other "stressors". In one of the strains, spontaneously hypertensive Wistar rats, the systolic blood pressure rose 10 to 40 mmHg during 30 s exposure, whereas it only rose 3 mm in the normotensive strain. Vibration was the most efficient component, but sound alone (of unspecified frequency or level) produced an effect nearly as great. Flashing light was least efficient. The data presented, however, do not allow for relevant intermodality comparison, since the stimuli were not sufficiently specified.

In conclusion, short-term studies establish that sound does cause adjustments of the cardiovascular homeostasis in man and animals with transient changes of blood flow and heart rate. The rate of habituation is under debate, but if sound acts as a conditioned stimulus, habituation will be delayed. Blood pressure is altered in animals. In man such effects have been found to be small and variable. The degree and kind of cardiovascular alteration is determined by the physical features of the sound, the combined effect of other environmental factors (e.g. mental or physical work, see below) and internal factors such as level of wakefulness, predisposition for blood pressure abnormalities, and neurotic personality. The most important cause of variability between studies is probably related to information content and ability to cope with the situation signalled by the sound (Williams et al., 1979).

2. Interaction with physical and mental work

Most investigations on the physiological effects of sound concern subjects in physical and mental rest. Unfortunately, very little is known about the combined effects of noise and physical work-load, although an increased interest has been focused on the topic recently. In two articles from 1964, Jansen, and Jansen et al., reported that sound-induced peripheral vasoconstriction, at least to some extent, persisted during physical activity. Quaas et al. (1971) studied the effect of sound on heart rate under conditions of moderate physical work. Four out of six subjects exhibited an increase in heart rate and two a decrease. No general conclusions could be drawn. A combined action of 3 h of sound (98 dB L_{eq}, airplane noise, traffic noise, and textile factory noise) and mental work was shown by Mosskov & Ettema (1977*a*, *b*, and *c*) and Schulte et al. (1977) to give a slightly greater rise of systolic blood pressure than did sound alone (81 dB traffic noise). Klotzbücher & Fichtel (1978, see also Klotzbücher, 1976) investigated the combined effect of white noise (50, 70, or 85 dB) and simultaneous work on a bicycle (15 or 30 W) on computing performance, heart rate, respiration rate and excretion of epinephrine and norepinephrine. The best computing performance was obtained with various combinations of sound and work: at high-level sound (70 dB or 85 dB) without physical work, at moderate sound level with moderate work and at low sound level with heavy work. The physiological reactions and hormone excretion were less during favorable (good performance) sound–work combinations than during unfavorable ones. The authors point out the need to plan work containing mental work, physical work and sound in such a way that the sum of the activation of sound and muscular work ranges within an optimal level. The additive effect of sound and physical work found by Klotzbücher & Fichtel (1978) is not supported by the findings in a similar study by Finkelman et al. (1979). Their subjects were exposed to random white noise bursts at 90 dB in various combinations with physical work-load and a test for information processing performance (delayed digit recall test). They found that noise deteriorated performance but did not affect heart rate. Physical work caused a rise of heart rate but did not affect mental work. There was no significant interaction between sound and physical work on either heart rate or mental performance. In a recent work Kryter & Poza (1980*a*, *b*) found no difference in peripheral vasoconstriction during broad-band noise exposure between conditions of physical rest or exercise.

No general conclusions can evidently be drawn from these investigations. However, the studies emphasize the need for further research to map the complex interactions between noise and physical and mental work. Most likely, the conditioning and information aspects in the acoustic environment are of great importance for these interactions.

3. Long-term exposure

In humans, no long-term laboratory studies on the effects of a well-controlled sound environment on cardiovascular functions have been fully reported. Indirect observations and a couple of preliminary reports are available. The findings of Jansen (1961) indicate that subjects working for a long time in high level sound exhibit peripheral vasoconstric-

tions (decline of finger volume pulse) after short sound bursts in a laboratory situation, as great as those of earlier non-exposed individuals. This finding can be interpreted to show a lack of habituation even after long exposures to high level sound. The experimental situation, as well as the sound used in the test, differ, however, from conditions in work to such extent that it is doubtful whether these observations are relevant for habituation to long-term exposure in a constant environment.

In a preliminary report, Hartmann & Hensel (1977) describe habituation of physiological responses, and subjective annoyance during intermittent sound exposure for up to 21 days. Each session was initiated with 30 min rest, followed by repeated 12–16 s exposures (100 dB (A), white noise) with 5-min intervals. The heart rate reaction adapted during the first experiment. The peripheral vasoconstriction declined during the first 10 days. The alteration of the electrical brain activity (EEG) had the slowest rate of adaptation. The authors conclude that the subjective and physiological reactions often had a different time course for their habituation. During a 3-h exposure to traffic noise with short periods of mental tests, a drop of the systolic, and a less than 10 mmHg rise of the diastolic blood pressure was observed (Mosskov & Ettema, 1977*c*).

In a recent German investigation, by means of interviews from areas with heavy traffic and quiet areas the incidence of treatment for hypertension was investigated. A higher percentage of treatment was observed in the exposed area, but only in some age groups (Eiff & Neus, 1980). It is to be noted that the exposed groups also smoked significantly more than controls. A 2–3 mmHg higher blood pressure was also observed in school children in noisy schools (close to airports). The difference tended to decrease beyond the first grades. Absenteeism, used as an indirect measure of health was, however, less in the noisy schools (Cohen et al., 1980).

The sparse observations on more prolonged sound exposures available from studies in man neither support nor disprove the possibility of permanent cardiovascular effects. An observation with relevance to the possibility of extrapolating the available data to very long exposure conditions should be mentioned. In a preliminary report of experiments on monkeys, Schreyer & Angelakos (1978) did not encounter any rise of blood pressure during acute exposure (400 Hz, 100 dB ± 4 dB SPL, 8 h daily, intermittent exposure). However, after 2 months in the experimental situation, a rise of blood pressure was observed, in contrast to a slight decline seen in the control group. Accordingly, the lack of acute effects does not exclude the possibility of chronic alterations. A considerable individual variability, both with respect to acute and presistent effects was found in a subsequent study (Schreyer & Angelakos, 1979).

Long-term experiments on the effects of sound exposure on physiological functions are available from experiments on rats, monkeys, rabbits, sheep, and pigs. A recent review with special reference to noise problems in animal quarters is given by Peterson (1980). Ames & Arehart (1972) studied the heart rate reaction in lambs exposed to 11 h a day of intermittent and dissimilar sound for 12 days. They found a complete habituation to music but not to white noise during the time of observation. This partly agrees with the results of Bolme & Novotny (1969). These authors showed a rapid habituation to sound with minimal information, but stable responses to sound signalling discomfort or physical work-load.

Peterson et al. (1978) followed heart rate in one unrestrained Rhesus monkey during several months. After a 4-month acclimatisation period, they exposed the animal 12 h a day to recorded traffic noise (10% of the time exceeding 84 dB (A)). Initially, they observed an increase of heart rate, which turned into a decrease after a few weeks. This decrease could have been due to a slow rise of blood pressure reflexively affecting heart rate via baroreceptors. The most interesting finding was an "anticipatory" heart rate reaction in the early morning before the start of the exposure. In an earlier study, they observed long-term changes in restrained monkeys, but could not, at that time, exclude the restraint as being the cause of the findings. This anticipatory reaction again emphasizes the potential significance of information and conditioning aspects.

The rat has been the favorite species for investigations of long-term effects to sound exposure. The majority of the grey Norwegian rats of Farris et al. (1945) suffered a rise of systolic blood pressure approximately 200 days after ongoing exposure to 5 min compressor sound (sound of an air blast, unknown level) per day, 5 days a week. Two out of the 10 animals were not affected, but these two

rats had low "emotional scores", whereas all "emotional" rats showed a rise of blood pressure.

Yeakel et al. (1948) used the same type of compressor sound for a 12-month exposure of domesticated grey Norwegian rats. The systolic blood pressure rose 30 mmHg on the average in the exposed animals, but only 2–3 mm in the control group. The technique used for blood pressure recording (tail plethysmography without heating) is however doubtful, and was shown by the authors to conform poorly with intra-arterial pressure values. The failure to obtain valid blood pressure values was probably due to the insufficient control of tail blood flow (Borg & Viberg, 1980). The direct systolic pressure of exposed and non-exposed rats did not differ significantly. Medoff & Bongiovanni (1945) continued the work of Farris et al. (1945) and used the same type of compressor sound. They exposed albino Wistar rats and grey Norwegian Wistar rats from the age of three weeks, 5 min per day, 5 days a week. About 70% of the grey rats reacted with seizures. A rise of blood pressure was only obtained in those so called "reactors", and then only after more than one year of exposure. In nearly all young animals and in "non-reactors", the systolic blood pressure was 140 mmHg or less. The albino animals seemed less affected than the grey rats, but the observations did not allow for definite conclusions.

In a continuation of this series of experiment, McCann et al. (1948) exposed 7 rats (males and females) to intermittent sound for one year. They observed an increase of systolic blood pressure from, on the average, 127 mm to 162 mmHg (with tail plethysmography). The control animals had a stable pressure at 127 mmHg. Adrenalectomy and substitution therapy normalized the pressure in the exposure group, which was interpreted as evidence for a key role of the adrenals in sound-induced hypertension.

In his review on the pathogenesis of hypertension, Smirk (1949) gave a short description of his own work with sound exposure in rats. Restal & Smirk (unpublished, cited by Smirk 1949) obtained an increase of blood pressure that was not influenced by ether anesthesia and persisted several months after the end of the exposure. A combination of sound and electric shocks caused a rise of blood pressure, but a smaller rise was obtained than by sound alone. No further specifications were given, neither about blood pressure levels nor the type or intensity of the sound.

Rothlin et al. (1953, 1956) did not succeed with a combined exposure to sound and light in producing hypertension in inbred albino rats. On the other hand, in cross-bred animals (a mixture of domesticated albino rats and wild rats), the pressure increased from 110 to 160 mmHg, with a delay of about 2 months. The animals were exposed 24 h per day; 5-s sound bursts with 30-s intervals. Bells, horns and pure tones in the frequency range 700–1 000 Hz were used (level unknown). In addition to the rise of blood pressure, which occurred in male as well as female rats, the relative heart weight increased somewhat in the exposed animals. Such differences between different strains of rats were further substantiated by the findings of Yamori et al. (1969). They found that a combined exposure of light, sound and electric shock (up to 11 weeks) was accompanied by a significant rise of systolic blood pressure in spontaneously hypertensive as well as normotensive rats. The spontaneously hypertensive animals, however, showed a greater increase.

The relative heart weight gives indirect information about the work-load on the heart, the peripheral resistance, and the blood pressure. Geber & Anderson (1967*a*, *b*) found a significant rise in heart weight already after 3 weeks of exposure to intermittent sound, thus further supporting the theory of sound as an etiological factor in hypertension.

An interesting series of experiments have been carried out by Buckley and co-workers (Hudak & Buckley, 1961; Rosecrans et al., 1966; Buckley & Smookler, 1970; Smookler et al., 1973). They exposed albino Wistar rats to intermittent "neurogenic stress". A combined exposure to light flashes, sound and vibration during 4 h a day, 3, 5, or 7 days per week (Rosecrans et al., 1966), or only 3 days per week (later experiments) was used. A moderate rise of blood pressure from 120–130 to 140–150 mmHg was seen after 8–10 weeks of exposure, independent of whether the animals were exposed 3, 5, or 7 days weekly. The rise of blood pressure was furthermore equal, irrespective of whether the animals were housed singly in the cages or in couples, or were kept in light or in darkness. The reaction observed thus seems to be of the all-or-none character. Evidence was also obtained showing that the blood pressure rise was more dependent on adrenal cortex than on adrenal medulla (see McCann et al., 1948). One interesting observation made in these studies was the influence of the age of the

animals on the possibility of inducing a rise of blood pressure. An influence of the environmental stimuli on blood pressure was noted only in animals raised in their own laboratory or delivered to the laboratory when weighing between 60 and 100 g (corresponding to an age of 4–6 weeks; cf. Medoff & Bongiovanni, 1945, who exposed rats at 3 weeks of age). It is relevant to point out the observation of Ackerman et al. (1977). They found that separation of rat puppies from their mother increases the risk of stress-induced ulcers. Such conditions may have increased the sensitivity of the rats to noise exposure to an abnormally high level.

Although the experiments of Buckley and co-workers were well conducted, certain limitations were at hand, which make interpretations unreliable with respect to the actual effects of the noise stimulus. First of all, the information on the effect of sound exposure alone is meager. The ten rats analysed with pure acoustic stimulation, however, showed a blood pressure development very similar to that of the animals exposed to the combined stimulation. Furthermore, the control animals were continuously housed in the animal department, whereas the exposed animals were transferred into sound-proof boxes for each session. Only in the final publication (Smookler et al., 1973), was it mentioned that the control animals were housed in an environment similar to that of the experimental animals and handled in a comparable fashion. Even though not clearly stated, it can be inferred from the experimental procedures that the exposed animals were shifted between different cages. Such a shift and exchange of cage mates can be stress factors themselves (Henry et al., 1967; Alexander, 1974). It has to be emphasized, though, that the experiments of Buckley and co-workers were not designed to investigate a possible physiological effect of long-term noise exposure, but rather to find a technique to produce neurogenic hypertension. The difficulties in applying some of their information to the present topic do not diminish the values of their experiments per se.

One typical feature of all the experiments is the use of intermittent stimulation with long and often irregular interstimulus intervals. Ising et al. (1974) point out the importance of exposure at random. They found morphological alterations in the heart muscle after 35 days of sound exposure, but only if the sound was randomly presented and not continuous, or periodic but regular (8 Wistar rats, 3 s per minute, 98–108 dB (A); 91 dB L_{eq} broad-band noise). Furthermore, Ising et al. (1976) found an increase of cardial fibrosis during intermittent (random) exposure to 1 s bursts of broad-band noise (duty cycle 10%) 80 dB (A) L_{eq}, but only in Mg^{++}-deficient rats.

In spite of technical inadequacies, these experiments support the idea that chronic sound exposure can cause a moderate (up to about 160 mmHg) rise of systolic blood pressure, at least in certain risk groups. One has to emphasize, though, that the handling of the control animals was poorly specified and that most likely, there were numerous factors other than the sound exposure that contributed to, or wholly explain, the findings, e.g. social interaction, transfers from home cage to exposure room, dietary factors etc.

A different approach to the role of sound environment for chronic, cardiovascular disturbances has been taken by Lockett & Marwood (1973), who selected especially quiet environments. The test animals were housed in a room with a sound level of 32–35 dB (unknown reference) in which the sound was largely generated by the rats themselves. The sound for the control animals had a level of approximately 75 dB and came mainly from a nearby highway. They obtained a rise of blood pressure only in the "sound-deprived" animals. This rise of blood pressure was dependent on the adrenal glands as in the sound-induced hypertension (see McCann et al., 1948), or neurogenic hypertension (Buckley & Smookler, 1970). Lockett & Marwood are of the opinion that "sound deprivation" hypertension has a unique pathogenesis.

The authors' interpretation of their findings is, however, not convincing. In an environment where sound is generated more or less exclusively by the animals themselves, the average level will be low, but will also be intermittent and probably informative about aggression and the extent of the activity of the surrounding animals. In the control box, road traffic noise (75 dB) may have masked most of these information-carrying sounds. The results can just as well be interpreted to show that information-carrying sound, even at low levels, causes hypertension, whereas non-informative sound, even at considerably higher levels, leaves the animals physiologically intact.

There are several experiments correlating sound alone or in combination with other sensory stimuli to alterations of blood pressure. The aim of most

of these experiments has been to produce "neurogenic" hypertension and not to analyse the possibility of the harmful effects of sound. Consequently, since differences in handling and housing of experimental and control animals have probably not been carefully considered, "neurogenic stress" may have been augmented by such procedures. Even the most efficient exposure situation, however, gave systolic blood pressure of only 140–160 mmHg, which is only slightly above that expected from middle-aged or older rats. An interesting feature of many of these studies is the low pressure values of the control animals (110–125 mmHg) which is closer to the mean blood pressure value than the systolic value in many other normative studies (McCarty & Kopin, 1978, see also Smookler et al., 1973, fig. 4). Especially, Kawasaki et al. (1979) pointed out that the *mean* intraarterial pressure never was below 122 mmHg in calm unrestrained rats. This corresponds to a systolic pressure of at least 160 mmHg. Even though no firm conclusion can be drawn from present data, it is tempting to suggest that intermittent, irregular sound exposure may cause an increase of blood pressure in certain, predisposed animals or animals reared under specified circumstances.

4. Epidemiological studies

For obvious reasons, controlled long-term studies on the effects of sound have not been performed on humans, certainly none comparable to the above-mentioned animal experiments. Several epidemiological investigations are, however, available on humans. As pointed out in the Introduction, sound and "noise" are multidimensioned concepts and complex sound situations may influence the organism in different ways, both on the physical, physiological and psychological level. It is sufficient to mention the information value of sound, which is not directly related to the level of sound but relates both to individual experiences and personality. Such aspects are difficult to quantify and evaluate in epidemiological studies, as are the effects of selection. It is particularly difficult to find population groups differing only in respect to their sound environment and to exclude the possibility of persons suffering from a noisy environment moving or changing to another profession.

In spite of the limitations in the interpretations, the epidemiological studies form a necessary and valuable part of the analysis of any environmental factor.

Psychological, psychiatric and medical problems in areas around airports and highways have been searched for in several field studies (Wilson, 1963; Abey-Wickrama et al., 1969; Cohen, 1971; Finke et al., 1975; Knipschild, 1977*a*, *b*, *c*; Knipschild & Oudshoorn, 1977; Müller & Bättig, 1977; Ettema & Zeilhuis, 1977*a*, *b*). In a recent study by Eiff & Neus (1980), a significantly higher proportion of subjects treated for hypertension was found in an area with high traffic volume than in an area with low traffic volume in Bonn. The incidence of several other diseases did not differ, nor did consumption of psychopharmacologic drugs. These findings seem to point to a hypertensive effect of noise. However, a similar study from the Netherlanders Knipschild & Sallé (1979) failed to find differences with respect to blood pressure and cardiovascular disease between high and low traffic areas. These studies will not be further analysed here, since the exposure situation is fundamentally different from that occurring in work environments. The most upsetting study has been presented by Meecham & Smith (1977) from an area near Los Angeles Airport. They found a higher mortality near the airport than in distant control areas, especially in stroke, cardiovascular disease and liver cirrhosis. In a reanalysis of the Meecham & Shaw (1980) data, Frerichs et al. (1980) found no difference when the confounding effects of age, race and sex were taken into account. In work soon to be published, however (Meecham & Shaw, 1980; Frerichs & Coulson, 1980) new evidence for increased rate of mortality will be presented.

Several field studies have shown a higher frequency of cardiovascular symptoms in factory workers exposed to high level sound than workers in low sound level environments. The following symptoms and findings have been most frequently described: Cardiac arythmias (Jansen, 1959, work in Russian cited by Cohen, 1968), hypertension (Andriukin, 1961, cit. by McLean & Tarnopolsky, 1977), and ECG abnormalities (Shatalov et al., 1962, cit. by McLean & Tarnopolsky, 1977; Anticaglia & Cohen, 1970). In a survey of over 1 000 industrial workers, Jansen (1959) observed a higher incidence of cardiovascular symptoms, disturbance of equilibrium and psychic instability in those working in high sound level than in those less exposed. In these publications from the 50's and the

early 60's, the symptoms observed were ascribed, without hesitation, to the acoustic environment. In recent publications, the cause-relationship has been more cautiously interpreted. Negative results from field studies have been reported by Glorig (1971) and Finkle & Poppen (1948).

In an investigation on jet-pilots, Brown et al. (1975) could not show any differences in heart rate, systolic or diastolic blood pressure, serum blood sugar or cholesterol level between professional pilots (exposed to high level sound) and non-flying personnel (less exposed). This study is one of the few where the control group and the exposure group are reasonably comparable, although the work environments of the two groups differ not only with respect to the sound level. Parvizpoor (1976) observed a higher incidence of hypertension among workers in a factory with high sound level (96 dB (A)) than among workers in industries with low level sound. The author is cautious in his interpretation and points out the multifactored cause-relationship in an industrial environment.

Kanevskaya et al. (1977) found a 20 to 30% higher incidence of high blood pressure among workers exposed to impulse noise than in controls. Other factors than noise do not seem to be adequately considered in this study and the data have to be interpreted carefully.

One difficulty in epidemiological studies extending over a very long time, is the estimation of the exposure dose. Hearing loss has been used to quantify exposure by several authors. Meinhart & Renker (1970) found that employees with a severe (noise-induced) hearing loss had a higher incidence of hypertension than did subjects with little or no hearing loss. There was no difference with respect to disturbances of peripheral blood circulation. In a similarly designed study, Jonsson & Hansson (1977) found that workers with a severe, "noise-induced" hearing-loss had a significantly higher blood pressure than did subjects with a small hearing-loss. These authors interpreted their findings as indicating that a large dose (exposure quantified as hearing-loss) also causes hypertension in humans. Takala et al. (1977), Hedstrand et al. (1977) and Lees & Roberts (1979) could not verify such a relationship between sound exposure and high blood pressure. Manninen & Aro (1979) found higher blood pressure in subjects with moderate hearing-loss than in normal hearing controls. There was, however, only a minimal difference between normal subjects and subjects with a severe hearing-loss. The work by Drettner et al. (1975) also has a relevance in this context. They found no correlation between cardiovascular risk factors and hearing-loss in men of 50. Even though these studies do not exclude the possibility of a relationship between sound exposure and blood pressure abnormalities, they tend to suggest that the relationship must be a complex one.

The most penetrating series of epidemiological studies has been presented by Cohen (Cohen, 1968; Cohen, 1973, cited by Kryter, 1976; Cohen, 1976; Cohen, 1977). In the first-mentioned study, Cohen (1973) found a higher incidence of diagnosed medical problems and absenteeism in a factory with high sound level (exceeding 95 dB (A)) than in a factory with low level (less than 80 dB (A)). The authors also showed that the frequency of recorded accidents was higher in the high level environment. This difference could be interpreted to show that high level sound increases the risk of accidents. The authors, however, present an alternative interpretation: the psychosomatic symptoms (stress symptoms) and the diagnosed medical problems were caused by worry about accidents and by the corresponding efforts to control the situation in order to prevent accidents. High sound level would be a concomitantly occurring phenomenon rather than a causative factor. In order to be able to separate the effects of the acoustics from the effects of other factors in the industrial environment, e.g. worrying about accidents, Cohen (1976) took the opportunity to utilize changes introduced in an industrial environment. In the factory under study, a propaganda campaign for general use of ear protectors was introduced. As a result, 80% of the employees always or often used protectors. After this change, a significant decline was observed with respect to absenteeism and incidence of diagnosed medical problems, whereas the frequency of psychosomatic problems was unchanged. However, the decline was equally great among the 20% not using protectors as among the users. Cohen's investigation does not support the assumption that the acoustic environment, quantified as dB (A), was the main factor behind the observed health problems. It was, of course, impossible to determine in advance who should use ear protectors and, therefore, the group of "non-users" might have contained a higher proportion of individuals insensitive to noise than the group of users. Alternately, the

ear protectors did not influence the specific aspect of the sound (if any) which is threatening to health. For example, the information content of the sound and not the level of the acoustic signal may be the important factor. In that case, the observed improvement of health status would be entirely independent of the sound attenuation provided by the protectors. The whole situation would then be misinterpreted. The preceding discussion—although full of speculations—illustrates the difficulties encountered in trying to obtain conclusive information regarding the role of "noise" from a medical point of view, even in very well conducted epidemiological studies. Regarding further pitfalls in epidemiological studies, especially with respect to the inquiries, the critical analysis by Tarnopolsky et al., (1978) is elucidating.

In a critical discussion, Kryter (1976) pointed out that the findings by Cohen (1976) can be interpreted to show a correlation, but not an interdependence, between sound level and general accident risks in an industry. The existence of such a parallelism renders the interpretation of epidemiological studies in industrial environments more difficult or even impossible. However, *rather firm support has been obtained for the assumption that work environments with high sound levels, are more threatening to health than such with low sound level. So far, animal experiments have not significantly contributed to the understanding of the role of noise and its relationship to health problems in work environment. In such studies, the sound has been of an outspokenly intermittent character and without consideration of the natural sleep–wakefulness cycle of the animals. Although these stimulus situations may have relevance for extreme physiological conditions and experimental production of "neurogenic" hypertension, they are of very little relevance for the evaluation of the industrial "noise" environment. In summary, it is not possible to state that sound is a threat to health* (in a recent tutorial, Kryter, 1980 arrives at a similar conclusion).

B. ENDOCRINE SYSTEM

1. Adrenal function

a. *Human studies*

The pituitary-adrenocortical system and the adrenal medulla play a central role in the adaptation to and defence against changes in external and internal milieu (Cannon, 1929; Selye, 1971). It has therefore been one of the main goals to elucidate adaptive changes during sound exposure and to determine to what extent "noise" is reacted upon as a threatening and harmful environmental phenomenon. No unequivocal picture of the adrenal reaction to sound is at hand. As for the cardiovascular effects, the contradictions are due to inadequately specified environmental situations, housing, differing exposure signals and individual differences. Often, relevant control groups have been lacking.

Argüelles (1967) and Argüelles et al. (1962, 1970) found an increase of hydrocorticoids in plasma and urine in young male subjects, and an increased urinary secretion of noradrenaline during a 1-hour exposure to 125 Hz, 1 kHz, 5 kHz, and 10 kHz sound at 63 or 93 dB (it can be inferred that the reference was HL). A tendency to frequency-specificity of the reaction was observed; the response being greatest at 10 kHz. A dependence on personality was also observed. Subjects with symptoms of anxiety-neurosis exhibited a more pronounced increase of hormone secretion than did the "normal" subjects.

Bugard et al. (1953) could not, on the other hand, find any change of 17-ketosteroids in subjects exposed to 130 dB jet engine sound (while wearing ear protectors). Nor could Brandenberger et al. (1977) find support for the hypothesis that noise is threatening to the organism in terms of adrenal activation. In a well conducted study, they exposed young men to different types of "probably meaningless" broad-band pink noise with levels up to 105 dB (A) for up to 120 minutes. The exposure was continuous or intermittent, using broad-band or narrow-band noise. Brandenberger et al. emphasize the outspoken normal diurnal variation in adrenal activity as a possible source of error in earlier studies (cf. Cartwright & Thompson, 1975, regarding the normal variation in blood pressure). The differences between the work of Bugard, Brandenberger and Argüelles et al. might be partly explained by the work of Atherley et al. (1970). They obtained direct support for the role of the information content of the sound, even in short-term reactions. Meaningless sound at 95 dB (A) (7 hours) did not induce significant alterations of 17-ketosteroids. Sound, perceived as meaningful, did, on the other hand, cause changes in the adrenal activity.

In a laboratory study, Arvidsson & Lindvall (1978) tested the effect of traffic noise (85 dB (A)) on perceived annoyance and physiological reac-

tions. They found no increase of urinary noradrenaline or adrenaline excretion, irrespective of whether the subjects were at rest or engaged in a mental task. However, if the reactions of the group of subjects who reported themselves annoyed were studied selectively, a tendency to physiological reaction was observed. This finding agrees with the observations of Argüelles et al. (1970) and further indicates the possible existence of a risk group. Numerous psychophysiological experiments indicated different reaction patterns in subjects with extrovert and introvert personality (Eysenck, 1980) and subjects classified as type A or B (Lovallo & Pishkin, 1980).

Slob et al. (1973) and Ortiz et al. (1974) encountered a rise of adreno-medullary excretion during exposure to sound at different frequencies, durations, and intensities in young test subjects. Ortiz et al. (1974) found a drop of corticosteroid level (plasma 11-OH-corticoids) during a 3-hour exposure, whereas Slob et al. did not find any alteration of adrenocortical activity.

A semi-long-term study has been performed with human subjects in a milieu laboratory (Cantrell & Hartman, 1974; Cantrell, 1974). Twenty healthy young male volunteers were confined in a dormitory for 55 days. They were intermittently exposed in a specially designed laboratory to a tone (increasing stepwise from 3.0 to 4.0 kHz) presented during 0.66 s with a 22-s interval, day and night. After being introduced into the laboratory, the subjects were given 15 days for acclimatization to the situation and to each other. After that period, the exposure sound was introduced and the level was increased stepwise from 80 to 85 and finally to 90 dB SPL with 10 days' interval. The results showed an increase of plasma cortisol level between the first two tests. Unfortunately, the first specimen was taken before the introduction into the milieu laboratory and no determination was made at the end of period of the acclimatization. The second specimen was taken after 5 days of exposure. During the subsequent 30 days, the cortisone level was stable, irrespective the sound level was raised from 80 to 90 dB SPL. The highest value was obtained a few days after the end of the exposure and returned slowly to base-line. These features in the design of the experiment unfortunately make conclusions regarding the effect of the sound exposure dubious. It is hard to see how the effects of sound can be separated from those of the psycho-social factors in the dormitory.

In conclusion, recent studies do not in general show adrenal activation during exposure up to 105 dB (A), up to 2 months. "Risk groups" formed by anxious and very annoyed subjects, may, however, exist.

b. *Animal experiments*

Adrenocortical reactions have been obtained during short-term as well as long-term sound exposure, mainly in rats and mice. Anthony & Babcock (1958) and Anthony et al. (1959) found that rodents exposed to extreme sound conditions (135–140 dB) showed a decreased adrenal weight and an increased adrenal activity. Since, in these experiments, the animals ought to have become deaf quite rapidly, the effects obtained could hardly have been transmitted via the auditory system. Henkin & Knigge (1963) also used sound levels (130 dB, 220 Hz, 0.5 to 48 h) which could have direct physical effects on the body (especially thorax and abdomen) as well as effects mediated by the auditory system. The latter authors observed an initial increase of OH-corticosteroid level in the adrenal vein in rats. The increase was followed by a decrease and finally a prolonged increase. The triphasic character of the response is probably due to the negative feedback of cortisone on the hypophysis. As well in this case, the sound used was of such a high level that the pain threshold was probably exceeded and deafness rapidly induced. In interpreting the studies mentioned above, the experiments of Busnel & Lehmann (1978) are elucidating. They studied the effect of low frequency sound (15–50 Hz, 115–118 dB) on normal-hearing and totally deaf mice. These two groups did not differ from each other in sensitivity to muscular fatigue in a swimming test. The exposed were, however, significantly more rapidly fatigued than control animals. Upon exposure to 2.5–10 kHz sound, the hearing mice were more easily fatigued than the deaf ones, which in this case did not differ from unexposed controls. These experiments nicely show that low frequency sound can affect the body through non-auditory routes.

However, animal experiments have provided unequivocal evidence for alterations of adrenal activity, even at moderate levels. Sackler et al. (1959) and later Geber et al. (1966) found an increased weight of the adrenal glands in rats after a few weeks' intermittent sound exposure. The animals were stimulated 5 min daily in a specially designed

exposure chamber. The control animals were simultaneously moved to new cages. An intermittent exposure at 95 dB during 6 h per day for 5 days with a 3-day pause was used in experiments on rats conducted by Hrubeš & Beneš (1965) After 2 to 4 weeks, they could observe an increased weight of the adrenals, an increase of catecholamine and free fatty acids in plasma. The handling of control animals was not specified, neither was the transfer and exchange of animals between cages during exposure clarified. A decrease of adrenal weight was observed by Osintseva et al. (1969) and a decreased content of ascorbic acid in rats exposed up to 126 days to 80 dB wide-band noise. This decrease was interpreted to show a fatigue during pronounced exposure. One month after the end of exposure, the conditions were nearly normalized. No details were given on sound exposure or treatment of control animals.

The great variation between the studies can be due to the existence of certain "harmful ranges" of sound frequency and intensity. The work of Ogle & Lockett (1968; see also Ogle & Lockett, 1966; Ogle, 1967; Lockett, 1970) is of relevance for this question. They compared urinary ion excretion in rats after exposure to 20 kHz at 90–100 dB and sound at 150 Hz (pure tone, 100 dB). They found a different excretion and differences in the hormonal reaction pattern between the two frequencies. It is also interesting to note that rats have some of their most relevant communication signals at 22 kHz (Barfield & Geyer, 1972; Anisko et al., 1978), and 20 kHz may indeed be, biologically, a quite interesting range for rats. Differences between frequencies, however, have to be interpreted carefully. For example, the hearing threshold curve of rats, is above 70 dB SPL at 150 Hz and 0–10 dB SPL at 20 kHz (Kelly & Masterton, 1977).

Collu & Jéquier (1976) found a small but not significant increase of corticosterone excretion (cannulated adrenal vein) in animals exposed to sound of an alarm clock for 30 min. Feldman et al. (1972) on the other hand, found a significant rise during a 30-min exposure to an alarm bell. They then managed to block this physiological reaction to sound by transecting certain afferent nerve pathways to the hypothalamus.

Cuha et al. (1975) described in an abstract a significant rise of corticosterone in plasma during a 1-h exposure to 80 dB sound. Pre-treatment with Chlorpromazine abolished this increase.

The majority of these experiments were conducted in mammals, but an acoustic activation of the adrenal glands of birds has also been described. Graul et al. (1976) exposed hens (Leghorn and Broiler) to 100 dB (no reference given) broad-band noise in a 30-min daily exposure for 7 days. They recorded an increase of 11-hydrocorticosteroid content in plasma. The response habituated upon repeated stimulation. A slow increase of baseline steroid level was simultaneously encountered in the Leghorns but not in the Broilers. This slow increase was interpreted as evidence for a chronic stress effect.

Studies by Buckley et al. on long-term effects of "neurogenic" stressors, include an analysis of adrenal function. Rats were exposed intermittently for 12 weeks in a special exposure chamber into which the animals were transferred for each exposure. Smookler et al. (1973) continued this experimental series and found a 90% increase of plasmacorticosterone level during the first week. The adrenal medullary hormones were either not at all or only mildly affected. The exposure consisted of sound (0.5–4.0 kHz, 100 dB), light-flashes and vibration. Only in a few experiments was sound alone used. The capability was shown in rats of sound alone (250–20 000 Hz noise, 100 dB SPL) to release ACTH as well as corticosterone during short term (30 min × 1 or 2 (Anthony et al., 1979)).

In the experiments by Briaud et al. (1971), it was shown that a 60-min exposure to 100 dB narrow-band noise initially gave an increase of corticosteroids in plasma in rats. At repeated exposure, the increase was smaller, indicating habituation. Kemper et al. (1976*a*, *b*) found an increase of plasma 11-OH-corticosterone and catecholamines during a 6-h exposure to 120 dB sound in pigs. Seventy-two hours' exposure to 108 dB engine sound on the other hand, produced a decline of corticosteroid level during exposure and an increase again immediately after the end of stimulation. An increase of catecholamines was, however, consistently observed. The authors discussed species differences and the role of the level and duration of the sound for the observed effects and conclude that the biphasic response may reflect a negative feedback effect on the hypophysis (cf. triphasic effects described by Henkin & Knigge, 1963). Further evidence for the critical role of temporal factors is obtained by Anthony (1973). He found an increase of adrenocortical activity (by measuring RNA content) at 8 or

48 hours after exposure but not at 1 or 4 hours after exposure.

An interesting attempt has been made to investigate the adrenocortical reaction to sound in wild animals under real-life conditions (Pritchett et al., 1976). Wild mice were caught in two areas, close to an airport, and in a less sound-polluted area. Basal corticosterone secretion in vitro was higher in the adrenal glands of the exposed animals compared to the control ones. On the other hand, a smaller response to an added ACTH dose was seen in the exposed mice. In addition, the total level (basal plus increment during ACTH stimulation) was smaller in the animals caught near the airport. The adrenal cortex thus had a smaller response capacity in the exposed than in the control animals. Even if this study represents one of the more realistic investigations in animals, the interpretation of cause-relationship remains obscure. Mouse populations near airports can be expected to be polluted not only by sound, but to a high extent also by combustion products of aeroplane fuel and by ground vibration during take-off and landing. In addition, only two groups of mice were compared, each one representing an individual colony. The differences obtained might therefore be due to chance.

There is one particular difficulty in conducting and interpreting studies of endocrine reactions to environmental stimuli, a difficulty that is often hard to circumvent. The pain and discomfort associated with the drawing of blood samples, decapitation etc. produce themselves, in many cases, more pronounced stress reactions than the environmental situation under study. Such stress effects have been analysed by e.g. Popper et al. (1977). They showed that lifting a rat by the tail increased secretion of adrenaline by 75% and immobilization increased secretion of catecholamines five to ten times. Decapitation, often used in hormone test, induced a tenfold increase of noradrenaline and an eightyfold increase of adrenaline secretion. Even if control and experimental animals had been subjected to the same procedure for obtaining specimens, possible differences obtained would have to be interpreted carefully knowing that the drawing of blood samples itself could cause a greater alteration than the experimental exposure. In a review about stress sensitivity in laboratory animals, Bronson (1967) further emphasized that transfers between cages can give a threefold rise of the cortisone level. Introduction of new individuals in a cage can also increase adrenal activity. Bronson also draws attention to the pronounced differences that exist between different mouse strains in the reactivity of their adrenal glands to various stressful stimuli. Another circumstance that may explain differences between studies is the diurnal variation in hormone levels and reactivity. Hiroshige et al. (1969) for instance, pointed out the well known fact that corticotropine activity in hypothalamus is low in the morning and high in the evening. An experimental stress situation (laparatomy under ether narcosis) caused a very strong rise of corticotropine activity in the morning, but a much smaller increase during the same exposure in the evening. The total level (background + increment during experimental stress) was, however, the same in both instances.

In the majority of studies, it has thus been shown that short-term exposure, even at levels corresponding to everyday industrial environment, activates the adrenal glands in experimental animals.

2. Reproductive system

a. *Observations on humans*

The possibility of experiments on the reproductive system in man is, for obvious reasons, limited.

In one of the few laboratory studies available, Beardwood et al. (1975*a*, *b*) exposed males and females to 2 h of intermittent sound (4.0 or 6.0 kHz pure tone, 85 or 95 dB) repeated for 4 days. They obtained an increase, both of LH (luteinizing hormone) and of the total urinary gonadotropine excretion.

In epidemiological studies, an increased rate of premature births and a delayed weight development has been observed in babies born close to airports (Takahashi & Kyo, 1968, cited by Algers et al., 1978). Ando & Hattori (1973, 1977) observed that birth weights were lower than normal in such areas. Ando & Hattori (1977) also found that human plasmalactogen was lower in pregnant women near airports than in controls, particularly after the 36th gestational week. Such hormonal alterations may explain the differences in birth weights. In their publication of 1973, Ando & Hattori also mention the interesting observation that newborn babies have subnormal reactions to sound, if the mother had been living in high level sound areas during pregnancy (conclusions are based on a questionnaire to the parents). In field studies of this type, it has, of course, not been possible to separate the possible effects of the sound itself from those as-

sociated with the information content of the sound or from other environmental or social factors occurring parallel. Selection effects between various residential areas are also difficult to exclude or evaluate. The observation of Mieszkowski & Saper (1978) that real estate close to airports is about 15% cheaper than houses in other areas may explain this.

A coefficient for the decline of house prices in the vicinity of airports was calculated by Nelson (1979) to be 0.5% per dB rise of noise level.

However, since airport sound is characteristically intermittent and occurring day as well as night, observations of such environments have a limited relevance for the occupational noise situation.

b. *Experiments in animals*

A review adequately covering these aspects of sound environment has been published (Algers et al., 1978). Only a few points will be mentioned here. In studies from the 60s the early 70s (e.g. Geber, 1966, 1973) it was shown, mainly in rats, that acute and chronic sound exposure influenced excretion of gonadotropic hormones and the function of ovary and testicles. A decrease of fertility and an increased rate of malformations was likewise found in laboratory studies. No effect on spermatogenesis in guinea-pigs was, however, found during 30 days of intermittent exposure to 110 dB acoustic stimulation (Günther, 1976). Kimmel et al. (1976) found a maternal and foetotoxic effect in mice, littel effect in rats and no teratogenic effect in either species (4 days, 6 min every half hour, 100 dB lin SPL, white noise).

Recently, direct evidence has been obtained for the influence of at least a few days' intermittent sound exposure on the secretion of hormones involved in the regulation of reproductive function (Beardwood et al., 1977*a*, *b*; Narendranath, 1976; Milin et al., 1979). Most studies have been aimed to investigate harmful effects of sound. A physiological role for acoustic reflexes has been described by Pollock & Hurnik (1977). They reported that the taperecorded sound of calves increased milk release in cows. This effect was probably due to secretion of oxytocin. It is again relevant to observe the role of information content in the sound.

It has earlier been claimed that rats kill their offspring if they are exposed to sound (Boutelier, 1968, cited by Algers et al., 1978). This behavior can be induced by an interrupted communication between the mother and the puppies due to auditory masking. Busnel & Lehmann (1977) however, found that deaf mice did not show a greater tendency to cannibalism than hearing animals (without sound exposure). This observation seems to indicate that the killing during sound exposure (Boutelier, 1968) was not due to auditory masking of ultrasonic communication signals from the baby rats, but was rather an expression of a direct auditory stress effect on the mother.

In most studies on reproductive functions, the animals were exposed to sound of a highly intermittent nature. The animals were not given any time to acclimatize to the experimental situation or to the sound before fertilization. Therefore, these studies are poor models of real-life situations. The possible effect of changing cages and environments must also be taken into account. The conclusions about the specific effects of the acoustic component of the environment are therefore dubious. *In a review from 1972 of field studies on supersonic booms on animals, Bell states that the support for an influence on the reproductive functions is meager or lacking.*

3. Further endocrine functions

a. *Body weight, growth and metabolism*

In a study on the growth of newborn infants, Salk (1961) found an increased weight development in babies stimulated by the sound of human heart beats. This finding, however, could not later be verified by Palmqvist (1975), nor by Schell (1979) who found a high correlation between birth weight and smoking habits but no difference between a community near an international airport and a less exposed control community.

In several animal experiments, it has been shown that intermittent sound exposure causes a decrease of bodyweight (Hrubeš & Beneš, 1965; Kaunitz et al., 1976; Fell et al., 1976) or a slower weight gain (Geber, 1966). Sackler et al. (1959) exposed rats to 110 dB sound in the frequency range 375 to 500 Hz, 1 to 5 min per day for 2 or 3 weeks. They observed a nearly significant decrease of growth rate. The weight of thymus, spleen, thyroid gland and hypophysis did not show significant alterations. On the other hand, faster weight gain in lambs under certain acoustic stimulus conditions, for example, during 12 days' exposure to white noise but not to music was seen by Ames & Arehart (1972). The weight of broiler chickens was not influenced by intermittent sound exposure (Stadelman, 1958,

cited by Algers et al., 1978). Kaunitz et al. (1976) in more elaborate analyses, found that the decreased weight of rats during exposure to intermittent sound (3 bell ringings per hour and white noise at 93 dB) was dependent on the content of fat in the diet. Only those animals fed on lard showed a decrease in weight, whereas those fed with 20% corn oil were uninfluenced. In general, the sound-exposed animals showed a higher open-field activity and furthermore, the lard-fed animals were more active than those fed on corn-oil. A potentiative interaction between dietary Mg^{++} and sound was found by Ising et al. (1976).

Doyle et al. (1977) found that the growth of long bones and teeth was retarded in rats exposed to intermittent sound (400–500 Hz, 100 dB, 3 exposures a week). That the growth was asymmetric had been observed earlier by Siegel & Smookler (1973) and Smookler et al. (1973) in rat pups exposed to sound, 500–4000 Hz, 100 dB, during the gestation period.

An increase of arteriosclerosis and a rise of plasmalipids was induced in rabbits by sound exposure (broad-band noise at 102 dB SPL and bursts of square waves at 114 dB SPL, Friedman et al., 1967). Vascular degeneration of this type may of course limit the life span of the animals, but can hardly be the explanation for the fatal outcome of the drastic experiments by Day et al. (1951). They exposed young albino rats to siren sound with maximum energy at 4 kHz (non-specified level). The animals died, on the average, after 36 min of exposure.

The mechanisms for these metabolic effects and the influence on body weight are largely unknown. It is reasonable to assume that growth hormone and thyroid hormones are somehow involved. Fell et al. (1976) showed that uptake of I^{131} decreased at least in some rat groups exposed to 1000 Hz pure tone 95 dB (A), 12 weeks, 15 min tone 15 min pause, 8 h daily. Females reacted more than male rats. I^{131} uptake was inhibited within 2 weeks of exposure, which corresponds to a decrease of thyroid secretory activity. Similar observations have been made in other types of "stress" situations (Brown-Grant & Pethes, 1960). Inhibition of thyroid hormone release may be caused by decline of hypothalamic-hypophysical stimulating hormones. However, Klein et al. (1979) observed an elevated level of thyroid stimulating hormone (TSH) in rats after 30 min audiogenic stimulation (bell at 100 dB for 10 weeks). Release of TSH can be inhibited by negative feedback from the adrenal cortical hormones.

Sackler et al. (1960) studied the influence of different types of sound (pure-tones, buzzer, alarm-bell), 5 min daily exposure for 3 weeks (115–120 dB, 400–600 Hz). The exposed rats, as well as the control animals, were transferred from the regular housing room to the exposure room and handled in a similar fashion. Different types of sound had surprisingly different effects on organ weights and on microscopically visible tissue changes. They obtained histological evidence for at least a mild increase of production of adrenal corticoids, inhibition of gonadotropins and possibly also of TSH and thyroid hormones. Furthermore, on the basis of a histological analysis Bugard & Romani (1957) and Bugard (1961) conclude that the thyroid gland is inactive after sound exposure.

Kemper et al. (1976*b*), on the other hand, found an increase of protein-bound iodine as an indication of increased thyroid activity during 72 h of exposure to 108 dB broad-band noise in pigs (see also Klein et al., 1979). The authors discussed species differences as a possible explanation for this unexpected finding, but the differences in exposure duration may also be a factor of importance. As pointed out above, the hormonal responses are often multiphasic due to negative feedback effects and typically show an initial increase of activity.

An increase in serum concentration of growth hormone in Rhesus monkeys (Meyer & Knobil, 1967) and of ACTH and MSH in rats (Kraicer et al., 1977) has been observed during short-term exposure. Collu et al. (1973) and Collu & Jéquier (1976) found, on the other hand, that venous concentration of growth hormone decreased during 30 min exposure to an alarm-bell (non-specified level). Only 8 rats were investigated, but specimens were sampled with chronically implanted cannulas, thereby circumventing a major source of measurement error (see above p. 23).

In conclusion, sound exposure, at least during a few weeks' duration, influences several hormonal systems. The complexity of hormone interactions and of control of secretion makes simplified statements impossible, at present.

b. *Electrolyte and water regulation*

Body fluid composition is determined by intake and excretion of electrolytes and water, functions influenced by upper brain-stem structures, pituitary

hormones and hormones from adrenals and kidney. The effect of sound exposure on water and salt balance can be expected to be complex, and dependent on many simultaneously varying parameter. Renin concentration in plasma was measured by Vander et al. (1977) after 30 min of pure-tone or broad-band noise exposure. None of the stimuli were effective for levels up to 100 dB (non-specified reference) at any stimulus signal. A 2 000 Hz tone was inefficient up to 105 dB, whereas a broad-band noise increased renin concentration from 6.3 to 9.4 nanograms/ml/hour. Animals kept on salt-restricted diets showed an increase already at 100 dB broad-band noise stimulation.

A marked increase of anti-diuretic hormone (ADH) in plasma was produced by a 5-min exposure to siren sound as well as by pain or violent vibration (Mirsky, 1955).

Ogle (1967) showed that natural thunder (150 Hz, 98–100 dB, unknown reference) caused an increase of oxytocin release from neurohypophysis in rats (see also Ogle & Lockett, 1966, 1968; Lockett, 1970).

On the basis of an electron microscopic analysis of the posterior lobe of the hypophysis, Miline et al. (1978) conclude that a combination of broad-band noise and vibration induces a pronounced secretion of oxytocin and vasopressin. The animals (rats) were housed in a factory in cages close to a machine with a sound level of about 100 dB. The control animals were housed in a similar environment but with a lower sound level. To what extent other factors of the milieu were controlled, e.g. air pollution, light, etc. is not, however, mentioned.

A different mode of interference with renal function was found by Caraffa-Braga et al. (1973) and later by Seal & Zbrożyna (1978) and by Hultcrantz (1978, 1979). They showed that renal blood flow decreased, in some cases with slow habituation, during sound exposure. Such an effect is expected to be followed by an increase of renin release (cf. Vander et al., 1977).

These findings together give a picture of salt and water retention, preservation of blood volume and of blood pressure, totally consistent with the preparation for fight or flight.

C. SOMATOMOTOR SYSTEM

Unexpected sounds elicit a "startle reflex" (Landis & Hunt, 1939), i.e. a generalized muscle response dominated by flexor muscle activity. Such reactions are part of everyday experience and have also been observed in humans both in the laboratory and in field studies, e.g. upon exposure to sonic booms (Rylander, 1974). On a more basic physiological level, it has also been shown in humans that monosynaptic quadriceps tendon reflex is increased after a one-second tone (Beale, 1971). Rossignol & Jones (1976) found a 185% facilitation of the H-reflex 110–130 ms after the start of a 100 ms 110 dB SPL burst of 1 000 Hz pure tone.

In animal experiments, a more profound analysis of the influence of sound on the somatomotor system has been possible. Gernandt & Ades (1964) and Wright & Barnes (1972) have shown in neurophysiological investigations on cats that sound can both increase and decrease spinal reflexes. The primary auditory cortex and the inferior colliculus mediate these reflex influences (Buser et al., 1966; Willott et al., 1979).

The startle reflex has been widely analysed with respect to the role of the acoustic features of the stimulus, e.g. in rat experiments (Hoffman & Searle, 1965, 1968; Fox, 1979). The magnitude of the startle response depends on sound level, and in addition on the interval between the stimuli. A sound burst of moderate intensity before the startle-eliciting stimulus decreased the response but shortened its latency. A background noise generally increased the response amplitude (Hoffman & Wible, 1969). The direction and size of this interaction depended in turn on stimulus parameters. The startle response habituates fairly rapidly, both intra- and intersessions (Korn & Moyer, 1966; Davis, 1970; Rossignol & Jones, 1976). The role of background noise for startle responses in gerbils was investigated by Galvani (1978) He found that 80 dB broad-band noise was more efficiently facilitating than was 67 or 90 dB SPL noise. The finding of an optimal level is in accord with observations on psychomotor and behavioral responses in humans at various sound levels (cf. Selye, 1971). Willott et al. (1979) found that a frequency of 10 kHz was more potent than 5 or 20 kHz in mice.

The startle reaction occurs simultaneously with autonomic and cardiovascular responses, and the relation between these different reactions has been discussed. It has been suggested that the defence reaction and the startle reaction are essentially responses mediated by the same mechanisms and that they should rather be regarded as two different outputs of one single reflex (Turpin & Siddle, 1978).

Sound-elicited generalized seizures, so-called "audiogenic seizures" have, for a long time, been known to occur in certain strains of rats and mice (Lindsley et al., 1942). Recently it has also been shown that seizure-resistant rats can be converted to sensitive ones, if they are exposed to sound in a priming session during a critical period of postnatal life (Henry & Bowman, 1970; Henry, 1973). This priming exposure probably causes a damage to the inner ear and an ensuing alteration in development of certain inhibitory neural pathways in the brain. Sound-elicited seizures have also been described in humans, but only in persons with other epileptic symptoms (Forster, 1970).

The major goal of these investigations has been to study increased motor activity during sound exposure. An inhibition of spontaneous movement during sudden unwarned sound stimulation has also been described (e.g. Anderson & Wedenberg 1965). Raynaud et al. (1968) investigated the effect of pure-tones at various frequencies and intensities on inhibition of motor activity in mice. They found the most efficient inhibition to occur at stimulus frequencies around 14 kHz, but they needed 110 dB (reference not specified) in order to obtain a reliable effect. These observations were substantiated (by Kneis, 1978), in EMG recordings on non-anesthetized guinea-pigs. He found a decrease of electrical activity during short sound bursts and interpreted these findings as a freezing reaction. The observations by Raynaud and by Kneis both seem to correlate well to the increased fatigability found in swimming experiments by Busnel & Lehmann (1978).

A related phenomenon was described by Rydén (1978). He found that juvenil birds of several species responded with immobility and persistent cessation of begging when exposed to species-specific alarm calls. The basic features of the behavior reaction was regarded to be innate, but it could be modified by manipulating the experimental situation (Rydén, 1978).

An interesting practical application of the audiogenic seizures has been suggested by Pinell (1972). He designed an ultrasonic rat trap. The theory behind the trap has, however, been repeatedly criticized (Morley & Abelson, 1975; Morley et al., 1977). They pointed out that habituation and selection would soon make the trap useless and possibly, in the long run, only create "a better rat".

Sound in the audible as well as in the infrasonic range has been found to decrease power of endurance in rats in a swimming test (Busnel & Lehmann, 1978). This effect, which is to be regarded as an acute reaction, is probably due to influences of the acoustic environment both on the cardiovascular and somatomotor systems.

D. SENSORY FUNCTIONS

Loeb et al. (1976) have presented an up-to-date review on the interaction of the auditory stimulus with other sensory processes. Most studies cited concern the vestibular system, vision and pain.

At very high level, exceeding 135 dB, sound was found to affect equilibrium (Ades, 1953; Parker, 1972), although nystagmus was not observed. Unsteadiness is observed for bursts of pure tone at 125–130 dB SPL, 1 000 or 2 000 Hz but only if rise time is below 25–50 ms (Rösler, 1981 p.c.). During acoustic stimulation at lower level stimulation around 90 dB, Nixon et al. (1966), Harris & Sommer (1968) and Harris (1972) found no deterioration of the ability to balance on narrow rails. In experiments on animals, Parker & von Gierke (1971) showed that slow pressure changes in the middle ear could induce neural activity in the vestibular nerve, thus corroborating the above-mentioned findings in humans. In a recent study in man by Vanderhei & Loeb (1976) and Loeb et al. (1976), unsteadiness during sound exposure could, however, not be verified. These authors studied the monaural and binaural effect of impulsive sound at 135 dB and continuous sound at 110 dB (A). No deterioration of performance in a rail balancing test was found. The effect of noise on sensorimotor performance has been investigated in several studies. In a recent work Pecenka (1979) found a great individual variability in the susceptibility to impact noise, and evidence for individual optimal noise levels.

Loeb et al. (1976) conclude that the "data are not indicative of intersensory interactions with important consequences for industrial safety or efficiency".

In the review by Loeb et al. (1976) it is pointed out that the intersensory effects described are small and variable, most studies are fragmentary and the results are difficult to reproduce.

The analysis of the effects of sound on pain sensation can be mentioned as an example of contradictory findings. Gardiner & Licklider (1959) found an analgesic effect of sound in dental practice, which could not be verified in better controlled experi-

ments by Carlin et al. (1962). Meltzak et al. (1963) conclude that the analgesic effect is only due to a "placebo mechanism" and is not the result of a specific sensory interaction. Audio-analgesia has, however, recently been viewed with renewed interest. Blass (1975) decided to reevaluate the earlier observations. Subjects in his study reported a clear decline in the painful sensation of electric shocks under various acoustic stimulus conditions. Music was found to be more efficient than white noise. In order to prevent the effects of suggestion and distraction, 8 subjects were selected who were minimally aware of the possible analgesic effects of sound. Even though there is a difference in the pain sensation, no statistical analysis has been performed, making the conclusions rather dubious. Furthermore, the assumption that the experimental subjects were unaware of the possible analgèsic effects was not analysed, much less proved. It could though be fruitful to reinvestigate audioanalgesia with respect to the endogenous morphines.

In their own experiments on the eye and visual functions, Loeb et al. (1976) found no more than marginal interactions. The only statistically significant reaction, even on high level sound exposure, was a pupil dilatation seen at 105 and 110 dB (A), continuous or impulsive sound. Such a reaction has been described earlier, e.g. by Clynes (1961) and Jansen (1969). A small influence on supposedly proprioceptive functions (tracking performance) was also seen. The effects of sound on sensitivity to visual flicker, a measure of visual temporal acuity, have been recently studied in three subjects by Harper (1979). Acuity was found to be dependent on environmental sound level and reached a maximum in the region of 70 dB SPL, but did not decline below control even at high levels. The influence on visual stereoscopic depth perception has been investigated by Hermann et al. (1979). They reject the earlier observations, e.g. by Slutsky (1975, cited by Hermann et al., 1979) and claim that there is no significant influence of sound up to 115 dB (A) on this aspect of visual perception.

In conclusion, most experimental evidence indicates that sound conditions meeting hearing conservation criteria do not seriously influence non-auditory sensory functions.

E. SLEEP–WAKEFULNESS

The most widely recognized, general physiological and/or behavioral effect of sound is interference with sleep. Such effects are well documented in laboratory studies, both in humans and animals under short-term conditions. It is also known that long-term forced wakefulness can cause mental disturbance and there is at least historical evidence for the use of elaborate acoustic stimulus schedules in torture. Whether sleep disturbance in an acoustic environment that has an acceptable similarity to a real-life situation leads to deterioration of somatic health is still unknown. Its effect on human performance and psyche is more well documented (e.g. Hartley & Shirley, 1977). It has also been found that REM-sleep deprivation leads to a lowering of pain threshold (Hicks et al., 1978). On the other hand intrauterine sound has a pronounced sedative effect on newborn (Muroka et al., 1976).

Reviews have recently been published on the effects of sound on sleep (e.g. Griefahn, 1977). Valuable work has also been done by Griefahn et al. (1976) in compiling results from 60 studies and comparing waking effects of seven kinds of sound exposure. White noise was the most efficient stimulus. They conclude that after-effects (decreased performance, functional or organic disease) can as yet not be related to the arousing effect of sound (see also Murat, 1979). De Camp (1977) points out in his review that, in spite of the great efforts made in laboratory studies, no information is available from studies on humans in their natural environments. He emphasizes that we do not know how, and even if, sound from airports and traffic influences sleep and health in a real living situation. Since the present study deals with effects of sound during worktime, the effects on sleep have little relevance in the present discussion.

Zung & Wilson (1961) showed on the one hand that sound can change sleep stage without causing wakefulness, and on the other hand that the arousal effect was dependent on the sleep stage. The most interesting observation, though, was the finding that the arousal effect of a certain sound could be manipulated. Some sound stimuli were given an information value by positive reinforcement, whereas others were not reinforced. The arousal effects of reinforced sound were considerably increased. This observation is an illustrative example of the great importance of keeping the information value of sound under control.

The vegetative reactions to sound persist during sleep (Johnson / Lubin, 1967; Griefahn, 1975) and are even claimed to be more resistant to habituation

during sleep than during wakefulness. This possibility is of course interesting with respect to long-term effects but no such reactions have been found.

In a study by Dittrichová et al. (1977) babies from 2 to 20 weeks of age were investigated with respect to their sleep stage and sensitivity to acoustic stimulation. They found that children below 6 weeks of age were much less sensitive than older babies.

In studies on chimpanzees Koestler & Dalton (1974) showed that animals exposed to 35 auditory disturbances each night habituated with respect to their psychomotor reactions during a prolonged (180 days) experiment.

In an investigation on rats Ribari & Knoll (1970) studied EEG arousal during exposure to various kinds of sound stimuli. High level fluctuating noise (about 100 dB) was most efficient in causing EEG-arousal. In spite of its relative efficiency, the arousal lasted only 34 min on the average.

In summary, a review by Griefahn & Muset (1978) can be cited. They state that "... it must be recognized that the most important problem—the significance of noise-induced sleep disturbances (for health, authors addition)—remains unsolved".

F. OTHER GENERAL PHYSIOLOGICAL EFFECTS

a. *Digestive system*

Non-propulsive contractions of the esophagus were observed during auditory stimulation and were concluded to form part of a defence reaction (Stacher et al., 1979*a*, *b*). Number and amplitude of contractions increased with increasing stimulus intensity (between 75 and 125 dB (A)) but were not dependent on rise-time (0 or 30 ms rise- and decay-time). There was, however, no difference between two levels of signal contents of the stimulus sound.

In 1930, Smith & Laird showed that sound exposure caused a decrease of gastric motility and secretion in humans. Other observations showed a decreased motility, whereas secretion seemed to vary individually (see also Jungmann & Venning, 1975, cited by Stacher et al., 1979*a*, *b*). Using external abdominal electrodes, Rougereau et al. (1976) showed that gastric and intestinal motility decreased in young subjects during short exposure to sound even at levels as low as 55 dB.

An accelerated intestinal crypt cell proliferation was observed in rats exposed to 4-hour intermittent acoustic stress. The animals were exposed during daytime, when they normally sleep, and the author suggests the shifted diurnal cycle to be the explanation for the changed growth of cells. Crypt cell proliferation is normally most rapid at night, when the animals are awake. Sound stimuli waking the animals in daytime thereby initiate this normal accelerated activity.

The influence of 14 days of 11-hour daily exposure to music, intermittent or continuous sound (100 dB or 75 dB) on gastric function and metabolism was investigated in sheep by Harbers et al. (1975). Minor changes in water and food intake were observed, but the animals mainly habituated during the experimental period.

A significant decrease of gastric secretion in rabbits was described by Cuha et al. (1975). The animals were exposed for one hour to intense sound (non specified) and secretion was sampled through a tube implanted chronically in the stomach. Treatment with a neuroleptic drug (Chlorpromazine) abolished this reaction to sound. Adaptation of the noise-induced release of free fatty acids was observed during exposure to noise 3 h per day for 10 days (Csalay et al., 1978).

b. *Hematology and immunology*

An increase of lymphocyte count concomitant with an increase of eosinophils during sound exposure was seen by Biro et al. (1959). Döpfner & Cerletti (1956) found that albino rats reacted with a more pronounced inflammatory reaction to a bacterial infection during the influence of sound than in silence. This difference was not seen after adrenalectomy or hypophysectomy. An interesting point was made: albino rats of the same breed did not react with a rise of blood pressure during the sound exposure (Rothlin et al., 1956). The physiological reaction in an acoustic environment was thus organ-specific and failure to show alteration in one organ system can thus not exclude alteration of other functions of the same organism.

An outspoken inhibition of the inflammatory response was, on the other hand, observed in rats by Billewicz-Stankiewicz & Krepinska-Urban (1974) after a 2-h exposure to 86 dB sound (or sound and vibration).

Jensen & Rasmussen (1970) showed that a 3-h exposure to 120 dB sound increased the sensitivity to microbial infections and the growth rate of tumors induced by polyoma virus whereas the pro-

gression rate of Rauscher virus leukemia was suppressed (see also Serafino et al., 1977).

Rodinov et al. (1977) induced auricular thrombosis by sound exposure in rats previously chemically sympathectomized.

Rogers et al. (1980) found an exacerbation of collagen-induced arthritis by auditory stress (100 dB wide-band noise, 5 s every min, 1 h daily for 7 days).

c. *Vocal functions*

An increase of voice problems and laryngeal malfunction is commonly encountered in workers exposed to high level sound. This general clinical observation has been confirmed in a closer analysis by Ferguson (1955) and Schleier (1977).

d. *Dental abnormalities*

Haskell (1975) reviewed different causes of stress-induced periodontal disease and presented his own observations on aircrew members. Pilots and crew on a propeller-driven aircraft showed a more extensive alveolar bone resorption and more frequent periodontal problems than jet pilots and controls. The authors interpreted the combination of propeller aircraft noise and vibration as inducing inflammation to a greater degree than jet noise which is less intermingled with vibrations. A simpler explanation would be that vibrations alone are responsible for the decalcification.

G. MECHANISMS FOR NON-AUDITORY EFFECTS OF SOUND

Sound at the low frequency extreme, "infra-sound" may directly influence tissues through acoustic resonance phenomenon (e.g. Lockett, 1970; Busnel & Lehmann, 1978), or by activation of spinal reflexes. Such resonances have been studied in the human thorax and abdomen by von Gierke (1964, 1973). Some studies, particularly those of an earlier date, have been performed at sound levels at or above threshold for aural discomfort and pain (e.g. Anthony et al., 1959). At such levels a direct acoustic activation of the labyrinth cannot be excluded (Ades et al., 1960; Parker & von Gierke, 1971; Bleeker et al., 1980). The specific contribution of these pathways needs to be further investigated in selectively deafferented animals. The majority of reactions, however, observed under the influence of audible sound are mediated via the ear and the central nervous system.

Simple acoustic reflexes, exemplified by the acoustic middle ear muscle reflex are mediated by pauci-neuronal pathways in the lower brain-stem (Borg, 1973; Browner & Webster, 1975). The accuracy of head orientation towards a sound source relies upon lemniscal pathways to the inferior colliculus (Thompson & Masterton, 1978) and tegmental pathways beyond the superior colliculus. The more nonspecific component of the orienting response, initial reflexive movements of the head toward a sound source (Thompson & Masterton, 1978) and peripheral vasoconstriction, remains after lesions to the inferior colliculus (Borg, unpublished). The startle reflex remains after decerebration, but it is abolished in animals with lesions to the inferior colliculus, the mesencephalic reticular formation or the nucleus reticularis pontis (Fox, 1979). Willott et al. (1979) found a good agreement between firing of units in the pericentral and/or external nuclei of the inferior colliculus and startle responses under different stimulus conditions. A less precise relation to units in the ventrolateral division was found.

In experiments on chronically decorticated cats Bard & Rioch (1937) showed that emotional excitement such as fear and rage can be evoked by sound and often become exaggerated after operation(s) (see also Bard & Macht, 1958). Important centers for integration of vegetative reactions are situated in the upper brain-stem, the mesencephalon, the hypothalamus and other structures belonging to the limbic system. Significant parts of these structures remain after decortication. Simple responses like pilo-erection during sound exposure have, however, been described to occur even in decerebrate animals (intercollicular decerebration, Forbes & Sherrington, 1914).

Electrical stimulation of certain brain regions can furthermore elicit different types and components of aggressive reactions; flight or fight behavior, such as cutaneous vasoconstriction, rise of blood pressure, and an increase of muscle blood flow (Abrahams et al., 1960). Electrical stimulation of hypothalamus in rats for several weeks has been found to give rise to an increase in blood pressure outlasting the stimulus period by several weeks (Folkow & Rubinstein, 1966). In a later more elaborate analysis with electrical stimulation, several different hypothalamic structures were found to induce a rise of blood pressure and a decline of heart rate (Faiers et al., 1976). If the vagal nerves were blocked, activation of the same areas produced an

increase of heart rate. Stimulation of adjacent areas was followed by a decrease of blood pressure and a lowering of heart rate. The role of the vagal nerve for sound-induced release of free fatty acids has recently been pointed out by Csalay et al. (1979) and chemical sympathectomy decreases the resistance of rats to "noise stress" (Rodinov et al., 1977).

Even though there are connections in the lower brain-stem mediating general physiological effects of sound, such reactions are of course highly dependent on control from higher centers. The decorticated cats of Bard & Macht (1958) showed, for example, a lowered threshold for emotional reactions to sensory stimulation. The reactions were poorly controlled, more violent and badly directed. As has been pointed out repeatedly, the information content of the acoustic stimulus is of great importance, particularly for prolonged physiological reactions and habituation. Such mechanisms heavily rely on higher brain-stem and cortical functions. The role of frontal cortical areas in establishment of habituation was defined by Glaser & Griffin in 1962. Lesions in septo-hippocampal connections influence responses to repetitive stimulation without blocking habituation (Miller & Treff, 1979). Small lesions in the orbital cortex, however, abolish the orienting reflex to sound (Petrek et al., 1970).

The response characteristics to auditory input of those particular neurons directly responsible for the reactions described in this review are not known. There is, however, at least circumstantial evidence from anatomical and physiological studies that several "non-auditory" brain-stem structures receive input from the classical auditory pathway, e.g. the reticular formation (amygdala, septum) and central grey matter (Green, 1969, p. 285 in Haymarker, Anderson and Nauta).

A relatively short latency activation of neurons in the hypothalamus and the limbic midbrain area on somato-sensory, visual and auditory stimulation has been described by Dafny et al. (1965) and Dafny & Feldman (1970). They analysed single cells in the posterior hypothalamus and found that nearly 80% of the cells were excited or inhibited by sound. Short latency responses to acoustic stimulation were recorded in the pineal body and ventromedial hypothalamus in freely moving rats by Daphny (1977). These response patterns were also found to be modulated from adjacent brain-stem structures, e.g. the caudate nucleus. In nucleus ruber, in the upper brain-stem, "evoked potentials" have been recorded during sound stimulation (Massion & Albe-Fessard, 1959).

Recently, short-latency responses (less than 12 ms) to auditory signals of neurons in the dorsal and medial raphe nuclei have been recorded in non-anesthetized rats (Le Moal & Olds, 1979). The respones were resistant to habituation and may be responsible for the autonomic reactions to sound observed in the decerebrate animals (Forbes & Sherrington, 1914).

Further information on the neuronal mechanisms involved in the non-auditory reactions to sound is gained from specific lesion studies. Interruption of the anterolateral and posterolateral connections to the hypothalamus (Feldman et al., 1972) blocked the acute sound-elicited corticosterone excretion. Ether-induced adrenocortical activation was not influenced by these lesions. Nor did lesions of the anterior afferents affect the sound-elicited hormone release. In a neuropharmacological study Collu & Jéquier (1976) found evidence that sound-elicited inhibition of growth hormone release was mediated by a non-catecholaminergic pathway. The findings indicate, however, the existence of a central catecholaminergic tonic drive (see also Collu et al., 1973).

The neuroanatomical and neurophysiological knowledge available at present, indicates that sound produces vegetative, hormonal and somatomotor responses via connections at several levels of the brain-stem. The inferior colliculus, the reticular formation, the limbic midbrain area and the hypothalamus thereby play crucial roles. Higher, cortical centers exert a modulatory influence of importance for the size, and habituation of the reaction as well as for the handling of the information value of the acoustic signal and constitute questions for further research.

H. SUMMARY

The review presented reveals a multitude of non-auditory effects of sound. Even though information is often contradictory there can be little doubt that most physiological systems can be influenced by environmental sound. No simple theory can be presented that completely explains the findings, but the following statements on short-term (1–5) and long-term (5–8) effects have a fair experimental support.

1) Short-term sound exposure can influence autonomic nervous functions and thereby alter cardio-

vascular and gastro-intestinal homeostasis and adreno-medullary activity.

2) Short-term sound exposure can alter excretion of hormones, especially those regulated from the hypothalamus–hypophysis system.

3) Unexpected sound elicits a generalized skeletomotor activation, a "startle" reaction.

4) The reactions are sensitive to habituation during prolonged, or repetitive exposure to similar acoustic stimuli.

5) The reactions are elicited through the auditory influences at several levels of the brain-stem including the hypothalamus and reticular formation.

6) Long-term exposure to an environment, a component of which is highly intermittent acoustic stimulus presentation, can produce a moderate rise of blood pressure in experimental animals (up to 150–160 mmHg).

7) In industrial environments with high sound levels, there is a higher incidence of medical and psychosomatic problems than in industries with low sound levels. (There is, however, no acceptable evidence that the sound itself is responsible for these health problems.)

8) Differences between species and individuals are pronounced (age, personality, etc.).

An inappropriate design of experiments and technical shortcomings limit the possibility of interpreting the results of many previous studies. Some commonly encountered difficulties can be enumerated.

1) The acoustic stimulus has been poorly designed and described with respect to its physical properties, and poorly adapted to the auditory functions of the experimental animal.

2) The acoustic stimulus has either an obvious but not quantified information value, or a hidden information value which can be inferred from the description of the experimental procedures.

3) Experimental subjects and controls (if any) differ not only with respect to sound exposure, but also with respect to other factors, such as intentional exposure to light or vibration or unintentional exposure to handling and housing.

4) The physiological state of the subjects differs; the basic levels of hormone secretion, blood flow or blood pressure have been different or not controlled. Normal diurnal or annual variations in physiological parameters have not been considered.

5) Only a few biological parameters have been investigated in each experiment and the question of whether observed reactions are to be regarded as normal physiological response or part of a process leading to damage or disease has not been tested or adequately considered.

Numerous questions can be raised with the aim of creating a better understanding of the acoustic environment as a threat to health.

1) What particular conditions must be fulfilled if the sound is to have a harmful chronic effect on health (except for hearing loss)? Can these conditions be fulfilled in a real-life situation, or in the laboratory?

2) Are there any physical characteristics of a sound making it particularly potent in influencing non-auditory, physiological systems?

3) Do information-related aspects and physical aspects of the sound interrelate in the creation of short-term and long-term physiological and pathophysiological effects?

4) Does sound interact with other physical or chemical factors in the environment? Is there an additive effect, a potentiation or a partial cancelling?

5) Do chronic alterations of the physiological homeostasis also imply a threat to health, a decrease of well being, an increase of disease incidence or a shortened life span?

6) Do risk groups exist with respect to harmful aspects of sound?

7) Can the risk groups be identified, e.g. on the basis of their short-term reactions?

8) What are the neuronal mechanisms responsible for the short- and long-term non-auditory effects of sound?

III. Personal Investigations

Two questions raised on the basis of the literature survey have become the goal for a series of experiments on animals.

1. How do the acute physiological reactions in the acoustic environment depend on the physical properties of the sound?

2. Which physiological and patho-physiological effects occur during lifelong exposure to sound simulating a work environment?

The investigation was performed as a model study on rats. This animal species was chosen for the following reasons:

1. Physiological response is accessible to non-invasive studies, i.e. the blood flow in the tail.

2. Blood pressure can be repeatedly measured by a non-invasive technique.

3. Hearing thresholds can be determined by a behavioral technique.

4. This species has a life span of only 2 to 3 years.

5. Several strains of rats are avilable and can form a basis for different risk groups.

A. ACUTE REACTIONS TO SOUND

1. Aims

a) To select a model organ where the sympathetically controlled activity can be recorded noninvasively without the use of anesthesia.

b) To quantify the relation between acoustic features and size of vegetative reaction.

c) To specify the influence of various external and internal factors on the vegetative reaction to sound.

2. Methods

The experiments were performed on a total of 80 Sprague-Dawley rats, the majority of them males. In addition, a number of spontaneously hypertensive Wistar rats were included.

The tail plays an important role in temperature regulation in rats. The blood flow is continuously adjusted reflexively in accordance with the demands of heat dissipation over a range of 100 times (Johansen, 1962). The arterial blood flow can be semiquantitatively recorded as volume pulsations obtained by using a rubber balloon overlying the central tail artery on the ventral side of the tail (Fig. 1). In order to establish a stable initial value of the pulse volume (blood flow), the rat was always mildly warmed until pulse volume reached maximal value. The animal rested on a temperature-regulated pad in an individually adjusted wiremesh tube. Before the start of the experimental session, the animal was allowed to acclimatize to the mesh tube in 1-h sessions for 5 days. The measuring session was started by warming the animal for 30 to 60 min until pulse volume reached a stable maximal value. At this state, any sound or other sensory stimulus was followed by a decline in pulse volume, often to less than 10% of the prestimulus value. This decline in pulse volume was interpreted as due to a vasoconstriction.

The stimulus sound consisted of a broad-band noise with maximum energy between 5 and 15 kHz. The signal was presented either as a 1 s burst with a rise and decay time of 20 ms, or as a constant noise in which short pauses or increments were introduced. All intermittent signals were presented with a varying interval of 10 to 20 min. The validity and reproducibility of this technique for measuring vascular reactions to sound has been analysed and presented separately (Borg, 1977).

3. Results

a. *Role of stimulus features*

The vascular reaction to sound was graded and systematically dependent on the acoustic properties of the stimulus.

A sequence of typical recordings of pulse volume and sound-elicited vasoconstrictions is illustrated in Fig. 2. One second after the onset of the sound (a 1 s burst of noise), the pulse volume drops and reaches a minimum after 10 to 20 s. Approximately 1 min later, the blood flow is again seen to normalize. The most relevant way of quantifying this reaction is to determine its duration and not just measure decline in pulse volume as such. The measure of duration used ($T\frac{1}{2}$) was defined as the time from onset of sound to a point where the pulse volume

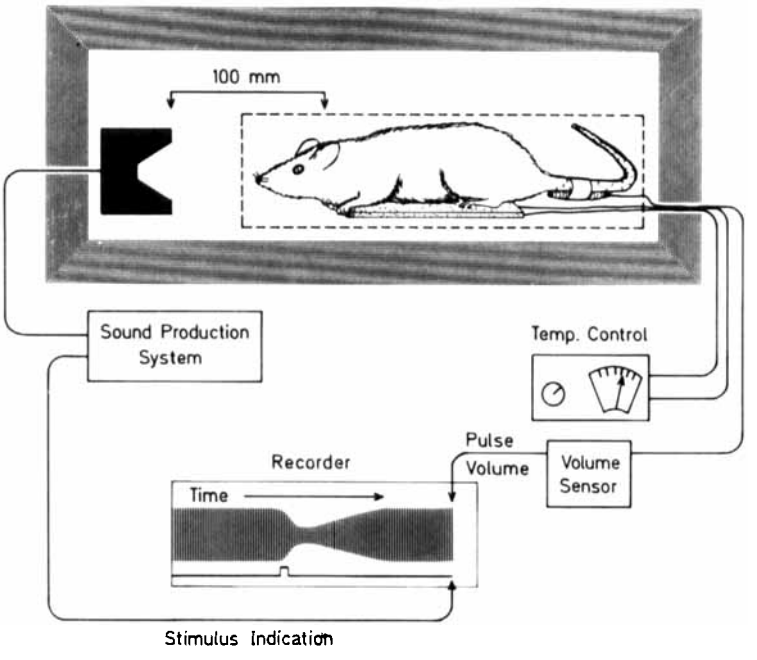

Fig. 1. Experimental set-up for study of tail artery response to sound. The rat rests on a temperature-regulated pad in a wiremesh cage. A short sound burst from the speaker, 10 cm in front of the rat's head, elicits a vasoconstriction evident as a decline in amplitude of pulse volume recorded from the tail of the animal.

had returned halfway to prestimulus value. It is seen in Fig. 2 that the vasoconstriction increased in size and duration as the level of the burst increased, and the response (quantified as $T\frac{1}{2}$) was a nearly linear function of sound level. The variability was appreciable both inter- and intra-individually and therefore, a fairly large series of measurements had to be made in order to ascertain differential sensitivity to various features of the sound (Fig. 3). The main findings regarding the role of acoustic properties for the size of the response are summarized in Fig. 4. This figure illustrates the following features.

1) The duration of the vasoconstriction increased in direct proportion to the sound level up to at least 90 dB SPL (re. 20 μPa) for 1 s noise bursts.

2) After approximately 1 h exposure to 80 dB SPL constant noise, the response was completely habituated, i.e. the pulse volume reached prestimulus value in spite of ongoing sound stimulation.

3) An increment of the noise level during 1 s was followed by a renewed vasoconstriction. In this case, the size of the vasoconstriction was related to the total sound level (background + increment) and not to the size of the increment itself. The reaction was independent of the size of the change as long as the change exceeded 5 dB (an increase from 50 to 80 dB SPL gave the same response as an increment from 70 to 80 dB SPL).

4) The higher the total level, the greater was the

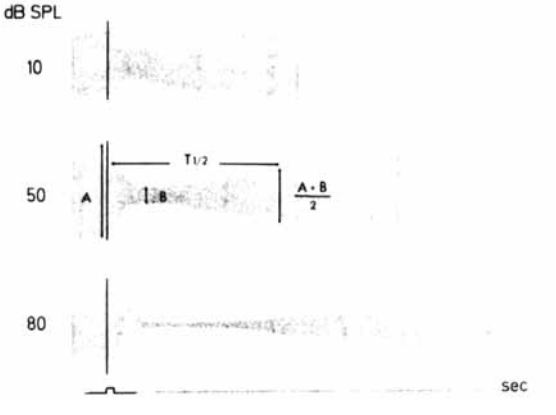

Fig. 2. Pulsations recorded from the surface of the tail of a non-anesthetized rat. A one-second noise burst elicits a decline in pulse amplitude, the degree and duration of which depend on sound level. The vasoconstriction is quantified by $T\frac{1}{2}$, the time from stimulus onset to recovery to $(A+B)/2$, where A is pre-exposure amplitude and B is minimum pulse amplitude. (From Borg 1977, *Acta Physiol Scand 100*, 129–138.)

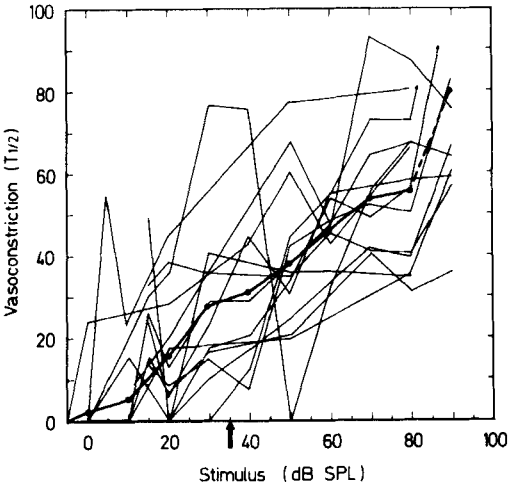

Fig. 3. Duration of vasoconstriction as a function of the level of a 1 s noise burst (stimulus–response curves) in 14 rats. At 80 dB up to 10 responses were obtained for each animal; at other levels 1–3 determinations were available. Solid line shows average calculated for each 10 dB step. Arrow shows hearing threshold obtained by traditional behavioral technique (Gourevitch 1965). (From Borg 1977, *Acta Physiol Scand 100*, 129–138.)

response to changes in sound level of equal size (10 dB), i.e., an increase from 70 to 80 dB SPL gave a larger response than an increase from 50 to 60 dB SPL, Fig. 4 C.

5) Noise bursts at 80 dB SPL shorter than 1.0 s gave significantly smaller responses than bursts with a duration exceeding 1 s.

6) Bursts with rapid rise and decay (1–100 ms) gave significantly larger vasoconstrictions than bursts with slow onset and offset (1 s).

7) An increase of sound level gave larger responses than did a corresponding decrease of sound level.

8) A pause in a constant noise gave (after habituation) rise to a renewed response even if the pause was of a duration less than 10 ms.

9) For short duration signals (e.g. 10 ms), a pause was more efficient than a noise burst in activating the vasoconstriction mechanisms.

b. *Habituation*

As mentioned above, vasoconstriction habituated during prolonged constant stimulation, i.e. the pulse volume increased gradually and finally reached pre-stimulus amplitude. In 80 dB SPL noise, the habituation was complete after about 1 h in spite of ongoing sound. During intermittent stimulation with 1 s 80 dB SPL bursts spaced 10–20 min, no habituation was observed as a rule, even during experimental sessions exceeding 8 h. Low-level bursts were more sensitive to habituation. This statement is, however, subjective and not based on a detailed analysis.

A number of animals were used several times with intervals varying from a few days to several months. A systematic investigation was made in seven rats subjected to identical experimental sessions with one week's interval. Responses to 1 s

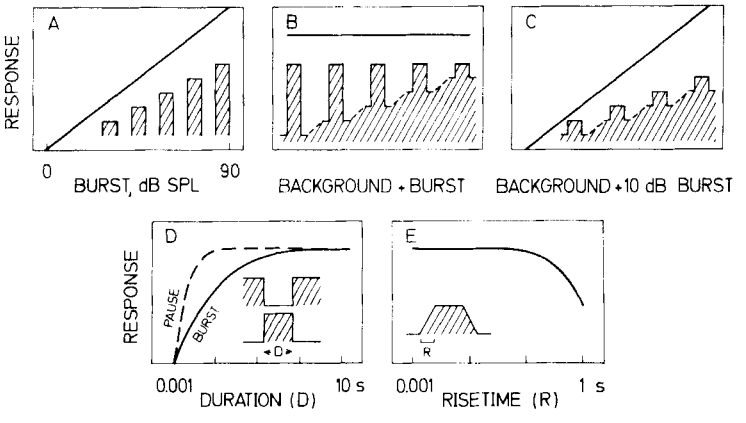

Fig. 4. Schematic presentation of the dependence of peripheral vasoconstriction on the physical properties of sound. (A) Stimuli (one s burst of broad-band noise, with maximum energy between 5 and 15 kHz) imposed on a quiet background. (B) Stimuli imposed on background with variable levels in such a way that the total level always reached 80 dB SPL. (C) Stimuli consisted of an one s 10 dB increase superimposed on a background. (D) Stimuli consisted of short bursts (—) and short pauses in an 80 dB SPL continuous sound (---). (E) Stimuli consisted of four s noise burst at 80 dB SPL with variable rise time. (From Borg 1979, *Acta Otolaryngol*, Suppl. 360, 80–85.)

bursts at various levels, intermittently presented with 10 to 20 min intervals were investigated. In 5 of the 7 rats, small differences were observed between the two sessions, but no tendencies to habituation could be seen. Two animals did not accept the measuring situation in the second session and therefore no measurements could be recorded. After an extended interval, however, the measurements could be completed. Response characteristics were then identical to those obtained in the first experiment. It can be inferred from these experiments that it is important to differentiate between a lack of response due to an aversion to the measuring situation and habituation in the usual sense of the word.

Under the present conditions of intermittent stimulation, habituation was thus not a factor of significance. It dit not interfere with the analysis of the role of acoustic features.

c. *Role of various external and internal factors for the vasoconstriction*

The temperature of the heating pad and the air in the sound-proof box was of great importance for the size of the pulse volume in non-stimulus conditions as well as after activation by sound. This dependence is to be expected since the tail is one of the effector organs for temperature regulation. Stable response conditions were only obtained in a narrow temperature range (about 0.5°C). An excessive increase of temperature led to overheating without further increase in pulse volume. On the other hand, the sound-induced vasoconstrictions declined. The gradual blocking of vasoconstriction during excessive heating was probably due to an overload of the vasodilatating signals from temperature-regulating centers. The signals from the auditory system could only induce a minimal vasoconstriction under these conditions. At subnormal temperature, on the other hand, the tail vessel was constricted, pulse volume was minimal, and sound could not reduce blood flow further.

The vasoconstriction elicited by a standardized sound (1 s burst of 80 dB SPL noise) was furthermore related to heart rate. There was a small, negative correlation between heart rate and vasoconstriction. At high heart rate, the reaction was smaller than at low heart rate. General skeleto-motor activity was also associated with a reduction of the response. Alternately, muscle activity itself produced maximal vasoconstriction.

4. Conclusions

These experiments show that acute sound stimulation induces reproducible reactions in the peripheral circulatory system. These responses are graded and depend systematically on the physical properties of the sound. They also undergo habituation and are influenced by a number of external and internal factors. One particularly noteworthy observation was that the size of the vasoconstriction was not determined by the size of the change in sound level, but rather by the total level reached during an incremental stimulation.

B. EFFECTS OF INTERMITTENT LIFELONG SOUND EXPOSURE

1. Aims

a) To follow selected physiological processes in animals subjected to an acoustic environment which simulates an occupational situation.

b) To observe changes in life span and morbidity in such an environment.

c) To observe the degree of hearing-loss after prolonged survival in this environment.

2. Methods

a) *Experimental animals*

The main experiments were performed in 115 Sprague-Dawley albino rats with normal blood pressure (normotensive animals; N) and 73 Wistar rats with a pre-disposition to hypertension (spontaneously hypertensive (SH) rats, Okamoto, 1969). 103 rats participated in 6 series of control experiments.

The Sprague-Dawley rats were obtained from the Anticimex stock in Sweden at about 1.5 months of age. The Wistar rats were supplied by Møllegaards Avlslaboratorium (generation F36, F37, F42, F43), Denmark and delivered at 1.5 to 3 months of age. At the age of approximately 3 months, the animals were introduced into one of three acoustic environments in which they stayed until the end of their lives.

b) *Housing of animals*

The animals were randomly distributed in one of three identical sound-proof boxes (manufactured by C. A. Tegnér AB, Stockholm, Fig. 5). These boxes had internal dimensions of 70×100×200 cm and contained up to 6 levels with two animal cages in each level.

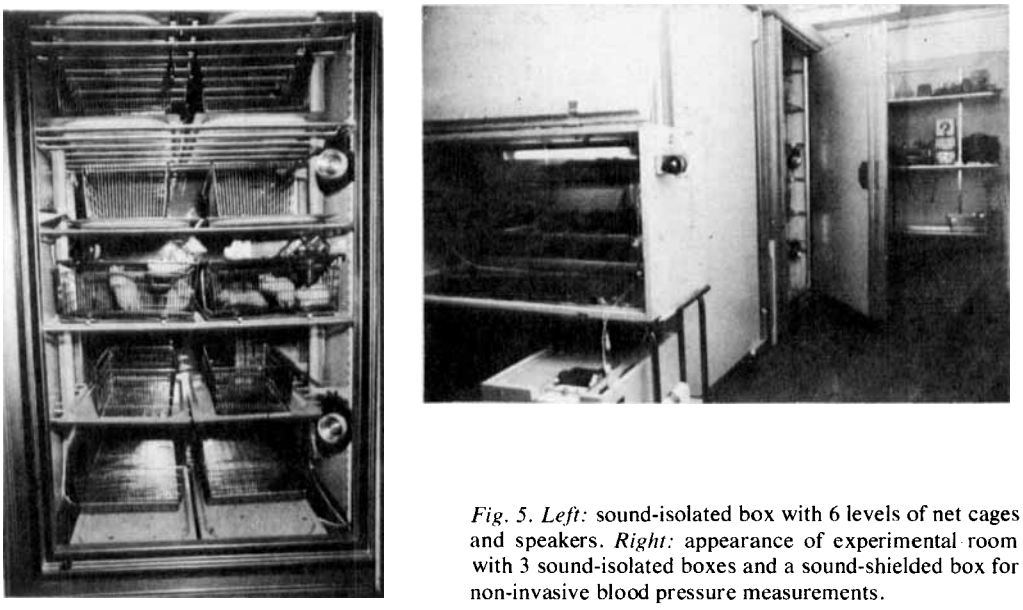

Fig. 5. Left: sound-isolated box with 6 levels of net cages and speakers. *Right:* appearance of experimental room with 3 sound-isolated boxes and a sound-shielded box for non-invasive blood pressure measurements.

The sound boxes were temperature-regulated and ventilated by a common air-conditioning system, maintaining the temperature between 22 and 23°C. Humidity was not regulated but was recorded together with temperature, during one week each month and was rarely outside the range of 30 to 60%. On one occasion (one night only) the ventilation system failed. Temperature increased to 28°C and three male SH-rats died, probably due to abnormal cardiovascular effects following overheating in these animals with cardiovascular disease. Each sound-box was fitted with three 24 W fluorescent tubes, set for an ordinary light/darkness cycle (light: 8 a.m. to 8 p.m.). Cleaning of cages was done once a week, during day-time. Food (R3, Ewos Sweden) and water were supplied *ad libitum*. During the first two years of the experiment, all routine handling and all measurements were made by one person (Agneta Viberg). She also made all physiological measurements, except hearing-threshold determination. During these first two years, the majority of the measurements were taken and about 50% of the original animal stock died. Later, the responsibility for animal care and physiological measurements was assumed by Gunilla Jalmarsson, Ulla Elmér and Ann Hagström.

c) *Sound exposure*

One of the three sound boxes (A) was used as a control environment and no sound was introduced. The background sound level present was generated by the rats themselves and by the ventilation system. While active, the rats produced a typically intermittent sound (Fig. 6 A) carrying information about their movements and activity, intermingled with vocalization and other acoustic signs of social interaction. Fig. 6 A shows sound level variations while the animals were asleep (during the day, left) and when they were highly active (at night, right).

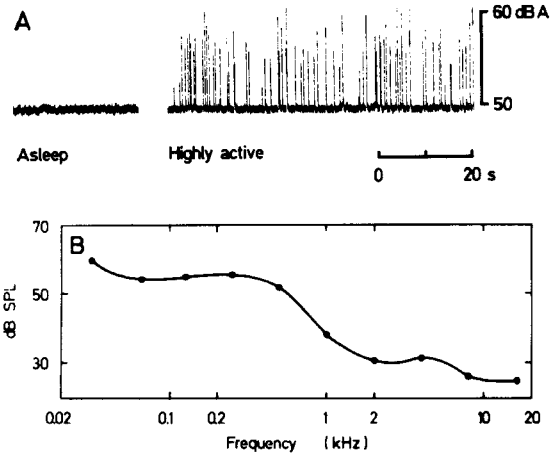

Fig. 6 A. Recording of sound level in box A (control); *left:* when animals were asleep; *right:* when they were very active.
Fig. 6 B. Octave spectrum of background noise (during low activity).

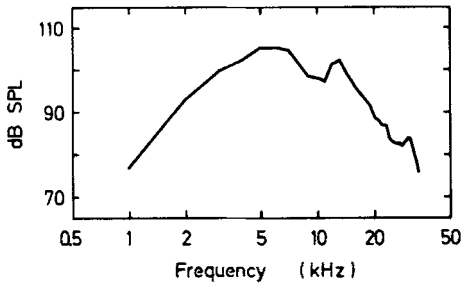

Fig. 7. Level of the ±840 Hz wide exposure noise band as a function of center frequency.

Octave-band spectrum obtained during a period of low activity is shown in Fig. 6B. During this time the dominating sound was generated by the low frequencies from the ventilation system.

The two remaining boxes (B and C) were each supplied with 4 Lancing L75 high-frequency horns. These horns were extended with a 1 cm aluminium ring to improve high-frequency sound characteristics. The exposure sound consisted of a narrow-band noise (±840 Hz width) frequency-modulated at 0.5 Hz between 3 and 30 kHz. The sound was, in addition, pulsating with a duty cycle of 50% (1 s on, 1 s off). Fig. 7 shows the noise level as a function of center frequency of narrow-band exposure noise. The spectrum is fairly flat between 3 and 15 kHz, with a maximum between 5 and 8 kHz at 105 dB SPL. The time course of the sound level variations is illustrated in Fig. 8 A as recorded by a B & K 1/4" microphone and B & K 2607 sound-level meter (RMS fast setting, 22.4 hZ HP-filter). The fine structure of the exposure sound was continuously variable and determined by the interfering action of the 0.5 Hz chopping and the 9.5 Hz frequency-modulation which were not of exactly the same frequency. An electronic clock regulated the sound presentation via a mechanical switch. Exposure was during the dark period between 8 p.m. and 8 a.m. This interval corresponds to the period of high activity of the rat diurnal cycle. During these 12 hours of exposure, a combined pause of a little over 2 hours was introduced (Fig. 8B). The pauses (1, 2, 4, 8, 16, 32, 64 min) were introduced in a pseudo-random fashion. The exposure schedule was predetermined from the beginning of the experiment (January 23, 1975). The mechanical switch of the timer generated transients with a level of 124 dB SPL (impulse hold setting, B & K 2607).

The frequency-modulated exposure noise was generated by folding a bandpass-filtered noise with a pure tone (Fonema bandpass-filter and noise generator, Wavetek 104 function generator). The sound was chopped with a 20 ms rise- and fall-time (Fonema timer circuit), amplified by a Quad 303B power amplifier and presented to four Lancing horns (L75) in each box.

The sound level was measured at varying positions throughout the boxes before the animals were introduced and it was monitored regularly after that time (Bruel & Kjaer 2607, 1/4 inch microphone fast). The sound level in box B went up to 85 dB SPL and in box C it reached 105 dB SPL in a frequency range of 5–15 kHz where the spectral energy was maximal. The variation between different microphone positions was within 3 dB when measured without the animals, but with food and water bottles in the cages. A subsequent introduction of the animals probably increased the variability in the sound field, but only in a random fashion. In order to further minimize the risk of systematic differences in sound level between the cages, the animals were repeatedly transferred to different locations in the boxes. The equivalent sound pressure level (L_{eq}) was determined (B & K 2218, ½ inch microphone, Lin, fast) during a 20 min sequence (without pauses) and found to be 100 dB in box C and 80 dB in box B. Taking in consideration that this level was presented 10 hours daily, the 8 hour noise dose will be approximately 101 dB (Lin).

d) *Physiological measurements*

In order to detect physiological changes of the presumably subtle nature expected in these experiments, measuring techniques themselves could only

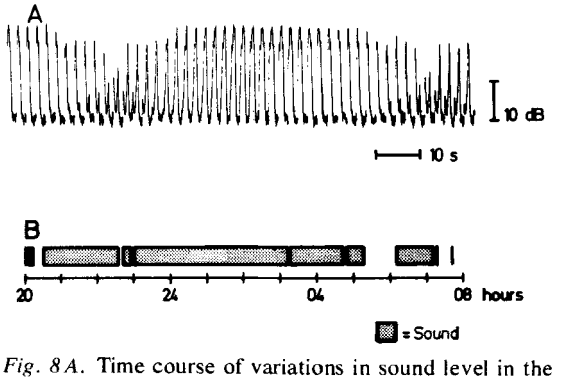

Fig. 8A. Time course of variations in sound level in the chopped frequency-modulated noise.
Fig. 8B. Temporal distribution of noise exposure between 8 p.m. and 8 a.m.

be allowed to have a minimal influence on the physiological system under study. Furthermore, accuracy of measurement and any possible "stress effects" had to be determined. Neither surgical procedures nor pharmacological agents have been used in any of the measurements. The only stressful events have been handling and the mild restraint during blood pressure measurements. The main parameters studied were blood pressure, body weight, water consumption and threshold of audibility.

α. *Indirect blood pressure measurements.* The tail of the rat has one large and two small vessels. The large central artery originates from the aortal bifurcation, and the two lateral arteries from the internal iliac artery. At room temperature blood pressure measured in the tail is usually lower than in the aorta due to pressure drop in the vessel. At room temperature the vessels are constricted but dilate drastically with heat (see section: Short-term experiments). The flow increases during warming, approximately a hundredfold (Johansen, 1962) and conditions for measurement of systolic blood pressure are thereby created (Borg & Viberg, 1980).

The measurements were performed using the Riva-Rocci technique for indirect blood pressure measurements: the tail of the rat was compressed and the blood flow was sensed peripheral to the cuff. The cuff pressure was decreased until the flow distal to the cuff was just measurable. The occluding pressure was usually lowered in steps of 5 or 10 mmHg in order to facilitate reading. This technique has been used for 40 years with different modifications. The technique as applied to these experiments has been evaluated especially with respect to the role of heating and tail blood flow (Borg & Viberg, 1980). During the measuring session, the rat rests in an individually adjusted wire-mesh tube. In order to minimize the stressful effect of this restraint, the animals are acclimatized to the measuring situation by daily one-hour training sessions for 5 days. Up to 24 rats can be measured simultaneously in a temperature-regulated box. Each animal is supplied with a cuff at the base of the tail for application of occluding pressure and a sensor, a small rubber balloon taped on the ventral side of the tail distal to the cuff. The sensor transmits the volume variations in the central tail artery and is connected to a pressure transducer (E 110C) and an ink recorder for read-out (Siemens 34T). In order to optimize measuring economy, a 24-channel pneumatic switch was interposed between the animals, the pressure and volume transducers. Pressure and volume pulse were displayed on an ink recorder. Four measurements were made per day for 5 consecutive days in each rat. The average of these 20 values formed the systolic blood pressure value used for further analysis. In a separate validity analysis (Borg & Viberg, 1980) it was shown that indirect blood pressure value obtained non-invasively from the tail correlates well to the iliac intra-arterial pressure, provided pulse volume used exceeded 25% of maximum obtainable pulse volume (i.e. 1 cm on the ink recorder). The blood pressure was initially determined at an age of 2–3 months, and thereafter with 1–4 months' intervals (4 daily measurements each time for 1 week).

β. *Body weight and water consumption.* The rats were regularly weighed on two following days with 1–4 months' interval. Water consumption was determined by weighing the water bottles for two consecutive days.

γ. *Hearing thresholds* were determined after the rats had spent 12 to 15 months in their respective sound environments. Thresholds were determined between 2 and 48 kHz with a modified conditioned suppression technique (Masterton et al., 1969; Kelly & Masterton, 1977). The animals were trained to assume a stereotype behavior, in the present situation, licking water from a spout. Each tongue movement interrupted a light beam and generated an impulse in a photo-cell circuit. An unexpected interference, e.g. a sound, induced an orientation reflex; the animal stopped drinking and looked for the source of the sound. Upon repetition of the sound, the orientation reflex habituated and the animal continued drinking, providing the sound did not carry information of value for the animal. On the other hand, if the sound was followed by an appropriately adjusted electric shock, a conditioned fear reaction was established, and whenever a tone was heard, the rats stopped drinking in order to be prepared for the shock. The tongue movements were recorded on an ink recorder and thereby positive or negative responses to the tone could easily be determined. A method of limits was used to obtain hearing thresholds at six frequencies in the range of 2 (in some animals 3) to 48 kHz.

e. *Autopsy and patho-anatomical organ studies*

Each rat in the main experimental group (188 animals) and 39 control animals living in the regular

animal department were autopsied at death. A few animals were sacrificed if they were judged to be suffering from advanced cancer or hind body paralysis. The autopsies were performed by Prof. Bertil Järplid, and Veterinarian Lena Renström at The Swedish National Veterinary Institute. The microscopic analysis of specimens from several organs was also performed by Prof. Järplid, thus ascertaining the primary cause of death, as well as the presence of additional pathological processes in a number of organs. Diagnosed organ lesions were classified into different groups related to organ systems and, if possible, to etiological factors. In addition, the weight of 5 organs was determined (heart, liver, kidney, adrenals, ovaries or testis). The pathologist was unaware of the strain of animal and the type of sound exposure used (see further Borg & Järplid, 1982).

The inner ear morphology including a counting of hair cell loss along the basilar membrane, was analysed in a small sample of rats.

f. *Statistical analysis*

Statistical analysis was performed with nonparametric methods (median test and the Kruskal-Wallis test). The blood pressure data was analysed by one-way test of variance and the life span and autopsy by median test, Fisher's exact test and the Kruskal-Wallis test (Siegel 1956). Mr Ulf Brodin and Mr Roger Skagerwall, the Biomedical Computercenter, Karolinska Institute, have been advicers for the statistical analyses.

g. *Control experiments*

The validity and reproducibility of the blood pressure measuring technique has been analysed and presented separately and will not be discussed here (Borg & Viberg, 1980 in preparation). In addition, the following control experiments were performed.

α. Forty SH (10 male and 10 female each, in boxes A and C) were followed with respect to blood pressure measurements up to 12 months of age. The aim was to establish the time course of the development of systolic blood pressure in detail for the initial part of the experiment.

β. Two groups of normotensive Sprague-Dawley rats (5 male and 5 female each) were housed in box A (no sound) and were subjected to blood pressure measurements only once, at 5 and 6 months of age respectively. The aim, with this control group, was to evaluate possible "stress effects" (on blood pressure) caused by the large number of physiological measurements.

γ. One group of normotensive Sprague-Dawley rats (5 male and 5 female) was housed in ordinary transparent plastic boxes with sawdust and placed in regular animal room where they were routinely handled and cared for by the animal department. These animals were subjected to blood pressure measurement according to the same schedule as the experimental animals (5 measuring sessions up to 9 months of age). The aim was to evaluate the role of the environment in the sound-insulated boxes as well as the handling of the animals (in contrast to the measurements).

δ. One group of normotensive rats (5 male and 5 female) was housed in the regular animal department and kept in plastic boxes like group γ. At the age of 6 or 7 months, the systolic blood pressure was determined in a single measuring series (four daily values for 5 days). The aim was to evaluate the total effect of experimental environment, handling and physiological measurements on the experimental groups in boxes A, B, and C.

ε. Four male Sprague-Dawley rats were selected for experiments conducted in a cage especially designed for ECG-recordings. They were tested one by one in the sound environment of box C. The heart rate reaction of these animals was studied before sound exposure, during the initial presentation of the exposure sound and during the habituation phase for up to 3 months. The animal was housed in the cage, the floor of which consisted of conducting plates. The plates were connected in such a way that the animal nearly always had one foot on plates connected to different inputs to an ECG amplifier.

η. Thirty-nine Sprague-Dawley rats have been housed in the animal department throughout their life-time, external controls. Life span and organ pathology have been determined in the same way as for the experimental animals. The aim of this group was to detect pathological changes possibly caused by the environment in the sound-isolated boxes but not related to the sound itself.

3. Results

a. *Physiology*

α. Blood pressure. The average systolic blood pressures of the rats in the three sound boxes from the age of 2–3 months up to the end of life are shown

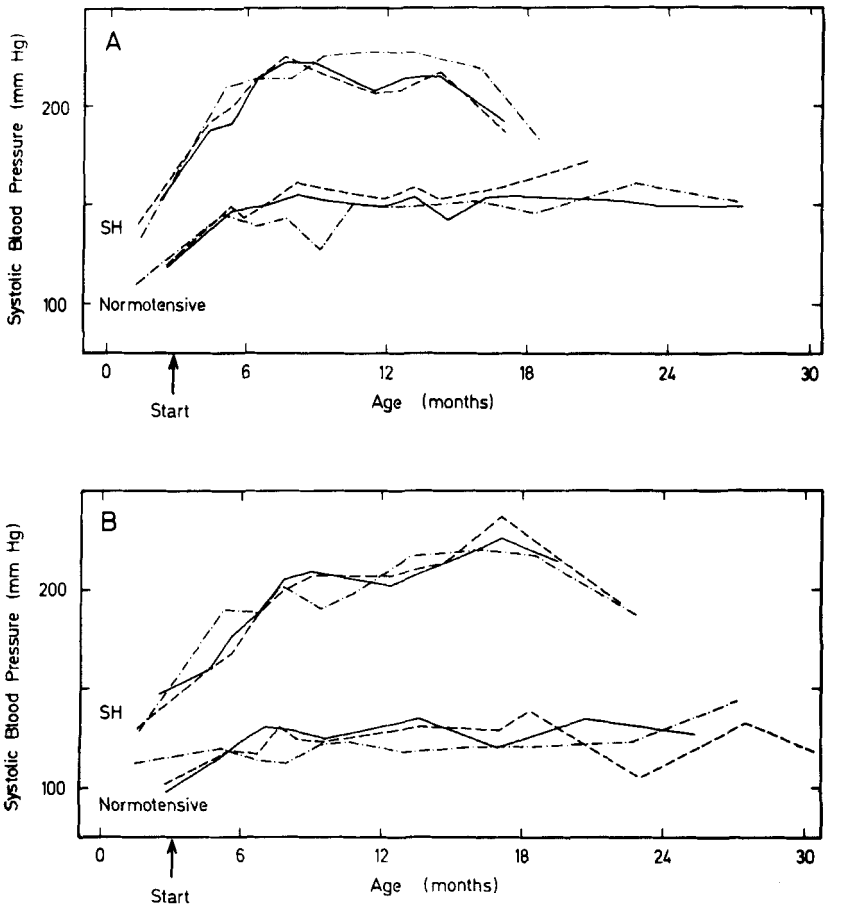

Fig. 9. Mean systolic blood pressure in male (A) and female (B) rats as a function of age in control environment (—), 80 dB L_{eq} sound exposure (---) and 100 dB L_{eq} sound (– · –). Arrow indicates start of experiment, i.e. when the animals were introduced into the sound-isolated boxes. Each group, at start, consisted of 7–8 animals.

in Fig. 9. Fig. 9A shows pressure values in males and Fig. 9B in females for normotensive (N) and spontaneously hypertensive (SH) animals. The continuous line shows the control animals (box A), the broken line represents animals in 85 dB SPL (box B) and the dash-dotted line represents the animals in 105 dB SPL (box C). The arrow shows the moment of introduction of the animals into the experimental boxes. It is seen that the SH animals have considerably higher blood pressure than the N ones. The rate of the rise in blood pressure was also considerably faster in the former strain. No systematic differences between the three groups in the three sound environments were, however, detected. A more rapid rise of blood pressure for the SH animals in box C may be the reason for the small difference in the initial shape of the curves. After the initial rise, the blood pressure reached a stable level for N as well as for SH animals. *No statistically significant differences were obtained between the three sound boxes ($p<0.01$, one-way analysis of variance).*

In order to establish the features of the initial phase of blood pressure development in detail, an additional series of measurements was carried out (control group α). Forty SH rats were introduced into the experimental boxes A and C and were subjected to repeated blood pressure measurements from 2 to 12 months of age. The average systolic blood pressure values as a function of age are shown in Fig. 10 (males and females). It is shown, beyond doubt, that sound-exposed (box C ---) and control animals (box A —) did not differ. Males tend to show a more violent blood pressure development than females, as also seen in Fig. 9. This sex difference may, partly or completely, be an artifact due to the non-invasive blood pressure measurement technique (Borg & Viberg, 1980).

Several control groups were investigated in order to evaluate other factors possibly influencing blood

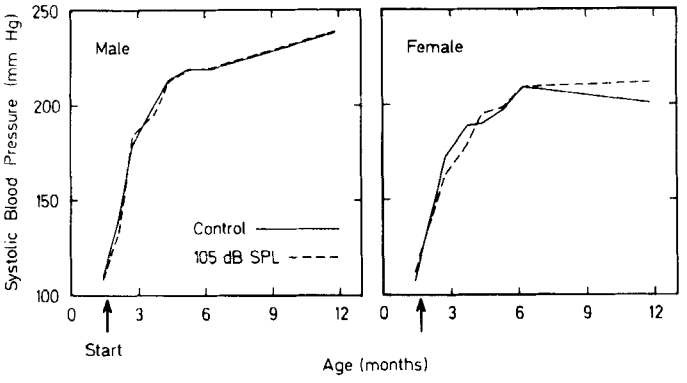

Fig. 10. Mean systolic blood pressure in 10 male and 10 female spontaneously hypertensive animals in each of the sound boxes A and C (control [—] and 100 dB L_{eq} [---]). Arrow indicates start of experiment.

pressure. The average systolic blood pressures (± S.E.M.) of these control groups are shown in Fig. 11 together with the corresponding pressure values in the main experimental groups (reproduced from Fig. 9 A and B). The animals housed in box A (no sound exposure) all had the same pressure, irrespective of whether they were subjected to repeated blood pressure measurements or only one single measurement (control group β). The animals housed in plastic boxes in the standard animal care unit showed a less unequivocal picture. All blood pressure values of female rat groups were identical, irrespective of housing conditions and measuring paradigm. Male rats housed in plastic boxes showed a tendency to lower pressure if measured only once (control group δ). The rate of increase in blood pressure for males was, furthermore, slower in the rats housed in plastic boxes compared to the experimental animals, housed in wiremesh cages. This difference was, however, not significant. Comparisons could also be made with a great number of male Sprague-Dawley rats housed in plastic boxes and subjected to direct blood pressure recordings in conjunction with other blood pressure experiments (e.g. validity study of Borg & Viberg, 1980). Those animals had systolic blood pressure values of 140 to 150 mmHg. Evidence for a pressure effect of the experimental situation as such is, at best, equivocal. *Some of the control experiments may thus be interpreted to show existence of some other environmental factors interacting with the acoustic milieu with respect to blood pressure, although the vast majority of data argue against such a possibility.*

β. *Water consumption.* The average volume of consumed water (ml/rat/24 h) in the experimental groups is shown in Fig. 12 (A = male, B = female). Initially, the SH animals had a lower water intake than the Sprague-Dawley animals. This difference, which may be due to a variance in size, tends to cancel out later in life. *No systematic, or even suggested, differences between the exposed and the non-exposed groups were observed.*

γ. *Body weight.* Mean weight of animals in the various groups is shown in Fig. 13 as a function of age. Pronounced differences between animals of different sex and strain are evident. At advanced age, the weight curves are more uncertain due to a decreased number of rats in the groups, but a tendency to decrease is seen, at least for normotensive

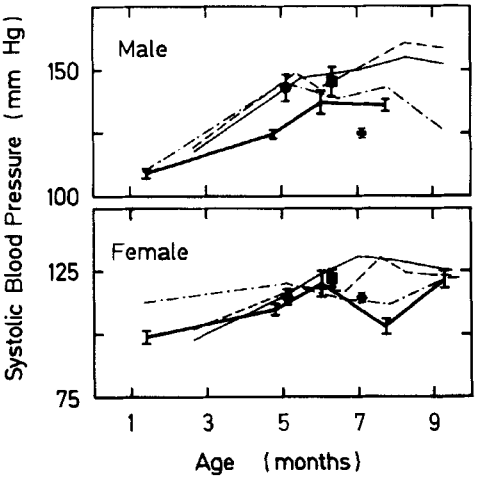

Fig. 11. Systolic blood pressure in male and female normotensive rats in the three sound environments (control [—], 80 dB L_{eq} [---], 100 dB L_{eq} [– · –]) compared with different control groups. Animals in plastic cages with wood carvings but only measured once (●), measured several times (—). Animals in the same environment as the long-term experiments but only measured once (■, ●). Mean ± S.E.M.

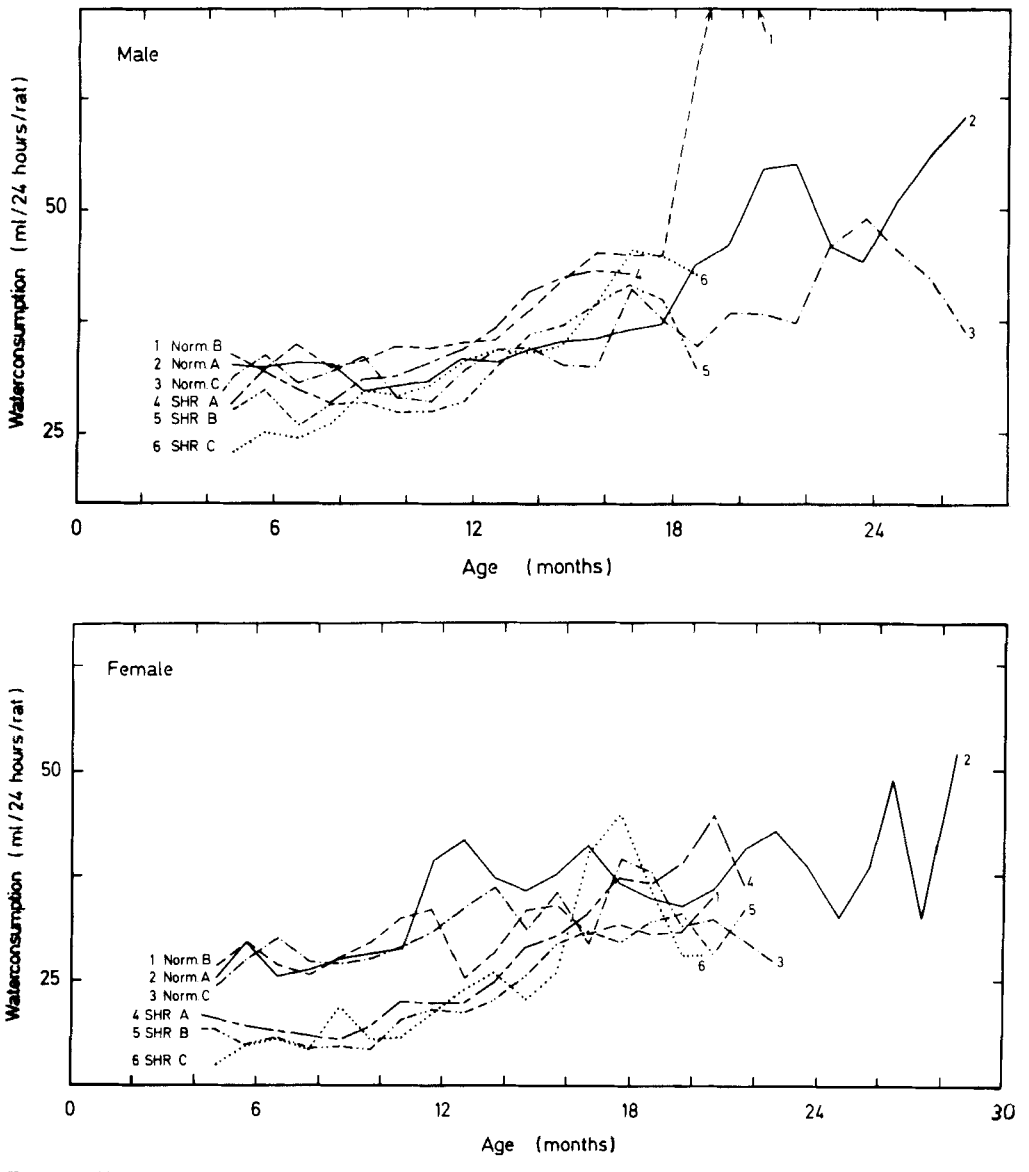

Fig. 12. Water consumption in male and female rats in ml/24 h/rat after introduction into the different sound environments. The different groups are identified by corresponding symbols at the beginning and at the end of the corresponding curve. A: control environment (—); B: 80 dB L_{eq} (---); C: 100 dB L_{eq} (— · —).

males. *No variance is, however, to be seen between differently exposed animals. In N males and SH females, the weight of the control animals is a little above the weight of the exposed animals. This difference was, however, already seen before exposure.*

δ. *Hearing thresholds.* After 12–15 months of sound exposure all animals were tested with respect to their hearing thresholds. A behavioral technique (conditioned suppression of licking) was used. The behavioral audiograms shown in Fig. 14 represent mean thresholds from animals in three sound environments, A for the N rats and B for the SH rats. It is seen that the control animals and the animals exposed to 85 dB SPL (box B) did not differ with respect to threshold. The animals exposed to 105 dB SPL suffered, on the other hand, from significant hearing loss. The normotensive rats had a 30–40 dB loss compared to the control rats in box A. *More remarkable was the finding of the very high degree*

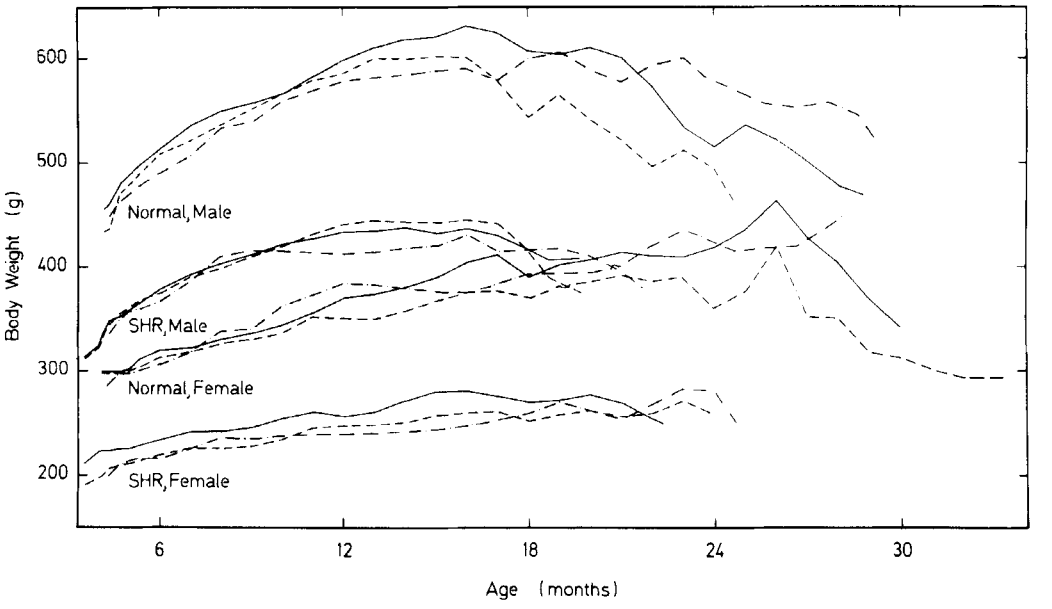

Fig. 13. Mean values of body weight of normotensive and spontaneously hypertensive male and female rats as a function of age after introduction into the different sound environments. Control (—), 80 dB L_{eq} (---), 100 dB L_{eq} (– · –).

of hearing loss in the SH animals in box C (105 dB SPL). The SH animals had at least a 60 dB hearing loss compared to the control animals for the frequencies 6 kHz and above.

The SH rats in 105 dB sound also showed a corresponding massive damage of the inner ear structures. In most of the basal turn there was a total loss of hair cells, in the second turn there was a partial loss and in the apical turn most cells were preserved. In spite of extensive inner ear damage the animals were not deaf, at least not up to the age of 15 to 18 months. It is seen that even control animals had some degree of hearing loss. This hearing loss can either be due to a degeneration of the inner

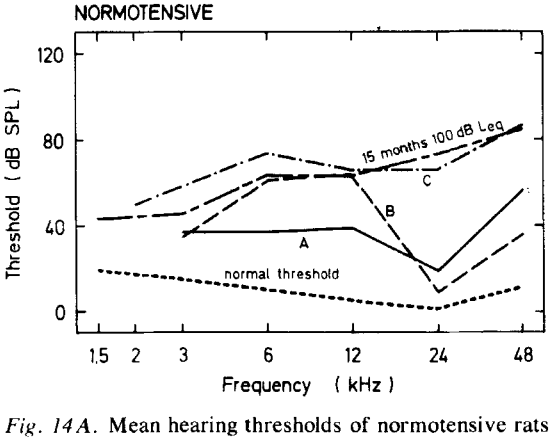

Fig. 14A. Mean hearing thresholds of normotensive rats (males and females) as a function of frequency after 12 months in the three sound-isolated boxes. For comparison, thresholds of non-exposed young normotensive rats are included (· · ·) and another group of long-term exposed rats (15 month, – –).

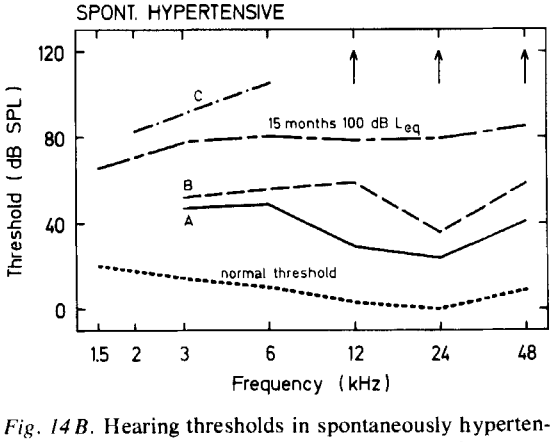

Fig. 14B. Hearing thresholds in spontaneously hypertensive (males and females) rats as a function of frequency after 12 months in the three sound-isolated boxes (A: control; B: 80 dB L_{eq}; C: 100 dB L_{eq}). For comparison, thresholds of non-exposed young spontaneously hypertensive rats are included (· · ·) and another group of long-term exposed rats (15 months, – –).

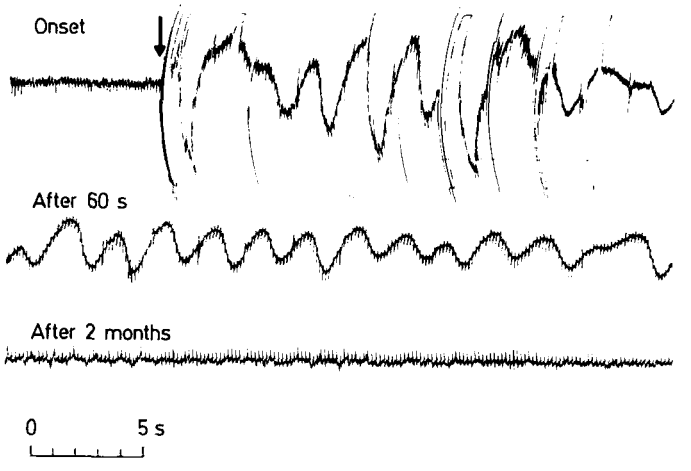

Fig. 15. Electrocardiographic recordings from a rat when initially (arrow) exposed to the 100 dB L_{eq} sound (top); after a primary violent twitch the animal moved synchronously with the variation in sound level (middle); after a few days no reaction was seen (recording after 2 months).

ear due to age or other factors, or to poor performance in the measuring situation due to advanced age. The animals were 14–17 months of age at the initial behavioral training. This possible methodological error is at any rate the same for all groups of rats. The hearing loss as shown in Fig. 14 may thus be somewhat overestimated for all groups. The loss of auditory sensitivity in Box C (100 dB L_{eq}) has been extensively studied in later experiments, with an improved behavioral technique. The normal thresholds for young non-exposed N and SH rats are indicated as well as thresholds of rats exposed 15 months in Box C. *These additional experiments indicate that the hearing loss measured in the original groups was overestimated.*

ε. *Habituation to the acoustic environment.* At the initial presentation of the exposure sound in box C, a pronounced jerk, in some cases a jump, was observed. This reaction was succeeded by a catatonic behavior. The rats were standing rigidly, often facing the loudspeaker and swaying synchronously in time with the variations in sound level. On succeeding nights, the reactions were gradually reduced, and after about 1 week it was usually impossible to see any behavioral response at all when the sound began at 8 p.m. The animals in the control group ε were followed in more detail. A series of ECG recordings are illustrated in Fig. 15. At the first confrontation with the sound, a violent startle response, as well as the successive oscillatory baseline indicating body sway, is clearly seen. A definite increase in heart rate, in some but not all of the animals, was observed at the onset of sound during the first few nights (Fig. 16). The heart rate reaction was less pronounced as the night progressed and was not seen at all after 1 week of exposure. Minor muscular reactions (a twitch-like disturbance of recording base line) was observed at sound onset on several occasions for weeks after onset of the experiment. *In conclusion, a rapid habituation was seen both for behavioral and cardiac responses.*

b. *Life span and patho-anatomic observations*

α. *Life span.* The mean (± S.E.M.) life span of N and SH rats in the different sound environments is illustrated in Fig. 17. The SH animals are seen to have a somewhat shorter life span than the N ones ($p<0.004$ for males). The SH males have a shorter life span than SH females ($p<0.0002$). No significant difference between the different sound environments is present (Fisher's exact test).

A more detailed picture of longevity is given in Fig. 18. Survival rate as a function of age is shown

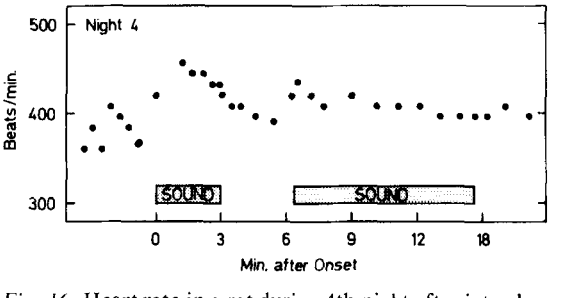

Fig. 16. Heart rate in a rat during 4th night after introduction into box C (100 dB L_{eq} sound). The dots to the left of time zero have been obtained at different periods during the day, i.e. during sound-free conditions.

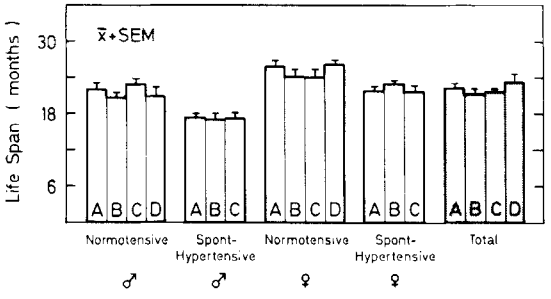

Fig. 17. Mean life span (+ S.E.M.) of 227 rats living since 3 months of age in the different sound environments. A: sound-isolated box, non-exposed; B: sound-isolated box, 80 dB L_{eq}; C: sound-isolated box, 100 dB L_{eq}; D: external controls, ordinary animal room.

for the SH and the N animals in the three sound environments. All curves follow each other closely. During the second year a tendency towards a deviation from that of the control animals and the animals in the environment C can be seen for the rats in environment B. *The median life span for the N females in environment B is shorter (not significant, Fisher's exact test) that the corresponding females in the control environments (A). There were no other trends visible in the statistical analysis.*

β. Disease panorama. At autopsy all pathologic organ lesions were noted. Since the pathologist was unaware of the animal strain and the exposure history, it seemed possible to obtain significant information merely by comparing the total number of diagnosed disorders in the different groups. Fig. 19 shows the mean values (+ S.E.M.) of the total number of diagnosed organ lesions in the two strains of rats in the different sound environments. *It is clearly seen that there are no differences with respect to sound environment, neither for N nor SH animals.* The SH animals, however, had a higher incidence of organ pathology than the N ones, irrespective of environment. In order to establish differences with respect to specific diseases a considerably larger amount of material would have to be available. Some information can, however, be obtained from a closer study of the present material, i.e. by looking at classes of diseases rather than individual entities.

The distribution of autopsy data from the total number of 225 animals autopsied is illustrated in Table I. The number of animals with organ lesions in 12 main diagnostic groups is illustrated for N and SH animals in the three sound environments. There is a higher incidence of cardiovascular disease in the SH groups and in the N males. Renal disease (chronic nephrosis) is most common in N females and is also frequent in N males. Endocrine disorders (adenoma, bleeding) are found in 50–70%

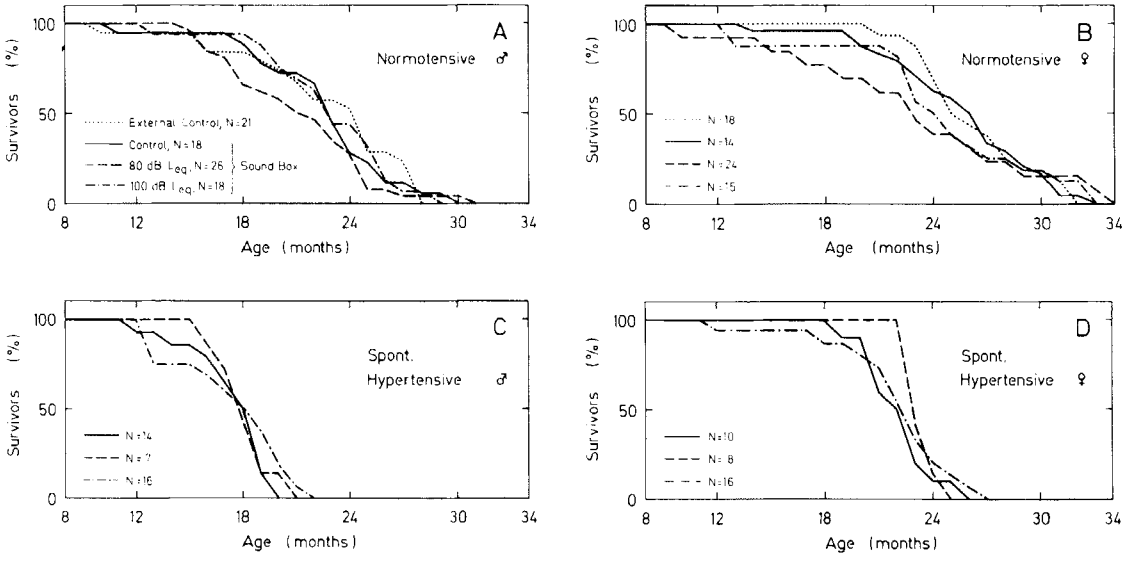

Fig. 18. Survival rate (percentage of animals living as a function of age) in a total of 227 normotensive and spontaneously hypertensive rats living in one of four environments from the age of 3 months. A: normotensive males; B: normotensive females; C: spontaneously hypertensive males; D: spontaneously hypertensive females.

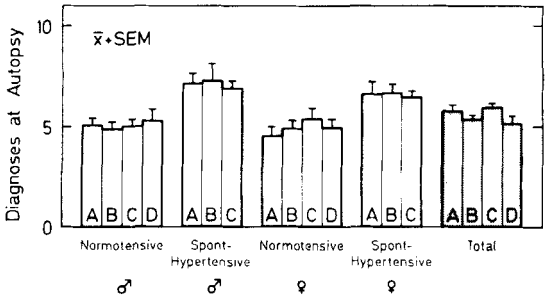

Fig. 19. Mean (+ S.E.M.) of number of diagnosed organ lesions at autopsy of 227 rats living in different acoustic environments from 3 months of age. A: sound-isolated box, non-exposed; B: sound-isolated box, 80 dB L_{eq}; C: sound-isolated box, 100 dB L_{eq}; D: external controls, ordinary animal room.

of the animals at the time of their natural death. Benign tumors are common in females. This category is constituted nearly exclusively of mammary fibroadenoma. Malignant tumors are rare among SH rats partly, at least, because they die early of cardiovascular disease. In the N groups 20–40% of the animals have malignant tumors. The differences between groups were statistically tested (median test). SH animals had significantly more cardiovascular disease than N rats. The difference with respect to liver thrombosis was especially pronounced ($p<0.00001$). The N females had little heart disease [less than N males ($p<0.0003$) and SH females ($p<0.0002$)]. The SH females, however, had more benign tumors than N males ($p<0.01$) and N females ($p<0.05$). The N males had more malignant tumors than the females ($p<0.05$).

The animals from the three sound environments differed only in a few cases with respect to the incidence of organ pathology. There was a tendency to a higher incidence of heart disease in N males in C than in A ($p<0.1$). The most remarkable difference was seen for malignant tumors. N males in C had significantly more malignant tumors than the control rats in A ($p<0.02$). However, the highest incidence was seen in the control rats in the ordinary animal department ($p<0.003$ compared to the N animals in A). It might not be possible to completely disregard the difference between A and C but the investigation would have to be redone on a very much larger number of animals before firm conclusions could be drawn. At present, little if any weight should be given to this observation.

No systematic differences with respect to organ weight have been observed (Table II).

In summary, the present findings show that rats

Table I. *Organs lesions at autopsy* (%)

Rat group		Number of animals	Cardiac	Periph. vasc.	Endocrine	Gastro-int.	Genital	Renal	Pulmonary	Other diagnoses	Mal. tumor	Ben. tumor	Liver	Infection
Male														
Normotensive	A	18	89	50	89	22	28	94	33	17	0	22	11	17
	B	26	6°	65	65	27	19	100	8	19	15	23	12	19
	C	18	67	44	61	11	17	100	17	28	39	11	22	39
	D	21	62	52	67	14	10	91	14	14	43	19	24	38
Spont. hypertensive	A	14	100	86	64	57	64	93	86	7	0	7	14	29
	B	7	100	100	86	71	29	100	71	0	0	14	0	43
	C	16	100	100	69	38	38	100	88	0	0	13	13	31
Female														
Normotensive	A	14	29	43	50	29	29	71	7	29	29	79	36	7
	B	24	29	46	54	29	50	63	13	50	17	67	25	13
	C	15	40	47	60	30	53	80	7	30	27	80	30	7
	D	18	6	61	67	17	44	50	28	6	17	78	28	11
Spont. hypertensive	A	10	100	80	70	40	20	100	30	30	10	50	30	10
	B	8	100	88	88	50	25	100	38	0	13	13	63	13
	C	16	88	86	88	31	19	100	63	31	0	38	13	0

Table II. *Organ weights (g)*

		Body	Heart	Adrenal glands	Kidneys	Liver	Spleen
N ♂	A	443±20.5	2.46±0.12	0.102±0.009	5.27±0.31	20.2±1.5	0.995±0.119
	B	395±15.9	2.36±0.07	0.182±0.032	5.15±0.22	18.9±1.7	0.876±0.132
	C	448±37.3	2.50±0.09	0.134±0.010	5.75±0.35	21.3±1.7	0.933±0.083
	D	418±32.3	2.34±0.14	0.176±0.062	4.69±0.33	18.1±1.3	0.879±0.095
SH ♂	A	340±10.4	2.84±0.13	0.101±0.009	3.25±0.11	15.9±1.3	0.475±0.061
	B	346±16.7	3.34±0.19	0.104±0.003	3.73±0.13	17.0±1.7	0.437±0.092
	C	350±13.4	2.68±0.10	0.096±0.006	3.04±0.08	15.4±0.8	0.375±0.027
N ♀	A*	350±28.7	1.71±0.14	0.173±0.054	2.77±0.23	14.9±1.8	0.826±0.166
	B*	349±36.4	1.86±0.11	0.127±0.012	2.95±0.16	14.2±1.4	1.146±0.320
	C*	453±37.7	1.89±0.13	0.121±0.014	3.01±0.15	16.5±1.5	0.792±0.117
	D*	453±37.0	1.88±0.08	0.116±0.009	2.87±0.22	17.4±1.4	1.585±0.371
SH ♀	A	223±12.9	1.94±0.13	0.113±0.012	2.13±0.07	10.1±0.8	0.479±0.069
	B	223±18.4	2.03±0.17	0.117±0.012	2.18±0.12	11.5±1.6	0.446±0.071
	C	203±10.4	1.79±0.13	0.112±0.007	1.99±0.08	9.4±0.7	0.282±0.036

* Including mammary fibrom.

housed in an environment for most of their lives where they were exposed to sound of 85 or 105 dB SPL for ten hours a day did not show any significant changes in blood pressure, body weight, water consumption, life span or disease panorama. Hearing loss and lesions to the sensory cells of the inner ear were related to exposure level, duration and strain of the animals.

C. GENERAL DISCUSSION

1. Summary of experimental results

a) Short-term sound bursts induced a peripheral vasoconstriction, the size of which depended systematically on the acoustic features, sound level, duration, rise time and temporal pattern.

b) The acute reactions habituated, on the average after 1 hour, during continuous exposure at 80 dB SPL. Irregularity of sound stimulation delayed habituation considerably.

c) Repeated exposure to an interrupted frequency-modulated sound 10 hours per night (i.e. when the animals were normally awake) induced a transient response but no permanent physiological adjustments, organ pathology or change of life span. These findings were valid in a "risk group" of spontaneously hypertensive rats, as well as for rats with normal blood pressure.

d) Various degrees of hearing loss were observed after 1 year of exposure. The loss increased as function of exposure level and was more pronounced in the spontaneous hypertensive than in the normotensive animals.

2. Short-term reactions

The present results lend further support for the existence of "reflexive" reactions of the autonomic nervous system elicited by acoustic stimuli. The reactions obtained, however, were sensitive to habituation and were markedly dependent on non-acoustic features of the environment (e.g. temperature). A few points will be discussed below:

a) The graded, or all-or-none, nature of the autonomic reactions to sound.

b) The existence of particularly efficient "key"-sounds.

c) The habituation and the possibility of predicting long-term reactions (in the field) from short-term laboratory investigations.

The present results clearly indicate, in agreement with several earlier studies, that, on the average, the responses depend in a graded way on stimulus features (see e.g. Hovland & Riesen, 1940; Jansen & Rey, 1962; Berlin, 1963) but are in contrast to Sokolov (1963) and Gogan's (1970) viewpoint and also to some extent to that of Rosecrans et al. (1966). A scrutiny of single responses shows, however, that faint stimuli can give pronounced responses even if the average response value based on several stimuli in the same session, becomes low. The low mean values obtained at low sound level may be due to a more rapid habituation in this range, or the large responses might express

random variations. These large responses do not occur exclusively at the beginning of an experimental session, indicating that habituation is probably not the main reason. From a practical point of view, it is of little importance if responses are graded either because the reflex is indeed of a graded nature, or because there is a variable, intensity-dependent habituation phenomenon continuously modulating the responses. The total autonomous activation is likely to be very much the same in a variable acoustic environment.

"Key"-sounds, acoustic stimuli with extraordinary efficiency in activating the autonomous nervous system, are, if they exist, important to identify, both from the theoretical and the practical viewpoint. It is well known that specific sounds can elicit particular behavioural reactions in lower animals (e.g. frogs, Capranica, 1965; birds, Rydén, 1978). Such an acoustic feature, extraction and reflexive reactivity, is to be regarded as primarily innate. The responses to the "key"-sounds can, however, be modified, e.g. weakened by experience and conditioning procedure (Rydén, 1978).

Sound communication has also been analysed in lower mammals, e.g. rodent (Smith, 1975). A 22 kHz ultrasonic signal plays a particular role in communication and behavior in rats (see e.g. Anisko et al., 1979). Comparisons between sound of different frequencies have to include a compensation for the ear's sensitivity curve and also to the fact that sound at very low frequency may act directly on the body, and compare to the effects of infrasound on humans.

Sound at 50–200 Hz (100 dB) was found to be more efficient, than 20 kHz (100 dB) pure tones in rats (Lockett, 1970) in spite the auditory threshold at 150 Hz is at least 70 dB higher than at 20 kHz (Kelly & Masterton, 1977). In humans, Argüelles et al. (1962) found that highpitched sounds were more efficient than 150 Hz sound with respect to adrenocortical activation. Speech sounds are more annoying than e.g. fan noise (Purcell & Thorne, 1977). The differences may be due both to the information in the conversation heard and to the acoustic features of the speech sounds themselves. Comparison of speech sounds with different types of information content is an important task for future research (cf. Hormann, 1970, cit. by Cantrell, 1979).

A baby's cry or babbling has a profound effect on most humans, and a finger scraping on a wet glass surface causes most humans to shiver. The autonomic reactions to such "natural" sounds still have to be investigated and related to artificial sounds of similar acoustic features and to occupational sounds. A common feature of all such acoustic signals is the content of repetitive acoustic transients, slowly modulated in amplitude and modulation frequency.

Two important features separate short-term laboratory studies from long-term field studies. First of all, the temporal factors and thereby the possibility of developing habituation and sensitization. Secondly, the degree of complexity differs. In the field situation, numerous uncontrollable factors are likely to modify the reactivity of the organism to the acoustic stimuli. In the present study, we have observed the influence, e.g. of ambient temperature and general motor activity of the animal. The degree of the predictability and the control of the noise situation have been found to influence both physiological reactions and annoyance (Glass & Singer, 1972; Geer & Maisel, 1972). The acute response and the rate of habituation depend on the physiological state of the organism at the time of the exposure (the "Law of initial value", Wilder, 1950). Several pieces of experimental evidence can be mentioned in support of this law. Graul et al. (1976) tested the effect on plasma glucose and free fatty acids in *Gallus gallus* of 30-min daily exposure to 100 dB sound. The size, as well as the direction, of the reaction was markedly dependent on the initial value of the parameters. A saturation phenomenon in the release of corticotropine was found in experiments by Hiroshige et al. (1969). They showed that a standardized stress test resulted in a smaller physiological reaction if instituted when baseline activity in the system under study was high, rather than when it was low. The total level (background+increment) attained, however, was the same in both cases. The direction of change for blood pressure in rats exposed to shock was found, both with the respect to size and direction, to be dependent on the initial blood pressure value. Evidence was also presented for a different pattern of sympathetoadrenal response leading to a decrease, or an increase of blood pressure in relation to level of peripheral sympathetic activation during coping behavior or adreno-medullary activity related to disorganized escape behavior (see Mason, 1968).

The "Law of initial value" also has a relevance in the summation of simultaneous "stress factors".

Most investigations have been performed on the basis of a background of physical and mental rest. Such a condition is of course not representative for an occupational situation. Our observations indicate that rats in a relatively high degree of motor activity show smaller vasoconstriction responses to sound than rats at physical rest. There is also a negative correlation between heart rate and vasoconstriction which points in the same direction. These observations, however, have not been statistically analysed. The series of publications presented by Buckley et al. (p. 16 in the literature survey) also gives indirect support to this view. They used a combination of different neurogenic stimuli (light, sound and vibration, see also Hallbäck & Folkow, 1974). It was found that sound alone initiated a blood pressure response in rats (for several weeks) identical to that obtained during combined stimulation. The three simultaneous stressors gave a combined response considerably smaller than the algebraic sum of the responses to the stimuli separately presented. On the other hand, in other experiments, e.g. by Humphrey & Keeble (1975), a "background stress" has been found to increase response to an added stimulus. They observed discomfort reactions in monkeys subjected to various combinations of sound and light. A more detailed analysis of summation phenomena has been performed by Lind (1976). He investigated weak electric shocks, alone or in various combinations with broad-band noise with regard to avoidance reactions. The results showed that sound at 85 to 105 dB was more efficient than sound at 75 or 115 dB. Adding the electric shock did, however, not further increase the effect. The author concludes that summation of different stress stimuli is not linear. Since, in addition, a decline of response was seen at the highest sound level, prediction about the effects of complex stress situations would be very difficult. The role of background sound and the interaction of temporally spaced sounds is also supported by investigations of the startle reaction in rats. Various combinations of stimuli will result in an inhibition or a facilitation depending on level and temporal relation (Hoffman & Searle, 1968; Davis & Gendelman, 1977).

In order to utilize results of short-term studies for the evaluation of risks and prediction of chronic effects, habituation mechanisms have to be known in detail. Habituation is unfortunately not a phenomenon that is determined once and for all by the stimulus, or by the physiological process under study. It is influenced by numerous factors in the same way as the response itself. The "background stress" acts to slow down habituation as shown e.g. by Maltzman et al. (1971) and by Humphrey & Keeble (1975). This resistance has been further emphasized in experiments by Carroll & Pokora (1976). They showed that the habituation of physiological reactions in humans to a 75 dB sound was considerably delayed if the subjects were under stress (the fear of receiving an electric shock). On the other hand habituation to one sound does not reduce response to another sound (Rossi et al., 1959, cit. by Cantrell, 1974) or even to the same sound at a higher level (short-term reactions). Strangely enough, a situation which can be presumed to be associated with low background stress has also been found to delay habituation. Johnson & Lubin (1967) found that heart rate and finger vasoconstriction were slower during sleep than in wakefulness. The role of the information content of the sound stimulus or of the experimental procedures must be emphasized again. Since such features are difficult to control, some of the contradictory results may be explained on the basis of different information contents that have not been observed or described by the experimenter (see discussion by McLean & Tarnopolsky, 1977). The work by Bolme & Novotny (1969) showed very well how habituation to a sound was abolished when it signalled an electric shock or a period of physical work.

The experiments of Schreyer & Angelakos (1978) can be interpreted to show existence of a sensitization process. They found a slow rise of blood pressure in monkeys after several months in a noise situation in spite of the fact that no acute reactions were observed at all. Further substantiation of these results has to be accomplished.

In conclusion, it is doubtful if it is at all possible to use short-term experiments to predict chronic effects of sound in a complex work environment situation. Predictions may be possible if the environment is very carefully analysed with respect to physical sound properties, other environmental factors, information contents, personal control of the sound sources and estimation of background stress for each subject. The basic principles for interaction between these factors can be established in short-term and laboratory studies in man and animals, but the situation is far too complex to allow for predictions at present. Long-term stud-

ies are needed and are strictly possible only in model experiments on animals. A logical first step in such an analysis is to investigate if in a sound environment, as far as possible freed from other stressors and with a minimum of information contents, long-term physiological effects would appear. This has been the goal of the second part of the present study.

3. Long-term effects

a. *The validity of the long-term study*

Only small and unsystematic dissimilarities between exposed and non-exposed animals were observed in the present study except for a different degree of hearing loss. This "failure" can be due to:

1) Some factors in the experimental situation had blocked or were masking pathological effects of the sound exposure.

2) The animals in the control environment were subjected to factors having an effect comparable to the effect of sound.

3) The animals rapidly became deaf and therefore could not be affected by the sound.

4) The sound used was erroneously designed and "biologically inefficient", i.e. a sound with other physical parameters would have given persistent effects.

5) The animals had habituated completely to the exposure sound.

All handling and measurements constitute potential stress factors for the animals (see e.g. Popper et al., 1976). These factors form a background stress, equal for all animals (see 1 and 2 above). As pointed out above, the summation and interaction of different stress factors are very complex. Substantial precautions have been taken to minimize the differences between sound-exposed and non-exposed groups with respect to handling and other nonacoustic factors. In one respect, however, there was a difference, the rat's selfproduced sounds. Since the exposure sound was switched on during the rat's active time of the diurnal cycle (at night) the sound produced by the rats themselves was masked by the exposure sound in environment B and C. The self-produced sound carried information about events in the environment, e.g. about aggressiveness, and could possibly be a source of stress for the control rats (see comments to the work of Lockett & Marwood, p. 17). However, animals in environment B (85 dB SPL sound) hear the same type of information-carrying sound but only for approximately 2 hour a day, and in a prominently intermittent fasion (during the exposure pauses). The animals in environment C (105 dB SPL) probably had a temporary and permanent hearing loss sufficient to make acoustic perception of these relatively faint signals impossible. It is not possible to exclude this source of error. Since, however, the three groups did not differ with respect to the physiological parameters studied, this error is probably negligible.

Efforts were made to estimate the role of environmental factors in the experiment, as well as handling and measuring procedures. The most obvious factor that had to be considered was the blood pressure measurements. They involved a certain degree of restraint in wiremesh cages. Restraining is often used as a neurogenic stress stimulus and could therefore be expected to influence the blood pressure. However, it was found that the blood pressure of rats living to the age of 6 or 7 months in the sound-insulated boxes, but only subjected to one final blood pressure measurement had the same pressure as those rats subjected to repeated measurements during the same period. In a further control study, it was however, found that a group of male rats living in the department's ordinary animal room, and only subjected to one blood pressure measurement, had a slightly lower pressure than the experimental animals. No difference was found with respect to the female rats. A large number of rats were used for other blood pressure studies. The systolic pressure of these adult male rats was, on the average, 138 mmHg. In the literature, the systolic blood pressure of "normotensive rats" is usually around 140 mmHg (Borg & Viberg) or on the average up to 150 mmHg (young Sprague-Dawley rats, 250–300 g, Williams et al., 1979). Some older studies have shown considerably lower systolic pressure values, but the techniques used have been hampered by the poor control of tail blood flow (probably being artificially low, see Borg & Viberg, 1980). The blood pressure of our male rats is in the upper normal range, whereas the females had a pressure in the medium or low normal range. The large variability of normal systolic blood pressure values seen in different studies can be explained if one assumes that environmental factors and measuring procedures may cause a rise of blood pressure of 20–30 mmHg from the lowest value or 110–120 up to the highest, 140–150 mmHg.

The acoustic environment in an ordinary animal

department is determined by the activity of the personnel as well as that of the animals. According to Jobst-Schenk et al. (1977) sound level is about 70 dB (reference not given) during service work with peaks up to 100 dB. Upon completion of work sound level was 65 dB. They also identified peaks at 20 kHz (80–85 dB) generated by vocalization of the rats. The animals in the experimental group (box A) probably have had an environment with much less frequent disturbances, acoustic or otherwise, than the control animals in the animal room of the Physiology department. If the sound environment is of importance, one would thus expect the animals in box A to have a lower pressure than the animals in the animal department. This was not the case. *If the lack of difference between the animals in boxes A, B and C was due to the presence of blood pressure elevating factors, which in themselves so profoundly raised the pressure that further rise due to sound was negated (according to the "law of initial value") then it must mean that sound cannot under any circumstances cause a rise of blood pressure above about 150–160 mmHg, even in the presence of other "stress factors". A pressure of 160 mmHg is hardly to be regarded as pathologic in an adult or senescent animal.*

A further possibility for the lack of difference between exposed and non-exposed rats was "biological inefficiency" of the sound used. There are two reasons for discarding this possibility: 1) the behavioral reactions at the onset of the exposure were prominent; 2) the sound exposure caused a hearing loss.

A rapidly developing hearing loss indicating biological efficiency of the sound exposure may on the other hand abolish persistent effects of the sound on general body homeostasis. After 1 year's exposure, the animals in 85 dB sound had nearly normal hearing thresholds. The normotensive rats in 105 dB sound had a moderate hearing loss, while the spontaneously hypertensive ones had a severe loss. Since, however, hearing thresholds of the SH rats were obtained, at least up to 6 kHz, the animals could not be considered deaf in the frequency range of interest. In a more detailed follow-up study on the development of hearing loss in normotensive and spontaneously hypertensive rats, it was found that the hypertensive rats had a hearing loss of 50–70 dB at 12 kHz and above after 3 months, whereas thresholds at 3 kHz were practically unaffected (Borg, 1979). Even though hearing loss at the end of their lives might have been so severe that the hypertensive rats were on the border-line of deafness, *we found sufficient hearing during most of the exposure period to be able to exclude hearing loss as an explanation for the lack of long-term effects.* The highest threshold in SH rats after 15 months in Box C was 86 dB SPL (6 kHz). An inner-ear damage by noise is furthermore characterized by a considerable recruitment of loudness. A few dB above hearing threshold, the sound is perceived equally loud as in normal-hearing subjects but distorted and usually more uncomfortable. If recruitment does exist in rats with noise-induced hearing loss, loudness ought to be similar, irrespective of hearing loss, throughout the exposure period. Observations on the size of vasoconstriction in animals with noise-induced hearing loss support the idea of recruitment in these animals (Borg, unpublished). In those animals, the threshold for sound-induced vasoconstriction was 70–80 dB. Ten to 20 dB above this threshold the vasoconstriction reached a size comparable to that seen in normal-hearing animals 80–90 dB above threshold.

A rapid habituation with respect to behavioral and physiological reactions to the exposure sound remains as an explanation. Approximately 1 week after being in a noise environment, no movements could be observed when the sound was switched on in the evening according to schedule. Even 2 months after the initiation of the experiment, electric recordings of the animals housed in an especially designed cage (control group ε) showed a small artifact indicative of minimal muscle activity at the start of the sound in the evenings, but no alterations of heart rate were seen at that stage. *There is little doubt that habituation was fast enough to completely explain a lack of long-term physiological effects.* The rate of habituation observed in the present experiments seems to correlate well with the findings of Borrell et al. 1980. They studied brain dopamine and serum corticosterone in rats exposed 15 min daily to 110 dB at 500 or 4000 Hz. They found an initial effect which completely habituated within 6 to 8 days.

b. *Comparison with other long-term studies on animals*

The present investigation is unique in that the animals were followed from maturity to their natural death. It also differs from earlier studies in being designed to simulate a work environment from an

acoustic point of view as well as to pattern the procedure to the experimental animal's physiology (hearing range, sleep–wakefulness cycle). Some earlier studies indicate differences between exposed and non-exposed animals but do not provide a means of interpreting the observations in terms of health and disease. In the present study, a wider range of physiological parameters was studied in the same animals and moreover, life span and morbidity were determined for each individual animal, as an indicator of whether observed physiological changes implied abnormal conditions, or merely represented a physiologic range of variations. Earlier long-term studies in animals have attempted to furnish maximal—"neurogenic"—stimulation for the investigation of the mechanisms behind hypertension. In most studies the animals were subjected to a combination of various stimuli on an extremely intermittent and irregular schedule, usually both at night (during the normal waking-period for the animal) or during the day, when the animals were asleep. Detailed comparisons are therefore very difficult to establish.

In the literature survey several investigations from the 1940's and 1950's were reviewed (Medoff & Bongiovanni, 1945; Farris et al., 1945; Yeakel et al., 1948; Rothlin et al., 1953, 1956). In certain groups of animals, an intermittent noise exposure was followed by a moderate rise of blood pressure, usually not exceeding 160 mmHg. Rothlin et al. (1956) observed hypertension only in animals crossbred between wild rats and albino laboratory animals but not in albino animals. Farris et al. (1945) likewise found a rise of blood pressure only in "emotional" rats. Buckley & Smookler (1970) on the other hand, saw a rise of blood pressure in all Wistar albino rats, provided they were introduced into their experiments when still very young. The pressure in the exposed rats of Buckley & Smookler (1970) did not, however, differ from the pressure of the control rats (130–150 mmHg) followed for 6 weeks in later experiments by Smookler et al. (1973). The lack of effect in most studies on "ordinary" rats is consistent with our results on normotensive animals. The spontaneously hypertensive rats were included as a "risk" group of emotional animals, since they had been shown to be hyperexcitable in neurogenic stress situations (Hallbäck & Folkow and others). On the basis of Rothlin's observations on the "emotional" rats, one would expect a pronounced rise of blood pressure in the spontaneously hypertensive animals. No such effect was observed in our experiments.

The dissimilarities between the present results and those of some earlier studies have several explanations. The most significant reason is, as pointed out above, the nature of the acoustic environment. Intermittent exposure, day and night, can be expected to give rise to a less pronounced habituation than a more continual type of noise (Ising et al., 1974). This is also supported by the results of the present short-term experiment showing a very slow habituation to intermittent bursts in contrast with the fairly rapid habituation to a constant noise.

Another possible explanation for effects on blood pressure seen in some earlier studies is the existence of differences in handling and housing of control and experimental groups in these studies. Rats were exposed only a few times a week and the animals were transferred into a special exposure cage for a short period (Hudak & Buckley, 1961; Buckley & Smookler, 1970) or for longer periods (Farris et al., 1945; Yeakel et al., 1948; Rothlin et al., 1956). The control animals, on the other hand, stayed in unchanged housing conditions (Smookler, 1973 is an exception). It is therefore doubtful to what extent conclusions can be drawn from these earlier studies regarding the specific effects of sound. As pointed out above evidence exists that *optimal neurogenic stimulation can rise blood pressure to 160 mmHg at maximum.*

A transfer of animals between cages in connection with exposures may raise the level of "background stress" (Bronson, 1967) which in turn may slow down rate of habituation. Such a transfer is likely to be combined with a change of cage-mates, another potential stress factor (Henry et al., 1967; Alexander, 1974). The findings of Gardiner (1977) may also be of importance in this connection. She showed that social isolation, for as short as 5 days, induced a rise of blood pressure from 100 to 157 mmHg. In experiments where exposed and control animals have not been treated in exactly the same way such factors may have created differences between groups.

The technique for blood pressure measurements also differs between studies. Several earlier experiments are based on measurements of blood pressure in the hind foot of the non-anesthetized rat (Rothlin et al., 1956; Buckley & Smookler, 1970), whereas the present study utilized measurements in

the tail. No direct comparison between these two techniques has been presented. It has, however, been shown that the indirect pressure obtained in the tail of full grown male rats is 5–10% above the intra-arterial pressure, whereas it is 5–10% below the intra-arterial pressure in females (Borg & Viberg, 1980). Such systematic errors may explain the difference between males and females and also be the reason for the fairly high pressure of male control animals in the present study (140–150 mmHg), but not the lack of difference between exposed and non-exposed rats.

As pointed out above, a possible reason for the lack of difference between the control and the exposed animals might be an uncontrolled stress factor giving rise to physiological reactions blocking the effect of the sound. Even though the background has not been stress-free, which besides being unrealistic was never intended, nothing has appeared which makes it likely that "background stress" differs between exposed and unexposed animals. Even though the question of the effect of background stress can never be fully elucidated in the present experiments, it should be noted that blood pressure did not exceed 150–160 mmHg even in senescent normotensive animals. Therefore, two possibilities remain: a) Sound does cause a small rise in blood pressure, but this rise is obscured by minimal background stress (or other environmental factors) blocking the increase of pressure; b) Sound does not produce any long-term changes at all. In either case, *sound environment cannot be regarded as harmful, since 150–160 mmHg of systolic blood pressure can by no means be regarded as pathologic in old individuals.* It should be especially noted that even those animal experiments, in which effects of intermittent sound exposure were shown, the systolic blood pressure did not exceed approximately 160 mmHg.

c. *Longevity and pathology in comparison with other rat colonies*

The life span of rats is dependent on numerous factors making only rough comparisons possible. It is known that dietary factors (e.g. Dalderup & Visser, 1971), both qualitative and quantitative, influence longevity. McCay et al. (1943) found a median life span of 531 to 680 days for male and 610 to 737 for female rats on "normal" diets with a somewhat different composition. Animals with restrained diets lived considerably longer (McCay et al., 1943; Nolen, 1972). Male rats allowed to mate once a week had an average life span of 734 days whereas unmated groups only lived for 578 days (Drori & Folman, 1969). For large groups of "normal" Wistar rats median life span of 710 days was given for males and 805 days for females (Gsell, 1964) and 645 and 749 by Festing & Blackmore (1971). Berg & Harmison (1957) obtained median values for a colony of 850 Sprague-Dawley rats to about 750 days for males and 900 days for females. They, however, excluded rats with symptoms of respiratory disease and insufficient weight development. It is evident that our control groups (box A) compare very well with these data (about 700 days for males and 800 for females, especially considering lack of mating experience).

The spontaneously hypertensive rats were more shortlived, an average of 520 days for males and 650 days for females. This is in the upper range of the interval of 3 to 20 months given by Okamoto (1969, see also Okamoto et al., 1973).

The incidence of chronic disease and cause of death in the control groups can be compared e.g. with the data presented by Simms & Berg (1957), Berg (1967) and Simms (1967) and for spontaneously hypertensive animals by Okamoto (1969, 1973). The Sprague-Dawley rats have, to a very large extent, renal disease (polycystic nephrosis, chronic nephrosis) which agrees with Simms & Berg (1957) and Cotchin & Row (1967). Myocardial degeneration and fibrosis is common especially in hypertensive male rats (Berg, 1967; Simms, 1967; Okamoto, 1969). Muscular degeneration was not searched for in our autopsies, but hindlimb paralysis was a common clinical finding in old Sprague-Dawley rats which agrees with the observations of Berg (1956) and Nolen (1972).

The only pathological feature where a tendency to difference could be traced between exposed and unexposed animals was the incidence of tumors. The high incidence of endocrine tumors in all groups agrees well with the values given by Davis et al. (1956) and McKenzie & Garner (1973). The higher incidence of tumors in 105 dB sound should be interpreted with great care, both due to the small number of diagnosed tumors, and with regard to the fact that the largest number of tumors was observed in the control group housed in the department's ordinary animal room.

In conclusion, no difference has been found between the present rats and rats analysed in other

long-term studies, with respect to life span, biological development, physiological function, incidence of disease and cause of death.

d. *The validity of the acoustic environment as a model for occupational noise exposure*

Two main factors limit the application of the present results to work environment:

a) Differences (simplifications) in the acoustic environment.

b) Species differences, discussed on page 55.

Occupational noise is not a uniform and simple phenomenon, and therefore, the exposure sound in the present model is designed to simulate only some characteristics, regarded as essential and common to most real "noise environments".

The following features may be observed:

1) Individuals are sound-exposed only when fully awake.

2) The fine structure of the acoustic environment is continuously varied.

3) There are predictable pauses in the sound.

4) The frequency and intensity range is adjusted to the hearing range of the animal.

5) The sound environment causes damage to the inner ear.

The aim has been to simulate only some basic features of the acoustic environment and it is self-evident that the industrial noise situation cannot be totally simulated in experiments on rats in cages. Some obvious differences can be mentioned:

1) Real occupational environments may have more variable—or more stationary—acoustic features.

2) The sound in the model does not carry information (at least not intentionally).

3) The sound does not mask communication sounds (neither warning signals nor speech) to the same extent as in a human work environment.

4) The distracting effect and the masking of "inner speech" also differs.

5) The sound in the exposure boxes is generated by horns always located in the same place. The animals have been shifted between various positions in the cages but they most likely had no difficulty in localizing the sound source from new positions. The real "noise sources" are often, but not always stationary and habituation can be expected to be delayed by changes in location.

6) An occupational environment possesses a much greater variety of other factors which can interact increasing or decreasing the effects of the stimulus sound. Likewise the model contains a much smaller range of individual variations, only one risk group is included.

It is at present impossible to evaluate the role of these differences. They have to be investigated in further experiments. It is only with respect to the degree of intermittency and predictability that some data are available. In earlier animal experiments, the sound exposure used has been highly intermittent, having very little similarity with a work environment where sound is both fairly continuous and for the most part predictable. The most important difference between the sound model in the present study and a real-life situation is probably related to the information contents of the sound. In the model, sound only informs about its own presence and not about any other event in the environment that the animals have to observe or react to. Evidence exists that information-carrying sound is prone to generate more pronounced and more slowly habituating physiological responses (Aceto et al., 1963; Bolme & Novotny, 1969; Herd et al., 1969) than neutral sound. The role of the information aspect has to be evaluated more fully in future experiments.

In conclusion, the exposure used forms a reasonable model for the acoustic aspects of an occupational environment. It should be noted that the present environment is not designed to be optimal for production of "neurogenic" hypertension.

4. Animals–humans, role of species differences

Most studies of physiological reactions to sound, both short-term and long-term, have been performed on rats and humans, a few on monkeys, dogs, sheep, rabbits, mice and fowl. Differences between species have been observed. Even within the most used species, *Rattus norvegicus*, differences have been found between various types and strains. In the literature survey it was e.g. pointed out that Farris et al. (1945), Medoff & Bongiovanni (1945), Rothlin et al. (1953, 1956) only observed an effect of blood pressure in certain strains characterized as "emotional" or "reactors", or cross-bred between laboratory rats and wild Norwegian rats. This pronounced, constitutional component can thus be observed in the pattern of reactions to "noise" and is further emphasized by the existence

of strains of animals sensitive to audiogenic seizures (see also Hallbäck & Folkow, 1974). The observations of Morley & Abelson (1975) and Morley et al. (1977) further support the role of genetic factors. They have succeeded in breeding a strain of rats showing abnormally strong averse reactions to sound. On the other hand, it is clear that certain basic reactions to sound occur in most species (see literature review).

The two strains of rats used in the present study were selected to represent both average and "high risk" individuals. The spontaneously hypertensive ones are characterized by exaggerated short-term reactions to sound and constitute a group of "reactors", in a way similar to humans with latent hypertension (Argüelles et al., 1970; Lorimer et al., 1971). These rats are regarded as a good animal model for "essential hypertension" in humans and probably constitute the most sensitive risk group regarding cardiovascular reactions to sound in animals.

The validity of a model must be assessed on the basis of comparisons of predictions based on the model and observations on the "original". Since a comparable long-term study on humans has not been made—and cannot be made—it remains only to compare short-term data. Peripheral vasoconstriction is one common physiological reaction which can be observed in humans and animals under similar circumstances. The rat has been found to be far more sensitive to sound than humans with respect to this system. The threshold is lower and the size of the responses is much larger in the rat (see Jansen, 1974 and Borg, 1977 for a comparison). Most observations on other physiological systems also indicate that humans and animals react in the same way to sound stimuli, but animals are usually more sensitive.

In conclusion, species differences with respect to physiological reactions to sound exist and point towards a higher sensitivity in animals than humans. The model work presented in this study obviously supports the idea that an environment with pseudo-constant, "neutral" sound, exposing humans while awake and active, is no threat to health except for a loss of hearing sensitivity.

IV. General Summary

The acoustic influence on various somatic functions (excluding the auditory system proper) and the possible effects on health, especially with regard to conditions in occupational life have been reviewed. A description of a series of experiments on rats aimed at detecting the physiological and pathogenic effects of sound has been presented. Since the concept "noise" defined as unwanted sound has been unsuitable and inapplicable within the context of these animal experiments, the discussions, therefore, were referred to sound in general.

While the literature survey shows a large number of contradictory ideas and information, there is little doubt that cardiac and vascular, as well as hormonal, somatic and somato-sensory systems can be influenced by short unexpected bursts of sound. No direct evidence for chronic influences on humans has been established, but, in some animal experiments, extremely intermittent sound exposure, day and night, has been found to cause a moderate rise of blood pressure. Several field studies indicate that employees in industries with high sound levels have a higher incidence of disease than employees in industries with low sound level, but little evidence exists for sound being anything more than an epiphenomenon without direct responsibility for generation of disease.

In the present study it has been shown that sound induces alterations in peripheral blood flow in non-anesthetized rats, and that the magnitude of these effects is systematically dependent on the properties of the sound as well as on other external and internal factors such as habituation and level of motor activity. In a milieu experiment including life-long exposure to meaningless sound simulating an occupational situation, rats were studied from the physiologic and patho-anatomic view. No difference with respect to blood pressure, body weight, water consumption, life span and incidence of disease between control animals and exposed animals was observed. This was true both for the "normal animals" and for "risk animals", i.e. rats with genetic disposition for high blood pressure. Hearing loss of various degrees was observed indicating that the environment, at least from one point of view was realistic.

In conclusion, in spite of the fact that sound gave very pronounced short duration reactions in rats, no chronic effects were observed during prolonged exposure. This observation suggests that any possible harmful effects of sound, if they exist, may be searched in relation to information content of the sound—information pertaining to risky actions or masking significant information—rather than to sound itself.

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