GUIDELINES FOR THE CONTROL

OF

HAEMOGLOBIN DISORDERS

This document was initiated at the VIth Annual Meeting of the
WHO Working Group on Haemoglobinopathies
held in Sardinia, April 1989

and edited by

Professor Bernadette Modell
WHO Collaborating Centre for the Control of Hereditary Diseases
Department of Obstetrics & Gynaecology
School of Medicine
University College London
London
UK

The assistance of Dr Beatrix Wonke, Consultant Haematologist,
Whittington Hospital, UK, is also gratefully acknowledged.

Participants in the VIth Annual Meeting of the WHO Working Group on Haemoglobinopathies
Cagliari, Sardinia
8-9 April 1989

Dr O. Akinyanju, Lagos, Nigeria
Dr M. Angastiniotis, Nicosia, Cyprus
Dr M. Brozovic, London, UK
Dr V. Boulyjenkov, Geneva, Switzerland
Dr A. Cao, Cagliari, Sardinia
Dr P. Colonna, Alger, Algeria
Dr S. Fucharoen, Bangkok, Thailand
Dr R. Girot, Paris, France
Dr H. Granda-Ibarra, Havana, Cuba
Dr A. Kuliev, Chicago, USA
Dr D. Loukopoulos, Athens, Greece
Dr G. Masera, Monza, Italy
Dr B. Modell, London, UK
Dr P. Naoum, Sao Jose do Rio Preto, Brazil
Dr P.G. Natrajan, Bombay, India
Dr J. Rosa, Paris, France
Dr G.R. Serjeant, Kingston, Jamaica
Dr Y. Tokarev, Moscow, Russian Federation
Dr WU Guanyun, Beijing, People's Republic of China

List of Contents

/...

List of Contents, continued

1. INTRODUCTION

Haemoglobin disorders, which include sickle cell disorders and the thalassaemias, are the commonest of human inherited diseases. They can be treated effectively, and also represent the first group of common inherited disorders for which prevention is possible at the community level.

Though indigenous in the tropics and sub-tropics, due to global migrations haemoglobin disorders now occur in most countries of the world. In many developing countries they are emerging rapidly as an important health problem, because as infant mortality falls, more affected children survive, are diagnosed and require treatment. In more developed countries treatment and prevention of haemoglobin disorders should already be a component of existing health services. Thus most countries need to assess the present and probable future burden of the haemoglobin disorders for patients, families and society, develop a rational strategy, and include it in health service planning.

To date, the best model for such services are the disease-orientated "thalassaemia control programmes" organised in some countries of the mediterranean area where thalassaemia is particularly common. These embody the WHO concept of a control programme for a hereditary disorder, i.e., "a comprehensive strategy combining the best possible patient care, with prevention by community information, carrier screening and counselling and the offer of prenatal diagnosis". They have proved to be effective, acceptable and highly cost-beneficial (1-2). However, progress in developing such programmes is impeded by the fact that medical genetics is a relatively new branch of medicine, and as yet few health systems include a recognised structure, either to ensure equitable services for people with inherited disorders, or for delivering genetic screening at the population level (3). Development of an effective programme requires recognition by the health authorities that the haemoglobin disorders are a public health problem, motivated health workers, and recognised expert centres. Each country will need to develop an individual strategy appropriate to the local epidemiology, current service structure and available economic resources. WHO monitoring shows that it is easiest to organise an effective programme in a relatively small population where the disorders are common, and a specific disease-oriented programme is required. It is more difficult to develop a national programme in large countries, since it must be integrated into the general health system, and a large element of professional and public education is needed (4-7).

This manual is intended to help with planning services in both more and less developed countries. It is limited to practical aspects of setting up and running a control programme for haemoglobin disorders: data on the molecular basis, clinical features and management of the haemoglobin disorders will not be duplicated here. The manual includes recommendations for the best approaches possible, taking into account the different conditions prevailing in various countries. It draws largely on the experience of existing disease-oriented services, with the objectives of assisting the development of (a) similar services in high incidence areas, and (b) equally high-quality services integrated into the general health system in areas where haemoglobin disorders are less common.

2. OUTLINE OF A PROGRAMME

Figure 1 shows that a control programme for haemoglobin disorders includes many elements and involves numerous groups of health workers, Patients' and Parents' Support Associations, and the whole community. Because of its scope and complexity, involvement of the public health authorities and rational planning are required.

A programme must start with ensuring the best possible service for patients, and the affected child and family should be the primary focus. It will then become clear that prevention is wanted by many families. Taking into account a limited health budget, it is likely also become clear that for existing patients are to be well treated, it is necessary to provide prevention. The programme leading to the rapid decrease in the birth incidence of thalassaemia in Cyprus was developed in the following sequence (8-9).

(a) *Improving curative services.* This required agreement between the health professionals involved, adoption of a common management protocol, a united approach to the health authorities, and their support for specialist centres.

(b) *Availability of adequate safe blood.* Difficulty in meeting patients' transfusion requirements is usually an indication that the blood transfusion service needs to be improved. Patient Support Associations can do much to assist with voluntary blood donation campaigns. In turn, a campaign that takes patients' needs into account increases public awareness of haemoglobin disorders.

(c) *Availability of obstetric and laboratory facilities for prenatal diagnosis.* Without this option, carrier screening and counselling are of limited value.

(d) *Population screening and counselling.* This needs to be integrated into basic health services, and requires training of primary health care and maternal and child health staff.

(e) *Community involvement, public information and education.* The activities of the mass media can only sensitize the public. True success in informing the population and encouraging carrier screening requires (1) educating primary care and maternal and child health professionals so that they offer information and screening, (2) providing carriers with accurate information so that they become an information resource within the community, (3) teaching in schools, (4) contacts with smaller groups and (5) the involvement of Support Associations in all the above areas.

(f) *Evaluation.* It is necessary to measure and report progress in patient care and prevention from time to time, in order to stimulate all relevant professionals, locate problems, and ensure continuing support from health authorities and the public. Evaluation can be done most effectively through maintaining registers of patients and of prenatal diagnoses, as an integral part of the national programme.

In high-incidence areas disease-oriented services including all these elements usually need to be planned from the beginning. In more developed countries most of the technical elements usually exist, but service quality suffers from lack of integration, planning, professional and community education, and audit at regional or national level (10).

The first step in implementing a programme, i.e., obtaining the support of the public health authorities, can be difficult. It is greatly helped by the following steps.

(a) Formation of a regional or national group of experts involved in the service, speaking with a single voice (a "Working Group on Haemoglobin Disorders" on the WHO model).

(b) Formation of a Parents' and Patients' Support Association, collaborating with the professional Working Group and in contact with the Thalassaemia International Federation (TIF).

(c) Collection of local information on epidemiology and health burden of the haemoglobin disorders.

It may be necessary to enlist other sources of help in relating with the Ministry of Health, e.g., a WHO consultancy, support for the necessary research from other funding bodies, etc.

Additional important points:

(a) The national or regional working group needs *a programme co-ordinator*, who can act as a central reference point. This person must be highly motivated, have a good understanding of the haemoglobin disorders and the principles of genetics and public health, be acceptable to professional colleagues and have a collaborative outlook. His or her chief responsibilities should be organizing co-operation, carrying out evaluation, and providing information at all levels. The development of an official national policy leads more readily to recognition of a programme co-ordinator.

(b) Research is vital for a control programme, so whenever possible there should be strong links with university centres. Every programme has to start with research on the frequency and distribution of the common disease mutations, the demographic structure of the population, frequency of consanguineous marriage, correlation between local mutations and severity of the disorders, level of demand for prenatal diagnosis etc. It is essential for centres to continue to do research to retain staff interest and dedication, and to ensure that the country keeps abreast of developments in treatment and prevention.

(c) National and international co-operation is necessary to maintain standards, to develop and test new methods in diagnosis and treatment, and to assess the impact of haemoglobin disorders on human populations on a global scale. Many research studies require co-operation on a national or international level because single centres have too few

patients with the problem under study: setting up such co-operation is an important function of the national working group.

The broad scope of control programmes for haemoglobin disorders and the range of countries that need them means that service requirements, organization and costs differ widely. This manual can only provide general guidance. It is divided into sections covering the principle elements of the service. Each section aims to summarize *underlying principles*, *methods* and *requirements*. It is not possible to describe *costs* in different countries in comparable terms, as labour costs and working hours vary widely, though costs of equipment and consumables are more comparable. Requirements are therefore, as far as possible, described in terms of staff, equipment and consumables: when possible, costs are also illustrated from existing examples.

3. ASSESSING EPIDEMIOLOGY AND HEALTH BURDEN

In order to win the support of public health authorities, it is necessary to provide figures on the frequency of haemoglobin disorders in the relevant country or area. This section gives guidance on how to do this.

The main haemoglobin disorders are listed in Table 1. To estimate their frequency and health burden in a given area requires the following steps.

i. Collect basic demographic data - population number, birth rate, infant mortality. Is the population homogeneous or heterogeneous? If the latter, the calculations outlined below must be done separately for each sub-group. What are the numbers and nature of the different groups?

ii. Establish the carrier frequency. In most populations local surveys have been done. Data published before 1984 collected by Livingstone (11) has been amalgamated with more recent data and summarized in country tables by WHO (4,12). Updated estimates for each country are given in Annex 1. Such estimates however, can only be as accurate as the data available. Data for abnormal haemoglobins are in general accurate, though in some surveys frequency is not clearly separated by population group. Surveys of α or ß thalassaemia trait are often unreliable and likely to give underestimates unless accurate HbA_2 estimation has been assured. Where no surveys have been done, minimum estimates of carrier frequency may be possible, from the observed birth rate of affected infants (13-14).

iii. Establish the birth incidence of affected children (births/1,000). This is the most valid way to describe the frequency of a genetic disease. Updated WHO estimates are also given in Annex 1. Birth incidence of affected infants can be estimated in two ways.

   (a) By establishing a local/national patient register and observing how many patients are born per year. This is reliable only if most patients are diagnosed and treated. It gives a minimum figure.

   (b) By calculating birth-rate from the carrier frequency, when this is known. Classically, the calculation is based on the gene frequency and the Hardy-Weinberg equation. The calculations are given in Annex 1. For simplicity, the approximate affected birth rate can be read off from the carrier frequency using the curves in Figure 2 (4).

3.1 Factors affecting calculation of birth incidence

The prevalence and main types of haemoglobinopathy genes

Most populations include carriers of a variety of haemoglobin disorders. Alpha gene disorders (mostly alpha thalassaemias) and beta gene disorders (beta thalassaemia, Hb S, Hb C, Hb D, Hb E, etc.) do not interact, so the two groups must be handled separately. For calculation of the birth incidence of major beta-globin disorders, use the sum of all types of beta haemoglobinopathy traits. This is important because a

small increment, like the 1-2% ß-thalassaemia trait in the example below, makes a significant difference to the affected birth rate.

Example. In the Caribbean area, AS = 8-10%, + AC = 2-3%, + ß-thalassaemia trait = 1-2%. Total carriers = 11-15%.

If beta thalassaemia trait is not included
Total Carrier Frequency = 12%, homozygote births = 3.6/1,000

If beta thalassaemia trait is included
Total Carrier Frequency = 13%, homozygote births = 4.2/1,000

i.e., at this level of frequency, a 1% difference in carrier rate makes a 16% in homozygote birth rate.

Calculate alpha thalassaemia separately, as it does not interact with beta haemoglobin disorders.

Other common conditions (e.g., hereditary elliptocytosis in parts of Malaysia) may appropriately be included in the calculations.

The particular mix of haemoglobinopathy genes present

Different combinations may produce syndromes of differing severity. For example, where HbE and beta thalassaemia trait co-exist, different proportions of infants with homozygous beta thalassaemia (severe), HbS/beta thalassaemia (variable) and homozygous HbE (usually harmless) will be born. Only the first two should be included in the calculation of health burden. The relative proportions of the different syndromes can be calculated using the WHO nomogram in Annex 1, Figure 2.

The presence or otherwise of customary consanguineous marriage

Customary consanguineous marriage increases the frequency of homozygote births for a given carrier frequency (1,15). The effect on affected birth incidence can be estimated using the curves in Figure 2. For example, when 30% of marriages are between 1st cousins, the birth incidence of homozygotes for a given heterozygote frequency is represented by a point 30% of the distance between the lower line (unrelated parents) and the upper line (100% 1st cousins).

In this calculation the following should be used.

(a) the frequency of first cousin marriage (which has a far greater effect than less closely consanguineous marriage).

(b) the proportion of cousin marriages in the general population, not among the parents of affected children.

Current figures must be used, as marriage customs can differ quite widely with social class and between generations. If reliable current

figures are not available they can be readily obtained by interviewing women in a government hospital after delivery (when they are accessible and have time to talk) (16). A method is given in Annex 2.

3.2 Use of epidemiological data in calculating health burden

The birth incidence/1,000 of children with different haemoglobin disorders can be related to the total annual number of births, to calculate ***the number of new affected children born annually*** in the country, administrative area or population group.

This figure may then be compared with the age-distribution of known patients to assess the quality of diagnosis and treatment. If the number of known patients in each yearly cohort is less than the calculated affected birth-rate, probably many are not being diagnosed and treated. Alternatively (though this is less common) the carrier frequency may have been overestimated.

The ***future cumulative patient numbers*** (assuming all are diagnosed and treated, and there is no prevention) can be calculated by extrapolation for 10, 20 and 30 years' time.

The ***rising costs of treatment*** for e.g., beta thalassaemia may then be calculated from the future cumulative patient numbers, and the requirements for blood and iron chelation therapy given in Tables 2 and 3.

The number of patients does not describe the ***health burden*** of the disorder. This can be evaluated only by direct study of affected families. Where prenatal diagnosis is not available, an enquiry should be conducted on parents' attitudes towards it. Where it is available, families' use of it should be assessed. Such studies can provide a reasonably objective measure of the perceived burden of the disorder.

3.3 How common must haemoglobin disorders be for a control programme to be indicated?

There is no simple answer to this question. It requires careful evaluation of the birth-rate of affected infants, the local mix of haemoglobin disorders, the level of development of the country and the organization of health services.

In more developed countries carrier screening, counselling and prenatal diagnosis should be provided as part of the health service, whatever the frequency of the disorders.

Wherever automated cell counters are available a diagnosis should be made for all microcytic samples, and consequently thalassaemia carriers should be detected and counselled. Similarly, electrophoresis should be available for groups at risk for sickle cell disorders. When carriers are rare it is preferable to send suspect samples to a reference centre for definitive diagnosis, to ensure quality assurance and efficiency. Prenatal diagnosis can also be arranged by sending fetal samples to an

expert centre. In countries where specific ethnic groups are at risk, some groups may gain access to the service only if genetic counselling is provided in the appropriate language and context.

In less developed countries it has been noted that the need for a *national* control programme begins to be widely recognised when the infant mortality has fallen to the range of 20-40/1,000, as many affected infants survive, are diagnosed and need treatment at about this point, however please note (c) mentioned below (1). The urgency of the perceived need for a programme then depends on:

(a) The birth-rate of affected infants ("high" if about 0.5/1,000 or more). When the affected birth-rate is high a disease-oriented programme is indicated: when lower, the programme may be integrated in general health services. Primary health care, pregnancy services and family planning services, and specific programmes, e.g., for handicap, voluntary blood donation, anaemia screening may all be involved.

(b) The nature of the condition. Thalassaemia major is more "visible" than sickle cell disorders as patients are hospital-dependent and treatment is expensive. Sickle cell disorders are less visible and be neglected for longer because they often cause early death, and many patients can survive without diagnosis and specific treatment. However, a relatively small investment in sickle cell disorders has a high pay-off in terms of lives saved, and improved quality of life for affected families.

(c) The level of development of the country. In most developing countries the published infant mortality figure is the average for very diverse population groups. Infant mortality is usually highest in rural areas, while among the educated urban minority it is often as low as in more developed countries: e.g., in Nigeria the infant mortality is estimated to range from about 20 to about 180/1,000 in different groups (1). Thus in most countries where haemoglobin disorders are common, a section of the population seeks treatment, carrier screening and prevention. If it is unavailable within the country they are likely to seek it abroad: but this is a relatively inefficient use of resources.

(d) The infrastructure of the health system. Where primary health care is well organised at a national level and basic WHO programmes are implemented, chronic childhood disorders tend to emerge across the community as infant mortality falls, e.g., Cuba, The Maldives, Palestinian refugees. In such communities the need for a national programme becomes clear at an early stage: it is also easier to implement where a primary care infrastructure is in place. Where health services are mainly privately organised (e.g., much of Latin America) public health programmes are more difficult to implement.

Where infant mortality is very high and government health services are focused on basic primary care (as in much of sub-Saharan Africa and parts of South East Asia) it is important to evaluate both the present and the potential future role of haemoglobin disorders.

Example. In West Africa sickle cell disorders are estimated to contribute 10-20% of the present infant mortality (1) and are destined to become a priority health problem as infectious diseases are controlled. It is thus indicated for each country in this area to encourage at least one expert centre to develop expertise and approaches that can be extended to the whole population in due course.

The way in which a programme develops depends on local circumstances. However, the following is generally viewed as the appropriate sequence of priorities.

(a) Correct diagnosis of affected infants (requires education of health personnel and a reference laboratory).

(b) Provision of basic management: blood transfusion for thalassaemia, prophylactic penicillin, information and surveillance for sickle cell disorders. More sophisticated forms of treatment will follow.

(c) Genetic counselling and prenatal diagnosis for affected families.

(d) Carrier screening, counselling and prenatal diagnosis for the general population.

4. CENTRES FOR HAEMOGLOBIN DISORDERS

A centre may be primarily concerned with thalassaemia, or sickle cell disorders or both. The aim of a centre is to ensure adequate services for treatment and prevention for the local population. It needs to include expertise and facilities for accurate carrier and patient diagnosis, the best possible patient care including management of difficult clinical problems, and genetic counselling for carriers, patients and families. Selected centres also need to include obstetric and laboratory aspects of prenatal diagnosis. Every country or region needs at least one haemoglobinopathy reference centre, since haemoglobin disorders occur in all populations, and can cause particular problems when they are rare. Centres are most often created by recognising experts who have already developed a wide range of services for the haemoglobin disorders.

In areas where haemoglobin disorders are common special dedicated centres are required, in appropriate numbers and appropriately situated, and with a high degree of autonomy. Where the disorders are uncommon the reference centre may be integrated into a specialist haematology or medical service.

Whether a centre is dedicated to haemoglobin disorders or integrated into the general medical service, continuity of patient care in the same out-patient and in-patient facilities is essential. Patients with chronic disease who require frequent hospital care should be dealt with rapidly and efficiently by a member of staff who knows them, rather than being mixed with general emergency cases.

The relationship of expert haemoglobinopathy centres to the general health service must be flexible. For instance, a specialist centre should not insist on exclusively treating patients if this requires them to travel long distances regularly. Patients can be treated well at peripheral centres providing these are in close touch with an expert centre to which they can refer patients when necessary. Doctors at peripheral centres need to be regularly updated in patient management, encouraged to use standard treatment protocols and record systems, to participate in audit (e.g., using a patient register), and to attend meetings of the local or national "Working Group". Transfusion-dependent patients should be treated at blood transfusion centres only if there is no alternative, as these have very limited expertise.

A centre for haemoglobin disorders cannot exist in isolation, as a multi-disciplinary "therapeutic team" is required. Input is needed from, e.g., endocrinologists (including diabetologists and reproductive endocrinologists), ophthalmologists, orthopaedic and general surgeons, hepatologists, neurologists, and obstetricians with a special interest in haemoglobin disorders (16-20). With modern management most patients with haemoglobin disorders survive into adult life: it is therefore essential to have strong links with adult physicians who may take over patient care in due course. Specialist units should include both paediatricians and adult clinical haematologists or specialists in internal medicine.

The staff of specialist centres require a career structure with promotion possibilities and regular contact with other branches of medicine; otherwise

doctors and nurses can be afraid of losing skills and missing promotion opportunities, and can be unwilling to work in the centre. They should also be made clearly aware of the wide range of clinical experience that can be gained through working with patients with haemoglobin disorders. It is inadvisable for the physician in charge to rotate between the centre and other services because of the overwhelming importance of continuity of care: however, this option should be open to more junior staff.

Staff requirements are higher for treating patients with thalassaemia than for treating patients with sickle cell disorders. Staff requirements for screening, counselling and prenatal diagnosis are the same for the two groups of conditions, but neonatal diagnosis may also be indicated for sickle cell disorders.

4.1 The role of support associations

An active support association is an essential component of a programme. In many countries formation of a support association has been the first step towards developing effective services.

Support associations provide psychological support by putting families in touch. They identify families' concerns, and collaborate with health workers in improving services. They identify research needs, and raise funds for research they consider relevant to the needs of patients and families. They support public health enterprises such as screening, and are one of the most important resources for informing and educating the public and health professionals. Conversely, screening increases public concern for patients and support for associations, by promoting awareness.

In many countries there are national support associations. National Thalassaemia Associations are federated internationally through the TIF (the Thalassaemia International Federation), which organizes international meetings bringing together patients and doctors, and provides information, encouragement and support in developing appropriate services. Annex 3 gives a list of existing National Thalassaemia Associations affiliated to TIF.

5. TREATMENT

In general, management of thalassaemia major is highly predictable and can be planned (17). By contrast, acute problems are common in sickle cell disorders and patients often require emergency treatment (18-20). These differences affect both requirements for care and the impact on the family.

The following basic laboratory facilities must be available for both thalassaemia and sickle cell disorders.

(a) Basic haematology, including automated measurement of red cell indices and electrophoresis, Kleihauer test, HbF estimation, HbA_2 estimation.

(b) Blood banking technology, including extended blood grouping facilities, testing for hepatitis B, hepatitis C, HIV antibodies, indirect antiglobulin test, and red cell antibodies. Laboratory aspects of blood transfusion are given in standard texts, and summarised in an Annex to the Physicians' Guide to the Management of Thalassaemia (17).

(c) Quality control of all laboratory methods. The WHO document "quality assurance in haematology" (21) can be very helpful and the WHO laboratory programme provides useful reference standards. Standards for Hb A_2 and Hb F have recently been included.

Individual requirements for thalassaemia and sickle cell disorders are given separately below.

Availability of treatment facilities differs widely between countries. Recommended management of both thalassaemia and sickle cell disorders includes basic steps that should be taken in all cases, and sophisticated interventions (e.g., radical cure by bone marrow transplantation) that can be provided only within highly developed health systems. The full range of desirable services is given here, followed by comments on priorities and approaches in countries with more limited resources.

5.1 Requirements for treating thalassaemia major

A special transfusion facility (day hospital) is needed when more than two transfusions are required per working day, e.g. when the number of patients exceeds 20-40 (depending on the local transfusion frequency).

Requirements per 50-100 patients (based on the mediterranean experience):

Staff

1 doctor
3 nurses
1 technologist equivalent (divided between haematology, blood banking, and biochemistry)
1 counsellor/psychologist
1 secretary/administrative assistant

Treatment protocols. Many centres develop local protocols. Protocols sponsored by the WHO are (a) The Thalassaemia International Federation's "Physician's Guide to the Management of Thalassaemia 1992 edition" (17), which includes details of treatment and references for all recommendations in this section, and (b) "What is Thalassaemia?" (22)[1]. This includes recommendations written in simple terms, and has proved particularly useful in developing countries and for general staff involved with thalassaemia patients.

Patient records are essential for satisfactory care. Model flow charts and annual summary chart are included in the Physician's Guide to the Management of Thalassaemia. A model patient record is also available through WHO. Patient records are often held in the treatment centre rather than with the general hospital records. Where there is no organised hospital record system, records should be held by the families. Staff must have adequate time to keep records up-to-date, and to review them annually. A computerised patient record for IBM compatible PCs[2] is available.

Equipment for measuring height and weight

Laboratory Tests

(i) Routine

- Haemoglobin estimation: at least x 24/patient/year.
- Ferritin estimation x 2-3/patient/year.
- Urinary iron estimation (especially if ferritin measurement is not possible) 2-12/patient/year.
- Transaminases, bilirubin x 4/patient/year.
- Hepatitis markers when indicated.
- Every 1-2 years X-ray of hand and wrist for bone age and bone change to age 12, then X-ray of knee till fusion of epiphyses.

(ii) Special tests in older patients

- Endocrine studies: thyroid function tests; glucose tolerance test; pubertal growth and function tests.

Transfusion. For transfusion-dependent thalassaemic patients the mean haemoglobin should be maintained at about 12g/dl, because this keeps patients in good health and reduces the frequency and severity of hypersplenism (23). This is called "high transfusion". Patients who have

---

1 Both booklets are available from most national Thalassaemia Associations (see list in Annex 4), or from the Thalassaemia International Federation (TIF), P.O. Box 8503, Nicosia, Cyprus.

2 English language version available from Dr A. Piga, University of Torino, Istituto di Clinica Pediatrica, Piazza Polonia 94, I-10126 Torino, Italy.

not been splenectomised and are not hypersplenic require on average 1.25 to 1.3 times as much blood as splenectomised patients. The annual blood requirement to maintain a mean haemoglobin of about 12 g/dl is shown in Table 2, in terms of donor blood, prepared whole blood, and pure red cells.

Requirements for blood and iron chelation therapy depend on the patients' weight and Desferal. Table 3 gives approximate age-related requirements. The annual blood requirement for an entire centre can be calculated from the patients' splenectomy status, the sum of their weights and the figures in Tables 2 & 3.

Blood requirement for 100 patients ranges from 500-1,500 litres of donor blood/100 patients/year, depending on age-distribution.

Blood transfusion depends largely on human resources, and costs vary substantially by country, depending on whether there is a voluntary blood donation programme etc. No attempt has been made to provide costings here.

Leucocyte-depleted blood should be used whenever possible. Leucocyte filters cost from US$ 9.00-20.00 each, and many can be used for two units. Average cost = US$ 14.00-30.00/transfusion = US$ 170-360/patient/year.

Filters for 100 patients = US$ 17,000-36,000/year.

If filters are not available, anti-histamines and steroids should be used at the time of transfusion to control reactions.

Desferal. Transfusion-dependent thalassaemic patients require from 30-60[3] mg/kg/day infused subcutaneously = 200-900 g/patient/year depending on weight (see Table 3). Cost of Desferal in 1989 = US$ 6,000 per kg.

100 patients require 20-90 kg of Desferal year depending on their age-distribution = US$ 120,000-540,000/year.

Infusion pumps. One is required per patient, plus 10% reserves. Cost = US$ 350-530.00/pump.

For 100 patients, one-off cost = US$ 38,500 - 58,300.

Disposables for Desferal infusion. Each patient requires 300 syringes, needles, infusion sets, and vials of 10 ml of distilled water/year.

For 100 patients = 30,000 of each/year.

---

3 The recommended dose for controlling iron-overload in a well chelated patient with classical thalassaemia major is 40-50 mg/kg/day. Patients with a lower blood requirement will need less, and those who are grossly iron-overloaded will need more.

Endocrine replacement treatment may be required, especially for diabetes and disturbances of pubertal growth and development.

Immunizations

(i) Hepatitis B Vaccine should be provided for all patients as soon as the diagnosis is made (approximate cost per course of 3 injections is US$ 3.00 in developing countries and US$ 50.00 in developed countries).

(ii) Anti-pneumococcal vaccine presplenectomy (2-3% of patients per year).

(iii) Haemophilus influenzae vaccination.

Splenectomy. On average 2-3% of patients require splenectomy each year. However, when a group of patients who have received sub-optimal treatment are first put on standard treatment the proportion found to need splenectomy can be very high, e.g., 30% in the first 1-2 years.

Interferon therapy. This is now indicated for patients with chronic active hepatitis.

Bone Marrow Transplantation. HLA typing must be available. Marrow transplantation is possible only for patients with a fully matched HLA-compatible, related donor, and who are free of complications (no chronic hepatitis; minimal iron overload (ferritin less than 2,000 ng/ml). (Example: only 10-15% of Italian patients meet these criteria.) The success rate varies by centre, but with appropriate patient selection can reach 90% disease free survival.

Cost = US$ 30-75,000 /patient, depending on the centre.

Other procedures. A limited number of patients have now had a liver transplant for liver failure, or a heart transplant for intractable heart failure. Heart + lung + liver transplant has also been successful in at least one case.

Psychological support. The first requirement is to provide treatment to the recommended standard: without this, attempts at specific psychological support are irrelevant. The next requirement is to provide continuity of care, and time for each family to discuss their problems with the physician-in-charge or a trained, dedicated nurse, counsellor or psychologist. Expert psychological assessment and support should be available for families, adolescents and adult patients with serious problems. It is essential for families to be able to communicate freely, and when necessary trained interpreters or genetic counsellors should be available.

Summary of requirements for treating 100 patients with thalassaemia

		Cost, US$/year
Staff	1 doctor, 3 nurses, 1 technologist, 1 counsellor/ psychologist, 1 secretary/administrative assistant.	7 salaries
Blood	500-1,500 litres/year	differs locally
Filters	1,200-1,800/year	17,000-36,000
Desferal	av 45 mg/kg/day	120,000-540,000
Disposables	infusion sets, syringes, needles, water, 30,000/year	
Endocrine replacement therapy		
Additional immunisations (Hepatitis B, Pneumovax)		
Interferon therapy for chronic active hepatitis		
One-off		
	100 pumps	38,500-58,300
Bone marrow transplantation/patient		30,000-75,000

5.2 Treating thalassaemia in developing countries

When resources are very limited, and especially if large numbers of patients are involved, the requirements listed above will be considerably modified. It should be possible to provide the following in most situations.

Staff Senior doctor in charge; clinical assistance; clerical help especially in organizing transfusions, contacting families and keeping records.

Basic blood taking facilities.

Basic laboratory facilities.

Treatment protocol.

Standard patient records, and yearly analysis to identify problems.

6-monthly measurement of height and weight.

Regular transfusion (monthly or more often) with safe blood to maintain a mean Hb of 12g/dl. ***This is the most cost-effective scheme under all circumstances.*** Lower transfusion schemes lead to the same or higher average blood consumption. Maintaining a lower haemoglobin level in order to save blood is a false economy (see Figure 5).

Control of transfusion reactions by antihistamines and steroids.

Immunizations; especially against hepatitis B.

Ferritin estimation annually.

Desferal. High cost and the inconvenient mode of administration makes Desferal unavailable for most patients in many countries. It is therefore necessary to consider how to make the best use of a limited amount of Desferal.

The minimum effective dose of Desferal is not known. It is likely that even small amounts of Desferal can help to postpone the toxic effects of iron overload. When treatment was first started, it was found that intramuscular injection of quite small doses stabilizes body iron load at a level corresponding to a ferritin of 4,000-7,000 ng/ml, and also protects against iron toxicity (16). This may be because regular administration of a small dose removes the most easily chelateable, (i.e., the most toxic) iron fraction. Small doses of Desferal are reasonably effective when given by intramuscular injection.

When resources are very limited (e.g., patients can obtain less than five 500mg vials of Desferal a week), it is best to buy as much Desferal as possible and take it in small regular intramuscular injections of half a vial or a vial at a time, with one vial intravenously during each blood transfusion.

When more than five 500mg vials are available per week, Desferal is best given regularly with a pump.

However, the evolution of iron overload is slow, and research on cheaper oral iron chelating drugs is promising. In this situation transfusion treatment should be provided to the best possible level in a spirit of optimism, because of its effect in improving quality of life for the child and the family.

5.3 Requirements for treating sickle cell disorders

It should be possible to meet the needs of patients with sickle cell disorders for basic out-patient and in-patient care wherever primary and secondary health services are available. Requirements given are for day hospital, in-patient and out-patient care for a "unit" of 200 patients, either adults or children but not mixed. (Costs given below are based on experience in London and Paris).

Staff

2 doctors
2 nurses
1 technologist equivalent, (divided between haematology, blood banking, and biochemistry)
1 counsellor/psychologist,
1 secretary/administrative assistant
access to a social worker

= 7 salaries

Management Protocols. Comprehensive guidance has been provided by Serjeant (18). WHO documents include Guidelines for the Management

of Sickle Cell Disorders (20). Specific protocols are required for casualty departments, to ensure rapid appropriate treatment, especially of pain.

Patient care

(a) Basic out-patient care: All patients with sickle cell disorders should make *regular out-patient* visits including physical examination, measurement of height and weight, blood count, urine tests, check-ups for eyes and bones, penicillin, pneumovax, dressings for ulcers, etc.). The ideal frequency of out-patient visits depends on the age of the patient as follows:

Younger than 6 months	every 4-8 weeks
6 months to 5 years	every 3-6 months
Older than 5 years	every 3 months-1 year

Average cost = US$ 250-500/patient/year

(b) Basic in-patient care: 85% of patients need only out-patient visits plus basic in-patient care when indicated for vaso-occlusion, aplastic crisis, infective episodes, etc. Average cost = US$ 2,500-5,000/patient/year.

Additional problems

(c) 5-10% of patients require regular transfusion for stroke, pulmonary hypertension, etc., at US$ 25,000/patient/year.

(d) 10% of patients have an exceptional problem e.g., require splenectomy, or elective orthopaedic or abdominal surgery, or incur pregnancy-related costs etc, at US$ 8-10,000/year.

Estimated total annual costs for 200 patients		
200 x a	=	$ 50,000-100,000
170 x b	=	$ 425,000-850,000
10 x c	=	$ 250,000
20 x d	=	$ 160,000-200,000
TOTAL	=	$ 885,000-1,400,000

Average/patient/year = US$ 4,425-7,000.

The type and severity of problems encountered varies very considerably with ethnic group, and geographical location. In general sickle cell disorders seem to be most severe in North-west Europe and Africa. The treatment available also differs substantially in countries at different levels of economic development. For example, in Jamaica Dr Serjeant's research unit provides only out-patient care (equivalent to (a) above). It follows 4,000 patients and manages 2,000 regularly with a staff of 6 doctors (2 for adults and 4 for children). The unit budget

(including research costs) is US$ 600,000 (= about US$ 300/patient/year). This is not greatly different from the cost of basic out-patient care in developed countries.

5.4 Neonatal Diagnosis of Sickle Cell Disorders (24)

Without neonatal diagnosis, mortality from sickle cell disorders in the first few years of life ranges from 10% in more developed countries to nearly 100% in rural areas of Sub-Saharan Africa. Neonatal diagnosis with prophylactic penicillin treatment, appropriate counselling and follow-up can greatly improve patient survival, e.g., in developed countries it reduces early mortality from about 10% to nearly zero.

Neonatal diagnosis is useful only when there is appropriate counselling for the parents and adequate primary care for the patients detected. Infants who are healthy carriers of an abnormal haemoglobin are also identified by neonatal screening and it may be difficult to decide how or whether use this information. When antenatal screening is routine most carrier mothers will already have been detected and counselled and many parents may already be prepared to understand information about a baby's carrier status. However, difficulties can arise when universal neonatal screening is introduced without antenatal screening and counselling. The families of carrier infants should be counselled, and other family members including both parents offered testing, but ability to do this depends on resources.

A neonatal screening programme should be accompanied by basic education of primary and maternal child health workers so that they can provide correct information. All programmes should have an audit component, e.g., assessment of patient survival.

Neonatal screening is helpful for epidemiological studies, and for quality control of prenatal diagnosis, as follow-up of the newly-diagnosed affected babies can show gaps in the screening and counselling programme (see section 10).

There are two possible strategies for neonatal screening:

(a) Selective testing of babies born (i) to couples already known to be at risk because of antenatal screening or because they already have an affected child, and (ii) to women who are known to carry a haemoglobin disorder, e.g., through antenatal screening. Selective testing is usually preferred in developing countries and in populations where sickle cell disorders are relatively uncommon.

(b) Universal screening of all newborns. This may be indicated in populations where sickle cell disorders are common, as in such circumstances a significant number of affected babies may be missed by selective testing.

Neonatal screening for sickle cell disorders may be done using cord blood (though there is a risk of contamination with maternal blood), or fresh or dried blood samples taken by heel-prick.

When a programme for neonatal screening for phenylketonuria and congenital hypothyroidism, already exists, the laboratory aspect of universal screening for sickle cell disorders can conveniently be attached to it. Neonatal screening may also be set up as an independent programme in areas where sickle cell disorders are common.

Requirements for neonatal screening for sickle cell disorders

Laboratory costs vary depending on method (cellulose acetate/agar electrophoresis or isoelectric focusing) or whether reagents are home-made or commercial, the number of tests per week, and cost of technologist's time. In the UK in 1988, the estimated cost for 1,000 neonatal samples (cord or heel prick, including equipment, maintenance, reagents, technologist's time, and repeat tests) was US$ 500-800 (US$ 0.5-0.8/ sample).

Laboratory costs represent less than a third of the total cost. Costs of collecting samples, filter papers or containers, transport or postage, reports, other administration, educational and information materials, counselling parents of affected and carrier babies, follow-up and family studies, training technologists and quality control, rent of premises, electricity, telephone etc. must all be taken into account.

6. CARRIER SCREENING

The aim of screening for haemoglobin disorders is to offer carrier testing to every member of the population (or to one member of each couple), ideally before they have children. The purpose is to identify carrier couples and inform them of their risk, and the options for avoiding it. The prime targets of screening are haemoglobins S,C D, E and ß- and α^0 thalassaemia traits. A fully-fledged prevention programme combines the following approaches.

Family-centred approach. Parents with affected children have a 1 in 4 recurrence risk in each pregnancy. They should be informed of this risk and of the possibility of prenatal diagnosis, and doctors in treatment centres should be well versed in genetic counselling. Genetic counselling for couples who already have an affected child is called "retrospective" genetic counselling. The parents' other children and relatives should also be informed of their high risk of being carriers (50% for siblings) and offered testing and counselling.

Family-centred counselling is a priority. However, it has a limited effect on the number of new affected births, since many affected children are born to couples with no family history of a haemoglobin disorder. To achieve a major effect on numbers it is necessary to provide population screening.

Population screening. Members of the public with no known affected relative are offered testing and counselling. Identifying carriers before they have an affected child is called "prospective" carrier diagnosis. The relatives of carriers detected by population screening should also be informed of their risk of being carriers (e.g., 50% for siblings) and offered testing and counselling. Population screening is inseparable from community information and genetic counselling, and should be decentralised to be easily available to the community.

It is recommended to start a programme with counselling families of affected children. This allows the team to gain experience with families already familiar with thalassaemia, and to verify their laboratory technology for carrier and prenatal diagnosis, and obstetric techniques, in cases that are definitely at risk (because there is already an affected child). A family-centred approach is indicated and should be feasible in almost any circumstances.

Starting population screening, on the other hand, requires careful planning in view of the need for organization, adequate resources, training and quality control, and the risk of errors in carrier or prenatal diagnosis (3).

As many variables affect the design of a screening programme, a first step is for the national or regional reference centre to carry out research on the most appropriate and cost-effective screening strategies in relation to local carrier frequencies, types of abnormality, and health service structure. It should be emphasized that screening for haemoglobin disorders is a form of anaemia screening, an aspect that is particularly important in less developed countries.

Screening may be provided by dedicated screening units, or integrated into the general haematology service. Very small dedicated screening units with

only one technician are undesirable. Two or more staff are required, and research must be carried out to maintain the morale of the team.

6.1 Choice of screening strategy

Screening should be delivered equitably to the target population regardless of social class, ethnic group, or locality. There is no single "right" approach, a number of complementary strategies may be needed, and it is necessary to start with what is possible. As more and more carriers are diagnosed and counselled, community involvement, understanding and support increase, and the strategy is likely to evolve.

In theory screening can be offered at many points in life e.g., in schools, premaritally, in family doctors' clinics, family planning clinics, antenatal clinics, or in the newborn period. Models for most of these approaches exist. In high risk areas it is possible to set up a special service oriented to screening before marriage or reproduction. However, in areas where screening must be integrated into the general medical service, it is usually necessary to offer it when people come into contact with the medical system for some aspect of routine care.

A screening infrastructure is required (Table 4). In most countries the rudiments of such an structure exist in the antenatal and newborn periods, as all pregnant women and newborn babies require basic, routine medical services. Hence it often proves necessary to start by offering screening to pregnant women (providing prenatal diagnosis is available), especially as some screening and counselling for reproductive risk is already part of antenatal practice.

Antenatal screening involves screening pregnant women when they first present for antenatal care, and offering testing to the partners of carriers so detected. It requires an education campaign for obstetricians, nurses and midwives. Providing women attend reasonably early, most couples at risk can be identified in time for the offer of prenatal diagnosis. This strategy has the advantages of equity and starting with the group most in need of the service: it has the disadvantages that options other than prenatal diagnosis are excluded, and that risk is usually identified too late for prenatal diagnosis in the first trimester, in the presenting pregnancy. (In theory, the latter problem might be overcome by encouraging women to report a pregnancy as soon as it is suspected, and training primary care workers to organise carrier testing.) However, antenatal screening allows experience to be gained on the implications of screening for the population, and is a starting point for developing the most appropriate service. Antenatal screening will always be needed as a back-up to other, earlier approaches.

Premarital testing is the official policy in Greece and parts of Italy. However, in practice most couples come for testing only when the woman is already pregnant. Premarital testing is unlikely to suit communities in which identification of a genetic risk prior to marriage can lead to stigma, especially for the woman. In this situation screening young couples prior to reproduction or in early pregnancy may be preferable.

Village screening In rural areas (e.g., in Sardinia), whole villages may be targeted by a visiting team; testing is particularly focused on young people and couples of reproductive age.

Screening in high school may ultimately be an ideal strategy. It requires a well-informed population, enthusiastic teachers, and a developed infrastructure. It is offered in Latium (Italy) and Montreal (Canada) (25,26), and in the near future may become the policy of choice in Cyprus and Sardinia (7).

Cascade screening. The classical medical genetic approach to carrier detection based on family studies ("cascade screening") has been relatively under-used for haemoglobin disorders, probably because where the carrier frequency is high population screening is the simplest and most effective strategy. Where the carrier frequency is lower (e.g., less than 5%) as in Portugal or among many groups of Asian Indians, once a carrier is identified follow-up of other family members may greatly increase the efficiency of screening. Once identified, carriers should be clearly informed that siblings have a 1 in 2 risk, uncles and aunts a 1 in 4 risk, and cousins a 1 in 8 risk of being carriers, and that testing is available for other family members. Cascade screening may be particularly effective in populations where consanguineous marriage is common (15): this aspect requires further study.

Neonatal screening is sometimes visualised as a strategy for identifying at risk couples for reproductive counselling, by following up the parents of carrier children. This opportunity should of course be taken, especially when neonatal screening is used for sickle cell disorders. However, neonatal screening is a very inefficient approach for genetic counselling, as by definition 50% of at risk couples are either missed, or not detected in time for reproductive choice (25% will already have an affected baby by the time they are detected, and the 25% who have a normal baby remain undetected).

6.2 Identifying carriers

The basic screen to identify carriers is shown in Figure 3.

The following technologies must be available:

(a) Measurement of red cell indices using a reliable electronic counter (cost US$7,000 upwards). Alternatively a one-tube osmotic fragility test with 0.36% saline (28) may be used in peripheral centres as a simple primary screen for thalassaemia traits. This test is not adequate for a reference centre.

(b) Electrophoresis for abnormal haemoglobins and raised HbF (usually on cellulose acetate) followed by electrophoresis on citrate agar if indicated. A one-tube turbidity test may be used as a simple screen for sickle haemoglobin in peripheral centres. This test is not adequate for a reference centre.

(c) Measurement of haemoglobin A_2. This may be by cellulose acetate electrophoresis with elution and colorimetry, or by a separate microcolumn method. Direct densitometry following cellulose acetate electrophoresis is not considered sufficiently reliable.

When screening for genetic counselling, a diagnosis is *desirable* for all samples tested and is *necessary* when both of a couple have an abnormality on the above tests.

The basic screening tests are, in general, straightforward and accurate, and screening for haemoglobin disorders is considered one of the simplest forms of genetic screening. However, a proportion of samples give intermediate or ambiguous results, and achieving correct diagnosis in all cases requires DNA and sometimes globin biosynthesis techniques (29). Common problems are as follows.

(i) Samples with a mean cell haemoglobin (MCH) below 27pg[4] should be investigated further (Figure 3). The differential diagnosis includes iron deficiency, α-thalassaemia trait and ß-thalassaemia trait. The proportions of people with these diagnoses differ greatly between populations. For example, in the Mediterranean area ß-thalassaemia trait is the commonest cause of marked microcytosis. By contrast, in South Asians iron deficiency and α^+ thalassaemia predominate, and often occur together particularly in pregnant women, over 25% of whom may be iron deficient. It is necessary to measure serum iron or ferritin to differentiate α-thalassaemia from iron deficiency in these groups. Note: iron deficiency rarely if ever interferes with the diagnosis of ß-thalassaemia trait (30).

(ii) Ethnic group may need to be taken into account in deciding whether to proceed with further investigations. The commonest cause of microcytosis in people of South Asian or African descent (apart from iron deficiency) is α^+ thalassaemia trait, which is almost always harmless in these populations. In these circumstances, it can do more harm than good to pursue the finding of microcytosis once ß thalassaemia trait and iron deficiency have been excluded.

(iii) Hb A_2 estimation may give intermediate results (e.g., 3.2-3.4%). This may indicate the coincidence of ß and α or δ thalassaemia traits in the same person, or the presence of a mild ß thalassaemia gene, or severe iron deficiency and ß thalassaemia trait, or the person may not be a carrier.

---

[4] In fact, it is hard to give a definite cut-off point as MCH can vary with the instrument used and the type of mutation present.

Other technologies

Iron-deficiency screening using measurement of red cell Zinc protoporphyrin has been recommended, especially when testing women and children. The equipment costs US$7,000, large numbers can be screened and running costs are low. Comparison with serum ferritin estimations indicate that only marked iron deficiency is detected, but the method can be very useful, especially where iron deficiency is common.

Isoelectric focusing (IEF) improves screening for abnormal haemoglobins, but is economical only where there is a large volume of work. IEF is easy using commercially available pre-poured plates, over 200 samples can be analyzed per day and, for example, haemoglobins E and C are readily distinguished. IEF is particularly suitable for neonatal diagnosis where large numbers of very precise tests are required, but for adults, cellulose acetate electrophoresis is cheaper.

HPLC has great advantages because it allows measurement of abnormal haemoglobins and Hb A_2 in a single step *on all samples*.

Automated quantitation of haemoglobin A_2 is expensive, fast and extremely precise. The (Biorad) machine is not expensive, but columns have a short life and cost US$ 400 each, and a high level of technical skill is required, so running costs are very high. The approach might be appropriate for reference laboratories in developed countries.

Measurement of abnormal haemoglobin. Monoclonal anti-HbS antibody, using a colour change is becoming available, and is very useful for confirming positive results in neonatal screening for sickle cell disorders.

Diagnosis of α thalassaemia. This is now largely by DNA methods (29).

Discriminant functions. There have been numerous attempts to integrate data obtained with automated counters to discriminate between iron deficiency and thalassaemia traits. This approach allocates individuals to one diagnosis or the other, though they often have both, and is not useful for screening. The main value of discriminant functions may be to alert staff in routine haematology laboratories in low incidence areas to the possibility of thalassaemia trait.

6.3 Requirements for carrier screening

Many variables must be taken into account in estimating requirements:

(a) Dedicated versus integrated screening service. In high incidence areas dedicated screening centres may be needed, but in lower incidence areas carrier screening is integrated into the general haematology service, and it may be difficult to identify costs.

Requirements for a dedicated screening unit are given below. Requirements for screening integrated into general haematology services can be estimated from these, on the basis of the weekly number of tests.

(b) The prevalence and mix of haemoglobin disorders and iron deficiency. All samples require measurement of red cell indices and Hb electrophoresis. Further costs depend on the prevalence of microcytic samples needing HbA_2 estimation and assessment of iron deficiency. In the UK, HbA_2 is measured only when the MCH is 27pg or less (selective testing), while in Greece, with a very complex genetic picture including "silent" ß-thalassaemia trait, and in Sardinia, haemoglobin A_2 is measured on every sample (universal testing). Screening can be particularly complex and therefore more expensive in e.g., South and South-east Asian populations because of the high prevalence of iron deficiency anaemia and α-thalassaemia trait.

(c) Labour costs. In more developed countries labour costs may be reduced by using automated methods, while in less developed areas more labour-intensive methods using traditional equipment are appropriate.

Example of a dedicated screening unit in Greece, where all samples have indices, electrophoresis and HbA_2 estimation.

Staff: (30-hour week, 9 salaries): 1 doctor, 1 nurse, 1 biochemist, 4 technicians, 1 secretary, 1 cleaner.

This staff can deal with 250-500 samples per week (13,000-26,000/year) depending on facilities and local conditions.

Estimated cost including personnel = US$ 20-30/test (US$ 260,000/year).

If HbA_2 is measured only on samples with MCH <27pg, as in the UK, costs/sample are less.

In the Sardinian programme (29), automated laboratory and computer methods are being integrated to obtain faster, cheaper carrier diagnosis combined with highly reliable recording of results. When the patient is first seen, details are logged onto a personal computer that is linked to the automated equipment in the laboratory. Carrier screening is by automated haematological indices and HPLC analysis (allowing quantitation of abnormal haemoglobins and Hb A_2 in a single step *on all samples*). The results are transferred automatically to the patient's computer record, and are also printed onto magnetic cards. All Sardinian centres for large-scale population screening have magnetic card decoders. This highly automated approach may well prove to be the most efficient, reliable and cost-effective in the long-term.

SCREENING IN LESS DEVELOPED COUNTRIES

Costs can be reduced very considerably by using a 1-tube osmotic fragility test to identify individuals who may have ß thalassaemia trait or iron deficiency, a simple 1 tube sickling test to pick up HbS, and a basic turbidity test for HbE (in areas where this is common). These tests can be done on finger-prick blood, and detect over 95% of carriers. Samples with a positive result are sent to a reference laboratory for more detailed investigation. Partners of all carriers identified should be tested by the reference laboratory. A pilot study using such a simplified approach is planned in southern Thailand.

7. GENETIC COUNSELLING

Information and genetic counselling must be available wherever carrier screening is done. Different levels of information and counselling are required at the various stages of a screening programme (Table 5).

(1) ***All primary care workers*** involved in offering the initial screening test need to be able to provide simple, clear and correct information, and basic counselling about the reasons and objectives. They need to know that testing should not be forced on people, and to be able to inform carriers about their result and its implications.

(2) ***Counselling by a trained expert*** should be available for all at risk couples and families with an affected member, and for people with unusual carrier states or particular problems or concerns.

For most health workers genetic counselling is a new art and training is needed. In particular, counselling at-risk couples requires experience and can be very labour-intensive. Genetic counselling involves a one-to-one encounter and requires correct information, time, and the ability to communicate.

Counselling for other genetic risks should be associated with counselling for haemoglobin disorders as far as possible. Counsellors should be trained to enquire about maternal age and about possible genetic abnormalities in the family, and should have direct contact with the local genetics service where one exists.

7.1 Counselling Carriers who do not yet have a partner, or whose partner is not a carrier (single carriers)

It is difficult to generalize about requirements for counselling carriers as they vary with the population concerned, the level of risk, the level of public education about haemoglobin disorders, and the way screening is organised. Carriers should be given simple written information and a clear record of their diagnosis. It is always best for them to have some discussion with a counsellor or their own (informed) doctor or practice nurse whenever possible. The time required for counselling carriers is inversely proportional to the level of public information: there is most need for face-to-face discussion when the population is uninformed, but there may be relatively little need in a well-informed population.

When screening is provided in dedicated centres, it is natural for carrier counselling to be provided in the same place. When screening is integrated into the general haematology service it is essential to ensure that counselling is also available. This can be done by providing trained haemoglobinopathy counsellors (as in the UK). When there are language problems it is particularly important for counsellors of the same ethnic group as those screened to be available. The screening centre should provide training for obstetricians, midwives, general practitioners, nurses, and other health workers in counselling single carriers. Informed doctors and nurses working in maternal and child health and primary care can then counsel single carriers in the community, or in antenatal clinics.

Group counselling of single carriers is possible in some communities, e.g., in Jamaica and Cuba, but is not acceptable to many, for fear of loss of confidentiality. In the Sardinian "village screening programme" a team visits the village, gives an initial educational session and offers carrier testing. Three days later sealed written results are handed out and a group information session is provided - a version of group counselling without loss of confidentiality.

7.2 Counselling carrier couples

At-risk couples should always be counselled by a specialist, not necessarily a doctor, who understands the disorders in depth. Counselling at this level of risk takes time, and several visits may be needed. Details of the disorder involved, the risks of the obstetric procedure and the possibility of prenatal misdiagnosis must be included in counselling. Written information for couples on their particular risk is essential, and records of counselling choices should be kept.

The transfer of knowledge transfers much of the responsibility for its use. Moral and psychological problems are inevitable when reproductive choices and prenatal diagnosis are involved, because once the inheritance pattern is explained to a couple at risk (or to the parents of an affected child), they cannot escape from the responsibility of choosing among the options in Table 6. The choices are all difficult, and all have ethical implications because they involve other people. Consequently people faced with the same objective risks can make very different choices. The genetic counsellor's first responsibility is to provide accurate and comprehensible information which will allow people to make a choice they feel they can live with for the rest of their life. Consequently the core ethical principles of genetic counselling are (31):

(a) The autonomy of the individual or couple
(b) Their right to full information
(c) The highest standard of confidentiality

Clearly, for people to be autonomous they must be fully informed, and counselling must be "non-directive". Non-directive counselling does not mean simply telling people the facts and leaving them to make their own decision: it involves actively helping them to reach a decision that is right for them, in the context of their unique medical, moral and social situation.

7.3 Requirements

For counselling carriers

Because of the large number of variables it is only possible to give examples. In the Sardinian population of 700,000 with a high prevalence of abnormal genes, 4 doctors and 4 nurses are required. At the reference centre in Cagliari four nurses deal with all comers. There are about 100 tests per day, and on average 13 carriers are detected daily and counselled. The staff also see people referred by other doctors. Two

doctors are responsible for counselling at risk couples at the centre, and two for counselling outside the centre.

The Brent Sickle Cell Centre (UK) is a regional centre responsible for providing counselling for a mixed population of 3.5 million with an average 3% heterozygotes, and universal neonatal and antenatal screening. Five nurses are required. They have, on average, 500 counselling sessions a year, including 20-30 at-risk couples.

In Cyprus there is a long-standing public and professional education programme and both the population and health professionals understand the implications of thalassaemia. Single carriers are given their result by letter, and rarely require specialist counselling as they can discuss problems with their own doctor. Individual counselling is offered for unusual carrier states and at risk couples.

For counselling at-risk couples

Dedicated screening services. In Sardinia two doctors see 350 at risk couples per year. In Athens one social worker counsels 500 at-risk couples per year. In Cyprus, all at-risk couples are counselled by doctors who are also responsible for the care of thalassaemic patients, one at each of the three main thalassaemia centres.

Screening integrated into the general health system. In the UK, two specialist centres for prenatal diagnosis of haemoglobin disorders are associated with specialist fetal medicine units (both in London). At risk couples living in London are referred from antenatal clinics or by haemoglobinopathy counsellors or general practitioners. They are seen by highly qualified counsellors who also accompany couples through prenatal diagnosis, and termination of pregnancy when that is requested. In other parts of the country couples detected by antenatal screening are counselled by haemoglobinopathy counsellors, obstetricians or haematologists. Those requesting prenatal diagnosis are referred to the regional fetal medicine centre for fetal sampling, and samples sent to a national reference laboratory (in Oxford) for analysis. It can be difficult to ensure the recommended standard of counselling with this "postal" type of prenatal diagnosis.

The cost of carrier counselling = the salaries of the above staff, transport if necessary, secretarial support, and educational materials for health workers, carriers and the general population. The costs of training health workers in carrier counselling should be part of the programme budget.

8. PRENATAL DIAGNOSIS

A prenatal diagnosis service must include the following, on the same site whenever possible:

- Risk assessment, counselling, and the opportunity for free informed choice for couples at risk
- An experienced and safe fetal sampling service
- Laboratory prenatal diagnosis
- Support during and after therapeutic abortion.
- Follow-up of babies born, whether or not prenatal diagnosis was performed
- Careful records
- Collaboration in a prenatal diagnosis register

Prenatal diagnosis for haemoglobin disorders should be centralised in a minimum number of expert centres, as the optimum number of diagnoses (prenatal tests plus others) should be over 200/year: expertise is lost with less than 100 samples/year. A high level of laboratory expertise is required, as there may be errors in referral of couples at risk, a large number of different mutations are involved, and some diagnoses may be very difficult. Incorrect risk assessment, the commonest cause of misdiagnosis, can have medico-legal implications.

8.1 Obstetric aspects

All fetal sampling procedures must be done by an expert in fetal medicine, with high quality ultrasound guidance. Chorionic villus (placental) material and fetal blood are suitable for analysis by modern DNA methods. Amniocentesis samples are less suitable because of the small quantity and poor quality of the DNA obtained. Fetal sampling can be carried out at any gestational age after 10 weeks, the earlier the better. At risk couples have a strong preference for prenatal diagnosis in the first trimester; e.g., the uptake of prenatal diagnosis is higher when couples are counselled in the first, rather than the second trimester (32,33).

Chorionic villus sampling (CVS) can be done transcervically up to 12 weeks' gestation, or transabdominally at any stage, providing the placenta is within reach. At many centres the approach is selected according to the conditions of each case. The associated risk of miscarriage is estimated to be 1-2% in experienced hands. There is a very small risk of fetal malformation if CVS is done before 10 weeks' gestation, but there is no convincing evidence of additional risk of malformation after this stage (34).

Fetal blood sampling (FBS) can be done safely only after 18 weeks' gestation. It is used for DNA diagnosis when the placenta cannot be reached transabdominally, or in the now rare situations when the diagnosis cannot be made by DNA and globin biosynthesis must be used. The current method is by direct needle puncture of the umbilical cord insertion under real-time ultrasound guidance. The associated risk of miscarriage is thought to be about 1% with an expert operator. Fetal blood sampling

under direct vision using a fetoscope carries a risk of from 2-7% depending on the operator's experience. It is no longer an acceptable method.

The upper limit of gestational age for fetal sampling is set by local laws governing legal abortion, which differ considerably by country. When there is risk of alpha thalassaemia hydrops fetalis, which poses a direct threat to the health of the mother (as it causes pre-eclampsia, eclampsia, obstructed labour and ante- and post-partum haemorrhage (35)), there can be no upper limit of gestational age for fetal diagnosis.

The method used for terminating a pregnancy depends on the stage of gestation. If the abortion is performed before the end of the 13th week of pregnancy the standard "suction method" is used. For abortion after the 14th week, usually labour is induced using prostaglandins. Alternatively, the fetus and placenta may be removed surgically. Whatever method is used, termination of pregnancy for fetal abnormality is distressing. Parents who have a genetic abortion suffer a bereavement and need sensitive emotional support and counselling.

8.2 Laboratory aspects

New prenatal diagnosis programmes should be started using DNA since modern techniques such as the polymerase chain reaction (PCR), and the amplification refractory mutation system (ARMS) or reverse dot blot hybridisation, are fast, do not need radioactivity, are suitable in almost all cases, and are appropriate for other types of genetic diagnosis. Techniques for globin synthesis should be viewed only as back-up. The programmes in Cuba and China were both begun with DNA. The main problem is the cost of reagents.

Errors are known to have occurred for the following reasons:

(a) Incorrect diagnosis in the parents, e.g., misdiagnosis of normal or alpha thalassaemia as beta thalassaemia trait, or of HbS/ß thalassaemia or Hb SC disease as sickle cell anaemia (SS).

(b) Contamination of the fetal sample with maternal tissue. Chorionic villus material usually includes fragments of endometrium that must be meticulously removed under a microscope before DNA is extracted for fetal diagnosis.

(c) Mixing up samples, technical errors, and misinterpretations of results.

(d) Non-paternity (of the fetus or other family member).

Because of the high level of responsibility in prenatal diagnosis, and because of the possibilities for error, it is common practice to analyze two separate samples by two different laboratory methods, for internal verification.

8.3 Requirements

For obstetric fetal sampling service

When prenatal diagnosis for haemoglobin disorders is part of an existing genetic and prenatal diagnosis service, only additional (marginal) costs for fetal sampling are required. However, the haemoglobin disorders are often the first conditions requiring a prenatal diagnosis service to be set up. In this case, the whole cost of training and establishing a reliable fetal sampling service is an integral part of the prevention programme for haemoglobin disorders. Requirements are

Staff

2 obstetricians trained in fetal medicine (ultrasound diagnosis and a variety of fetal sampling techniques)
1 ultrasound operator
1 nurse

High quality ultrasound equipment
Sampling equipment (disposable and re-usable)
Suitable sterile facilities for fetal sampling
Suitable facilities for termination of pregnancy in the first and second trimesters
Bereavement counselling for women undergoing termination of pregnancy (ideally this will be provided by the counsellor with whom the couple discussed prenatal diagnosis)

For laboratory prenatal diagnosis

For a dedicated service carrying out 100-500 prenatal tests/year (based on Sardinia).

Staff

1 director of the unit
A counsellor (nurse-specialist, social worker or other)
1 molecular geneticist
1 technician per about 100 tests/year, including family studies

Appropriate equipment. Automated PCR machines are essential.

Restriction enzymes, DNA polymerase and DNA probes are expensive. Even if they are synthesised locally, as in China, costs of DNA diagnosis remain high because the nucleotides must be bought in hard currency. Costs may be reduced by automated equipment and kits for common mutations. Availability of a DNA synthesizer may also decrease costs, e.g., one laboratory could synthesize DNA primers and probes for a whole country.

However, because DNA methods are much faster and less labour intensive than older methods total costs are lower, and are likely to fall

further in the future. In the examples below costs have been calculated by dividing the entire laboratory unit budget including salaries, reagents, maintenance of equipment, etc. by the number of samples run.

(a) PCR with non-radioactive probes (eg. ARMS technique). 1 person can run more than 50 samples per week. Cost = approximately US$ 50/sample.

(b) Polymerase chain reaction (PCR) and oligonucleotide probes. Using 4 main probes plus radioactivity, 1 person can run 20 samples per week (manually). If 8 oligonucleotides are used, 5 samples can be run per week. Cost = approximately US$ 100 per sample.

(c) Analysis of RFLPs. 1 person can study 1 family per week (not complete haplotyping). Cost per family = US$ 200-250.

(d) Denaturing gels. 1 person can run 50 samples per week. Cost = much less than US$ 50/sample.

(e) Direct blot-dot analysis is used in Sardinia where 97% of mutations can be diagnosed by 8 oligoprobes, and 350 prenatal diagnoses are done per year.

Example from China

The Chinese make their own Taq polymerase at a quarter of the cost of imported enzyme. The 200/250 units required per test cost US$ 1.6 if imported, and 40 cents if home-made. The Chinese also synthesize their own primers but this reduces cost only slightly because nucleotides must be bought from the USA. Total cost per family studied (materials only, excluding staff) = US$ 30.

9. EDUCATIONAL COMPONENT

A control programme for haemoglobin disorders depends on adequate education of the public and health professionals, and collaboration with Health Education specialists is very helpful. It has been suggested that approximately 10% of the budget of a haemoglobinopathy control programme should be set aside for providing educational materials and professional training. However, few ongoing programmes have a specific budget for community and professional education.

9.1 Professional education

(a) Training counsellors

Whether counselling is done full-time or as part of a professional's work, counsellors need (a) a source of correct information, (b) training in techniques of non-directive counselling, and (c) opportunities for continuing in-service training. Specific training courses for haemoglobinopathy counsellors exist in the UK, the USA and Nigeria (36). Once trained counsellors are available, they in turn can train other health workers in haemoglobinopathy screening and counselling.

(b) Doctors and nurses

The medical and nursing curriculum should be updated to ensure appropriate teaching.

Specific professional targets include obstetricians, midwives, general practitioners, nurses working in primary care, and family planning doctors and nurses. Regular updating courses should be run for these health workers by specialists and haemoglobinopathy counsellors. Professional education should include general aspects of genetic disease, not only the haemoglobin disorders.

9.2 Public education

The following are appropriate:

Teaching in Schools. In high incidence areas such as Cyprus, Greece and Sardinia specific teaching on haemoglobin disorders is included in the school curriculum. Now that carrier detection for cystic fibrosis and other inherited disorders is becoming feasible, it is desirable to include teaching on recessively inherited disorders in the school biology curriculum in most countries.

Posters and leaflets displayed in key places, e.g., antenatal clinics, general practitioners' surgeries, family planning clinics.

Patients' and Parents' Associations maintain public awareness through their publications and through their newsworthy activities

and meetings: e.g., in Cyprus they hold an anti-anaemia week every year.

The media are usually involved in reporting newsworthy events such as policy decisions, the opening of a centre, or activities of the parents' and patients' associations, as well as producing special programmes.

9.3 Educational materials

Table 7 shows the availability of WHO sponsored educational materials (and the languages in which they are available). Such materials need to be available in sufficient quantities for use by haemoglobinopathy counsellors and other health workers.

Even when appropriate materials are available there can be many difficulties. The standard of material may be uneven; materials may not be available for rarer carrier states such as Hb Lepore, Hb D C or E trait, or α thalassaemia; centres may find materials difficult to acquire in sufficient quantities, or to replace when they run out; materials may have to be paid for so that poor quality photocopies are used. A comprehensive and renewable resource of basic information materials for use by centres and counsellors is under development.

9.4 Requirements

In each country one designated centre for health education for haemoglobin disorders is needed, with the resources to:

(a) Write and produce a range of appropriate, high-quality information materials on treatment and prevention of the haemoglobin disorders (WHO and TIF materials may be used as a starting-point)

(b) Develop other materials suited to the needs of the population (e.g., videos)

(c) Continually update information materials, as methods for treatment and prevention develop, experience is gained, and public awareness increases.

10. EVALUATION

A programme has two main targets: all patients should benefit from the best possible treatment, and all at risk couples should be identified and offered informed reproductive choice before they have an affected child. Progress towards these targets should be evaluated at a national level, and programme monitoring should be an integral part of a national programme. The health service structure may be favourable or unfavourable for such co-operative activities; it may be necessary for the Ministry of Health to request evaluation for it to be carried out. A unit capable of performing evaluation needs to be identified and supported appropriately.

The most powerful tools for evaluation are registers of patients and prenatal diagnoses (see below). A national patient register keeps the organisers of a national programme in touch with the great majority of doctors treating patients, and creates a network that can be used to inform them of advances in treatment and prevention, and to disseminate eg. WHO-sponsored management protocols, standard record systems, information materials for patients and newsletters from support groups. Ideally there should be an annual meeting of participants in the network. It is proposed that steady improvements in quality of care can be brought about in this way.

10.1 Methods

Collect epidemiological data in order to define numbers and distribution of people requiring the service, and to generate projections of future need as outlined in Section 3.2.

Describe the structures and services presently available. Is there:

a national co-operative group?
a support association?
recognised haemoglobinopathy centres?
reference laboratories?, etc.
What is the level of activity of each?

Initiate national registers of patients, and prenatal diagnoses.

Evaluate quality of patient diagnosis. The calculated birth rate is compared with the observed birth rate using the patient register. A deficiency of known patients indicates under-diagnosis.

Evaluate Treatment. Some very simple indicators can be used as a broad guide to the quality of treatment in the country. For example information on the amount of blood provided annually for thalassaemia nation-wide may be obtained from blood banks, and compared with the estimated requirement. Similarly, figures on the amount of Desferal imported into the country annually may be obtained from the Government or Ciba-Geigy. The standard patients' record allows assessment of the mean haemoglobin maintained by transfusion, and other indicators of how far current recommendations are followed in treating thalassaemia (23).

Evaluate patient survival. WHO has shown that ***a regularly-updated patient register*** is a simple tool for evaluating treatment and prevention of haemoglobin disorders (5). Annex 4 gives suggestions for data that can usefully be included. Figure 4, the age-distribution of patients in the Italian National Register, illustrates this function. There are relatively few patients over 25 years old. This is not because most patients die at around 20: it is because effective management only became available about 25 years ago and severely affected children born before that time died in infancy. (Most Italian patients over 25 have thalassaemia intermedia, which allowed them to survive with minimal treatment in the past.) When the register is regularly updated, to the extent that older patients survive, the "leading" edge of the age distribution moves to the right, and is a measure of survival. Enquiries into the causes of deaths can be used to locate problems in treatment (37).

Evaluate prevention. If prenatal diagnosis is not available, it may be necessary first to investigate whether it is wanted or not. This can be done by interviewing the parents of affected children.

If prenatal diagnosis is available, its quality can be monitored through a register of prenatal diagnoses (including misdiagnoses and the causes). Relatively few diagnostic laboratories are involved in each country. As all keep good records and their data is usually complete and reliable, this information is relatively easy to collect.

The extent of informed reproductive choice can be assessed through the patient register. The "trailing" edge of the age distribution in Figure 4 shows the number of new patients born each year, and measures the effect of prevention (with a 2-year lag-time, as some patients do not present until they are 2-3 years old). New births, once identified, can be followed up with an enquiry into the surrounding circumstances, to see if parents had informed choice. A WHO pilot study showed that for thalassaemia, the majority of new births were associated with lack of awareness of the potential problem and failure to screen and inform on the part of the doctor, rather than refusal of prenatal diagnosis on the part of the parents (5). The objective of maintaining registers is to report back to collaborating doctors, so that deficiencies in service delivery can be corrected.

10.2 Cost/benefit analysis

The aim of cost-benefit analysis is to describe the financial and non-financial costs and benefits of services, and to determine the most efficient ways to deliver them. Figure 5 compares the costs and benefits of the minimalist approach to treating thalassaemia that is common in many less developed countries (low transfusion and no splenectomy) with the management recommended by WHO (high transfusion and splenectomy when blood consumption rises above the standard level). In this example involving siblings, the low-transfused older sibling suffered chronic ill-health and was only two-thirds the size of the younger high-transfused sibling, but had required twice as much blood by the time she died at 8 years of age. The high transfused sibling survives in good health

at 14 years of age. The blood given to the high transfused sibling has been used over twice as effectively in health terms, as that given to the low-transfused child, which has been largely wasted. (The figure is intended to demonstrate a non-financial method of cost-benefit analysis, not to answer all questions related to transfusion policy.)

A full cost-benefit analysis can be difficult and time-consuming (38). Often as a short-cut, only financial costs and savings are considered i.e., only a cost analysis is done. The projections of patient numbers described in Section 3.2 and the estimates of treatment costs in Section 5 can be used to perform cost analyses of services for haemoglobin disorders. In almost every country the number of living patients with haemoglobin disorders is increasing because of improved survival, and as treatment is expensive future projections for service requirements can be quite alarming. The results of cost analyses therefore usually strongly support provision of prenatal diagnosis within the health service, because it reduces the number of affected children born, and increases the possibilities for treating those who already exist.

However, this type approach can cause misunderstandings because it may seem to imply that prenatal diagnosis is an alternative to patient management, rather than as a complementary aspect of a control programme. It is therefore necessary to take care to present cost analyses sensitively, taking into account the non-financial costs and benefits of a prevention programme. Outstanding benefits are an informed population, informed choice for couples at risk, the birth of healthy infants or of accepted affected ones, and replacement of affected fetuses with healthy infants (38).

10.3 Requirements

It is necessary for one or more designated individuals to be responsible for collecting epidemiological data and maintaining registers of patients and prenatal diagnoses - an appropriate role for a programme co-ordinator. The person carrying out this function must be acceptable to colleagues and the work requires support by the public health authorities.

Cost/country for evaluation

½ doctor; ½ clerical assistant
computer, software, and programming advice
running costs: office and travel
an annual or biennial national meeting

11. SUMMARY OF REQUIREMENTS FOR A CONTROL PROGRAMME FOR HAEMOGLOBIN DISORDERS

A control programme for haemoglobin disorders involves health workers, patients' and parents' support associations, and the whole community. Because of its scope and complexity, involvement of the public health authorities and rational planning are required.

TREATMENT

Requirements for treating 100 patients with thalassaemia

		Cost, US$/year
Staff	1 doctor, 3 nurses, 1 technologist, 1 counsellor/ psychologist, 1 secretary/administrative assistant.	7 salaries
Blood	500-1,500 litres/year	differs locally
Filters	1,200-1,800/year	17,000-36,000
Desferal	av 45 mg/kg/day	120,000-540,000
Disposables	infusion sets, syringes, needles, water, 30,000/year	

Endocrine replacement therapy

Additional immunisations (Hepatitis B, Pneumovax)
Interferon therapy for chronic active hepatitis

One-off	100 pumps	38,500-58,300
Bone marrow transplantation/patient		30,000-75,000

Treating thalassaemia in less developed countries

It is possible to provide the following in most situations.

- Staff - Senior doctor in charge; clinical assistance; clerical help especially in organising transfusions, contacting families and keeping records
- Basic blood taking facilities
- Basic laboratory facilities
- Treatment protocol
- Standard patient records, and yearly analysis to identify problems
- 6-monthly measurement of height and weight
- Regular transfusion (monthly or more often) with safe blood to maintain a mean Hb of 12g/dl. Maintaining a lower haemoglobin level in order to save blood is a false economy
- Control of transfusion reactions by anti-histamines and steroids
- Immunizations; especially against hepatitis B
- Ferritin estimation annually

Desferal. Even when Desferal is not available, high transfusion should be provided in a spirit of optimism, because of its effect in improving quality of life

for the child and the family. In addition, the evolution of iron overload is slow, and research on cheaper, oral, iron chelating drugs is promising.

Requirements for treating 200 patients with Sickle Cell Disorders

Requirements for day hospital, in-patient and out-patient care for a "unit" of 200 patients, either adults or children but not mixed. (Based on experience in London and Paris).

Staff = 7 salaries

2 doctors
2 nurses
1 technologist equivalent, (divided between haematology, blood banking, and biochemistry)
1 counsellor/psychologist
1 secretary/administrative assistant
access to a social worker

Management Protocols. WHO documents available include Guidelines for the Management of Sickle Cell Disorders (20). Specific protocols are required for casualty departments, to ensure rapid appropriate treatment, especially of pain.

(a) *Out-patient* visits should include physical examination, measurement of height and weight, blood count, urine tests, check-ups for eyes and bones, penicillin, pneumovax, dressings for ulcers, etc.). The recommended frequency of out-patient visits depends on age as follows:

Younger than 6 months	every 4-8 weeks
6 months to 5 years	every 3-6 months
Older than 5 years	every 3 months-1 year

Average cost = US$ 250-500/patient/year

(b) Basic in-patient care: 85% of patients need only out-patient visits plus basic in-patient care when indicated for vaso-occlusion, aplastic crisis, infections etc. Average cost = US$ 2,500-5,000/patient/year.

Additional problems

(c) 5-10% of patients require regular transfusion for stroke, pulmonary hypertension, etc. at US$ 25,000/patient/year.

(d) 10% of patients have an exceptional problem eg. require splenectomy, or elective orthopaedic or abdominal surgery, or incur pregnancy-related costs etc., at US$ 8-10,000/year.

Estimated total annual costs for 200 patients		
200 x a	=	US$ 50,000-100,000
170 x b	=	US$ 425,000-850,000
10 x c	=	US$ 250,000
20 x d	=	US$ 160,000-200,000
TOTAL	=	US$ 885,000-1,400,000

Average/patient/year = US$ 4,425-7,000.

Treating sickle cell disorders in less developed countries

In most situations it is possible to provide basic out-patient care as in (a) above. However, the possibilities of in-patient care may vary very much. In Jamaica Dr Serjeant's research unit provides only out-patient care. It follows 4,000 patients and manages 2,000 regularly with a staff of 6 doctors (2 for adults and 4 for children). The unit budget (including research costs) is US$ 600,000 = about US$ 300/patient/year.

Requirements for neonatal screening for sickle cell disorders

Laboratory costs vary depending on method (cellulose acetate/agar electrophoresis or isoelectric focusing) number of tests etc. In the UK in 1988, cost for 1,000 neonatal samples (including equipment, maintenance, reagents, technologist's time, and repeat tests) was US$ 500-800 (US$ 0.5-0.8/sample).

Laboratory costs are thought to represent less than a third of the total cost of neonatal screening. Costs of collecting samples, transport, reports, administration, information, counselling, follow-up and family studies, training, quality control, rent of premises etc must also be taken into account.

CARRIER SCREENING

Example from Greece, of a dedicated screening unit dealing with testing and counselling for 250-500 samples per week (13,000-26,000/year). All samples have indices, electrophoresis and HbA_2 estimation.

Staff (30-hour week): 1 doctor, 1 nurse, 1 biochemist, 4 technicians, 1 secretary, 1 cleaner. = 9 salaries

Cost including personnel = US$ 260,000/year: i.e., US$ 20-30/test.

If HbA_2 is measured only on samples with MCH <27 pg, as in the UK, costs per sample are less.

Screening in less developed countries

Costs can be reduced very considerably by using simple preliminary screening tests. A 1-tube osmotic fragility test can be used to identify

individuals who may have ß thalassaemia trait or iron deficiency, a simple 1 tube sickling test to pick up HbS, and a basic turbidity test for HbE.

COUNSELLING

Counselling carriers

Because of the large number of variables it is only possible to give examples. In Sardinia (population 700,000, average 12% heterozygotes) 4 doctors and 4 nurses deal with counselling associated with about 100 tests and 13 carriers detected daily, and referrals from other doctors.

The Brent Sickle Cell Centre (UK) requires 5 nurses for counselling associated with universal neonatal and antenatal screening in a mixed population of 3.5 million, average 3% heterozygotes. They have about 500 counselling sessions a year including 20-30 at-risk couples.

In Cyprus, due to a long-standing education programme the population and health professionals understand the implications of thalassaemia. Results are sent by letter and single carriers rarely require specialist counselling as they can discuss problems with their own doctor. Individual counselling is offered for unusual carrier states.

Counselling at risk couples

This should always be done by experts (not necessarily doctors). For example in Sardinia two doctors see 350 at risk couples per year. In Athens one social worker counsels 500 at-risk couples per year. In Cyprus, all at-risk couples are counselled by doctors who are also responsible for the care of thalassaemic patients, one at each of the three main thalassaemia centres.

The cost of counselling carriers and at risk couples = the salaries of the above staff, transport if necessary, secretarial support, and educational materials for health workers, carriers and the general population. Costs of training health workers in carrier counselling should be part of the programme budget.

PRENATAL DIAGNOSIS

Obstetric prenatal diagnosis service

Staff

2 obstetricians trained in fetal medicine (ultrasound diagnosis and a variety of fetal sampling techniques) (part time)
1 ultrasound operator
1 nurse

High quality ultrasound equipment
Sampling equipment (disposable and re-usable)
Suitable sterile facilities for fetal sampling
Suitable facilities for termination of pregnancy in the first and second trimesters
Bereavement counselling for women undergoing termination of pregnancy.

Laboratory prenatal diagnosis service

For a dedicated service carrying out 100-500 prenatal tests/year (example of Sardinia).

Staff

1 director of the unit
A counsellor (nurse-specialist, social worker or other)
1 molecular geneticist
1 technician per about 100 tests/year, including family studies

Appropriate equipment. Automated PCR machines are essential.

Restriction enzymes, DNA polymerase and DNA probes.

EDUCATION

In each country one designated centre for health education for haemoglobin disorders is needed, with the resources to:

(a) Write and produce a range of appropriate, high-quality information materials on treatment and prevention of the haemoglobin disorders (WHO and TIF materials may be used as a starting-point).

(b) Develop other materials suited to the needs of the population (e.g., videos).

(c) Continually update information materials, as methods for treatment and prevention develop, experience is gained, and public awareness increases.

EVALUATION

Cost/country

- doctor at 50%; clerical assistant at 50%
- computer, software, and programming advice
- running costs: office and travel
- an annual or biennial national meeting.

12. REFERENCES

1 WHO 1985. Report of a WHO Advisory Group on Hereditary Diseases (HMG/WG/85.10).

2 WHO 1983. Community control of hereditary anaemias: Memorandum from a WHO meeting. 1983. Bulletin of the World Health Organisation 61:63-80.

3 WHO 1992. Modell B, Kuliev AM, Wagner M. Community Genetics Services in Europe. WHO Regional Publications, European Series No 38. WHO Regional Office for Europe.

4 WHO 1985. Report of the Third and Fourth Annual Meetings of the WHO Working Group for the Community Control of Hereditary Anaemias. (HMG/WG/85.8).

5 WHO 1987. Report of the Vth WHO Working Group on the Feasibility Study on Hereditary Disease Community Control Programmes, Herakleion, Crete, 24-25 October 1987 (WHO/HDP/WG/HA/87.5).

6 WHO 1989. Report of the VIth WHO Working Group on the Feasibility Study on Hereditary Disease Community Control Programmes (Hereditary Anaemias), Cagliari, Sardinia (WHO/HDP/WG/HA/89.2).

7 WHO 1993. Report of a joint WHO/TIF Meeting on the Prevention and Control of Haemoglobinopathies, Nicosia, Cyprus, 3-4 April 1993 (WHO/HDP/TIF/WG/93.1).

8 Angastiniotis MA, Hadjiminas MG. Prevention of thalassaemia in Cyprus. Lancet 1; 369-370, 1981.

9 Angastiniotis MA, Kyriakidou S, Hadjiminas M. How thalassaemia was controlled in Cyprus. World Health Forum 7:291-297, 1986.

10 WHO 1987. The Haemoglobinopathies in Europe. WHO Regional Office for Europe, unpublished document IPC/MCH 110.

11 Livingstone FA. Frequencies of haemoglobin variants. Oxford University Press, New York and Oxford, 1985.

12 Modell B, Bulyzhenkov V. Distribution and control of some genetic disorders. World Health Statistics Quarterly 41:209-218, 1988.

13 Modell B, Benson A, Payling-Wright CR. 1972. Incidence of Beta thalassaemia trait among Cypriots in London. British Medical Journal ii:737.

14. Modell B, Berdoukas VB. The clinical approach to thalassaemia. Grune & Stratton, 1984.

15 Modell B, Kuliev AM. Social and genetic implications of customary consanguineous marriage among British Pakistanis. Galton Institute Occasional Papers, Second Series, No 4, 1992. The Galton Institute, 19 Northfields Prospect, Northfields, London SW18 1PE, UK.

16 Darr A, Modell B. The frequency of consanguineous marriage among British Pakistanis. Journal of Medical Genetics 25:186-190, 1988.

17 Cao A, Gabutti V, Masera G, Modell B, Sirchia G, Vullo C, Wonke B. 1992 Management Protocol for the Treatment of Thalassemia Patients. Obtainable from Cooley's Anaemia Foundation, 105 East 22nd St, New York, NY 10010, USA and the Thalassemia International Federation, PO Box 8503, Nicosia, Cyprus.

18 Serjeant GR. Sickle Cell Disease. Oxford University Press. Oxford, New York, Tokyo. 2nd edition, 1992.

19 Davies SC, Brozovic M. The presentation, management and prophylaxis of sickle cell disease. Blood Reviews 3:29-34, 1989.

20 WHO 1991. Brozovic M, Stephens A. Guidelines for the Management of Sickle Cell Disease (WHO/HDP/SCD/GL/91.2).

21 WHO 1992. Quality Assurance in Haematology (WHO/LBS/92.4).

22 Vullo C, Modell B. What is Thalassaemia? The Thalassaemia International Federation. Obtainable from most Thalassaemia Associations, and the Thalassemia International Federation, PO Box 8503, Nicosia, Cyprus.

23 Rebulla P, Modell B. Transfusion requirements and effects in patients with thalassaemia major. The Lancet 337:277-280, 1991.

24 Neonatal screening for sickle cell disease. Pediatrics 83:Supplement, 1989.

25 Bianco I, Graziani B, Lerone M, Congedo P, Ponzini D, Braconi, Aliquo C. A screening programme for the prospective prevention of mediterranean anaemia in Latium: results of seven years' work. Journal of Medical Genetics 21:268-271, 1984.

26 Ostrowsky JT, Lippman A, Scriver CR. Cost-benefit analysis of a thalassemia disease prevention programme. American Journal of Public Health 75:732-736, 1985.

27 Cao A, Rosatelli C, Galanello R. Population-based genetic screening. Curr. Opinion in Genetics and Development, 1:48-53, 1991.

28 Kattamis C, Efremov G, Pootrakul S. Effectiveness of one-tube osmotic fragility screening in detecting ß-thalassaemia trait. Journal of Medical Genetics 18:266-270, 1991.

29 Cao A, Rosatelli. Screening and prenatal diagnosis of the haemoglobinopathies. Balliere's Clinical Haematology 6, 1993 (in press).

30 Galanello R, Ruggieri R, Addis P, Paglietti E, Cao A. Hemoglobin A_2 in iron deficiency ß-thalassemia heterozygotes. Hemoglobin 5:613-618, 1981.

31 Fletcher JC, Berg K, Tranoy KE. 1985. Ethical aspects of medical genetics. A proposal for guidelines in genetic counselling, prenatal diagnosis and screening. Clinical Genetics 27:199-205, 1985.

32 Cao A, Cossu P, Monni G, Rosatelli C. Chorionic villus sampling and acceptance rate of prenatal diagnosis. Prenatal Diagnosis 7:531-533, 1987.

33 Petrou M, Brugiatelli M, Ward RHT, Modell B. Factors affecting the uptake of prenatal diagnosis for sickle cell disease. Journal of Medical Genetics, 29:820-823, 1992.

34 WHO 1992. Report of a WHO Consultant on Current Trends in Prenatal Diagnosis (WHO/HDP/CONS/92.5).

35 WHO 1990. Educational Materials on the Thalassaemias (WHO/HDP/HB/EMT/93.6).

36 Akinyanju OO, Anionwu EN. Training of counsellors on sickle cell disorders in Africa. The Lancet i:653-654, 1989.

37 Zurlo MG, De Stefano P, Borgna-Pignatti C, Di Palma A, Piga A, Melevendi C, Di Gregorio F, Burattini MG, Terzoli S. Survival and causes of death in thalassaemia major. The Lancet ii:27-30, 1989.

38 Drummond MF. Principles of economic appraisal in health care. Oxford Medical Publications. Oxford University Press, Oxford/New York/Toronto Melbourne. 1980.

Table 1

THE MAJOR HAEMOGLOBIN DISORDERS

Alpha globin chain disorders	Beta globin chain disorders
Alpha thalassaemias	Sickle cell disorders:
Haemoglobin H disease Alpha thalassaemia hydrops fetalis (= Hb Bart's hydrops fetalis)	. Sickle cell anaemia (Hb SS) . Haemoglobin S/ß thalassaemia . Haemoglobin SC disease . Haemoglobin SD disease . other rare sickling disorders
	Beta thalassaemias:
	. ß thalassaemia major . ß thalassaemia intermedia . Hb E/ß thalassaemia . other rare thalassaemias

Table 2

Amounts of blood required to maintain a mean haemoglobin of 12g/dl in a transfusion-dependent thalassaemic patient

Splenectomy status	Donor blood ml/kg/year	Prepared whole blood ml/kg/year	Pure red cell equivalent ml/kg/year
Splenectomised patient	300	360	135
Unsplenectomised patient	375	450	170

Table 3

Basic annual requirement for treating one patient with thalassaemia major, related to age

Age group	Mean wt Kg	Units of donor blood/year *	Desferal Kg (at 45 mg/kg/d)	Desferal Cost US$ (at US$ 12/gram **)
1-5	15	10	0.22	2,600
6-10	25	17	0.37	4,400
11-15	40	27	0.58	7,000
16-21	55	37	0.8	9,600
Adult	60	40	0.88	10,500

* at minimum requirement of 300 ml/kg/years. 1 unit = 450 ml donor blood

** 1993 Cost of Desferal, depending on area = US$ 4.2-6/500mg vial

Table 4

REQUIREMENTS FOR GENETIC POPULATION SCREENING

(1) Agreed policy with a sound research basis.

(2) Adequate diagnostic facilities.

(3) Information for the population.

(4) A system for collecting samples from a cohort of the population prior to reproduction, and delivering them to a laboratory.

(5) A network of diagnostic laboratories with a quality control system.

(6) A system for reporting results to doctors and "patients".

(7) An information storage and retrieval system.

(8) Information and counselling for carriers.

(9) Facilities for counselling at-risk couples and providing prenatal diagnosis.

(10) A monitoring (or audit) system.

Table 5

Needs for information and counselling at different stages in screening

Stage	Requirement
Sensitising the population to the existence of the problem and the value of screening	Basic information on the test its possible implications and its optional nature, by a trained health worker
Carriers detected	Clear written information Face-to face explanation when possible with a trained health worker
Couples at risk carriers of unusual mutations	Discussion with an expert genetic or haemoglobinopathy counsellor Clear written information

Table 6

POSSIBILITIES OPEN TO CARRIERS OF AN INHERITED DISEASE, TO AVOID HAVING AFFECTED CHILDREN

TIME OF DISCOVERING RISK	POSSIBLE ACTION
Before marriage (uncommon)	1. Remain single (uncommon). 2. Avoid selecting another carrier as partner (very uncommon). 3. Select partner in the usual way. (the commonest choice).
After marriage (more common)	4. Remain childless (common only for severe disease when PND[1] impossible). 5. "Take the chance" (common for less severe diseases). 6. Use prenatal diagnosis (very common). 7. Use AID[2] or other form of "assisted reproduction" (very uncommon). 8. Separate and find another partner (very uncommon indeed).
After birth of an affected child (commonest)	Options 4-8 above for further reproduction, plus: 9. Accept infant and treatment (usual). 10. Accept infant, but reject treatment (occasional). 11. Reject infant (can happen).

[1] PND = Prenatal diagnosis
[2] AID = Artificial insemination by donor

Table 7

EDUCATIONAL AIDS REQUIRED FOR A HAEMOGLOBINOPATHY CONTROL PROGRAMME

1. Poster to inform people of the existence and nature of the disorder.
2. Simple information leaflets to encourage requests for testing.
3. Information booklet for carriers.
4. Detailed booklet for families and patients.
5. Guidelines on management (for doctors).
6. Guidelines on screening and counselling (for doctors and nurses).

Information available from The Hereditary Diseases Programme, WHO

1. Educational materials for carriers of (a) alpha-thalassaemia and (b) beta-thalassaemia.
2. Information about prenatal diagnosis for (a) thalassaemia major and (b) sickle cell disorders.
3. Guidelines on the Management of Sickle Cell Disorder.
4. Information for the Community:
   Posters
   Counselling booklet for single heterozygotes
   Counselling booklet for married couples of heterozygotes
   Cartoon book for young thalassaemic patients
   A treatment record book for thalassaemic patients
   A booklet on consanguineous marriage

   Information for Professionals:
   Screening for heterozygotes
   Consanguineous marriage: booklet for counsellors

Information available from the Thalassaemia International Federation (TIF)

1. What is thalassaemia? (A detailed booklet for families and patients) (by R. Vullo and B. Modell).
2. 1992 Management Protocol for the Treatment of Thalassaemia Patients (A. Cao, V. Gabutti, G. Masera, B. Modell, G. Sirchia, C. Vullo, B. Wonke).
3. 100 Questions sur la Beta-Thalassemie (R. Girot) - in French.
4. TIF Newsletter.

* * * * *

LEGENDS FOR FIGURES

1. Outline of the components of a programme for the control of haemoglobin disorders.

2. Curve showing the relationship of carrier frequency (% of the population) to the birth-rate of affected infants (births/1,000). The lower curve shows the relationship in populations where consanguineous marriage is uncommon. The upper curve shows the theoretical relationship if all marriages were between first cousins. If the proportion of first cousin marriages in a population is known, the affected birth rate can be calculated using both curves. For example, if the frequency of thalassaemia trait in the population is 6% the affected birth-rate is about 0.9/1,000. However, if 50% of marriages are between first cousins, 50 of the difference between the two curves must be added: in this case the affected birth incidence should be about 2.6/1,000.

3. The basic "haemoglobinopathy screen".

4. The age distribution of Italian patients with thalassaemia major, derived from the Italian national patient register. The figure shows the year of birth of the patients. The arrow indicates that as the register is regularly updated, the patient cohort moves to the right. The progress of the "leading edge" can be used to monitor survival, the progress of the "trailing edge" can be used to monitor prevention.

5. An example of non-financial cost-benefit analysis of two different treatment policies for thalassaemia. The "minimal intervention" policy common in many developing countries is (a) to give blood only when the haemoglobin is very low with the objective of minimizing blood consumption, and (b) to maintain a conservative policy on splenectomy because of fear of infections. The policy recommended by WHO involves high transfusion to maintain a normal haemoglobin level and prevent hypersplenism. The two policies were compared in Thai siblings with thalassaemia major. When high transfusion was first tested in Thailand, it was first tried in younger siblings of patients already on the "conventional" low transfusion scheme. The results in the siblings described here were typical for the whole group. The younger high-transfused sibling required more blood than her low-transfused sister only in the first year of treatment. Her blood consumption has remained constant and she remains in good health at 14 years old. She was started on Desferal treatment at 8 years of age. The low-transfused sibling's blood requirement increased steadily with time as her spleen enlarged. When she died of anaemia aged 8 years, her growth was stunted (she was only two-thirds as heavy as her sister at the same age) and had consumed twice as much blood as her sister. Data kindly provided by Professor Voravarn Tanphaichitr.

* * * * *

Components of Genetic Services Needed at National or Regional Level

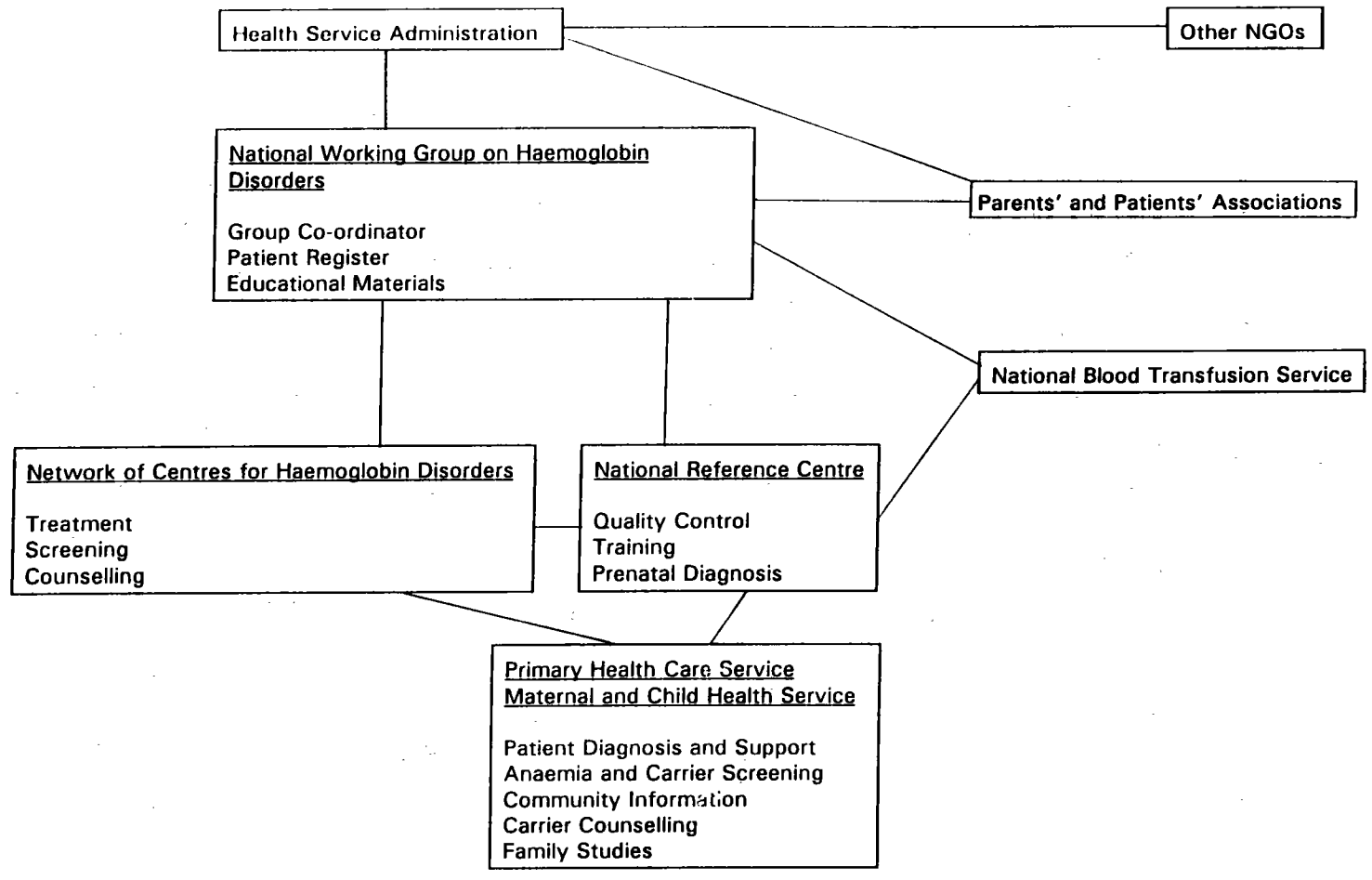

FIG. 1

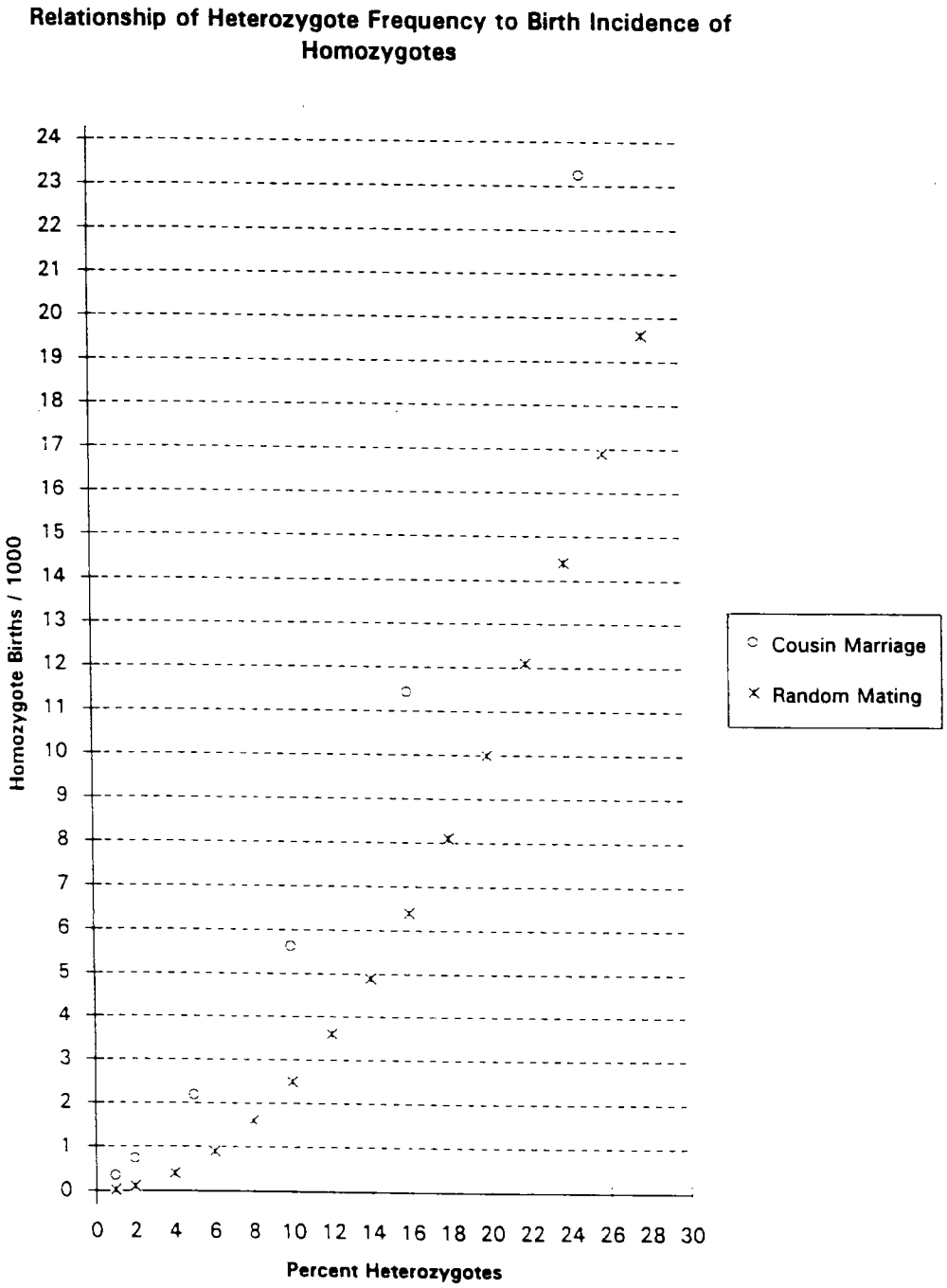
Relationship of Heterozygote Frequency to Birth Incidence of Homozygotes
Homozygote Births / 1000
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Percent Heterozygotes
Cousin Marriage
Random Mating

FIG. 2

THE HAEMOGLOBINOPATHY SCREEN

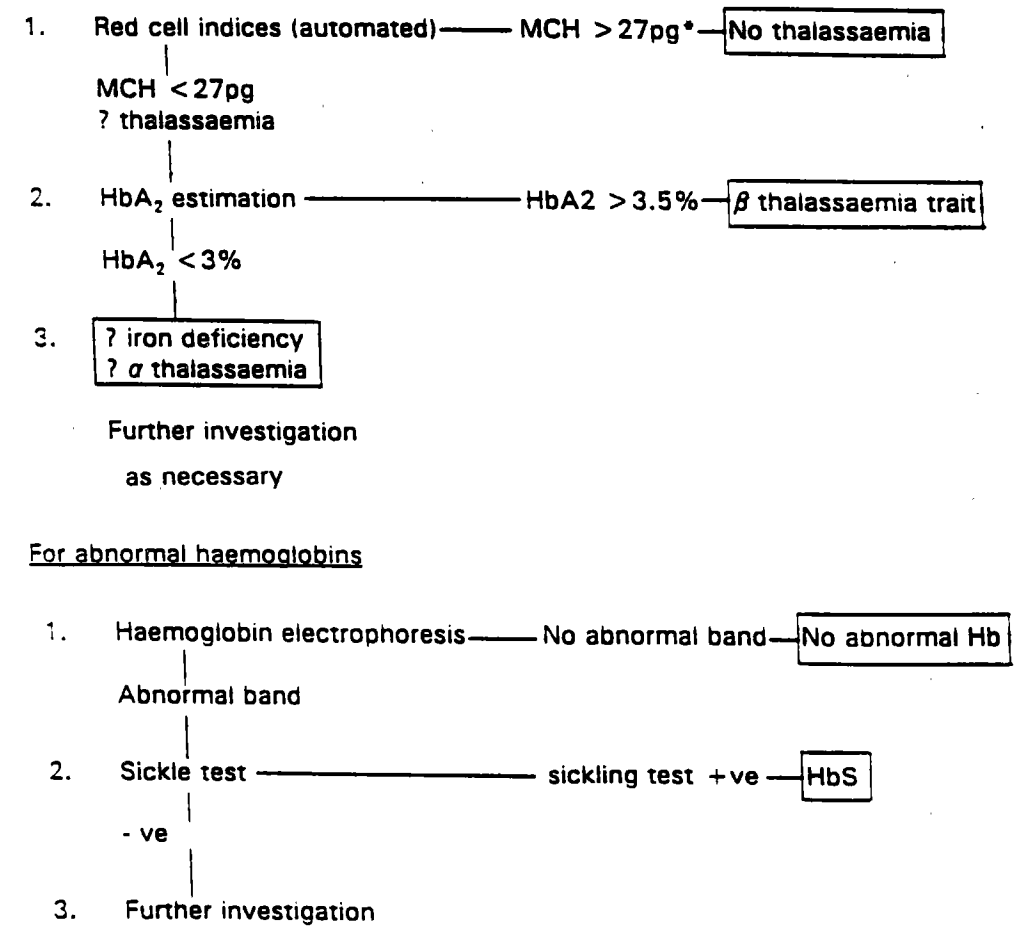

Fig. 3

Age Distribution of Italian Patients

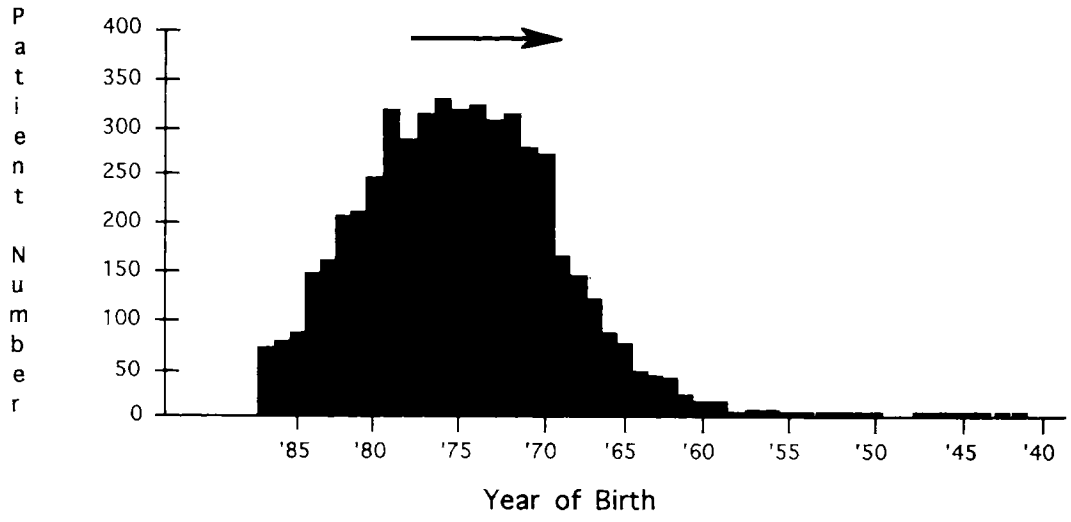

FIG. 4

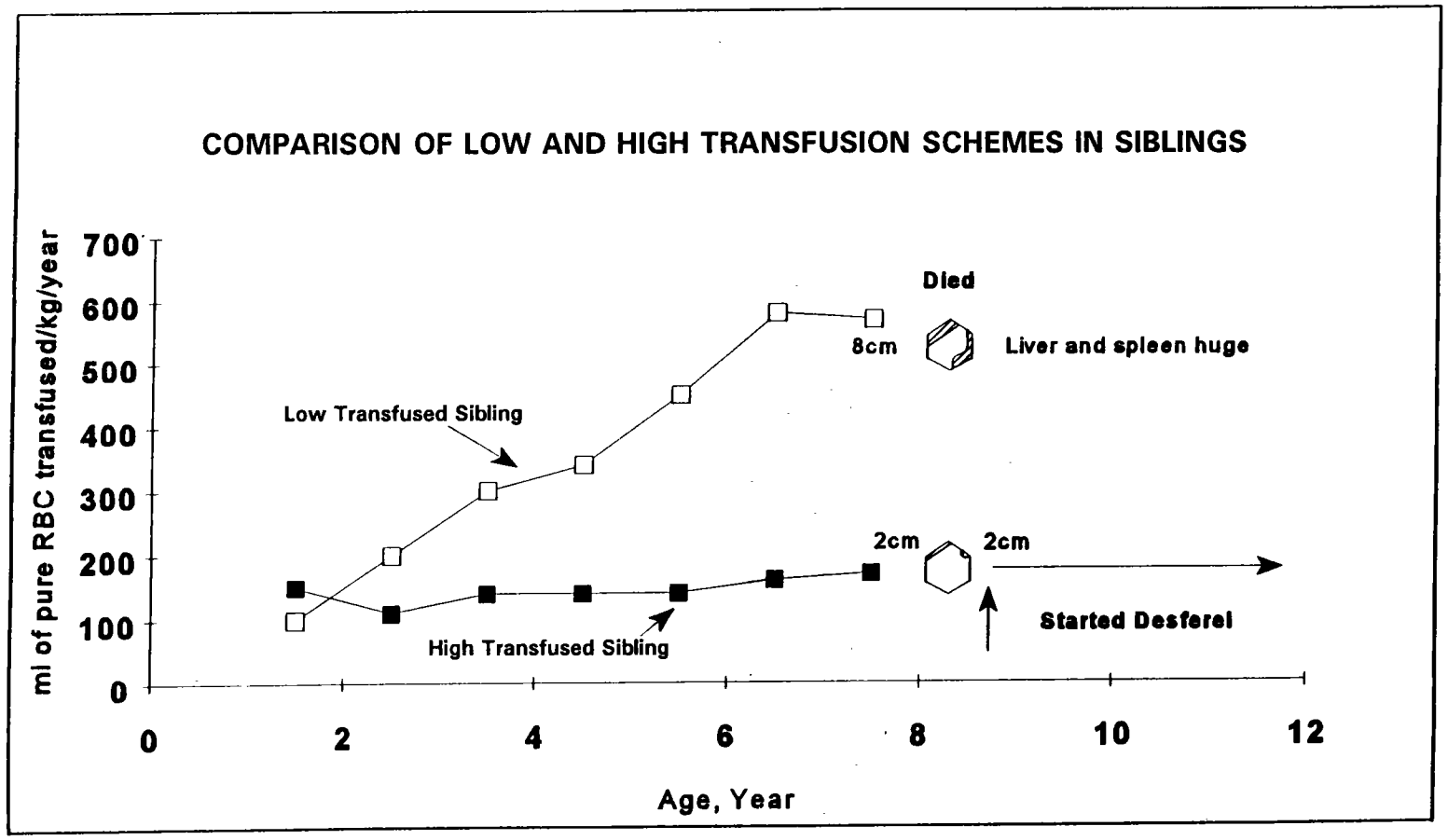
COMPARISON OF LOW AND HIGH TRANSFUSION SCHEMES IN SIBLINGS
ml of pure RBC transfused/kg/year
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
Age, Year
Died
8cm
Liver and spleen huge
Low Transfused Sibling
2cm
2cm
Started Desferel
High Transfused Sibling

FIG. 5

ANNEX 1

UPDATED ESTIMATES OF THE FREQUENCY OF THE HAEMOGLOBIN DISORDERS IN EACH COUNTRY

Summary of Global Distribution of Major Haemoglobin Disorders

The Global Summary Table on page 5 indicates that at least 4.5% of the world population carry a significant haemoglobinopathy trait, and the global birth rate of infants with a major Hb disorder is at least 2.0/1 000.

1. General principles

These tables present cautious estimates based on existing information, some of which may be inaccurate. Demographic data is from the 1991 United Nations Demographic Year Book. Figures for carrier frequency are based on the published survey data collected by Livingstone (see ref. 11), unpublished data provided by many colleagues, and calculations according to the Hardy-Weinberg equation:

$$p^2 + 2pq + q^2 = 1$$

The Hardy Weinberg equation is based on the gene frequency, where

p = the Hb A gene frequency
q = the haemoglobinopathy gene frequency.

Usually $q = 1-p$.

The Hardy-Weinberg equation derives the birth incidence of the different gene combinations in the population from the gene frequencies as follows:

p^2 = the frequency of homozygotes without haemoglobinopathies
$2pq$ = the frequency of heterozygotes
q^2 = the frequency of homozygous with haemoglobinopathies

Example;

q = 0.085
p = 1-.085 = 0.915
q^2 = 0.0072 = proportion of homozygotes at birth
= .72%
or 7.2/1,000
$2pq$ = 0.1555 = proportion of heterozygotes at birth = 15.6%
p^2 = 0.8372 = proportion of normals at birth = 83.7%

However, if the percentage of heterozygotes in a population is known and the frequency of the gene is not high, an approximate frequency of such a recessive gene can be calculated as a half frequency of the heterozygotes who carry it (Cavalli-Sforza, Bodmer, 1971). Figure 2 gives the homozygote birth

rate in relation to carrier frequency based on this calculation. It can be used to estimate affected birth rate rapidly.

These equations hold true only if there is essentially "random" mating in the population. Corrections for frequent consanguineous marriage can also be made from Figure 2.

The figures given in the tables should be viewed as approximations: in many cases it would be desirable to confirm them by further studies. Tables are presented in the United Nations style, each country being listed alphabetically within the African, American, Asian, European, and Oceania Regions.

The birth rate of homozygotes or compound heterozygotes has been calculated for each country, from the known heterozygote frequency. The calculations take account of the effects of: (a) the coexistence of two or more haemoglobinopathy alleles in a population; (b) uneven distribution of populations particularly at risk; and, (c) the existence in many populations of a tradition of consanguineous marriage.

Figure 2 shows the standard relationship between heterozygote frequency and the birth rate of homozygotes, when there is random mating and when cousin marriage is common. It is used as in the legend.

2. The Regional Tables show:

   1. Population size and presence of consanguineous mating.

   2. Present information on the frequency of different ß-haemoglobinopathy alleles. When conflicting information is available, the lowest figure within a reasonable scientific basis has been used, to avoid over-estimates. Future improved surveys are likely to increase the estimates proposed for some countries, such as Pakistan.

   3. The estimated frequency of homozygote births per 1,000, calculated using the above approach. In populations where HbC or HbE are common, since homozygous HbC, HbC/ß-thalassaemia and homozygous HbE are asymptomatic states, the number of homozygotes with a major pathological syndrome is expressed separately. This is taken as the significant figure.

   4. The estimated number of births of infants with each type of major syndrome.

The figures for the European Region have been calculated differently. Because the haemoglobinopathies are found among the ethnic minorities of North-west European countries, the calculation is based on the size of these groups in the different countries and on the known or probable frequency of haemoglobinopathy genes in these groups. This subject has been considered separately by the WHO European/Mediterranean Working Group (see ref. 10).

The problems inherent in this type of calculation may be illustrated by reference to Africa and America.

In Africa there are some remarkable limitations in the information available. For instance, there has been no good large-scale survey of the frequency of thalassaemia in Egypt, while the Sudan illustrates the difficulty of dealing with a large country. Since the frequency of sickle cell trait varies greatly, with a minimum towards the East and a maximum towards the West, but there has been no micro-mapping, it is impossible to make even reasonable estimates of the number of affected births for the whole country.

Consanguineous marriage is common in North Africa. It has been estimated that this marriage pattern approximately doubles the birth-rate of affected children in the countries where it is common. Most offspring of consanguineous marriages would be homozygous for the gene in question. This has been allowed for by estimating that approximately 50% of the affected children are the offspring of consanguineous marriages (and will therefore be homozygous) and that the other 50% will be the offspring of random mating.

For convenience, East and South Africa has been divided into three areas: a north-eastern area including Ethiopia and Somalia; a southern area, including South Africa,, Botswana, Lesotho and Swaziland where haemoglobin disorders are uncommon; and an intermediate area including all the remaining East African countries where sickle cell disorder is common. The numerical calculations relate only to the African population, but there is also a sizeable Asian population originating from India in East and South Africa, 3-6% of whom probably carry ß-thalassaemia trait. However, in the absence of fuller information about this population, actual figures for the births of thalassaemic children have not been proposed.

Probably the major limitation for Sub-Saharan Africa is the lack of information on the frequency of ß-thalassaemia trait. It probably occurs with a low frequency in other countries in addition to the Ivory Coast, Liberia, Upper Volta, Guinea and Guinea Bissau.

In North America information on haemoglobinopathies among the black population is sound. ß-thalassaemia occurs among Americans of Southern European and Asian origin, but with population mixing, the birth-rate of children with thalassaemia major is dropping. An increase may be expected following the recent influx of refugees from South-east Asia.

The populations of all the countries of central America are a mixture of Caucasian, Amerindian and Black. The Caucasian population of most central American countries originated from Spain and would be expected to have a frequency of ß-thalassaemia trait of 0.5% or less, so haemoglobin would be predominantly found among the black and mulatto populations. The approximate size of the "relevant" population is given in the tables. Most of the calculations are based on this sub-set of the population, and their birth-rate is assumed to be the same as the population average, though this is probably incorrect.

The populations of the South American countries are very complex: some have a substantial "black" population and some have none: and some have a 50:50 mixture of blacks and Asians originating from different parts of South Asia. The Caucasian population is also very mixed. In many countries people of Spanish origin predominate, but in Venezuela and Brazil the Caucasian population came mainly from Portugal where 1-3% of the population carry a haemoglobinopathy trait. In Brazil, Venezuela and Argentina there are also large groups of Italian extraction, 2-7% of whom may carry ß thalassaemia trait, depending on their place of origin; a conservative estimate would be about 3%. In the absence of further information, good estimates can be made for very few South American countries.

Sufficiently detailed data is available to deal with similar problems in a number of other large countries, where the haemoglobinopathy distribution is complex. Separate calculations (not shown here but available on request) have been made for Brazil, Saudi Arabia, India and Thailand.

GLOBAL SUMMARY TABLE

REGION	POPULATION MILLIONS	ANNUAL BIRTHS (THOUSANDS)	HETEROZYGOTES (THOUSANDS)	% OF POPULATION HETEROZYGOTE	ANNUAL HOMOZYGOTE BIRTHS		% OF AFFECTED BIRTHS	AFFECTED BIRTHS /1 000
					TOTAL	PATHOLOGICAL		
Africa (ß)	664.33	29,802	88,355.8	13.3	226,991	216,439	73.50	7.26
America (ß)	731.20	17,174	14,938.5	2.0	5,181	5,181	1.76	0.30
Asia: ß	3,149.94	83,487	117,465.0	4.1	105,978	57,875	24.13	0.85
a			12,966.0		13,186	13,186		
Europe (ß)	780.50	11,053	6,862.0	0.9	1,620	1,620	0.55	0.15
Oceana (ß)	26.82	524	351.0	1.3	174	174	0.06	0.33
	5,346.0	142,040	240,938.0	4.5	353,130	294,475	100.0	2.07

Over 4.5% of the global population carry a haemoglobinopathy trait.
The global birth rate of affected infants is over 2.0/1 000.

Almost three-quarters of affected births are in Africa.

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% OF POPOPULATION HETEROZYGOUS FOR				TOTAL HETS. x10³	HOMOZYGOTE BIRTHS PER THOUSAND		HOMOZYGOTE ANNUAL BIRTHS		% OF HOMOZYGOTE ANNUAL BIRTHS:				
				S	C	S Th	Total		Total	Total Path.	Total	Total Path.	CC & C/Th	SC	SS	S/Th	S Tm
North Africa																	
Algeria	25.66	35.5	911	1.0	0.7	2-3.0	4.0	1,026.4	0.8*	0.72*	729	656	10	7		16	67
Egypt	54.69	37.9	2,073	0.2	0.1	2.5	2.8	1,531.3	0.39*	0.37*	808	767	5	4		6	86
Libyan Arab Jamahiriya	4.71	44.0	207	2.0	0.5	1-2	4.0	188.4	0.8*	0.66*	166	137	18	38		18	27
Morocco	25.70	35.5	912	1.5	2.0	3.0	6.5	1,670.5	2.0*	1.2*	1,824	1,094	39	16		10	35
Sudan	25.94	44.6	1,157	2.25	-	4.0	6.25	1,621.5	2.0*	2.0*	2,314	2,314	-	37		25	37
Tunisia	8.36	31.1	260	2.3	+	3.0	5.5	459.8	1.5*	1.5*	390	390	-	32		24	44
Western Sahara	0.18	-	-					-									
Sub-total	145.24		5,520				4.5	6,497.9	1.13	0.97	6,231	5,358					
North-east Africa																	
Ethiopia	53.38	48.6	2,594	0	-	1.2	1.0	533.8	0.025	0.025	65	65	-	-	-	-	100
Somalia	7.69	50.1	385	0	-	-	-	-	-	-		-	-	-	-	-	-
Sub-total	61.07		2,979				+	533.8	-	0.02		65					
East Africa																	
Kenya	25.91	47.0	1,218	3-30	-	+	7.0	1,813.7	-	1.23		1,498	-	-	98	-	+
Malawi	8.56	56.3	482	8	-	+	8.0	684.8	-	1.6		771	-	-	98	-	+
Mozambique	16.08	45.0	724	1-40	-	+	10.0	1,608.0	-	2.5		1,810	-	-	100	-	-
United Republic of Tanzania	28.36	50.5	1,432	5-20	-	+	15.0	4,254.0	-	5.6		8,019	-	-	100	-	-
Uganda	19.52	52.2	1,019	9-20	-	+	16.0	3,123.2	-	6.4		5,706	-	-	98	-	+
Zambia	8.78	45.6	400	10-21	-	+	15.0	1,317.0	-	5.6		2,204	-	-	98	-	+
Zimbabwe	10.02	41.7	418	2-6	-	+	4.0	400.8	-	0.4		167	-	-	98	-	+
Sub-total	117.23		5,693			+	11.3	13,201.5	-	3.6		20,175	-	-			
South Africa																	
Botswana	1.35	48.5	65	0.5	-	-	0.5	6.8	-	0.006		+	-	-	98	-	-
Lesotho	1.83	40.8	75	-	-	-	-	-	-	-			-	-	-	-	-
South Africa	36.07	32.1	1,158	-	-	+	+	4.1	-	-		+	-	-	98	-	-
Swaziland	0.82	46.8	38	0.5	-	-	0.5	+	-	0.006			-	-	?	-	+
Sub-total	40.07		1,336	-	-	+	+	>10.9	-	-		+					
Islands																	
Cape Verde	0.38	37.9	14	6.0	-	-	6.0	22.8	-	0.9		13	-	-			
Comoros	0.57	47.5	27	2-4.0	-	-	4.0	22.8	-	0.4		11	-	-	100	-	-
Madagascar	11.49	45.8	526	2-20		-	10.0	1,149.0	-	2.5		1,315	-	-	100	-	-
Mauritius	1.09	20.7	23	2.0	-	2.0	4.0	43.6	-	0.8*		18	-	-	28	44	28
Réunion	0.61	23.5	14	2.0	-	2.0	4.0	24.4	-	0.8*		11	-	-	28	44	28
Sao Tome and Principe	0.12	35.0	4				16.0	19.2		6.4		26	+	+	+	+	-
Seychelles	0.07	25.1	2				1.5	1.1		0.06		0.1	-	-	100	-	-
Sub-total	14.33		610	-	-	-	9.0	1,282.9	-	2.29		1,394	-	-			

* Estimates from Hardy-Weinberg equation, multipled by 2, to allow for effects of customary consanguineous marriage.

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% OF POPULATION HETEROZYGOUS FOR					TOTAL HETS. x10³	HOMOZYGOTE BIRTHS PER THOUSAND		HOMOZYGOTE ANNUAL BIRTHS		% OF ANNUAL BIRTHS OF HOMOZYGOTES WITH:				
				S	C	STh	E	Total		Total	Total Path.	Total	Total Path.	CC & C/Th	SC	SS	S/Th	S Tm
Angola	10.30	47.2	486	25	-	-	-	25	2,575.0	15.6	15.6		7,582	-	-	100	-	-
Benin	4.89	49.2	241	22	10	-	-	32	1,564.8	25.6	23.0	6,170	5,543	10	42	48	-	-
Burkina Fasso	9.24	47.1	435	5-25	10-30	+	-	23	2,125.2	13.2	8.6	5,742	3,741	35	48	17	+	+
Burundi	5.26	47.6	268	10	-	-	-	10	562.0	2.5	2.5		670	-	-	100	-	-
Cameroon	12.24	47.5	581	5-25	+	-	-	15	1,836.0	5.6	5.6		3,254	-	-	100	-	-
Central African Republic	3.13	45.5	142	12	-	-	-	12	375.6	3.6	3.6		511	-	-	100	-	-
Chad	5.82	44.2	257	1-20	-	-	-	10	582.0	2.5	2.5		643	-	-	100	-	-
Congo	2.35	46.1	108	25	-	-	-	25	587.5	15.6	15.6		1,685	-	-	100	-	-
Equatorial Guinea	0.36	43.8	16	20	-	-	-	20	72.0	10.0	10.0		160	-	-	100	-	-
Gabon	1.21	39.4	48	25	-	-	-	25	302.5	15.6	15.6		749	-	-	100	-	-
Gambia	0.88	47.4	42	15	2-3	-	-	18	158.4	8.1	7.9	340	332	3	27	70	-	-
Ghana	15.51	44.4	689	12	12	+	-	24	3,722.4	14.4	10.8	9,922	7,441	25	50	24	+	+
Guinea	5 93	51.0	302	10-30	+	2	-	26	1,541.8	16.9	16.6	5,104	5,013	2	26	71	+	+
Guinea-Bissau	0.98	42.9	42	2-24	2	1	-	11	107.8	3.0	2.9	126	122	4	30	67	+	+
Ivory Coast	12.46	49.9	622	2-15	1-18	3-4	-	20	2,492.0	10.0	8.7	6,220	5,411	13	46	40	+	+
Liberia	2.71	47.3	128	15	1-2	3	-	20	542.0	10.0	9.9	1,280	1,267	1	18	80	+	+
Mali	9.51	48.7	463	10	0-10	-	-	18	1,711.8	8.1	6.4	3,750	2,963	21	49	30	-	-
Mauritania	2.04	46.2	94	5	-	-	-	5	102.0	0.63	0.63		59	-	-	100	-	-
Namibia	1.84	44.0	81	0-9	-	-	-	3	55.2	0.23	0.23		19	-	-	100	-	-
Niger	7.98	51.7	413	5-24	5-10	-	-	21	1,675.8	10.0	9.3	4,130	3,841	7	38	55	-	-
Nigeria	112.16	48.5	5,440	10-30	2-8	-	-	28	31,404.8	19.6	19.2	106,624	104,448	2	20	77	+	+
Rwanda	7.49	51.2	383	7	-	-	-	7	524.3	1.2	1.2		460	-	-	100	-	-
Senegal	7.53	45.5	343	5-20	2	-	-	16	1,204.8	6.4	6.3	2,195	2,161	2	23	75	-	-
Sierra Leone	4.26	48.2	205	17-30	3-4	-	-	26	1,107.6	19.6	19.2	4,018	3,936	2	20	78	-	-
Togo	3.64	44.7	163	6-26	8-14	-	-	20	728.0	10.0	8.3	1,630	1,353	17	48	42	-	-
Zaire	36.67	45.6	1,672	5-40	-	-	-	25	9,167.5	15.6	15.6		26,083	-	-	100	-	-
Sub-total	286.39		13,664					23.3	66,828.8	14.6	13.9	199,126	189,447					
AFRICA TOTAL	664.33		29,802					13.3	88,355.8	7.6	7.3	226,991	216,439					

COUNTRY	POP. IN MILLIONS	% OF BLACK	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% OF HETEROZYGOTES	TOTAL HETEROZYGOTES x10³	HOMOZYGOUS BIRTHS PER THOUSAND	HOMOZYGOTE ANNUAL BIRTHS	% ANNUAL BIRTHS OF HOMOZYGOTES WITH:					
									CC & C/Th	SC	SS	S/Th	S Tm	E/Th
North America									average					
Canada	26.99	?	15.30	413	?	?		?	6	25	55	12	1.5	+
Greenland	0.06	0	21.8	1	-	-		-						
USA : white	223.89		16.3	3,649	1.0	2,239.0	0.025	91					most	
black	28.80	11.4		469	11.0	3,163.0	3.0	1,407	6	25	55	12	1.5	+
Sub-total	279.74			4,532		>5,402.0		1,498						
Central America									overall average					
									6	25	55	12	1.5	
Belize	0.19	50.0	31.1	6	12.0*	11.4	3.6*	11						
Costa Rica	3.06	5-10	27.4	84	11.0*	33.7	3.0*	25						
El Salvador	5.38	few	36.3	195	+	+	+*	+						
Guatemala	9.47	few	39.3	372	+	+	+*	+						
Honduras	5.27	2.0	39.8	210	11.0*	11.6	3.0*	13						
Mexico	87.84	0.08	29.0	2,547	11.0*	773.0	3.0*	76						
Nicaragua	4.0	>10.0	41.8	167	11.0*	44.0	3.0*	50						
Panama	2.47	15.0	26.7	66	17.0*	63.0	7.2*	71						
Sub-total	117.68			3,647		>937.0		246						
South America														
Argentina	32.71	-	21.7	710	>1.0	327.1	0.025	18					most	
Bolivia	7.61		46.6	355	2.0	152.2	0.1	36					most	
Brazil: white	85.85		28.6	2,455	1.0	858.5	0.025	61					most	
black	67.46	44.0		1,491	4.4	2,968.3	0.5	745	6	25	55	12	1.5	+
Chile	13.39	-	22.2	297	0.2	26.8	-	-						
Colombia	33.61	15.0	27.4	921	7.5*	378.1	1.4*	193	6	25	55	12	1.5	-
Equador	10.86	-	32.9	357	1.5	162.8	0.06	21					most	
French Guyana +	0.10	100.0	25.2	3	6.0	6.0	0.9	3					most	
Guyana +	0.80	100.0	26.9	22	6.0	48.0	0.9	20					most	
Paraguay	4.40	-	34.8	153	+	+	+	+					most	
Peru	22.00	-	34.1	750	>1.0	220.0	0.025	19					most	
Suriname +	0.43	100.0	31.0	13	11.0	47.3	3.0	39					most	
Uruguay	3.11	-	18.3	57	1.0	31.1	0.025	1					most	
Venezuela: white	18.24		28.0	511	1.0	182.4	0.025	13					most	
black	2.03	9.0		57	8.5	172.6	1.8	103	6	25	55	12	1.5	
Sub-total	302.59			8,152		5,581.2		1,272						

* = % of heterozygote or homozygote birth-rate in the relevant part of the population.
+ In these 3 countries, 50% of the population is of African and 50% of Asian origin.

COUNTRY	POP. IN MILLIONS	% OF BLACK	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% OF HETEROZYGOTES	TOTAL HETEROZYGOTES x10³	HOMOZYGOUS BIRTHS PER THOUSAND	HOMOZYGOTE ANNUAL BIRTHS	% ANNUAL BIRTHS OF HOMOZYGOTES WITH:					
									CC & C/Th	SC	SS	S/Th	S Tm	E/Th
<u>Caribbean</u>									Overall average					
									6	25	55	12	1.5	+
Antigua	0.08	most	13.1	1.1	11	8.8	3	3.3						
Aruba	0.06	most	15.6	0.9	11	6.6	3	2.7						
Bahamas	0.26	most	19.2	5.0	17	44.2	7.2	36.0						
Barbados	0.26	most	15.7	4.1	11.5	28.9	3.3	13.5						
Bermuda	0.06	most	14.8	0.9	11	6.6	3.0	2.7						
Cuba	10.74	50	16.2	174.0	6.5*	349.1	1.0*	87.0						
Dominica	0.08	75	21.3	1.7	14*	8.4	3.7*	6.3						
Dominican Republic	7.32	most	31.3	229.1	11	805.2	3.0	687.3						
Grenada	0.08	most	24.5	2.0	11	8.8	3.0	6.0						
Guadeloupe	0.35	most	17.9	12.7	11	38.5	3.0	38.1						
Haiti	6.63	100	36.2	240.0	14	928.2	3.0	720.0						
Jamaica	2.37	most	24.6	58.3	14	331.8	4.5	262.4						
Martinique	0.34	most	17.8	6.1	11.5	39.1	3.2	19.5						
Netherlands Antilles	0.19	most	18.9	3.6	12	22.8	3.6	13.0						
Puerto Rico	3.61	50	18.5	66.8	11*	198.6	3.0*	100.2						
St. Lucia	0.15	most	21.3	3.2	15	22.5	3.6	11.5						
St. Vincent	0.12	most	24.5	2.9	14	16.8	5.6	16.2						
Trinidad & Tobago	1.25	most	20.7	25.9	10	125.0	4.9	126.9						
US Virgin Islands	0.12	most	16.3	2.0	11	13.2	2.5	5.0						
The rest +	0.12	most	20.0	2.4	11	13.2	3.0	7.2						
Sub-total	31.19			843		3,017.3		2,165						
TOTAL AMERICAS	731.20			17,174		14,938.0		5,181	423		6,536		336	+

+ Only islands with a population of over 50,000 are treated separately. "The rest" includes Anguilla (7,000), British Virgin Islands (13,000), Cayman Islands (26,000), Montserrat (12,000), St Kitts & Nevis (44,000), St Pierre & Miquelon (6,000), Turks & Caicos Islands (10,000): total = approximately 118,000.

* Figures for <u>the relevant part of the population</u>.

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% HETEROZYGOTES	TOTAL HETEROZYGOTES THOUSANDS	HOMOZYGOUS BIRTHS PER THOUSAND	TOTAL ANNUAL HOMOZYGOTE BIRTHS	% ANNUAL BIRTHS OF HOMOZYGOTES WITH:			
								SS	S/Th	S TM	E/Th
<u>West Asia</u>											
Afghanistan	16.43	49.3	810	3.0	493	0.45*	365	-	-	100	-
Bahrain	0.520	28.4	15	13.0	68	8.5*	128	67	18	15	-
Cyprus	.71	18.6	13	17.0	121	7.2	94	+	5	95	-
Iran	55.76	42.5	2,370	4.0	2,230	0.8*	1,896	16	18	66	-
Iraq	19.58	42.6	834	6.0	1,175	1.8*	35	38	24	38	-
Israel	4.98	22.2	111	+	+	+	+	+	+	+	-
Jordan	4.15	38.9	161	3.5	145	0.6*	97	9	21	70	-
Kuwait	2.10	28.0	59	4.0	84	0.8*	47	64	18	18	-
Lebanon	2.75	31.7	87	4.0	110	0.8*	70	17	17	66	-
Oman	1.56	45.6	71	6.0	94	1.8*	128	77	12	11	-
Palestinians +	2.25	40.0	90	3.5	79	0.6*	54	11	+	89	-
Qatar	0.38	22.7	9	6.0	23	1.8*	16	36	28	36	-
Saudi Arabia	14.69	42.1	618	9.6	1,410	4.6*	2,842	74	14	12	+
Syrian Arab Republic	12.99	44.6	579	6.0	779	1.8*	1,042	10	40	50	-
Turkey	60.78	26.1	1,586	2.5	1,520	0.32*	508	12	16	72	+
United Arab Emirates	1.63	22.8	37	5.0	82	1.25*	46	27	17	56	-
Former Dem. Rep. of Yemen	2.76	47.3	131	7.0	193	2.45*	322	55	17	28	-
Former Arab Republic of Yemen	9.55	53.6	512	6.0	573	1.8*	922	55	17	28	-
Sub-total	213.57		8,093		9,179		8,612				

+ "Palestinians" = population of West Bank (approximately 1.25 million) and Gaza Strip (approximately 1 million)
* Corrected for consanguineous marriage

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% OF HETEROZYGOTES	TOTAL HETEROZYGOTES x 10³	HOMOZYGOTE BIRTHS /1 000	ANNUAL HOMOZYGOTE BIRTHS		% OF ANNUAL BIRTHS OF HOMOZYGOTES WITH:			
							Total	Total Path.	SS + S/Th	Tm	E/Th	EE
South Asia												
Bangladesh	118.75	42.2	5,011	5.0	5,938	0.625/0.41	3,132	2,055	-	17	48	35
Bhutan	1.55	38.3	59	4.0	62	0.4	24	24	-	+	+	100
India	849.64	29.9	25,404	3.9	33,135	0.92[a]	23,372	23,372	68	32	+	+
Maldives	0.22	41.2	9	15.0	33	5.6	50	50	3	95	2	+
Nepal	19.61	39.6	777	4.0	784	0.4/0.2	311	155	-	16	36	48
Pakistan	115.52	30.3	3,500	4.5	5,198	0.9[b]	3,150	3,150	+	98	+	+
Sri Lanka	17.24	21.3	367	3.5	603	0.62/0.5	228	184	-	34	49	17
Sub-total	1,122.53		35,127		45,753		30,267	28,990				
East Asia: North												
China - 70%	809.10	21.2	17,153	-	+	-	-	-	-	-	-	-
Democratic People's Republic of Korea	22.19	23.5	521	-	-	-	-	-	-	-	-	-
Japan	123.92	9.9	1,227	-	-	-	-	-	-	-	-	-
Mongolia	2.25	36.1	81	-	-	-	-	-	-	-	-	-
Republic of Korea	43.27	14.5	627	-	-	-	-	-	-	-	-	-
Sub-total	1,000.73		19,609									
East Asia: South												
Brunei Darussalam	0.27	27.8	8	2.0	5	0.1	1	1	-	+	+	+
Cambodia	8.44	41.4	349	33.0	2,785	27.2/5.2	9,493	1,815	-	1	18	81
China 30%	346.70	21.2	7,350	4.0	13,868	0.4	2,940	2,940	-	98	2	+
East Timor	0.75	43.8	33	7.0	53	1.23/0.86	41	28	-	21	49	30
Hong Kong	5.91	11.7	69	3.0	177	0.23	16	16	-	98	2	+
Indonesia	187.77	28.6	5,370	6.0	11,266	0.23/0.17	1,235	913	-	25	50	25
Lao People's Democratic Republic	4.26	45.1	192	35.0	1,491	30.6/8	5,875	1,536	-	2	24	74
Macau	0.39	16.9	7	3.0	12	0.23	2	2	-	98	2	+
Malaysia	18.33	28.0	513	7.7	1,411	1.5/0.56	770	287	-	7	21	72
Mayanmar	42.56	30.6	1,302	28.0	11,917	19.6/4.7	25,519	6,119	-	2	22	76
Philippines	62.87	33.2	2,087	2.0	1,257	0.1/0.08	209	167	-	25	50	25
Singapore	2.76	17.8	49	3.0	83	0.23/0.19	11	9	-	40	40	20
Thailand	56.92	20.4	1,161	26.0	14,799	16.9/4.8	19,621	5,573	-	4	19	77
Viet Nam	68.18	31.8	2,168	5.0	3,409	0.63/0.4	1,366	867	-	16	48	36
Sub-total	806.11		20,658		62,533		67,099	20,273				
TOTAL ASIA	3,142.94		83,487		117,465		105,978	57,875				

[a] Global figure, allowing for very unequal distribution of genes, and customary consanguineous marriage in large sub-groups of the Indian population.
[b] A cautious estimate, allowing for customary consanguineous marriage and uneven distribution of thalassaemia genes in the population of Pakistan.

α^0 thalassaemia in Asia:
Estimates of the number of α-thalassaemia heterozygotes,
and the birth rate of affected infants (α thalassaemia hydrops fetalis and Hb H disease)

COUNTRY	POPULATION (MILLIONS)	BIRTH RATE /1 000	ANNUAL BIRTHS x10^3	% OF POPULATION HETEROZYGOUS FOR:			NO. OF α^0 THALASSAEMIA HETEROZYGOTES (THOUSANDS)	BIRTHS/1 000 OF INFANTS WITH:			NUMBERS/YEAR BORN WITH:	
				α^0 thal	*α^+ thal*	*total*		*Hydrops Fetalis $\alpha^0\alpha^0$*	*Hb H $\alpha^0\alpha^+$*	*Total Patho-logical*	*α thal hydrops*	*Hb H Disease*
China[1]:												
Guangdong	59.30	25.0	1,482	5.0	3.5	8.5	2,965	0.6	0.6	1.2	890	890
Guangxi	36.40	27.3	994	8.8	14.2	23.0	3,203	1.9	6.2	8.1	1,890	6,160
Cambodia	8.44	41.4	349	4.0	16.0	20.0	336	0.4	3.2	3.6	140	1,120
Hong Kong	5.91	11.7	69	3.5	3.5	7.0	207	0.3	0.6	0.9	21	42
Lao People's Democratic Republic	4.26	45.1	192	4.0?	20.0	24.0	172	0.4	4.0	4.4	77	768
Malaysia	18.33	28.0	513	3.5	5.0	8.5	64	0.3	0.9	1.2	154	462
Philippines	62.87	33.2	2,087	2.0	?	>2.0	1,258	0.1	?	>0.1	>209	?
Singapore	2.76	17.8	49	3.5	3.5	7.0	98	0.3	0.6	0.9	15	29
Thailand	56.92	20.4	1,161	4.0	16.0	20.0	2,276	0.4	3.2	3.6	464	3,715
Viet Nam	68.18	31.8	2,168	3.5	?	>3.5	2,387	0.3	?	?	650	?
Total	323.37		9,064				12,966				>4,510	>13,186

[1] Information based on adequate screening is available only for Guangxi (personal communication with Dr Wu Guanyun) and Guangdong. Therefore the figures quoted are minimum figures only.

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% OF GROUPS "AT RISK"		HETEROZYGOTES x10³	ANNUAL HOMOZYGOTE BIRTHS	% OF ANNUAL BIRTHS OF HOMOZYGOTES WITH:		
				IN THE POPULATION	AT BIRTH			SS, SC, S/Th	Tm	E/Th, EE
Northern and Central Europe										
Austria	7.82	12.0	94	2.6	4.6	4.0	1.0	+	98	-
Belarus	9.99	15.0	150	-	-	-	-	-	-	-
Belgium	9.84	12.0	118	5.8	7.8	31.0	9.0	55	45	+
Former Czechoslovakia	15.58	13.3	207	-	-	-	-	-	-	-
Denmark	5.15	12.4	64	0.8	2.0	2.0	2.0	60	40	-
Estonia	1.59	14.2	23	-	-	-	-	-	-	-
Finland	5.03	13.1	66	-	-	-	-	-	-	-
France	57.05	13.3	759	8.7	12.6	195.0	>135.0	60	40	-
Germany	80.33	11.5	924	5.0	11.5	69.0	>22.0	50	50	-
Hungary	10.34	12.2	126	-	-	-	-	-	-	-
Iceland	0.26	17.6	5	-	-	-	-	-	-	-
Ireland	3.52	14.9	52	+	+	-	-	-	-	-
Latvia	2.59	14.5	38	-	-	-	-	-	-	-
Lithuania	3.74	15.0	56	-	-	-	-	-	-	-
Luxembourg	0.37	13.0	5	15.3	18.6	0.9	+	50	50	-
Netherlands	15.07	13.2	199	3.8	7.2	25.0	12.0	70	30	+
Norway	4.26	14.2	60	0.3	0.6	0.6	0.5	-	100	-
Poland	38.24	14.3	547	-	-	-	-	-	-	-
Republic of Moldova	4.36	18.9	82	+	+	+	+	-	+	-
Russian Federation	143.59	14.6	2,096	+	+	+	+	-	+	-
Sweden	8.64	14.3	124	1.9	3.6	8.0	6.0	60	40	-
Switzerland	6.79	12.6	86	8.7	11.1	27.0	4.0	-	100	-
Ukraine	50.92	12.7	647	-	-	-	-	-	-	-
United Kingdom	57.37	13.8	792	6.0	11.0	169.0	203.0	79	20	1
The rest*	0.38		5	+	+	+	+	-	+	-
Sub-total	542.82		7,325			531.5	395.0			

* The rest includes states with very small populations (Andorra 58,000, Channel Islands 140,000, Faroe Isles 47,000, Gibraltar 30,000, Holy See 1,000, Isle of Man 70,000, Liechtenstein 28,000, Monaco 28,000, San Marino 23,000, Svalbard & Jan Mayen's 3,400).

EUROPE I: "NON-ENDEMIC" AREAS

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS x10³	% HETEROZYGOTES	TOTAL HETEROZYGOTES x10³	HOMOZYGOTES /1 000	ANNUAL HOMOZYGOTE BIRTHS	% OF ANNUAL BIRTHS OF HOMOZYGOTES WITH:	
								SS, SC, S/Thal	Tm
Southern Europe									
Albania	3.3	24.7	82.0	8.0	264	1.6	131	50	50
Bulgaria	8.98	10.7	96.0	2.4	216	0.14	13	-	100
Greece	10.06	10.1	102.0	8.0	805	1.6	163	13	87
Italy	57.05	9.8	559.0	4.8	2,852	0.58	324	4	96
Malta	0.36	15.2	5.5	3.0	11	0.23	1	-	100
Portugal	10.58	11.0	116.0	1.5	159	0.06	7	85	15
Romania	23.19	13.6	315.0	1.0	232	0.03	10	-	100
Spain	39.03	10.2	398.0	0.5	195	0.002	1	+	98
Former Yugoslavia	23.93	14.0	335.0	1.8	431	0.1	34	-	100
Sub-total	176.48		2,008.5		5,165		684		
Transcaucasus & Central Asia & Republics of the Former USSR									
Armenia	3.34	22.9	76.0	2.0	67	0.1	8	-	100
Azerbaijan	6.66	25.6	170.0	6.0	400	1.0[2]	170	10	90
Georgia	5.22	16.7	87.0	3.0	157	0.23	20	-	100
Kazakhstan	15.94	23.0	367.0	?	?	?	?	-	?
Kirghizistan	4.01	30.4	122.0	?	?	?	?	-	?
Tadjikistan	4.57	38.7	177.0	5.0	229	1.0[2]	177	-	100
Turkmenistan	3.23	34.9	113.0	1.2	39	0.07[2]	8	-	100
Uzbekistan[1]	18.23	33.3	607.0	3.0	274[1]	0.52[2]	158[1]	-	100
Sub-total	61.2		1,719.0		1,166		541		
TOTAL EUROPE	780.5		11,053.0		6,862		1,620		

[1] Only 50% of population of Uzbekistan are Uzbeks.
[2] Corrected for customary consanguineous marriage.

EUROPE II: "ENDEMIC" AREAS

COUNTRY	POP. IN MILLIONS	BIRTH RATE /1 000	ANNUAL BIRTHS $x10^3$	% OF HETEROZYGOTES	TOTAL HETEROZYGOTES $x10^3$	HOMOZYGOUS BIRTHS /1 000	ANNUAL HOMOZYGOTE BIRTHS	% ANNUAL BIRTHS OF HOMOZYGOTES WITH:		
								Tm	E/Th	EE
Australia	17.34	15.4	267	0.5	87	0.006	>16	100	+	+
Fiji	0.78	24.9	19	?						
French Polynesia	0.21	27.9	6	?						
Guam	0.12	26.5	3	?						
Federated States of Micronesia	0.1	? 26.0	3	?						
New Caledonia	0.17	24.6	4	?						
New Zealand	3.38	17.8	60	?						
Papua New Guinea	3.77	34.2	129	7.0	264	1.23	158	100	+	+
Samoa	0.17	31.0	5	?						
Solomon Islands	0.33	42.0	14	?						
Tonga	0.09	28.9	3	?						
Vanatu	0.16	? 30.0	5	?						
Other*	0.20	? 30.0	6	?						
Sub-total	26.82		524		351		174			

* Other = numerous islands with small populations.

OCEANIA

ANNEX 2

Measuring the frequency of customary consanguineous marriage

This varies with urban/rural residence and social class. It is important to study a sample that truly represents the relevant population, namely people having babies today. A good, accessible group to study are women in hospital after having a baby: they have time to talk, and are usually slightly more knowledgable than men about details of family relationships. In a small country or area, a study at one or two large public hospitals may give a quick answer. In a larger country a co-operative study at a set of hospitals in different areas will be needed.

Questions should be asked by a woman, with care and delicacy, and it is necessary to sit down and take adequate time. It must be made clear that consanguineous marriage is viewed in a positive rather than a negative light ("we" have this custom, rather than "some people" have this custom). The aims of the research should be explained. The woman should then be asked whether her husband is related to her or not, and if so, the type of relationship. Descriptions such as "mother's brother's son" are easier and more accurate than descriptions such as 1st or second cousin etc. The researcher may then work out exact relationship at leisure.

Additional useful information on trends in consanguineous marriage can be obtained by asking the woman whether her own parents are/were relatives, and if so their exact relationship. In a study of British Pakistanis, it was found that women had more accurate knowledge of their own parents' relationship than of their husband's parents' relationship, though this information may also be requested.

Eliciting this information and being sure of its accuracy can take 15-20 minutes/woman.

* * * * *

ANNEX 3

National Thalassaemic Support Associations

Argentina

Dra Aurora Feliu Torres
Hospital de Pediatria Dr JP Garrahan
Haemato-Oncologia
Pichincha 1850
Buenos Aires

Tel: +54 1 941 8532

Australia

Miss Christine Savva
Thalassaemia Society of Victoria
6 Tiernan Street
Footscray 3011, VA

Tel: +61 3 687 4777
Fax: +61 3 687 4295

Ms Patricia Fleming
Australian Thalassaemia Association
Haematology Department
ICPMR, Westmead Hospital
Westmead, NSW 2145

Tel: +61 2 633 7034
Fax: +61 2 891 5376

Miss Jenny Kelly
Thalassaemia Society of New South Wales
P.O. Box 80
Marrickville, SW 2204

Tel: +61 2 871 1701

Dr Sylvia Barber - President
Australian Thalassaemia Association
c/o The Queen Elizabeth Hospital
28 Woodville Road
Woodville South, SA 5011

Tel: +61 8 450 222
Fax: +61 8 243 6806

Miss Irene Triantafillidis
Thalassaemia Society of South Australia
288 Franklin Street
Adelaide, SA 5000

Tel: +61 8 231 1132

Azerbaijan

INSAN
Social and Charitable Centre
Azerbaijan Talassaemia Society
ab/box N70
Baku Centre 370000

Tel: +7 8922 663 048
Fax: +7 8922 923 297

Bahrain

Mr Abdulla Saif
President
Bahrain National Hereditary Anaemia Society
P.O. Box 11399
Manama

Tel: +9 73 529 500
Fax: +9 73 643 579

Belgium

Mrs Oriella di Stefano
President
Ligue des Jeunes Thalassemiques
88/5 Rue Waleffe
4220 Seraing-Jemeppe

Tel: +32 41 333 977

Brazil

Mrs Neuza C. Cattassini - President
Abrasta Associacao Brasileira dos
Talassemicos
113 Rua da Quitanda
6 andar, Sala 62
CEP 01012-010
Sao Paulo SP

Tel: +55 11 366 151
Fax: +55 11 524 902/341 712

Mr Luis Carlos Salvaterra
Associacao de Pais
e Amigos dos Thalassemicos
R Parana 203
Bairo Sao Benardo
Campinas SP 13030

Tel: +55 192 391 301

Canada

Ms Naushy Mullani
Ontario Thalassaemia Association
3 Massey Square, No 2901
Toronto, Ontario

Tel: +1 416 694 6796 (home)

Mrs Mary Sammarco
The Vancouver Thalassaemia Society of BC
6620 Bouchard Court
Richmond, British Columbia
BC V7C 5H5

Tel: +1 604 274 1052

Mrs A.C. Kritikos
Quebec Society of Thalassaemia Inc.
505 Jean Talon East
Montreal, Quebec
H2R 1T6

Cyprus

The Cyprus Thalassaemia Association
1 Philippou Hadjigeorgiou
Flat 5
P.O. Box 8503
Nicosia

Tel: +357 2 429 141
Fax: +357 2 315 792

Egypt

Dr M. Gadalla
Egyptian Thalassaemic Friends Association
c/o. Ciba-Geigy Scientific Office
P.O. Box 1071
Cairo 11511

Tel: +20 2 919 388/917 143
Fax: +20 2 919 388

France

Mr Louis Thiemongue
President
France Hemoglobinoses
(Alpes-Maritimes)
Centre de Transfusion Sanguine
Avenue de Docteur Donat
F-06700 Saint Laurent du var

Tel: +33 932 23750
Fax: +33 932 23783

Mr Elias Benamou
Association France Hemoglobinoses
86 Avenue du Rove, Bât. D
F-13015 Marseille

Tel: +33 91 60 91 00

Greece

Mr Dimitris Paspalis
Association of Parents and
Patients of Thessaloniki
T. Papageorgiou 2
Thessaloniki 54 631

Tel: +30 31 228 931

Miss Evgenia Georganda
Panhellenic Thalassaemia Patients'
Association
1 Tzavella Street
GR-106 81 Athens

Tel: +30 1 364 4682
Fax: +30 1 645 0510

Costas Papageorgiou
Panhellenic Association for the Protection of
Thalassaemia Patients
Akadimias 64
T.T. 106 79 Athens

Tel: +30 1 362 5102/325 2547
Fax: +30 1 323 6115

Mr Elias Sofianos
President
Panhellenic Thalassaemia Federation
Tzavella 1
Z.P 106 81 Athens

Tel: +30 1 364 4682
Fax: +30 1 645 0510

Mr Karnaros
Panellina Kinisi yia ti Mesogiaki Anemia
P.O. Box 70014
16610 Glyfada
Athens

Tel: +30 1 894 7395/681 5605

Thalassaemia Parents' Association
Kassavitti 4
KA 38221
Magnisia

Mr Anastasios Eliopoulos
Thalassaemia Parents' Association
Antonopoulos 98
KA 38221
Volos

Miss Georgia Galanopoulou
Sylogos Pashontou apo Mesogiakin
Iera Metropoli Korinthou
Metropoliticos Naos Ayiou Pavlou
P.O. Box 303
Korinthos 20 100

Tel: +30 741 23324

Hong Kong

Mrs Ngan-Wah Yeung
The Cooley's Anemia Foundation of
Hong Kong
P.O. Box 44379
Block A, Flat G, 21st Floor
Shau Ki Won Centre
9 Factory Street
Shau Ki Won

India

Mr Tapas Sengupta
The Thalassaemia Society of India
1/B Grant Street (Nr. Chandni Market)
Culcutta 700 013

Mr Varsha Bihani
Bhoruka Research Centre for
Haematology and Blood Transfusion
Futnani Chambers, Gat 4
Corporation Place
Calcutta 87

Tel: +91 33 449 619/448 902

Mr Thakorbhai B. Desai
Parents' Association Thalassaemic Trust Unit
Kanji Khetshi New Building, 3rd Floor
Tatya Gharpure Marg
Bombay 400 004

Tel: +91 22 363 347

Dr M.B. Agarwal
Thalassaemia & Sickle Cell
Society of Bombay
Vijay Sadan, Flat No. 1
168B Dr Ambedkar Road
Dadar TT, Bombay

Tel: +91 22 414 2272/4453
Fax: +91 22 414 0058

Mr Chandrakant Koticha
Rajkot Voluntary Blood Bank
and Research Centre
c/o Jayshree Traders "Ajay Mansion"
P.O. Box 508
Malaviya Road
Rajkot 360 002

Tel: +91 281 82636/82176
Fax: +91 281 47015/47016

Dr J.S. Arora
National Thalassaemia Welfare Society
KG 1/97
Vikas Puri
New Delhi 110018

Tel: +91 11 550 7483

Dr S.M. Merchant
Research Laboratories BJ Wadia Hospital
for Children
Acharya Donde Marg
Parel
Bombay 400 012

Tel: +91 22 413 7000/412 9786

Mr C.L. Juneja
The Thalassaemia Foundation of India
181/B, MIG
DDA Flats
Rajouri Garden Extension
New Delhi 110027

Tel: +91 11 502 367

Mr Guninder Singh Chandok
Thalassaemia and Sickle Cell Society
of Bangalore
Jai Rattan Nivas
11 A/22, Cunningham Road
Bangalore 560 002

Tel: +91 812 258 661

Mr M.S. Rekhi
Thalassaemia Children Welfare Association
3047, Sector 20-D
Chandigarh

Mr Deepak Chopra
Thalassaemics India (Regd)
C-1/59 Safdarjung Development Area
New Delhi 110016

Indonesia

Mr Ruswandi
Yayasan Thalassaemia Indonesia
J1 Melat No. 40
Gilandak Barat
Jakarta Selatan 12430

Tel: +21 750 0788/799 5936

Iran

Dr Mina Izadyar
Director
Iranian Thalassaemia Society
Apt. 10, No. 113
Ghaem Farahani Avenue
P.O. Box 15875 6156
Teheran

Tel: +98 21 646 2977
Fax: +98 21 677 094

Israel

Mr Gilad Silberstein
M. Jakobsohn Ltd.
38 Kalisher St.
P.O. Box 29096
Tel Aviv 61290

Tel: +972 3 510 3131
Fax: +972 3 517 3585

Italy

Mr Silvano Fassio
Lega Italiana Per La Lotta Contro Le Emopatie E Tumori Dell'Infanzia
Via Giobert 27
I-14100 Asti

Tel/Fax: +39 141 557 034

Ms Silvia Olla
President
Nuiva Associazione Talassemici Italiani
Lungotevere Flaminio, 48
I-00 196 Rome

Tel: +39 6 322 4823
Fax: +39 6 482 0974/503 7923

Kuwait

Dr Laila Al-Fezae
Pediatric Department
Sabah Hospital
P.O. Box 25328
13114 Safat

Tel: +965 254 3377/531 2400
Fax: +965 531 9533

Lebanon

Mrs Randa Daouk
Chronic Care Center
P.O. Box 213
Hazmieh
Beirut

Tel: +961 1 868 109
Fax: +961 1 866 301/866 302

Mr Samih Shahine
Lebanese Association
Mea Eng Department
Lim, Beirut

Tel: +961 1 316 316 Ext. 2854

Malaysia

Malaysian Association of Thalassaemia
Jabatan Pediatrik
University Kebangsaan Malaysia
Salam reja Mude
50300 Kuala Lumpur

Ms Khee Swee Hong
President
Pertubuhan Thalassaemia Pulau Pinang
56 Jalan Gen Guan He
11400 Penang

Tel: +60 4 686 412

Rep. of Maldives

Dr Naila Firdous
Society for Health Education
M Kothanmaage (South)
Maaveyo Magu
Male 20-03

Tel: +960 327 117
Fax: +960 322 221

Malta

Mrs Simone Buhagiar
President
Thalassaemia Awareness Maltese Association
Comprehensice Genetics Programme
University of Malta
Tal-Qroqq
Msida

Tel: +356 314 392/239 807
Fax: +356 310 577

Pakistan

Mr Amin Bandhani
Fatimid Thalassaemia Centre
393 Britto Road, Garden East
P.O. Box 3412 (New Town)
Karachi

Tel: +92 21 716 733

Lt. Gen. (Rtd) Fahim Ahmad Khan
Pakistan Thalassaemia Welfare Society (Regd)
22 Ata-ul-Haq Road
Westridge-I
Rawalpindi

Tel: +92 51 862 227/862 393
Fax: +92 51 565 206

Romania

Mrs Michaela Dogaru
Asociata Romania Pentrou Protectia
Bolnavilor de Thalasemie Majora
50 Vioiceni Street
Bloc A 15 bis, so 1
Ap 18, Sector 2
73418 Bucharest

Russia

Professor Yuri N. Tokarev
Research Institute for Pediatric Haematology
Ministry of Health of the Russian Federation
113 Leninsky Drive
Moscow 117513

Tel: +7 095 434 8141
Fax: +7 095 434 8678

Saudi Arabia

Professor Mohsen A.F. El-Hazmi
National Working Group
WHO Collaborating Centre
College of Medicine and
King Khalid University Hospital
P.O. Box 2925
Riyadh 11461

Tel: +966 1 467 0830
Fax: +966 1 467 2575

Saudi Thalassaemia Friend's Society
King Abdulaziz University
King Fahd Medical Research Centre
P.O. Box 9029
Jeddah 21413

Tel: +966 2 688 1821/2057

South Africa

Mr D. Brijball
President
South African Thalassaemia Association
26 Robin Street
Kharwastan, Durban 4092

Tel: +27 31 413 442

Thailand

Prof. Voravarn S. Tanphaichitr
Secretary
Thalassaemia Foundation of Thailand
Department of Pediatrics
Siriraj Hospital
Bangkok 10700

Tel: +66 2 411 3010
Fax: +66 2 412 1371

Tunisia

Professor Slaheddine Fattoum
A.L.P.H.A.T.T.
Hôpital d'Enfants
Bab Saadoun-1007
Tunis

Tel: +1 262 521/663 500/
664 125
Fax: +1 262 521/572 572

Turkey

Professor Ayten Arcasoy
Ankara Thalasemia Society
Kibris Sok 10/5
Guvenevieri
Asagni Ayranci
Ankara

Tel: +9 319 1440

Opr Dr Duru Malyali
TADAD
Thalassemi Dayanisma Dernegi
Posta Kutusu 403
Kadikoy
81310 Istanbul

Tel: +1 358 0071/512 6819
Fax: +1 339 9496/991 1934

Professor Huseyin Sipohioglu
President
Akdeniz Talasemi Dernegi
Anafartalar 15/8
07050 Antalya

Tel: +31 124 400/128 158

United Kingdom

Mr Costa Paul
United Kingdom Thalassaemia Society
107 Nightingale Lane
GB-London
N8 7QY

Tel: +44 81 348 2553
Fax: +44 81 348 0437

United States of America

Lucille Gash
President, Thalassemia Action Group
c/o Daniele
25 Bassett Lane
Palm Coast, 33137-8823

Tel: +1 904 446 3442
Fax: +1 201 935 3366

Mr Robert Ficarra
Cooley's Anemia Foundation, Inc.
Suite 911
105 East 22nd Street
New York, NY 10010

Tel: +1 212 598 0911
Fax: +1 212 944 7327

West Indies

Mrs I. Rampaul
The Society for Inherited and Severe
Blood Disorders (Trinidad & Tobago) Ltd
Haematology Treatment Centre
General Hospital
P.O. Box 421
Port of Spain
Trinidad

Tel/Fax: +1 809 625 4765

Mrs L. Bhagwandin
Thalassaemia Association of
Trinidad & Tobago Ltd
352 Southern Main Road
Enterprise, Chaguanas
Trinidad

• • • • •

Annex 4

SUGGESTIONS FOR A REGISTER OF PATIENTS WITH HAEMOGLOBIN DISORDERS

It will not be possible to collect all the recommended data at the beginning. However, with the passage of time and increasing co-operation, it will become possible gradually to develop more complete recording.

Family register number
Patient's register number
Name, date of birth, address etc.
Hospital where treated
Hospital number and file number

Responsible doctor: address: phone number
Any other doctors including primary care doctor

Genotype: results of conventional laboratory and DNA studies
Age at presentation
Blood group (extended)

Date of first transfusion
Transfusion interval (weeks)
Pre-transfusion Hb (mean)
Amount of blood transfused each time
Transfusion reactions?
Red cell antibodies?
Hepatitis B, C, antigen positive?

Splenectomy yes/no: date

Desferal (a) pump yes/no
(b) number of vials used/year

Vaccinations: normal childhood vaccinations
hepatitis B
pneumovax
haemophilus influenzae

Bone marrow transplantation: yes/no: date: outcome.

Family: Family tree
any other affected children, living/dead? Patient number.

Death: Date of death
Causes of death

* * * * *