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Concerning The Need for More Sophisticated Animal Models in Sensory Behavioral Toxicology

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It is necessary but not sufficient to develop laboratory animal models in sensory behavioral toxicology for screening toxic substances and for the analysis of sensory impairment at threshold levels of stimulation. It is important to develop more thorough and quantitative tests of impairment which in their greater complexity more accurately reflect the conditions and environmental demands of day-to-day life. Such greater complexity in stimulus conditions and behavior may also aid in monitoring not merely the state of the receptor organ but more central nervous processes which are the focus of assault by many known toxic substances. Techniques are described for studying such acoustic behaviors as intensity discrimination and frequency selectivity in guinea pig and monkey by use of operant conditioning procedures coupled with sensory testing (psychophysical) methods. Impaired auditory selectivity and discrimination is shown to be correlated with histopathological changes in the inner ear. Slight modification of these procedures in animals may be used to investigate acoustically more intricate behaviors such as sound localization and the perception of frequency modulated acoustic signals as elements of speech and communication sounds.

One class of animal models in the study of behavioral toxicology has an obvious appeal because of its simplicity. The canary in the coal mine is an old and familiar example: it was an all-or-nothing proposition. If the carbon monoxide in the mine reached a certain level, the canary died, and it was time for the men to get out of the mine. This was not, however, a model which invited further and more detailed analyses of the behavioral effects of the toxic substance. The canary did not stop singing, for example, at lower levels of carbon monoxide, nor were there observed changes in other forms of canary behavior as a consequence of the pollutant. It provided a simple, reasonably effective model for behavioral toxicology but one with a somewhat limited scope.

To better understand the effects of toxic substances on behavior and the toxic process, we need a more informative canary—one that can tell us not only that things are getting bad before they have gone beyond the point of no return, but also one that tells us where it hurts so that we can discover specific processes and physiological mechanisms which may represent target sites for the toxic substance in question. Put in another way, we need a more sophisticated canary trained to answer in a quantitative fashion a number of very specific questions about the continually deteriorating state of its health brought on by exposure to some poison.

Clearly, animal models can serve a variety of very different functions in behavioral toxicology. For example, one essential approach involves the development of simple, highly analytic measures of behavior which are employed as baselines for the study of the effects of known or presumed poisons. Such behavioral measures as general activity, eating and drinking, seeing and hearing may be readily obtained, in some instances, from large numbers of animals, and may serve in the screening of a wide variety of toxic substances.

With regard to hearing, for example, we may be

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concerned simply with whether normal sound levels are audible to an animal without regard to the intensity or other characteristics of the acoustic signal. Observations of the pinna (ear flap) reflex, startle, or escape from a sound which foretells of impending electric shock all give us at least "rough and ready" measures of hearing in a more general sense. Few would question the need for such measures which may provide us with clear indications that something has gone awry in the environment. The advantages of such measures reside in the ease and relative quickness with which they may be obtained. Lengthy training time and complicated equipment are not necessary. Secondly, such measures can serve as an early warning system for the build-up of toxic substances in the environment and in the bodily tissues. Unfortunately, in return for speed and ease of training, some sacrifices must be made in the level of sophistication and complexity of the information obtained by these procedures and sometimes even in its validity and reliability.

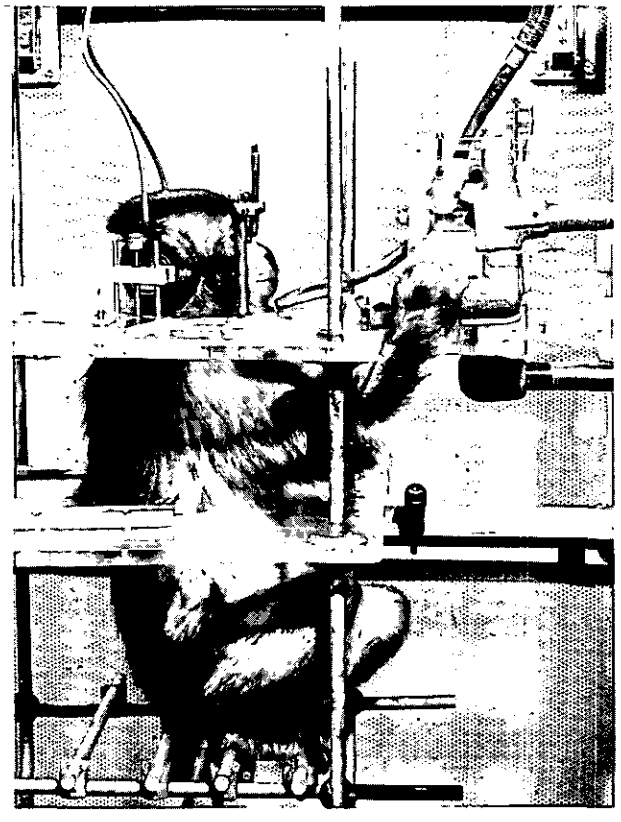

FIGURE 1. Subject, a macaque monkey, seated in restraining chair for hearing testing. Earphones, cylindrical response tube, and feeder tube are shown. The monkey is in listening position with his hand grasping the response tube prior to tone stimulation (*2*).

It becomes important to probe further once it is clear on the basis of the preliminary results obtained from these simpler screening procedures that some form of behavioral impairment has resulted from exposure to a toxic agent. Some form of scale is necessary which will relate the degree of impairment to the quantity of and duration of exposure to the poison. Its time course of action is equally important and makes this more than a simple dose-effect curve. Daily or even hourly monitoring will reveal the earliest signs of damage, but such extensive testing precludes mass screening with large numbers of animals. The hope is for a much more detailed behavioral profile of action of the toxin. To establish such a scale in an animal model requires lengthy behavioral training regimens and often fairly elaborate instrumentation. There is presently no viable alternative.

A particularly relevant example may be found in the threshold testing of monkeys by using simple operant conditioning methods with food reinforcement (*1*). In about two months, animals fresh from the jungle learn to report through a computer when an acoustic stimulus, briefly presented, is just audible. The monkey seated in a chair (Fig. 1) responds to a flashing light by touching a metal tube. Contact with the tube is maintained until the sound is presented through earphones. If the animal then removes its hand from the tube while the sound is on, reinforcement in the form of a small food tablet follows immediately. Time-out from the experiment—a delay in food availability—is a form of punishment given for responding when the sound is off. Thresholds are determined by reducing the intensity of the stimulus after it is correctly detected and increasing its intensity following the subject's failure to respond to it. A tracking method is used in which there is a feedback loop between subject

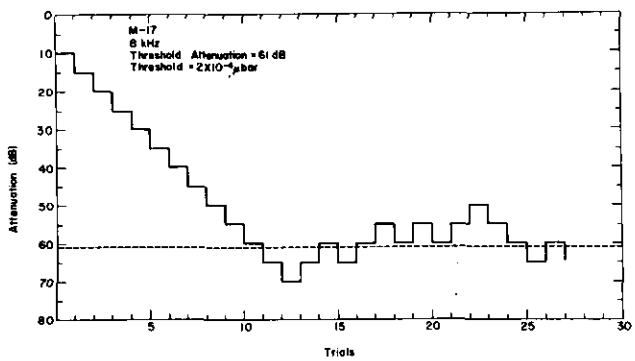

FIGURE 2. Use of the tracking method for audiometric testing of monkeys. Correct detections cause the tone to be attenuated in 5 dB steps, while failure to hear produces a subsequent 5 dB increase in tone intensity (*3*).

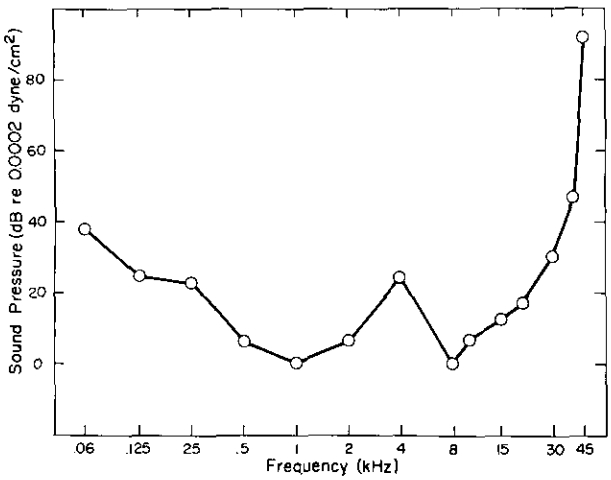

FIGURE 3. Threshold of hearing function for macaque monkey (2).

and stimulus; the record of responses to the stimulus resembles an up-and-down staircase (Fig. 2). Threshold represents the stimulus value to which the subject responds correctly 50% of the time. Such thresholds are determined over a wide range of frequencies resulting in a function like the one in Figure 3, in which sound intensity at threshold is shown to vary over the animal's audible frequency range.

Threshold or the minimum detectable level of acoustic stimulation is affected by a variety of poisons and environmental pollutants. Aging in man brings with it a loss in sensitivity to high frequencies. The aminoglycoside antibiotics produce a similar effect, although in a much briefer time period. The characteristic picture of progressive hearing loss is seen in an experimental animal treated with the antibiotic, kanamycin (Fig. 4). The inexorable progression of the impairment from high to low frequencies is evident in this example. At a certain point in time, treatment is discontinued, and the subject tested over a further time interval for any delayed effects of the drug on hearing. The animal is then sacrificed and its temporal bones taken for microdissection and histopathological analysis of the organ of Corti of the inner ear. The results together with the terminal threshold measurements are shown in Figure 5. There is a striking correlation between the extent and pattern of receptor cell loss along the basilar membrane in the inner ear and the high frequency hearing impairment. The receptor cells and perhaps their supporting cells and the fibers of the auditory nerve are clearly implicated as targets for the site of action of this ototoxic drug (4).

Thresholds for tonal stimuli at minimum detectable levels of stimulation provide an important measure of hearing and may even offer some insight into underlying mechanisms particularly, as just described, for those agents whose primary destructive focus is within the inner ear. Such threshold measures, however, are limited in terms of the information they offer about the overall performance of the auditory system.

A primitive function of the auditory system is its ability in detecting low level acoustic energy—heavy feet on the substrate. In insects, most fish and in our early land-dwelling vertebrate ancestors, detection was the primary if not the sole function of the auditory system. Its currency pur-

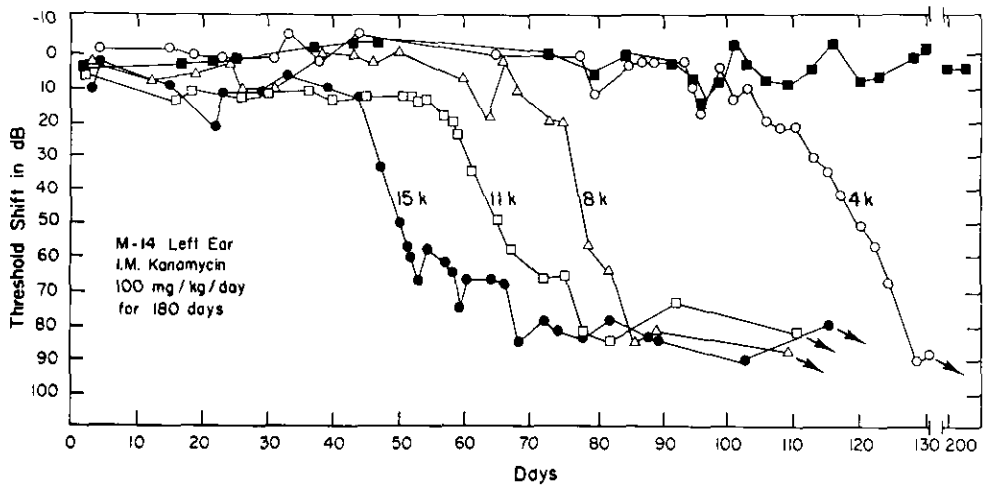

FIGURE 4. Progressive changes in threshold for one macaque monkey for different acoustic frequencies during daily kanamycin treatment. The zero line represents normal hearing at all frequencies prior to drug treatment (4).

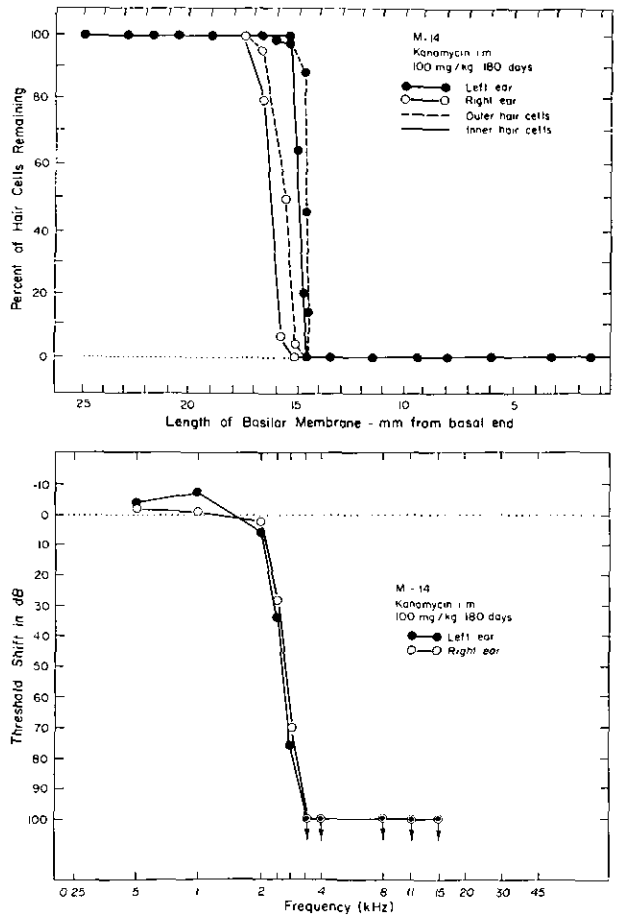

FIGURE 5. Auditory threshold shift for the monkey represented in Fig. 4 after 180 days of daily kanamycin (lower panel); hair cells remaining as a function of position on basilar membrane (upper panel) (*3*).

chased a mate, a meal, and on many occasions helped an animal avoid being included on someone else's menu. In the living mammals, particularly the primates including man, a more highly evolved auditory system plays a much more complex and diverse role. Beyond simply detecting acoustic events in, for example, an early warning mode, it is highly discriminating on the basis of acoustic frequency, intensity, time and timbre or acoustic complexity. Effective communication assumes that the normal listener is able to make fine discriminations in all these dimensions. The physical distinction between "bad" and "dad", for example, lies in the initial 50 msec frequency transition upward or downward depending on whether the first letter is a "b" or a "d". The putative higher vertebrates also are very accomplished in locating with considerable precision the source of a sound in three-dimensional space, a skill which has given them the edge over their less capable forebears in capturing prey, avoiding predation, and finding a mate.

In order to comprehend fully the normal or the impaired auditory system, it is essential to examine functions other than those involved in the simple detection of acoustic signals. The questions assume a higher level of complexity and, in so doing, approach more closely the state of affairs in the real world. Many signals, for example, are clearly audible to us, but it is often important that we be able to locate their source and accurately determine their direction of movement. These are biologically important activities in daily use and they assume an intricate interplay between the auditory system and the rest of the central nervous system. Deterioration in the skill with which these activities are performed implies something regarding the nature and location of the deficit in the nervous system. If, in addition, the responsible agents are neurotoxic substances, we stand to gain information regarding their locus and mechanism of action.

A broad spectrum of biologically relevant acoustic behavior should be considered for study and use as baselines for toxicological intervention. In addition to sound localization, these behaviors include differential acuity for acoustic frequency and intensity, discrimination of the complex acoustic signals used in speech and communication, judgment of loudness, and the ability to extract a signal from a noisy background. All are functions, which like sound localization, play a substantial role in our daily lives. Although their impairment is seldom life-threatening it may presage far more harmful consequences to other bodily systems as a result of continued exposure to the noxious substance.

Only recently have the conditioning techniques which have been applied successfully to the measurement of thresholds in experimental animals been extended to the analysis of more complex auditory functions. It is a major purpose of this paper to describe some of the experiments that have been carried out in order to demonstrate their potential for a full scale analysis of hearing and ototoxic hearing loss in animal models. Again, these are not procedures which lend themselves easily to the screening of large numbers of chemical substances in large numbers of animals. The procedures described here are arduous, time-consuming, and heavily instrumented. Their virtue lies in their ability to provide exact quantitative behavioral measures of a variety of hearing functions. Together with physiological, biochemical, and anatomical measures they can aid in pinpointing basic mechanisms and thus offer a logical and far more detailed follow-up of basic toxicological screens than simple threshold detection functions.

Operant conditioning procedures, together with sensory testing (psychophysical) methods, provide an effective means of questioning a nonhuman animal about the limits of its sensory experience. A slight modification in the basic threshold testing protocol described earlier permits the sampling and accurate measurement of a wide range of such experiences. For example, the ability to discriminate small differences in the various parameters of an acoustic signal (i.e., intensity, frequency, etc.) permits an animal or man to respond to the most subtle differences in communication sounds or language. Loss of this ability in the hearing impaired produces a distinct handicap and may or may not be correlated with a significant loss in detection threshold. In evaluating the limits of this ability, the subject is asked to report the smallest discriminable differences between two sounds (usually tones).

In a recent experiment (*5*), guinea pigs were trained to report such minimal differences in the intensity of a pure tone. Their pure tone detection thresholds were also determined. The animals were operantly conditioned to depress a small switch in the floor of their test cage in response to a flashing light. Depression of the switch initiated a trial which included a series of tone pulses at fixed intensity. After a brief but varying time interval a tone pulse of higher or lower intensity alternated twice with those pulses in the initial pulse train. If the animal responded to this change in sound intensity by releasing the switch, it was reinforced with food. Release of the switch at any other time was followed by punishment in the form of a time-out from the experiment. When the intensity difference was correctly reported by the animal, that difference was reduced on the subsequent trial; however, if the animal failed to report the intensity difference by continuing to depress the switch, the difference was subsequently increased. The testing procedure was a variation on the original threshold procedure described earlier and yielded a quantitative measure of intensity difference threshold as that difference correctly reported by the animal on 50% of the trials. Normal values obtained from several animals were found to be reliable and stable and only slightly larger than values obtained for human subjects.

The guinea pigs were then treated daily with the antibiotic kanamycin for about two months. Their hearing was assessed daily either by the conventional threshold procedure or by the intensity discrimination threshold method. Typical results are presented for one animal. (Fig. 6). In the lower function, the detection threshold results are displayed. At this test tone frequency of 8 kHz, the animal experienced a rather sudden and precipitous

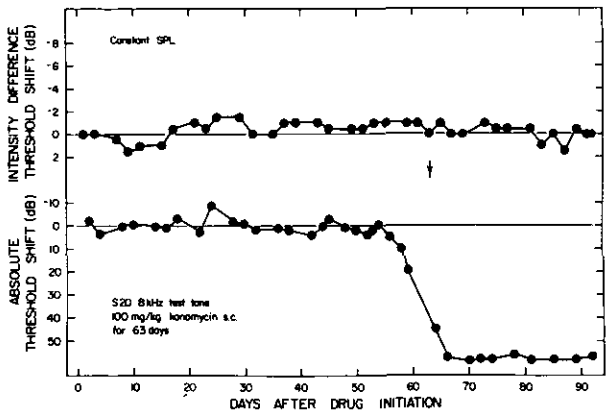

FIGURE 6. Intensity difference threshold shift (upper panel) and pure tone detection threshold shift (lower panel) at 8kHz as a function of days after initiation of treatment with kanamycin for one guinea pig. Arrow indicates cessation of drug treatment at 63 days (*5*).

hearing loss just prior to the end of the drug treatment. Although the hearing loss was considerable (about 70 dB), it was not complete. A particularly interesting finding, which was observed for all treated subjects, is seen in the upper function which represents the intensity difference threshold obtained during and after drug treatment for the same animal. The results merely reflect the stability of the measure over time, for no significant departure from baseline (at 0 dB on the figure) and thus no loss in intensity discrimination is evident throughout the treatment period or thereafter. Differential acuity for sound intensity was tested at sound levels well in excess of the threshold of hearing (70 dB) before drug treatment and thus only slightly above threshold (20 dB), which had been markedly altered, after drug treatment.

These results have important implications for behavioral toxicology, for they clearly indicate that, as a consequence of exposure to a toxic substance, one function of a sensory system may be drastically altered while another, seemingly closely related function, remains intact. Of further interest are the subsequent histopathological findings in the inner ears of those treated guinea pigs. Of the two populations of morphologically different receptor cells in the organ of Corti, the outer hair cells were missing from the basal half of the cochlea in these animals while the inner hair cells remained intact and appeared normal and were probably functional. It would be premature to state at this point that the missing outer hair cells reflect the considerable threshold shift, while the inner hair cells still in place, play an important role in acoustic intensity discrimination. The findings are suggestive, but

more importantly they exemplify the kind of conceptual issues which arise when behavioral toxicologists go beyond routine screening and simple detection measures. The basis for the effect of the toxic substance may now be explored more fully.

The ability to resolve small frequency differences in acoustic stimulation may be measured by a frequency discrimination paradigm similar to the one for intensity discrimination just described for the guinea pig. Another strategy involves the masking of one pure tone by another with the subject trained to respond when one tone, the test tone, is just audible above the second tone, the masker (*6*). A test tone, always of the same frequency and intensity (usually slightly above detection threshold), is presented together with the masker, a tone which is varied systematically in both intensity and frequency. Often the masker begins at a frequency well below that of the test tone; its intensity is adjusted by the tracking or staircase method and a threshold level of the masker is determined as that level that enables the subject to respond correctly to the test tone on 50% of the trials. The masker frequency is then changed and a new threshold for detection of the test tone is determined. The process is continued until an entire function—a psychophysical tuning curve—is generated. For animal subjects the conditioning procedure is a simple adaptation of the one described previously. The subject makes a contact response, holds, and then breaks contact when the test tone can be heard over the level of the masker. A psychophysical tuning curve for a monkey is shown in Figure 7. The test tone was at 2 kHz, 10 dB above the animal's threshold at that frequency. The masker frequency was varied from about 300 to 3000 Hz. A measure of tuning or frequency resolution is provided by the Q metric which is usually the test tone frequency divided by the frequency bandwidth of the function 10 dB above the tip. A family of psychophysical tuning curves obtained at different test tone frequencies for one monkey is shown in Figure 8, together with the underlying pure tone detection function.

These double-barrelled functions, measuring both frequency selectivity and threshold in the monkey, and intensity discrimination and tone detection threshold in the guinea pig, are distinctly advantageous, for two very different characteristics of the same subject's acoustic behavior may be evaluated simultaneously under normal conditions and following exposure to a toxic substance. Recent findings (*7*) indicate that frequency selectivity as measured by psychophysical tuning curves in chinchillas treated with kanamycin is unaffected at acoustic frequencies where the loss in threshold sensitivity is as great as 50 dB. Greater shifts in threshold were correlated with severely distorted tuning curves. Related histopathological findings from the inner ears of these animals suggest that when outer hair cells are missing from the cochlea no changes are observed in frequency selectivity; however, when inner hair cells in addition to outer hair cells are destroyed, impairment of frequency selectivity follows; psychophysical tuning curves are drastically altered.

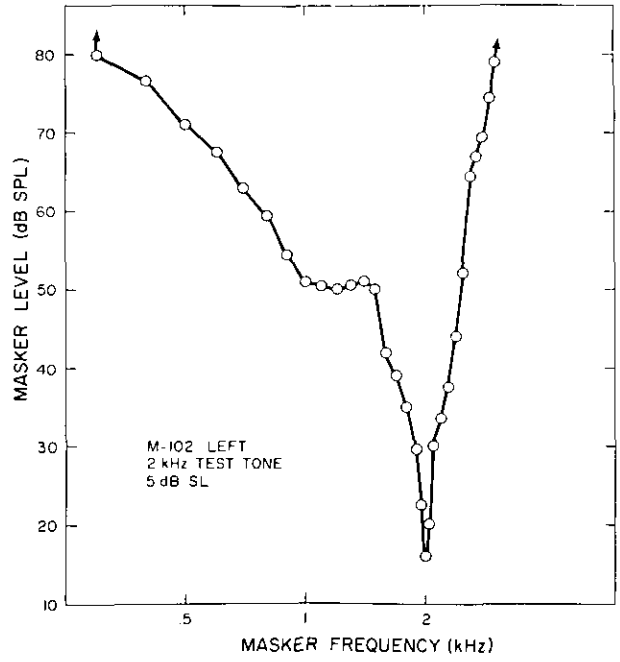

FIGURE 7. Psychophysical tuning curve for a macaque monkey (1).

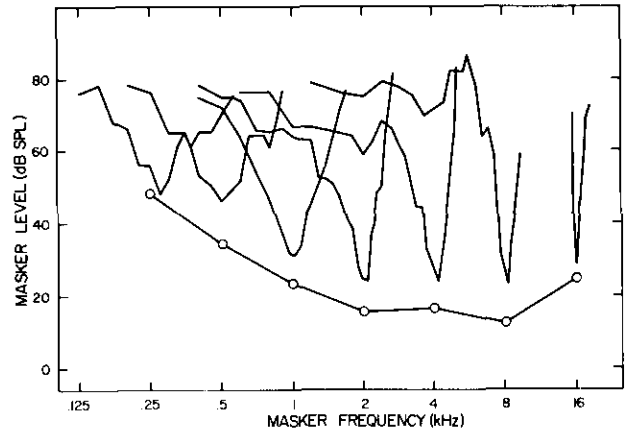

FIGURE 8. A family of psychophysical tuning curves shown with underlying pure tone threshold function for a macaque monkey.

Certain toxic substances, such as the aminoglycoside antibiotics, are highly specific in their action, which is confined to only one or two target sites such as the auditory periphery and the kidney. The behavioral measures just described reveal this form of specificity. Other substances—for example, those that affect the nervous system—appear to produce considerably more diffuse effects that are reflected in a broad spectrum of behavioral changes, often difficult to evaluate in a rigorous, quantitative manner. Some acoustic behaviors are under more central nervous system control and may be severely altered by auditory system changes which are not simply confined to the inner ear. The accurate localization of sound which requires the two ears depends on the integrity of certain structures in the brain stem and on higher levels in the nervous system. Discrimination of speech and communication sounds and other complex biologically relevant signals also appears to rely more on the integrity of central than peripheral structures. Sites in auditory and adjacent cortical regions have been implicated in both sound localization and in the perception of these complex signals (*8*, *9*). In attempting to understand more fully behavioral changes influenced by toxic substances and their underlying target sites, animal models must be developed for these more complex acoustic behaviors.

A procedure for studying sound localization in monkeys shows promise as a potential baseline for behavioral toxicological investigation (*10*, *11*). The procedure is yet another variant on those already discussed and requires the animal to respond whenever an acoustic signal changes location from a standard reference position in front of the animal. Sound sources are located on an arc partially surrounding the animal so that localization acuity may be measured by reference to the angular distance separating any given source from the reference. For example, with the reference sound source at the end of an imaginary line extending from the center of the animal's head between the two eyes to a position directly in front (in the line of regard or 0 degrees azimuth) and a second source at the end of a similar length line extending from the center of the head through one ear, the calculated angle would be 90°.

The preparation is pictured in Figure 9. The animal responds to a light, indicating the beginning of a trial, by closing a switch, and a series of sound pulses is produced from the reference sound source at zero degrees azimuth. In time, the sound shifts briefly to another location on the arc and then returns to the reference position. If the subject breaks contact by removing its hand from the switch when the sound source changes position, food reinforcement is given immediately. On subsequent trials the position to which the sound shifts is varied; acuity of sound localization is taken as the minimum audible angle—the angle in degrees between the reference and the new sound source location on the arc to which the subject responds correctly on 50% of the trials.

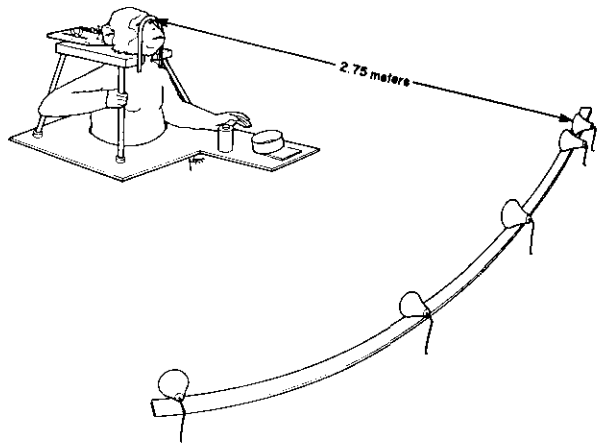

FIGURE 9. Schematic representation of a monkey in restraining chair. Response disk and feeder cup are shown together with arc containing loudspeakers. Reference speaker is indicated by the straight line extending from the center of the animal's head (*11*).

In Figure 10 the percentage of correct responses is plotted for three monkeys as a function of the angular separation in degrees of arc between the reference location and the other positions on the arc to which the sound was shifted. In this particular instance the acoustic signal was a pure tone at 8000 Hz. The acuity of sound localization as measured by the minimum audible angle was about 10° for the three animals. The small number of responses at zero degrees reflected the animals' guessing rate when the position of the source had not changed. It is well known that experimental lesions in the auditory portion of the nervous system will produce severe deficits in sound localization ability (*12*); however, the use of the sound localization paradigm in behavioral toxicology has not yet been entertained.

The processing and perception of complex biologically salient acoustic signals like sound localization is a form of acoustic behavior which is of critical importance in the daily life of man and other mammalian vertebrates. Like localization this behavior shows evidence for central as opposed to peripheral nervous control. Animal models for the analysis of this form of behavior in the laboratory have been and are currently being developed. We know that some animals, other than man, have

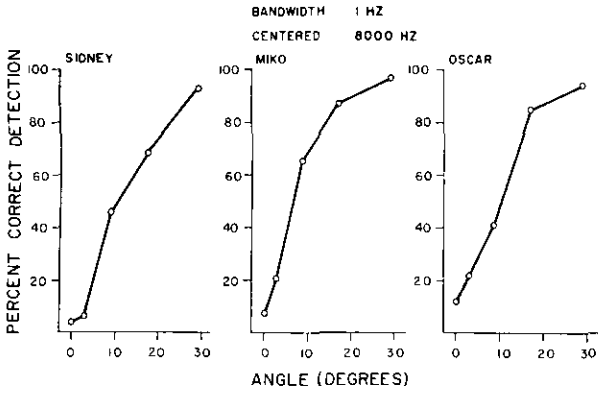

FIGURE 10. Percent correct detection of a change in the location of an 8000 Hz tone as a function of the horizontal displacement of the tone in degrees of arc for three macaque monkeys (*10*).

little difficulty discriminating between, for example, basic human consonant-vowel pairs (phonemes) such as "ba" and "da" (*13*) and between certain variations in their own communication sounds (*14*). The experiments apply operant conditioning principles and represent slight modifications of those procedures described earlier.

An important property of human speech and many animal communication sounds and one that clearly conveys information regarding message content and perhaps also speaker identity is the slow or quite rapid frequency changes that occur so often in the communication process. As with sound localization, there is compelling evidence that perception of these frequency shifts is mediated by the central nervous system (*15*, *16*). In our laboratory, we have isolated the frequency shift from communication, speech, or other complex acoustic signals and have presented it to monkeys and guinea pigs as a simple pure tone time varying in frequency. The signal is actually synthesized by computer. The animals are asked to discriminate the frequency-modulated (FM) tone from a simple steady-state pure tone. The FM tone can be varied in rate and extent of modulation (that is, how fast the frequency shift occurs and how far it sweeps across the frequency spectrum). Threshold for FM detection represents that modulation to which the subject responds on half of the trials. Several experiments are planned for this particular preparation. In one series we hope to replicate some interesting findings for human subjects which indicate that exposure (or adaptation) to a frequency-modulated tone can markedly increase the FM detection threshold, thus suggesting the possibility of either channels or perhaps even feature extractors in the nervous system for FM (*15*, *17*, *18*). Subsequently, the FM detection baseline is one which should be tested for its sensitivity as a baseline for behavioral toxicology.

I am not familiar with any epidemiological evidence from man suggesting that such complex acoustic behaviors as sound localization or the perception of complex biologically relevant signals are adversely affected by exposure to particular toxic substances. Yet, to my knowledge, the specific questions have not been asked. The effects we hope to pick up are sufficiently small that it is somewhat unlikely that they would have been observed earlier without employing the kinds of procedures that we have described here.

The purpose of this paper has been to call attention to a somewhat different strategy for examining the effects of toxic substances on behavior and on the nervous sytem. The procedures suggested are by way of example and are, in no way, intended to limit the possible techniques that might be applied. The basis of the approach argued here is the analysis of behaviors and the elaboration of behavioral baselines that go beyond toxicological screens and detection of simple stimuli. The use of animal models under stimulus conditions which more closely approach those important in real life situations such as perception of communication signals and of their critical elements or the ability to locate the source of a sound in space is advocated in this paper. Perception and discrimination of such complex biologically significant stimulus events is under central nervous system control, and it is well known that many chemical and other poisons exert their toxic effect on the central nervous system (*19*). Perhaps then, the study of experimentally induced perceptual disabilities in these animal models may aid in our understanding of the nature and extent of the disabilities themselves as well as their physiological and morphological basis.

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