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JOINT WHO/TIF MEETING ON THE
 PREVENTION AND CONTROL OF HAEMOGLOBINOPATHIES

(7th Meeting of the WHO Working Group
 on the Control of Hereditary Anaemias)

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1. INTRODUCTION

Haemoglobinopathies - thalassaemias and sickle cell disorder (SCD) - are widespread recessive inherited diseases. At present, about 250 million people (4.5% of the world population) carry a potentially pathological haemoglobinopathy gene. Each year about 300,000 infants are born with major haemoglobinopathies. The hereditary anaemias were originally confined to the sub-tropics and tropics, their high incidence being due to the fact that healthy carriers are protected against lethal effects of malaria. However, increasing global migration has introduced the haemoglobinopathies into many areas where they were not originally endemic. In the USA, 10% of the population is at risk for SCD, and in North-West Europe, between 2% and 9% of most populations now belong to ethnic minorities at risk for the haemoglobinopathies. In some South-East Asian countries, population movement could increase the potential birth-rate of infants with thalassaemia. Globally, there are more carriers of thalassaemia than of SCD, but the high frequency of the sickle cell gene in certain areas leads to a high birth rate of homozygotes. As a result, SCD accounts for about 70% of haemoglobin disorders worldwide. Nearly 70% of affected births occur in sub-Saharan Africa where up to 2% of all children are born with SCD. This high frequency makes the African Region a global focus of haemoglobin disorders^{1,2,3}.

Haemoglobinopathy control programmes based on WHO approaches and recommendations have been established in different countries of each WHO Region, and have shown successful management of the problem. In many developing countries, the haemoglobinopathies are the first condition to draw attention to the need to develop genetic approaches for the control of chronic childhood disease^{4,5,6}.

This first joint WHO/Thalassaemia International Federation (TIF) meeting was convened to review the following areas relevant to control programmes for haemoglobin disorders: progress in ongoing programmes in different regions (including possibilities for extension of working groups on haemoglobin disorders/hereditary disease to the WHO regional level); finalization of educational materials, and guidelines for control programmes for haemoglobin disorders at the country level.

This report is concerned primarily with the first topic. The approved educational materials and guidelines are listed in Annexes 1 and 2. They will be produced separately as unpublished WHO documents, and will be available, upon request, either through the WHO Hereditary Diseases Programme or from TIF, which supports this WHO activity.

2. PROGRESS IN ONGOING PROGRAMMES FOR THE CONTROL OF HAEMOGLOBIN DISORDERS

2.1 Africa

60-70% of all births of children with major haemoglobin disorders occur in Africa², the region with the least resources for coping with the problem, and numbers are rising steadily as developments in primary health care lead to increased survival of patients with sickle cell disorder. Several motivated clinicians are making efforts to provide some services, and to sensitize governments and the WHO Regional Office for Africa (AFRO) to the importance of the problem. Because of the global economic downturn some gains that had been made are being lost: e.g., malnutrition is increasing, and many trained people have left the region because of political or economic turmoil. In 1987 WHO proposed a plan to develop services for sickle cell disorder throughout the African continent which would require US\$ 3 million to carry out. However, to date, it has not

been possible to identify a donor. In 1991 WHO/AFRO brought together eight African experts (4 francophone, 4 anglophone) to plan a meeting to include representatives from all AFRO countries and initiate a regional working group on sickle cell disorder. Unfortunately, this meeting could not take place in 1992 as planned due to lack of funds.

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

The Nigerian Experience

An extended survey of 16,000 randomly selected individuals over the age of 15 from the 30 states confirms that 25.3% are AS, AC, SS or SC (Table 1). Beta thalassaemia trait could not be evaluated in these surveys: its prevalence is thought to be about 1%. The figures are considered generally representative for sub-Saharan Africa.

The Sickle Cell Club of Lagos organizes support for parents and patients. Providing counselling proves to be the least expensive and most accessible helpful activity under African conditions⁷. Counselling for sickle cell disease includes both psychological support for families and genetic counselling. In developing countries it is initially focused on affected families. The Sickle Cell Club of Lagos has now held five annual counselling training courses, and so far 152 counsellors from Nigeria and some from other parts of Africa have been trained. Follow-up studies have shown a decrease of morbidity and mortality in families with affected children, decreased hospital attendances and happier people with greater self-esteem.

Other activities of the centre include training doctors in "understanding sickle cell", in order to avoid inappropriate treatment and excessive medical dependency of the patients. The centre also provides correct information to the public and to journalists. However, less emphasis is now placed on the public information campaign, as without appropriate facilities for treatment and prenatal diagnosis it can lead to frustration.

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

2.2 The Americas

Hereditary anaemias are highly prevalent in the French-speaking and English-speaking Caribbean nations, which are geographically and ethnically related to some Latin American populations. However, social, political and health care differences require separate analyses for each country, which will not be done here. Problems for all genetic diseases revolve around lack of treatment, counselling and prenatal diagnosis facilities, and the fact that termination of pregnancy is illegal in most Latin American countries.

However, there is encouraging progress in individual countries, including several where haemoglobin disorders are common, and a high level of expertise is available in the region. It was suggested that a Pan American Health Organization (PAHO) Working Group on Haemoglobin Disorders, including the active countries of the Caribbean, Brazil and other Latin American countries where the disorders are common, could be extremely valuable. Although in the past decade PAHO has convened two advisory groups in genetic health services for the Region^{8,9}, this issue has not yet been assigned the importance it deserves.

The Brazilian Experience

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

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

The Cuban Experience

Cuba is the only Latin American country that provides a comprehensive community-based medical genetics programme with the assistance of the WHO Collaborating Centre for the Development of Genetic Approaches for Health Promotion in Havana. This work, including development of appropriate technologies, has been reported previously¹⁰. Services for treatment of sickle cell disease are available; thalassaemia major is not a problem.

The Cuban prevention programme for sickle cell disorders¹¹ is based on screening pregnant women at 16+ weeks of gestation (when maternal serum AFP screening is also provided), then offering testing to partners of carriers, and offering DNA-based prenatal diagnosis to couples at risk. There is one DNA laboratory in Havana for the whole country. Obstetric sampling (by amniocentesis) is available in each province, and CVS is now available in three provinces.

80-90% of the partners of women found to be carriers come for testing, and 95% of couples at risk ask for prenatal diagnosis. 90% of those in whom an affected baby is found decide for, and 10% decide against termination of pregnancy. Though in principle this high uptake should lead to a marked fall in affected births, in practice the affected births have fallen by only 32% (Fig. 1). This is mainly because with the present screening strategy many at-risk couples are detected too late for prenatal diagnosis in the presenting pregnancy. Screening policy has now been changed and blood samples will be taken at first booking, in order to deliver prenatal diagnosis in the first trimester. In 1992 the fall in affected births was only 22% because of incoordination associated with this policy change. There remains a great need for education of the population and doctors.

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

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

2.3 The Eastern Mediterranean

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

The Bahrain Experience

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

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

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

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

The Cyprus Experience

The Cyprus thalassaemia programme, based on the experience of the WHO Collaborating Centre for the Community Control of Thalassaemia in

been extensively reported¹². Though prevention is in general complete, five new thalassaemic children were born in 1991. Residual births are mainly for social reasons, including births to single mothers (three cases). This is a relatively new issue in Cyprus:

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

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

The Egyptian Experience

High rates of β -thalassaemia are known to occur in Egypt.

A heterozygote carrier frequency of 2.6-4% has been reported, although in a more recent study a carrier rate of 13% among a random sample of Egyptians aged between 1-59 years was noted. As consanguineous marriages occur at a high frequency (28-33%) in urban areas and more frequent in rural areas, a high frequency of homozygosity for the β -thalassaemia gene is expected. About 1,000 children affected with β -thalassaemia are expected to be born yearly in Egypt based on the birth of 1.5 million annually which poses a significant health problem.

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

Cases with α -thalassaemia have also been identified in Egypt. In a study comprised of 545 neonates taken randomly from various regions in Egypt, the incidence of α -thalassaemia was found to be 10%.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is by far the most common enzyme abnormality in man with the highest frequency in Mediterranean countries. In Egypt, regional variations are prominent and the percentage of G6PD deficiency ranges between 0.9-9.2%.

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

The Iranian Experience

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

The national programme for prevention calls for mandatory heterozygous detection screening for marrying couples in the endemic regions. Couples who both have thalassaemia minor are advised not to marry.

There has been a breakthrough also in the field of prenatal diagnosis. DNA-based diagnostic tests were introduced to the private health service over a year ago. Since then more than 50 at-risk pregnancies have been screened. The only drawback is that this highly needed service is not supported by the national health system and is therefore available only to those who can afford it.

The Pakistan Experience

A national thalassaemia programme in Pakistan is still in an early stage of development. Modern surveys show 8% beta-thalassaemia trait in Pathans and 3.3% in Punjabis. Taking an average figure of 5% for carrier prevalence, there are six million carriers in Pakistan. Allowing for the high frequency of consanguineous marriage, the expected birth rate of thalassaemic children is about 1.3/1,000. In the province of Rawalpindi, 120 new cases of beta-thalassaemia major are diagnosed per year. Fourteen cases of HbH disease have also been diagnosed in the last five years, and Hbs S, C, and D are also seen (1.2% of Punjabis carry HbD).

National blood transfusion services are poorly developed, and resources available for patient care are limited to: (a) Blood transfusion services through the Fatimid Foundation, a charitable nongovernmental organization (NGO) with centres in Karachi, Lahore and Islamabad; (b) A comprehensive service for a limited number of patients through the more recently-formed Pakistan Thalassaemia Welfare Society (PATHWELL) in Rawalpindi.

PATHWELL is starting a national thalassaemia registry and has so far registered 600 cases. Family studies and genetic counselling are provided for the parents and extended family of patients. The Society has the following aims:

- (1) To improve blood transfusion services;
- (2) to improve the level of information among health-workers by providing lectures in Medical Schools;
- (3) to recruit 100 patients to be entered in trials of management by the end of 1993. Forty patients have been recruited so far. Iron chelation and other specialist services will be provided, as well as blood transfusion;
- (4) to provide a prenatal diagnosis service and genetic counselling; training has already been arranged with University College Hospital, London. There is a consensus in Pakistan that therapeutic abortion is permissible in exceptional severe cases such as thalassaemia;
- (5) to establish a bone-marrow transplantation centre.

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

The Saudi Arabian Experience

The WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies in Riyadh is being developed as a national and regional resource for patient care, laboratory diagnosis, and educational activities. A national survey of the prevalence of haemoglobin disorders has been conducted¹³, and a substantial number of educational materials in Arabic has been developed. The materials are being disseminated within Saudi Arabia and are available for the whole Eastern Mediterranean region.

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

An important problem in organizing service delivery in Saudi Arabia, as in many other Middle Eastern countries, is fragmentation of the health care system between the public service, private hospitals, and hospitals supported by the military, the security services, companies etc. A database of national expertise and facilities has been established, and national registration of patients with thalassaemia and sickle cell disorder is under way. The Saudi centres have agreed to develop a network, with a newsletter produced in Riyadh as a "messenger" between the groups. There are plans to build on the experience with haemoglobin disorders to develop a molecular genetic laboratory resource for genetic diseases in general.

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

The Tunisian Experience

Beta thalassaemia trait is slightly more common than sickle cell trait in Tunisia. Systematic surveys have shown a total prevalence of 4.5% haemoglobinopathy traits, with some areas with a prevalence as high as 10%. The mutations present have been defined at the molecular level. To date, 33 prenatal diagnoses have been performed, 15 for risk of beta thalassaemia and 18 for risk of sickle cell disease¹⁴. A Tunisian Association for Haemoglobinopathies and Thalassaemia has recently been started.

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

2.4 Europe

Political change means that the countries of the European Region now fall effectively into four groups: North-west, Southern, Eastern and Turkic-speaking, and this change affects the approach to haemoglobin disorders in the region. They present an important health problem in Turkic-speaking areas, and their significance is increasingly recognized in Azerbaijan and Turkey. Though they are generally uncommon in Eastern Europe, there is a significant problem in Romania (over 400 known thalassaemic patients), Bulgaria (over 300 known thalassaemic patients) and particularly in Albania. All these countries need special help in ensuring that services for these disorders are developed and supported.

A regional (European/Mediterranean) Working Group on Haemoglobin Disorders, initiated in 1986, has reported on epidemiology and available services in the Region⁶. The Working Group meets at approximately 2-yearly intervals, and has two sub-groups. One is concerned with psychosocial aspects (co-ordinator Dr John Tsiantis) and the other with identifying problems and evaluating service delivery (co-ordinator Dr Bernadette Modell, Head, WHO Collaborating Centre for the Control of Haemoglobinopathies in London). The current objective of the latter group is to promote development of national collaborative groups, and registers of patients and prenatal diagnoses. Short-term support for a European Community Concerted Action on this topic was obtained in 1991. The Concerted Action, limited to countries within the European Community (EC) and so to North-Western and Southern Europe, is now finished and the final meeting of the EC group was held prior to the meeting reported here. It has shown that registers are a useful means of contacting all doctors involved in service delivery, helping them improve their skills, identifying weaknesses in the programme, and promoting collaborative research. Key conclusions of the EC study are summarized in Tables 2-6.

Table 2 shows the estimated number of carriers of haemoglobin disorders in participating countries. Among indigenous northern Europeans thalassaemia is a typical rare inherited disease, the prevalence of carriers (mainly of beta thalassaemia) probably being about 1/1,000, corresponding to a homozygote birth rate of about 1/million, though it may be higher in some populations e.g., the Irish and the Dutch. Migration has now raised the general homozygote birth rate in North-West Europe to about 0.4/1,000.

Table 3 shows that there are now more patients with haemoglobin disorders living in North-west than in Southern Europe. There are several reasons for this rather surprising fact. Firstly, the majority of patients in North-west Europe have sickle cell disorder, in which untreated survival can be far longer than in thalassaemia. Hence, by contrast with thalassaemia, migrants included patients with sickle cell disorder. Secondly, majority of patients born in the 1950s and 60s are still alive. Thirdly, migrants from sub-Saharan Africa have a very high birth incidence of children with sickle cell disorder. Fourthly, screening and prenatal diagnosis at the community level are developing more slowly in North-West Europe than in the South, particularly for sickle cell disorder.

Table 4 shows that in the absence of prevention there would be more affected births/year in the South. However, the disease-oriented programmes of Southern Europe have been extremely effective in preventing thalassaemia (Table 5), and there are now more affected births in North-West than in Southern Europe (Table 6).

Equitable delivery of carrier screening and counselling is more complex in North-West than in Southern Europe: (a) in Northern Europe the predominant problem is sickle cell disorder, for which genetic counselling is particularly difficult, owing to its unpredictability; (b) it is difficult to deliver a specific genetic counselling service to diverse ethnic groups scattered in a large population not at-risk. For success it is necessary to integrate carrier screening and counselling into general medical services at the primary health care/mother and child health level. This requires a large-scale effort to educate health workers currently in practice in the principles of "community genetics"¹⁵; (c) because of cultural and linguistic diversity, a core of specially-trained ethnic genetic counsellors is required.

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

The French Experience

The number of subjects with heterozygous β thalassaemia and sickle cell anaemia in metropolitan France has been evaluated by the distribution and the birth rate of populations originating from countries with a high prevalence of haemoglobinopathies⁶. Taking into account the recent movements of these populations and an unevaluable immigration from Subsaharan Africa, these are probably under-estimates. A national programme for treatment and prevention of thalassaemia and sickle cell disorder is progressing steadily. Neonatal screening in Paris has shown one newborn with sickle cell disorder/1,500 pregnancies. SCD is considered a significant public health problem, as there are several thousand patients. Since 1987, a Working Group on Sickle cell Disease has been established in the region of Paris. It consists mainly of paediatricians but with the passage of time, new members, particularly adult haematologists, are being recruited. The group now numbers more than 40. Patient data are entered on a computer for prospective follow-up.

The Greek Experience

According to the experience of the WHO Collaborating Centre for the Community Control of Hereditary Diseases in Athens, about 150 new thalassaemic children would be born each year in Greece, in the absence of prevention. New births have fallen to 10-20% of expectation, and now seem to have reached a plateau. The causes of new births have been investigated: they are mainly due to complacency and lack of co-ordination between centres and between government and private health services (Table 7). For example, the government programme identifies only about 50% of carriers. The rest go to private laboratories, and most of the 10-20 annual affected births are due to carrier misdiagnosis in a private laboratory. A major deficiency is the lack of official evaluation of effects and cost-effectiveness by the Ministry of Health.

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

The Russian Experience

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

The Sardinian Experience

In the dedicated, expert and well-supported Sardinian programme in Cagliari (where the WHO Collaborating Centre for the Community Control of Hereditary Diseases is located), automated laboratory and computer methods are being introduced to obtain faster, cheaper analysis and more reliable recording of results. Carrier screening will be by haematological indices and automated HPLC analysis, which allows measurement of abnormal haemoglobins and Hb A₂ in a single step on *all samples*. Recording of patients' results on magnetic cards is now being introduced: other centres in Sardinia will have magnetic card decoders. The current plan is summarized in Figure 2.

Figure 3 shows that there are very few residual births: the main cause is still lack of information. To ensure universal information, a health education module, supported by a special budget from the Regional Ministry of Health, will be introduced in secondary schools starting from September 1993, and will consist of a book for the pupils, a book for the teachers and a video-tape.

Optional carrier screening will be offered to the pupils a few months later: informed consent will be obtained from the parents. However, screening in schools is unlikely to become universal because of differences of opinion among school directors. In parts of Italy where they have given permission in the past, screening of senior school children (with their parents' informed consent) has been reported as being very successful¹⁶.

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

2.5 South-East Asia

The majority of countries in the South-East Asian region (SEARO) find that thalassaemia is a growing problem, and in some (e.g., the Maldives¹⁷) is a recognized priority problem.

The Thai Experience

The haemoglobinopathy situation in Thailand has been reported¹. Up to 40% of the population carry one or another potentially significant haemoglobin mutation, and the major disorders, i.e., homozygous beta thalassaemia, HbE/beta thalassaemia, alpha-zero thalassaemia hydrops fetalis, and HbH disease are all common¹⁸. Estimates of the annual numbers of couples at-risk and of affected births, and rough estimate of the number of living patients in Thailand are given in Table 8. The difficulties of introducing a programme (ignorance, incurability, unpopularity with doctors, and lack of recognition by health authorities, lack of infrastructure and organization) have all been previously noted. However, considerable progress is being made.

The Thalassaemia Association of Thailand, formed under the chairmanship of Dr Soodsarkorn Tuchinda, now has more than 3,000 members including doctors, interested people and parents of affected children. National registration of patients has begun, but this will be a slow process, as they are not specifically identified in most hospital records. Molecular technology is available at the Thalassaemia Centre at Siriraj Hospital, and the types of beta and alpha thalassaemia mutations have been defined. To date, 181 prenatal diagnoses (mostly retrospective) have been carried out, 45 for risk of Hb Bart's hydrops fetalis, 46 for homozygous beta thalassaemia and 90 for HbE/beta thalassaemia. Haemoglobin disorders have been introduced into the national five-year plan for the first time, but with low priority.

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

2.6 The Western Pacific

The Chinese Experience

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

(1) A study of the distribution and frequency of α and β thalassaemia and mutation types in Southern China. Five common mutations account for over 90% of Chinese beta thalassaemia genes; the frequency of hydrops fetalis in Southern China is 1/500 newborns (2/1,000). 50% of patients with HbH disease have a non-deletional form of alpha-thalassaemia in association with the South-East Asian type of α^0 -thalassaemia: 66% are Hb Constant Spring, 16% Hb Guangxi, and the remainder are unknown. Patients

with non-deletion HbH disease in South China are usually transfusion-dependent.

(2) Development of prenatal diagnosis. The most appropriate DNA detection methods for use in China have been investigated and developed. The centre prepares kits for prenatal diagnosis; 30 professional staff have now received training by the Beijing team; a training course for up to 100 participants is held on an annual basis in the collaborating centre. 10 provinces and cities have started prenatal diagnosis for haemoglobin disorders, but chemicals are difficult to obtain.

(3) A book entitled "Techniques of gene diagnosis and its application" was published at the end of 1992. 5,000 copies have been distributed.

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

3. CONCLUSIONS AND RECOMMENDATIONS

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

The Headquarters of WHO has summarized world experience in community control of hereditary anaemias and outlined the objectives of such programmes. WHO has made the case for global comprehensive approaches (improve curative services, establish prenatal diagnosis, develop carrier detection and counselling, improve education) and the need to establish some reference centres. At the same time, the usefulness of voluntary groups and community organizations is emphasized to ensure that approaches are appropriate to individual local social-cultural-political situations.

Following WHO recommendations the health burden of hereditary anaemias could be significantly reduced in those countries and regions willing to participate. Each WHO Regional Office should support and develop regional and interregional working groups on the prevention and control of haemoglobinopathies.

WHO and TIF should collaborate in the preparation and international dissemination of information on thalassaemia and sickle cell disorder, as well as in possible strategies for their control. Such information must be regularly updated and revised in the light of research developments and experience.

WHO and TIF should stimulate funding for research projects targeted at reducing the burden of haemoglobinopathies in countries with different requirements, customs and resources.

WHO and TIF should assist in the organization of training programmes for technical and health care workers involved in haemoglobinopathy control programmes, in the light of new knowledge and possibilities.

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Fig. 1 Prenatal diagnosis of sickle cell disorder in Cuba

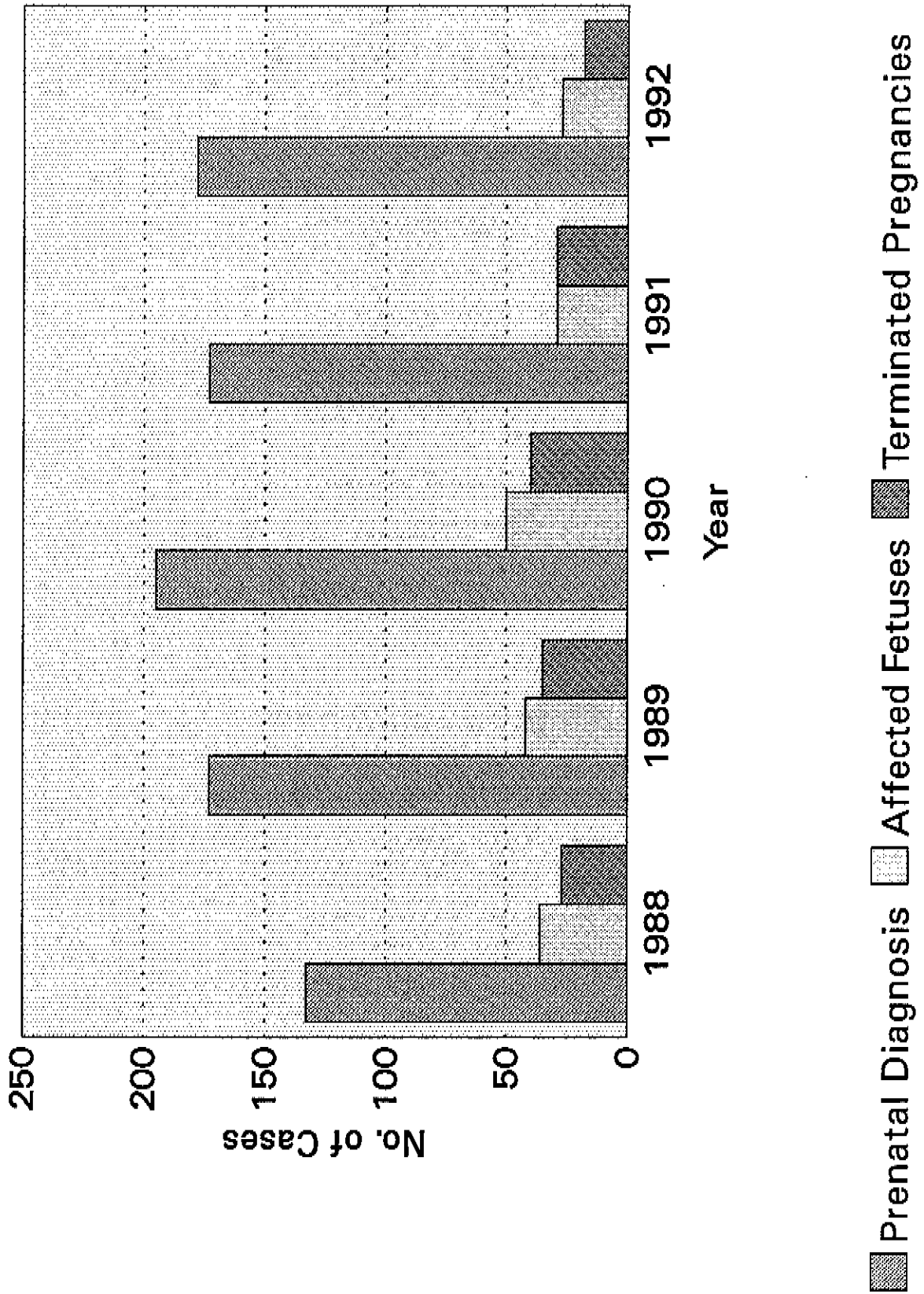


FIG. 2

ADVANCES AND ADVANTAGES IN BETA THALASSAEMIA PREVENTION IN SARDINIA

<u>METHOD</u>	<u>ADVANTAGES</u>
<p>CARRIER SCREENING</p> <p>2 automated steps: RBC indices Hb pattern analysis by HPLC</p> <p>PC programme linking patient data and lab results</p> <p>Molecular globin gene analysis Beta mutations: reverse dot-blot ARMS Alpha mutations: PCR</p>	<p>No electrophoresis, fast less expensive</p> <p>No errors, fast, easy data storage and retrieval</p> <p>No radioactivity, simple, rapid, cheap</p>
<p>PRENATAL DIAGNOSIS</p> <p>Reverse dot-blot: ARMS VNTRs</p>	<p>↓</p> <p>No mistakes</p>

New strategy: health education and screening in state secondary schools

Fig. 3 Fall in the birth rate of homozygous β -thalassaemia in Sardinia

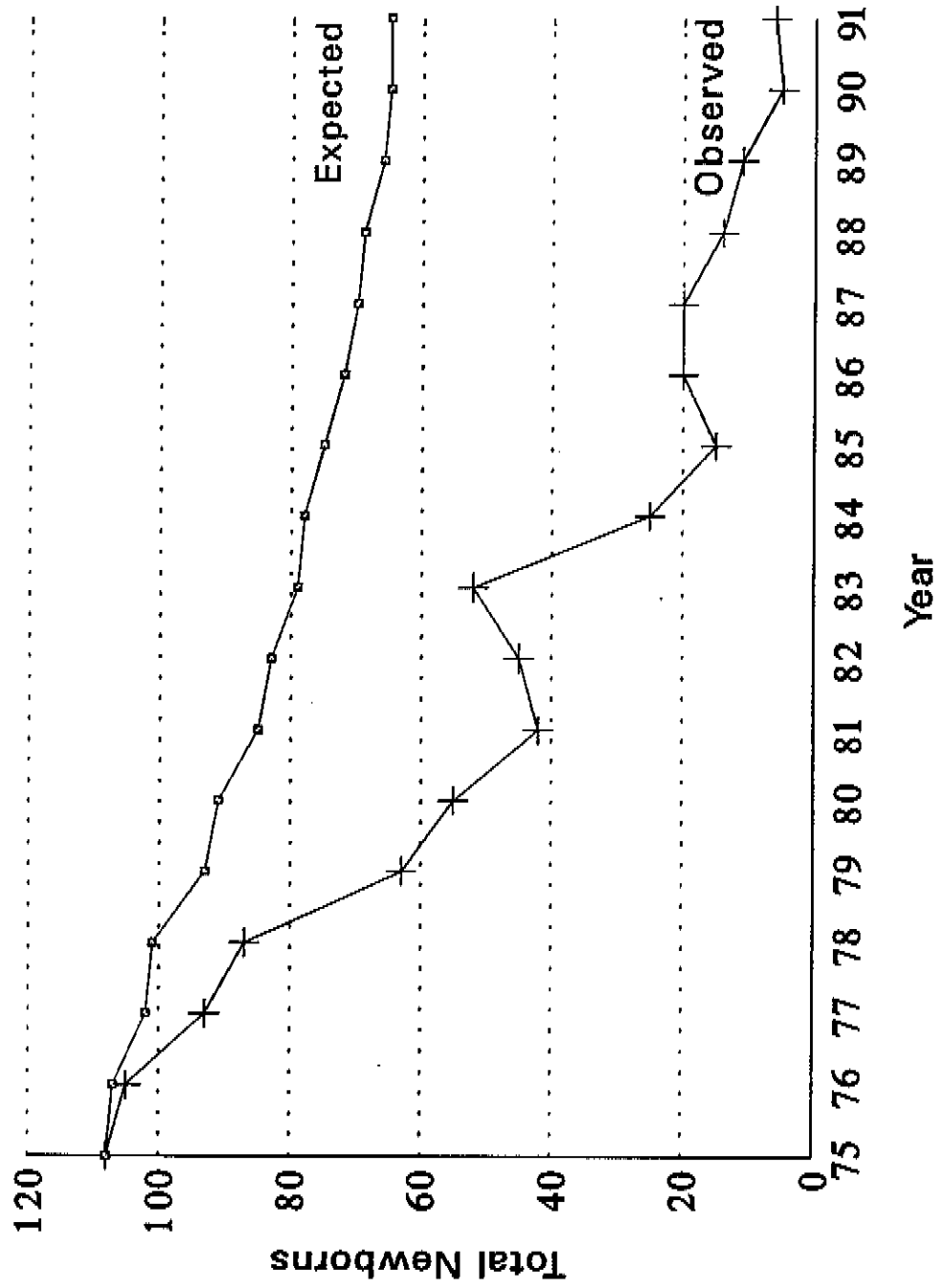


Table 1

RESULTS OF A NIGERIAN NATIONAL SURVEY OF THE PREVALENCE OF
HAEMOGLOBIN DISORDERS AMONG 16,000 ADULTS (>15 YEARS OLD)

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

Comment

The survey gives the following gene frequencies: A = .871
S = .119
C = .01

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

Table 2

ESTIMATED NUMBERS OF CARRIERS OF THALASSAEMIA AND
SICKLE CELL DISORDERS IN EUROPEAN COMMUNITY COUNTRIES

COUNTRY	CARRIERS IN GROUPS AT RISK	IN INDIGENOUS POPULATION, ASSUMING 1/1,000	PER CENT OF POPULATION CARRIERS
Belgium	30,900	9,850	0.41
Denmark	2,000	5,110	0.14
France	195,000	54,940	0.46
Germany	69,000	78,160	0.19
Netherlands	25,000	14,420	0.27
UK	170,000	55,620	0.41
Subtotal	491,900	218,100	
Greece	888,000		9.0
Italy	2,850,000		5.0
Portugal	153,000		1.6
Spain	193,500		0.51
Subtotal	3,946,800		

Table 3

KNOWN LIVING PATIENTS IN THE EUROPEAN COMMUNITY (APPROXIMATE NUMBERS)

Country	Beta Thal	SCD	Total	% SCD
Belgium	54	76	130	59
Denmark	14	10	24	42
France	350	2,500	2,850	88
Germany	296	68	364	19
Netherlands	25	27	52	51
UK	598	4,000	4,600	87
Subtotal	1,337	6,691	8,023	83
Greece	1,528	406	1,934	21
Italy	4,475	400	4,875	8
Portugal	72	218	290	75
Spain	94	7	101	7
Subtotal	6,169	1,031	7,200	14
TOTAL	7,506	7,722	15,228	51

At least 53% of the total are Northern Europe

Table 4

ESTIMATED ANNUAL AFFECTED BIRTHS IN THE EUROPEAN COMMUNITY
 IN THE ABSENCE OF GENETIC COUNSELLING
 (potential births)

Country	Beta Tm	Alpha Tm	SCD	Total
Belgium	3	-	6	9
Denmark	0.7	+	1.1	1.8
France	15	>3	82	100
Germany	11	-	+	11
Netherlands	3.5	1	7.5	12
UK	40	>6	115	161
Subtotal	73	>10	212	>295 (38%)
Greece	130	+	20	150
Italy	303	-	11	314
Portugal	2	-	11	13
Spain	3	?	+	>3
Subtotal	438	+	42	480 (62%)
TOTAL	511	>10	254	>775

Table 5

**% OF FALL IN AFFECTED BIRTHS IN THE EUROPEAN COMMUNITY
DUE TO GENETIC COUNSELLING**

(Calculated from observed or estimated births,
and known prenatal diagnoses)

Country	Beta Thal	SCD	Total
Belgium	11%	80%	57%
Denmark	>50%	70%	50%
France	27%	20%	21%
Germany	36%	33%	35%
Netherlands	?	?	?
UK	50%	22%	30%
Greece	85%	85%	85%
Italy	79%	40%	78%
Portugal	13%	7%	8%
Spain	20%	-	17%

Table 6

MAXIMUM FALL IN ANNUAL BIRTHS OF CHILDREN WITH
MAJOR HAEMOGLOBIN DISORDERS IN EUROPEAN COMMUNITY COUNTRIES

(Calculated from estimated or observed births, and prenatal diagnoses)

Region	Beta Thal	SCD	Total	% Fall
Northern Europe	73 - >43	216 - >170	289 - >212	(27%)
Southern Europe	438 - >86	43 - >19	481 - >110	(77%)
TOTAL	511 - >129	259 - >189	770 - >322	(58%)

* 212/322 annual affected births (65%) are in Northern Europe

Table 7

CAUSES FOR THE PLATEAU IN THE BIRTH-RATE OF
THALASSAEMIC INFANTS IN GREECE

(Analysis of Dr D. Loukopoulos)

Decreased interest of the public health authorities

- Increased pressure for better patient care
- Increased costs
- Logistic problems and lack of administrative support
- Underestimation of the problem, overconfidence and complacency

Decreased enthusiasm of medical and paramedical staff

- Lack of a career structure
- Negative, long-lasting administrative problems

Lack of co-ordination

- A national thalassaemia committee exists but has no real power
- A powerless "central" unit
- Independent units with more interest in research than service

Confusion/misunderstanding of the borders between treatment, prevention and research

- Misunderstanding of the roles of academic institutions, clinicians, social workers and scientists
- Possessiveness about results

Lack of evaluation and assessment of cost-effectiveness

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Table 8

ESTIMATES OF THE FREQUENCY OF THE
FOUR COMMONEST HAEMOGLOBINOPATHIES IN THAILAND

DISEASE	COUPLES AT RISK (per year)	BIRTHS (per year)	LIVING PATIENTS
1. Homozygous β -thalassaemia	2,500	625	6,250 ¹
2. β -thalassaemia/Hb E	13,000	3,250	97,500 ²
3. Hb Bart's Hydrops Fetalis	5,000	1,250	0
4. Hb H Disease	28,000	7,000	420,000 ³

^{1,2,3} Estimated life expectancy are 10, 30 and 60 years, respectively.

ANNEX 1

EDUCATIONAL MATERIALS ON HAEMOGLOBIN DISORDERS

- A The following educational materials are available from the Hereditary Diseases Programme, World Health Organization, CH-1211 Geneva 27, Switzerland. These documents provide information in a simple, clear written form. They are intended to be used only as a basis for developing appropriate local materials. Within each country, they should be adapted by appropriate experts, with regard to content and length, the local educational level and cultural approaches.
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. Guidelines on the Control of Haemoglobin Disorders.
 5. 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
- B The following information is available from the Thalassaemia International Federation (TIF), P.O. Box 8503, Nicosia, Cyprus
1. What is thalassaemia? Available in English and Italian. A detailed booklet for health workers, 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.

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ANNEX 2

GUIDELINES FOR THE CONTROL OF HAEMOGLOBIN DISORDERS

This document provides guidance on the requirements for a control programme for haemoglobin disorders, in terms of the basic epidemiological information required, service structure and development, staff, equipment, and costs as far as possible. The contents are as follows:

1. INTRODUCTION
 2. OUTLINE OF A PROGRAMME
 3. ASSESSING EPIDEMIOLOGY AND HEALTH BURDEN
 - 3.1 Factors affecting calculation of birth incidence
 - 3.2 Use of epidemiological data in calculating health burden
 - 3.3 How common must haemoglobin disorders be for a control programme to be indicated?
 4. CENTRES FOR HAEMOGLOBIN DISORDERS
 - 4.1 Role of support associations
 5. TREATMENT
 - 5.1 Requirements for treating thalassaemia major
 - 5.2 Treating thalassaemia in developing countries
 - 5.3 Requirements for treating sickle cell disorders
 - 5.4 Neonatal diagnosis of sickle cell disorders
 6. CARRIER SCREENING
 - 6.1 Choice of screening strategy
 - 6.2 Identifying carriers
 - 6.3 Requirements for carrier screening
 7. GENETIC COUNSELLING
 - 7.1 Counselling single carriers
 - 7.2 Counselling carrier couples
 - 7.3 Requirements
 8. PRENATAL DIAGNOSIS
 - 8.1 Obstetric aspects
 - 8.2 Laboratory aspects
 - 8.3 Requirements
 9. EDUCATIONAL COMPONENT
 - 9.1 Professional education
 - 9.2 Public education
 - 9.3 Educational materials
 - 9.4 Requirements
 10. EVALUATION
 - 10.1 Methods
 - 10.2 Cost/benefit analysis
 - 10.3 Requirements
 11. SUMMARY OF REQUIREMENTS FOR A CONTROL PROGRAMME FOR HAEMOGLOBIN DISORDERS
 12. REFERENCES
- TABLES
- FIGURES
- ANNEX 1 Country estimates of prevalence of haemoglobin disorders
- ANNEX 2 Measuring the frequency of consanguineous marriage
- ANNEX 3 List of national thalassaemic support associations
- ANNEX 4 Suggestions for a register of patients with haemoglobin disorders

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ANNEX 3

LIST OF WORKING PAPERS AVAILABLE UPON REQUEST

1. Progress on sickle cell disorders in Africa. A Nigerian Perspective.
Professor O.O. Akinyanju.
2. Genetic Services for the Haemoglobinopathies in Latin-America.
Dr V. Fenchaszadeh.
3. The National Thalassaemia Programme in Pakistan. Dr M. Saleem.
4. Progress Report on Haemoglobinopathies in Tunisia.
Professor S. Fattoum.
5. Progress Report on Haemoglobinopathies, Thalassaemias and Enzymopathies in
Saudi Arabia. Professor M.A.F. El-Hazmi.

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