NUCLEAR JAUNDICE AND DEAFNESS

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THE first case of deafness associated with kernicterus was recorded by Coquet (1944). Lande (1948), Evans and Polani (1950), Crabtree and Gerrard (1950), Hazell (1950) and Goodhill (1950), more recently, have also observed deafness in children with kernicterus. Perlstein (1950) suggests that it occurs in about 40 per cent. of cases, Evans and Polani (1950) consider the incidence is rather less, namely, 20 per cent.; in the experience of Crabtree and Gerrard (1950), who have recorded the greatest number, it is present in 80 per cent. of cases. The incidence may be even greater, for of 24 children whom we have now seen with neurological sequelae to Rh iso-immunization, aged 5 years or more, and who have been submitted to a full audiometric examination, 22 have a perceptive deafness, one has a conductive deafness and one child only has a normal range of hearing.

Although kernicterus commonly occurs in association with Rh incompatibility it may occur independently and is then usually associated with prematurity (Zuelzer and Mudgett, 1950; Aiden *et al.*, 1950). But whether it occurs with the former or with the latter its neuropathology is identical and lesions of the cochlear nuclei are common.

Method

With a view to finding out if perceptive deafness, associated with a severe neonatal jaundice and either Rh incompatibility or prematurity, was a common cause of deafness in the deaf population, I approached Mr. Cockersole, the Headmaster of the Royal School for the Deaf, Birmingham, and Miss Lack and Miss North, the Headmistresses of the two city council schools for the deaf. They kindly agreed to forward a questionnaire to the parents of their deaf children.

Four hundred and seven questionnaires were despatched; three hundred and sixty replies were received. Thirty-three deaf children were stated to have been jaundiced in infancy. These children were visited, blood was taken from the child and from his or her mother, and a careful record of the family history was taken. The blood from the mother and child was grouped and the maternal serum was tested for Rh antibodies against a battery of Rh positive and Rh negative cells suspended in saline and in bovine albumin. One mother refused to co-operate; her daughter, she said, was too highly strung; a second family could not be investigated as the mother was no longer alive.

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The incidence of deafness associated with Rh iso-immunization

Of the thirty-three children who had been jaundiced in infancy the jaundice in five was associated with Rh iso-immunization, these five were all mild cases of kernicterus, i.e. they were excitable and they exhibited involuntary movements of a choreic character. Five cases in a population of 407 (although only 360 answered the questionnaires) is not a large number but it reveals a greater incidence of cases of kernicterus than occurs in the population at large, where the incidence is no greater than one per 3,000, and is highly significant (P less than 0·001). These five children all had a high-frequency perceptive deafness.

The number of children, however, with a perceptive deafness following hæmolytic disease of the newborn in the schools for the deaf in Birmingham is rising, and for three main reasons. 1. We have been able to show that some children who were thought to be mentally retarded are in fact deaf. 2. Children with kernicterus are given a full audiometric examination as soon as they are old enough to co-operate (usually at the age of 4 or 5), deafness when present is therefore detected early and arrangements can be made for the child to have suitable tuition ; he is not allowed to languish untutored at home. 3. We consider that many such children derive more benefit by education in a school for the deaf, or partially deaf, than in a school for the physically handicapped unless special tuition for the partially deaf is available in the latter.

The incidence of deafness associated with prematurity

The birth weight of the deaf child was known in 181 instances ; in 33 instances the child weighed 5½ lb. or less at birth, i.e. 18·3 per cent. were born prematurely. This contrasts with an incidence of premature births of 6·9 per cent. in Birmingham as a whole (Crosse, 1949). This increased incidence of premature births among the deaf children is highly significant (P less than 0·01). Premature babies usually exhibit an obvious physiological jaundice, whether deafness becomes apparent later or not. Of the 26 children who were jaundiced in infancy and who did not have hæmolytic disease the deafness in one was probably familial (his mother, father and grandmother were all deaf), in another it was probably due to maternal rubella at the tenth week of gestation, and in two others was associated with chronic middle-ear disease ; one child is mentally retarded, not deaf. Details of the remaining 21 cases are given in the accompanying table.

Eleven of these cases were jaundiced for 14 or more days, none became noticeably pale and in no instance was the family history suggestive of hæmolytic disease of the newborn. Eight (Cases A, B, D, E, G, R, S, and U) were late in learning to walk, i.e. they did not learn to walk until they were at least 2 years old ; six (Cases A, B, D, E, R, and S) are clinically

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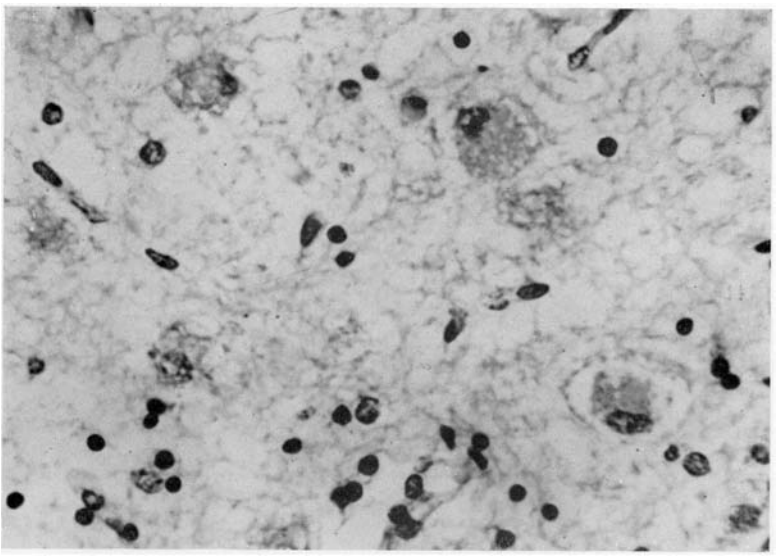


Fig. 1.

Dorsal cochlear nucleus, showing extensive cell destruction (H. and E. × 600).

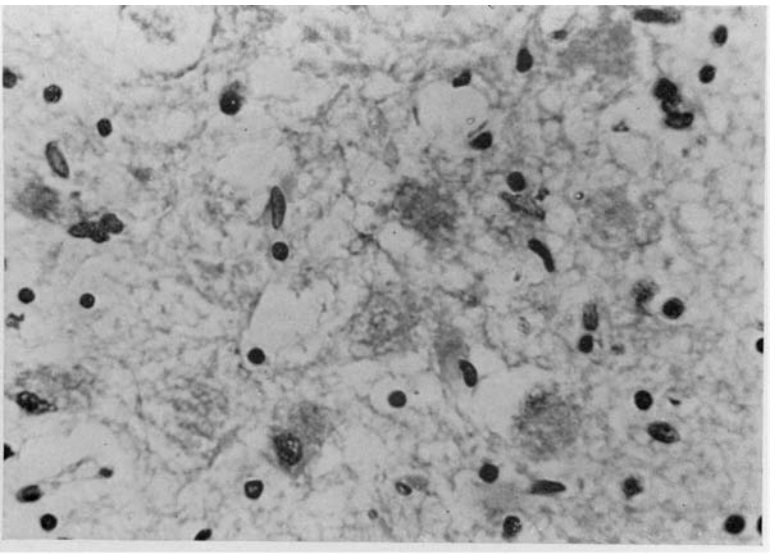


Fig. 2.

Ventral cochlear nucleus, showing extensive cell destruction (H. and E. × 600).

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TABLE.

Case	Age in years	Birth wt. lb.	Birth wt. oz.	Jaundice Onset	Jaundice Duration	First sat up	First walked	Comments	Deafness
A	14	4	8	3rd day	14 days	18 months	3½ years	Choreic and excitable	H.F.P.
B	14	7	8	Not certain		?	2½ years	Ataxic initially, now normal	H.F.P.
C	14	6	0	1st day	3 days	6 months	13 months	Excitable	Severe P.
D	7	5	8	1st day	4 days	15 months	2 years	Ataxic and excitable	H.F.P.
E	10	7	8	Birth	42 days	?	5 years	Choreic and excitable	H.F.P.
F	8	6	8	Birth	14 days	6 months	14 months	Normal	H.F.P.
G	10	7	12	2nd day	3 months	9 months	24 months	Normal	Severe P.
H	15	4	12	2nd day	4 days	6 months	14 months	Normal	H.F.P.
I	8	7	4	1st day	7 days	9 months	15 months	Normal	H.F.P.
J	10	7	2	Birth	35 days	7 months	18 months	Excitable	Perceptive
K	10	7	8	Birth	14 days	5 months	12 months	Normal	Perceptive
L	10	4	12	2nd day	10 days	11 months	22 months	Normal	H.F.P.
M	11	6	8	2nd day	21 days	6 months	12 months	Normal	H.F.P.
N	14	6	8	Birth	42 days	6 months	12 months	Normal	H.F.P.
O	13	Less than 3 lb.		2nd day	4 days	8 months	16 months	Excitable	Total P.
P	9	6	8	2nd day	3 days	6 months	13 months	Excitable	Total P.
Q	11	4	0	Birth	14 days	7 months	14 months	Excitable	H.F.P.
R	4	4	5	Birth	35 days	12 months	24 months	Choreic and excitable	Too young
S	9	7	8	1st day	5 days	11 months	24 months	Ataxic and excitable	Unco-operative
T	6	6	6	Birth	35 days	6 months	18 months	Normal	Unco-operative
U	7	7	0	Birth	7 days	9 months	24 months	Normal	?

The Table above gives relevant details of the children in three schools for the deaf whose deafness was associated with neonatal jaundice but not with Rh iso-immunization.
P.—perceptive deafness.
H.F.P.—high-frequency perceptive deafness.

indistinguishable from mild cases of kernicterus; seven (35 per cent.) weighed 5½ lb. or less at birth.

Four of these children were admitted to hospital soon after birth because the jaundice had become deep and their general condition critical, in one (Case R) it was possible to obtain a detailed history. This child's general condition, as is so often the case in this type of kernicterus, was satisfactory, apart from deepening jaundice, until the seventh day of life, when he became drowsy, developed head retraction and refused feeds. In the course of the next few days he gradually improved and again, as so often happens, he appeared to be normal when he was discharged home; involuntary movements and deafness only became apparent later.

The pathological anatomy of the high-frequency deafness

Attention has already been drawn (Crabtree and Gerrard, 1950) to the probable site of the lesion responsible for the high-frequency deafness in these cases.

Crowe, Guild and Polvogt (1934) have, however, shown that the organ of Corti, in the basal coil of the cochlea, is often abnormal in cases of high-frequency deafness; but in 17 of 46 such cases which they investigated both the organ of Corti and the spiral ganglion of Corti were normal; they suggested that the deafness in these cases might be due either to a lesion in the central nervous system, or to an atrophy, which they were unable to demonstrate, of the non-medullated collateral and terminal nerve fibres in the organ of Corti itself.

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Impulses received by the organ of Corti are transmitted along the auditory division of the VIIIth nerve ; on entering the medulla each fibre divides (Lorente de Nó, 1933) ; one branch passes to the dorsal and the other to the ventral cochlear nucleus. Lorente de Nó (1933) did not consider that there was a point-to-point representation of the cochlea in the cochlear nuclei, but Lewy and Kobrak (1936) have been able to demonstrate that, in the rabbit, nerve fibres from the inferior turns of the cochlea, i.e. those mediating the higher frequencies, end dorsally, and those from the superior turns end ventrally in the cochlear nuclei. From the latter second-order neurones cross the midline and ascend in the lateral lemniscus to the inferior colliculus ; third-order neurones ascend further to the medial geniculate body. The inferior colliculus is probably not concerned with hearing as such, but with reflex mechanisms by which, for example, the head and neck and eyes are directed towards auditory stimuli when they are heard. The medial geniculate body is the final relay station on the auditory path to the cerebral cortex, and in it, as Ades *et al.* (1938) have demonstrated—in cats—there is a well marked localization of frequencies ; those, for example, of 8,000 cycles per second are mediated in the dorsal region, and those of 4,000 cycles per second in the anterior quadrant. From the medial geniculate body nerve fibres fan out to a circumscribed area of the temporal cortex (Poliak, 1932) which lies, in primates, in the superior temporal gyrus in the floor of the Sylvian fissure. The auditory cortex has its own characteristic cyto-architecture and has been further localized, in the monkey, by recording cortical responses to auditory stimuli (Ades and Felder, 1942, and McCulloch *et al.*, 1942). Locklider and Kryter (1942) have found that frequencies are localized more sharply in monkeys than in cats, indicating a more highly developed acoustic centre in the former.

There is not only a point-to-point relation between the cochlea and the cochlear nuclei, as already indicated, but also between the cochlea and the auditory cortex (Woolsey and Walzl, 1942) and between the auditory cortex and the medial geniculate body (Walker, 1938). The higher frequencies, mediated by the basal coil of the cochlea, are transmitted in the dorsal cochlear nucleus, the dorsal region and the anterior quadrant of the medial geniculate body, to the rostral part of the auditory or koniocortex. Symmetrical high-frequency perceptive deafness might, therefore, be due to a bilateral lesion in any of the above areas or in the interconnecting neurones. Cortical lesions may produce deafness, but disorders of hearing, for example, tinnitus, are more common (Frazier and Rowe, 1934).

I have been able to examine the cochlea in two cases of kernicterus who died during the neonatal period. Serial sections were taken and no abnormality was detected either in the organ of Corti—the basal coil was examined with especial care—or in the spiral ganglion of Corti. The

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latter is analogous to the dorsal root ganglia (Fulton, 1949) ; no pathological lesions of the dorsal root ganglia have been observed in cases of kernicterus. In these two cases, where the organ of Corti and the spiral ganglion of Corti were normal, extensive destruction of the nerve cells in the cochlear nuclei was present (Figs. 1 and 2). In some instances the nerve cells had disintegrated completely, in others the nuclei had faded away leaving only a cell outline or " ghost " cell to mark their original position, in yet other instances the cytoplasm had a homogeneous appearance, staining a uniform pink with eosin, and the nucleus was hyperchromatic, shrunken and in some instances fragmented. The cell destruction was, in each case, bilateral, and involved both the ventral and dorsal cochlear nuclei ; a few scattered normal cells remained. I had hoped to find the ventral cochlear nucleus unaffected and the cell destruction limited to the dorsal nucleus, but this was not the case. In retrospect this is not surprising, as the cases were so severely affected that death was inevitable. Even in those who survive the neonatal period the lesion is sometimes sufficiently extensive to cause total deafness, and in most the nucleus must be partially destroyed.

In one case sections were also taken through the inferior colliculus, the medial geniculate body and the temporal cortex ; the nerve cells in these regions were essentially normal.

That the cochlear nuclei may be damaged in kernicterus has been noted by a number of authors (Beneke, 1907 ; Esch, 1908 ; Potter, 1947 ; Bertrand, 1946 ; and Dereymaeker, 1949). Many others (Orth, 1875 ; Schmorl, 1903 ; Pfannenstiel, 1908 ; Pfältzer, 1915 ; Ylppö, 1918 ; Palm, 1919 ; Hawkesley and Lightwood, 1934 ; Forster and McCormack, 1944 ; Stiller, 1947 ; and Becker and Vogel, 1948) have noted icteric pigmentation of the floor of the fourth ventricle and the underlying cranial nerve nuclei. The cochlear nuclei are, therefore, not infrequently damaged in cases of kernicterus, and it is this lesion, I think, which is responsible for the high-frequency perceptive deafness which is such a common finding in this condition. It is, perhaps, not without significance that the pigmentation seen on cross section of the medulla is more marked in the floor of the fourth ventricle than in the deeper substance of the medulla ; if pigmentation is indicative of neural damage, and there are grounds for believing this to be so, this would suggest that lesions of the dorsal cochlear nuclei are more common and more severe than lesions of the ventral nuclei, thus correlating the pathological with the clinical findings. There have as yet been no recorded cases where a child with kernicterus, and known to have been deaf, has come to autopsy and the cause of the deafness verified microscopically.

I do not think that the neurological lesion is due either to the jaundice or, directly, to Rh iso-immunization, but whatever is responsible for the neurological lesion is probably an important cause of high-frequency

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deafness both in children who have had hæmolytic disease of the newborn and in others who may have been born prematurely. In these cases the high-tone loss is due to a lesion of the cochlear nuclei, and is probably acquired during the first week of life.

Discussion

Whatever the metabolic process in kernicterus by which nerve cells are destroyed this process frequently gives rise to lesions in the cochlear nuclei especially the dorsal cochlear nuclei and those fibres mediating tones of the higher frequencies. Occasionally in our experience this nucleus, and this nucleus alone, may show evidence of permanent damage, as Goodhill (1950) also has noted, and the only persisting neurological sequel is a perceptive high-tone deafness.

Hiller (1950), in Tasmania, has recently analysed 42 congenitally deaf children. In 32 instances the deafness was due to maternal rubella ; in those cases, although the high-tone loss was greater than that of the low tones, the fall, as shown in the audiometric charts, was not steep, nor did the charts exhibit a uniform pattern. In the remaining 10 cases, in six of which the deafness was probably hereditary, the audiometric charts were more uniform and the fall was steeper. Hiller virtually suggests that congenital deafness is due either to maternal rubella or to a hereditary factor. This may be so in a small isolated country like Tasmania but in this country, where most women acquire their rubella in childhood, many cases of congenital deafness are still unexplained.

Attention has already been drawn (Crabtree and Gerrard, 1950) to the association of a severe neonatal jaundice with perceptive deafness ; this jaundice may be associated with Rh incompatibility or with prematurity, but this is not always so. In my experience the very small babies with kernicterus, not associated with Rh incompatibility, usually die, whereas the babies who weigh 5 or more pounds at birth and who develop kernicterus often survive and present with deafness later. A careful enquiry into the early progress of these children often reveals a sudden deterioration between the third and seventh days of life when the child becomes critically ill. A spontaneous and apparently complete recovery may then take place, but the child is usually late in sitting up, standing and walking.

Hiller has rightly stressed the roles of maternal rubella and heredity in the production of congenital deafness, but some cases of perceptive deafness may be thought, wrongly, to be congenital when they are, in fact, acquired soon after birth ; in these the deafness is associated with lesions of the cochlear nuclei and not with any developmental defect and it can be distinguished by its frequent association with a severe neonatal jaundice, Rh incompatibility or prematurity.

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Summary

1. An investigation has been carried out into the part played by Rh iso-immunization and prematurity in the production of perceptive deafness.

2. This deafness was associated in five, and possibly six, of 407 children with kernicterus due to Rh iso-immunization.

3. In a further 17 cases there was a comparable perceptive deafness associated not with Rh iso-immunization but with a high incidence of severe neonatal jaundice and prematurity.

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