microscopy appearances are normal and that enzyme levels are low.

After her later relapse, which occurred when whole proteins, egg and chicken, were introduced into her diet, some success was obtained with a completely synthetic diet, Intralipid, fructose and L-amino acids. Its use was prompted by our experience and that of others (Cash & Berger 1969) in use of intravenous fat emulsions, combined with the knowledge that resolution often occurs with oral feeds of breast milk. Again relapse occurred on the introduction of whole proteins. A lasting remission was obtained using lactase-treated EBM.

There are complex biochemical dissimilarities between human milk, cow's milk and synthetic feeds such as Galactomin. For example, in cow's milk 20% of calories are derived from protein, whereas in human milk only 8% of calories come from protein. There are also differences in the relative amounts of lactalbumin and casein as well as species specific structural differences (Barness 1961).

The nutritional management of some cases of acrodermatitis enteropathica is complex, the role of protein and lipid metabolism is yet to be fully elucidated and this case seems to show the importance of considering all aspects of the child's nutritional status together with specific treatment.

The child is now receiving lactose-treated EBM and Diodoquin 7.2 g daily. We do not believe that there is any disturbance of tryptophan metabolism.

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DISCUSSION

Dr E J Moynahan: We have now had the opportunity of seeing four children with acrodermatitis enteropathica who presented with sugar intolerance due to deficiency of the enzyme lactase. Three of these infants were unable to transport glucose into the villus cell and the remaining child could not transport fructose, but could absorb glucose.

Most mammals are unable to digest milk sugar (lactose) after weaning, so that liquid milk is an unnatural food for mammals; it may not be well known that this also holds for the majority of the human race. The capacity to digest milk sugar is restricted to cultures based on cattle and horses, e.g. Central Asian Mongols, and is very rare in purely agrarian cultures. Our patients are of Italian, Armenian or Persian origin, and many of the inhabitants of these regions cannot digest milk in late childhood or adult life. Patients of British ethnic origin with acrodermatitis enteropathica do not show this intolerance for milk sugar or indeed any other sugars. A recent report from Nigeria (Kretchmer N, Ransome-Kuti O, Hurwitz R, Dungy C & Alakija W, 1971, *Lancet* ii, 392–5) shows that there are in the same country two genetically different populations, the distribution of the gene for lactase being determined by the length of time that liquid milk has been consumed in different regions of the country.

Our patient did very well on lactase-treated breast milk and was discharged home on a synthetic amino acid diet to which Intralipid and vitamins were added with fructose as the only sugar.

Waardenburg's Syndrome in Two Siblings, Both Parents and Their Maternal Grandmother

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Case 1 Boy aged 11. Brother of Case 2
Congenital deaf-mute. Small white forelock. Gross lateral displacement of medial canthi with normal interpupillary distance and inter-inner canthal distance increased to above two standard deviations over the normal for his age (i.e. typical dystopia canthorum medialis lateroversa). Congenital bilateral blockage of nasolacrimal ducts, requiring a left dacryocystorhinostomy four years ago. Normal nasal root with very hypoplastic alæ nasi. Leukotrichia of the medial eyebrows which were not hyperplastic. Blue irides. Patches of white skin symmetrically over the backs of the elbows, the outer aspect of the forearms and the front of the ankles. Bilateral short fourth metacarpals and bilateral clinodactyly of the fifth fingers.

Case 2 Girl aged 17. Sister of Case 1
Congenital deaf-mute. Small white forelock. Gross lateral displacement of the medial canthi as in Case 1. Normal nasal root with very hypoplastic alæ nasi. Normal eyebrows. Blue irides. Patches of white skin with identical distribution to Case 1. Bilateral short fourth metacarpals and bilateral clinodactyly of the fifth finger.

Case 3 Woman aged 42. Mother of Cases 1 & 2. Housewife
Congenital deaf-mute. Large white forelock. Marked lateral displacement of medial canthi.

Normal nasal root with hypoplastic alæ nasi. Normal eyebrows. Blue irides. Born with a soft tissue deformity of her left cervical region, corrected by surgery in infancy.

Case 4 Man aged 44.
Father of Cases 1 & 2
Ex-husband of Case 3. Violent and aggressive. Possibly below average intelligence. Congenital deaf-mute. Marked lateral displacement of medial canthi. Normal eyebrows and no white forelock. Heterochromia iridium. Broad nasal root with normal alæ nasi.

Case 5 Woman aged 72. Mother of Case 3.
Housewife
Congenital deaf-mute. Very little hair on scalp, and wears a wig, but used to have a small white forelock. Sparse eyebrows. Marked lateral displacement of medial canthi. Normal nasal root with very hypoplastic alæ nasi. Blue irides.

Family history: Cases 1 and 2 have no siblings, and their mother had no abortions or stillbirths. Case 3, their mother, has no siblings. Case 5 has no siblings; her first marriage to a normal man resulted in a normal male offspring, and her second marriage was to a deaf-mute not suffering from Waardenburg's syndrome. No reliable family history was forthcoming from Case 4, except that he probably came from Ireland; he was not related to Case 3 except by marriage.

Investigations: Palmar dermatoglyphics of all 5 cases were normal. Lymphocyte karyotypes of Cases 1, 2, 3 and 5 are normal (Case 4 refused to co-operate). Radiographs of the chest, cervical spine and skull of Case 3 are all normal.

Discussion

All five cases have Waardenburg's syndrome. Eyebrow hyperplasia was the only feature absent in all, although Case 4 was the only one to have a broad nasal root. Other features which have been described in this condition are hypopigmented mottled retinæ, premature greying of the hair, cleft palate and congenital heart disease (usually ventricular septal defect). None of these was present in our patients.

Waardenburg's syndrome is inherited as an autosomal dominant, and about one-third of all cases represent new mutations. The penetrance for the various features is different, being highest for the displaced medial canthi (99%) and lowest for the white forelock (20%). This family is possibly unique because two people with Waardenburg's syndrome have married one another. Such an occurrence is not altogether unexpected since deaf-mutes tend to mix exclusively with, and marry, other deaf-mutes. It is possible that Cases 1 or 2, or both, are *homozygous* for the Waardenburg's syndrome gene, and if this is the case then this has had no obvious phenotypic effect.

The most striking feature of Cases 1 and 2 is that they have an identical distribution of white patches of skin, these being a well-recognized but unusual feature of Waardenburg's syndrome. This identical distribution is unlikely to be a coincidence and resembles the inherited distribution of piebald spotting in animals. Both single or multiple genes may be involved. For example, in the mouse 'light head, white face' is a single recessive gene which probably acts only in the presence of the gene for recessive spotting (Pincus 1931). However, if one compares mice of a given spotted strain it will be found that certain areas are always white and others are always pigmented. If the frequency of pigmentation for a large number of skin areas has been decided then contour lines can be plotted enclosing areas which are pigmented in a certain percentage of cases. Different genotypes produce different fields of pigmentation, and a set of 'k' genes has been suggested as the ultimate cause of these white areas and therefore of the field distribution (Charles 1938). It appears that these 'k' genes can interact with a recessive spotting gene 's' to produce a white forehead, also confusingly called 'white face' although different from the single gene condition described above. It is firmly established that specific genes regulate the differentiation of pigment cells in mice, and it is probable that comparative systems operate in man.

Congenital deafness may be associated with many dermatological conditions, including pigmentary disorders. There seems to be a continuum of diseases involving both hereditary hypopigmentation (both patterned and unpatterned), varying degrees of eye colour dilution, and deafness. No satisfactory explanation exists to account for all the features of Waardenburg's syndrome, although a neural crest defect could explain the combination of pigmentary disorder with perceptive deafness. Even harder to explain embryologically is the association of Waardenburg's syndrome with palmo-plantar hyperkeratosis combined with severe mental retardation (Amini-Elihou 1970). It may be that unrecognized genetic heterogeneity, allelic or nonallelic, exists in families where certain features (e.g. hypoplastic alæ nasi, leukoderma, palmo-plantar hyperkeratosis) clearly segregate with the Waardenburg's syndrome phenotype.

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