DEAFNESS AS PART OF AN HEREDITARY SYNDROME

By L. FISCH (London)*

I. Introduction

THE syndrome which is the subject of this paper consists of the following symptoms or signs:

(1) Malformation of the inner angles of the eyelids.
(2) Congenital perceptive deafness.
(3) Differently coloured eyes (heterochromia iridium).
(4) A white forelock.

Not all these signs are always present, and various combinations of two or more may occur. Less frequently additional signs crop up, and these will be mentioned later.

The syndrome is hereditary, and was described fully by P. J. Waardenburg (1951) although the association of some of the signs with congenital deafness was recognized before.

The aspect of deafness was not studied previously in detail, and Waardenburg mentioned in his paper in 1951 that he hoped someone would undertake this special study, and we have done so.

Besides detailed information concerning the types and degrees of deafness our study revealed some additional information and this modified the significance of our study. Accordingly the scope of this paper can be summarized in the following points:

(1) Our investigation revealed new and so far unknown aspects of the types and degrees of deafness associated with this syndrome,

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and this has important bearings on the knowledge of congenital perceptive deafness in general.

(2) Histological description is given for the first time.

(3) An explanation of the mechanisms of the developmental abnormality is suggested, including an explanation for the association of a congenital abnormality in the inner ear and abnormalities of body pigmentation.

(4) The large number of cases which was available for a detailed study revealed new aspects, and the investigation of family groups led to the discovery of what we think is a new syndrome, although related to this one.

(5) Previously it was thought that this was a comparatively rare condition, but, although almost unknown to those who are interested in problems of deafness, we found that it was common, and played an important part in the recognition of the aetiology of deafness.

(6) Certain differential diagnostic aspects of practical importance are pointed out.

II. Material and Methods

Initially 81 cases (probands) were collected for the survey, and out of these, 35 were selected for the present study. Many parents and relations were examined in detail, and this considerably increased the total number of observed subjects who had signs of the syndrome.

In a few of the remaining 46 cases no further co-operation was forthcoming, or we were not able to get enough detailed information in good time before the study had to be concluded. Some were not included because it was found that they belonged to a different genetic or ætiologic group. They showed certain features which merit a separate study.

Some of the cases were found among patients attending for investigation at the Audiology Unit, and some were discovered as a result of an appeal in the journal *Teacher of the Deaf* (1956) which resulted in reports from various deaf schools where these children were pupils.

In most cases photographic evidence was obtained, and frequently, from old family photographs, pictorial evidence was available extending to several generations. Some of these were selected for a more detailed investigation, and visited in their homes by a team (otologist, geneticist, audiometrician), and as many members of the family as possible were examined.

Because the most penetrating sign of the syndrome (which is nearly always present) is the easily detectable eyelid deformity, special attention was paid from this point of view to all children attending at the Audiology Unit. It soon became clear that careful observation revealed unexpectedly

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large numbers of these cases, and therefore the number for the purpose of this investigation had to be limited to a representative group, large enough for a detailed clinical study (that is 35 cases). At this stage, the purpose was not to study the incidence, and therefore only those family groups for which detailed information was available were included.

Considerable pictorial material was collected for further study, and many coloured pictures were later found to be invaluable for a more detailed examination of some disorders of pigmentation. It is impossible to reproduce in an article even a small fraction of the photographic material, but some of it was used for an exhibit which was prepared for the Scientific Exhibition of the B.M.A. at Birmingham in July, 1958. This gives a complete pictorial review of the syndrome, and is available for inspection at the Audiology Unit, London.

III. Results

OBSERVATIONS CONCERNING SIGNS AND SYMPTOMS

Deafness is numerically the most significant *disabling* symptom of this syndrome and when medical advice is sought, these subjects frequently come under the care of an E.N.T. Specialist. It is important that they should possess an accurate knowledge of the signs, for important differential diagnostic aspects are involved.

Waardenburg (1951) discussed in detail all the characteristics of this syndrome and here we give only a brief description. This is, however, based entirely on our own cases and differs in some details from Waardenburg's description.

1. The eyelid deformity.

The eyelids are joined at the inner canthus almost at the level of the medial side of the cornea. Normally the amount of sclera visible on the lateral and medial side is the same. In the case of this eyelid anomaly hardly any sclera is visible at the medial side. The upper eyelid comes down in an almost vertical curve at the level of the medial limit of the cornea to fuse with the lower eyelid, thus forming an unusual type of medial palpebral commissure.

The condition may create the illusion of a wide nasal bridge and of squinting. Careful inspection shows that the eyes are straight, and there is no displacement of the eyeballs. The nasal bridge, which is frequently depressed in these cases, is not necessarily abnormally wide. The drawing in Fig. 2 illustrates this. The distance between the centre of the pupils is identical in both the normal and abnormal set of eyes.

The eyelid deformity is, genetically, the most "penetrating" sign of the syndrome and is almost always present. There are, however, cases where several of the other signs are present without the eyelid deformity.

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This anomaly should not be confused with an epicanthic fold. An epicanthus (plica orbitalis) is a true vertical fold, either an inner one, by the nose, or a median one extending from the nasal fold into the upper eyelid (Fig. 1). Such folds are normal during fœtal development from the third to the sixth month and usually disappear by the time the child is born, although occasionally they may persist for a while. It is not uncommon in small children as a temporary structure. In the Mongolian races the condition persists into adult life giving rise to the typical Mongolian eye.
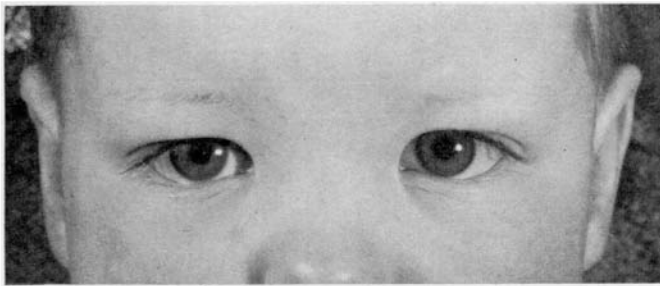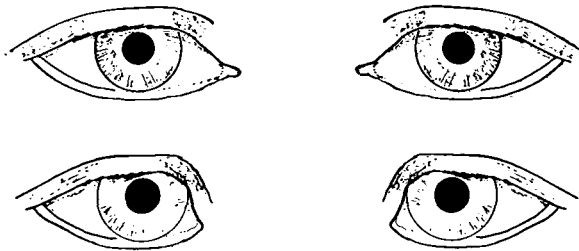

FIG. 1.
An epicanthal fold in a normal child.

FIG. 2.
A comparison of distances between normal eyes and eyes in this syndrome. 1. The eyeballs are *not* displaced laterally. They are in normal position. 2. The distance between the centres of the two corneas is normal. 3. The distance between the two medial angles of the eyelids *is increased* by the peculiar eyelid deformity.

2. The colour of the eyes.

The original colour of the iris is deep blue. If there is an inherent fault in pigment development, the eyes retain their original deep blue colour.

Faulty pigmentation of the iris occurs in this syndrome either as a result of complete lack of pigment development in both eyes (the iris is then of a deep blue colour), or only in one eye (one iris is blue and the other one brown—heterochromia iridium). Heterochromia may also be partial, where one eye is brown and in the other one part of the iris is

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brown and part is blue. Occasionally partial heterochromia occurs in both eyes. In other cases some melanin develops in both eyes and the deep blue iris is speckled with dark dots or patches.

Numerous variations were observed (Fig. 3) indicating various degrees of pigmentation. Indeed, this *graduation from minimal to more pronounced degrees of the various signs is characteristic of this syndrome.*
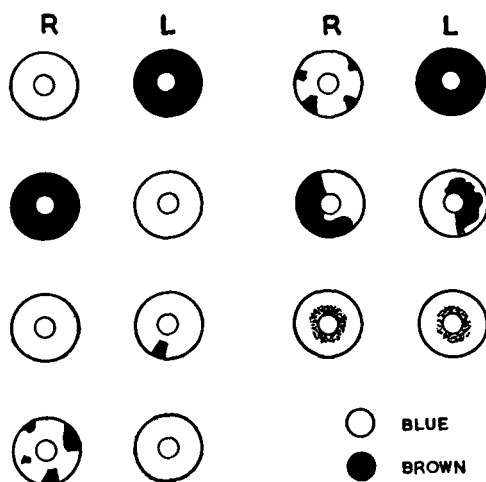

FIG. 3.

Various degrees of heterochromia iridium observed in our cases.

3. White forelock.

This is present as a streak of white hair, originating from the middle of the forehead at the margin of the hairline, or a little above it, or slightly off the centre (Fig. 4). It may occur in the form of a few strands of white hair, or as a sharply outlined thick forelock.

We must bear in mind that a white forelock in the middle of the hairline is not by itself a very rare phenomenon. It may occur as a hereditary sign through many generations, and is genetically different from this syndrome. A well documented case is the family of Percy, Dukes of Northumberland. A white forelock has occurred for over 500 years in this family. The first time it was noticed in a Percy was in the 15th century.

4. Configuration of the skull.

Undoubtedly a typical configuration of the skull is part of the syndrome. When the pictures of all our probands are grouped together, the similarity is quite striking, and the impression is given that these children are siblings of one family.

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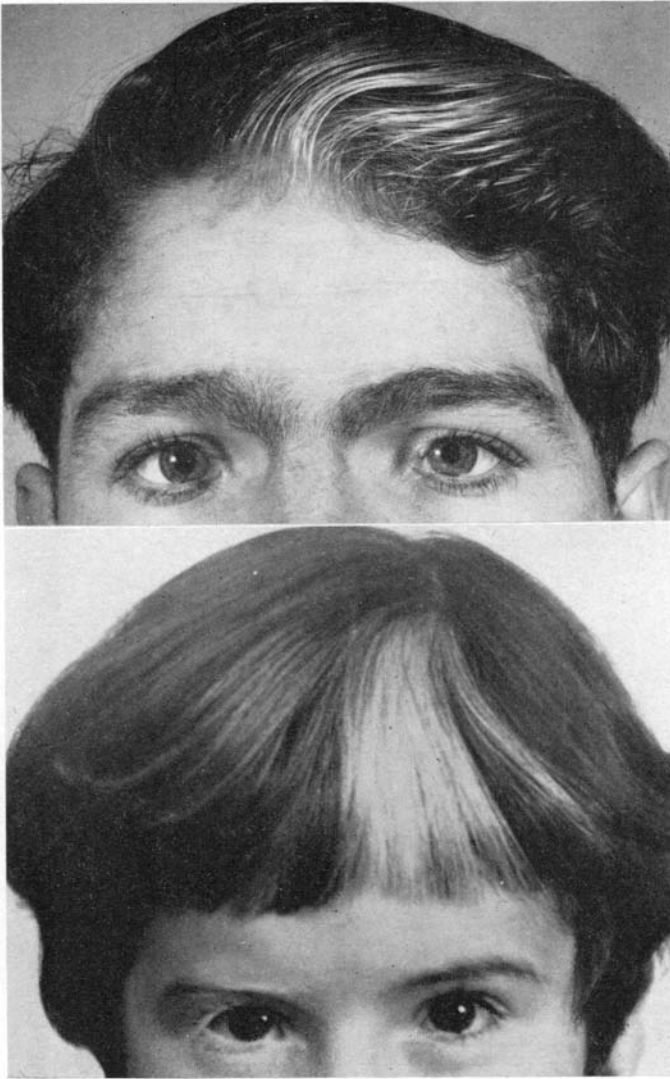
FIG. 4.
Examples of a white forelock. Also note the typical anomaly at the inner angle of the eyelids. Both children were severely deaf.

The profile is typical. Often the nasal bridge is depressed. Chronic sinusitis and nasal obstruction is frequent during childhood.

X-Ray examinations were carried out only in a small number of cases. We did not feel justified in subjecting these children to exposure for this purpose, but in the limited number of X-Rays which was carried out for diagnostic reasons (sinusitis, etc.) it was interesting to find that a *metopic*

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suture was present in many cases. It is interesting to note in this connection that one of the signs observed in some cases and described by Waardenburg (1951) was a faintly marked furrow in the forehead extending to the tip of the nose. We observed this in only one case.

The jaw is massive, and this largely contributes to the characteristic appearance. The outlines of a large number of pictures of these children were superimposed and they were almost identical.

5. *Deafness*.

The following distinctive patterns of audiographs were observed:

Type 1. An almost *total deafness* with a little residual hearing for the lower range of frequencies (Fig. 5, Audiographs 1-6).
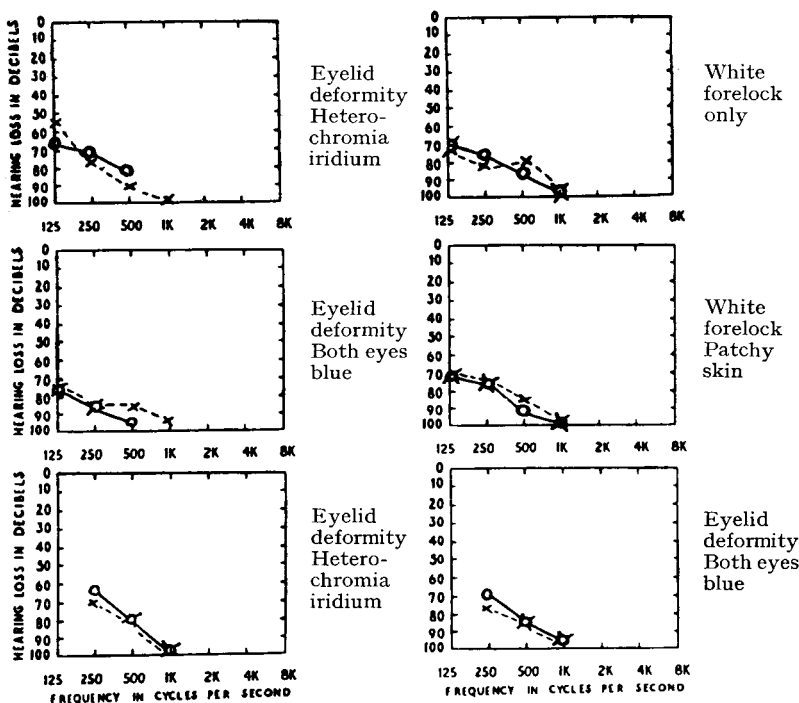
FIG. 5.

Type 2. A *moderate degree of deafness* with uniform hearing loss for the lower and middle ranges of notes with a remarkable improvement for the higher ones, often with normal hearing for 6,000 c.s. and 8,000 c.s. (Fig. 6, Audiographs 11, 12).

A combination of both types is possible in a single individual, showing Type 1 in one ear and Type 2 in the other one (Audiograph 11). The severe variety—Type 1—occurs most frequently as unilateral deafness.

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FIG. 8.

Various degrees of "patchy skin". The fourth picture illustrates a marked degree of this dappling effect. The whole body is covered by similar patches of brown skin. His mother was similarly affected. The child was totally deaf.

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The moderate type of hearing loss, in which hearing for the higher frequencies is better, is so distinct and characteristic that in several cases, since the investigation began, the suspicion of the presence of the syndrome was aroused because of this unusual pattern in the audiograph in a congenital perceptive deafness.

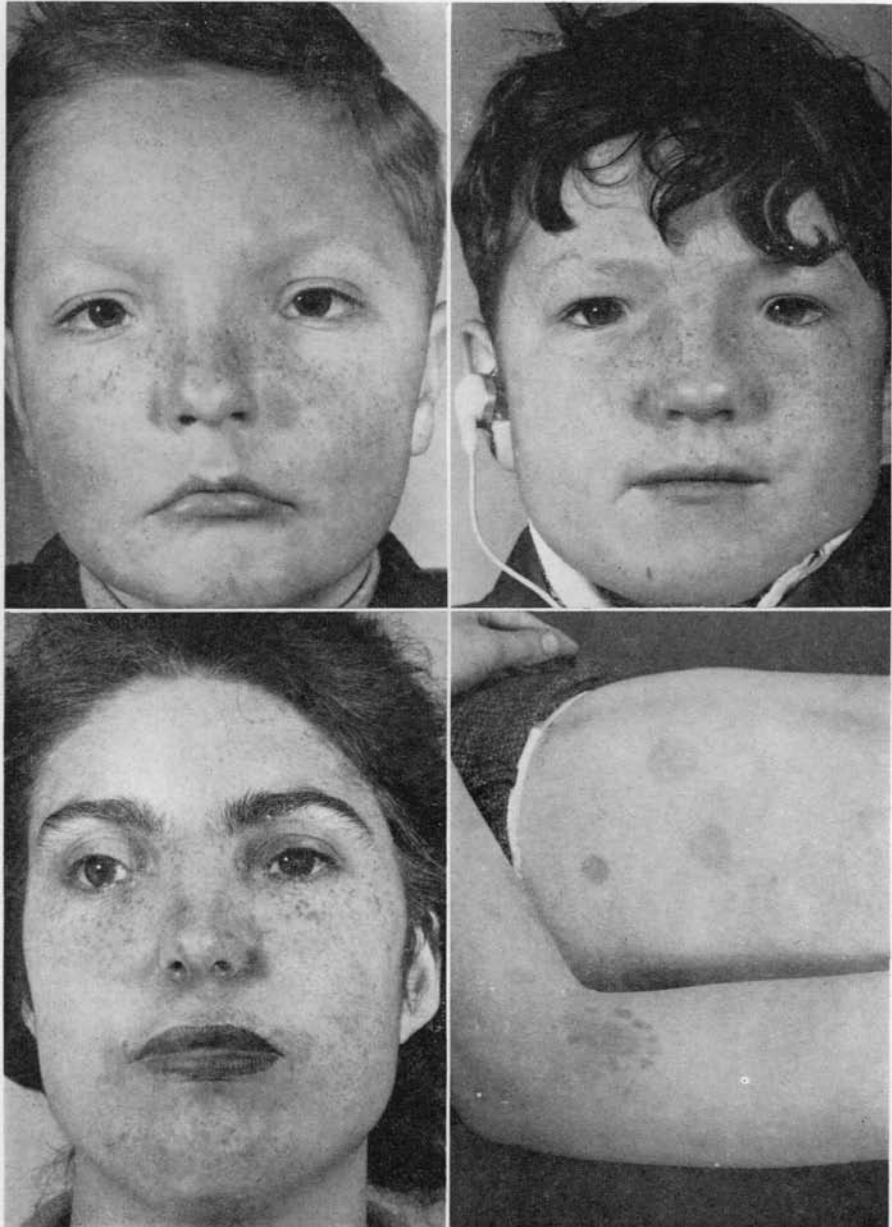Deviations from the two distinctive patterns were very few, and in our 35 probands there was only one case significantly different. There was a severe hearing loss from 70 to 90 db. for all frequencies, but in spite of the severity, residual hearing was present through the whole range of notes (See Audiograph No. 8, Fig. 7).

6. *Patchy skin.*

Regions of depigmented and brown patchy skin, giving a dappling appearance, is another sign of this syndrome.

We observed a family with a pronounced degree of this sign. The proband had an extreme degree of white forelock. He also had white eyebrows and white eyelashes on both sides. His eyes were of a clear blue colour. He was very, almost totally deaf. There were numerous patches of varying intensity on his legs, face and body. All members of the family group had these circular patches of skin. Many were deaf and some had a white forelock (See pedigree No. 1, Fig. 9).
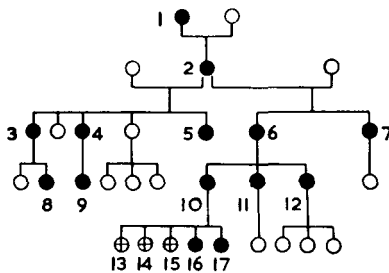
FIG. 9.

Pedigree No. 1.

●—affected by one or more signs of the syndrome.

No. 13 was stillborn.
No. 14 died soon after birth.
No. 15 died at the age of 3 weeks.
All affected subjects had "patchy" skins, mostly circular patches of brown skin of varying sizes and intensity in colour.

Patchy skin is undoubtedly one of the fairly frequent signs of the syndrome, although not in such a pronounced degree. We could not extend our study to investigate this sign in detail. Only after examining our pictorial material was it noticed how frequently the skin of the face was affected. Flash light used for photography contains a large element of

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ultraviolet which made this sign visible, although hardly noticeable on examination of the patient. A detailed investigation would be required by full ultraviolet photography.

There is a considerable genetic interest in this sign because it is known to occur in some animals, and it is most probable that the syndrome of deafness, white forelock, etc., in man, is closely related to the "dapple" carrier state in dogs (Sorsby and Davey, 1954).

In dogs, dappling appears for example, in the harlequin marking in Great Danes, which is occasionally associated with heterochromia iridium. Although these are minor anomalies, it is important to note, as Sorsby pointed out, that the gene in the duplex state (that is in homozygotes) leads to more extensive anomalies, including discoloration of the fur, deafness, and blindness from ocular malformations. What is even more important, gross malformations may appear, leading to still-birth or early death. This acquires special significance when our pedigree is examined. It will be noted that in the 5th generation in one family, there were five siblings. One was still-born, two died in early infancy, two survived but were affected by the syndrome and were deaf.

Early death in infancy in families affected by this syndrome was recorded in another of our groups studied. In this family (see Pedigree No. 2, Fig. 10) deafness, white forelock, eyelid deformity and heterochromia occurred in several members through several generations.
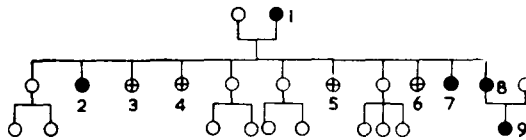
FIG. 10.

Pedigree No. 2.

●—affected by one or more signs of the syndrome.
No. 2. Severe deafness, white forelock.
No. 3 and 4 died at the age of ten months of "wasting disease" (atresia of the œsophagus?)
No. 5. Sudden death at the age of five months.
No. 6. Died at the age of six months of "wasting disease".
No. 7. Eyelid deformity, white forelock, severe deafness.
No. 8. White forelock, deafness.
No. 9. White forelock, deafness, eyelid deformity, heterochromia iridium.

In one generation of 11 siblings, four died during infancy. The cause was given as "wasting disease" in three, and "sudden unexpected death" in one.

The question arises of what is the possible congenital malformation which leads to early death. The study of another family group gave us an indication of at least one malformation, that is, atresia of the lower part of the œsophagus, which led to early death.

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7. *Congenital atresia of the lower part of the œsophagus.*

The proband was a girl who came under our care at the age of about 2 years 9 months because of deafness.

She had a typical eyelid anomaly; the right eye was blue and the left one had partial heterochromia (the outer two-thirds of the iris being brown and the inner one-third blue); she was deaf and spent almost all her life in hospitals because of her œsophageal atresia.

She also had a large Meckel's diverticulum in the lower ileum of the size 8 cm. by 3 cm. The X-Ray of her skull showed a metopic suture. At the age of $3\frac{1}{2}$ she died of bronchopneumonia, which had arisen as a complication after a transthoracic approach for surgical repair of stenosis.

Her mother was not deaf, but had an eyelid deformity, white forelock and heterochromia. Her 6 year old brother was severely deaf, and had an eyelid deformity.

The genetical aspect of congenital pyloric stenosis has been discussed by various authors in the past (Cockayne and Penrose, 1943) but so far it has not been recognized as part of a hereditary syndrome associated with deafness, and as far as we know, has not yet been described, as part of this syndrome. However, the association of deafness with congenital œsophageal stenosis was recorded before.

It is probable that in the previous mentioned families (Pedigree Nos. 1 and 2, Figs. 9 and 10) the cause of early death in infancy, given as "wasting disease" in one of the families, was in fact, congenital atresia of the œsophagus and that *these children had the gene in the duplex state (homozygotes)*.

8. *Combinations of signs of the syndrome.*

In our sample of probands (that is those subjects who came to us because of deafness, and not including their relations) various combinations of the signs of the syndrome were observed.

The most frequent combination was *deafness, eyelid deformity* and *deep blue eyes* (14 cases). All the other combinations were less frequent (see Table I, Fig. 11).

In eight cases there was no eyelid deformity.

The combination of *all* signs of the syndrome in a single individual is comparatively rare.

The hearing loss in the great majority of the 35 probands was of the severe, almost total type, showing only some residual hearing for low frequencies in the audiograph. Only in two cases was the hearing different. In one it was *unilateral*. In another case it was of the severe type in one ear, and of moderate in the other one.

Different sets of combinations may occur in subjects who are not deaf, and a large variation was observed in our series of families. Frequently

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TABLE I.

COMBINATIONS OF SIGNS OF THE SYNDROME.

Cases with deafness and eyelid deformity.			
1.	Deafness—eyelid deformity—blue eyes		14 cases
2.	,, ,,	brown eyes	4 cases
3.	,, ,,	blue eyes—white forelock	3 cases
4.	,, ,,	heterochromia iridium	3 cases
5.	,, ,,	partial heterochromia	1 case
6.	,, ,,	partial heterochromia—white forelock	1 case
7.	,, ,,	partial heterochromia—atresia of œsophagus	1 case
Cases with deafness but no eyelid deformity.			
a.	Deafness—blue eyes—white forelock		3 cases
b.	,, brown eyes—white forelock		1 case
c.	,, partial heterochromia		3 cases
d.	,, blue eyes—white forelock—marked patchy skin		1 case
		Total 35	

FIG. 11.

only the eyelid deformity is present as a single sign of the syndrome in an individual.

The best practical illustrations of typical cases can be given by a short description of sets of parent-child, siblings or other relations.

Parent and Child.

A. *Mother;* 1. White forelock. *Son:* 1. Eyelid deformity.

2. Heterochromia iridium. 2. Severe deafness.

3. Severe deafness.

The interesting point in this case was that the mother had *no eyelid deformity,* which appeared however in the child, who on the other hand, had no white forelock and no heterochromia iridium.

B. *Mother:* 1. Eyelid deformity. *Daughter:* 1. Eyelid deformity.

Normal hearing. 2. Deep-blue eyes.

3. Severe deafness.

The interesting point in this case was that the eyelid deformity in the mother cropped up suddenly without being inherited. There were no signs at all in any relations in three preceding generations. The mother was perfectly normal in every other aspect.

C. *Father:* 1. Eyelid deformity. *Son:* 1. Eyelid deformity.

2. White forelock. 2. Deep-blue eyes.

3. *Unilateral deafness* of a typical 3. Severe deafness in
pattern observed in this syndrome. both ears.

In this case the existence of unilateral deafness in the father, but severe, almost total, bilateral deafness in the child should be noted. Both had several signs of the syndrome, but the only one which was common to both was the eyelid deformity.

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Siblings.

D. *A boy:* 1. Eyelid deformity.   *His sister:* 1. Eyelid deformity.
        2. Typical *unilateral deafness.*   2. Blue eyes.
                                                 3. Severe deafness.

E. *A boy:* 1. Eyelid deformity   *His sister:* 1. Eyelid deformity.
        2. Blue eyes.   2. Partial heterochromia iridium.
        3. Severe deafness.
                                               3. Severe deafness.
                                             4. Œsophageal atresia.

Their *mother* had a white forelock, eyelid deformity, but *had normal hearing* in both ears.

Relations.

F. *A boy:* 1. Eyelid deformity.   *His Aunt:* 1. White forelock.
        2. Heterochromia iridium.   2. Eyelid deformity.
        3. Severe deafness.   3. Normal hearing in both ears.

Mutation

Example B is of special interest because there are indications that a sign of the syndrome (eyelid deformity) appeared suddenly, by mutation. It was not inherited but undoubtedly of genetic origin because it was passed on to the child who had several signs of the syndrome, including severe deafness.

This was not the only family in our series in which the syndrome cropped up, most probably, by mutation. We will mention specially one case because of its practical importance.

In a boy, the syndrome appeared, without any trace of it in previous generations or relations. He had an eyelid deformity, heterochromia iridium, and severe bilateral deafness. His father had a spine injury during the war, and had no less than 40 major X-Ray examinations. His son was born a few years after the war. It is feasible to assume that mutation was induced by radiation.

We had the impression that the mutation rate in this syndrome was high, but further detailed investigation of this aspect is necessary.

A New Syndrome?

During our investigations we came across a family with signs which we think represent a different syndrome.

The proband was a boy of 3, brought to us for investigation because his parents suspected deafness. He was initially included in the group

for the study of our syndrome because it was observed he had a wide nasal bridge.

Further examination showed that he had no eyelid deformity, but the history disclosed deafness in the family and also partial heterochromia iridium. Several branches of the family lived in the same vicinity, and therefore they were visited in their homes by our team. They were all examined, their hearing tested, and they were photographed. The results are shown in Pedigree No. 3 (Fig. 12). Twenty-one subjects of the family
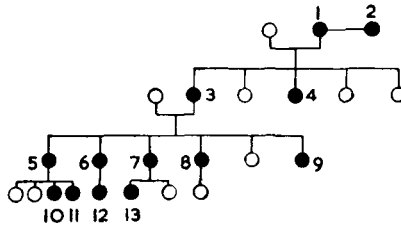

FIG. 12.
Pedigree No. 3.

●—Affected subjects.
No. 1, 3, 5, 7, 8, 12, 13. Early greying.
No. 2 and 4. Early greying and deafness.
No. 9 and 11. Deafness (young children, early greying did not appear yet).
No. 6 and 10. Partial heterochromia iridium.
No. 12 at the time of examination was a 15 years old girl and already had streaks of grey hair.

group are represented, and in 13 there was one or more of the signs of what we now call provisionally the "early greying" syndrome.

The most prominent sign was *early and pronounced greying*.

For example a girl of 15 years already had several strands of completely grey hair. In other members, considerable greying was present in their early twenties.

Impaired hearing was present in four cases, and in two of them early greying was also present. In two cases the subjects were children and too young for us to say whether early greying will appear or not.

The type of deafness was also different as compared with the main syndrome under study. The audiograph of the proband (see Fig. 13, Audiograph No. 14) showed a moderately severe loss for all frequencies, with

FIG. 13.

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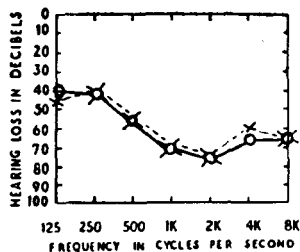
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a little better hearing for the lower notes. This type of hearing loss was not observed at all in our cases of the main syndrome under study.

Several other similar cases were observed, since this family was noted. This group merits a separate study because we think that this is a different, and genetically distinct syndrome, although related to the one under study.

Differential Diagnosis

It is important not to confuse this syndrome with two conditions which may superficially resemble it, and these are:

(1) *mongolism* and (2) *hypertelorism*.

In fact, in our series, in three cases the initial diagnosis was mongolism, and in three cases hypertelorism. Both these conditions are associated with mental deficiency. It is known that severe deafness, because of absence of speech, or late speech development, has often been misdiagnosed as mental deficiency. If such a deaf child has also a facial appearance which superficially may resemble mongolism (because of the eyelid anomaly) or hypertelorism (because of a superficial appearance of a very wide interocular space) incorrect conclusions may be drawn, and valuable time may be lost before a correct diagnosis is established. *Mental deficiency is not part of this syndrome.*

It has already been mentioned that the eyelid deformity is not an epicanthal fold. The *mongoloid* child may have an epicanthal fold, and a wide depressed nasal bridge, but there is no eyelid deformity.

In *hypertelorism* there *is* a considerably increased interocular space because of the lateral displacement of the eyeballs. As the drawing illustrating the eyelid anomaly indicated, the interocular space in our syndrome is normal, and there is no displacement of the eyeballs and no evidence of bony abnormalities typical of hypertelorism (Grieg, 1924).

Histology

One of the patients in our series died at the age of $3\frac{1}{2}$ years. She was a girl who was profoundly deaf, had a partial heterochromia iridium, and a typical eyelid deformity. She also had a congenital atresia of the lower part of the œsophagus.

She died from bronchopneumonia as a result of complications following an operation. The temporal bone was taken out a few hours after death and immediately fixed. The brain, including the root of the eighth nerve was also removed and immediately placed in a fixative solution.

Not only the temporal bone was examined, but also the whole auditory pathway. This is important because *the investigation of a peripheral sensory organ without the whole pathway cannot be considered as complete.*

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The histological examination of the temporal bone was undertaken by Dr. I Friedman, Pathologist at the Institute of Laryngology and Otology, London, and the brain was examined at the Burden Neuropathological Laboratory (Bristol) by Dr. R. M. Norman and Dr. H. Urich.

Dr. I. Friedman's Report

"Temporal bone received in formol saline was decalcified in Formic acid—368 ccs., sodium formate—86 ccs., and tap water—2,000 ccs., embedded in Low Viscosity Nitrocellulose and stained with Hæmatoxylin and Eosin and Van Gieson. No nerve stain was attempted.

Microscopy shows a good deal of non-specific inflammatory granulation tissue in the periantral cells of the mastoid process. There is also some frank pus in the tympanic cavity and Eustachian tube and there are adhesions around the ossicles. The inner ear is fully developed, the maculae of the utricle and sacule appear to be normal. Hair cells are visible, covered by the otolithic membrane. The semi-circular canals show no abnormality.

Cochlea.—The Organ of Corti is absent in all coils. The basilar membrane is slightly thickened and smooth, except in a small area covered by atrophic limbus-type cells.
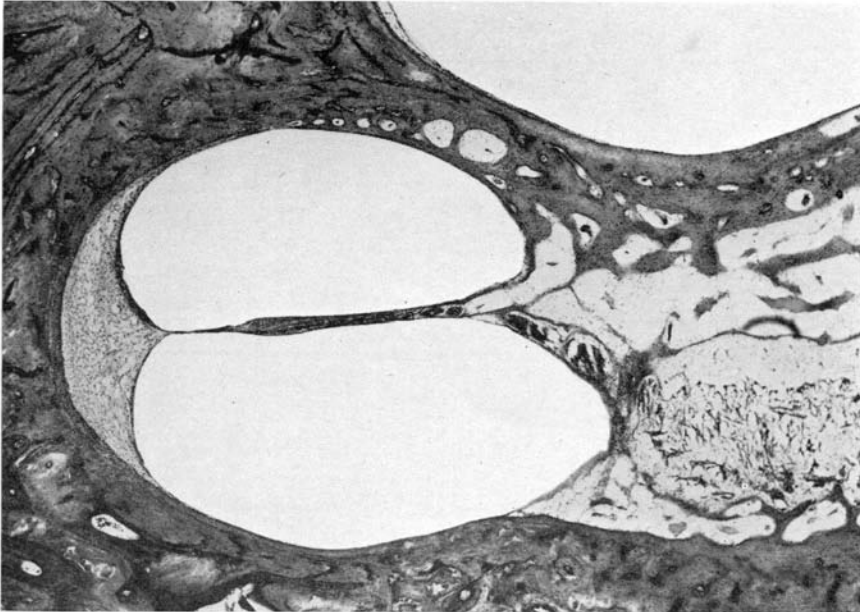
Fig. 14.
Cochlear canal.
The Organ of Corti is absent.

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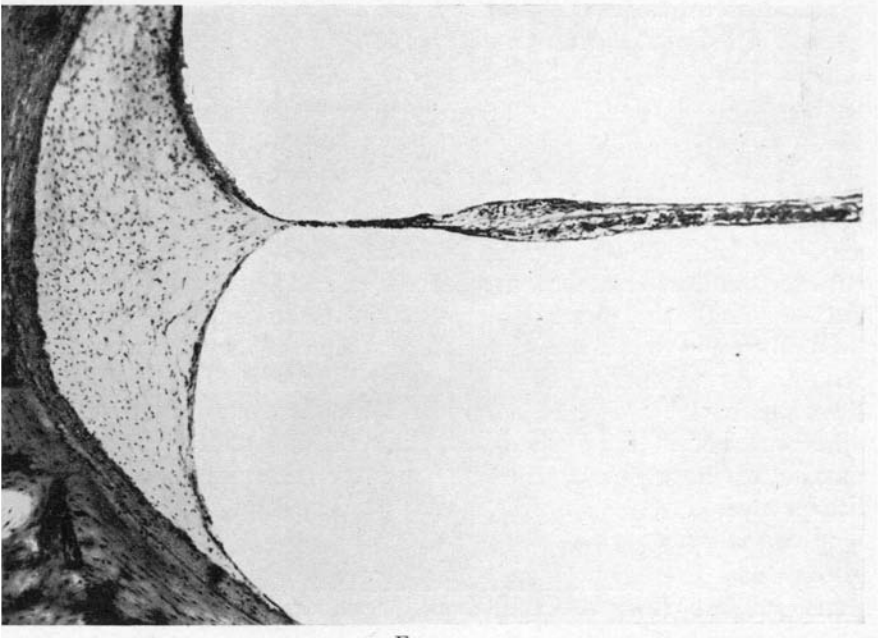
FIG. 15.
An enlarged section of cochlear canal showing the basilar membrane and absence of the Organ of Corti.

FIG. 16.
The spiral ganglion contains only few ganglion cells. The nerve fibres are sparse and appear to be slender.

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The spiral ligament is normal but the vascular stria is atrophic and contains one or two dilated vessels. The spiral ganglion contains only few ganglion cells, the nerve fibres are sparse, appear to be slender, although bundles of nerve fibres can be seen entering the basilary membrane in a fairly normal fashion (See Figs. 14, 15, 16).

Conclusions.—In view of the good preservation of the sensory epithelium of the vestibular apparatus, it is considered that the absence of the Organ of Corti in the sections is not an artefact. That is further supported by the obvious atrophy of the spiral ganglion and nerve. Subacute Suppurating Otitis Media was almost certainly a terminal event."

DR. NORMAN'S AND DR. URICH'S REPORT

"*Methods.*—Representative blocks were taken from the frontal, central, parietal, occipital and temporal cortex, the basal ganglia and the cerebellum. Those from the left hemisphere were used for frozen sections which were stained with carbol azure for cells, Kultschitsky-Pal's method for myelin and Holzer's stain for fibrillary glia. The material from the right hemisphere was embedded in celloidin and cut serially from the mid-medullary level to the metathalamus. At the levels of the cochlear nuclei every twentieth, in other parts every fortieth section was stained for myelin. In addition, selected sections were stained with Gross-Bielschowsky's method for neurofibrils.

Cerebral Hemispheres.—The cerebral cortex, white matter and basal ganglia were normal throughout. In all areas examined, the cortex showed a normal cytoarchitectural pattern. Myelination was normal. There was no gliosis.

Brain Stem.—The following nuclei of the auditory pathway were examined: the ventral and dorsal cochlear, the trapezoid, the superior olive, the ventral and dorsal nuclei of the lateral lemniscus, the inferior colliculus and the medial geniculate body. The tracts examined included the roots of the eighth nerve, the internal fibre systems of the cochlear nuclei, the trapezoid body, the fibre systems of the superior olive, the lateral lemniscus and the brachium colliculi inferioris. All these structures were found to be normal with the exception of the cochlear root of the eighth nerve which was thin, poorly myelinated and contained sparse nerve fibres."

This is of great interest, particularly when it is related to the findings in the inner ear. There is no doubt according to these histological findings that deafness was caused by the lesions in the end organ and the peripheral neurone without involvement of the central pathway. This is not an uncommon pattern, as transneuronal or chain degeneration in the

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auditory pathway is rather rare. In particular, malformations which develop in embryonic or early fœtal life do not as a rule give rise to transynaptic degeneration as the various parts of the pathway develop independently of each other and do not depend on synaptic connections for their growth.

Histological evidence from animals

As already mentioned, the association of congenital deafness with signs similar to those which exist in our syndrome in humans was detected in animals. It was observed a long time ago that in cats abnormalities of pigmentation in the iris were frequently associated with an absence of the organ of Corti (Alexander, 1900; Crowe, 1934).

Davis, Derbyshire and Lurie (1934) in their classical paper on the electric responses of the cochlea, studied a cat which had one blue and one yellow eye. Action currents were studied in both ears. The ear on the side of the yellow eye gave normal electric responses in respect to threshold, magnitude and wave form. On the blue eye side no electric responses were obtained, and no action potentials in the auditory pathway. Both inner ears were examined histologically. The responsive ear was essentially normal. In the unresponsive ear, the ossicles, membrane of the oval window and round window, saccule, utricle and semi-circular canals were essentially normal. But in the cochlea, the hair cells and supporting cells were absent; the tunnel was absent; Reissners membrane was adherent to the basilar membrane; *the number of nerve fibres in the spiral lamina was markedly reduced*. This histological finding is essentially the same as the one in our case, namely, *an absence of the Organ of Corti and reduction of nerve fibres*.

Discussion

PIGMENT AND THE INNER EAR

There is nothing new in the observation that development faults in the inner ear are occasionally associated with developmental faults in pigmentation in some animals, and in humans. Waardenburg (1951) himself reviewed this subject, and provided an extensive bibliography of the published literature. However, no explanation of this phenomenon has been attempted.

From the genetical point of view, *the question arises whether there is a common cause or association due to separate but linked factors*. The common embryological origin of the ear vesicle and body pigment, and *functional link*, in my opinion, indicates that *the cause is common, due to a developmental fault in the neural crest*.

The cells of the neural crest, during the earliest stages of development, border the neural plate like a bond. The dorsal ectoderm forms the neural

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plate. Eventually the neural ridge develops, and from this the neural plate and neural folds. These fuse, and a wedge-shaped cell mass is formed, called the neural crest. The crest cells leave the tube and migrate in a lateral and ventral direction between the epidermis and spinal cord. Within a short time, all the crest cells have left the neural tube and the neural crest ceases to exist as a structure.

Observations resulting from embryological extirpation experiments suggest that the neural crest is active in determination of the auditory organ. For example, in one set of experiments, large ear vesicles developed in the absence of the hindbrain (Horstadius, 1950).

If the crest of the head also was removed, the auditory vesicles were absent. Ear vesicles can develop in spite of a complete absence of the brain, and this indicates that the neural crest is in some way involved in the complex process of determination of ear vesicles.

There is good evidence to show that the neural crest is also the source of pigment cells (Du Shane, 1943 and 1944; Rawles, 1948). *Prospective pigment cells in all vertebrates are derivatives of the neural crest.*

For example, pigmentation of the eye (specially relevant in the context) was investigated in many experiments. In transplantation experiments when the host was deprived of its neural crest, no pigment appeared in a transplanted eye. Undoubtedly pigment cells in the choroid and iris arise from the migratory cells of the neural crest.

The Function of Pigmentation and Auditory Function

Although at first it is difficult to see a close relationship between body pigmentation and the organ of hearing, further analysis shows that it is *not only the common early embryological origin which links them, but there is also a functional link and a common functional development.* Both body pigment and hearing have fundamentally *a protective function*, essential for survival of the species. It is interesting to observe the close relationship in the animal world between the development of pigment and the function of hearing after birth. We cannot describe it in detail here, but will indicate a few examples.

At the time of birth, the young of various species have attained different states of development which generally correspond to the length of gestation (although this rule has some exceptions). In other words, birth occurs at different ages not only in the *chronological* but also in the *developmental* sense, and this enables us to study, postnatally, the various final stages of development of organs and functions.

Because we are interested here in *protective functions*, let us consider the various ways in which the new-born and very young in the mammal world are protected.

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In this respect the young can be divided into the following groups:
1. (1) The pouch young and the nest young.
2. (2) Runners.
3. (3) Swimmers.
4. (4) Breast young.
5. (5) Human infant.

There is no need to consider separately the pouch young in this connection because they are delivered in an embryonic stage, and the pouch fulfils later the function of the nest.

The nest young are usually born in a well hidden nest at the end of tunnels or under dense vegetation. The ears, for example in mice, are solidly sealed by the growth of the epidermal surface layer called periderm. The ears *close up* during the 18th day of pregnancy, that is, four days before birth, and remain closed during the first two weeks after birth. *The ear duct is covered* by the distal, folded over part of the pinna, till about the fifth postnatal day, but the peridermal plug persists up to the 15th day. Obviously, whatever hearing there is must be dulled, because the young must remain quiet and not disperse. As soon as they open up, the young make excursions from the pouch or nest. *They are also born naked, without fur, and the body pigment has not been formed.*

It must be understood that pigment cells which migrate from the neural crest in a colourless state, produce their pigment only as a result of interaction with the cells of the other tissues or between themselves, and so pigment itself is formed rather late in embryonic development. Melanophores are held over in undifferentiated (unpigmented) state until activated by the metabolic changes accompanying maturation. Presumptive pigment cells in the early stages cannot be distinguished from other mesenchyme cells. In other words, there is a definite stage during development when pigment is formed, and pigmentation assumes its protective function. It is interesting to observe that similarly hearing assumes its protective *function* at a definite stage of development, and this is achieved *simultaneously with the function of pigmentation. Mice* are naked and unpigmented at birth, and also the cochlea is incompletely developed. These important protective organs start functioning only in the weanling. The young mouse crawls away from the nest when he is pigmented and is able to hear. *Suckling rats* are also unpigmented and naked and their hearing is not functional. The cochlea, particularly the area of neuroepithelium is incompletely developed and unevenly differentiated (Bélanger, 1956). In the weanling of 20 days, when it becomes furred and pigmented, the cochlea, also seems to have reached functional maturity.

Rabbits are born in a more mature state, but are still naked, unpigmented and *deaf.* The ears become free of peridermal plug and the young are pigmented at about the 8th day.

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Hares are born with fully pigmented fur and open, fully functioning ears. Even on the first day after birth, the young run off if they are frightened by noise. But this protection by hearing would be useless without the protection of the fully pigmented fur, and both functions are necessarily very closely linked.

The hare belongs to the group of "runners". Several runners are born with fully coloured juvenal pelages, and fully functioning hearing. For example, like the hare, the young *eland* at birth have the coloured pattern of the adult female. Hearing is very important for the young eland, and almost the only means of finding the mother after running away (they can run in a matter of hours after birth). The young bleat like a domestic calf, the mother answers with a soft bleating note.

The human infant is born after one of the longest gestation times. The ears open up (free from peridermal plug) about the middle of the gestation period. At birth human infants *are covered with* first generation lanugo (or even with second generation hair) and *functioning inner ears.* His helplessness is not proof of absence of the protective function of hearing. It is not a primitive condition, but a secondary regression which may have developed when primitive ancestral man became a cave dweller. A good example of the inherent abilities is the way in which a very young human infant is able to support its own weight when hanging from a stick by its hands.

We can see then, that the two most important protective functions (body pigmentation and hearing) not only have a common origin from the neural crest, but also closely related from the functional point of view and they both assume their functions at the same critical stage of development.

Because of this common functional link and embryological origin it is not surprising that a genetical fault produces anomalies in both systems.

THE EXPLANATION OF THE WHITE FORELOCK

The explanation of a common genetical fault, giving rise to developmental errors in two different systems which are linked functionally and from the embryological point of view, does not yet explain why certain signs of the fault are consistently localized in a particular region of the body. For example, how to explain the strange location of an unpigmented area in the middle of the forehead?

An explanation is attempted here to show how a wider biological approach may help to form a hypothesis, which could provide the initial step to a better understanding of the mechanisms involved. This could then lead also to an explanation of some other pathological conditions in other regions, for example, in the inner ear.

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The melanoblasts (early undifferentiated stage of melanophores which produce melanin) are endowed with a complement of genes, and development and ultimate differentiation are dependent upon the activity of these genes, subject all the time to correlative influences from adjacent or contiguous tissues (Rawles 1948). It means that the neuroblasts possess certain reaction potencies which determine the particular type of response elicited by a particular tissue substrate (Willier, 1948).

In other words, the process of pigmentation has to be initiated also by some factors outside the pigment forming cell.

This physiological condition of the substrate may be influenced by numerous factors, among them by certain biochemical influences.

It is known for example, that the pigment pattern in the iris is controlled by factors located in the iris (Barden, 1942).

Similarly it may happen that one particular fairly well circumscribed region at the hair line in the middle of the forehead remains unpigmented because of a local influence.

It is then quite possible that the melanoblasts which already have certain abnormal reaction potencies (conditioned by their genetic make up) are at this particular region prevented from being ultimately differentiated into melanophores by a factor located in the substratum.

Now—what kind of peculiarity could be ascribed to this small circumscribed area in the middle of the forehead at the hairline?

Firstly, when we consider the frontal bone, one peculiarity of the frontal plate which comes into mind is the metopic suture, occasionally present, more or less complete, running up the frontal plate in the middle line, indicating the fact that the frontal bone was originally formed from two parts which eventually fused into one.

Rarely the fusion is not complete and the metopic suture may remain unclosed, forming a metopic fontanelle.

On the cerebral surface there are several depressions, for arachnoidal granulations, but about at the level of the hairline in the middle, there is frequently a marked circular depression not quite of the same character as those for arachnoidal granulations.

Secondly, apart from the anatomical considerations, could one find anything particular to this region when the long developmental history of vertebrates is examined? As a matter of fact, there *is* something, and it is of great interest from the point of view of our subject. This is the region where once, at the early stage of development of vertebrates, the *third, median eye was situated*.

In their early history, the ancestral vertebrates had a third eye, medially situated on the forehead and directed upwards in almost all the older amphibians and early reptiles, including most of the mammal-like types. Today we find medial eyes present only in lamprey, Sphenodon, and some lizards; buried beneath the skin they can presumably do little

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more than detect the presence or absence of light. In frogs there may be a vestigial external structure of dubious nature; in all other groups the remains of such organs are no more than glandular material in the brain-case.

Such dorsal eyes spring from the roof of the diencephalon and hence, like lateral eyes, are essentially part of the brain. The medial eye may develop either of two outgrowths—the parietal organ (or parapineal organ) and the pineal organ. Despite loss of eye function, the pineal organ persists in higher vertebrates as a glandular structure (A. S. Romer, 1955, also S. Duke-Elder, 1958).

Is there a possibility that the old connections between this region of the forehead and the pineal body are maintained in the form of certain hormonal (biochemical) or nervous influences which can so change the substrate that it prevents the formation of pigment by the genetically abnormal melanoblasts, in the same way as it does in the existing fully developed eye?

Although this suggestion, at this stage, may be in the realms of speculation, it certainly merits further detailed investigation. The locality of this abnormality of pigment development at the forehead, associated with a similar lack of pigmentation in the iris of the eye, suggests that this is a feasible explanation of this puzzling abnormality. It becomes even more feasible when the causation of heterochromia iridium is considered in greater detail.

We already mentioned that the process of pigmentation depends both on the activity of genes and on the physiological condition of the substrate. What can change physiologically the substrate in the iris (and possibly in a certain area in the middle of the forehead)?

There are other possible causes of heterochromia apart from inherited ones. An acquired cause is heterochromic cyclitis, a disease of young adults in which an atrophy of iris tissue causes it to appear much paler than the other eye. Another cause is a *one-sided paralysis of the cervical sympathetic nervous system* as Colhoun (1919) noted a long time ago. How would a non-functioning cervical sympathetic system influence this and some other regions? In a preliminary communication Burn and Rand (1958) pointed out that degeneration of the postganglionic sympathetic fibres causes a super-sensitivity of the denervated iris to noradrenaline and adrenaline. This is due to loss of the noradrenaline normally present in the iris. Undoubtedly this changes profoundly the physiological condition of the substrate.

There is no evidence so far to show what is the state of the cervical sympathetic system in subjects affected by our syndrome, but there is a definite developmental link and that is the fact that all the elements of the cervical sympathetic system originate also from the neural crest, as the inner ear does. *The neural crest is the exclusive source of the sympathetic*

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elements (Van Campenhout, 1930). This presents us with a complex picture of the possible defect involving (a) the cervical sympathetic system, (b) abnormality of pigmentation in certain parts of the body (where the physiological changes occurred in the substratum), and (c), inner-ear defects, in different degrees.

It is interesting to note in this context the already well-known connection between the cervical sympathetic system and the inner ear, which was the subject of many detailed investigations. Therapeutic (pharmaceutical and surgical) measures, taken as a result of this connection were however leading to puzzling and contradictory results which indicated that many unknown factors were involved.

Investigations concerning this complex problem are only in the initial stages and therefore we put forward this hypothesis here only as a preliminary communication and mainly to show how a seemingly rare or specialized aspect of investigation of deafness, when subjected to more detailed study and viewed from a wider biological aspect, opens up the possibility for better understanding of a wider sphere of phenomena concerning the ear.
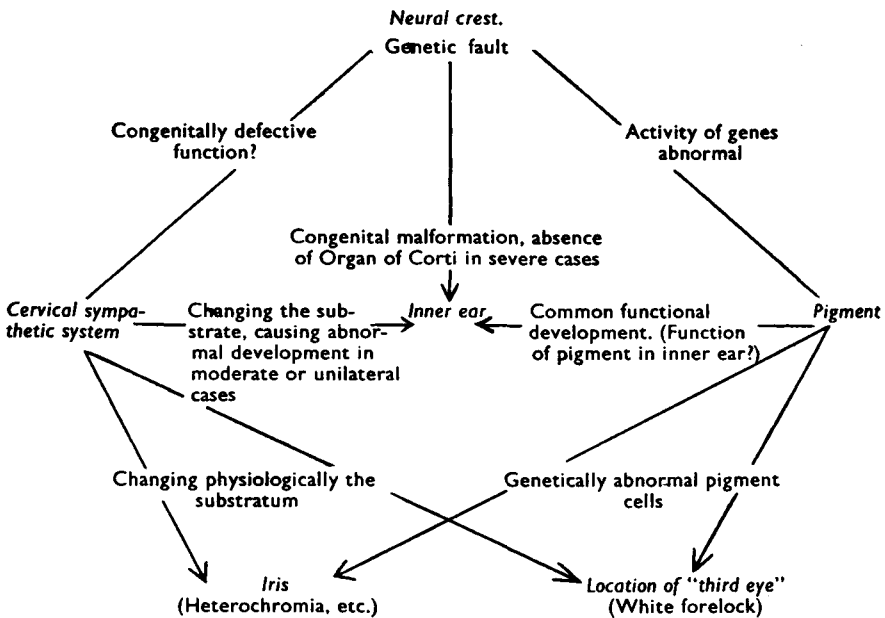
Summary

A hereditary syndrome, with deafness as clinically the most significant symptom, is the subject of this paper.

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This syndrome, although known to geneticists for some time, has not been described in detail in this country, and all cases remained undetected, or occasionally, misdiagnosed.

Our investigations disclosed that this is not a rare condition but a relatively common one. It plays an important role, as ætiological factor within the group of congenital deafness.

Important differential diagnostic aspects are involved, and it is pointed out that the syndrome should not be confused with mongolism or hypertelorism.

The types of deafness are either a very severe, almost total hearing loss, or a moderate one. In this moderate type it is frequently observed that the hearing for high frequencies is better than for the lower ones, although this is undoubtedly perceptive in type.

It was possible, as a result of histological examinations, to show that the lesion was in the inner ear, and that the auditory pathway was intact.

This study made possible a better understanding of the relation between body pigmentation and hearing. These two systems are closely linked developmentally and functionally, and this link may explain some of the mechanisms involved which lead to anomalies appearing simultaneously in both systems.

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