ABNORMAL HAEMOGLOBINS

A Symposium

organized by

THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

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Edited by

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FOREWORD

The Council for International Organizations of Medical Sciences groups fifty international voluntary associations of specialists belonging to all the medical disciplines. It is concerned with assistance to member-organizations, with co-ordination and multidisciplinary activities, and with the study of questions which do not fall within the competence of any one member but are of interest to all.

From its inception, the Council has arranged symposia to provide opportunities for the careful analysis and discussion of scientific subjects on the fringe of several medical disciplines. As a rule these meetings are held in connection with international congresses from which they draw part of their membership but from time to time they are organized in countries where international meetings are less frequently held, in order to provide a stimulus for research.

The symposium on 'Abnormal Haemoglobins' took place in Istanbul since the Near East appears to be a sort of haemoglobin crossroads. A practical training course on laboratory methods, open to young research workers from the Near and Middle East region, followed the symposium and was organized under the auspices of the Unesco Middle East Science Co-operation Office.

These two closely integrated meetings were only made possible thanks to a generous grant from the Rockefeller Foundation and to the close co-operation and support of Unesco. The C.I.O.M.S. wishes to put on record its appreciation for the help received from these two organizations.

Sincere thanks are also due to the local organizing committee, the Faculty of Medicine of Istanbul, and in particular to the Acting Dean, Professor Üveis Maskar, for the gracious hospitality which was offered to all who took part in the meetings.

Drs Inceman, Ulutin, Visser and Sijpesteijn contributed largely to the success of the meeting by attending to all details of organization and Mr W. J. Bishop was kind enough to see the manuscript through the press and to compile the index. May they find here the expression of the Council's gratitude.

During the week September 15th-21st, 1957, all the various aspects of the haemoglobinopathies were reviewed and discussed—biochemistry, genetics, clinical aspects, geographic distribution and relationship to other diseases. This volume is a record of the meeting: may it be of use to those who are investigating this rapidly expanding field of molecular biology.

J. F. DELAFRESNAYE
Secretary, C.I.O.M.S.

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THE GEOGRAPHY OF HAEMOGLOBINS

GENETIC AND PHYSICAL FACTORS IN THE HETEROGENEITY OF HAEMOGLOBIN

HARVEY A. ITANO

I. Introduction

1. *Historical Considerations*

Early investigators of the properties of the haemoglobin molecule were aware of the possibility that it may exist in more than one molecular form in the same individual or in different individuals of the same species. The question, 'Is the oxyhaemoglobin of the blood of any individual a single substance?' was discussed by Reichert and Brown (1909) in their impressive volume on the crystallographic properties of the haemoglobin of many vertebrates. These authors observed that the oxyhaemoglobin of several species crystallized in more than one form and cited earlier observations of the same phenomenon by other workers. Using the ratio of affinities of haemoglobin for oxygen and carbon monoxide as their criterion, Douglas, Haldane and Haldane (1912) stated, '... the average constitution of the globin part of the molecule varies, not only in different species, but also in different individuals of the same species'. More recent results on the effect of type and concentration of small ions and molecules on crystal form and oxygen affinity have raised some doubt concerning the usefulness of these criteria in detecting differences between haemoglobin molecules (Itano, 1956). Nevertheless, the question of Reichert and Brown and statement of Douglas and co-workers contain the essential elements of the current approach to the study of the human haemoglobins, namely, the consideration of differences in the haemoglobin of an individual and between individuals of the same species on the basis of inherited differences in the control of its synthesis.

One type of difference in the haemoglobin of individuals of the same species was discovered by Körber in 1866, who published data in his doctoral thesis (cited in Krüger, 1887) which indicated that haemoglobin from human placental blood is more resistant than the haemoglobin of adult blood to denaturation both by alkali and by acid. In subsequent years, other investigators have confirmed this finding and have also demonstrated that other species also have a foetal and an adult form of

haemoglobin. Haurowitz (1929) applied kinetic methods to the denaturation of haemoglobin by alkali and showed that the haemoglobin of a newborn infant is a mixture of adult and foetal forms. Lemberg and Legge (1949) have summarized other studies that suggested the existence of heterogeneity in the haemoglobin of a species or of an individual. In most cases the results were not conclusive in the light of present knowledge concerning the methods employed (to be discussed in a later section), and in no case was the heterogeneity analysed in terms of genetic control.

In 1948 and 1949, two papers called attention to the important contributions of genetic factors in giving rise to physically different haemoglobin molecules. Hörlein and Weber (1948) reported that the ferrihaemoglobin of individuals afflicted with a rare type of congenital ferrihaemoglobinaemia has an abnormal absorption spectrum. Pauling, Itano, Singer and Wells (1949) demonstrated that the haemoglobin in sickle-cell anaemia is electrophoretically abnormal and that the haemoglobin in individuals with sickle-cell trait, an asymptomatic condition, is a mixture of the abnormal form and normal adult haemoglobin. The genetic relationship between the anaemia and the trait (Neel, 1949) indicated that a single abnormal gene induces the synthesis of the abnormal haemoglobin. The discovery of sickle-cell haemoglobin stimulated a widespread search for other electrophoretic differences in human haemoglobin, and by now at least nine or ten inherited forms have been reported.

Replacement of foetal haemoglobin by adult haemoglobin is complete or nearly complete in most infants by the end of the first year of postnatal life. Singer, Chernoff and Singer (1951) found varying amounts of an alkali-resistant haemoglobin in the blood of older individuals with severe anaemia. Examination of this component by several independent techniques has established to the satisfaction of most investigators that foetal haemoglobin persists beyond infancy in some types of severe, chronic anaemia. Observations of minor heterogeneities in the haemoglobin of normal adults have been reported from time to time, and the isolation of two such components by Kunkel and Wallenius (1955) provided conclusive evidence of their identity as haemoglobin.

The usefulness of human haemoglobin for studies of the heterogeneity and inheritance of proteins lies in the large number of inherited alterations to which it is known to be susceptible. It is too early to state whether the wide diversity of genetic control of the synthesis of human haemoglobin is a unique one among mammalian species. Reports of

inherited differences in other mammalian proteins have appeared; however, to date no more than two inherited types are known in any of these instances. The present picture may be distorted because of the fact that human haemoglobin has been more intensely surveyed than any other protein from the point of view of finding inherited differences.

Several other factors favour the use of haemoglobin for studies of the heterogeneity and inheritance of proteins. The cell in which its biosynthesis occurs is present in large quantity in each individual, and protein remains in the cell after completion of the biosynthetic process. Since haemoglobin comprises nearly all of the soluble protein mass of the red blood cell, it can be prepared in large quantity and nearly free of other proteins from the red cells of one individual and without the use of procedures for fractionation. Thus, ambiguity from the loss of components during preparation and from the pooling of samples pose no problems. But for its size, which renders the determination of its complete amino-acid sequence a formidable if not insurmountable problem, haemoglobin would be the ideal protein for the investigation of the biochemical genetics of protein synthesis.

The physical chemist is primarily interested in the end-product of a fractionation procedure: is a protein prepared from individual or pooled samples according to certain specified methods a homogeneous entity of identical molecules? The biochemical geneticist may regard homogeneity in terms of how the structure of a protein corresponds to genetic information: does each gene contain specific information concerning the polypeptide sequence of a protein molecule, and if so, how accurately is this information transmitted? Studies on the inherited forms of human haemoglobin have considerable bearing on these questions. The current status of the problem of obtaining homogeneous preparations of proteins for physical and chemical studies has been reviewed by Low and Edsall (1956), and the relationship of the template theory of gene action to the one gene–one enzyme hypothesis has been discussed by Horowitz and Fling (1956).

2. *Nomenclature*

The various compounds of haemoglobin may be designated in accordance with the nomenclature proposed by Pauling and Coryell (1936). Deoxygenated haemoglobin and oxidized haemoglobin, commonly called haemoglobin and methaemoglobin, respectively, are assigned the more descriptive names, ferrohaemoglobin and ferrihaemoglobin. The

compounds of ferrohaemoglobin with oxygen and with carbon monoxide are designated oxyhaemoglobin and carbonmonoxyhaemoglobin, respectively. The word 'haemoglobin' will be used whenever a more specific designation is not required, for example, in discussions of amino-acid analyses. When physical differences of two different inherited forms of haemoglobin are discussed, it is understood that both are examined as the same compound of haemoglobin.

The molecular species of haemoglobin unique to man are designated by capital letters (Chernoff *et al.*, 1953). Normal adult and foetal haemoglobins are haemoglobins A and F, respectively, and the abnormal haemoglobin of sickle-cell disease is sickle-cell haemoglobin or haemoglobin S. The other abnormal haemoglobins have been named haemoglobins C, D, E, G, etc., in order of discovery. The letter B was omitted in order to avoid confusion with haemoglobin b, which had been proposed by the author for sickle-cell haemoglobin (Itano, 1951, 1953a). Two minor components of normal red cells have been named haemoglobins A_2 and A_3 respectively (Lehmann, 1957b). Haemoglobin F, the abnormal haemoglobins, and the minor components, all differ from haemoglobin A in their electrophoretic behaviour. Other differences in properties have also been observed, and these will be described.

It is convenient to divide the sources of heterogeneity in the haemoglobin molecule to those associated with the haem or with the globin portions. Examination of the haems prepared from the haemoglobins of different species and of haemoglobins A and S have not revealed any differences (Lemberg and Legge, 1949; Pauling *et al.*, 1949), and it is likely that interspecies and intraspecies differences reside in the protein portions of the molecules, the globins. Thus, when we speak of genetically controlled differences in the properties of haemoglobin, we are referring to differences in the globins. It has been shown that haemoglobins A, S and C are produced under the control of genes that are transmitted as alleles (Ranney, 1954), so that haemoglobins S and C may be regarded as adult types. A homozygous individual has only one of these forms, and a heterozygous individual has two, and no more than two. Most of the other abnormal forms are probably controlled at the same locus, although complete genetic data are not yet available. The designation Hb has been given to this locus (Allison, 1955). Neel (1957) has proposed a more complex scheme which takes into account the possibility that other loci may be found that affect the synthesis of abnormal haemoglobins. If more than two components are present in the same individual, these components may be derived from the two

adult forms by chemical or physical processes, or other genetic loci may perhaps be involved. For example, an infant heterozygous for the adult forms has foetal haemoglobin in addition to two adult forms (Schneider and Haggard, 1955). Foetal haemoglobin may be present in addition to two adult forms in some forms of anaemia (Singer *et al.*, 1951). Partial conversion to ferrihaemoglobin also results in electrophoretic inhomogeneity (Itano and Robinson, 1956); however, the difference in mobility between the ferrihaemoglobins of two adult forms is the same as the difference between the corresponding oxyhaemoglobins or carbonmonoxyhaemoglobins. Presence of the same minor component in association with each of the adult forms, as is the case with foetal haemoglobin, suggests that the genetic locus responsible for this component is different from that for the adult globins. The genetic control of the component now designated A_2 (Lehmann, 1957) is probably also independent of the Hb locus.

The clinical conditions associated with inherited abnormalities of haemoglobin are designated in accordance with the haematologic manifestations and with the type of abnormal haemoglobin present. In general, the terms anaemia and disease are associated with the presence of two abnormal genes, like or unlike; and the term trait, with the presence of a single abnormal gene. The condition associated with homozygosity and heterozygosity in the thalassaemia allele are called thalassaemia major and thalassaemia minor respectively.

II. Bases for Differences among Haemoglobins

Certain structural alterations of the haemoglobin molecule can be directly correlated with alterations of a genetic locus that apparently controls globin synthesis and are incorporated into the structure of the molecule at the time of synthesis. Other alterations occur after the molecule has been completed. For the considerations of the causes of heterogeneity, the two groups of alterations will be discussed under genetic bases and physical bases respectively. The latter group includes reactions and alterations that all haemoglobin molecules can undergo. Since the ability to undergo these processes is inherent in the structure of haemoglobin, as distinguished from other proteins, the division into genetic and physical bases may appear to be an arbitrary one. Actually, the distinction is a valid one that must be taken into consideration in the planning of experiments and the interpretation of data. If the object of an experiment is to demonstrate inherited differences, all samples used

for comparative purposes should be converted to the same compound, for example, carbonmonoxyhaemoglobin. If the object is to demonstrate heterogeneity caused by a general reaction to which all haemoglobins are susceptible, the use of a mixture of inherited haemoglobins would complicate the data unnecessarily.

1. *Physical Bases*

Haemoglobin is the intraerythrocytic respiratory protein of vertebrates and consists of a protein, globin and a ferrous-protoporphyrin complex, ferrohaem. Its iron content is 0.335-0.340%, and its molecular weight of about 67,000 corresponds to the presence of four haems per molecule. Oxygen and carbon monoxide combine with ferrohaemoglobin in the ratio of one gas molecule per ferrohaem. The oxidation of ferrohaem to ferrihaem produces ferrihaemoglobin, a derivative that combines with a number of anions but not with oxygen or carbon monoxide. These reactions are reversible, the globin being unaffected in each case, and each of the compounds has a characteristic absorption spectrum. While it is conceivable that a mutation might produce marked alterations in the properties summarized above, no such instance has been established; and inherited differences such as those between species and between two haemoglobins of the same species have been demonstrated by the observation of differences in other properties. Degradative changes such as oxidation of protoporphyrin and denaturation of globin are associated with radical changes in the properties of the molecule and are not completely reversible.

Since the various compounds of haemoglobin differ in physical properties, ambiguous results may be obtained from the study of preparations that are partially oxidized to ferrihaemoglobin or incompletely saturated with oxygen or carbon monoxide. Partial conversion to ferrihaemoglobin results at acid pH in an additional positive charge for each haem oxidized and causes electrophoretic inhomogeneity (Itano and Robinson, 1956). Cannan and Redish (1942) observed that oxyhaemoglobin deoxygenated with sodium dithionite and then recombined with oxygen would not crystallize as readily as untreated oxyhaemoglobin. Thus, in this instance, a reagent for the preparation of a sample homogeneous with respect to deoxygenation induces another type of heterogeneity. The observation by Brenner and Allison (1953) that catalase inhibition causes denaturation of haemoglobin in red cells suggests that the denaturing action of dithionite is an effect of the

peroxide formed in the reduction of oxygen. Carbonmonoxyhaemoglobin is a common contaminant in the blood of tobacco smokers and of individuals exposed to exhaust fumes, and ferrihaemoglobin is produced in nitrite poisoning and in toxic reactions to oxidizing drugs. Denaturation or conversion from one haemoglobin compound to another may take place in the course of an analysis and induce heterogeneity not present in the original sample.

Human haemoglobin is a relatively labile protein, and repeated crystallization may increase rather than decrease heterogeneity. The precipitation of insoluble material with prolonged storage may be due, at least in part, to the formation of intermolecular disulphide bonds (Riggs and Wolbach, 1956). The determination of type and proportions of all components present is an important aspect of the study of human haemoglobin, and stroma-free haemolysates of washed cells are used in most cases. For chemical analyses that require the use of homogeneous preparations, samples from individuals, homozygous for the gene which controls a given haemoglobin should be used, and further purification by crystallization and electrophoretic separation should be attempted. Further details of the preparation and storage of haemoglobin solutions have been reviewed elsewhere (Itano, Bergren and Sturgeon, 1956).

2. *Genetic Bases*

Observations to date indicate that both interspecies and intraspecies differences are ascribable to inherited alterations in the globin portion and not in the haem (Lemberg and Legge, 1949; Pauling *et al.*, 1949; Havinga and Itano, 1953; Ingram, 1956, 1957b). The genes that control the synthesis of haemoglobins A, S and C are allelic, the genes for S and C presumably being mutants of the gene for A. Homozygous individuals have only one of these haemoglobins, and heterozygous individuals have two. Although most of the other abnormal forms of human haemoglobin are known to be transmitted from parent to offspring, the available familial data are not sufficiently complete to localize their genetic control. Considerations to be discussed in the section on genetic control, based on electrophoretic and chemical data, suggest that the genes controlling their synthesis are also allelic with the gene for haemoglobin A. The structure of foetal haemoglobin is also an inherited characteristic since the properties of this form are characteristic for a given species; however, the control of its synthesis appears to differ from that of the normal and abnormal adult haemoglobins since

an individual may have foetal haemoglobin in addition to two of the inherited adult forms.

The existence of more than one haemoglobin component in a given individual does not always indicate that a different gene is responsible for each component. The modifications to which all haemoglobin molecules are susceptible have been discussed in the preceding section. In addition, other modifications characteristic of certain species may occur. Svedberg and Hedenius (1934) observed that the haemoglobin of amphibia and reptiles contains a rapidly sedimenting component, presumably a dimer of the haemoglobin molecule. The proportion of dimer increased as the samples aged. These investigators also reported that the haemoglobin of several species of birds sediments as a single component; on the other hand, Dunlap *et al.* (1956) and Rodnan and Ebaugh (1957) found the haemoglobin of a large number of species of birds, including some that are closely related to the species examined by Svedberg and Hedenius, can be separated into at least two components by electrophoresis. The same heterogeneity was found in all individuals of a given species, so that these examples of heterogeneity differ from those caused by mutations at a single locus. Mutant forms are transmitted in accordance with Mendelian laws, so that although each form in an offspring is present in one of the parents, the mixture in the offspring need not be the same as that in either parent. The occurrence of the same heterogeneity in all individuals suggests either that two or more genetic loci are operating simultaneously or that in some species the haemoglobin molecule undergoes modification following initial synthesis. While the tendency to undergo modification is an inherited characteristic of a particular species, the mechanism must be different from that which produces the abnormal haemoglobins of man.

Hereditary ferrihaemoglobinaemia (Barcroft *et al.*, 1949) is an example of an inherited mechanism that results in heterogeneity after completion of synthesis of the haemoglobin molecule. An inherited defect in the enzyme-controlled reducing mechanism of the red cell permits the accumulation of ferrihaemoglobin and results in heterogeneity with respect to the oxidation state of the iron in the haems. This form of inherited ferrihaemoglobinaemia differs from that described by Hörlein and Weber (1948), in which the globin is apparently affected. Since red cells are produced by a continuous process of cell division, it is also conceivable that a mutation in a proerythroblast can result in a gene-controlled heterogeneity not transmissible from parent to offspring.

III. Genetic Control of Haemoglobin Synthesis

Highly significant findings of a chemical difference between haemoglobins A and S have been reported by Ingram (1956, 1957b). Each of these molecules is a symmetrical dimer, and the molecules appear to be identical except in one position of each half-molecule. A valine residue in each half-molecule of haemoglobin S takes the place of glutamic acid residue in the same position in haemoglobin A. Therefore, a whole molecule of haemoglobin S contains two fewer glutamic acid residues and two more valine residues than a molecule of haemoglobin A. The experimental procedures used by Ingram include partial tryptic hydrolysis into peptides, combined electrophoretic-chromatographic separation of the peptides, and sequential analyses of the peptides. The findings of Ingram re-emphasize the importance of physical and chemical methods for the study of inherited differences among the haemoglobins and of the significant role assumed by the abnormal haemoglobins as experimental tools in the elucidation of the genetic control of protein structure.

The specific methods that have proven useful for the identification of abnormal haemoglobins will not be discussed here as these will be described in greater detail elsewhere in this symposium. The clinical and haematologic findings in the abnormal haemoglobin syndromes will also be discussed by other speakers.

The remainder of this paper will be devoted to a consideration of the significance of chemical and physical findings in relation to current concepts of the genetic control of protein synthesis. Other papers will be devoted to different aspects of the genetics of the abnormal haemoglobins. The author will therefore not present a general review of the clinical, haematologic and anthropologic implications of the genetic data. Instead, an attempt will be made towards reconciling the available findings with biochemical concepts and theories.

1. *Control of Differences in Physical Properties of Haemoglobin*

(a) *The normal haemoglobins.* Foetal haemoglobin is structurally dissimilar to haemoglobin A, and the same foetal haemoglobin is found in all infants in severe, chronic anaemia, whether or not abnormal haemoglobins are present. The A_2 component likewise occurs in the presence or absence of abnormal haemoglobins or of anaemia. We have mentioned that since the foetal haemoglobin of different species differs one from the other, some form of genetic control must be exerted over its synthesis. This control is obviously different from that which