

Reviews/Analyses

Prevention and control of haemoglobinopathies*

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In many developing countries the haemoglobinopathies (thalassaemias and sickle-cell disorder) are so common that they provide a convenient model for working out a genetic approach to control of chronic childhood diseases. At present, about 250 million people (4.5% of the world population) carry a potentially pathological haemoglobinopathy gene. Each year about 300 000 infants are born with major haemoglobinopathies. Haemoglobinopathy control programmes, based on WHO approaches and recommendations, have been established in different countries in all WHO Regions and have been successful in management of the problem. Following WHO recommendations the health burden of hereditary anaemias could be significantly reduced. This article summarizes the presentations and discussions made at a joint WHO/TIF (Thalassaemia International Federation) meeting, held in Cyprus in April 1993, and reviews the experiences of programmes in several countries for the control of haemoglobinopathies in the world.

* This article is based on the report of the Joint WHO/TIF (Thalassaemia International Federation) Meeting on the Prevention and Control of Haemoglobinopathies, Nicosia, Cyprus, 3-4 April 1993 (unpublished document WHO/HDP/TIF/HA/93.1). The participants at this meeting were Professor O.O. Akinyanju (Nigeria), Dr S. Al-Arrayed (Bahrain), Dr Al-Attar (Iraq), Dr M. Angastiniotis (Chairman) (Cyprus), Professor M.A.F. El-Hasmi (Saudi Arabia), Professor M. El-Khateeb (Jordan), Professor D.D. Farhud (Islamic Republic of Iran), Professor S. Fattoum (Tunisia), Professor S. Fucharoen (Thailand), Professor R. Galanello (Italy), Professor R. Girot (France), Dr L. Heredero (Cuba), Dr A. Kullev (USA), Dr D. Loukopoulos (Greece), Professor B. Modell (Rapporteur) (United Kingdom), Dr A.M. Mohammad (Bahrain), Dr S. Papagallo (UNRWA, Jordan), Dr V. Penchaszadeh (USA), Dr M. Saleem (Pakistan), Professor S. Temtamy (Egypt), Professor Y.N. Tokarev (Russian Federation), and Dr Wu Guanyun (China). TIF Secretariat: Mr P. Englezos and Mr G. Constantinou (Cyprus), and Mr R. Ficarra (USA). WHO Secretariat: Dr H.A. Gezairy, Regional Director, and Dr A. Alwan, Regional Adviser on Noncommunicable Diseases (WHO Regional Office for the Eastern Mediterranean, Alexandria, Egypt), and Dr V. Boulyjenkov (Secretary).

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Reprint No. 5610

Introduction

Haemoglobinopathies — i.e., the thalassaemias and sickle-cell disorder (SCD) — are recessive inherited diseases which are globally widespread. At present, about 250 million people (4.5% of the world population) carry a potentially pathological haemoglobinopathy gene. Each year about 300 000 infants are born with a major haemoglobinopathy (Table 1, Fig. 1). These hereditary anaemias were originally confined to the subtropics and tropics, with a high incidence because healthy carriers were protected against the lethal effects of malaria. Owing to increasing global migration, however the haemoglobinopathies have appeared in many areas where they were not endemic. In the USA, 10% of the population is at risk for SCD, and in north-west Europe between 2% and 9% of most populations now belong to ethnic minorities who are at risk for the haemoglobinopathies. In some south-east Asian countries, population movements could increase the rate of infants born with thalassaemia. Globally, there are more carriers of thalassaemia than of SCD, but the high frequency of the sickle-cell gene in certain areas leads to a high birth rate of homozygotes. As a result, SCD accounts for about 70% of haemoglobin disorders worldwide. Nearly 70% of affected births occur in sub-Saharan

Table 1: Global distribution of haemoglobinopathies, by region^a

Region	Population (millions)	Annual births (thousands)	Heterozygotes (thousands)	Heterozygote (% of population)	Annual homozygote births		% of affected births	Affected births per 1000
					Total	Pathological		
Africa (β)	664.33	29 802	88 355.8	13.3	226 991	216 439	73.50 ^b	7.26
America (β)	731.20	17 174	14 938.5	2.0	5 181	5 181	1.76	0.30
Asia (β)	3 149.94	83 487	117 465.0	4.1	105 978	57 875	24.13	0.85
Asia (α)			12 966.0		13 186	13 186		
Europe (β)	780.50	11 053	6 862.0	0.9	1 620	1 620	0.55	0.15
Oceania (β)	26.82	524	351.0	1.3	174	174	0.06	0.33
Total	5 346.00	142 040	240 938.0	4.5	353 130	294 475	100.00	2.07

^a Over 4.5% of the global population carry a haemoglobinopathy trait. The global birth rate of affected infants is over 2.0/1000.

^b Almost three-quarters of affected births are in Africa.

Africa where up to 2% of all children are born with SCD (1),^{a,b}

Haemoglobinopathy control programmes based on WHO recommendations, which have been established in countries in all six WHO Regions, have shown success in the management of the problem. In many developing countries, the appearance of a haemoglobinopathy is the first indicator of the need to develop genetic approaches for the control of chronic childhood diseases.^{c,d,e}

This article summarizes the presentations and discussions at the first joint WHO/Thalassaemia International Federation (TIF) meeting, which was convened in Cyprus to review the progress in ongoing programmes in the different WHO Regions.

Situation in the African region

Some 60–70% of all births of children with a major haemoglobin disorder occur in Africa,^b the region

with the least resources for coping with the problem; the numbers are rising since developments in primary health care have increased the survival of patients with sickle-cell disorder. Several motivated clinicians are making efforts to provide some services, and to sensitize the governments and the WHO Regional Office for Africa (AFRO) to the importance of this problem. Because of the global economic downturn some of the gains are being lost, e.g., malnutrition is increasing, and many trained people have left the region for political or economic reasons. In 1987 WHO proposed a plan to develop services for sickle-cell disorder throughout the African continent which required US\$ 3 million to carry out, but so far there has been no donor. In 1991 WHO/AFRO brought together eight African experts (4 francophone, 4 anglophone) to plan a meeting to include representatives from all countries and initiate a regional working group on sickle-cell disorder. Unfortunately, this meeting could not take place in 1992, as planned, owing to lack of funds.

Future proposals for action by AFRO could involve:

- making efforts to find a donor, perhaps through the United Nations Children's Fund (UNICEF) or the Food and Agriculture Organization of the United Nations (FAO);
- establishing a position with respect to sickle-cell disorder in each country within AFR;
- identifying key workers;
- convening the AFRO meeting, as planned, to initiate an AFRO Working Group on Sickle-Cell Disorder.

Nigerian experience

An extended survey of 16 000 randomly selected individuals over the age of 15 from the 30 states

^a Report of the Third and Fourth Annual Meetings of the WHO Working Group for the Community Control of Hereditary Anaemias (unpublished WHO document HMG/WG/85.8, 1985). Requests for should be sent to the Hereditary Diseases Programme, World Health Organization, 1211 Geneva 27, Switzerland.

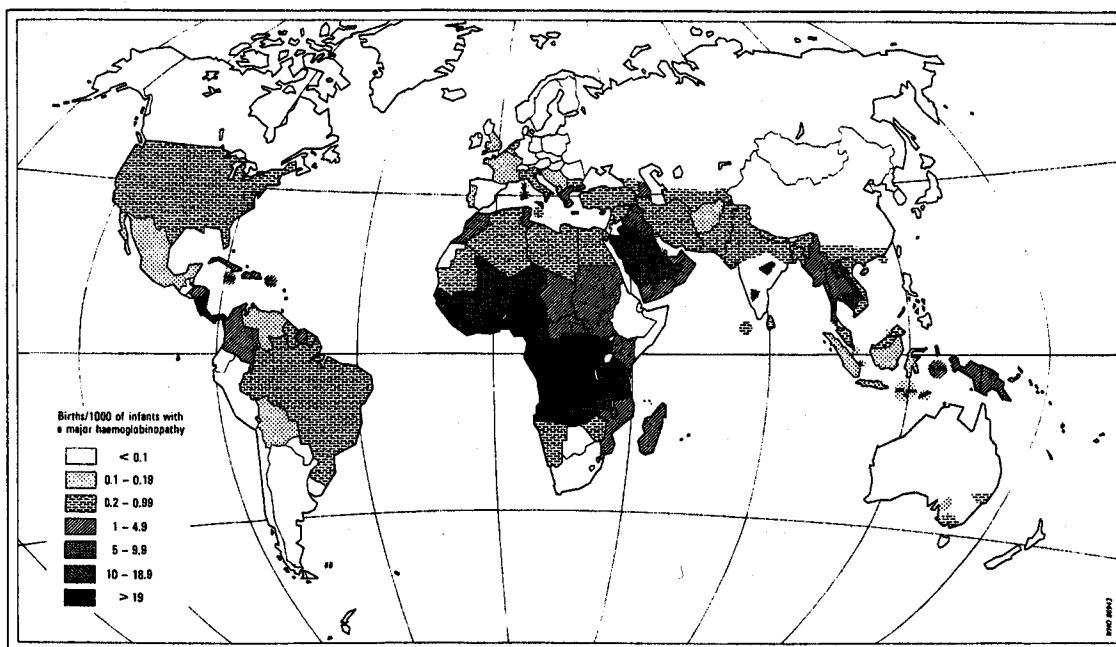
^b Report of a WHO informal consultation for a feasibility study on the control of sickle cell disease in Africa, Geneva, 2–7 February 1987 (WHO/HDP/SCD/87.3).

^c Report of the Vth Annual Meeting of the WHO Working Group on the Feasibility Study on Hereditary Disease Community Control Programmes (Hereditary anaemias: alpha-thalassaemia), Herakleion, Crete, 21–24 October 1987 (WHO/HDP/WG/HA/87.5).

^d Report of the Vth Annual Meeting of the WHO Working Group on the Feasibility Study on Hereditary Disease Community Control Programmes (Hereditary anaemias), Cagliari, Sardinia, Italy, 8–9 April 1989 (WHO/HDP/WG/HA/89.2).

^e Report of the WHO/EURO meetings on the Haemoglobinopathies in Europe, 1987 (EUR/IPC/MCH 110).

Fig. 1. Global distribution of haemoglobinopathies (thalassaemias and sickle-cell disease).



showed that 25.3% had the AS, AC, SS or SC Hb genotypes (Table 2). Beta-thalassaemia trait could not be evaluated in these surveys: its prevalence is thought to be about 1%. These figures are considered to be generally representative for sub-Saharan Africa.

The Sickle Cell Club of Lagos organizes support for parents and patients. Providing counselling

proves to be the least expensive and most accessible helpful activity under African conditions (2). Counselling for sickle-cell disease includes both psychological support for families and genetic counselling, which in developing countries is initially focused on affected families. The Sickle Cell Club of Lagos has now held five annual counselling training courses, and so far 152 counsellors from Nigeria and some from other parts of Africa have been trained. Follow-up studies have shown a decrease of morbidity and mortality in families with affected children, decreased hospital attendances, and more understanding and greater self-esteem.

Other activities of the Club include training doctors in "understanding sickle cell", in order to avoid inappropriate treatment and excessive medical dependency of the patients. The Club also provides correct information to the public and to journalists. However, less emphasis is now placed on the public information campaign, because the absence of appropriate facilities for treatment and prenatal diagnosis can lead to frustration.

The Nigerian government has formed a new Expert Committee on Noncommunicable Diseases including sickle-cell disorder, and is producing a booklet for primary health care workers on these topics.

Table 2: Nigerian national survey of the prevalence of haemoglobin disorders among 16 000 adults (>15 years old)

Hb genotype ^a	Frequency (%)	Estimated numbers among the adult population
AA	74.7	35 400 000
AS	23.0	10 900 000
AC	1.8	858 000
SS ^b	0.3	123 000
SC ^b	0.2	114 000

^a The survey gives the following gene frequencies: A = 0.871, S = 0.119, C = 0.01.

^b Using the Hardy-Weinberg equation, the expected birth incidence of "homozygotes" with SS or SC is 1.44%, equivalent to 230 in the 16 000 sample. Of these, 14.3% should be SC, equivalent to 33 in the 16 000 sample. In fact, 80 homozygotes were found, 48 SS and 32 SC. This suggests an 80% mortality before 15 years of age among people with SS, but little early mortality among those with SC disease.

% of affected births	Affected births per 1000
73.50 ^b	7.26
1.76	0.30
24.13	0.85
0.55	0.15
0.06	0.33
100.00	2.07

its is over 2.0/1000.

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Situation in the Americas

Prevalence of hereditary anaemias is high in the French-speaking and English-speaking Caribbean nations, which are geographically and ethnically related to some Latin American populations. Owing to social, political and health care differences, however, separate analyses are required for each country. In general, the problems for these genetic diseases arise from the lack of facilities for treatment, counselling and prenatal diagnosis, and the fact that termination of pregnancy is illegal in most Latin American countries.

Nevertheless, there is encouraging progress in some countries, including several where haemoglobin disorders are common, and a high level of expertise is available in the region. It was suggested that a Pan American Health Organization (PAHO) Working Group on Haemoglobin Disorders, including representatives from the active countries in the Caribbean, Brazil and other Latin American countries where the disorders are common, could be extremely valuable. Although in the past decade PAHO has convened two advisory groups in genetic health services for the Region (3),¹ this matter has not yet been assigned the importance it deserves.

Brazilian experience

The Brazilian Ministry of Health has set up a committee for haemoglobin disorders, and is identifying a number of reference centres, with the objective of standardizing diagnosis and management, to improve the health care of affected people. Prenatal diagnosis is available for wealthy patients in private clinics in all the major cities in Brazil. Frequent political change is another problem, because the amount of support for programmes varies with different governments.

The Brazilian committee identifies reference centres based on their ability to carry out diagnosis, treatment and health education: these centres are being provided with centrally-produced information materials to help in health education. The Thalassaemia International Federation (TIF) and Cooley's Anaemia Foundation in the USA have sent delegations on two occasions to Brazil, and there has been a marked improvement in the patients' quality of life in the last two years.

¹ Report of a Pan American Health Organization (PAHO) Expert Group in Medical Genetics on the Delivery of Genetic Services in Latin America and the Caribbean, Havana, Cuba, 9-11 October 1987.

Cuban experience

Cuba is the only Latin American country to provide a comprehensive community-based medical genetics programme, with the assistance of the WHO Collaborating Centre for the Development of Genetic Approaches for Health Promotion in Havana. This work, including development of appropriate technologies, has been reported previously.² Services for the treatment of sickle-cell disease are available: thalassaemia major is not a problem.

The Cuban prevention programme for sickle-cell disorders (4) is based on screening pregnant women at 16+ weeks of gestation (when maternal serum AFP screening is also provided), then offering testing to the partners of carriers, and offering DNA-based prenatal diagnosis to couples at risk. There is one DNA laboratory in Havana for the whole country. Obstetric sampling (by amniocentesis) is available in each province, and chorionic villus sampling (CVS) is now available in three provinces.

Some 80-90% of the partners of women found to be carriers come for testing, and 95% of couples at risk ask for prenatal diagnosis; 90% of those in whom an affected baby is found decide in favour of termination of pregnancy, and the rest are against it. Though in principle this high uptake should lead to a marked fall in affected births, in practice the affected births have fallen by only 32%. This is mainly because with the present screening strategy many at-risk couples are detected too late for prenatal diagnosis in the presenting pregnancy. Screening policy has now been changed and blood samples will be taken at first booking, in order to deliver prenatal diagnosis in the first trimester. In 1992 the fall in affected births was only 22% because of incoordination associated with this policy change. There remains a great need for education of the population and doctors.

The initial screening approach was to combine universal antenatal and universal neonatal screening, in order to detect and inform all homozygotes and heterozygotes. For reasons of efficiency neonatal screening is now limited to selective testing of all babies of mothers who are found to be carriers during pregnancy.

The cost of the total programme is uncertain. However, imported materials for the whole Cuban genetics programme cost about US\$ 1 million per year.

² Report of a WHO Consultation on the Human Genetics Programme in Cuba: present status and further developments, Havana, Cuba, 1984 (HMG/Cons/84.1).

Situation in the Eastern Mediterranean region

The importance of hereditary disease (including haemoglobin disorders) in the Eastern Mediterranean region is recognized, and the first meeting organized by the WHO Eastern Mediterranean Regional Office on hereditary disorders took place following the global meeting on haemoglobin disorders which is reported here.

Bahraini experience

Information on the frequency of the haemoglobin disorders is based on a neonatal screening project involving 10 000 newborns; 2.1% had sickle-cell disorder (SS or S/ β -thalassaemia) and 11.2% were AS; Hb Barts was present in 24.3%, and G6PD (glucose-6-phosphate dehydrogenase) deficiency in 24% of males. There are still no reliable figures for β -thalassaemia trait, but more than 100 patients with transfusion-dependent β -thalassaemia major are regularly treated on high transfusion and receive Desferal chelation therapy. HbH disease is common. Some cases are very severe, requiring maintenance transfusion as for β -thalassaemia major; some have an intermediate disease like thalassaemia intermedia; and some very mildly-affected adults have been detected only by antenatal screening. Hydrops fetalis is so far unknown in Bahrain.

Some 90% of sickle-cell mutations are of the "Indo-Asian" variety and the rest are of the Benin type. Most cases of sickle-cell disorder are considered "not very severe".

There is as yet no systematic national programme for haemoglobin disorders, but a Bahrain National Hereditary Anaemia Society has recently been initiated. Screening and counselling for couples prior to marriage in health centres is being started but there is a need for identification and training of genetic counsellors. Currently most people who present for genetic counselling already have the problem in their family: under these circumstances, many couples have separated when both parents are found to be carriers.

The issue of prenatal diagnosis and therapeutic abortion is not settled in the Middle East, and current practice differs between Muslim countries. In Bahrain, abortion is allowed within the first three months for serious risks to the mother or fetus, as ensoulment is considered to occur at about 120 days of fetal life, and the law permits therapeutic abortion. Three consultants are required to sign the consent form. Consequently, prenatal diagnosis is expected to be accepted, and is foreseen.

Cypriot experience

The Cyprus thalassaemia programme, based on the experience of the WHO Collaborating Centre for the Community Control of Thalassaemia in Nicosia, has previously been reported (5). Though prevention is in general complete, five new thalassaemic children were born in 1991. Residual births are mainly for social reasons, including births to single mothers (three cases). This is a relatively new issue in Cyprus.

Though premarital carrier testing in the government laboratory is effectively mandatory (through a church ruling), much carrier screening is done in the private sector. Quality control of private laboratories is arranged in the following way. When a couple who have already been screened in a private laboratory present for a premarital certificate, a further test is carried out. The government and private laboratory results are compared, and in case of a discrepancy the laboratory concerned is informed. Couples diagnosed as at-risk are both re-tested. Updated observations confirm that only 3% of at-risk couples identified prior to marriage separate. There is now some pressure in the community for schoolchildren to be screened, and this programme will be developed.

G6PD deficiency. Though 7–10% of Cypriot males are G6PD-deficient, it is not thought necessary to introduce G6PD screening into the programme. Neonatal jaundice is routinely controlled, and favism has been very uncommon since 1954, when a health education campaign discouraging parents from giving fava beans to young boys was started. No induced haemolytic crises have been observed on the island, except in association with fava beans.

Egyptian experience

High rates of β -thalassaemia are known to occur in Egypt. A heterozygote carrier frequency of 2.6–4% has been reported, although in a more recent study a carrier rate of 13% among a random sample of Egyptians aged between 1 and 59 years was noted. As consanguineous marriages occur frequently (28–33%) in urban areas and even more in the rural areas, a high frequency of homozygosity for the β -thalassaemia gene is expected. About 1000 children affected with β -thalassaemia are expected to be born every year in Egypt (based on 1.5 million births annually), which poses a significant health problem.

Molecular studies of β -thalassaemia were mainly conducted in two centres: the National Research Centre in Cairo and the Children's Department located at Mansura University in Mansura. Results of these studies showed that 80% of thalassaemias in Egypt have classical Mediterranean mutations, the rest are non-Mediterranean.

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Cases with α -thalassaemia have also been identified in Egypt. In a study comprising 545 neonates taken randomly from various regions in Egypt, the incidence of α -thalassaemia was found to be 10%. Glucose-6-phosphate dehydrogenase deficiency is by far the most common enzyme abnormality in man with the highest frequency in Mediterranean countries. In Egypt, regional variations are prominent and G6PD deficiency is in the range 0.9–9.2%.

The application of new DNA techniques for the screening of the most common mutations in the β -globin gene are now undertaken in the National Research Centre. Screening programmes for the detection of carriers, followed by molecular prenatal diagnosis in at-risk families, need to be established in Egypt for the ultimate goal of prevention of this disease.

Iranian experience

The major type of haemoglobinopathy in Iran is β -thalassaemia, and 15 000 patients are registered. Although the distribution of carriers is countrywide, some areas have a particularly high prevalence. It is estimated that the carrier frequencies in Fars Province and among the population of the Caspian littoral are close to 10%.

The national programme for prevention calls for mandatory heterozygous detection by screening of couples before marriage in the endemic regions. Couples who both have thalassaemia minor are advised not to marry. Another breakthrough in the field of prenatal diagnosis was the introduction of DNA-based diagnostic tests by the private health service over a year ago. Since then, more than 50 at-risk pregnancies have been screened. The only drawback is that this highly needed service is not supported by the national health system and is therefore available only to those who can afford it.

Pakistani experience

A national thalassaemia programme in Pakistan is still in an early stage of development. Modern surveys show 8% β -thalassaemia trait in Pathans and 3.3% in Punjabis. Taking an average figure of 5% for carrier prevalence, there are six million carriers in Pakistan. Allowing for the high frequency of consanguineous marriage, the expected birth rate of thalassaemic children is about 1.3/1000. In the province of Rawalpindi, 120 new cases of β -thalassaemia major are diagnosed per year, 14 cases of HbH disease have also been diagnosed in the last five years, and HBs S, C, and D are also seen (1.2% of Punjabis carry HbD).

National blood transfusion services are poorly developed, and resources available for patient care

are limited to blood transfusion services through the Fatimid Foundation, a charitable nongovernmental organization (NGO) with centres in Karachi, Lahore and Islamabad, and the more recently-formed Pakistan Thalassaemia Welfare Society (PATHWELL) in Rawalpindi, which offers a comprehensive service for a limited number of patients.

PATHWELL is starting a national thalassaemia registry and has so far registered 600 cases. Family studies and genetic counselling are provided to the parents and extended families of patients. The Society's aims are to: improve blood transfusion services; improve the level of information among health-workers by providing lectures in medical schools; recruit 100 patients to be entered in trials of management by the end of 1993 (40 patients have been recruited so far, iron chelation and other specialist services will be provided, as well as blood transfusion); provide a prenatal diagnostic service and genetic counselling (training has already been arranged with University College Hospital, London, and there is a consensus in Pakistan that therapeutic abortion is permissible in exceptionally severe cases such as thalassaemia); and establish a bone-marrow transplantation centre.

The scale of the thalassaemia problem in Pakistan is so great that NGOs alone cannot handle the situation; involvement of the Ministry of Health is therefore essential.

Saudi Arabian experience

The WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies in Riyadh is being developed as a national and regional resource for patient care, laboratory diagnosis, and educational activities. A national survey of the prevalence of haemoglobin disorders has been conducted (6), and a substantial number of educational materials in Arabic has been developed. The materials are being disseminated within Saudi Arabia and are available for the whole Eastern Mediterranean region.

Studies have been conducted within Saudi Arabia on the epidemiology of thalassaemia and sickle-cell disorder, their clinical features, laboratory parameters, natural history, and the feasibility of screening for carriers. Clinical trials of hydroxyurea to treat sickle-cell disease are under way. DNA laboratory diagnosis for haemoglobin disorders has been set up, and is available as a resource for the whole Eastern Mediterranean region.

An important problem in organizing service delivery in Saudi Arabia, as in many other Middle Eastern countries, is the fragmentation of the health care system between public services, private hospi-

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tals, and hospitals supported by the military, the security services, companies, etc. A database of national expertise and facilities has been established, and national registration of patients with thalassaemia and sickle-cell disorder is under way. The Saudi centres have agreed to develop a network, with a newsletter produced in Riyadh to link the groups. There are plans to build on the experience with haemoglobin disorders in order to develop a molecular genetic laboratory for genetic diseases.

Strategies for delivering population screening and genetic counselling are being investigated. Optional premarital screening is available, but so far few couples have taken advantage of this service. Day-care clinics for patient care are being promoted.

Tunisian experience

β -Thalassaemia trait is slightly more common than sickle-cell trait in Tunisia. Systematic surveys have shown a total prevalence of 4.5% haemoglobinopathy traits (in some areas, as high as 10%). The mutations present have been defined at the molecular level. To date, 33 prenatal diagnoses have been performed, 15 for risk of β -thalassaemia and 18 for risk of sickle-cell disease (7). A Tunisian Association for Haemoglobinopathies and Thalassaemia has recently been started.

There are many difficulties in the care of patients and in understanding the nature of the problem, and in the need for carrier screening and counselling. A national plan for education, screening and issue of a premarital certificate has been submitted to the Ministry of Health; preliminary indication of support has been given. The establishment of a thalassaemia centre to treat patients according to standard WHO protocols is desirable, and attention at the national level to these activities should be further increased.

Situation in the European region

Considering the recent political changes the countries of the WHO European Region now fall effectively into four groups: north-western, southern, eastern, and Turkish-speaking, which influence the approach to haemoglobin disorders in the region. They present an important health problem in Turkish-speaking areas, and their significance is increasingly being recognized in Azerbaijan and Turkey. Though they are generally uncommon in Eastern Europe, there is a significant problem in Romania (over 400 known thalassaemic patients), Bulgaria (over 300 known thalassaemic patients), and particularly in Albania. All these countries need special help in

ensuring that services for these disorders are developed and supported.

A regional (European/Mediterranean) Working Group on Haemoglobin Disorders, initiated in 1986, has reported on epidemiology and the available services in the Region.^h The Working Group meets at approximately 2-year intervals, and has two subgroups concerned with psychosocial aspects (coordinator, Dr John Tsiantis) and with identifying problems and evaluating service delivery (coordinator, Dr Bernadette Modell, Head, WHO Collaborating Centre for the Control of Haemoglobinopathies in London). The current objective of the latter subgroup is to promote development of national collaborative groups, and registers on patients and prenatal diagnoses. Short-term support for a European Community Concerted Action on this topic was obtained in 1991, which is limited to countries within the European Community (EC), i.e., north-western and southern Europe. This has shown that registers are a useful means of contacting all doctors involved in service delivery, helping them to improve their skills, identifying weaknesses in the programme, and promoting collaborative research. Key conclusions of the EC study are summarized in Tables 3 and 4.

Table 3 shows the estimated number of carriers of haemoglobin disorders in the participating countries. Among indigenous northern Europeans thalassaemia is a rare inherited disease, the prevalence of carriers (mainly of β -thalassaemia) probably being about 1/1000, corresponding to a homozygote birth rate of about 1/million, though it may be higher in some populations, e.g., Irish and Dutch. Migration has now raised the general homozygote birth rate in north-west Europe to about 0.4/1000.

There are now more patients with haemoglobin disorders living in north-west than in southern Europe. There are several reasons for this: (1) the majority of patients in north-west Europe have sickle-cell disorder, in which untreated survival can be far longer than in thalassaemia (hence, by contrast with thalassaemia, migrants included patients with sickle-cell disorder); (2) the majority of patients born in the 1950s and 60s are still alive; (3) migrants from sub-Saharan Africa have a very high birth incidence of children with sickle-cell disorder; and (4) screening and prenatal diagnosis at the community level are developing more slowly in north-west Europe than in the south, particularly for sickle-cell disorder.

In the absence of prevention there would be more affected births/year in the south. However, the disease-oriented programmes of southern Europe have been extremely effective in preventing thalassaemia.

^h See footnote e on page 376.

Table 3: Estimated numbers of carriers of thalassaemia and sickle-cell disorders in European Community countries

Country	Carriers in groups at risk	Carriers in indigenous population (assuming 1/1000)	Carriers (as % of population)
Belgium	30 900	9 850	0.41
Denmark	2 000	5 110	0.14
France	195 000	54 940	0.46
Germany	69 000	78 160	0.19
Netherlands	25 000	14 420	0.27
United Kingdom	170 000	55 620	0.41
Subtotal	491 900	218 100	
Greece	888 000		9.0
Italy	2 850 000		5.0
Portugal	153 000		1.6
Spain	193 500		0.51
Subtotal	3 946 800		

saemia (Table 4), and there are now more affected births in the north-west than in southern Europe.

Equitable delivery of carrier screening and counselling is more complex in north-west than in southern Europe: (a) in northern Europe the predominant problem is sickle-cell disorder, for which genetic counselling is particularly difficult, owing to its unpredictability; (b) it is difficult to deliver a specific genetic counselling service to diverse ethnic groups scattered in a large population not at risk (for success it is necessary to integrate carrier screening and counselling into the general medical services at the primary health care/mother and child health level, which requires a large-scale effort to educate

Table 4: Percentage of fall in affected births in the European Community due to genetic counselling^a

Country	β -Thalassaemia	Sickle-cell disease	Total (%)
Belgium	11%	80%	57
Denmark	>50%	70%	50
France	27%	20%	21
Germany	36%	33%	35
Netherlands	?	?	?
United Kingdom	50%	22%	30
Greece	85%	85%	85
Italy	79%	40%	78
Portugal	13%	7%	8
Spain	20%	-	17

^a Calculated from observed or estimated births, and known prenatal diagnoses.

health workers in the principles of "community genetics" (8); and (c) because of cultural and linguistic diversity, a core of specially-trained ethnic genetic counsellors is required.

The importance of trained haemoglobinopathy counsellors is clearly shown in the results from the United Kingdom, where genetic counselling and prenatal diagnosis for thalassaemia are well delivered to people of Cypriot extraction, but is not reaching people of Asian origin; this is largely because of lack of trained Indian and Pakistani haemoglobinopathy counsellors. It has also been found in the United Kingdom that people's choice of having a prenatal diagnosis for sickle-cell disorder has risen steadily in relation to the availability of trained counsellors for the relevant ethnic groups. The provision of more counsellors, in addition to ensuring equitable services, should therefore be cost-effective.

French experience

The number of subjects with heterozygous β -thalassaemia and sickle-cell anaemia in metropolitan France has been evaluated by the distribution and the birth rate of populations originating from countries with a high prevalence of haemoglobinopathies.¹ Taking into account the recent movements of these populations and the unknown numbers of immigrants from sub-Saharan Africa, these are probably underestimates. A national programme for treatment and prevention of thalassaemia and sickle-cell disorder is progressing steadily. Neonatal screening in Paris has shown one newborn with sickle-cell disorder/1500 pregnancies. Sickle-cell disease is considered a significant public health problem, as there are several thousand patients. In 1987, a working group on sickle-cell disease was established for the Paris region, consisting mainly of paediatricians but also haematologists; the group now numbers more than 40. Patients' data are entered on a computer for prospective follow-up.

Greek experience

According to the experience of the WHO Collaborating Centre for the Community Control of Hereditary Diseases in Athens, about 150 new thalassaemic children are likely to be born each year in Greece, in the absence of prevention. New births have fallen to 10-20% of this number, and now seem to have reached a plateau. The reasons for such births have been investigated, and are mainly due to complacency and lack of coordination between centres and be-

¹ See footnote e on page 376.

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tween government and private health services. For example, the government programme identifies only about 50% of carriers; the rest go to private laboratories, and most of the 10–20 affected births in a year are due to carrier misdiagnosis in a private laboratory. A major deficiency is the lack of official evaluation of the programme effects and cost-effectiveness by the Ministry of Health.

Plans for the future include improved information for, and emphasis on, training of personnel; quality control of all laboratories performing carrier screening, through the Greek Society of Haematology; provision of a carrier identification card; and evaluation of end results.

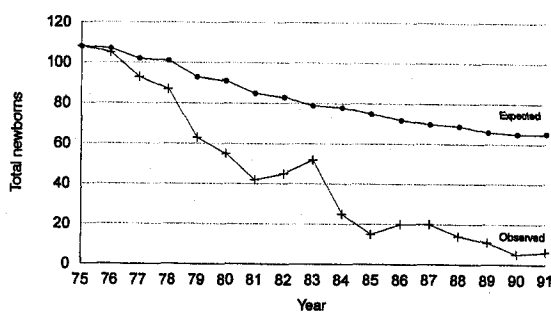
Russian experience

The objective of the WHO Collaborating Centre on Community Control of Haemoglobin Disorders, established in Moscow in 1986, was to assist the Republics of the former USSR and other countries (such as Vietnam), where haemoglobin disorders are common, with diagnosis and treatment. The dissolution of the USSR has made these objectives unattainable, and has also created severe medical problems within the country. Public health services have disintegrated and services are now more or less through private practice only. As it is now more difficult for patients to travel to the WHO Collaborating Centre in Moscow, the quality of care for at least some patients has decreased. Activity on the control of haemoglobin disorders has ceased in all Republics of the former USSR except Azerbaijan. The Collaborating Centre now has limited staff and equipment. In 1992, the Centre identified 31 patients with haemoglobinopathies among 139 Russians with different forms of anaemia. Five new patients were diagnosed with homozygous β -thalassaemia. The nature of the mutations are under study (in collaboration with Professor T.H.J. Huisman, Georgia, USA). The Centre is currently studying a small population in the Russian Federation at risk of haemoglobin disorders, haemochromatosis, erythrocytosis, etc.

Sardinian experience

In the expert and well-supported Sardinian programme in Cagliari (where the WHO Collaborating Centre for the Community Control of Hereditary Diseases is located), automated laboratory and computer methods are being introduced to obtain faster, cheaper analysis and more reliable recording of results. Carrier screening will be by haematological indices and automated HPLC analysis, which allows measurement of abnormal haemoglobins and Hb A₂ in a single step on all samples. Recording of patients'

Fig. 2. Fall in the birth rate of homozygous β -thalassaemia in Sardinia, 1975–91.



results on magnetic cards is now being introduced; other centres in Sardinia will have magnetic card decoders.

There are very few residual births in Sardinia (Fig. 2); the main cause is still lack of information. To ensure universal information, a health education module, supported by a special budget from the Regional Ministry of Health, was introduced in secondary schools in 1993, consisting of a book for the pupils, a book for the teachers and a video-tape. Optional carrier screening is offered to the pupils after a few months, with informed consent from the parents. However, screening in schools is unlikely to become universal because of differences of opinion among school directors. In parts of Italy where they have given permission in the past, screening of older schoolchildren (with their parents' informed consent) has been reported as being very successful (9).

Bone marrow transplantation has just started in Cagliari, and a research project on gene therapy is foreseen.

Situation in the South-East Asian region

The majority of countries in the WHO South-East Asian region (SEARO) find that thalassaemia is a growing problem, and in some (e.g., the Maldives (10)) it is a recognized priority problem.

Thai experience

The haemoglobinopathy situation in Thailand has been reported.¹ Up to 40% of the population carry a

¹ See footnote a on page 376.

potentially significant haemoglobin mutation, and the major disorders, i.e., homozygous β -thalassaemia, HbE β -thalassaemia, α -zero thalassaemia hydrops fetalis and HbH disease, are all common (11). Estimates of the annual numbers of couples at risk and of affected births, and a rough estimate of the number of living patients in Thailand are given in Table 5. The difficulties of introducing a programme (ignorance, incurability, unpopularity with doctors, lack of recognition by health authorities, and lack of infrastructure and organization) have all been previously noted. However, considerable progress is being made.

The Thalassaemia Association of Thailand, formed under the chairmanship of Dr Soodsarkorn Tuchinda, now has more than 3000 members including doctors, interested people and parents of affected children. National registration of patients has begun, but this will be a slow process, as they are not specifically identified in most hospital records. Molecular technology is available at the Thalassaemia Centre at Siriraj Hospital, and the types of β - and α -thalassaemia mutations have been defined. To date, 181 prenatal diagnoses (mostly retrospective) have been carried out, 45 for risk of Hb Bart's hydrops fetalis, 46 for homozygous β -thalassaemia, and 90 for HbE/ β -thalassaemia. Haemoglobin disorders have been introduced into the national five-year plan for the first time, but with low priority.

A pilot community-based project of screening and genetic counselling based on the one-tube osmotic fragility test is planned for a defined area in southern Thailand. A target population of 500 000 people will receive a programme of public health education and back-up laboratories will be developed. In the first year, all pregnant women will be offered testing and advice. In the second year, military recruits and school-leavers will be involved. The success of the education programme and the results of screening will be evaluated at regular intervals.

Table 5: Estimates of the frequency of the four commonest haemoglobinopathies in Thailand

Disease	Couples at risk (per year)	Births (per year)	Living patients
Homozygous β -thalassaemia	2 500	625	6 250 ^a
β -thalassaemia/Hb E	13 000	3 250	97 500 ^b
Hb Bart's hydrops fetalis	5 000	1 250	0
Hb H disease	28 000	7 000	420 000 ^c

^{a,b,c} Estimated life expectancies are 10, 30, and 60 years, respectively.

Situation in the Western Pacific region

Chinese experience

Haemoglobin disorders are common in six provinces in southern China. The following activities were undertaken by the WHO Collaborating Centre for the Community Control of Hereditary Diseases (Thalassaemia) in Beijing:

(1) A study of the distribution and frequency of α - and β -thalassaemia and mutation types in southern China. Five common mutations account for over 90% of Chinese β -thalassaemia genes; the frequency of hydrops fetalis in southern China is 1/500 newborns (2/1000); 50% of patients with HbH disease have a non-deletional form of α -thalassaemia in association with the south-east Asian type of α^0 -thalassaemia: 66% are Hb Constant Spring, 16% Hb Guangxi, and the remainder are unknown. Patients with non-deletion HbH disease in South China are usually transfusion-dependent.

(2) The most appropriate DNA detection methods for prenatal diagnosis in China have been investigated and developed. The centre prepares kits for prenatal diagnosis; 30 professional staff have now received training by the Beijing team; a training course for up to 100 participants is held on an annual basis in the collaborating centre. Ten provinces and cities have started prenatal diagnosis for haemoglobin disorders, but chemicals are difficult to obtain.

(3) A book entitled "Techniques of gene diagnosis and its application" was published at the end of 1992, and 5000 copies have been distributed.

(4) A project on prevention of thalassaemia is under development in Guangxi province in South China, where α -thalassaemia trait (15%, of which 9% is α^0 -thalassaemia trait and 6% α^+) and β -thalassaemia trait (3-4%) are present. A suitable county has been identified and a training course held, but more resources are needed to develop the programme further.

Conclusions

The hereditary anaemias constitute a significant community health problem in a number of countries in the WHO Regions. Some countries have already embarked on successful control programmes, while others are beginning to organize the resources in this direction. The poorest and least developed nations have not yet acknowledged the need for a control programme, even when the problem is of great magnitude.

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WHO, having summarized global experience in community control of hereditary anaemias and outlined the objectives of such programmes, has made a case for comprehensive approaches (improve curative services, establish prenatal diagnosis, develop carrier detection and counselling, improve education) and the need to establish reference centres. The usefulness of voluntary groups and community organizations has also been emphasized to ensure that the approach is appropriate to individual sociocultural and political situations.

Recommendations

- The health burden of hereditary anaemias could be significantly reduced in those countries and regions that are willing to participate. The WHO Regional Offices should support and develop regional and interregional working groups on the prevention and control of haemoglobinopathies.
- WHO and the Thalassaemia International Federation (TIF) should collaborate in the preparation and widespread dissemination of information on thalassaemia and sickle-cell disorder, and in possible strategies for their control. Such information must be regularly updated and revised in the light of research developments and experience.
- WHO and TIF should stimulate funding for research projects targeted at reducing the burden of haemoglobinopathies in countries with differing requirements, customs and resources.
- WHO and TIF should assist in the organization of training programmes for technical and health care workers involved in haemoglobinopathy control programmes, in the light of new knowledge and possibilities.

Acknowledgements

We are very grateful to the WHO Regional Offices for Africa, the Americas and the Eastern Mediterranean for financial support towards this meeting. We thank Dr A. Eleftheriou and Dr P. Ioannou (Cyprus), Dr D.F. Tricta (Brazil), Dr H. Petros and Dr E. Georganda (TIF, Cyprus), Dr F. Madanta (Jordan), and Dr S. Al-Awadi (Kuwait) for contributing to the discussion.

Résumé

Lutte contre les hémoglobinopathies

Dans de nombreux pays en développement, les hémoglobinopathies (thalassémies et drépanocytoses) sont si répandues qu'elles constituent un modèle commode pour l'élaboration d'approches

de lutte contre les maladies chroniques de l'enfance. Actuellement, quelque 250 millions de personnes sont porteuses d'un gène d'hémoglobinopathie potentiellement pathogène. Chaque année, environ 300 000 enfants naissent avec une hémoglobinopathie majeure. Des programmes de lutte contre les hémoglobinopathies, fondés sur les approches et recommandations de l'OMS, ont été établis dans différents pays de toutes les Régions de l'OMS et donnent de bons résultats dans la prise en charge de ce problème. En suivant les recommandations de l'OMS, il serait possible de réduire dans des proportions importantes la charge que représentent les anémies héréditaires. Le présent article résume les exposés et les discussions d'une réunion conjointe OMS/TIF (Thalassaemia International Federation) qui s'est tenue à Chypre en avril 1993, et présente les activités de programmes de lutte contre les hémoglobinopathies menés dans plusieurs pays des différentes Régions de l'OMS.

Les anémies héréditaires constituent un important problème de santé publique communautaire dans divers pays de toutes les Régions de l'OMS. Certains pays ont déjà des programmes de lutte qui donnent de bons résultats, tandis que d'autres commencent seulement à mobiliser des ressources dans ce but. Les pays les plus pauvres et les moins développés n'ont pas encore reconnu la nécessité des programmes de lutte, même lorsque ces maladies posent un problème important.

L'OMS, ayant passé en revue les expériences menées dans le monde entier pour combattre les anémies héréditaires et exposé les objectifs de ces programmes, a plaidé pour une approche globale (amélioration des services curatifs, création de services de diagnostic prénatal, développement de la détection des porteurs et du conseil génétique, amélioration de l'éducation) et a insisté sur la nécessité d'établir des centres de référence. Elle a reconnu l'utilité des groupes bénévoles et des organisations communautaires qui permettent d'assurer que l'approche est adaptée aux diverses situations socioculturelles et politiques locales.

Recommandations

- L'impact des anémies héréditaires pourrait être sensiblement réduit dans les pays et régions désireux de participer à la lutte. Les Bureaux régionaux de l'OMS devraient soutenir et développer des groupes de travail régionaux et interrégionaux sur la prévention des hémoglobinopathies et la lutte contre ces affections.

• L'OMS et la TIF (Thalassaemia International Federation) devraient collaborer à la préparation et à la diffusion d'informations sur la thalassémie et les drépanocytoses et à l'élaboration de stratégies de lutte. Ces informations devraient être régulièrement mises à jour et révisées à la lumière de l'expérience et des progrès de la recherche.

• L'OMS et la TIF devraient stimuler le financement de projets de recherche visant à réduire la charge que représentent les hémoglobinopathies dans des pays ayant des besoins, des coutumes et des ressources différents.

• L'OMS et la TIF devraient apporter leur aide à l'organisation de programmes de formation destinés aux agents de santé et aux personnels techniques des programmes de lutte contre les hémoglobinopathies, à la lumière des nouvelles connaissances et possibilités.

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