The Auditory Pathway of the Epileptic Waltzing Mouse

II. PARTIALLY DEAF MICE [1]

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ABSTRACT This study deals with degeneration occurring in the auditory pathway of the partially deaf epileptic waltzing mouse. Cellular changes include loss of Nissl material and swelling of the neurons. The fibers lose their myelin sheaths and ultimately disappear. These changes occur gradually and throughout the system, so that the animals slowly lose their hearing and finally become deaf. Tests given to three of the four animals reported here show that the high tones are most affected, but the low tones are lost to a lesser extent. The specific locations of degenerative changes in the acoustic centers are described and related, as far as possible, to the tonotopic pattern in the auditory system as reported in the literature.

This comparison brings out a caudorostral relationship between the medial geniculate and the primary auditory cortex.

The auditory centers of older, deaf epileptic waltzing mice were compared with those of normal mice of the same species, Peromyscus maniculatus, in Part I of this report (Ross, '62) and an anatomical basis for the deafness was established. Part II will be concerned with a study of the auditory centers of young, partially deaf, epileptic waltzing mice.

The various nuclei associated with the auditory system have the same extent in the partially deaf animals as in the normal animals previously reported (Ross, '62) and this data will not be repeated here. However, much recent work has shown the advantage of dividing the ventral cochlear nucleus into posteroventral and anteroventral nuclei. These nuclei were not described in Part I of this report. In order to determine their presence or absence in the mouse a number of preparations used previously were re-examined and several mouse brain series, both transverse and longitudinal, from the permanent Huber Comparative Collection of brains at The University of Michigan, Department of Anatomy were studied with the following results.

At least four regions or subnuclei of the ventral cochlear nucleus of the normal mouse may be differentiated with cresyl-violet or toluidin blue staining techniques. The division of the ventral cochlear nucleus into rostral and caudal parts occurs at the level of the entrance and bifurcation of the cochlear nerve. Caudal to this level lies the posteroventral nucleus, and rostral to it is the anteroventral nucleus (Rose, Galambos, and Hughes, '59; Harrison and Warr, '62). Each of these subnuclei in turn may be divided into at least two parts because of major differences in cell morphology and spatial arrangement, dorsally and ventrally. Harrison and Warr ('62) subdivide the anteroventral nucleus of the rat into two parts, dorsal and ventral, but do not distinguish two separate regions in the posteroventral nucleus of this form. However, their cytoarchitectonic description of the posteroventral nucleus is in agreement with the following description of this nucleus as it is found in the normal mouse.

The posteroventral nucleus is first seen caudally as a few large neurons located deep to the ventral part of the acoustic tubercle and almost enclosed by numerous small, round, dark-staining cells. As the ventral cochlear nucleus increases in size, this portion of the nucleus remains interposed between the acoustic tubercle and restiform body and comprises the so-called "tail" of the ventral cochlear nucleus (Ramon y Cajal, '09). Here the neurons are widely spaced, large, multiangular, and contain much Nissl material. These cells take on a characteristic violet color in Nissl stain and comprise a distinct cellular aggregate, which will be called the dorsal group, within the posteroventral nucleus. As the posteroventral nucleus lengthens ventrally, medium-sized, more closely spaced neurons (some of which are spindle shaped) appear in this ventral portion and represent the most caudal extent of the second cell cluster in this subdivision, the ventral group

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(figs. 1 and 3). The large neurons remain dorsally disposed, becoming less numerous as the hillock shape is assumed, and finally terminate as a small, rounded mass of neurons slightly caudal to the level of the cochlear nerve (fig. 3). In some series a fibrous lamella is interposed between the dorsal and the ventral groups (fig. 3). The medium-sized, more closely arranged neurons of the ventral subnucleus increase numerically and make up the entire posteroventral subdivision immediately caudal to and at the level of the cochlear nerve. Here the neurons are more closely spaced dorsally than ventrally.

Rostral to the level of the cochlear nerve lies the anteroventral subdivision of the ventral cochlear nucleus; it is narrower dorsally than ventrally. The neurons are ovoid appearing and closely spaced dorsalward and triangular or spindle shaped and more scattered ventralward (fig. 7). These cytological differences are obvious in both transverse and longitudinal sections through the ventral cochlear nucleus and probably warrant subdividing the anteroventral portion into dorsal and ventral subnuclei (Harrison and Warr, '62).

It will be shown in this report that partial degeneration occurs throughout the auditory system in these young epileptic waltzing mice. In the cell-stained material the degeneration is exemplified by large, ovoid, and very pale-staining cells with eccentric nuclei. In the Weil stained series there is a reduction in total number and myelination of fibers in the various auditory centers.

The small cells with dark-staining, round, conspicuous nuclei, which were found scattered in the normal mouse brain and which were greatly increased numerically in the deaf brain series, are found in the preparations of the partially deaf mice. These may be phagocytic microglia, especially since Nissl granules have not been demonstrated in their ill-defined cytoplasm. However, as differential stains for glia were not used, these cells will be referred to simply as "small, round cells" or "granule-type" cells.

MATERIALS AND METHODS

This report is based upon a study of four series of brains from young, partially deaf epileptic waltzing mice. Two of the brains, no. 96050 and no. 96836, were stained with toluidin blue; and two, no. 96362 and no. 96835, were prepared according to Weil's method for fibers. Three of the mice were tested for range of hearing using equipment described previously by Dice and Barto ('52).

Dice and Barto ('52) found that young epileptic waltzers gave ear twitch responses to a range of frequencies between 500 and 95,000 cycles/sec. With vibrissae clipped to the length of the surrounding fur, Mouse no. 96835 heard frequencies ranging between 300 and 65,000 cycles/sec; under similar conditions Mouse no. 96362 heard frequencies between 4,000 and 60,000 cycles/sec, and Mouse no. 96836 recognized tones of frequencies between 500 and 55,000 cycles/sec. All of the animals except Mouse no. 96835 gave ear twitch responses to a slightly wider range of frequencies with the vibrissae intact. This may have been due to a change in position of the animal in the box at the time of the second testing or may indicate that the vibrissae reinforce sound vibrations.

All of the mice waltzed when exposed to the stimulus of jingling keys; and, in two cases, a similar response was evoked by certain pure tones of low frequencies. Effective pure tones in the case of Mouse no. 96836 were 8,000, 10,000, and 20,000 cycles/sec. The time of exposure in each case was 240 seconds, 140 seconds, and 60 seconds, respectively. Exposure to a frequency of 18,000 cycles/sec for 40 seconds resulted in a convulsion. Dashing and then stupor followed the waltzing at 10,000 cycles/sec after exposure to the stimulus for 175 seconds. In the case of Mouse no. 96835 effective frequencies were 6,000 and 8,000 cycles/sec. Both waltzing and dashing ensued after 65 and 55 seconds, respectively. Mouse no. 96362 was tested with a frequency of 16,000 cycles/sec for a period of 180 seconds but showed no abnormal behavior.

Mouse no. 96050 was not tested with the electrical equipment for range of hearing but was considered partially deaf because she did not twitch her ears in response to a squeak, nor did she waltz when stimulated with the jingling keys. The sounds of jingling keys and of metal striking glass did cause a positive ear twitch, however. This animal had been considered a high grade waltzer previously.

DESCRIPTION OF MATERIAL FROM ABNORMAL MICE

Primary auditory centers

Dorsal cochlear nucleus. The acoustic tubercles of the abnormal mice exhibit a partial loss of fibers and of lamination which is most evident ventrally throughout the caudorostral extent of the nucleus. The ventral portion of the acoustic tubercle generally shows some degree of atrophy, its lateromedial dimension being much more narrow than in the normal mouse. Small, round cells are more numerous than normal in the delaminated portions of the acoustic tubercles and in the region of nucleus proprius, and occupy the most ventral part of the tubercle when it is atrophied. Anteriorly, in some cases, de-

generation also occurs dorsally, so that a better preserved area remains between atypical dorsal and ventral portions.

In Mouse no. 96836, small, round cells fill the nucleus proprius and the ventral portions of both acoustic tubercles at all levels; also, the ventral part is atrophied on the left. Small, round cells increased numerically in a dorsalward direction in the rostral third of the tubercle on the right; but on the left side these cells become numerous far dorsalward rostrally, sparing the midportion of the tubercle.

Both acustic tubercles of Mouse no. 96050 are more distinctly laminated and contain more typical cells than is the case in Mouse no. 96836. In the caudal two-thirds of both nuclei in Mouse no. 96050, granule-type cells increase ventrally in Layers II, III and IV and in nucleus proprius (figs. 2 and 4). Anteriorly, such cells become numerous dorsally as well as ventrally; there is a normal area between dorsal and ventral portions of each acoustic tubercle.

In both Mouse no. 96835 and Mouse no. 96362, the posterior third of the acoustic tubercles lacks fibers and appears degenerated. In each case the ventral portion of each dorsal nucleus is especially affected at all levels and, except for the left acoustic tubercle of Mouse no. 96835, is atrophied. Elsewhere in the dorsal nuclei fibers are not so numerous as in the normal brain, ramifying in approximately the dorsal half of the left nucleus in Mouse no. 96835, and in the dorsal portion of the acoustic tubercle on both sides in the brain of Mouse no. 96362 (fig. 6). In the latter series the left nucleus is more atypical than the right. In Mouse no. 96835, on the right (fig. 5), fasicles occupy only the midportion of the nucleus anteriorly, resembling the distribution of the better preserved elements in the cell material described above.

Ventral cochlear nucleus. There is general agreement on location of degeneration within the ventral cochlear nuclei of all four abnormal mouse brains reported here, although the degree of this degeneration varies from one specimen to another and may be related to total hearing loss. The most typical portions in the posteroventral subdivision of the ventral cochlear nucleus lie within the "tail" or dorsal group (figs. 2, 5 and 6) and at levels near the entrance of the cochlear nerve where the entire posteroventral subdivision consists of the ventral group (fig. 4). Because of the marked preservation of the dorsal group in these abnormal brains, this cell cluster appears to comprise a distinct functional, as well as morphological, subnucleus of the posteroventral subdivision. In figures 5 and 6 the relatively good fiber supply of the dorsal group is demonstrated. The ventral group is severely degenerated in Mouse no. 96362, shown in figure 6. In Mouse no. 96835, shown in figure 5, there is a loss of fibers ventrolaterally and medially in the ventral group and a thinning of the myelin on those fibers still present in the better preserved midportion.

This distribution of degeneration along lateral and medial borders of the ventral group is common to most of the abnormal mice studied and reported here. In cell stained material, small, round cells are more numerous than normal laterally and medially in the ventral group with bettter preserved neurons lying in between them. Near, and at the level of, the entrance of the cochlear nerve, the posteroventral subdivision of the ventral cochlear nucleus broadens into a hillock; but its smaller than normal size is indicative that some degenerative changes are in progress. The neurons within the hillock are not entirely typical; they appear larger and more lacking in Nissl substance than comparable neurons in normal material. The small, round cells are slightly increased numerically, being most numerous at the lateral and medial borders of the hillock (fig. 4). Degeneration of both dorsal and ventral groups of the posteroventral nucleus decreases in a caudorostral direction.

In the anteroventral subdivision, loss of fibers and changes in cell morphology are usually well distributed throughout but increase in intensity in a caudorostral direction. This means that the ventral cochlear nucleus on the whole exhibits least structural changes at and on either side of the level of the cochlear nerve. The anteroventral subdivision is more narrow in a lateromedial direction than normal (fig. 8), and the lateral border may be concave rather than straight, especially rostralward. The neurons remain more closely grouped dorsally than ventrally in the anteroventral subdivision, so that dorsal and ventral subnuclei may be distinguished.

In brain no. 96362, on the left side, the ventral cochlear nucleus assumes a triangular shape near the level of entrance of the cochlear nerve; this is reminiscent of the changes which ultimately occur in the ventral cochlear nucleus as the abnormal animals become old and deaf (Ross, '62). In Mouse no. 96050, the ventral tip of the anteroventral nucleus is severely degenerated rostrally on the right side but is almost typical in appear-

ance on the left. This is the only specimen which shows this variation.

Secondary auditory centers

Superior olivary complex and adjacent gray. The superior olivary nucleus is atrophied and is not laminated in the four specimens reported here. Many of the cells are round or ovoid in shape, possess very pale nuclei and pale-staining cytoplasm (fig. 10). The cells are more closely arranged than in the normal superior olive, and granule-type cells are more prominent. The accessory superior olive varies greatly in extent of degeneration; in two series the nucleus is distinct, and in the two remaining series the accessory superior olive is not separated from the superior olive. The medial nucleus of the trapezoid body and the parolivary nuclei tend to be less degenerated than the rest of the complex.

In Mouse no. 96050 the accessory superior olive is not separated from the superior olive. The parolivary nuclei are small, ill-defined gray masses and the medial nucleus of the trapezoid body is composed of light-staining, round, closely grouped cells. In Mouse no. 96835 the accessory superior olive merges with the superior olivary nucleus. Fiber losses in the nucleus of the trapezoid body and the parolivary nuclei are more marked on the right side than on the left. In Mouse no. 96362 and Mouse no. 96836 the accessory olive is distinct from the superior olivary nucleus but is rounded in outline and smaller than normal.

Inferior colliculus. The cells of the inferior colliculus are more closely grouped than in the normal mouse and frequently take little stain due to a loss of Nissl substance (fig. 12). The small, round cells are more numerous than normal in both nuclear and capsular portions. In Weil stained material, fibers course through the nucleus and the capsule of the inferior colliculus but are less numerous than normal. The inferior colliculi of the abnormal mice are slightly smaller than those in the normal animal but are equally atrophied on the two sides.

Medial geniculate nucleus. For convenience of comparison, both the medial geniculate nucleus and the auditory cortex will be divided into caudal, middle, and rostral thirds. In all four abnormal mouse brains, the caudal third of pars principalis is atypical in shape, being flattened in a lateromedial direction (fig. 15). Degeneration is most obvious in the dorsal third or one-half of pars principalis and in a strip along the lateral border. The small, dark-staining, spindle-shaped cells of the dorsal group are rarely found in this caudal portion of pars principalis in abnormal material. There are a few typical, polygonal, well-spaced neurons ventrally and ventromedially in pars principalis in that part called the "chief" or "main mass." In the "c" group, the neurons are swollen and the small, round cells increased numerically. The caudal third of pars principalis is more atypical on the left side than on the right in every case but one (no. 96835).

The middle third of pars principalis is always less affected than the caudal portion in the abnormal material (fig. 17) and may even assume a characteristic bean-shape. The ventral portion of the chief nucleus contains some typical cells and has the best fiber supply. Occasionally, the dorsal group of neurons is well-defined (fig. 17). A few, flat, spindle-shaped neurons of the "c" group are observed at times, but this subdivision of pars principalis is usually indistinguishable from the chief nucleus.

The rostral third of pars principalis varies most in degree of degeneration from one specimen to another. It is completely degenerated in one case, almost typical in another, and in the remaining two cases morphological changes are most pronounced dorsally and laterally.

In Mouse no. 96835, on the right, pars principalis has atrophied to such an extent caudally that it is triangular in shape.

Pars principalis is typically bean-shaped for 75 μ near the anterior end of its middle third in the brain of no. 96836 on the right (fig. 17). On the left side in Mouse no. 96050, anteriorly in the middle third of its caudorostral extent, pars principalis is typical in shape, the cells are well spaced, and small, round cells are not numerous. Near the midpoint of the extent of pars principalis on the right in Mouse no. 96362, there are few fibers in any of its subnuclei.

The entire pars principalis is atypical in its rostral third on both sides in the brain of no. 96836. The neurons are pale-staining, closely spaced, and almost masked by the numerous small, round cells so that it is impossible to trace the nucleus far orally. In contrast, in this portion of pars principalis on both sides of Mouse no. 96050, the neurons are well spaced and the small cells are not numerous (fig. 19). In the two Weil preparations the dorsal and lateral portions of pars principalis show the major fiber losses, more severe on the left than on the right in both brains. In the brain of no. 96362, on

the right side, a narrow border is degenerated ventrally, also.

The neurons of the magnocellular portion of the medial geniculate nucleus are mostly ovoid and "ghost-like," and the small, round cells have increased numerically. This nucleus is rarely distinct in the abnormal material. The levels at which it assumes a more typical appearance vary greatly from one specimen to another and are given below.

Pars magnocellularis is obvious only in a few sections in the middle third of its caudorostral extent in the brain of no. 96836 (fig. 17), but in the brain of no. 96050 there are some typical cells in the caudal two-thirds on the left and the caudal one-half on the right. The Weil stained material shows a general loss of fibers throughout the nucleus. Portions best supplied with fibers in the brain of no. 96835 lie caudally and near the middle third of the extent of pars magnocellularis. In brain no. 96362, on the right, fibers are more numerous in the rostral third than in more caudal portions of pars magnocellularis; on the left, the nucleus has a good fiber supply in only two places — near the middle of its extent and at its rostral tip.

Auditory cortex. Lamination typical of auditory cortex is obscured in certain parts of the area in these abnormal brains by the swelling of the neurons which renders their morphological differentiation impossible. This delaminating process in auditory cortex is not accompanied, however, by a great increase in small, round cells. In Weil stained material, fibers are delicate and diminished in number in the degenerating parts; often they extend only into Layers VI and V of the auditory cortex.

In all four specimens, degeneration is widespread in caudalmost sections of the primary auditory area. The left side is more atypical than the right in every case but one (no. 96835), which agrees with findings in the caudal part of pars principalis in these series of mouse brains. Delamination is frequently confined to dorsal and ventral borders, with the latter being more extensively affected as a rule.

Middle and rostral thirds of the primary auditory cortex vary greatly in degree of degeneration, and individual differences will be cited below. However, it is worthy of note that the middle third is generally better preserved than the caudal portion of the primary auditory area and that the rostral third of the area shows the greatest degree of variation from one specimen to another.

In Mouse no. 96835, the right primary auditory cortex is more affected than the left in its caudal third; there are few fibers in any stratum of auditory koniocortex on the right, although delamination is most evident dorsally and ventrally. On the left, in the no. 96835 series, fibers are generally more numerous and some knobs are apparent in the fourth lamina along the ventral border of the primary auditory area. In the no. 96362 series, the dorsal and the ventral parts of the caudal third of auditory koniocortex are poorly supplied with fibers on both sides, but there are more fascicles in the intervening portion. In Mouse no. 96836, there are a few scattered pyramidal cells denoting Layers II and III throughout most of the caudal third of the right auditory koniocortex, the other laminae being undifferentiated except near the anterior end of this portion. On the left side, at the anterior end of the caudal third, some better preserved cells are found ventrally. In brain no. 96050, on the right, the cellular changes are confined to the ventral one-half of the primary auditory area in its caudal third (fig. 16); but, on the left side, both the dorsal and the ventral borders are severely affected.

The middle third of the auditory koniocortex shows great variation in position and extent of degeneration. The dorsal border of the area is well laminated on the right in the no. 96836 series; on the left, immediately anterior to the midpoint of the area, the dorsal half of the field shows some typical pyramidal cells in combined Layer II and III and some clusters of neurons in Layer IV. This region of better preserved cells is 150 μ long. The rest of the middle third of the auditory koniocortex in this brain consists largely of inflated ovoid neurons, although laminae may be distinguished at times (fig. 18). In the no. 96050 series, posteriorly in the middle third the dorsal half of the right primary auditory area is well developed and there are clusters of cells in Layer IV. Midway in the right auditory koniocortex all except the far dorsal part is degenerated, but better-preserved neurons are again evident throughout the field more rostrally. On the left side in this series, lamination of the primary auditory area improves so that the entire auditory koniocortex assumes a typical appearance. However, midway in the extent of the left auditory koniocortex the ventral border becomes atypical and slightly more rostralward the laminae become indistinct along the dorsal border, also. In brain no. 96362, on the right, the upper two-thirds of the field are most affected; on the left, a narrow zone dorsally and the entire ventral one-half of the primary auditory area are degenerated in the middle third of the caudorostral extent of auditory koniocortex. On the right side of brain no. 96835, fibers gradually increase numerically up to the rostrocaudal midpoint of the auditory koniocortex. Just anterior to this level there are knobs in Layer IV dorsally, but ventrally the fibers are delicate and not numerous in any of the laminae. On the left, the ventral border is delaminated posteriorly in this

middle third of the auditory area; the rest of the auditory koniocortex is better preserved. The fiber supply increases from section to section until it becomes rich near the midpoint of the left auditory area, where all of the primary auditory area except the dorsal border appears typical. Degeneration then gradually spreads from the dorsal border, so that anteriorly in this third only the ventral half of the field has an abundant fiber supply.

In the rostral third of the no. 96836 and the no. 96050 series of brains there is delamination of the ventral border on the right side. The more dorsal portion is well laminated and exhibits many typical cells (fig. 20). The degeneration spreads dorsalward to envelope most of the right auditory koniocortex at the rostral tips of these two series. Pale-staining, ovid cells occupy much of the primary auditory area rostrally on the left side of brain no. 96836. The left auditory koniocortex is well developed rostrally in the brain of no. 96050, delamination being confined to the dorsal border. In brain no. 96835 there are knobs in the fourth lamina throughout this rostral third of the right auditory koniocortex, but the fibers are usually thicker and more numerous dorsally than ventrally. On the left in this series the fibers are delicate and few in number dorsally, but the ventral half of the field has an abundant fiber supply; most rostrally, the entire primary auditory area is richly supplied with fibers. This latter distribution of better preserved fibers is also seen in brain no. 96362 on the right, although the fascicles are fewer in number. The ventral one-half of the auditory koniocortex is delaminated on the left side, rostrally, in the brain of no. 96362.

Delamination is more advanced in the secondary auditory area than in auditory koniocortex. Frequently the degeneration occurs in a reverse location from that in the primary auditory cortex.

Delamination of the right secondary auditory area occurs along the dorsal border caudally in brain no. 96836 and more rostrally involves the entire area except for a few sections in which the ventral portion is laminated. The cortical layers are not differentiated through most of the left side.

In brain no. 96050 there are five isolated places on the right in which normal appearing cells occur in the secondary auditory area: one small zone far caudally, two in the middle third, and two in the rostral third. Far caudally, on the left, the entire area is laminated but only along the dorsal border at other levels.

Although fibers are delicate throughout the right secondary auditory area in the no. 96835 series, they are most numerous in the dorsal part of both the caudal and the middle thirds, and in the entire region far rostrally. On the left, there are three locations of degeneration: (1) in the midportion of the field far caudally, (2) at the junction of the caudal and the middle thirds where the dorsal part is atypical, and (3) in the anterior part of the middle third where the fibers are extremely delicate dorsally.

The entire caudal half of the right secondary auditory cortex is devoid of lamination in brain no. 96362, and the delicate fibers reach only the deepest part of the cortex. The anterior half of the area is laminated. One the left side the layers are mostly run together, delicate fibers being generally dorsally disposed.

GENERAL DISCUSSION

Research on a wide variety of forms indicates that there is an interrelationship between specific portions of the auditory system. Among the many workers who have contributed to our knowledge may be mentioned Poliak ('26, '27, '32), Mettler ('32), Guild ('32), Lorente de Nó ('33a, b), Lewy and Kobrack ('36), Walker ('37, '38), Waller ('34, '40), Licklider and Kryter ('42), Ades and Felder ('42, '45), Ades ('41, '43), Rasmussen ('42, '53), Barnes, Magoun and Ranson ('43), Tunturi ('44, '50), Walzl ('47), Rose ('49), Rose and Woolsey ('49), Ades and Brookhart ('50), Portmann and Portmann ('54), Harrison and Warr ('62), and Powell and Cowan ('62).

The pattern of projection in the acoustic system appears to be as follows. Fibers originating in the basal coil of the cochlea transmit tones of high frequency, and those from the apical coil carry tones of low frequency. The tones of the middle range are carried over fibers from the midportions of the cochlea (Crowe, Guild and Polvogt, '34; Stevens, Davis and Lurie, '35; Davis, Dworkin, Lurie and Katzman, '37; Culler, '35; and others). Tasaki ('54 has indicated that the fibers arising in the apical turn respond only to low frequencies, whereas the fibers arising in the basal turn may respond to tones of low frequency as well as those of high frequency, if the intensity of the stimulus is high enough. In the primary acoustic nuclei the tonal pattern may vary from one form to another, but most commonly the higher frequencies project to the more dorsal portions of the dorsal and ventral cochlear nuclei and lower frequencies to more ventral and ventromedial portions of these centers (Lewy and Kobrack, '36; Rose, Galambos and Hughes, '59). Many nuclei associated with the acoustic pathway receive connections from the primary acoustic nuclei: the trapezoid gray, the nuclear complex of the superior olive, the reticular formation, the nuclei of the lateral lem-

niscus, and the inferior colliculus (Ades and Brookhart, '50; Barnes, Magoun and Ranson, '43; Harrison and Warr, '62; Harrison and Irving, '64). Axons of third order (and possibly even fourth order) neurons in these nuclei join second order neurons from the opposite primary acoustic nuclei in the lateral lemniscus to ascend to the medial geniculate nucleus. Fibers may cross the midline in the trapezoid body, in the commissure of Probst, or in the commissure of the inferior colliculus, so that both cochleae come to be represented in the medial geniculate nucleus and auditory areas of each side.

Barnes, Magoun and Ranson ('43) believe that all of the direct fibers which ascend to the inferior colliculus or to the medial geniculate nucleus from the primary acoustic nuclei are crossed, having gained the opposite side through the trapezoid body. Homolateral representation in the medial geniculate nucleus and in auditory cortex, according to them, is due to synapses which occur in the ipsilateral superior olivary nucleus, with third order neurons from this nucleus constituting an important link to the homolateral medial geniculate nucleus. They also believe that auditory information originally sent contralaterally may be projected back to the homolateral side through the commissure of Probst or the commissure of the inferior colliculus. Later work of Ades and Brookhart ('50) shows also that the direct fibers from the dorsal cochlear nucleus to higher acoustic centers are crossed.

Possibly because of the many centers to which the primary acoustic nuclei project, aside from their direct fibers to the medial geniculate nucleus, no pattern of projection has been demonstrated between the primary centers and the medial geniculate nucleus. There is, however, much evidence of a direct relationship between the medial geniculate body and the auditory cortex (Mettler, '32; Waller, '34; Le Gros Clark, '36; Walker, '37, '38; Ades, '41; Rose and Woolsey, '43, '49, '58; Neff and Diamond, '58).

In lower forms, Rose and Woolsey ('49, '58) concluded that the pars principalis (at least its anterior part) is related to the primary auditory area and that area AI receives essential projection fibers from pars principalis. Their earlier work indicated that pars principalis projects from along its long axis in orderly sequence along the long axis of the primary auditory area, while its lateromedial extent projects in a direction at right angles to the long axis of the primary auditory area. In their more recent work these authors ('58) raise the possibility of a projection pattern such that each cross section of pars principalis receives information from all turns of the cochlea, and the anteroposterior dimension of pars principalis projects in a dorsoventral sequence on the primary auditory area. Neff and Diamond ('58) are in agreement with Rose and Woolsey that removal of AI alone in the cat causes retrograde degeneration in approximately the anterior half of the pars principalis of the medial geniculate nucleus. Earlier investigations of Poliak ('26, '27, '32) and Walker ('37, '38) emphasized that in the monkey, due to a rotation of the auditory radiations in primates (Poliak, '32), the dorsorostral portion of the medial geniculate body projects to the posterior part of the auditory area; and the ventroposterior portion of the nucleus projects to the anterior part of auditory koniocortex. The lateromedial extent of the medial geniculate nucleus according to this theory is related to the lateromedial extent of auditory koniocortex (Walker, '38).

According to Knighton ('50) and Waller ('40), the magnocellular division of the medial geniculate nucleus projects to the secondary auditory area. Rose and Woolsey ('49, '58) found no retrograde degeneration in pars magnocellularis when the secondary auditory areas were involved in their lesions. Neff and Diamond ('58) found magnocellularis to be degenerated only when areas ventral to AII and EP were ablated. Rose and Woolsey have suggested that, in the cat, pars magnocellularis is related to primary and secondary auditory areas, the third auditory area (EP), and to adjacent temporal and insular cortical areas by a sustaining projection.

There may be two, three, or four auditory areas in the cerebral cortex depending upon the form studied and some investigators would include still more portions of the cortex as auditory in function. Rose

('49) described three auditory fields in the cat on a cytoarchitectural basis. In the cat, physiological studies show that high tones project to the rostral part of the primary auditory area and to the caudal part of the secondary area for hearing. Low tones project to the caudal part of the primary auditory area and to the rostral portion of the secondary auditory area (Woolsey and Walzl, '42). In the third area as found in the cat (Rose and Woolsey, '49; Downman, Woolsey, and Lende, '60) and in the dog (Tunturi, '44), responses to high frequencies occur superior to those for low frequencies. In the monkey (Licklider and Kryter, '42) and in the chimpanzee (Bailey, Bonin, Garol and McCullock, '43) a tonotopic pattern has been described on the primary auditory area, such that low ones project anterolaterally and high tones posteromedially. The pattern appears to be reversed in the secondary auditory area (Woolsey, '47) as compared with the tonotopic pattern in the primary area for hearing. There is some evidence that the secondary area may receive connections from the primary auditory area (Ades, '43).

Aside from the ascending system, the acoustic pathway is complicated further by the presence of a descending system (Ades, '41; Rasmussen, '42, '53; Portmann and Portmann, '54). The descending system is not dealt with in this study.

One of the most interesting features of the degeneration in the primary acoustic nuclei is the difference between the actual location of the cellular and fiber changes and the expected position, using the tonotopic pattern found in higher forms. This study of the cochlear nucleus in partially deaf mice indicates that it is the ventral portion of the dorsal cochlear nucleus which is usually degenerated and sometimes atrophic through the series. The dorsalmost part of the nucleus may be atypical also, but this is inconstant. In the ventral cochlear nucleus, however, the changes are laterally and medially disposed posteriorly but are distributed throughout the nucleus rostrally. In only one instance is the ventral tip of the anteroventral nucleus more atypical than the more dorsal portions. The three mice tested were shown to have lost the high tonal range particularly, but some loss of low tone was also demonstrated. On the basis of Lewy and Kobrack's ('36) findings and those of Powell and Cowan ('62), one would expect the most dorsal portions of both the dorsal and the ventral cochlear nucleus to be severely degenerated, while minor losses should have been observed ventrally in these nuclei. Of interest, also, is the fact that approximately the middle third of the ventral cochlear nucleus is less affected than the more caudal or rostral portions. This finding is in contrast with that of Powell and Erulkar ('62), who describe the portion of the nucleus near the entrance of the cochlear nerve as being initially most subject to gliosis in the case of transneuronal degeneration in the acoustic nuclei of the cat. This may mean that we are not dealing with transneuronal degeneration in these abnormal mice, although further studies must be made to clarify this point. One last feature deserving mention is the fact that the acoustic tubercle is always in a more advanced stage of degeneration than the ventral cochlear nucleus, which indicates that degenerative processes begin here earlier or, for some reason, advance more rapidly.

A study of the various accessory nuclei — the nucleus of the trapezoid body, the nuclear complex of the superior olive, the nuclei of the lateral lemniscus, and the nucleus of the inferior colliculus — is inconclusive with respect to their specific relationship to the acoustic system. Some of the fibers of the trapezoid (or ventral acoustic) decussation appear to be internuclear components passing between the nuclei of the trapezoid body, for the decussation is always well represented. Also, there exists a rather thick internuclear bundle between the inferior and superior nuclei of the lateral lemniscus, as these fascicles are largely present in the abnormal mouse brains. Of interest is the fact that losses are evenly distributed throughout the inferior colliculi; one side never appears more atypical than the other, even though the primary acoustic nuclei are usually more degenerated on one side than the other. Several comparisons between the location of degeneration in the pars principalis of the medial geniculate nucleus and in the primary auditory area

may be made to show that a caudorostral projection pattern exists. Among these are the following examples. In Mouse brain no. 96835, the right pars principalis has an atrophied, triangular-shaped caudal tip; in the corresponding portion of auditory koniocortex there are few fibers, even in Layer VI. On the left side of this series, near the midpoint of pars principalis, only the dorsalmost portion appears degenerated and near the middle of the extent of the primary auditory area only the dorsal border is delaminated.

The right pars principalis and the right koniocortex of brains no. 96362 and no. 96836 are less affected than the left. In the no. 96362 series, the fibers are extremely delicate caudally in the left pars principalis; and approximately the caudal sixth of the left primary auditory area is abnormal. The most normal part of the left pars principalis lies just anterior to its midpoint; and it is at a similar level of the left primary auditory area that fibers are numerous in Layers II, III and IV, as well as V and VI. In brain no. 96836, the cells of the right pars principalis become crowded orally and it is difficult to trace the nucleus far rostralward. Similarly the entire rostral end of the right primary auditory area is delaminated. The left pars principalis broadens for a short distance near the midpoint of its extent; the left primary auditory area is laminated for about 50 μ just anterior to the midpoint, although there are no knobs in the fourth layer. It is extremely difficult to trace the left pars principalis rostralward, and the anterior third of the left auditory koniocortex is atypical to its oral tip.

The right pars principalis and the right primary auditory area are better preserved caudally in brain no. 96050 than in the previous brains. The rostral third of the nucleus is fairly normal in appearance on this side, also, and the rostral third of the auditory koniocortex is generally well represented. The caudal end of both the pars principalis and the primary auditory area are more affected on the left than on the right. The anterior half of the nucleus is nearly normal in appearance, and the rostral half of the auditory koniocortex is laminated except at its far dorsal border.

The lamination of pars principalis observed in higher forms is not so evident in this material. The ventral and the ventromedial portions of the nucleus are generally less degenerated than the dorsal portion and the lateral border; yet, the ventral part of the primary auditory area is more atypical than the dorsal border. The dorsal third or more of pars principalis is nearly always degenerated and may be atrophied. The dorsomedial cells and fibers are included in this atypical portion. This may indicate that, in the rodent, the cells which project to the ventral part of the primary auditory area are dorsomedially situated.

The dorsal part of pars principalis appears to project along its entire caudorostral extent to corresponding portions of the ipsilateral primary auditory cortex. Degeneration is not confined to the anterior half of pars principalis in these abnormal mice, as it was in the retrograde degeneration studies carried out on the cat by Neff and Diamond ('58). Since the ventral and ventromedial portions of the "chief mass" of pars principalis are least affected in the animals reported here, it may be that this ventral region of pars principalis in the mouse corresponds in its projection pattern to the caudal portion of pars principalis in the cat. The dorsal region, which is most atypical in these abnormal animals, would then correspond in its projection pattern to the anterior portion of pars principalis in the cat.

A relationship between pars magnocellularis and the secondary area is not evident. It may be that in the rodent, as in the cat (Rose and Woolsey, '58), pars magnocellularis is related to the secondary auditory area by sustaining fibers. One feature of the degeneration in the secondary area for hearing is that it sometimes appears in exactly reverse location from that in the primary area. For example, on the right side of brain no. 96836, the ventral border of the auditory koniocortex anteriorly and the dorsal border of the secondary area posteriorly are degenerated; on the left, the ventral part of the primary and the dorsal portion of the secondary area for hearing are atypical. In brain no. 96050, on the left, the dorsal border of the primary and the ventral

border of the secondary areas are atypical throughout. Whether or not this indicates a projection from auditory koniocortex to the secondary auditory area cannot be stated at this time.

The extreme behavior observed in the abnormal mice in response to audiogenic stimuli — waltzing, dashing, and loss of consciousness — appears to be similar to the "grand mal" type of epilepsy encountered in man. During such a seizure, the animal falls on its side, sometimes with the forelimbs flexed and the hind limbs extended. The mouse may be picked up and handled during this time. There is no resistance to passive movement of its limbs. It recovers from the seizure quickly, but its movements are not well coordinated at first and the animal seems sluggish.

The exciting cause of a convulsive seizure in these mice is an auditory stimulus; and, hence, the locus of the disease appears to be within the degenerating auditory area of the cerebrum. This cannot be stated with absolute certainty, however, as Beach and Weaver ('43) were able to demonstrate that the epileptic response to audiogenic stimuli in susceptible rats was increased in intensity and that the time interval between the onset of the stimulus and the seizure was shortened following removal of all or part of the neocortex. Unfortunately, histological studies of the brains of the rats used by Beach and Weaver were not reported. We have no way of knowing the possible site of origin of the massive responses shown by these animals once neocortex was removed.

In the case of the mice used in our studies there can be no doubt that the impulses set up by the sound of jingling keys is highly disorganizing and distressing to the animal when it reaches higher auditory centers. It must be noted that such sounds (jingling keys) are not distressing to normal animals with intact auditory systems nor are the abnormal animals subject to epileptic seizures once the auditory pathways are nearly completely degenerated so that the animals are deaf (Ross, '62).

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The author is extremely indebted to Dr. Lee R. Dice of the Laboratory of Vertebrate Biology for having provided an abundance of mice for study and to him and Dr. Elizabeth Barto who spent much time in testing the abnormal animals for range of hearing. She is also deeply grateful to Dr. Elizabeth C. Crosby and Dr. Edward Lauer for their constructive criticisms of this paper.

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Abbreviations

AT, Acoustic tubercle
Avn, Anteroventral nucleus of ventral cochlear nucleus
"c" Group "c" of pars principalis of the medial geniculate nucleus
cm, "Chief mass" of pars principalis of the medial geniculate nucleus
dg, Dorsal group of pars principalis of the medial geniculate nucleus
d. grp., Dorsal group of cells in the posteroventral nucleus of the ventral cochlear nucleus
IC, Inferior colliculus
l, Lateral group of pars principalis of the medial geniculate nucleus
LC, Lamina cellularis of the dorsal cochlear nucleus
LL, Lateral lemniscus
M, Pars magnocellularis of the medial geniculate nucleus
MGN, Medial geniculate nucleus
NP, Nucleus proprius
PvN, Posteroventral nucleus of the ventral cochlear nucleus
SO, Superior olive
TB, Trapezoid body
v. grp., Ventral group of the ventral cochlear nucleus
I, Lamina I of the primary auditory cortex
II + III, Lamina II + III of the primary auditory cortex
IV, Lamina IV of the primary auditory cortex
V, Lamina V of the primary auditory cortex
VI, Lamina VI of the primary auditory cortex

PLATE 1

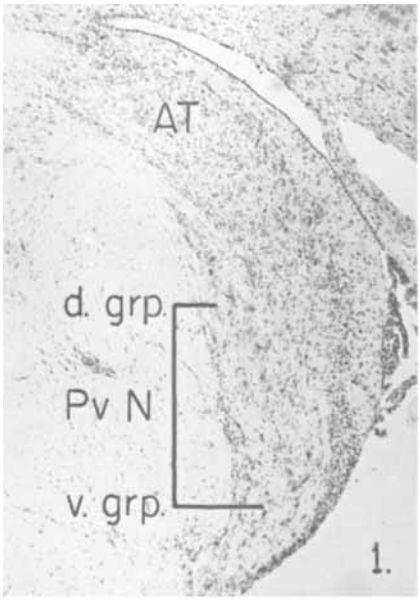
EXPLANATION OF FIGURES

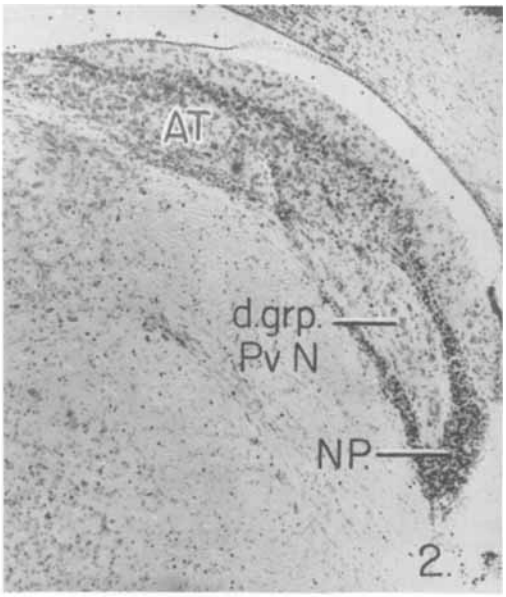
1 In this transverse section through the dorsal and ventral cochlear nuclei of the normal mouse, the acoustic tubercle (AT) is well developed and laminated. The ventral cochlear nucleus consists of the posteroventral subdivision (PvN), and dorsal (d. grp.) and ventral (v. grp.) groups are readily distinguished within it. Cresyl-echt-violet preparation. × 50.

2 This transverse section through the dorsal and ventral cochlear nuclei of partially deaf Mouse no. 96050 is slightly posterior to the plane shown in figure 1. The increase in the small, round cells of nucleus proprius (NP), as well as elsewhere in the acoustic tubercle, is apparent. Only the dorsal group (d. grp.) of the posteroventral subdivision (PvN) of the ventral cochlear nucleus is present at this level. The neurons of the dorsal group are paler staining, due to a loss of Nissl substance, in this abnormal brain than in the normal material shown in figure 1. Toluidin blue preparation. × 50.

3 In this photomicrograph, the dorsal (AT) and ventral (PvN) cochlear nuclei of the normal mouse are shown near the level of the entrance of the cochlear nerve. The posteroventral nucleus (PvN) has a rounded, hillock shape. The dorsal group (d. grp.) is terminating as a small mass of neurons, while the ventral group (v. grp.) is large and well developed. Note that the neurons of the ventral group are separated into laminae by the cochlear nerve fibers coursing posteriorly through the nucleus. Cresyl-echt-violet preparation. × 50.

4 Figure 4 should be compared with figure 3, as both are sections from approximately the same levels. Note the general thinning of both the dorsal and the ventral cochlear nuclei in this abnormal brain (no. 96050) together with a prominence of small, round cells. Only the ventral group (v. grp.) is found in the posteroventral subdivision (PvN) of the ventral cochlear nucleus in this transverse section, and its neurons are pale-staining and ovoid. Toluidin blue preparation. × 50.


AT
d. grp.
Pv N
v. grp.
1.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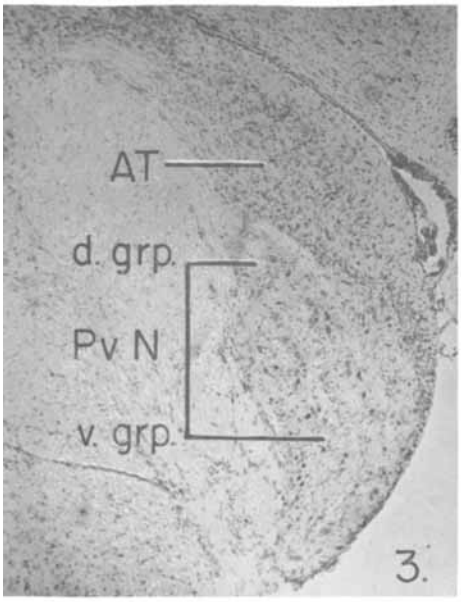
AT
d. grp.
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v. grp.
3.

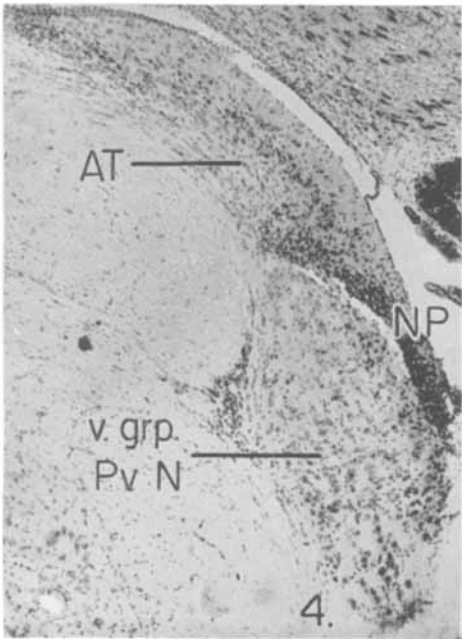
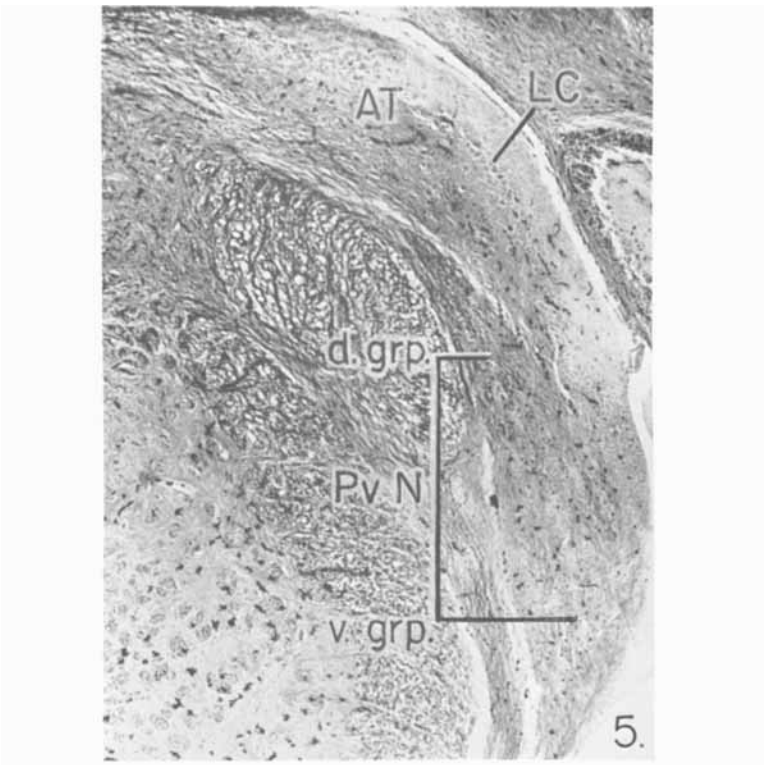

AT
NP
v. grp.
Pv N
4.

PLATE 2

EXPLANATION OF FIGURES

5 In this transverse section through dorsal and ventral cochlear nuclei of Mouse no. 96835, the general loss of fibers is evident. The ventral group (v. grp.) of the posteroventral subdivision of the ventral cochlear nucleus sustains greater losses than the dorsal group (d. grp.), which has a good fiber supply. Nucleus proprius appears "granular" even in this fiber-stained preparation. The neurons of lamina cellularis (LC) are prominent, and the acoustic tubercle exhibits fiber losses dorsally and ventrally. Weil stained preparation. × 40.

6 Fibers ramify in the dorsal portion of the acoustic tubercle (AT) in Mouse no. 96362 and are more numerous in the dorsal group (d. grp.) than in the ventral group (v. grp.) of the posteroventral subdivision of the ventral cochlear nucleus. Nucleus proprius (NP) is not so severely atrophied in this series as in Mouse no. 96835. Weil stained preparation. × 40.


AT
LC
d. grp.
Pv N
v. grp.
5.

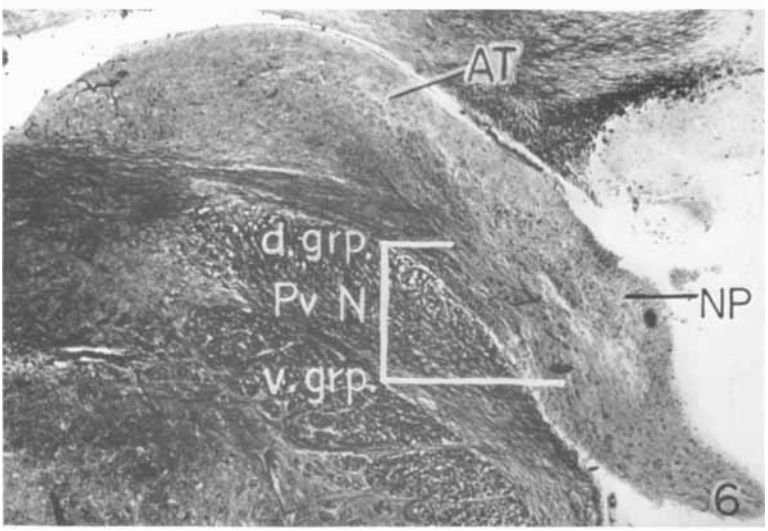

AT
d. grp.
Pv N
v. grp.
NP
6

PLATE 3

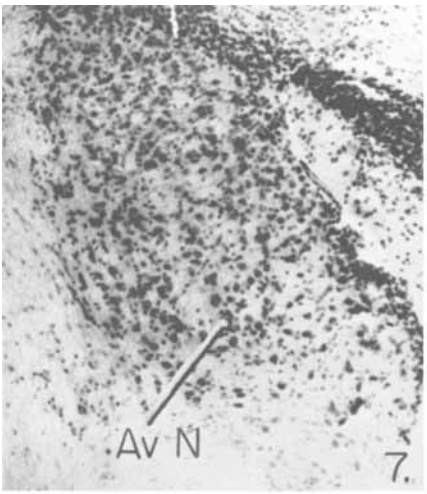
EXPLANATION OF FIGURES

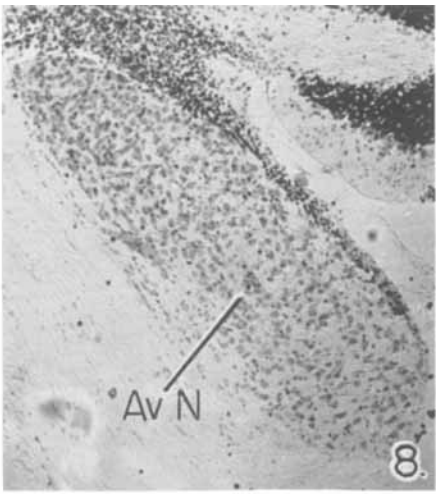
7 The normal anteroventral nucleus (AvN) is shown in this photomicrograph as it appears in transverse sections just rostral to the level of the cochlear nerve. The cells dorsally disposed are ovoid in shape and more closely spaced than the more ventral neurons. Cresyl-echt-violet preparation. × 75.

8 This transverse section showing the anteroventral nucleus of abnormal Mouse no. 96836 lies at approximately the same level as that shown in figure 7. The nucleus is thinner than normal, and the neurons are much more closely grouped than in the normal material. The change in staining quality of the cells is also evident. Toluidin blue preparation. × 75.

9 A transverse section of the normal superior olivary nucleus at the level of the left facial nerve. The neurons of the superior olive (SO) are dark-staining, spindle-shaped or multiangular, and are arranged in folds. The nucleus of the trapezoid body (TB) is shown to the right on the photomicrograph. Cresyl-echt-violet stained preparation. × 75.

10 The superior olivary nucleus (SO) of abnormal Mouse no. 96836 exhibits enlarged, pale-staining cells which are not arranged in conspicuous folds at the level of the facial nerve. The cells of the nucleus of the trapezoid body (TB), at the right of the photomicrograph, are also swollen and closely spaced. Compare this section with figure 9. Toluidin blue stain. × 75.


Av N
7.


Av N
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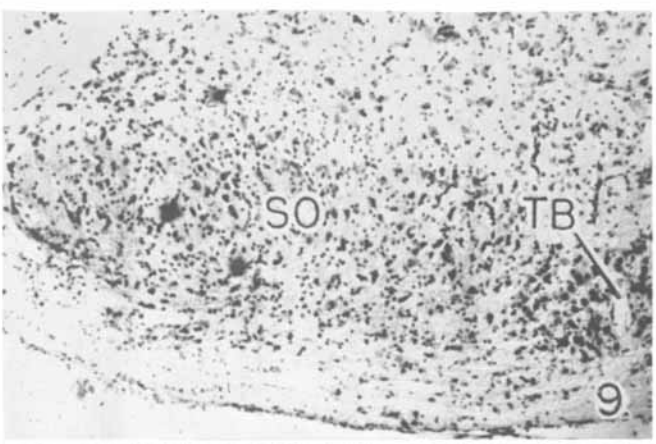
SO
TB
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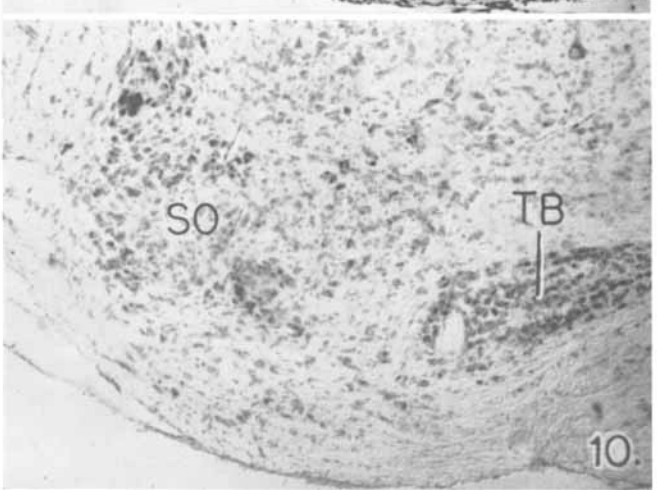
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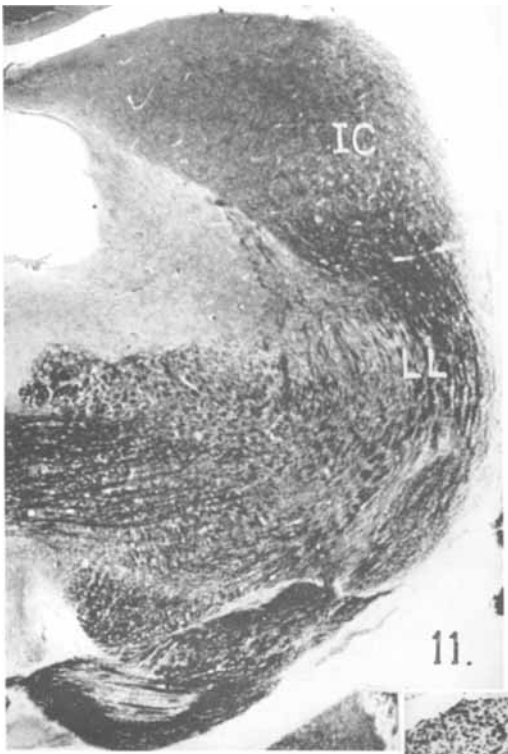
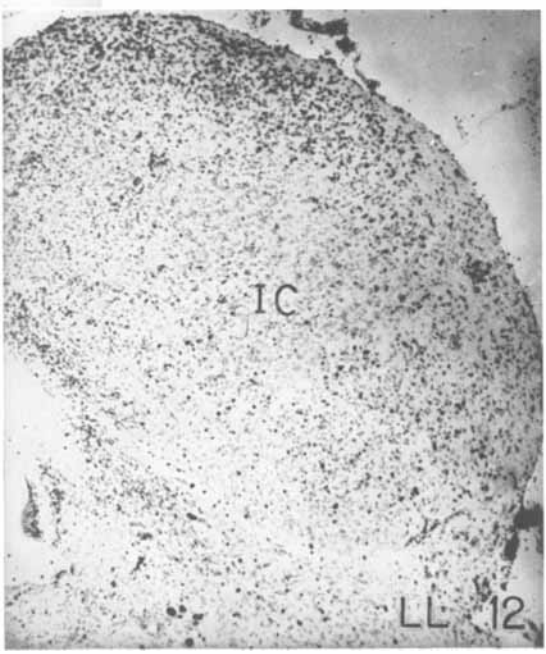
PLATE 4

EXPLANATION OF FIGURES

11 This photomicrograph shows the well-developed normal inferior colliculus (IC) as it appears in transverse section. The large lateral lemniscus (LL) is entering the colliculus. Weil stained preparation. × 32.

12 The inferior colliculus (IC) of abnormal Mouse no. 96050 is greatly magnified to show the close spacing of the neurons and the increase in small, round cells which gives a granular appearance to the nucleus. The inferior colliculus is more nearly round and smaller than in the normal mouse. The lateral lemniscus (LL) is also shown in this transverse section. Toluidin blue preparation. × 48.


IC
LL
11.


IC
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12

PLATE 5

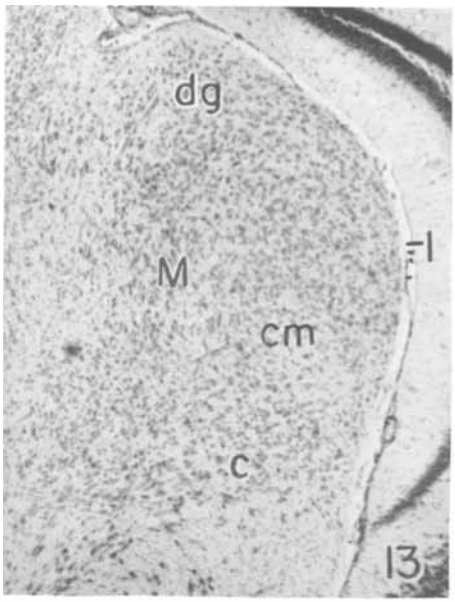
EXPLANATION OF FIGURES

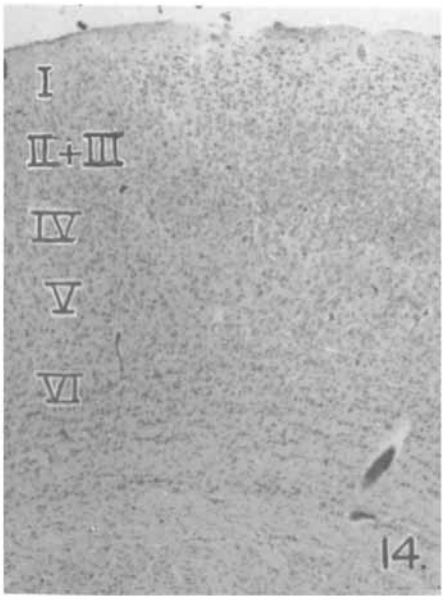
13 The normal medial geniculate nucleus has a bean shape in this transverse section taken from the middle third of its caudorosral extent. This section shows all of the various subdivisions of pars principalis clearly: the dorsal group (dg), the lateral division (l), the chief mass (cm), and the "c" group (c). Pars magnocellularis (M) is also evident. Toluidin blue preparation. × 46.

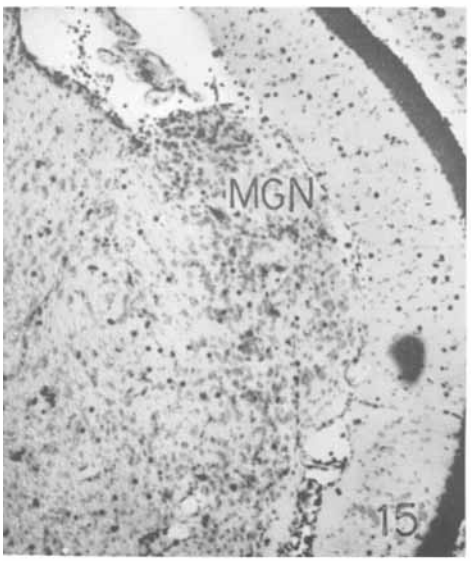
14 The primary auditory cortex of the normal mouse shows a six-layered plan of organization (I–VI) with a clustering of cells in the fourth lamina. Toluidin blue preparation. × 55.

15 In Mouse no. 96050, the medial geniculate nucleus (MGN) appears caudally as a thin band of neurons which are enlarged and pale-staining. Small, round cells are more numerous than in normal material. Toluidin blue preparation. × 50.

16 This protomicrograph illustrates the general thinning of the auditory koniocortex in its caudal third in Mouse no. 96050. This transverse section shows the dorsal portion of the area in which numerous typical appearing cells are present. Toluidin blue preparation. × 60.


dg
M
cm
c
13.


I
II+III
IV
V
VI
14.


MGN
15.

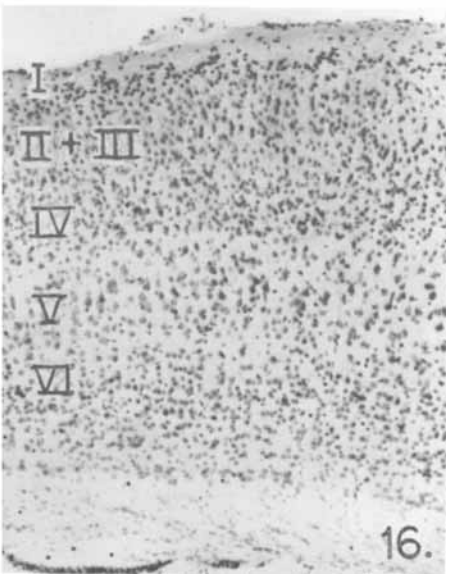

I
II + III
IV
V
VI
16.

PLATE 6

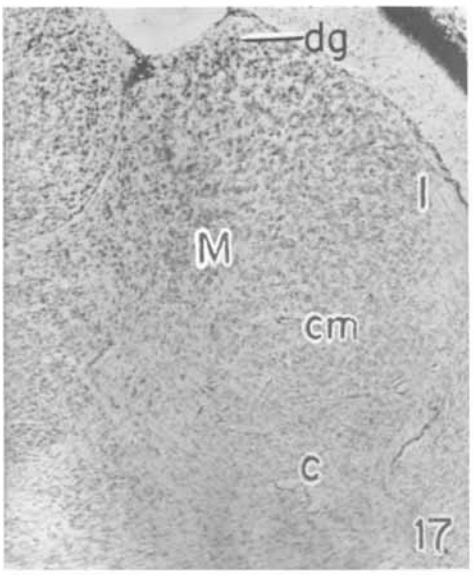
EXPLANATION OF FIGURES

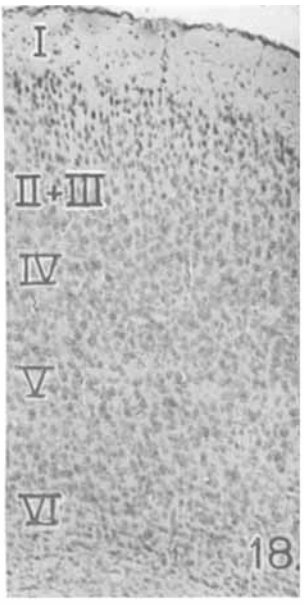
17 A transverse section through the middle third of the caudorostral extent of the medial geniculate nucleus of Mouse no. 96836. The various subdivisions of the nucleus are present. The shape of the nucleus is typical. The neurons are somewhat enlarged, however, and more closely arranged than in normal material. Compare with figure 13. Toluidin blue preparation. × 60.

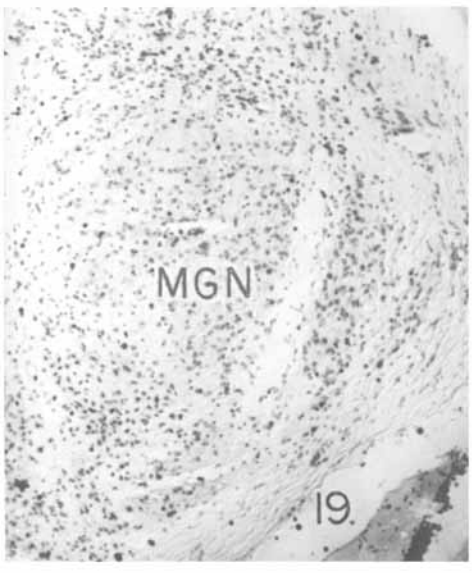
18 The primary auditory area of Mouse no. 96836 is laminated in the middle third of its caudorostral extent, but many of the cells are swollen and pale-staining. Toluidin blue preparation. × 75.

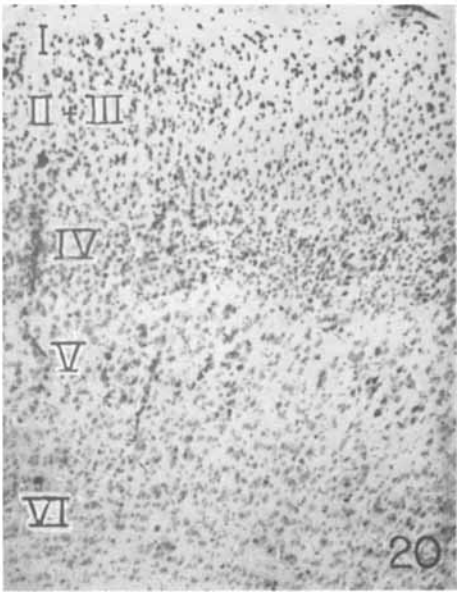
19 The medial geniculate nucleus is shown in its rostral third where it is situated deep to the lateral geniculate nucleus, pulvinar, and lateral nucleus of the thalamus. The ovoid neurons with pale-staining Nissl granules suggest degeneration. This transverse section is taken from the Mouse no. 96050 series. Toluidin blue preparation. × 60.

20 The cortical laminae are more distinct rostrally than caudally in the primary auditory cortex in Mouse no. 96050 (compare fig. 20 with fig. 16). Many typical cells are found, and the clustering of neurons in Layer IV is observed. Toluidin blue preparation. × 75.


dg
I
M
cm
c
17


I
II+III
IV
V
VI
18


MGN
19


I
II+III
IV
V
VI
20