the jaw, upper cervical region, and concha is due to involvement of the auricular branch of the vagus nerve. We did not observe overflow to the cheek, nose, or eyes. Bohm and Strang (1962) subdivided their series into two groups—oropharyngeal and aural—according to the main symptomatology, but patients usually present with pain in both zones concurrently. Typically there is no sensory impairment in the area of pain, as there usually is when tumours of the cerebellopontine angle or base of the skull are present.

The clinical picture of "idiopathic glossopharyngeal neuralgia" is so characteristic that diagnosis is seldom difficult. Glossopharyngeal neuralgia, however, may be confused with trigeminal neuralgia in patients with pain in the region of the tragus or deep to the angle of the jaw.

There is some evidence that glossopharyngeal neuralgia may be controlled by medication—for example, vitamin B complex, Tegretol (carbamazepine)—but no proof that the relief is lasting. Treatment of this neuralgia is essentially surgical. It has passed through various stages from dissection and avulsion of the glossopharyngeal nerve and pharyngeal branch of the vagus nerve in the neck to the intracranial section of the glossopharyngeal nerve alone or combined with the upper two rootlets of the vagus nerve. However, the avulsion of nerves in the neck has often been followed by recurrence of pain over a period of time—for example, Case 1—as has avulsion in the tonsillar fossa (Case 7). The treatment of choice remains the intracranial section of the glossopharyngeal nerve and upper two rootlets of the vagus nerve, as we feel that the latter nerve is also implicated. In skilled hands this operation carries a negligible mortality and can be performed on elderly patients.

Surgical Approach

This is essentially the approach by Dandy (1927), though nowadays it is facilitated by operating on the patient in the upright position. The legs should also be raised or bandaged in elderly patients to prevent postural arterial hypotension. The procedure is carried out through a small suboccipital craniectomy under endotracheal anaesthesia. Enough bone is removed to expose the lateral sinus above and the sigmoid sinus laterally—that is, about 3–4 cm. diameter. The dura is opened, with a small flap swung laterally over the sigmoid sinus. The cerebellopontine angle is opened up after the posterior fossa has been slackened either by slipping a retractor over the cerebellar hemisphere and opening the cisterna magna or by releasing a previously placed lumbar puncture needle. The rootlets of the ninth, tenth, and eleventh cranial nerves are seen arranged in a vertical column from above down. The ninth cranial nerve is a single filament normally separated from the multiple filaments of the tenth nerve by a dural isthmus as the nerves pass out through the jugular foramen. The ninth cranial nerve is hooked up and sectioned at this position, followed by section of the upper two rootlets of the vagus. In closing the craniectomy the dura is sutured back into position. The patient is usually sitting out of bed on the first day, and relieved of pain from the time of operation.

Summary

Ten cases of glossopharyngeal neuralgia have been studied and the literature has been reviewed. A more correct classification would be to describe the condition as "glossopharyngeal and vagal neuralgia." Evidence is given to support this view. Intracranial section of the glossopharyngeal nerve and the upper two rootlets of the vagus nerve is the operation of choice.

We wish to thank Mr. P. H. Schurr and Mr. J. J. Maccabe for permission to include their cases, and also our various neurological colleagues, particularly Dr. M. J. McArdle, for entrusting us with patients under their care.

References

Adson, A. W. (1924). *Arch. Neurol. Psychiat. (Chic.)*, **12**, 487.
Bohm, E., and Strang, R. R. (1962). *Brain*, **85**, 371.
Dandy, W. E. (1927). *Arch. Surg.*, **15**, 198.
—— (1945). Reprinted in 1966 as *The Brain*, p. 191. Hagerston, Maryland.
Harris, W. (1926). *Neuritis and Neuralgia.* New York.
—— (1937). *The Facial Neuralgias.* London.
Keith, W. S. (1932). *Brain*, **55**, 357.
Love, J. G. (1944). *Surg. Clin. N. Amer.*, **24**, 959.
Sicard, R., and Robineau, M. (1920). *Rev. neurol.*, **36**, 256.
Weisenburg, T. H. (1910). *J. Amer. med. Ass.*, **54**, 1600.
Wilson, C. P., and McAlpine, D. (1946). *Proc. roy. Soc. Med.*, **40**, 82.

Haemoglobin F Hull (γ 121 Glutamic Acid → Lysine), Homologous with Haemoglobins O Arab and O Indonesia

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Brit. med. J., 1967, **3**, 531–533

A haemoglobin variant is the result of an amino-acid substitution in one of the two pairs of polypeptide chains which constitute the haemoglobin molecule. Foetal haemoglobin (Haemoglobin F) has a pair of α-chains and a pair of γ-chains, and is denoted as $\alpha_2\gamma_2$. Variants of Haemoglobin F may thus be divided into two groups, those with abnormal α-chains and those with abnormal γ-chains.

An α-chain substitution gives rise not only to a variant of Haemoglobin F but also to a variant of Haemoglobin A ($\alpha_2\beta_2$) and a variant of Haemoglobin A_2 ($\alpha_2\delta_2$) in the same individual. A γ-chain substitution, in contrast, can give rise only to a variant of Haemoglobin F. In the same way a β-chain substitution can give rise only to a variant of Haemoglobin A ; most of the common haemoglobin variants—for example, Haemoglobins S, C, D, and E—are β-chain variants.

Few γ-chain variants have been described, and in only one case, that of Haemoglobin F Texas I, has the amino-acid substitution been identified (Schneider and Jones, 1965 ; Jenkins, Beale, Black, Huntsman, and Lehmann, 1967). We here describe a new γ-chain variant and define its amino-acid substitution. The variant, which is designated Haemoglobin F Hull, was first found as an electrophoretically slow component of the cord-blood haemoglobin of a normal baby of native English stock (Fig. 1). It made up 14% of the total haemoglobin, determined by the method of Marengo-Rowe (1965). It was found again in the cord blood of a subsequent baby

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born to the same parents, comprising 9% of the total haemoglobin. This baby was born after 30 weeks of gestation and died of prematurity after a few days. A third example of the variant was found in a healthy baby born to parents who are, so far as is known, unrelated to the first family, though both families live in the same town (Kingston-upon-Hull). The variant comprised 7% of the cord-blood haemoglobin of this baby. Although twice found in Hull families, the variant has not been observed again during a survey of 12,000 cord bloods in Britain.

Fig. 1

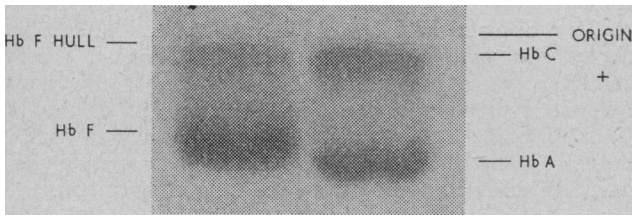

Fig. 2

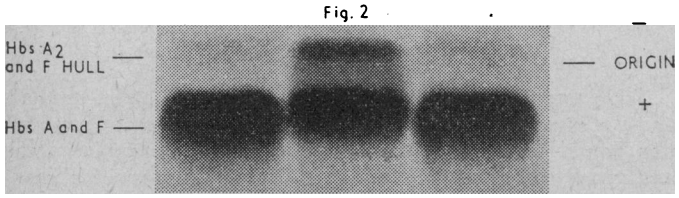

FIG. 1.—Haemoglobin electrophoresis on paper at *p*H 8.9 (barbiturate buffer). Left: cord blood containing Haemoglobin F Hull. Right: adult heterozygous for Haemoglobin C.

FIG. 2.—Haemoglobin electrophoresis on paper at *p*H 8.9 (tris buffer). Centre: cord blood containing Haemoglobin F Hull (near origin). Left and right; blood from the parents of this infant; Haemoglobin A_2 is shown near origin. The electrophoretic mobilities of Haemoglobins A, and F Hull are similar.

The abnormal haemoglobin was thought to be a variant of Haemoglobin F for the following reasons:

(1) It was absent from the blood of the parents (Fig. 2) in both families. An examination of the antigens of nine blood group systems in parents and children failed to provide evidence of aberrant paternity in any of the three cases.

(2) The ultraviolet spectrum of the isolated variant haemoglobin showed a clearly resolved tryptophan fine structure band at 289 mμ (Fig. 3). This is a characteristic feature of Haemoglobin F and its γ-chain variants.

(3) The amount of the variant present in the blood of the two surviving infants declined during the first few months of life.

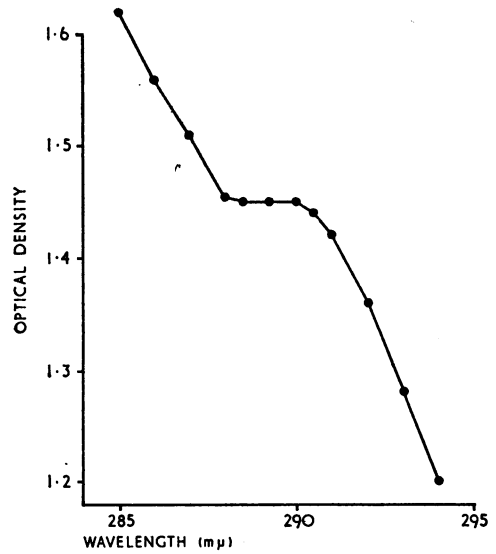

FIG. 3.—Ultraviolet spectrum of the isolated haemoglobin variant, showing the tryptophan fine structure band.

On paper electrophoresis at *p*H 8.9 Haemoglobin F Hull moved slightly more slowly towards the anode than Haemoglobin C (Fig. 1). The distance between the variant and Haemoglobin F was approximately the same as that between Haemoglobin C and A. If this difference in mobility is due to a single mutation it can be assumed that, as in Haemoglobin C, a positively charged amino-acid residue has taken the place of a negatively charged residue in each of the two abnormal polypeptide chains. The nature of the genetic code (Nirenberg *et al.*, 1965) is such that a charge change of this type is due to a substitution of glutamic acid by lysine (Beale and Lehmann, 1965).

In order to define the amino-acid substitution more fully, the haemoglobin was converted to globin, and peptide maps ("fingerprints") were prepared according to the procedures of Ingram (1958) and Baglioni (1961); these procedures have been described in detail by Beale (1966). Fingerprints of pure Haemoglobin F, isolated from normal cord blood by chromatography at pH 6 according to Huisman and Prins (1955), were prepared simultaneously with those of the variant.

Fingerprints of the variant when compared with those of Haemoglobin F (Fig. 4 A and B) showed that the spot corresponding to the thirteenth tryptic peptide of the γ-chain (peptide γTpXIII), marked 1 in Fig. 4 A and B, was absent in the variant. This peptide (γTpXIII) contains residues 121–132 of the 146 composing the γ-chain. Number 121, the first in this sequence, is a glutamic acid residue. Two abnormal peptide spots, which are marked 2 and 3 in Fig. 4, had appeared. Peptide 2 is positively charged, while peptide 3 is neutral. The abnormal peptides were eluted with constant-boiling HCl and analysed for their amino-acids (Spackman, Stein, and Moore, 1958). The results are shown in Table I. The abnormal positively charged peptide contains one extra lysine and one glutamic acid residue less when

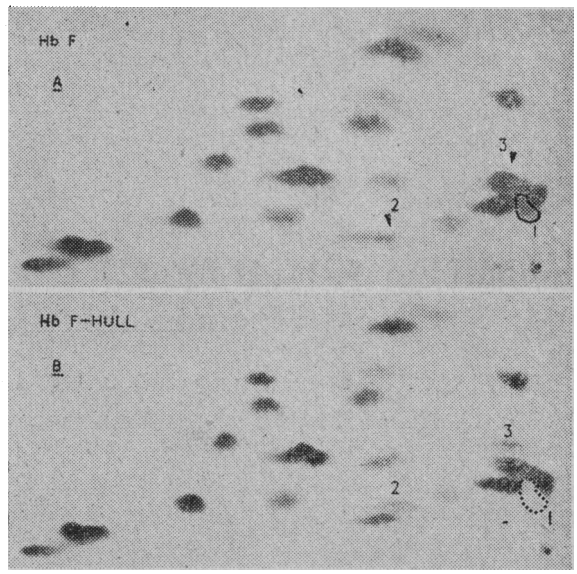

FIG. 4.—Fingerprints of (A) Haemoglobin F and (B) Haemoglobin F Hull.

TABLE I.—*Amino-acid Composition of the Hydrolysates of the Two Abnormal Peptides in the Fingerprints of Haemoglobin F Hull*

	Peptide 2 (Positively Charged)		Peptide 3 (Neutral)	
	μmole	Molar Ratio	μmole	Molar Ratio
Thr	0·015	1·2	0·012	1·1
Ser	0·021	1·3	0·015	1·4
Glu	0·049	3·0	0·030	2·7
Pro	0·014	0·9	0·014	1·3
Ala	0·016	1·0	0·013	1·2
Val	0·018	1·1	0·009	0·8
Phe	0·015	0·9	0·008	0·7
Trp	+	(1)	+	(1)
Lys	0·030	1·8	0·011	1·0
Total ..		12		11

TABLE II.—*Amino-acid Sequences of the Two Abnormal Peptides in the Fingerprints of Haemoglobin F Hull, Compared with the Normal Peptide γTpXIII of Haemoglobin F According to Schroeder, Shelton, Shelton, Cormick, and Jones (1963)*

	121	122	123	124	125	126	127	128	129	130	131	132
γTpXIII	glu	phe	thr	pro	glu	val	gln	ala	ser	trp	gln	lys
Peptide 2 (positively charged)	lys	phe	thr	pro	glu	val	gln	ala	ser	trp	gln	lys
Peptide 3 (neutral)		phe	thr	pro	glu	val	gln	ala	ser	trp	gln	lys

compared with the peptide γTpXIII (Table II). This indicates that a glutamic acid→lysine substitution has occurred. The abnormal neutral peptide has one glutamic acid residue less than γ TpXIII. This can only be explained by a glutamic acid→lysine substitution at position 121 in the γ-chain. The presence of two abnormal peptides in place of γTpXIII indicates that tryptic digestion results in partial cleavage only between residues 121 and 122 of the variant haemoglobin.

Baglioni and Lehmann (1962) described two types of Haemoglobin O which they designated O Arab and O Indonesia. Haemoglobin O Arab bears a glutamic acid→lysine substitution at position 121 in the β-chain, while Haemoglobin O Indonesia bears a glutamic acid→lysine substitution at position 116 in the α-chain.

In a model of the haemoglobin molecule (Perutz, 1965) each polypeptide chain is divided into segments denoted by letters. The eight helical regions are lettered from A nearest the amino end to H nearest the carboxyl end, while the interhelical regions are lettered according to the adjoining helical regions—that is, AB, BC, CD, etc. The residues within each region are given numbers from 1 to n. By this notation the residues α116, β121, and γ121 are homologous, all three being designated GH4. Haemoglobins O Arab, O Indonesia, and F Hull are therefore variants of haemoglobin which bear identical substitutions at homologous positions in different polypeptide chains of human haemoglobin.

This is the first example of such a situation, and its interpretation is uncertain. It is possible that mutations affecting this position are unusually common ; indeed, another haemoglobin variant, Haemoglobin D Punjab, has a glutamic acid→glutamine substitution at position 121 in the β-chain (Baglioni, 1962).

Summary

An identical variant of foetal haemoglobin was found in two unrelated families in Hull. It has not been seen again in a survey of 12,000 cord bloods in Britain. Haemoglobin F Hull differs from Haemoglobin F ($\alpha_2\gamma_2$) by the substitution of lysine for glutamic acid in position 121 of the 146 amino acid residues of the γ-chain. The same substitution occurs in the homologous position in the α- and β-chains of human haemoglobin, giving rise to Haemoglobins O Indonesia and O Arab respectively. The addition of glutamine in this position of the β-chain characterizes the common variant Haemoglobin D Punjab.

We are grateful to Mr. D. Irvine, Miss M. Joyce, and Miss P. M. Kynoch for technical assistance. Two of us (R. G. H. and A. J. B.) thank the Endowment Fund of St. Thomas's Hospital for financial support.

We gratefully acknowledge the co-operation of the nursing staff, obstetricians, and pathologists of the following hospitals who have sent us cord-blood samples: Copthorne Hospital, Shrewsbury ; Coventry and Warwickshire Hospital ; Dulwich Hospital, London ; Guy's Hospital, London ; General Lying-in Hospital, London ; Hull Maternity Services ; Lambeth Hospital, London ; Lewisham Hospital, London ; North Middlesex Hospital, Edmonton ; Oldchurch Hospital, Romford ; Plaistow Maternity Hospital ; Queen Mary's Maternity Hospital, Hampstead ; Royal Free Hospital, London ; St. Alfege's Hospital, Greenwich ; St. Andrew's Hospital, Bow ; St. Bartholomew's Hospital, London ; St. Thomas's Hospital, London ; The Lister Hospital, Hitchin ; The London Hospital, London ; Victoria Maternity Hospital, Barnet ; Waltham Maternity Hospital ; Westminster Hospital, London ; Wexham Park Hospital, Slough ; Windlesham Maternity Hospital ; Woking Maternity Hospital.

REFERENCES

Baglioni, C. (1961). *Biochim. biophys. Acta (Amst.)*, **48**, 392.
—— (1962). Ibid., **59**, 437.
—— and Lehmann, H. (1962). *Nature (Lond.)*, **196**, 229.
Beale, D. (1966). In Lehmann and Huntsman's *Man's Haemoglobins*, p. 299. Amsterdam.
—— and Lehmann, H. (1965). *Nature (Lond.)*, **207**, 259.
Huisman, T. H. J., and Prins, H. K. (1955). *J. Lab. clin. Med.*, **46**, 255.
Ingram, V. M. (1958). *Biochim. biophys. Acta (Amst.)*, **28**, 539.
Jenkins, G. C., Beale, D., Black, A. J., Huntsman, R. G., and Lehmann, H. (1967). *Brit. J. Haemat.*, **13**, 252.
Marengo-Rowe, A. J. (1965). *J. clin. Path.*, **18**, 790.
Nirenberg, M., *et al.* (1965). *Proc. nat. Acad. Sci. (Wash.)*, **53**, 1161.
Perutz, M. F. (1965). *J. molec. Biol.*, **13**, 646.
Schneider, R. G., and Jones, R. T. (1965). *Science*, **148**, 240.
Schroeder, W. A., Shelton, J. R., Shelton, J. B., Cormick, J., and Jones, R. T. (1963). *Biochemistry (N.Y.)*, **2**, 992.
Spackman, D. H., Stein, W. H., and Moore, S. (1958). *Analyt. Chem.*, **30**, 1190.