

The Interaction of Noise and Aspirin in the Chick Basilar Papilla

Noise and Aspirin Toxicity

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• The possible synergism between noise and aspirin for causing cochlear damage was examined histologically. Six chicks fed aspirin for five days and five chicks fed a normal diet only were paired and placed in sound chambers. They were exposed to a 1500-Hz tone at 115 dB sound pressure level for eight hours. The mean serum salicylate level just before noise exposure was 24 mg/dL (1.74 mmol/L). Ten days later they were killed, and the temporal bones were processed. Hair cell counts were made at 100- μ m intervals throughout the length of the basilar papilla (cochlea). The noise produced a discrete cochlear lesion centered about 30% of the distance from the base to apex. The addition of aspirin did not significantly alter the extent or location of this lesion. One aspirin-fed chick had a unilateral middle ear effusion, and a striking shift in the center of damage toward the apex was noted in this cochlea.

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It is well established that both noise and certain drugs can damage the cochlea. The effects of combining

more than one such ototoxic agent, though, are less well documented. Several recent studies have shown definite synergism between some ototoxic drugs (eg, aminoglycosides) and noise in causing cochlear damage in experimental animals.^{1,3} Given those findings, possible interactions between noise and aspirin, the most commonly ingested ototoxic drug, represent an important area for study.

For at least a century it has been recognized that aspirin can cause tinnitus and hearing loss. One of the earliest studies attempting to document aspirin-induced hearing loss was by Macht et al⁴ in 1920. These authors gave aspirin to themselves and to medical students and, using a watch tick in a quiet room, determined that salicylates decreased hearing acuity. Subsequent studies have demonstrated that when serum salicylate levels exceed 20 mg/dL (1.45 mmol/L), tinnitus and hearing loss often occur in normally hearing individuals.⁵⁻⁷ In general, as the salicylate level increases to 40 mg/dL (2.90 mmol/L), the hearing loss becomes more pronounced, usually reaching a maximum of about 40 dB.

The precise nature of hearing losses due to salicylates has not been firmly established. For example, there is disagreement over whether the thresh-

old shift caused by aspirin is flat across frequencies or predominantly at high frequency.^{5,6,8} There is a consensus, however, that all hearing loss, as well as tinnitus, is completely reversible, usually within 24 to 72 hours after stopping salicylate ingestion. This seems to be true even when aspirin has been taken for many years.⁶

In most studies, the histologic changes in the cochleas of animals given salicylates have not been conspicuous. Covell⁹ reported changes in the shapes of mitochondria in basal outer hair cells and cells of the stria vascularis. Gotlib,¹⁰ however, detected no changes in the organ of Corti of guinea pigs given aspirin, although some alterations in the spiral and vestibular ganglion cells were noted. Myers and Bernstein¹¹ studied the temporal bones of monkeys given a single large injection of aspirin and found no light microscopic changes in the hair cells, spiral ganglion cells, stria vascularis, or cochlear nerve. Using transmission electron microscopy, Douek et al¹² recently reported changes in the stiffness of the stereocilia and vacuolation of the smooth endoplasmic reticulum of outer and inner hair cells after multiple doses of salicylate sodium.

This study examines the interaction

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between noise and aspirin. We reasoned that if aspirin has potential ototoxic effects, it, like other ototoxic agents, might potentiate the effects of noise. The chick basilar papilla (cochlea) is a convenient model to use in histologically examining this possible interaction. Prior studies have shown that the response of the chick's ear to acoustic trauma and to various ototoxic antibiotics is remarkably consistent across animals and is essentially the same as that in mammals.^{13,14} In addition, the short, uncoiled cochlea of the bird is convenient for histologic preparation and quantitative hair cell analysis. Therefore, in this study, histologic changes in the cochlea produced by intense noise in chicks given long-term aspirin were compared with those produced by the same sound exposure in normal chicks. Very young chicks, whose cochleas may be more susceptible to noise and aspirin toxicity, were chosen to maximize any potential interactions.

MATERIALS AND METHODS

Subjects

Eleven chicks were used and 19 cochleas were examined histologically (three cochleas were damaged during processing). Six chicks were fed aspirin by an orogastric tube two or three times daily from day 5 to day 9 after hatching. Each dose of aspirin consisted of a standard 15-mg aspirin tablet that was crushed and mixed with 1 mL of water, producing a slurry. Serum salicylate levels were obtained two hours after the last dose of aspirin had been given on the fifth day and just before sound exposure. Five control chicks were fed a normal diet only.

Sound Exposure

At 9 days of age each control and aspirin-fed chick was paired and placed in a transparent plastic (Plexiglas) cylindrical chamber positioned directly beneath a power horn inside an acoustic chamber. They were then exposed to a continuous 1500-Hz tone at 115 dB sound pressure level for eight hours. A 1500-Hz pure tone was selected because it is near the middle of the chick's frequency range and near its maximum sensitivity.^{15,16}

The tone was generated by an audio oscillator (Wavetek Model 134), amplified, and led to a free field speaker (IRS Power Horn 40-1238). The pure tone was calibrated to 115 dB using a 1.2-cm (half-inch) electret microphone (GR19-72). Spectral

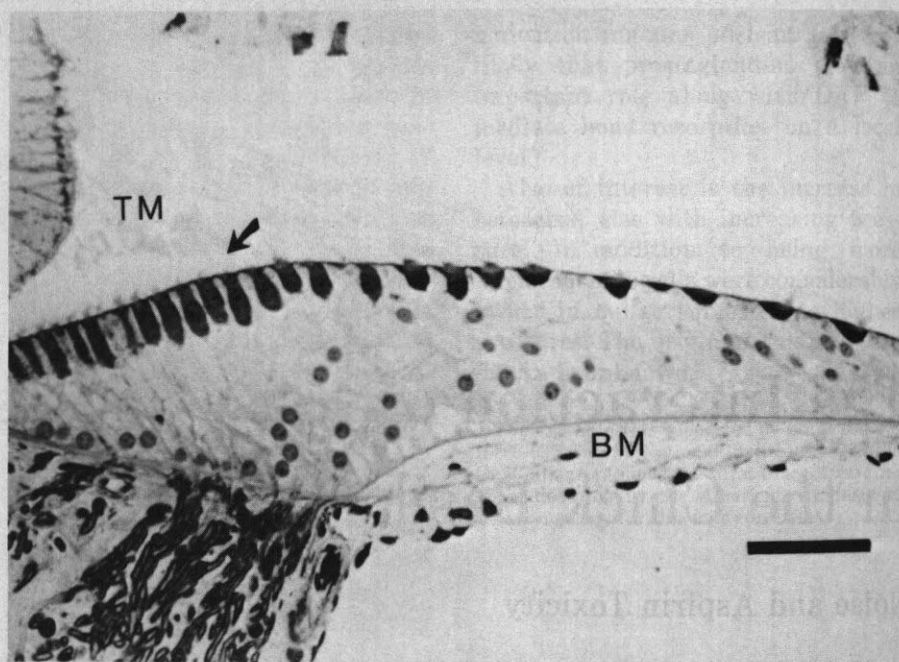


Fig 1.—Transverse section through normal cochlea in 19-day-old chick. Tall hair cells are present medially (arrow) and short hair cells predominate laterally (free edge of basilar membrane). TM indicates tectorial membrane; BM, basilar membrane; calibration bar, 0.05 mm.

analysis performed at the level of the chick's head showed that the first and second harmonics of the 1500-Hz tone were at least 30 dB below the fundamental frequency.

In one of the control chicks and in three of the aspirin-fed chicks, an earplug was used to protect one cochlea from acoustic overstimulation. This procedure has been shown to provide at least a 40-dB attenuation from 125 to 4000 Hz.¹⁶ After noise exposure, the earplugs were removed and all chicks were returned to their brooder and fed a normal diet. They were killed ten days later (19 days after hatching).

Tissue Preparation

The chicks were deeply anesthetized by intraperitoneal injection of pentobarbital sodium, then decapitated. A direct intralabyrinthine perfusion of 1% paraformaldehyde and 2.5% glutaraldehyde in 0.12M phosphate buffer (pH, 7.2) was immediately performed bilaterally. The entire head was then immersed in cold fixative for 48 hours. That portion of the skull containing each cochlea was removed, trimmed, and placed in new cold fixative for approximately one week. Specimens were then decalcified in either a formic acid—hydrochloric acid mixture (Richmand-Gelfand-Hill protocol) or formic acid—formaldehyde mixture (Schmorl protocol) for 60 to 90 minutes.¹⁷ After decalcification, the tissue was washed in running

tap water for one to two hours and post-fixed in 2% osmium tetroxide (in phosphate buffer, pH, 7.3) for one hour. The specimens were then dehydrated in a graded methyl alcohol series and embedded in epoxy resin (Epon). The embedded cochleas were sectioned transverse to the longitudinal axis in the distal to proximal (apical to basal) direction using an ultramicrotome (Servall LKB). A group of three or four sections, 3 μ m thick, were obtained at each 100- μ m interval throughout the length of the cochlea. They were then mounted in serial order, stained with toluidine blue, and covered with coverslips.

Hair Cell Counts

Sections from each level of the cochlea were viewed under a 40 \times objective at a total magnification of 500 \times . To maintain consistency and reliability between hair cell counts, specific counting criteria were established. A hair cell was counted when a cell body, cuticular plate, and stereocilia could be identified. The total number of hair cells was counted in each section. The hair cell counts from the three or four sections at each 100- μ m interval were averaged then plotted as a function of normalized distance (percentage of total basilar membrane length) from the proximal tip (base) of the basilar membrane.

Figure 1 is a photomicrograph of a transverse section through the cochlea of a normal chick. Two types of hair cells, tall

and short, are found arranged along the basilar membrane. The tall hair cells are located primarily along the medial portion of the basilar membrane and are often considered homologous with inner hair cells. The short hair cells are located toward the lateral edge of the basilar membrane and may correspond to outer hair cells.¹⁸ In this study, both cell types were combined to determine total hair cell counts.

RESULTS

Normative Hair Cell Counts

In three chicks that had been fed aspirin and in one chick that had received a normal diet, an earplug was used to protect one cochlea from the noise. The hair cells from these four cochleas appeared to be normal. Because there were no differences in the number of hair cells from these ears, the data were combined. Figure 2 shows the mean hair cell counts from these cochleas plotted as a function of percentage distance along the basilar membrane. These values are essentially the same as those previously reported from this laboratory for hair cell counts from normal 20-day-old chicks.¹³ They were, therefore, considered normal and used as normative hair cell counts in this study.

Hair Cell Loss After Noise Exposure

Figure 3 shows the mean hair cell counts as a function of distance along the basilar membrane for the five chicks (six cochleas) exposed to the 1500-Hz tone. This stimulus produced a discrete lesion centered approximately 25% to 30% of the distance from the base to apex. Around the center of damage, all hair cells were lost, and usually there was disruption of the basilar membrane. Where hair cell loss was not total, the short hair cells were more severely distorted than the tall hair cells. An example of a partially damaged area is seen in Fig 4.

The Table gives the spread of hair cell loss in both the apical and basal directions. An area was considered damaged if the hair cell count was decreased by 25% or more compared with the normative hair cell count at that particular position along the basilar membrane. Using this criterion, the mean area of hair cell loss ex-

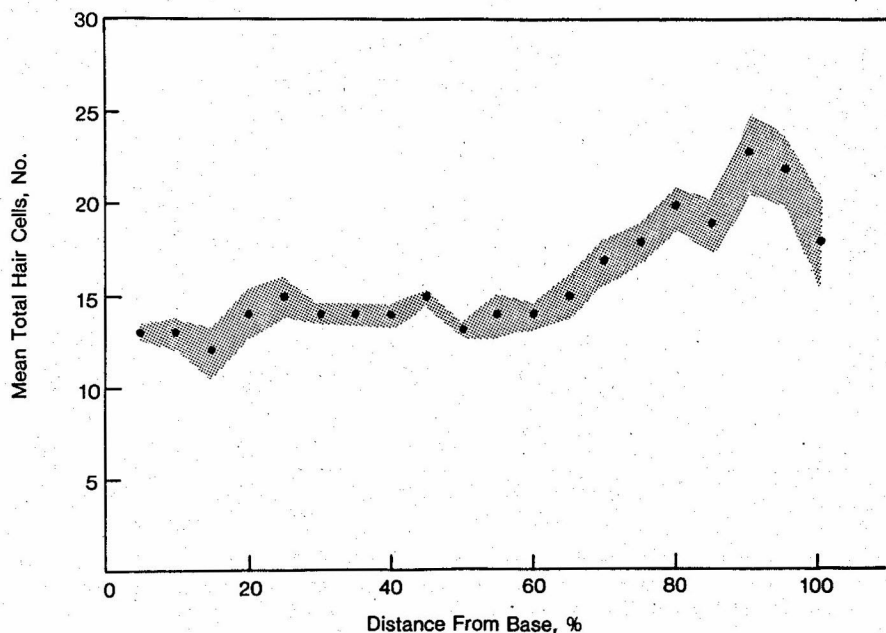


Fig 2.—Points show mean total hair cell counts and shaded area represents ± 1 SEM for chicks (four cochleas) receiving aspirin or exposed to noise but protected with earplug.

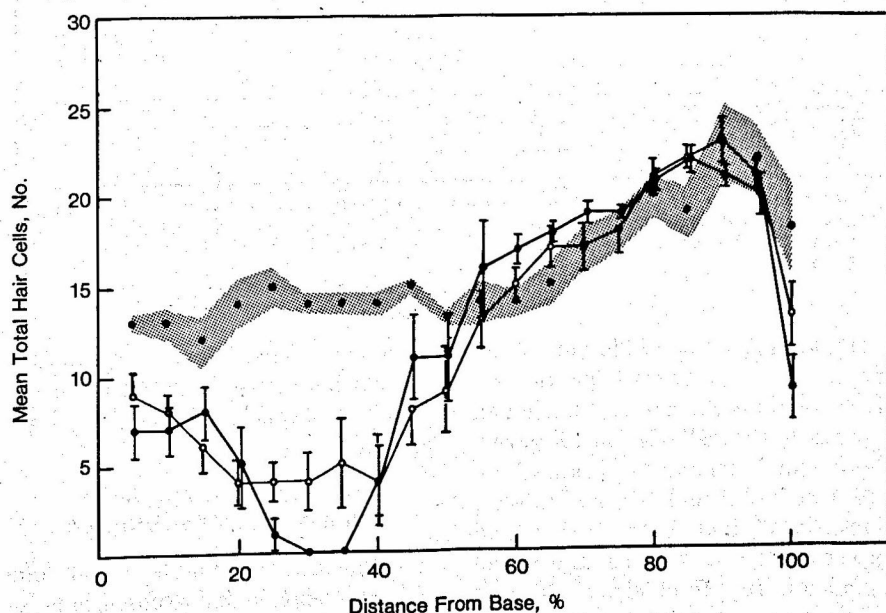


Fig 3.—Closed circles show mean (± 1 SEM) total hair cell counts for chicks (six cochleas) exposed to 1500-Hz pure tone. Chicks (eight cochleas) first fed aspirin then exposed to noise are represented by open circles. Shaded area shows normative mean total hair cell counts (± 1 SEM).

tended from 10% to 44% of the distance from the base to the apex of the cochlea. The mean loss in the total number of hair cells was 24%.

Hair Cell Loss After Aspirin Ingestion and Noise Exposure

The salicylate levels for the six aspirin-fed chicks were 26, 27, 30, 14,

31, and 15 mg/dL (1.88, 1.95; 2.17, 1.01, 2.24, and 1.09 mmol/L); the mean level was 24 mg/dL (1.74 mmol/L). These levels were all near the therapeutic range (15 to 30 mg/dL [1.09 to 2.17 mmol/L]) as determined for humans. The therapeutic range for chicks is unknown.

Figure 3 shows the mean hair cell

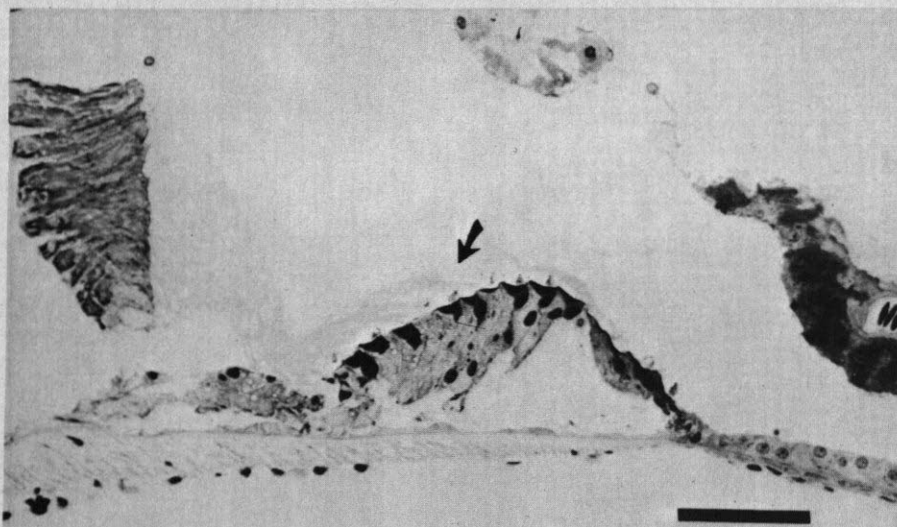


Fig 4.—Photomicrograph of cochlea from chick exposed to 1500-Hz tone for eight hours. Hair cells have been severely damaged, and supporting cells have separated from basilar membrane. A few damaged tall hair cells persist (arrow). Calibration bar is 0.05 mm.

Cochlear Damage From Ear Treated With Noise vs Noise Plus Aspirin*

	1500 Hz, Mean \pm SEM	1500 Hz + Aspirin, Mean \pm SEM
Center of damage	28 \pm 1.9	30 \pm 3.0†
Basal spread of damage	18 \pm 2.3	20 \pm 2.5
Apical spread of damage	16 \pm 2.3	15 \pm 2.2
Total hair cell loss	24 \pm 2.8	24 \pm 1.9

*Values for center of damage are in percentage of distance from base to apex; values for apical and basal spread of damage are in percentage of total length of basilar membrane; values for total hair cell loss are percentage, calculated using normative hair cell counts as reference.

† $P < .1$.

counts as a function of distance along the basilar membranes for the six chicks (eight cochleas) fed aspirin and exposed to the 1500-Hz tone. Figure 5 shows individual hair cell counts from two aspirin-fed and two normal-diet chicks that had been paired and exposed to the noise in the same sound chambers. In all chicks a discrete lesion occurred that totally eliminated hair cells in one region. There was more variability, however, in the location of the center of damage for the aspirin-fed chicks. This accounts for the apparent observation that the mean total hair cell counts for the aspirin-fed chicks in Fig 3 do not reach 0 at the center of damage.

Measurements of the center of damage, apical and basal spread of damage, and total hair cell loss are given in the Table. There was no significant difference in these values as compared with those from the chicks treated

with noise only. Also, no significant correlations were found between the salicylate levels and any of these damage values.

Hair Cell Loss in a Chick With a Middle-Ear Effusion

At death, the middle ear of one chick fed aspirin and exposed to noise was found to contain a serous effusion. The hair cell counts from this one cochlea are plotted in Fig 6, as compared with the hair cell counts in the opposite ear (without effusion). The mean hair cell counts from all of the aspirin-fed chicks are also shown.

As expected, the cochlear lesion in the ear with the effusion was considerably more discrete than the damage to the opposite cochlea. The total hair cell loss in the ear with effusion was the least for all chicks in this study. Although the amount of damage in

the ear with effusion was reasonably predictable, the position of the damage was quite unexpected. The point of maximal damage along the basilar membrane was markedly shifted toward the apex in this one cochlea. In all other ears, the center of damage was positioned between 20% and 40% from the base, whereas in this ear it was centered approximately 60% of the distance from the base to the apex. The damage in the opposite cochlea of this chick was positioned within the normal range.

COMMENT

The mechanism of hearing loss following salicylate ingestion is unknown. Although it has been shown in cats¹⁹ and guinea pigs²⁰ that salicylates do reach the inner ear, consistent histologic changes within the cochlea have not been reported. In this study, morphologic alterations were not seen by light microscopy in the hair cells of chicks fed aspirin and protected from noise. Salicylate levels were not measured in the perilymph of these chicks; however, the serum salicylate concentrations were similar to those levels that produce hearing loss in other animals, including chinchillas and man.

The findings in previous studies that have investigated the interaction of aspirin and noise have been conflicting.^{8,21-24} No interaction between the two agents, a simple summation of their effects, and a possible synergism between the two have all been reported. In only one of these studies was a histologic analysis of the cochlea performed.²¹

In 1978 Woodford et al²¹ reported on the interaction of salicylates in three different temporary threshold shift-producing noise paradigms. Auditory brain-stem responses were studied in chinchillas given one intramuscular injection of salicylate sodium (400 mg/kg) and then exposed to the noise two hours later. The median serum salicylate level was 65 mg/dL (4.71 mmol/L). In control chinchillas receiving only salicylate and not exposed to noise, temporary threshold shifts in the range of 10 to 20 dB, depending on the frequency, were noted two to six hours after injection.

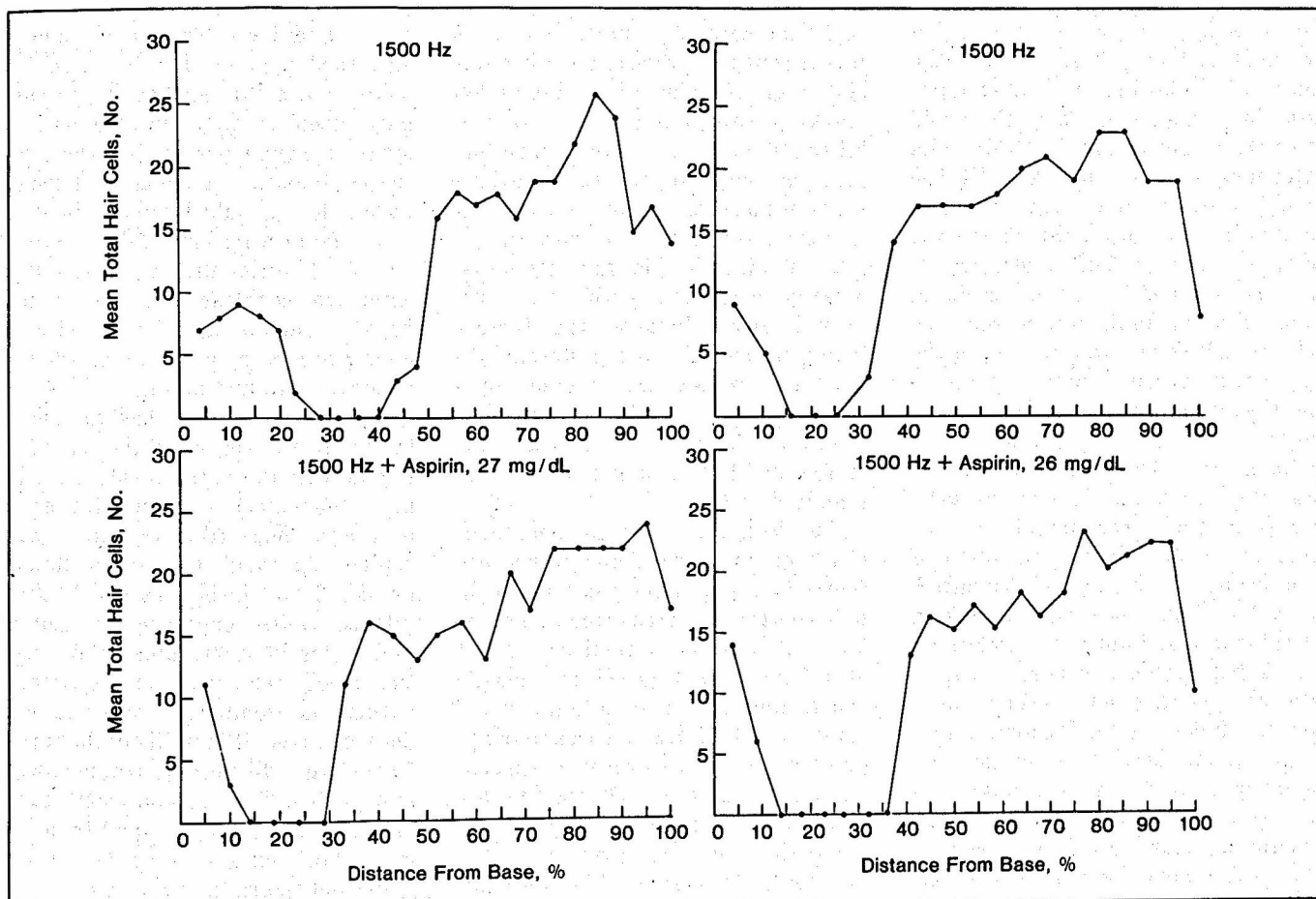


Fig 5.—Individual hair cell counts from two aspirin-fed and two normal-diet chicks that had been paired and placed in same sound chambers.

In chinchillas exposed to noise after salicylate injection, the maximum temporary threshold shift at any frequency was comparable with that produced by the single agent (salicylate or noise) causing the greatest threshold shift at that frequency. The implication was made, therefore, that the hazard to the auditory system for persons taking aspirin and then exposed to noise is no greater than the hazard of either agent alone.

In contrast to Woodford's data are the findings by Eddy et al,²² who studied the interaction of salicylate sodium and noise in seven adult chinchillas. The temporary threshold shift at 1000 Hz was measured by behavioral testing after noise exposure (85 dB broad-band noise for 48 hours), after salicylate sodium administration (200 mg/cm³, four times daily for three days), and after the combination of noise and salicylate sodium. The

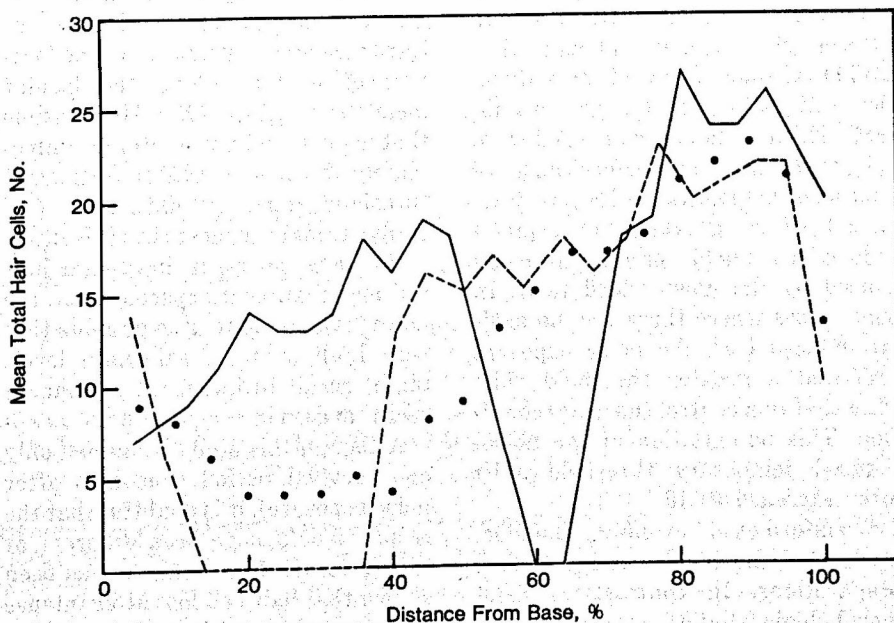


Fig 6.—Solid line shows hair cell counts from cochlea of aspirin-fed chick that had unilateral middle ear effusion. Dashed line represents hair cell counts from opposite ear (without effusion). Mean total hair cell counts for all chicks fed aspirin and exposed to noise are represented by closed circles.

serum salicylate levels ranged between 20 and 40 mg/dL (1.45 and 2.90 mmol/L). Following salicylate administration, the temporary threshold shift was approximately 30 dB, and after noise exposure it was 35 dB. The combination of noise and salicylate produced a temporary threshold shift of approximately 55 dB, a larger hearing loss than either agent produced alone. Similar findings were reported by Mitchell et al,²³ who measured the cochlear nerve action potential following the administration of aspirin and noise.

Chen and Aberdeen investigated the interaction of aspirin and noise by studying their concurrent use as priming agents for the induction of audiogenic seizures in BALB/c mice.²⁴ They found that oral administration of salicylate sodium (500 mg/kg) six hours before noise exposure had a greater priming effect than noise alone. From their experimental design it was possible to exclude any neurotoxic reaction to salicylate sodium as a contributing factor to the enhanced seizure risk. They concluded that salicylates seemed to sensitize the mouse cochlea, making it more vulnerable to acoustic trauma.

McFadden and Plattsmier⁸ suggested a possible synergism between aspirin and noise. They measured temporary threshold shifts in human subjects given aspirin and exposed to a 2500-Hz tone of ten minutes' duration (intensity varied for each subject). The aspirin dosage ranged from 0.5 g taken two hours before the noise exposure to 4 g/d taken for 2½ days. In all cases in which an aspirin-induced hearing loss occurred, the loss caused by the noise added to it. In some cases where there was no aspirin-induced loss, the noise exposure produced a greater threshold shift than that in a control (no drug) condition. This potentiation of the noise-induced temporary threshold shift often exceeded 10 dB.

Woodford et al²¹ examined the morphology of the cochlea using surface preparations. In contrast to most morphologic studies on aspirin ototoxicity, as well as the quantitative hair cell analysis of the present study, they found a mild loss, "less than

10%," of outer and inner hair cells throughout the entire cochlea in chinchillas given a single injection of 400 mg/kg of salicylate sodium and then killed 16 days later. In chinchillas given aspirin and exposed to various types of noise, the pattern of hair cell loss showed a simple superposition.

The findings in this study cannot be directly compared with those reviewed above because the factors being measured were different. In most prior studies, acute cochlear dysfunction was assessed behaviorally or electrophysiologically, whereas this study sought to document chronic histologic changes.

The chick inner ear is an ideal model for quantitative histology because there is remarkable consistency in hair cell counts across chicks. This is true not only for normal chicks but also for chicks exposed to acoustic overstimulation¹³ and to aminoglycosides.¹⁴ The 1500-Hz tone was found to produce a discrete cochlear lesion centered approximately 30% of the distance from the base to the apex. Approximately one quarter of the hair cells were destroyed by the noise. The administration of aspirin over a five-day period in amounts sufficient to achieve therapeutic blood levels did not significantly alter the mean location of this injury or the numbers of hair cells destroyed. It did, however, introduce more variability in the location of damage along the basilar membrane. Although it is possible that aspirin and noise interact immediately to cause a greater temporary threshold shift, the data from this study strongly suggest that this interaction does not result in greater hair cell loss than that expected from the noise trauma alone. It is possible that very high or toxic salicylate levels might result in increased permanent cochlear damage.

Although this study examined only one survival period (ten days after noise exposure), it is doubtful that the results would have been different at longer survival intervals. It has been shown that hair cell loss after intense noise exposure continues for approximately 30 days in the chick.¹³ The center of damage along the basilar membrane stays constant, but there is

apical and basal spread of damage with the longer survival times. In this study, hair cell loss most likely would have been slightly greater with a longer survival period, but the relative contribution of aspirin ototoxicity to this loss should be approximately the same at a ten- or 30-day survival period. Additionally, with the less extensive cochlear damage at ten days, it should have been easier to appreciate a synergistic effect between aspirin and noise.

Disruption of the basilar membranes in the center of the damaged region was consistently observed in both the chicks treated with noise only and those receiving noise plus aspirin. Although basilar membrane breaks have been described after intense noise exposure in guinea pigs,²⁵ this is a rare finding. Because the chick cochleas were sectioned within the temporal bone and not dissected free, it is unlikely that artifact from dissection trauma was responsible. The basilar membrane breaks were seen with equal frequency in both chicks exposed to noise alone and aspirin plus noise, so it does not appear that aspirin altered the physical properties of the basilar membrane, making it more susceptible to rupture. Additionally, disruption of the basilar membrane was never seen in ears without acoustic trauma (ear plugged).

The findings in the one chick with a middle ear effusion that had been given aspirin and exposed to the noise are noteworthy. There was less hair cell loss in that ear compared with the opposite ear, without effusion, and there was a striking shift in the position of damage along the basilar membrane toward the apex. One would expect an effusion to decrease the sound energy reaching the cochlea, and that did seem to occur to the extent that the lesion was much more discrete, with considerably less apical and basal spread compared with the opposite ear. This dampening effect was apparently insufficient, however, to totally prevent the loss of hair cells. The cause for the marked shift in the position of damage is unclear. It has been recently demonstrated by Rubel and Ryals²⁶ and by

Lippe and Rubel²⁷ that the position of frequency coding along the basilar membrane changes. One possible explanation, then, is that the middle ear effusion caused mechanical changes within the middle ear, particularly affecting the round window. The pressure changes then induced a temporary shift in the frequency coding along the basilar membrane, caus-

ing the maximum traveling wave of 1500 Hz to be more apically located.

A 1500-Hz tone produces a discrete lesion in the chick cochlea. The addition of aspirin at a therapeutic level does not significantly alter this lesion other than to introduce more variability in its location along the basilar membrane. This suggests that people taking moderate doses of aspirin and

being exposed to a noisy environment are not at an increased risk for permanent acoustic trauma.

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