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11. THE DISTRIBUTION OF ABNORMAL HAEMOGLOBIN IN THE INDIAN POPULATION

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ABSTRACT

The population of India is characterized by a high degree of ethnic heterogeneity. This has been well brought out by studies using well known genetic markers. Among these, the study of abnormal haemoglobins has been usefully utilized in population genetics to evaluate the nature and extent of selective forces operating in a population.

A brief review of the distribution of abnormal haemoglobins, including thalassaemia in different ethnic groups, is presented. Some of the commonly seen haemoglobin variants are Hb-S and Hb-E besides beta thalassaemia. Of these, haemoglobin S is seen mostly in Adivasis (tribes) and scheduled castes, while haemoglobin E is seen mostly in the eastern part of India. Limited data on beta thalassaemia show that this gene is confined to certain ethnic groups. The implications of these findings are discussed.

The salient features of abnormal haemoglobins and thalassaemia observed in the Bombay area are also given.

Haemoglobin consists of two pairs of identical polypeptide chains and each chain carries one haem group. One pair of chains, the α-chains, differ in amino acid sequence from the other pair, the ß-chains. The α-chain contains 141 and the β chain 146 amino acid residues. The iron atom of the haem is attached to a histidine group of the polypeptide chain by a covalent bond.

Normal adult haemoglobin consists of haemoglobin A ($\alpha_2\beta_2$), haemoglobin F ($\alpha_2\gamma_2$) and haemoglobin A_2 ($\alpha_2\delta_2$). Syntheses of the α, ß, γ and δ polypeptide chains are regulated by a structural gene and operator genes. A specific structural gene controls the amino acid sequence of each chain quantitatively. Mutation of the gene regulating structure of the polypeptide chain causes change in the coding system resulting in the replacement of an amino acid in the peptide chain. Examples of these changes are the electrophoretically detectable Hbs. S, D, E, etc. Mutations affecting the operator genes through special regulator genes result in quantitative difference in the syntheses of polypeptide chains. Examples of these are thalassaemias and their variants (Huisman, 1963; Lehmann and Huntsman, 1966).

The diverse population groups in India form very useful material for the study of various genetical characters. Recent advances in the knowledge about haemoglobin, with possible detection of mutation at molecular level, make it an immensely useful character in popu-

lation genetics. Various haemoglobins detected in India include Hbs. S, D, E, J, K, L, M and Q, thalassaemias and hereditary persistent foetal haemoglobin. Distribution of these haemoglobins varies in different ethnic groups.

HAEMOGLOBIN S

This is the most commonly found haemoglobin. Sickling was first demonstrated in India in the tribal groups of the Nilgiri hills in South India (Lehmann and Cutbush, 1952). A subsequent report confirmed the presence of Hb-S in these groups by electrophoretic studies (Lehmann and Sukumaran, 1956). Table 11.1 shows the presence of haemoglobin S in various groups from that area. Later studies showed sickling in Paniyan, Kurumba and other groups in Nilgiri district (Büchi, 1955, 1959; Kirk *et al.*, 1962; Das *et al.*, 1967). A low incidence of this trait was found in Shimoga district in Mysore (Swarup *et al.*, 1959). The Relli community in Vishakhanatnam in Andhra Pradesh showed a high incidence of sickle cell gene (Krishnamurthy and Subba Rao, 1973). Cases of Hb-S in families from Andhra Pradesh have been reported (Chatterjea, 1966; Sita Devi *et al.*, 1969). A detailed genetic study of some populations in Tamil Nadu revealed cases of Hb-S in Irula and Parayans and an isolated instance in Naidus.

TABLE 11.1

*Haemoglobin in the Nilgiris**

Community	Number examined	Sickling test positive	Haemoglobin	
			Normal adult haemoglobin only	Mixture of normal adult and sickle cell haemoglobins
Badaga	30	2	28	2
Irula	18	4	14	4
Kotha	22	0	22	0
Kurumba	26	7	19	7
Toda	50	1	49	1

* Ref. Lehmann and Sukumaran, 1956.

In Western India, sickling was found in some tribal groups from Broach, Surat and Baroda districts (Sukumaran *et al.*, 1956; Vyas *et al.*, 1962; Sayed and Amin, 1966). Table 11.2 shows the sickle cell trait in some groups from this area. A small endogamous community (Sorthi) near Bombay showed a high incidence of sickle cell gene which included sickle cell anaemia and sickle cell-thalassaemia (Mittal *et al.*, 1962). In a detailed population genetic study of the Parsi com-

munity, the presence of sickle cell trait in low incidence has been reported (Undevia, 1969). Some tribal groups, namely Kokna, Katkari and Warli from the Sahyadri section of Maharashtra showed Hb-S trait while this was seen in a low frequency in Mahar, a scheduled caste tested in Bombay (Sanghvi, 1962). Students belonging to scheduled castes from Aurangabad also revealed the presence of the sickle cell trait (Lele *et al.*, 1962). In a survey from Nagpur sickling was reported in a few scheduled caste groups (Shukla and Solanki, 1958; Das *et al.*, 1961). Although findings of Hb-S were confined mainly to tribal groups and scheduled caste populations, isolated cases of sickle cell-thalassaemia were found in Sindhi-speaking Lohanas, Khadaita vania, Desa vania and Bene-Israel Jews (Sukumaran, unpublished observation).

TABLE 11.2

*Sickle cell trait in some tribes and other groups in Western India**

Caste or tribe	No. of persons tested	No. of persons with sickling	Percentage incidence
Bhils	206	32	15.53
Dhodias	207	22	20.53
Dublas (Talavia)	211	20	9.48
Kolis	51	0	0.0
Naikas or Naikadas	90	20	22.22
Anavil Brahmins	53	0	0.0
Leva Patidars	150	0	0.0
Marathas	201	0	0.0
Mixed group	222	0	0.0

* Ref. Sukumaran *et al.* 1956.

From a survey in Mainpuri district in Uttar Pradesh sickle cell trait was reported in the Dhanukh caste (Bhatia *et al.*, 1955). In Madhya Pradesh, in and around Bastar and Koraput districts, sickling has been reported in varying frequencies (Negi, 1962, 1963, 1964; Chatterjea, 1966; Das *et al.*, 1967 and Kumar and Ghosh, 1967). In a study of 10,600 tribal people in Madhya Pradesh 10% sickle cell trait was found (Chatterjea, 1966). Two instances of Hb-S were reported from Indore (Salgia *et al.*, 1965).

Haemoglobin S was found to be extremely rare in Bengal. A few instances of sickle cell-thalassaemia were found in a Santhal tribe in Midanpur district (Chaudhari *et al.*, 1964). Isolated examples of sickle cell trait were reported from Calcutta (Chatterjea *et al.*, 1957b). Some tribes of the Andaman islands were investigated and found to be negative for sickling and other abnormal haemoglobins (Lehmann, 1954; Agarwal, 1968; Sukumaran, unpublished observation). Figure

11.1 shows the distribution of sickling in various tribes and scheduled castes in India.

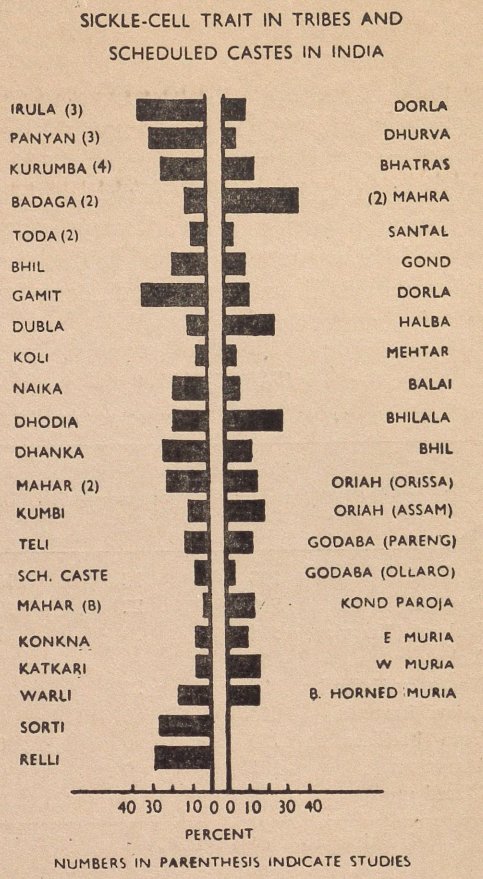


Fig. 11.1 Distribution of sickling in various tribes and scheduled castes in India.

HAEMOGLOBIN D

Haemoglobin D, found in India and known as Hb-D Punjab (Los Angeles), is a β-chain variant, and was first reported from Poona in a Sikh soldier (Bird *et al.*, 1955). Later investigations of unrelated members of the Sikh community showed Hb-D trait and one case of an apparently homozygous state of this haemoglobin, again in a Sikh soldier (Bird *et al.*, 1956; Bird and Lehmann, 1956a; Bird and Lehmann, 1956b). The latter case was subsequently found to be a case of Hb-D thalassaemia. A survey in Punjab revealed Hb-D in Sikhs and Punjabis (Saha and Banarjee, 1965).

Haemoglobin D has been reported in Gujarati school children from Kampala in Uganda (Jacob *et al.*, 1956; Lehmann, 1959). Cases

of Hb-D thalassaemia and Hb-D trait have been reported in Gujarati-speaking and Sindhi-speaking Lohanas from Bombay (Sukumaran *et al.*, 1960). An interesting case was reported of a pseudohermaphrodite girl suffering from testicular feminization syndrome in whose mother and brother the Hb-D trait was seen (Sukumaran and Shah, 1962). During a genetic study in different groups of Gujarati-speaking Lohanas, Hb-D was found in Halai, Cutchi and Goghari Lohanas (Sukumaran *et al.*, 1969). A similar study in a Muslim population from Bombay showed 2 instances of Hb-D trait in the Khoja community (Hakim *et al.*, 1972). An Audich Brahmin group in the Bombay area also showed this trait (Parikh *et al.*, 1969). In a study of Goan population, 0.3% Hb-D trait was found (Lessa and Desai, 1955). In two separate surveys, Hb-D trait was found, once in each, in individuals originating from Punjab and Madhya Pradesh, while cases of Hb-D trait and Hb-D thalassaemia were found in subjects from Uttar Pradesh (Pande *et al.*, 1972; Gupta *et al.*, 1972). An incidence of 0.4% of Hb-D trait was found in Indians in Singapore (Vella, 1962). Reports from Bengal include Hb-D trait, Hb-D thalassaemia and Hb-D E disease (Swarup *et al.*, 1966). Haemoglobin D-thalassaemia with severe anaemia and hepato-splenomegaly in a Sindhi child, and Hb-D only also with clinical manifestations, in a child originating from Kerala have been reported (Jain *et al.*, 1970; Jain, 1971). A case of Hb-D thalassaemia was reported in a Sikh from Punjab (Dutta *et al.*, 1972). Haemoglobin D trait in Muslims (Khoja and Memons) and Vania, and Hb-D trait and Hb-D thalassaemia in Sindhi-speaking Lohanas have been observed (Sukumaran, unpublished observation).

HAEMOGLOBIN E

This haemoglobin variant was described in Bengalees and Assamese and found in Hindus and Muslims alike in Bengal. In a study among unrelated Bengalee Hindus 3.9% showed this trait (Chatterjea *et al.*, 1956; Chatterjea *et al.*, 1957a). In Totos in Totopura in Assam a higher incidence of 19.8% was reported (Chaudhari *et al.*, 1964). Subsequent studies in Bengal showed cases of Hb-E trait, Hb-E disease (homozygous), Hb-E thalassaemia and Hb-DE disease (Chatterjea *et al.*, 1957b; Swarup *et al.*, 1960; Chatterjea 1965; Swarup *et al.*, 1966).

Isolated instances of Hb-E were reported from Agra, Uttar Pradesh, Patiala, in one Tamil-speaking family from Madras and one of a Bengal-Tamil ancestry and in a Muslim family from Aurangabad (Swarup *et al.*, 1960; Lele *et al.*, 1962; Mathur *et al.*, 1962; Kochar and Kathpalia, 1963; Pande *et al.*, 1972). Haemoglobin E-thalassaemia was reported in a Muslim (Bohra) family in Maharashtra

in which there was evidence of Bengalee admixture while two other examples of this condition were found, one with a local Muslim mother and a Pathan father and the other in a Bhayya from Gondia in Uttar Pradesh (Sukumaran and Randelia, 1967; Sharma *et al.*, 1963; Udani *et al.*, 1963). One case of Hb-E trait was observed in a Hindu male in Trivandrum, Kerala State and one case of Hb-E thalassaemia in a Tamil Christian family (Pillay *et al.*, 1972; Mehta *et al.*, 1973). In a study of Indians in Singapore, 4.5% showed Hb-E trait (Vella, 1962). Out of the nine families seen in Bombay, apart from the one reported earlier, one Maratha boy from Ratnagiri district, Maharashtra showed Hb-E disease. The remaining families all had instances of Hb-E thalassaemia, of which one family (Hindu-Kayasth) was from Uttar Pradesh; while all others were from different parts of Maharashtra with no evidence of admixture with populations from regions in north or north-east India. In each of these families more than one individual showed Hb-E thalassaemia. They included two Deshastha Brahmins, one each of Maratha and Mahar (a scheduled caste), two Muslims (Sunni sect) and three Muslims of other sects. One Brahmin family from Kerala State was found to have Hb-E trait (Sukumaran, unpublished observation).

HAEMOGLOBIN J

The first report of Hb-J trait in an Indian was in a Gujarati woman, detected in a survey of Indians living in and near Kampala, East Africa (Raper, 1957). In a study in Bombay this haemoglobin variant was recorded in two unrelated Gujarati-speaking Lohana families. In one of them, there was evidence of Hb-J trait associated with β-thalassaemia trait; this was proved by family studies (Sanghvi *et al.*, 1958). Another example of Hb-J trait was reported in a Harijan family from Nagpur (Subhedar *et al.*, 1961). Two members in a Bengalee family were reported to have the Hb-J trait and other members to have Hb-J interacting with β-thalassaemia, thus indicating that this haemoglobin was a β-chain variant (Swarup *et al.*, 1963). In a survey of Indians in Malaya, one example of Hb-J trait was found (Vella, 1962). Halai and Cutchi Lohanas in Bombay showed Hb-J trait. Hybridization of this haemoglobin showed this variant to be of α-chain type (Sukumaran *et al.*, 1969).

A new variant with mutation in the α-chain known as Hb-J Rajappan ($\alpha_2$90 Lys $\rightarrow$ Thr β_2) was observed in an Indian family belonging to a Tamil-speaking community in South India investigated at Southampton, England (Hyde *et al.*, 1971). Another example of Hb-J trait seen in a Mahar originating from Ahmednagar in Maharashtra was found to be a β-chain variant which on subsequent analysis showed a substitution at 126 position of β-chain with gluta-

mic acid replacing valine (Sukumaran *et al.*, 1974). A similar variant with identical substitution was designated as Hb-Hofu (Miyaji *et al.*, 1968). Yet another Hb-J with evidence of mutation in α-chain was observed in Bombay, and the structure of this haemoglobin was found to be $\alpha_2$120 (H3) Ala → Glu (Sukumaran, unpublished observation).

HAEMOGLOBIN K

Very few examples of this variant are seen in this country. The first report of its presence was in an East Indian family (Ager and Lehmann, 1957a). Subsequently instances of this variant were reported from Singapore in subjects originating from South India (Vella, 1962). One family with haemoglobins K and E and thalassaemia with all three abnormal genes in one individual, was reported from Bengal (Swarup *et al.*, 1963). Presence of Hb-K trait in Indians has been documented from Goa as well as from Madras city (Lessa and Desai, 1955; de Traverse *et al.*, 1963).

HAEMOGLOBIN L

Haemoglobin L, a slow-moving variant, was first reported from London in a Punjabi originating from Mianwali district in Pakistan (Agar and Lehmann, 1957b). Later this haemoglobin was seen in 8 individuals in three families of Gujarati-speaking Lohanas (Sukumaran *et al.*, 1959). Haemoglobin L seen in Bombay was found to be an α-chain variant with substitution in Tp 8-9 (Sukumaran and Pik, 1965). The presence of this haemoglobin was seen in Halai, Cutchi and Goghari Lohanas (Sukumaran *et al.*, 1969). Table 11.3 shows the distribution of abnormal haemoglobins in Lohanas investigated in Bombay. Two examples of Hb-L in Indians in Singapore have been recorded (Vella and Bhagwan Singh, 1959).

TABLE 11.3

*Haemoglobin genotypes of Gujarati-speaking Lohanas in Bombay****

Groups	Number tested	AA	AD	AJ	AL
Halai	253	248	3	1	1
Cutchi	237	233	2	1	1
Goghari	108	105	2*	—	1

* This includes one individual with Hb D-thalassaemia.
** Ref. Sukumaran *et al.* 1969.

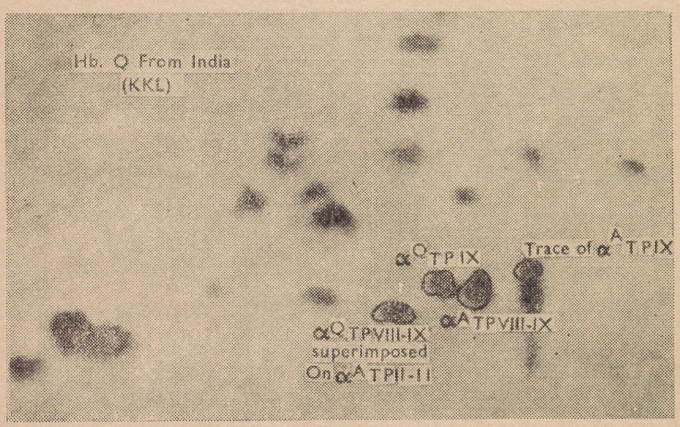
HAEMOGLOBIN M

Haemoglobin M was first described in a Punjabi family living in Amritsar. Haemoglobin M in a Muslim-Khoja (Ismaili Aga Khan sect) was reported with father and all four children being carriers

of this trait (Bajaj *et al.*, 1973). Structural studies showed that this variant was similar to Hb-M Boston (α 58 His →Tyr). Another example of Hb-M seen in a Punjabi-Hindu was found to be similar to Hb-M Iwate (Sukumaran and Das, unpublished observation).

HAEMOGLOBIN Q

This haemoglobin, a new variant with the structural formula α_2 64 (E13) Asp → His associated with β-thalassaemia, was reported in three Sindhi families from Bombay (Sukumaran et al., 1972). Figure 11.2 shows the finger print of the soluble tryptic peptide of this haemoglobin (Hb-Q India) from the father in one family. Recently Hb-Q was reported in two unrelated Sindhi families (Chouhan *et al.*, 1973). Haemoglobin Q was also reported from Goa (Lessa and Desai, 1955).



Fg. 11.2 Finger print (pH 6.4) of the soluble tryptic peptide of Hb-Q India.

THALASSAEMIA

Thalassaemia is not a single disease entity but a collection of them with varying severity. With the advance in the knowledge of the structure of the haemoglobin molecule it is now possible to distinguish a great majority of thalassaemias. The two commonly found thalassaemias are β-thalassaemia in which β-chain synthesis is reduced and α-thalassaemia where α-chain synthesis is affected.

BETA THALASSAEMIA

In India this condition was first recorded in a 2½ year old Bengalee boy (Mukherji, 1938). Since then several reports have appeared describing cases of thalassaemia from different parts of the country (Coelho, 1939; Napier *et al.*, 1939; Parekh, 1939; Dhaya-

gude, 1944; Malhotra and Chuttani, 1950; Patel and Bhinde, 1939; Chanda and Chaudhari, 1950; Pirzada and Kapur, 1951).

Collected series of cases have also been reported from time to time (Das Gupta *et al.*, 1954; Tiagi *et al.*, 1954). In a study in the Sikh community resident in Vancouver, Canada, 6% showed this trait (Sidoo *et al.*, 1956). Other reports on thalassaemia include 17 cases from Bombay (Coelho and Simmons, 1958), 7 cases from Delhi (Ghai, 1958) and 13 from Nagpur (Khandelwal and Solanki, 1959). 26 further cases were reported from Bombay describing thalassaemia syndromes in children (Udani *et al.*, 1961). Cases of thalassaemia seen at the J. J. Hospital revealed this disease in people coming from Gujarat, Maharashtra, Sind and Goa (Sharma *et al.*, 1963). In a study in Uttar Pradesh 68 cases of thalassaemia disease were recorded (Dube *et al.*, 1959). In extensive data collected by a group at the School of Tropical Medicine, Calcutta, thalassaemia major was seen in Hindus from Bengal, Bihar, Orissa, Sind and Punjab. Beta-thalassaemia, in combination with haemoglobin variants such as D, E, S and J, was also recorded during this study (Chatterjea, 1966).

Frequency of the thalassaemia trait to an extent of 3.7% was reported from Bengal (Chatterjea *et al.*, 1957b), and 0.6% among the random population in Trivandrum (Pillay and Krishna Das, 1972). Evidence of β-thalassaemia trait in Bene-Israel Jews from Bombay and Cochin Jews from Kerala has been recorded (Ramot *et al.*, 1964). Studies on thalassaemia in Bombay revealed 4.2% trait in Chitrapur Saraswats, 1% in Gaud Saraswats and 13.6% in Lohanas (Sharma *et al.*, 1971). The Bhanushali community, originating from North India, was reported to have 15% of this trait (Mehta *et al.*, 1971). A detailed investigation on 122 cases having β-thalassaemia disease (homozygous) with complete family studies along with adequate controls showed that 42% of cases belonged to Sindhi-speaking and Gujarati-speaking Lohanas (Sukumaram and Randelia, 1967). Preliminary studies on Sindhi school children in Ulhasnagar near Bombay showed 10 out of 82 children examined having β-thalassaemia trait (Sukumaran, unpublished observation). Table 11.4 shows the findings in this study.

HEREDITARY PERSISTENCE OF FOETAL HAEMOGLOBIN (HPFH)

Foetal haemoglobin, which forms the bulk of haemoglobin during the last two trimesters in intrauterine life, is sometimes found to be persistently high even in adult life. It is believed that in these cases the normal process of switching off the γ-chain production and turning on the β- and δ-chains fails to occur. When the switching mechanism fails, a high level of foetal haemoglobin continues in adult

TABLE 11·4

Haematological Data on 82 Sindhi Students

	R.B.C. $X10^6/mm^3$	Hb g/100 ml	P.C.V. %	M.C.V. cu m^3	M.C.H. pg	M.C.H.C. %	Fragility* %	Hb. F %	Hb. A_2 %
Normal (70)	4·60±0·04	13·30±0·14	42·5±0·20	92·0±0·73	28·9±0·29	31·4±0·42	80·5±1·18	0·77±0·03	2·26±0·03
Beta—Thal. Trait (10)	5·55±0·13	11·9±0·35	41·0±0·72	74·04±1·68	21·6±0·77	29·2±0·28	54·3±5·33	1·31±0·15	5·32±0·24
Hb. A+D									
Case 1	4·99	12·4	40·0	80·1	24.8	31.00	86.0	1·38	
Case 2	5·41	14·4	44·0	81·2	26.7	32·8	75.5	0.31	

Figures are Mean ± S. E., with number examined in parentheses.

* % Haemolysis in 0·4 Tyrode solution. (Normal 80—100)

life unassociated with anaemia. It has been shown that the γ-chain of the Hb-F exists in two forms, (1) with a glycine residue in the position 136, and (2) with an alanine residue in the same position of the polypeptide chain. Depending upon the nature of the γ-chain of Hb-F, carriers of HPFH may be classified as Hb Gγ, Hb Aγ and Hb GγHb Aγ (Schroeder *et al.*, 1968).

Cases of HPFH haemoglobin along with β-thalassaemia have been reported from Bombay (Sukumaran *et al.*, 1961). One of them, in a Christian family, was first investigated in 1953 and was reported as having interaction of thalassaemia with high foetal trait (Sukumaran *et al.*, 1959). Similar conditions were noticed in two Bengalee families (Chatterjea, 1966), and a later study in Bombay revealed this type of double heterozygous condition in two cases (Parekh *et al.*, 1963). Similar cases of HPFH with β-thalassaemia have been recorded by Barkhan and Adinolfi (1962) and Bird *et al.*, (1964). One Maratha family showing Hb-E with this gene has been described from Bombay (Sukumaran and Vengsarkar, 1972).

In view of the evidence of multiple structural genes for the γ-chain of human foetal haemoglobin, some of the HPHF already reported from Bombay were subjected to chemical analyses. In one case HPHF in homozygous state seen in a 9 year old boy was found to have Hb-F entirely of Gγ type. In addition the case of Hb-E with HPHF was also found to be Gγ type (Sukumaran *et al.*, 1972). A similar study of six individuals in four families showing HPHF were found to have two types of γ-chains (the Gγ chain with glycine in 136 position and the Aγ chain with alanine in the same position) which were present in the ratio of 70:30. It was suggested that these heterozygotes form a distinct sub-group of Hb GγHb Aγ class. Some members of this family carried β-thalassaemia gene along with the above abnormality (Schroeder *et al.*, 1973).

HAEMOGLOBIN LEPORE

This is a class of haemoglobins composed of α-chain and a hybrid of δβ-chains and can be designated $\alpha_2(\delta\beta)_2$.

In this country Hb-Lepore was found in 10 out of 23 members of a family studied (Chouhan *et al.*, 1971).

ALPHA THALASSAEMIA, HAEMOGLOBIN BART'S AND HAEMOGLOBIN H

There are two clinical forms of α-thalassaemia, (1) haemoglobin Bart's hydrops syndrome and (2) haemoglobin H disease, the former due to the polymerization of the excessive γ-chains to a tetrameric form Hb-γ_4 and the latter due to the excess of β-chains resulting in β_4 tetramer. Unlike the β-thalassaemia trait, the carrier state of

α-thalassaemia is difficult to diagnose. It is recognized by the presence of Hb-Bart's in a new-born. A case of Hb-H thalassaemia was reported from Calcutta (Chatterjea, 1961). Two cases of Hb-H disease from Western India have been reported (Parekh *et al.*, 1967; Chouhan *et al.*, 1970).

Haemoglobin Bart's to an extent of 2.4% was detected in cord bloods from Bengal (Swarup *et al.*, 1965). A survey in cord bloods carried out in Bombay showed presence of α-thalassaemia (Chouhan *et al.*, 1970). In another study of cord bloods in Bombay, 0.86% of Hb-Bart's with concentrations below 2% was observed (Sukumaran, unpublished observation).

OTHER THALASSAEMIA VARIANTS

In an attempt to differentiate various forms of thalassaemia on the basis of relative proportions of haemoglobin A, A_2 and F seen in Calcutta, various types of thalassaemias have been reported. They include ß-thalassaemia, ßδ-trait or α-trait, $\beta/\beta\delta$ or $\beta/\propto$, $\beta\delta/\beta\delta$ and α/β types (Swarup *et al.*, 1965). A case of βδ-thalassaemia in combination with β-thalassaemia trait resulting in a condition simulating thalassaemia disease was seen in a Marathi-speaking boy in Bombay (Sukumaran *et al.*, 1971). A Sindhi family with a child suffering from thalassaemia major showed one parent carrying β-thalassaemia trait and the other with elevated Hb-A_2 but not associated with any haematological stigmata. This trait was seen in other siblings as well (Sukumaran, unpublished observation). Instances of suspected 'silent carrier' of β-thalassaemia were also found in Bombay. These were in families where the children manifested mild or intermediate type of thalassaemia with only one parent showing the classical β-thalassaemia trait, while the other was almost normal with no haematological manifestations (Sukumaran, unpublished observation). Similar examples of double heterozygote for 'silent carrier' of β-thalassaemia and high A_2 thalassaemia resulting in mild manifestation of thalassaemia have also been reported (Chouhan, 1971). Figure 11.3 shows the distribution of abnormal haemoglobins and thalassaemia in India.

DISCUSSION

Haemoglobin S has been the most commonly found abnormal haemoglobin in this country. Severe to moderately severe clinical manifestations are associated with this haemoglobin when in a homozygous condition or in association with β-thalassaemia or other haemoglobin variants. The frequency of Hb-S varies in different ethnic groups, and in such groups where this gene is high, haemo-

lytic anaemia in childhood can be a public health problem directly attributable to this deleterious gene.

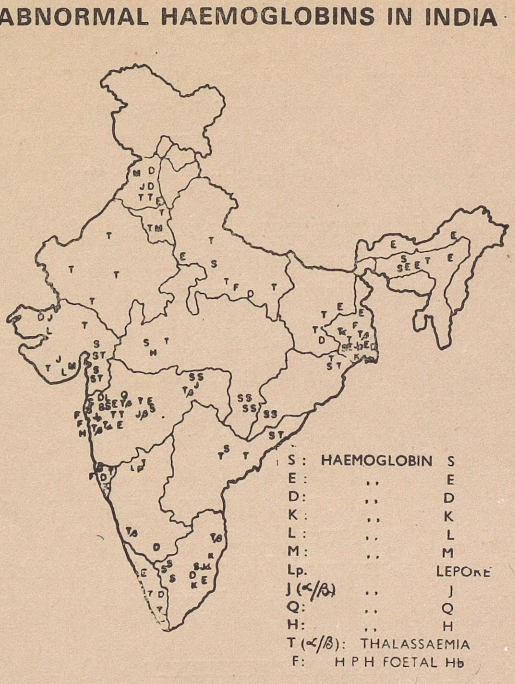


Fig. 11.3 Distribution of abnormal haemoglobins and thalassaemias in India.

Haemoglobin E, considered to be characteristic of the yellow race, has been seen mostly in Bengal and adjacent areas. A report of this haemoglobin in areas farther away from north-eastern region of this country with no possible evidence of migration, as in the remote villages, is interesting. It is worthwhile to ascertain whether Hb-E found in such areas are structurally similar to the one seen in Bengal, for there is another type of Hb-E with amino acid substitution at a different position (Vella *et al.*, 1967). This is particularly so in view of the hypothesis that the "entire area of Assam, northern Bengal and possibly parts of Nepal were inhabited in prehistoric times by a contingent population of matrilineal Austroasiatic tribes among whom Hb-βE spread after its introduction by migration from South-East Asia" (Flatz *et al.*, 1972).

Haemoglobin D-thalassaemia with evidence of interaction between them do not exhibit any clinical manifestations, as seen from earlier reports. Recently there are cases that do show evidence of varying degrees of anaemia and other associated conditions. Careful study of such families would be interesting.

Haemoglobin F manifested as hereditary persistence of foetal haemoglobin has not been a rare condition, at least in the Bombay region. Findings of variants of the gene based on structural differences of the gamma-chain, especially a homozygous form of haemoglobin Gγ and another in association with Hb-E, are of significance. Other types of γ-chains are also noticed in HPHF conditions. These findings including the heterozygotes with 25-30% foetal haemoglobin which form a distinct sub-group of the Hb Gγ Hb Aγ class are of anthropological importance (Schroeder *et al.*, 1970).

Haemoglobin J and its structurally different forms in the diverse population groups described need special attention as limited studies so far have revealed three distinct forms.

Data so far available show that it is not uncommon to find variants of thalassaemia though β-thalassaemia has been found to be most common. Again some ethnic groups showed a higher incidence of the latter condition though data available are inadequate for a meaningful conclusion. Considering the peculiarly heterogenous population divided into different endogamous groups, the origin and evolution of the majority of which are not traceable, data available on the distribution of abnormal haemoglobins in this country are inadequate. Systematic study in this direction can be rewarding.

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QUESTIONS

Chakravarti (Calcutta) : What do you feel is the reason for the association between sickling and malaria, and other such associations ? Is this true for haemoglobinopathies in general ?

Sukumaran : It has been postulated that in holoendemic or stable malarial areas the gene for Hb-S is maintained in high incidence because of partial protection of the heterozygote against P. *falciparum* malaria. There have been reports of Hb- C trait and E trait affording protection against similar types of malaria. There are equally contradictory reports on these claims.

Malhotra (Poona) : Could you please elaborate on why the sickling could not have spread from India to the Mediterranean area ? It is yet to be estab-

lished that the Indian tribal population, particularly Proto-Australoids, came from the Mediterranean area.

Sukumaran : It is believed that the gene for Hb-S originated in the Middle East and spread through migration. This does not rule out the possibility of an independent mutation the rate of which can be incredibly high. Other possibilities also exist. These are yet to be proved.

Mukherjee (Tirupati) : Do you think the hypothesis of heterozygous advantage fits with the high incidence of Hb-S in small inbred populations including subcastes of Mahars and tribes ?

Sukumaran : Yes. It happens that in families where children have died of sickle-cell anaemia, the two parents who are both Hb-S trait carriers, would have more heterozygote children, which would result in a greater number of sicklers in the next generation. It has been stated that parents who have lost childen through sickle-cell anaemia tend to replace them and might in fact over-compensate for their loss.

Sharma (Nagpur) : Have you come across any case of thalassaemia with hyper-triglyceridaemia ?

Sukumaran : Yes. We have seen a few cases in Bombay that were referred to us for investigations.

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