MALIGNANT EXOPHTHALMOS

The most effective treatment of malignant exophthalmos is orbital decompression. It should be considered if vision is threatened as a result of raised intraorbital pressure or from severe exposure keratitis. Corneal ulceration, papilloedema, or serious limitation of eye movements may also be indications for operation. There are various operations: in some the floor of the orbit is removed, in others the lateral wall, and in the Naffziger operation the roof. Operative interference is considered only in patients whose vision is threatened by extreme proptosis. In this condition, when retinal vein distension and papilloedema may be evident, lateral or even supraorbital decompression offers a predictable means of relief and a chance to preserve the eye. This is a major operation requiring an expert surgeon, but the results are often striking.⁴² The transantral approach to the floor and medial wall of the orbit by means of a Caldwell-Luc exposure has recently become favoured. It is simple, safe, and effective, and it has the additional advantage of not being an intracranial procedure.⁴³

Much debate has centred on the effect of different methods of treatment for thyrotoxicosis on the patient's exophthalmos. Exacerbation of exophthalmos may occur after any form of treatment of thyrotoxicosis—whether it is antithyroid drugs, subtotal thyroidectomy, or radioactive iodine therapy—though the incidence of deterioration is small, usually about 10%.^{19 44} It is important to avoid hypothyroidism, but there is no rationale for giving thyroxine to euthyroid patients. Even so, there may be an argument for controlling the hyperthyroid state cautiously. There is clinical evidence that in thyrotoxic patients treated by drug, surgery, or radiation there is a greater fall in the serum protein-bound iodine level and a greater rise in L.A.T.S. in those developing an exacerbation of exophthalmos than in those who do not develop this complication.⁴⁴

In conclusion, endocrine exophthalmos can usually be recognized clinically even in euthyroid patients. In a majority the diagnosis can be confirmed either by a failure of tri-iodothyronine to suppress the ¹³¹I uptake or by the presence of thyroid antibodies. As far as treatment is concerned it should always be remembered that time is on the patient's side and a conservative course should be pursued unless exposure keratitis or papilloedema constitute a threat to vision, when a more radical approach to decompress the orbit is indicated.

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Scientific Basis of Clinical Practice

The Haemoglobinopathies

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Haemoglobinopathies are inherited disorders of haemoglobin synthesis. They comprise, firstly, the thalassaemias, in which the synthesis of haemoglobin is impaired, and, secondly, the abnormal haemoglobin syndromes, in which normal haemoglobin is replaced by a structural variant.

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The Haemoglobin Molecule

The haemoglobin molecule consists of a protein, globin, to which is bound a prosthetic group, haem, an iron-porphyrin compound. The iron in haem is in the divalent (ferrous) state and is able to combine reversibly with oxygen to form oxy-haemoglobin without change in the valency of iron.

Much precise information has been obtained about the structure of haemoglobin.

It has a primary structure of two pairs of amino-acid chains; a secondary structure, which is a regular α -helical coiling of the

amino-acid chains; a tertiary structure formed by the folding of the coiled chains; and a quaternary structure pertinent to the relative positions of the four chains with particular reference to their points of contact. The position of the haem groups in relation to the amino-acid chains has been established.

The haemoglobin molecule is ellipsoidal and has a molecular weight of 64,458, of which about 97% is contributed by globin. It consists of two identical half molecules each made up of a pair of unlike amino-acid chains. The amino-acid chains consist of eight helical portions A-H; the interhelical portions are designated by the letters of the preceding and succeeding helicals—e.g., EF. Haem is situated in a crypt between the E and F helicals; it interacts with the globin molecule and stabilizes its structure. It is linked to a histidine residue situated at position F8 in both the α - and β -chains.

During oxygenation and deoxygenation changes take place in the quaternary structure of haemoglobin. The changes have been described as a kind of molecular respiratory movement. The movement is a to and fro rotation of the β -chains in the vicinity of the haem residues. The iron atoms become 7 Å closer together on oxygenation.

Normal Haemoglobins

Normal haemoglobins are normal adult haemoglobin (Hb A), a minor adult component (Hb A₂), normal fetal haemoglobin (Hb F), and an embryonic haemoglobin (Hb Gower-2). The haemoglobins have one pair of amino-acid chains in common: α -chains. In Hb A α -chains are paired with β -chains, in Hb A₂ with δ -chains, in Hb F with γ -chains and in Hb Gower-2 with ϵ -chains. Hb A therefore has the molecular formula $\alpha_2\beta_2$; the molecular formulae of the various normal haemoglobins is given in Table I. The α -chains contain 141 amino-acids, the non α -chains 146. The complete amino-acid sequence of the various chains has been established.

TABLE I—Normal Haemoglobins

Type	Symbol	Molecular formula
Adult haemoglobin	A	$\alpha_2\beta_2$
Minor adult component	A ₂	$\alpha_2\delta_2$
Fetal haemoglobin	F	$\alpha_2\gamma_2$
Embryonic haemoglobin	Gower-2	$\alpha_2\epsilon_2$

Hb F is readily distinguished from Hb A by electrophoresis in agar gel at pH 6.2. It is resistant to alkali or acid denaturation; this property forms the basis of various methods for the demonstration of Hb F, such as the Kleihauer test for fetal erythrocytes in the maternal circulation.

GENETIC CONTROL

Separate pairs of alleles control the structure of the α -, β -, γ - and δ -chains. In the fetus α -chains combine with γ -chains to produce Hb F. At term γ -chain synthesis is rapidly reduced, and in about twelve months Hb F becomes a minor haemoglobin component. In the normal adult Hb F amounts to less than 0.5% of the total haemoglobin.

The amount of globin chains synthesised depends on the amount of messenger RNA (m-RNA) which is produced¹ and the rate at which the chains are assembled on the m-RNA-ribosomal template. Haem synthesis is controlled by a feed-back mechanism, in which haem inhibits a critical enzyme step in its own synthetic pathway. Haem stimulates globin synthesis so that there is synchronous production of haem and globin. Furthermore, iron is involved in haemoglobin synthesis: it inhibits haem synthesis and maintains the stability of the polysomes (aggregates of four to six ribosomes) active in globin synthesis. The synthesis of a globin chain begins at the N-terminus and is continued by the sequential addition of amino acids coded in the m-RNA template as it moves along the polysome.

The Thalassaemias

There are two main types of thalassaemia: β -thalassaemia and α -thalassaemia, in which there is defective synthesis of β -chains and α -chains respectively.

β -Thalassaemias

In the β -thalassaemias there is synthesis of γ -chains after the neonatal period so that Hb F levels are raised. The unqualified term thalassaemia is usually applied to β -thalassaemia. The homozygous condition (thalassaemia major) was first described by Cooley and Lee² in a paper entitled "Series of Cases of Splenomegaly in Children with Anaemia and Peculiar Bone Change." The term thalassaemia was introduced by Whipple and Bradford,³ who had earlier used the term Mediterranean anaemia because the condition was found chiefly in children of Greek, Italian, and Syrian origin. $\Theta\alpha\lambda\alpha\sigma\sigma\alpha$ (thalassa) is Greek for sea, and to the Greeks the sea is the Mediterranean.

The term Cooley's anaemia is still widely used. This is unfortunate, partly because it relegates Lee to the limbo of the forgotten, and partly because Cooley⁴ described another anaemia, which is sex-linked and characterised by anaemia with elliptocytosis. If an eponym must be used for thalassaemia, Cooley and Lee's anaemia would be appropriate.

PATHOLOGICAL AND CLINICAL FEATURES

There is grossly defective synthesis of Hb A, impaired formation of erythrocytes, and increased haemolysis of the defective red cells. Erythropoiesis cannot compensate for increased cell destruction; this inadequacy is probably greater in thalassaemia than in any other haemolytic anaemia. Haem synthesis is impaired, protoporphyrin synthesis is slow, and there is an incomplete block in the combination of protoporphyrin with iron, probably owing to impaired activity of the appropriate mitochondrial enzyme. This defect, which causes iron granules to form in the cytoplasm of erythroblasts, places thalassaemia in the group known as sideroachrestic anaemias; nevertheless, thalassaemia is usually classified as a haemolytic anaemia.

The anatomical changes in thalassaemia fundamentally depend on the increased destruction of the defective red cells. There is erythropoietic hyperplasia of the bone marrow and extramedullary haemopoiesis. The destruction of the patient's red cells and those of transfused blood results in excessive deposition of iron in the tissues, such as the spleen, liver, kidneys, and other organs.

Thalassaemia major begins insidiously; it is recognized clinically after the age of 6 months.

Listlessness, fever, diarrhoea, a poor appetite, pallor, and splenic enlargement are presenting manifestations. There may be headache and precordial pain. When the anaemia is severe the facial appearance becomes characteristic: the head is large with prominent frontal and parietal bones, the malar eminences are prominent, the bridge of the nose is depressed, and the upper teeth protrude. A muddy complexion with a tendency to "slit-eyes" produces a characteristic mongoloid look.

The abdomen is protuberant because of enlargement of the spleen and often the liver. The heart is enlarged (Fig. 1a); haemic murmurs are common. Other features include pericarditis, gallstones and leg ulcers, haemosiderosis (after repeated transfusions) and poor growth after the age of 8-10 years; hypogonadism is a constant feature.

Bone marrow hyperplasia produces osteoporosis, thinning of the bone cortex, and widening of the medullary spaces. The thinning of the cortex is compensated for by numerous small trabeculae. The earliest changes are observed in the small bones, particularly in the metacarpals (Fig. 1b) and metatarsals, which often appear rectangular in X-ray films and show a mosaic pattern of trabeculation. Pathological fractures, chiefly of the long bones (Fig. 1c), may occur. The diploe of the skull are thickened. The outer and inner tables are thin. Perpendicular striations appear between the tables. The

Some clinical features of thalassaemia major (a) cardiac enlargement; (b) mosaic trabeculation of the small bones of the hand; (c) healed pathological fracture of the left fibula; (d) "hair on end" appearance in x-ray film of skull.

outer table is sometimes so thin as to be invisible; the perpendicular striations then give the "hair on end" appearance (Fig. 1d) which is characteristic of skull x-ray pictures in severe homozygous haemoglobinopathies. Retarded filling of the cranial air sinuses with air is common; this results from hyperplasia of marrow in the mastoids and paranasal sinuses.

HAEMATOLOGICAL PICTURE

There is a hypochromic microcytic anaemia. The haemoglobin ranges between 5 and 9 g/100 ml, and the red cells from 2.5 to 3.5 millions/mm³. Haemoglobin is mainly Hb F; there is some Hb A and Hb A₂; the amount of Hb A₂ is normal or low. The packed cell volume is reduced. The M.C.V., M.C.H., and, in many cases, the M.C.H.C. are decreased. The blood smear shows appreciable anisocytosis (cells 3-15 μ m in diameter), poikilocytosis, fragmentation, polychromasia, and punctate basophilia. Howell-Jolly bodies are occasionally seen.

The reticulocyte count is above normal; it may reach 10% or more. Leptocytes are numerous—pale flat cells, many of which show a peripheral rim of haemoglobin surrounding a central island of haemoglobin with a pale zone in between; such leptocytes are called target cells. Though target cells are a characteristic feature of thalassaemia they also occur in chronic iron deficiency, the abnormal haemoglobin syndromes, liver disease, severe dehydration, and after splenectomy. Nucleated red cells are always present. They vary in size and maturity, but are most often normoblasts. Moderate leucocytosis is present (15,000-30,000/mm³); granulocytes predominate. The platelets are normal. The bone marrow, in severe cases, shows primitive erythroid cells and a predominance of basophilic normoblasts. Many erythroblasts give a strongly positive P.A.S. (periodic acid Schiff) reaction.

The osmotic fragility is strikingly abnormal. Because of the high proportion of leptocyte stroma as compared to its volume, osmotic fragility is greatly decreased. The cells can imbibe a relatively greater quantity of water before bursting. Despite this, red cell survival time is shortened to 60-80 days; haemolytic anaemia results from increased fragmentation of the defective red cells.

The serum bilirubin may be raised. It is usually 1.5 to 3 mg/100 ml; when the upper limit is exceeded a haemolytic crisis or gallstones should be suspected. The serum iron is normal or increased; the serum iron binding capacity is fully saturated. The condition is easily distinguished from chronic iron deficiency, in which the serum iron is low.

The urine often contains slightly increased quantities of urobilinogen or urobilin. Occasional iron-containing kidney epithelial cells are found in the deposit. Urinary amino-acid levels are increased. The faeces contain greatly increased amounts of coproporphyrin.

The characteristic facies, the stunted growth, the protuberant abdomen, and the typical haematological and radiological findings make the clinical diagnosis quite simple to the experienced. Nevertheless, since the condition is inherited, a firm diagnosis cannot be made without a family study.

Interactions of thalassaemia with haemoglobin variants (for example, Hb S-thalassaemia), chronic severe iron deficiency, di

Guglielmo's disease (erythraemic myelosis), pyridoxine-responsive anaemia, and pseudothalassaemia (the sex-linked anaemia of Cooley), may show features similar to thalassaemia major.

PROGNOSIS

The outlook in thalassaemia major is poor. There is a definite susceptibility to infection. The children are feeble: their life, pleasures, and schooling are continually interrupted by illness or hospitalisation for transfusion. Repeated blood transfusion is required to maintain normal activity in the severe disease. In some patients there is a strong haemolytic component. In the less severe condition—the so-called intermediate type (thalassaemia intermedia)—transfusions are not required regularly; they become necessary only when there is exposure to infection or other stresses.

Many patients die before puberty. Whereas infection was the chief cause of death before the discovery of sulphonamides and antibiotics, heart failure is now the principal cause, being related to heavy deposition of iron in the myocardium. Once heart failure develops death results in about twelve months. The initial sign is a prolonged PR interval. Acute benign non-specific pericarditis sometimes occurs, particularly among patients who have undergone splenectomy. The cause of this susceptibility is unknown; spontaneous recovery takes place.

Since the condition is inherited, there is no cure. Transfusions are required to maintain reasonably good health and to enable the children to play and to attend school. Splenectomy is useful when there is an appreciable haemolytic component. Iron is contraindicated, but other haematinics may be given if actually deficient. Folic acid deficiency is present in some patients; in these folic acid (15-30 mg) daily brings about some improvement.

Other β -Thalassaemias

β -THALASSAEMIA MINOR

The heterozygous state, β -thalassaemia minor, is a relatively benign condition. The patient has a mild anaemia, which is often mistaken for iron-lack anaemia but does not respond to iron. Hb A₂ levels are raised from the normal 2-3% to 3-6%; Hb F levels may be slightly raised.

δ - β -THALASSAEMIA (F-THALASSAEMIA)

The clinical picture is similar to that of β -thalassaemia. In the homozygous state no β - or δ -chains are produced and Hb F is the only haemoglobin. In the heterozygote Hb A₂ levels are not raised but Hb F levels range from 5-30%.

δ -THALASSAEMIA

Homozygous δ -thalassaemia, with complete absence of Hb A₂, has been described in a Japanese family by Ohta *et al.*⁵

Hb Lepore Syndrome

Although Lepore haemoglobins are structurally abnormal, this condition is classified with the thalassaemias because it resembles β -thalassaemia clinically and haematologically.

In the Lepore haemoglobin the α -chains are normal but the non α -chains consist of the N-terminal portion of the δ -chain joined to the C-terminal portion of the β -chain. This composite chain is thought to have arisen as the result of crossing over at closely-linked loci for the δ - and β -chain genes.

Hereditary Persistence of Fetal Haemoglobin

Hereditary persistence of fetal haemoglobin (H.P.F.H.) is an inherited high level of Hb F which persists throughout life and is not associated with anaemia. Conley *et al.*⁶ have reported an individual homozygous for this condition; his haemoglobin consists entirely of Hb F without any Hb A or Hb A₂, and blood films showed microcytosis, target cells, and abnormal variations in the size and shape of erythrocytes.

H.P.F.H. may be distinguished from β -thalassaemia by the fact that in the former Hb F is present in all erythrocytes rather than in separate clones. The β - and δ -chain loci are closely linked and are believed to form an operon which is under the control of an operator gene. H.P.F.H. may be due to failure of the operon to "switch on" production of both β - and δ -chains. H.P.F.H. may interact with haemoglobin variants or with β -thalassaemia. At present three types of H.P.F.H. are recognized: African, Greek, and Swiss.⁷

 α -Thalassaemias

Since α -chains are common to all haemoglobins, decreased production of α -chains affects the production of Hbs A, F, and A₂ but their relative proportions are not appreciably changed. Homozygous α -thalassaemia gives rise to stillbirth with severe hydrops fetalis. During fetal life the decreased production of α -chains leaves an excess of γ -chains, which form tetramers known as Hb Barts (γ_4).

Heterozygous α -thalassaemia is recognized in the newborn by raised levels (5-20%) of Hb Barts. In adults it is not easy to recognize. When β -chain production takes over from γ -chain production tetramers of β -chains are formed (haemoglobin H). Hb H (β_4) is unstable and readily denatures within the red cell to form inclusion bodies.

In haemoglobin H disease β -chains are produced two or three times faster than α -chains. The β -chains combine to form appreciable amounts of Hb H. Nevertheless, since Hb H is so unstable the amount demonstrable in blood specimens does not give a true indication of the amount actually formed.

HAEMOGLOBIN HOMOTETRAMERS

As mentioned in the preceding section an excess of one kind of polypeptide chain may result in the formation of tetramers: Hb Barts (γ_4) and Hb H (β_4). Another tetramer is Hb Gower-I (ϵ_4), seen only in embryos.

Abnormal Haemoglobin Syndromes

In the abnormal haemoglobins there is variation in the primary structure of the α -, β -, γ - or δ -chains. Most haemoglobins

TABLE II—Amino-acid Substitution in Some Haemoglobin Variants

α -chain variants				β -chain variants		
Residue No.	Amino-acid substitution	Variant	Helical	Residue No.	Amino-acid substitution	Variant
16 23	Lys-Glu Glu-Gln	I Memphis	A3	6	Glu-Val	S
			A3	6	Glu-Lys	C
			A3	6	Glu-Val	C Georgetown*
			A6	9	Ser-Cys	Porto Alegre
			A14			
87	His-Tyr	M Iwate	B4	26	Glu-Lys	E
			B8	63	His-Arg	Zurich
			E7	6	Glu-Val	C Harlem
			E17	73	Asp-Asn	
			F8	92	His-Tyr	M Hyde Park
12	y-chain variant Thr-Lys	F Alex- andra	A9	121	Glu-Gln	D Punjab

*This variant has another amino-acid substitution

differ from normal haemoglobin by the substitution of a single amino-acid by another. A list of haemoglobin variants is provided by Lehmann and Carrell;⁸ those mentioned here are shown in Table II. The change may be so benign that the person is clinically or haematologically normal. On the other hand, the physical properties of some variants are so changed as to give rise to severe pathological effects.

The variation in primary structure probably depends on a variation in DNA coding. Amino-acid substitution can be explained by point mutations which result in the replacement of one of the three basic codings for the appropriate position on the amino-acid chain.

HAEMOGLOBIN S

In 1904 Herrick observed "freakish poikilocytosis" in the blood of a severely anaemic Negro. His observations were published six years later⁹ under the title "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anaemia." Evidence was later obtained that sickle-cell anaemia was hereditary.^{10 11}

Neel¹² suggested that sickle cell anaemia was due to homozygosity, and the sickle-cell trait, usually an asymptomatic condition, to heterozygosity for a sickle-cell gene; evidence in support of this view was published by Neel¹³ and by Beet.¹⁴ Striking support for the genetic theory was provided by the demonstration by Pauling *et al.*¹⁵ that sickle-cell trait carriers had two kinds of haemoglobin, one normal and the other abnormal, which could be separated by electrophoresis, whereas patients with sickle-cell anaemia had only a single abnormal haemoglobin.

Thus sickle-cell anaemia emerged as a molecular disease. The brilliant work of Ingram¹⁶ showed that Hb S (sickle-cell haemoglobin) differs from Hb A only in respect of a single amino-acid substitution in the β -chain. In Hb S a valine residue replaces glutamic acid in position 6. The molecular formula of Hb S is therefore $\alpha_2^A\beta_2^S$ or $\alpha_2^A\beta_2^{\text{glu} \rightarrow \text{val}}$. Valine has a negative charge less than glutamic acid so that Hb S migrates more slowly than Hb A in an electrophoretic field.

Sickle-cell Disease

The substitution of glutamic acid by valine involves only the β -chain. Children who are homozygous for Hb S do not show the sickling phenomenon until β -chain production predominates over γ -chain production. In the oxygenated state the single amino-acid substitution appears to have no physiological significance. In the deoxygenated state the solubility of Hb S falls to 2% of normal. Reduced Hb S forms a viscous semisolid gel, which consists of many thin filaments arranged parallel to one another (tactoids). A low pH hastens sickling.

The presence of sickle cells increases blood viscosity and slows its rate of flow.

In low pressure vascular areas, where blood flow is normally at its slowest, further slowing occurs. This predisposes to stasis, so that more oxygen is given up by red cells to meet tissue requirements. The sickling tendency is therefore enhanced and a vicious cycle established. Blood vessels may be occluded by a mass of distorted cells. Furthermore, sickle cells are particularly vulnerable to mechanical trauma and readily haemolyse.

Sickle-cell anaemia is a chronic, often fatal, haemolytic anaemia, almost entirely confined to Negroes. Virtually all its clinical features are attributable to increased blood viscosity. Dyspnoea, vomiting, epigastric pain, and chronic ulcers, chiefly of the legs, are common features. Jaundice may occur. Worsening of these symptoms constitutes a "crisis." Death may result from inadequate blood supply to a vital organ.

Apart from the tendency of red cells to sickle and its pathological consequences, the haematological and clinical features of sickle-cell anaemia are essentially the same as those of homozygous β -thalassaemia. A full description of sickle-cell disease is given in the book by Whitby and Britton.¹⁷

Haemoglobin S and Malaria

There is evidence that Hb S is relatively unsuitable for the development of *Plasmodium falciparum*. Thus, in a malarial area, the sickling gene has a selective advantage, so that there is a state of balanced polymorphism.¹⁸ Luzzato *et al.*¹⁹ observed in AS heterozygotes with *P. falciparum* malaria that parasitized cells were more prone to sickling than non-parasitized cells. They suggest that the parasitized cells, once sickled, are more easily removed from the circulation and that this is the chief mechanism which confers a selective advantage on the AS heterozygote.

Other Haemoglobins Which Induce Sickling

Capacity to induce the sickle-cell change is not confined, as generally believed, to Hb S. Hb C Harlem and Hb Memphis produce sickle cells by the same mechanism as Hb S. Hbs F Alexandra, Barts, C Georgetown, I, and Porto Alegre also induce sickling.

HAEMOGLOBIN C

In Hb C the amino-acid substitution also occurs in position 6 of the β -chain; lysine which carries a positive charge replaces the negatively charged glutamic acid. Hb C has a different electrophoretic mobility to Hbs A and S. It is less soluble than Hb A. Intra-erythrocytic crystals of Hb C may be seen in Hb C disease.²⁰ The signs and symptoms of Hb C disease are milder than those of sickle cell anaemia.

Double heterozygotes for Hb C and β -thalassaemia, and for Hb C and Hb S have been described.

HAEMOGLOBIN D

Hb D is a non-sickling haemoglobin variant²¹ with the same electrophoretic mobility on paper at pH 8.6 as Hb S. It can be distinguished from Hb S by its inability to cause sickling and by its greater solubility. The best known Hb D is Hb D Punjab.²²⁻²⁴ Hb D Punjab has been characterized as $\alpha_2\beta_2^{121} \text{glu} \rightarrow \text{gln}$. It is also known as D Los Angeles, D Cyprus, and D Chicago. Hb D has been found in many parts of the world; it is relatively common in North West India where it has a frequency in certain populations of about 2%.

HAEMOGLOBIN E

Hb E ($\beta_2\alpha\beta_2^{26\text{glu} \rightarrow \text{lys}}$) has a frequency of about 13% in some Far Eastern populations—for example, Indonesia, Thailand and Burma.²⁵ In Hb E homozygotes there is a mild haemolytic

syndrome. Hb E-thalassaemia is very common in South-East Asia. The clinical picture is similar to β -thalassaemia; Hb A is usually completely suppressed.

HAEMOGLOBIN M

The amino-acid substitution in Hb M occurs in the pocket of peptide which contains the haem molecule; methaemoglobin-aemia is therefore the sole feature of Hb M disease. Homozygosity for the Hb M gene is incompatible with life. In heterozygotes cyanosis is seen at birth when Hb M is an α -chain variant—for example, Hb M Iwatae. In β -chain variants—for example, Hb M Hyde Park—cyanosis appears after β -chain synthesis has reached a sufficient level.

There are no other clinical manifestations in Hb M disease and the prognosis is good.

HAEMOGLOBIN ZÜRICH

This is one of several unstable haemoglobins. Persons with a gene for Hb Zürich are predisposed to severe haemolytic episodes after ingestion of sulphonamides and other drugs. The erythrocyte is distorted and contains a large inclusion body.²⁶

Interactions

There are many clinical syndromes which result from the interaction of α - or β -thalassaemia, α - or β -chain haemoglobin variants, and H.P.F.H. Some of these interactions have been mentioned above. In some double heterozygotes—for example, Hb S and β -thalassaemia—the effects are additive; in others—such as the double heterozygote for α - and β -thalassaemia—the subject is as mildly affected as if he had inherited only one thalassaemia gene. Some interactions are beneficial: an individual with a combination of Hb S and H.P.F.H. is clinically well because the presence of Hb F in all cells counteracts the sickling tendency.

Conclusion

The study of haemoglobinopathies has provided one of the most fascinating applications of molecular biology to clinical medicine. Deep insight has been obtained into the structure and function of the haemoglobin molecule and into the genetic basis of thalassaemia and the abnormal haemoglobin syndromes. Much has to be omitted from a single paper: recent developments however have been well reviewed.^{1-7,8} It is true that many inherited haemoglobin abnormalities are almost entirely confined to remote populations. Nevertheless, because of large numbers of immigrants and foreign visitors, haemoglobinopathies are becoming of increasing importance in this country in the differential diagnosis of dyshaemopoietic or haemolytic anaemia.

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Medical Education

Closing the Gap between the Medical Researcher and the Literature

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For about five years in Britain it has been possible to transfer to a computer the formidable task of searching medical literature for articles on a particular topic. The computer searching system is known as MEDLARS and can cover all the medical literature appearing in *Index Medicus*, *Index to Dental Literature*, and *International Nursing Index* after 1963.¹⁻²

Up to the present the complexity of searching by computer has meant that any request for a literature search has had to be channelled through a trained librarian or search editor. This delegation of the task of searching always introduces certain difficulties no matter how the searching is done. The main difficulty is that to make a satisfactory search the librarian needs to know as much about the topic as the medical researcher and to have similar criteria for the rejection of references. Any deficiencies in these respects can be remedied only by constant reference back and consultation.

In addition to the possible misinterpretations resulting from delegation, the use of machine methods introduces further difficulties—particularly (1) the very formal and limited ways of communicating with a machine system; (2) the inability to alter the computer's search instructions, when the deficiencies of the output are seen, without expensive re-searching; and (3) the delay before enough searches can be gathered to make a complete search run economic. This precludes any immediate response to queries.

The difficulties mentioned above have now been largely overcome by a system set up and developed for medical and dental research workers by the Computing Laboratory of Newcastle University with funds provided by the Office for Scientific and Technical Information. Medical and dental research workers can now formulate their own MEDLARS search and see samples of the references it will retrieve immediately printed for them on a typewriter terminal attached to a computer. They can alter the search at any point to improve it as other possibilities occur to them just as they could if searching *Index Medicus* or *Index to Dental Literature* by hand.

Of course, any research worker wishing to use the system has to have some familiarity with the way in which *Index Medicus* treats its references and he also needs to know how to command the computer to do the necessary tasks. We have tried to simplify both these requirements as much as possible and to make the process of selecting a readable number of references from about 1 million on the MEDLARS files as easy as the *Index Medicus* indexing system will permit without sacrificing its great potential for precise searching.

Operation of System

The interaction or dialogue with the computer for an actual search is shown in Figs. 1 to 8. The excerpt in Fig. 1 shows the computer responding to the terminal being connected. The system normally prints in capitals, while entries from the user are in small letters. The user identifies himself to the system using the command "\$signon" and then requests the system to start obeying the programme he wishes to use with the command "\$run *medlars." The computer is, of course, at the same time obeying many different programmes for other users. This initial sequence is probably the least comprehensible part of the process; the remainder of the dialogue on the terminal is with the MEDLARS programme, which is specifically designed for medical users.

```
MTS (LA00-0087)
#$signon dlc4 pw=blank
***LAST SIGNON WAS: 10:03.47 07-07-71
# USER "DLCA" SIGNED ON AT 10:05.21 ON 07-07-71
#$run *medlars
#EXECUTION BEGINS
OPERATOR ASKED TO MOUNT MEDLARS DISK
DONE
```

FIG. 1—Start of terminal session with MEDLARS system.

A complete search done by a medical user as it appeared on the terminal is shown in Figs. 2 to 8. The explanatory comments are interspersed to ease the understanding of the process. In Fig. 2 the user requests help from the programme to ensure that he gets full messages rather than the brief version available to the experienced user. He gives his search a title to provide an identification for him should he wish to return to this search at a later date and amend it or merely run it again on a different file of references.

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