

## Appendix-A

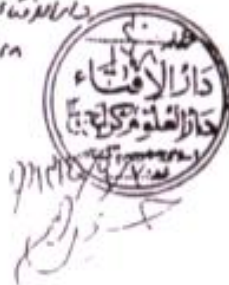
Opinion of Mr. Mohammad Taqi Othmani regarding termination of Pregnancy for a serious genetic disorder.

۱- حمل میں جب جان پڑ جائے (یعنی ۱۴ دن بعد) تو اسقاطِ حمل کی سزا عموماً بائبل  
 کے تحت نہیں ہے، اگرچہ طبی تحقیق کے ذریعہ حمل میں کسی بیماری کا لائق غالب ہی کیوں  
 نہ ہو جائے، مگر چونکہ جان پڑنے کے بعد اسقاطِ حمل قتل کے مشابہت اور زندہ بچہ کو  
 خواہ وہ کتنا ہی شدید بیمار اور معذور کیوں نہ ہو قتل کرنا کسی صورت جائز  
 نہیں ہے۔ اس طرح حمل میں جان پڑ جانے کے بعد اسقاط کرنا اور کر دانا بھی  
 جائز نہ ہوگا، بالخصوص جبکہ امکان موجود ہے کہ طبی رپورٹ پر ہی طرح درست  
 نہ ہو یا رپورٹ درست ہو مگر پیدائش کے بعد اللہ کا حکم ہے۔ یہ سزا نہیں ہے۔

۲- البتہ حمل میں جان پڑنے سے قبل اگر طبی تحقیق سے حمل میں کوئی  
 بیماری یا نقص کا علم ہو جائے اور ماہانہ اور طبیب کے اسقاط کا مشورہ دیا  
 تو والدہ کیلئے سزا عموماً اس قدر ہلکی نہیں ہے۔

في اثم ميتة قال في النهر لقي رجل يباح الاستسقاء بعد الحمل نعم يباح ما لم  
 يتحقق منه شيء وان يكن ذلك الا بعد مائة وعشرين يوما وهذا يقتضي انهم  
 ارادوا بالتخليق نفع الروح والآن فهو يخلط لأن التخليق يتحقق بالثابت بعدة قبل هذه  
 المدة كذا في الفتح والحلا فم يفتيه عدم توقف جوار استعاطها قبل المدة المذكورة  
 على اذن النروج. وحي كراهية التي نية فلا أقول بالجل انا ان لو كسر بعض العيب  
 ضمنه لأنه اصل العيب فلما كان يترأخه بالحياة فلا أقل من أن يلقها ثم هنا  
 اذا استقلت بغير عنده قال ابن وهبان ومن الأئمة أن ينقطع لبنها بعد ظهور  
 الحمل وليس ثوب العيب ما ليس جرمه العسر ونحوه لعله له شيء من ذلك

شعبہ معذوریت و طبی مشورہ  
 دارالافتاء - ۵، سیدنا بازار، کراچی  
 ۱۸/۹/۲۰۱۵ء



الحجرات  
 محمد تقی عثمانی  
 ۱۹-۹-۲۰۱۵ء  
 مفتی

## Appendix-B

### QUESTIONNAIRE FOR THE PARENTS OF THALASSAEMICS

Reference: \_\_\_\_\_

–

Father's education: [None] [Primary] [Matric] [Above matric]

Mother's education: [None] [Primary] [Matric] [Above matric]

Monthly income of the family: [< Rs. 5,000] [Rs. 5,000-10,000] [>Rs. 10,000]

Total No of children: [ \_\_\_\_\_ ]

No of thalassaemic children: [ \_\_\_\_\_ ]

Does thalassaemia affect your family life ? [A little] [Often] [A lot]

Does thalassaemia affect your financial situation ? [A little] [Often] [A lot]

Do you know that prenatal diagnosis is available in Pakistan ? [Yes] [No]

Who told you about prenatal diagnosis ?

[ \_\_\_\_\_ ]

Did you have a pregnancy in the last 2 years ? [Yes] [No]

If yes, did you request prenatal diagnosis ? [Yes] [No]

If no, then why not ?

[ \_\_\_\_\_ ]

Would you request prenatal diagnosis in your future pregnancies ?

[ \_\_\_\_\_ ]

Do you agree with termination of pregnancy for thalassaemia ? [Yes] [No]

## REFERENCES

- Altman DG (1991) Practical statistics for medical research. Chapman and Hall London.
- Al-Quran. Sura Al-Nisa: verse 22
- Al-Quran. Sura Al-Momenoon: verse 14
- Alwan AA and Modell B (1997) Community control of genetic and congenital disorders. EMRO Technical Publication Series 24. WHO regional office for the Eastern Mediterranean Region. ISBN 92-9021-220-9ISSN 1020
- Amselem S, Nunes V, Vidaud M, Estivill X, Wong C, d'Auriol L, Vidaud D, Gallbert F, Baiget M, Goossens M (1988) Determination of the spectrum of  $\beta$ -thalassaemia genes in Spain by use of Dot-Blot analysis of amplified  $\beta$ -globin DNA. *Am J Hum Genet* 43: 95
- Angastiniotis M and Hadjiminias M (1981) Prevention of thalassaemia in Cyprus. *Lancet* i: 369
- Angastiniotis M, Kyrikidou S, Hadjiminias M (1986) How thalassaemia was controlled in Cyprus. *World Health Forum* 7: 291
- Annual Report of Health Services in Pakistan (1995-96) Office of the Director General Health, Ministry of Health, Government of Pakistan.
- Antonarakis SE, Kazazian HH, Jr, Orkin SH (1985) DNA polymorphism and molecular pathology of the human gene clusters. *Hum Genet* 69: 1
- Antonarakis SE (1989) Diagnosis of genetic disorders at the DNA level. *N Eng J Med* 320: 153
- Anwar MJ, Saleem M, Anwar M, Ahmad S, Alvi EA, Khattak MF (1995) Comparison of indigenously prepared microcolumns for haemoglobin A<sub>2</sub> estimation. *Pak J Pathol* 6: 75
- Barrai I and Vullo C (1980a) Screening for  $\beta$ -thalassaemia heterozygotes. *Lancet* ii: 1257
- Barrai I and Vullo C (1980b) Assessment of prospective genetic counselling in the Ferrara area. *Am J Med Genet* 6: 195
- Basak AN, Ozeelik H, Ozer A, Tolun A, Aksoy M, Agaoglu L, Ridolfi F, Ulukutlu L, Akar N, Gurgey A, Kirdar B (1992) The molecular basis of  $\beta$ -thalassaemia in Turkey. *Hum Genet* 89: 315
- Bashi J (1977) Effects of inbreeding on cognitive performance. *Nature* 266: 440
- Basu SK (1975) Effects of consanguinity among North Indian Muslims. *J Pop Res* 2: 57
- Baysal E, Indrak K, Bozkurt G, Berkalp A, Aritkan E, Old JM, Ioannou P, Angastiniotis M,

- Droushiotou A, Yuregir GT, Kilinc Y, Huisman TJH (1992) The  $\beta$ -thalassaemia mutations in the population of Cyprus. *Br J Haematol* 81: 607
- Baysal E and Huisman THJ (1994) Detection of common deletional  $\alpha$ -thalassaemia-2 determinants by PCR. *Am J Haematol* 46: 208
- Baysal E and Carver MFH (1995) The  $\beta$ - and  $\delta$  thalassaemia repository (Eith edition). *Haemoglobin* 19: 213
- Baysal E, Kleanthous M, Bozkurt G, Kyri A, Kalogirou E, Angastiniotis M, Ioannou P Huisman THJ (1995b)  $\alpha$ -thalassaemia in the population of Cyprus. *Br J Haematol* 89: 496
- Beuzard Y (1996) Towards gene therapy of haemoglobinopathies. *Semin Haematol* 33: 43
- Bhatti FA, Amin M and Saleem M (1995) Prevalence of antibody to hepatitis C virus in Pakistani thalassaemics by particle agglutination test utilizing C-200 and C22-3 viral antigen coated particles. *J Pak Med Assoc* 45: 269
- Bianco I and Silvestroni E (1983) A highly cost effective method of mass screening for thalassaemia. *Br Med J* 286: 1007
- Bianco I, Graziani B, Lerone M, Congedo P, Aliquo MC, Ponzini D, Braconi F, Foglietta E, Modiano G (1985) Prevention of thalassaemia major in Latium (Italy). *Lancet* ii: 888
- Bittles AH (1980) Inbreeding in human populations. *Biochem Rev* L: 108
- Bittles AH (1990) Consanguineous marriage: current global incidence and its relevance to demographic research. Population studies centre, University of Michigan. Research report No 90-186.
- Bittles AH, Mason WM, Greene J, Rao AR (1991) Reproductive behaviour and health in consanguineous marriages. *Science* 252: 789
- Bittles AH, Grant JC, Shami SA (1993) An evaluation of consanguinity as a determinant of reproductive behaviour and mortality in Pakistan. *Int J Epidemiol* 22: 463
- Bittles AH (1994) The role and significance of consanguinity as a demographic variable. *Population and Development Review* 20: 561
- Bittles AH and Neel JV (1994) The costs of human inbreeding and their implications for variations at the DNA level. *Nature Genet* 8: 117
- Bittles AH (1995) When cousins marry: A review of consanguinity in the middle east. *Perspectives in Hum Biol* 1: 71
- Bodmer WF and Cavalli-Sforza LL (1976) Genetics evolution and man. W.H. Freeman and Company, San Francisco.

- Boehm CD and Kazazian HH Jr (1989) Examination of fetal DNA for haemoglobinopathies. In, Perinatal Haematology ed. Alter BP. *Methods Haematol* 21: 1
- Bokhari SHS (1975) History of Baluchistan (Taarikh-e-Baluchistan). United Booksellers Karachi.
- Bowden DK, Vickers MA, Higgs DR (1992) A PCR-based strategy to detect the common severe determinants of  $\alpha$ -thalassaemia. *Br J Haematol* 81: 104
- Brambati B, Lanzani A and Oldrini A (1988) Transabdominal chorionic villus sampling. Clinical experience of 1159 cases. *Prenatal Diagnosis* 8: 609
- Brittenham GM (1992) Development of iron-chelating agents for clinical use. *Blood* 80: 569
- Brown JM, Thein SL, Weatherall DJ, Mar KM (1992) The spectrum of  $\beta$ -thalassaemia in Burma. *Br J Haematol* 81: 574
- Bunday S, Alam AH, Kaur A, Mir S, Lancashire RJ (1991) Why do UK born Pakistani babies have high perinatal and neonatal mortality rates? *Paediatric and Perinatal Epidemiology* 5: 101
- Bunn HF and Forget BG (1986) Haemoglobin: Molecular, Genetic and Clinical aspects. WB Saunders, Philadelphia.
- Burney MI (1993) Health and medical profile of the Muslim world. COMSTECH Secretariat, Islamabad.
- Cai SP and Kan YW (1990) Identification of the multiple  $\beta$ -thalassaemia mutations by Denaturing Gradient Gel Electrophoresis. *J Clin Invest* 85: 550
- Cao M, Furbetta M, Galenello R, Melis MA, Anguis A, Ximenes A, Rosatelli C, Ruggeri R, Addis M, Tuveri T, Falchi AM, Paglietti E, Scalas MT (1981) Prevention of homozygous  $\beta$ -thalassaemia by carrier screening and prenatal diagnosis in Sardinia. *Am J Hum Genet* 33: 592
- Cao A, Falchi AM, Tuveri T, Scalas MT, Monni G, Rosatelli C (1986) Prenatal diagnosis of thalassaemia major by fetal analysis: experience with 1000 cases. *Prenatal Diagnosis* 6: 159
- Cao A (1987) Results of programmes for antenatal detection of thalassaemia in reducing the incidence of the disorder. *Blood Rev* 1: 169
- Cao A, Gabutti V, Masera G, Modell B, Sarchia G, Vullo C (1992) 1992 management protocol for the treatment of thalassaemia patients. Cooley's Anaemia Foundation of USA, New York.
- Cao A and Rosatelli MC (1993) Screening and prenatal diagnosis of the haemoglobinopathies. *Baillieres Clin Haematol* 6: 263

- Cao A, Galanello R Rosatelli MC (1994) Genotype-phenotype correlations in  $\beta$ -thalassaemias. *Blood Rev* 8: 1
- Census of Pakistan (1981) Bureau of statistics, Islamabad, Pakistan .
- Centre for Disease Control and Prevention (1995) Chorionic Villus Sampling and amniocentesis: recommendations for prenatal counselling. *Morbidity and Mortality Weekly Report* 44: 1
- Chan V, Chan TK, Chebab FF, Todd D (1987) Distribution of  $\beta$ -thalassaemia mutations in South China and their association with haplotypes. *Am J Hum Genet* 41: 678
- Chebab FF, Der Kaloustian V, Khouri FP, Deeb SS, Kan YW (1987) The molecular basis of  $\beta$ -thalassaemia in Lebanon: application of prenatal diagnosis. *Blood* 69: 1141
- Coleman D (1980) A note on the frequency of consanguineous marriages in Reading, England in 1972/1973. *Hum Heredity* 30: 278
- Collins FS Weisman SM (1984) The molecular genetics of human haemoglobin. Progress in Nucleic Acid Research and Molecular Biology (Ed Cohn WE and Moldave K) New York Academic Press.
- Committee on DNA technology in forensic science (1992) DNA technology in forensic science. National Academy Press, Washington, DC.
- Coquelet ML, Jaeger G, Brampt IC (1983) Detection of haemoglobin abnormalities in 35,000 exchange students. *Bull Soc Pathol Exot Filiales* 76: 183 (English Abstract).
- Craig JE, Kelly SJ, Barnetson R, Thein SL (1992) Molecular characterization of a novel 10.3 kb deletion causing  $\beta$ -thalassaemia with unusually high Hb-A<sub>2</sub>. *Br J Haematol* 82: 107
- Crowley JP, Sheth S, Capone RJ, Schilling RF (1987) A paucity of thalassaemia trait in Italian men with myocardial infarction. *Acta Haematol* 78: 249
- Cunningham JM Jane SM (1996) Haemoglobin switching and fetal haemoglobin reactivation. *Semin Haematol* 33: 9
- Dacie JV and Lewis SM (1991) Practical Haematology. Churchill Livingstone, London.
- Darr A and Modell B (1988) The frequency of consanguineous marriages among British Pakistanis. *J Med Genet* 25: 186
- Dash S (1985) Beta thalassaemia trait in the Punjab (North India). *Br J Haematol* 61: 185
- Deka R, Chakraborty R, DeCruo S, Rothhammer F, Barton SA, Ferrell RE (1992) Characterization of polymorphism at a VNTR locus 3' to the Apolipoprotein B gene in five human populations. *Am J Hum Genet* 51: 1325

- Dode C, Krishnamoorthy R, Lamb J, Rochette J (1992) Rapid analysis of  $-\alpha^{3.7}$  thalassaemia and  $\alpha\alpha^{\text{anti}3.7}$  triplication by enzymatic amplification analysis. *Br J Haematol* 82: 105
- Dozy AM, Kan YM, Embury SH, Mentzer WC, Wang WC, Lubin B, Davis JR, Koenig HM (1979) Alpha globin gene organization in Blacks precludes the severe form of  $\alpha$ -thalassaemia. *Nature* 280: 605
- Earley A, Valman HB, Altman DG, Pippard MJ (1990) Microcytosis, iron deficiency, and thalassaemia in preschool children. *Arch Dis Child* 65: 610
- Economic survey (1995-96) Government of Pakistan, Finance Division, Economic Advisor's Wing, Islamabad.
- Embury SH, et al (1980) Two different molecular organizations account for the single  $\alpha$ -globin gene of the  $\alpha$ -thalassaemia-2 genotype. *J Clin Invest* 66: 1319
- Engeleke DR, Hoener PA, Collins FS (1988) Direct sequencing of enzymatically amplified human genomic DNA. *Proc Natl Acad Sci, USA* 85: 544
- Europa World Year Book (1995) Pakistan: Statistical survey.
- Fairweather DVI, Model B, Berdoukas V, Alter BP, Nathan DG, Loukopoulas D, Wood W, Cleg JB, Weatherall DJ (1978) Antenatal diagnosis of thalassaemia major. *Br Med J* 1: 350
- Farzana F, Zuberi SJ, Hashmi JA (1975) Prevalence of abnormal haemoglobin and thalassaemia trait in a group of professional blood donors and hospital staff in Karachi. *J Pak Med Assoc* 25: 237
- Fessas P (1986) Prevention of thalassaemia and haemoglobin S syndromes in Greece. *Acta Haematol* 78: 168
- Flint J, Harding RM, Clegg JB, Boyce AJ (1993) Why are some genetic diseases common? Distinguishing selection from other processes by molecular analysis of globin gene variants. *Hum Genet* 92: 91
- Fodde R and Losekoot M (1994) Mutation detection by denaturing gradient gel electrophoresis (DGGE). *Hum Mutation* 3: 83
- Friedman MJ Traeger W (1981) The biochemistry of resistance to malaria. *Sci Am* 244: 154
- Galanello R, Ruggeri R, Paglietti E, Addis M, Melis A, Cao M (1983) A family with segregating triplicated alpha globin loci and beta thalassaemia. *Blood* 62: 1035
- Gallerani M, Scapoli C, Cicognani I, Ricci A, Martinelli L, Cappato R, Manfredini R, Dall'Ara G, Faggioli M, Pareschi PL (1991) Thalassaemia trait and myocardial infarction: low infarction incidence in male subjects confirmed. *J Intern Med* 230: 109
- Garewal G, Fearon CW, Warren TC, Marwaha M, Marwaha RK, Mahadik C, Kazazian HH

- (1994) The molecular basis of  $\beta$ -thalassaemia in Punjabi and Maharashtran Indians includes a multilocus aetiology involving triplicated  $\alpha$ -globin loci. *Br J Haematol* 86: 372
- Ghanem N, Girodon E, Vidaud M, Martin J, Fanen P, Plassa F, Goossen M (1992) A comprehensive scanning method for rapid detection of  $\beta$ -globin gene mutations and polymorphisms. *Hum Mutation* 1: 229
- Giardina PJ and Grady RW (1995) Chelation therapy in  $\beta$ -thalassaemia: The benefits and limitations of desferrioxamine. *Semin Haematol* 32: 304
- Gilman JG and Huisman THJ (1985) DNA sequence variation associated with elevated fetal  $\gamma$  globin production. *Blood* 66: 783
- Golbus MS and Appelman Z (1990) Chorionic Villus Sampling. In assessment and care of the fetus, physiological, clinical and methodological principles. Ed Eden RD and Boehna FH. Prentice Hall International (UK) Limited, London.
- Gonzalez-Redondo JM, Stoming TA, Lanclos KD, Gu YC, Kutlar A, Kutlar F, Nakatsuji T, Deng B, Han IS, McKie VC, Huisman THJ (1988) Clinical and genetic heterogeneity in Black patients with homozygous  $\beta$ -thalassaemia from the Southern United States. *Blood* 72: 1007
- Goossens M, Dozy AM, Embury SH, Zachariades Z, Hadjiminias MG, Stamatoyannopoulos G, Kan YW (1980) Triplicated  $\alpha$ -globin loci in humans. *Proc Natl Acad Sci USA* 77: 518
- Gosden C (1993) Cell Culture. In Prenatal Diagnosis and Screening, edited by Brock DJH, Rodeck CR, Ferguson-Smith MA. Churchill Livingstone. Edinburgh, London.
- Gringras P, Wonke B, Old J, Fitches A, Valler D, Kuan AM, Hoffbrand AV (1994) Effect of  $\alpha$  thalassaemia trait and enhanced  $\gamma$  chain production on disease severity in  $\beta$  thalassaemia major and intermedia. *Arch Dis Child* 70: 30
- Grompe M (1993) The rapid detection of unknown mutations in nucleic acids. *Nature Genetics* 5: 111
- Grosveld F, Blom van Assendelft, Greaves DR, Kollias B (1987) Position-independent, high-level expression of the human  $\beta$ -globin gene in transgenic mice. *Cell* 51: 975
- Gupta RB, Tiwary RS, Pande PL, Kutlar F, Oner C, Oner R, Huisman THJ (1991) Haemoglobinopathies among the Gond Tribal groups of Central India; interactions of  $\alpha$ - and  $\beta$ -thalassaemia with  $\beta$ -chain variants. *Haemoglobin* 15: 441
- Halliday T (1990) Insight guides: Pakistan. APA Publications (HK) Ltd.
- Hameed MA and Chaudhry KSA (1983) Hereditary persistence of fetal haemoglobin and thalassaemia trait in our population (a study of 300 adult subjects). *Rawal Med J* 13: 2
- Harper PS (1993) Practical genetic counselling. Butterworth-Heinemann London.



- Hashmi JA and Farzana F (1976) Thalassaemia trait, abnormal haemoglobins and raised fetal haemoglobin in Karachi. *Lancet* 1: 206
- Hassan K, Ikram N, Dodhy M, Burki UF, Tahir M (1997) Prevalence of  $\beta$ -thalassaemia trait in and around Islamabad. *J Rawalpindi Medical College* 1: 18
- Hathout H (1974) Induced abortion; In, Islam and Family Planning edited by Nazer IR, Karmi HS, Zayid MY. Imprimerie Catholique Beirut.
- Higgs DR, Hill AVS, Weatherall DJ, Clegg JB (1984) Independent recombination events between the duplicated human  $\alpha$ -globin genes; implications for their concerted evolution. *Nucleic Acids Res* 12: 6965
- Higgs DR, Vickers MA, Wilkie AOM, Pretorius I-M, Jarman AP, Weatherall DJ (1989) A review of the molecular genetics of the human  $\alpha$ -globin gene cluster. *Blood* 73: 1081
- Higgs DR, Wood WG, Jarman AP, Sharpe J, Lida J, Pretorius I-M, Ayyub H (1990a) A major positive regulatory region located far upstream of the human  $\alpha$ -globin gene locus. *Genes and Development* 4: 1588
- Higgs DR, Wood WG, Jarman AP, Vickers MA, Wilkie AOM, Lamb J, Vyas P, Bennett JP (1990b) The  $\alpha$ -thalassaemias. *Ann NY Acad Sci* 612: 15
- Hinchliffe RF Lilleyman JS (1995) Frequency of coincidental iron deficiency and beta-thalassaemia trait in British Asian children. *J Clin Pathol* 48: 594
- Horn GT, Richards B, Klinger W (1989) Amplification of a highly polymorphic VNTR segment by the polymerase chain reaction. *Nucleic Acid Res* 17: 2140
- Housman D (1995) Human DNA polymorphism. *New Engl J Med* 332: 318
- Hultman T, Stahl S, Hornes E, Uhlen M (1989) Direct solid phase sequencing of genomic and plasmid DNA using magnetic beads as a support. *Nucleic Acids Res* 17: 4937
- Huisman THJ (1990a) Frequencies of common  $\beta$ -thalassaemia alleles among different populations: variability in clinical severity. *Br J Haematol* 75: 454
- Huisman THJ (1990b) Silent  $\beta$ -thalassaemia and thalassaemia intermedia. *Haematologica* 75: 1
- Huisman THJ (1996) Molecular genetics of  $\alpha$ -thalassaemia. Educational programme of the 26<sup>th</sup> Congress of the International Society of Haematology, Singapore, 25-29 August: 233
- Ihsanullah S, Nawab SH, Rehman N (1985) Pattern of haemoglobinopathies in Karachi. Annual meeting of the Pakistan Association of Pathologists, Multan.
- Imaizumi Y (1986) A recent survey of consanguineous marriages in Japan. *Clin Genet* 30:

International Committee for Standardization in Haematology (1978) Recommendations for selected methods for quantitative estimation of Hb-A<sub>2</sub> and for Hb-A<sub>2</sub> reference preparation. *Br J Haematol* 38: 573

Jones JS and Rouhani S (1986) Human evolution: how small was the bottleneck. *Nature* 319: 449

Joshi LM and Singh F (1976) History of the Punjab. Everest Press Delhi.

Kan YW, Golbus MS, Klein P, Dozy AM (1975) Successful application of prenatal diagnosis in a pregnancy at risk for homozygous  $\beta$ -thalassaemia. *New Engl J Med* 292: 1096

Kanavakis E, Wainscoat JS, Wood WG, Weatherall DJ, Cao A, Furbetta M, Galanello R, Georgiou D, Sophocleous T (1982) The interaction of  $\alpha$  thalassaemia with heterozygous  $\beta$  thalassaemia. *Br J Haematol* 52: 465

Kattamis C, Efremov G, Pootrakul S (1981) Effectiveness of one tube osmotic fragility screening in detecting  $\beta$ -thalassaemia trait. *J Med Genet* 18: 266

Kattamis CA and Kattamis AC (1995) Management of thalassaemias: growth and development, hormone substitution, vitamin supplementation, and vaccination. *Semin Haematol* 32: 269

Kazazian HH, Jr, Orkin SH, Antonarakis SE, Sexton JP, Boehm CD, Goff SC, Waber PG (1984) Molecular characterization of seven  $\beta$ -thalassaemia mutations in Asian Indians. *EMBO Journal* 3: 593

Kazazian HH Jr and Boehm CD (1988) molecular basis and prenatal diagnosis of  $\beta$ -thalassaemia. *Blood* 72: 1107

Kazazian HH, Jr, Dowling CE, Boehm CD, Warren TC, Economou EP, Katz J, Antonarakis SE (1990) Gene defects in  $\beta$ -thalassaemia and their prenatal diagnosis. *Ann NY Acad Sci* 612: 1

Khan AZ (1980) History and culture of Sindh. Royal Book Company, Karachi.

Khan LR and Hayee A (1986) A study of haemoglobin Bart's in cord blood. *J Pak Med Assoc* 36: 285

Khattak MF (1987) Prevalence of heterozygous beta thalassaemia and abnormal haemoglobin genes in adult healthy Pakistani population. MPhil Thesis, Quaid-e-Azam University, Islamabad.

Khattak MF and Saleem M (1992a) Prevalence of heterozygous  $\beta$ -thalassaemia in the Northern areas of Pakistan. *J Pak Med Assoc* 42: 32

- Khattak MF and Saleem M (1992b) Structural haemoglobin variants in adult healthy population of Northern Pakistan. *Pak J Pathol* 3: 85
- Khlat M, Halabi S, Khudr A, Der Kaloustian VM (1986) Perception of consanguineous marriages and their genetic effects among a sample of couples from Beirut. *Am J Med Genet* 25: 299
- Kimpton CP, Gill P, Walton A, Urquhart A, Millican ES, Adams M (1993) Automated DNA profiling employing multiplex amplification of short tandem repeat loci. *PCR Methods Applications* 3: 13
- Kimura A, Matsunaga E, Takihara Y, Nakamura T, Tagaki Y (1983) Structural analysis of a  $\beta$ -thalassaemia gene found in Taiwan. *J Biol Chem* 258: 2748
- Klingberg MA, Chen R, Chemke J, Levin S (1971) An epidemiologic study of congenital malformations among different ethnic and social groups in Israel. *Med Dev Child Neurol* 13: 735
- Kolenda P (1978) Caste in contemporary India: beyond organic solidarity. Benjamin Cummings Publishing Co, London.
- Krawczak M and Schmidtke J (1994) DNA fingerprinting. bios Scientific Publishers, Oxford.
- Kuliev AM, Rasulov IM, Dadasheva T, Schwarz EI, Rosatelli C, Saba L, Meloni A, Gemidjioglu E, Petrou M, Modell B (1994) Thalassaemia in Azerbaijan. *J Med Genet* 31: 209
- Kulozik AE, Kar BC, Serjeant GR, Serjeant BE, Weatherall DJ (1988) The molecular basis of  $\alpha$ -thalassaemia in India. Its interaction with the sickle cell gene. *Blood* 71: 467
- Kwok S, Kellogg DE, McKinney N, Spasic D, Goda L, Levenson C, Sininsky JJ (1989) Effect of primer template mismatches on the polymerase chain reaction: Human immunodeficiency virus type 1 model studies. *Nucleic Acids Res* 18: 999
- Kwok S and Higuchi R (1989) Avoiding false positives with PCR. *Nature* 339: 237
- Labie D, Bennani C Beldjord C (1990)  $\beta$ -thalassaemia in Algeria. *Ann NY Acad Sci* 612: 43
- Latif Z (1983) Clinico-morphological study of beta thalassaemia syndromes and Hb-D. MPhil Thesis, University of Punjab.
- Lebel RR (1983) Consanguinity studies in Wisconsin. I: Secular trends in consanguineous marriages, 1843-1981. *Am J Med Genet* 15: 543
- Lewis D, Stockley RJ, Chanarin I (1982) Changes in the mean corpuscular red cell volume in women with  $\beta$ -thalassaemia trait during pregnancy. *Br J Haematol* 50: 423

- Liebbaber SA, Cash FE, Ballas SK (1986) Human  $\alpha$ -globin gene expression: The dominant role of the  $\alpha 2$ -locus in mRNA and protein synthesis. *J Biol Chem* 261: 15327
- Lie-Injo LE, et al (1981) Two types of triplicated  $\alpha$ -globin loci in humans. *Nucleic Acids Res* 9: 3707
- Lie-Injo LE, Cai SP, Wahidijat I, Moeslichan S, Lim ML, Evangelista L, Dorothy M, Kan YW (1989)  $\beta$ -thalassaemia mutations in Indonesia and their linkage to haplotypes. *Am J Hum Genet* 45: 971
- Longo MC, Beringer MS and Hartley JL (1990) Use of DNA glycosylase to control carry-over contamination in polymerase chain reactions. *Gene* 93: 125
- Loukopoulos D (1996) Current status of thalassaemia and the sickle cell syndromes in Greece. *Semin Haematol* 33: 76
- Lucarelli G, Giardini C, Baronciani D (1995) Bone marrow transplantation in thalassaemia. *Semin Haematol* 32: 297
- Lukens JN (1993) The thalassaemia and related disorders: quantitative disorders of haemoglobin synthesis; In, Wintrobe's Clinical haematology edited by Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN. Lee and Febiger, London.
- Makdur MS (1974) Sterilization and abortion from the point of view of Islam; In, Islam and Family Planning edited by Nazer IR, Karmi HS, Zayid MY. Imprimerie Catholique Beirut.
- Malhotra KC (1979) Inbreeding among Dhanger castes of Maharashtra, India. *J Biosoc Sci* 11: 397
- Mazza U, Saglio G, Caligaris-Cappio F, Camaschella C, Neretto G, Gallo E (1976) Clinical and haematological data in 254 cases of Beta-thalassaemia trait in Italy. *Br J Haematol* 33: 91
- Melis MA, Pirastu M, Galanello R, Furbetta M, Tuveri T, Cao A (1983) Phenotypic effect of heterozygous  $\alpha$  and  $\beta^0$ -thalassaemia interaction. *Blood* 62: 226
- Meloni A, Rosatelli MC, Faa V, Sardu R, Saba L, Murru S, Sciarratta GV, Baldi M, Tannoia N (1992) Promoter mutations producing mild  $\beta$ -thalassaemia in the Italian population. *Br J Haematol* 80: 222
- Modell B, Ward RHT, Fairweather DVI (1980) Effect of introducing antenatal diagnosis on reproductive behaviour of families at risk for thalassaemia major. *Br Med J* 280: 1347
- Modell B and Berdoukas V (1984) The clinical approach to thalassaemia. Grune & Stratton, London.
- Modell B, Petrou M, Ward RHT, Fairweather DVI, Rodeck C, Varnavides LA, White JM (1984) Effect of fetal diagnostic testing on birth-rate of thalassaemia major in Britain.

*Lancet* ii: 1383

Modell B and Kuliev AM (1992) Social and genetic implications of customary consanguineous marriage among British Pakistanis. Galton Institute Occasional Papers, Second Series No. 4, The Galton Institute, London.

Monk M and Holding C (1990) Amplification of a  $\beta$ -haemoglobin sequence in individual human oocytes and polar bodies. *Lancet* 335: 985

Mouzouras M, Camba L, Ioannou P, Modell M, Constantinides P, Gale R (1980) Thalassaemia as a model of recessive genetic disease in the community. *Lancet* ii: 574

Mullis KB and Faloona FA (1987) Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction. *Methods Enzymol* 155: 335

Myers RM, Fischer SG, Lerman LS, Maniatis T (1985) Nearly all single base substitutions in DNA fragments joined to a GC clamp can be detected by denaturing gradient gel electrophoresis. *Nucleic Acids Res* 13: 3131

Myers RM, Tilly K, Maniatis T (1986) Fine structure and genetic analysis of a  $\beta$ -globin promoter. *Science* 232: 613

Mayers RM, Maniatis T, Lerman LS (1987) Detection and localization of single base changes by denaturing gradient gel electrophoresis. *Methods Enzymol* 155: 501

Naderi S (1979) Congenital abnormalities in newborns of consanguineous and non-consanguineous parents. *Obstet Gynaecol* 53: 195

Neel JV and Schull WJ (1962) The effect of inbreeding on mortality and morbidity in two Japanese cities. *Am J Hum Genet* 48: 573

Nevins JRA (1983) The pathway of eukaryotic mRNA formation. *Annu Rev Biochem* 52: 441

Novelletto A, Hafez M, Deidda G, Rienzo AD, Felicetti L, Tahan HE, Morsi ZE, Ziny ME, Al-Tonbary Y, Sittien A, Terrenato L (1990) Molecular characterization of  $\beta$ -thalassaemia mutations in Egypt. *Hum Genet* 85: 272

Newton CP, Graham A, Heptinstall LE, Powell SJ, Summers C, Kalsheker N, Smith JC, Markham AF (1989) Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS). *Nucleic Acids Res* 17: 2503

Newton CR and Graham A (1994) PCR. Bios Scientific Publishers, Oxford, UK.

Old JM, Heath C, Fitches A, Thein SL, Weatherall DJ, Warren R, McKenzie C, Rodeck CH, Modell B, Petrou M, Ward RHT (1986a) First trimester fetal diagnosis for haemoglobinopathies: report on two hundred cases. *Lancet* ii: 763

- Old JM, Heath C, Fitches A, Thein SL, Jeffreys AJ, Petrou M, Modell B, Weatherall DJ (1986b) Meiotic recombination between two polymorphic restriction sites within the  $\beta$  globin gene cluster. *J Med Genet* 23: 14
- Old JM, Varawalla NY, Weatherall DJ (1990) Rapid detection and prenatal diagnosis of  $\beta$ -thalassaemia: studies in Indian and Cypriot populations in the UK. *Lancet* 336: 834
- Olivieri NF (1996) Reactivation of fetal haemoglobin in patients with  $\beta$ -thalassaemia. *Semin Haematol* 33: 24
- Orkin SH, Kazazian HH Jr, Antonarakis SE, Goff SC, Boehm CD, Sexton JP, Waber PG, Giardina PJV (1982a) Linkage of  $\beta$ -thalassaemia mutations and  $\beta$ -globin gene polymorphisms with DNA polymorphisms in human  $\beta$ -globin gene cluster. *Nature* 296: 627
- Orkin SH, Kazazian HH Jr, Antonarakis SE, Ostrer H, Goff SC, Sexton JP (1982b) Abnormal RNA processing due to the exon mutation of the  $\beta^E$ -globin gene. *Nature* 300: 768
- Orkin SH, Antonarakis SE, Kazazian HH Jr (1984) Base substitution at position -88 in a  $\beta$ -thalassaemic globin gene: Further evidence for the role of distal promoter element ACACCC. *J Biol Chem* 259: 8679
- Orkin SH, Cheng TC, Antonarakis SE, Kazazian HH Jr (1985) Thalassaemia due to a mutation in the cleavage-polyadenylation signal of the human  $\beta$ -globin gene. *EMBO Journal* 4: 453
- Ostrowsky JT, Lippman A, Scriver CR (1985) Cost-benefit analysis of a thalassaemia disease prevention programme. *Am J Public Health* 75: 732
- Panter-Brick C (1991) Prenatal responses to consanguinity and genetic diseases in Saudi Arabia. *Soc Sci Med* 33: 1295
- Park SS, Barnetson R, Kim SW, Weatherall DJ, Thein SL (1991) A spontaneous deletion of  $\beta$ 33/34 Val in exon 2 of the  $\beta$ -globin gene (Hb Korea) produces the phenotype of dominant  $\beta$  thalassaemia. *Br J Haematol* 78: 581
- Pasvol G, Weatherall DJ, Wilson RJM (1977) Effects of fetal haemoglobin on susceptibility of red cells to Plasmodium falciparum. *Nature* 270: 171
- Peschle C, Mavilio F, Care A, Migliaccio G, Migliaccio AR, Salvo G, Samoggia P, Petti S, Guerriero R, Marinucci M, Lazzaro D, Russo G, Mastroberardino G (1985) Haemoglobin switching in human embryos: Asynchrony of  $\zeta$ - $\alpha$  and  $\varepsilon$ - $\gamma$ -globin switches in primitive and definite erythropoietic lineage. *Nature* 313: 235
- Petrou M, Modell M, Darr A, Old JM, Kin E, Weatherall DJ (1990) Antenatal diagnosis: how to deliver a comprehensive service in the United Kingdom. *Ann NY Acad Sci* 612: 251
- Petrou M (1994) The UK control programme for the haemoglobin disorders. *Fetal Maternal Med Rev* 6: 191

- Piomelli S (1995) The management of patients with Cooley's anaemia: transfusions and splenectomy. *Semin Haematol* 32: 262
- Pirastu M, Galanello R, Doherty MA, Tuveri T, Cao A, Kan YW (1987) The same  $\beta$ -globin gene mutation is present on nine different  $\beta$ -thalassaemia chromosomes in a Sardinian population. *Proc Natl Acad Sci USA* 84: 2882
- Pirastu M, Ristaldi MS, Loudianos G, Murru S, Sciarratta GV, Parodi MI, Leone D, Agosti S, Cao A (1990) Molecular analysis of atypical  $\beta$ -thalassaemia heterozygotes. *Ann N Y Acad Sci* 612: 90
- PMRC (1982) Haemoglobinopathies in Multan. Pakistan Medical and Research Council Annual Report.
- Pootrakul P, Wasi P, Na-Nakoran S (1973) Haematological data in 312 cases of  $\beta$ -thalassaemia trait in Thailand. *Br J Haematol* 24: 703
- Punjabi IA (1976) Punjab Ki Aurat (The women of Punjab). The Pakistan Research Institute, Punjab.
- Quaife R, Al-Ghazi L, Abbas S, Fitzgerald P, Fitches A, Valler D, Old JM (1994) The spectrum of  $\beta$ -thalassaemia mutations in the UAE population. *J Med Genet* 31: 59
- Quddus SA (1987) The Pathans. Ferozsons Lahore.
- Qureshi TZ, Anwar M, Ahmed S, Khan DA, Saleem M (1995) Serum ferritin levels in carriers of  $\beta$ -thalassaemia trait. *Acta Haematol* 94: 7
- Raheemtoola RJ (1960) Cooley's anaemia in Pakistani children. *Medicus* 20: 101
- Rahimtoola RJ (1981) The thalassaemia (at Karachi). *Pak Pediat J* 5: 17
- Rapson EJ (1962) The Cambridge history of India. Chand and Company Bombay.
- Ratip S, Petrou M, Old JM, Wonke B, Porter JB, Modell B (1997) Relationship between the severity of  $\beta$ -thalassaemia syndromes and the number of alleviating mutations. *Eur J Haematol* 58: 14
- Reddy PH (1994) Haemoglobin disorders among the tribal population "The Baiga" of Madhya Pradesh, India. PhD Thesis, London University.
- Rodeck CH and Nicolini U (1989) Obstetric approaches to fetal haematology. In, Perinatal Haematology ed. Alter BP. *Methods Haematol* 21: 1
- Rosatelli C, Falchi AM, Scalas MT, Tuveri T, Furbetta M, Cao A (1984) Haematological phenotype of the double heterozygous state for alpha and beta thalassaemia. *Haemoglobin* 8: 25

- Rosatelli MC, Tuveri T, Scala MT et al (1992a) Molecular screening and fetal diagnosis of  $\beta$ -thalassaemia in the Italian population. *Hum Genet* 89: 585
- Rosatelli MC, Dozy A, Faa V, Meloni A, Sardu R, Saba L, Kan YW, Cao A (1992b) Molecular characterization of  $\beta$ -thalassaemia in the Sardinian population. *Am J Hum Genet* 50: 422
- Rao VB (1994) Direct sequencing of Polymerase Chain Reaction Amplified DNA. *Analytical Biochem* 216: 1
- Rund D, Filcon D, Dowling C, Kazazian HH, Rachmilewitz EA, Oppenheim AP (1990) Molecular studies of  $\beta$ -thalassaemia in Israel: mutation analysis and expression studies. *Ann NY Acad Sci* 612: 98
- Sahih Al-Bukhari Vol: 8 Hadith 593
- Saiki RK, Gelfand DH, Stofel S, Scharf R, Higuchi R, Horn GT, Mullis KB, Erlich HA (1988) Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 239: 487
- Saleem M (1974) Haemoglobinopathies. *Pak Armed Forces Med J* 25: 9
- Saleem M, Ahmed PA, Mubarik A (1985) Distribution pattern of haemoglobinopathies in the Northern areas of Pakistan. *J Pak Med Association* 35: 106
- Saleem M (1996) An overview of thalassaemia in Pakistan. Proceedings of the PMA International Seminar on thalassaemia, Lahore.
- Sanger F, Nicklen S, Coulson AR (1977) DNA sequencing with chain-termination inhibitors. *Proc Natl Acad Sci, USA* 74: 5463
- Sanghvi LD (1966) Inbreeding in India. *Eugen Q* 13: 291-301
- Scerri CA, Abela W, Galdies R, Pizzuto M, Grech JL, Felice AE (1993) The  $\beta^+$  IVSI-NT no 6 (T-C) thalassaemia in heterozygotes with an associated Hb Valletta or Hb S heterozygosity in homozygotes from Malta. *Br J Haematol* 83: 669
- Schull WJ and Neel JV (1972) The effects of parental consanguinity and inbreeding in Hirado, Japan. V. Summary and interpretation. *Am J Hum Genet* 24: 425
- Semenza GL, Delgrosso K, Poncz M, Malladi P, Schawartz E, Surrey S (1984) The silent carrier allele:  $\beta$ -thalassaemia without a mutation in the  $\beta$ -globin gene or its immediate flanking regions. *Cell* 39: 123
- Shafi M (1980) Tafseer Sura Al-Momenoon. Moaraf Al-Quran Vol: 6. Idara Al-Moaraf Karachi.



- Shami SA and Zahida (1981) Risks in consanguineous marriages: an isonymic study. *J Pak Med Association* 31: 269
- Shami SA and Zahida (1982) Study of consanguineous marriages in the population of Lahore (Panjab), Pakistan. *Biologia* 28: 1
- Shami SA and Iqbal I (1983) Consanguineous marriages in the population of Sheikhpura (Panjab), Pakistan. *Biologia* 29: 231
- Shami SA and Hussain SB (1984) Consanguinity in the population of Gujrat (Panjab), Pakistan. *Biologia* 30: 93
- Shami SA and Minhas IB (1984) Effects of consanguineous marriages on offspring mortality in the city of Jhelum (Panjab), Pakistan. *Biologia* 30: 153
- Shami SA and Siddiqui H (1984) The effects of parental consanguinity in Rawalpindi city (Panjab), Pakistan. *Biologia* 30: 189
- Sharma NP, Gupta SC, Atal RR, Melhotra TN, Agarwal AK, Kapoor KK (1976) Abnormal haemoglobins in the Pakistan Armed Forces personnel. *Indian J Med Res* 64: 883
- Sharma V and Litt M (1992) Tetranucleotide repeat polymorphism at the D21S11 locus. *Hum Mol Genet* 1: 67
- Shapiro MB and Senapathy P (1987) RNA splice junctions of different classes of eukaryotes: sequence statistics and functional implications in gene expression. *Nucleic Acids Res* 15: 7155
- Shivdasani RA and Orkin SH (1996) The transcriptional control of haematopoiesis. *Blood* 87: 4025
- Sinclair S (1972) Familial mental retardation and parental consanguinity. *Indian J Med Res* 60: 1718
- Slatis HM and Hoene RE (1961) The effects of consanguinity on the distribution of continuously variable characteristics. *Am J Hum Genet* 13: 28
- Smith RN (1995) Accurate size comparison of short tandem repeat alleles amplified by PCR. *Biotechniques* 18: 122
- Southern EM (1975) Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J Mol Biol* 98: 503
- Spritz RA, Jagadeeswaran P, Choudary PV et al (1981) Base substitution in an intervening sequence of a  $\beta^+$ -thalassaemic human globin gene. *Proc Natl Acad Sci USA* 78: 2455
- Spritz RA and Orkin SH (1982) Duplication followed by deletion accounts for the structure of an Indian deletion  $\beta$ -thalassaemia gene. *Nucleic acids Res* 10: 8025

- Steinberg MH and Adams III JG (1991) Haemoglobin A<sub>2</sub>: Origin, evolution and aftermath. *Blood* 78: 2165
- Stern MA, Kynoch PMA, Lehmann H (1968)  $\beta$ -thalassaemia, glucose-6-phosphate-dehydrogenase deficiency, and haemoglobin D-Punjab in Pathans. *Lancet* i: 1284
- Strickberger MW (1968) Genetics. The Macmillan Company, New York.
- Tariq WZ and Hussain SZ (1995) Potential of future spread of HIV/AIDS in Pakistan. Proceedings of COMSTECH symposium on policy briefing on AIDS prevention and control.
- Teebi AS (1994) Autosomal recessive disorders among Arabs: an overview from Kuwait. *J Med Genet* 31: 224
- Thein SL, Old JM, Wainscoat JS, Petrou M, Modell B, Weatherall DJ (1984) Population and genetic studies suggest a single origin for the Indian deletion  $\beta^0$  thalassaemia. *Br J Haematol* 57: 271
- Thein SL, Wainscoat JS, Sampietro M, Old JM, Cappellini D, Fiorelli G, Modell B, Weatherall DJ (1987) Association of thalassaemia intermedia with a beta-globin gene haplotype. *Br J Haematol* 65: 367
- Thein SL and Weatherall DJ (1988) The thalassaemias; In, Recent Advances in Haematology edited by Hoffbrand AV. Churchill Livingstone London.
- Thein SL, Hesketh C, Wallace RB, Weatherall DJ (1988) The molecular basis of thalassaemia major and thalassaemia intermedia in Asian Indians: application to prenatal diagnosis. *Br J Haematol* 70: 225
- Thein SL, Hesketh C, Taylor P, Temperley IJ, Hutchinson RM, Old JM, Wood WG, Clegg JB, Weatherall DJ (1990) Molecular basis for dominantly inherited inclusion body  $\beta$ -thalassaemia. *Proc Natl Acad Sci USA* 87: 3924
- Thein SL, Best S, Sharpe J, Paul B, Clark DJ, Brown MJ (1991) Haemoglobin Chesterfield ( $\beta$ 28 Leu-Arg) produces the phenotype of inclusion body  $\beta$ -thalassaemia. *Blood* 77: 2971
- Thein SL and Hinton J (1991) A simple and rapid method of direct sequencing using Dynabeads. *Br J Haematol* 79: 113
- Thein SL (1992) Dominant  $\beta$ -thalassaemia: molecular basis and pathophysiology. *Br J Haematol* 80: 273
- Trecartin RF, Liebhaber SA, Chang JC, Lee KY, Kan YW (1981)  $\beta^0$  thalassaemia in Sardinia is caused by a nonsense mutation. *J Clin Invest* 68: 1012

- Treisman R, Orkin SH, Maniatis T (1983) Specific transcription and RNA splicing defects in five cloned  $\beta$ -thalassaemia genes. *Nature* 302: 591
- Tuan D, Solmon W, Li Q, London IM (1985) The " $\beta$ -like globin" gene domain in human erythroid cells. *Proc Natl Acad Sci USA* 82: 6384
- Urquhart A, Kimpton CP, Downes TJ, Gill P (1994) Variation in short tandem repeat sequences - a survey of twelve microsatellite loci for use as forensic identification markers. *Int J Leg Med* 107: 13
- Varawalla NY, Old JM, Sarkar R, Vankatesan R, Weatherall DJ (1991a) The spectrum of  $\beta$ -thalassaemia mutations on the Indian subcontinent: the basis for prenatal diagnosis. *Br J Haematol* 78: 242
- Varawalla NY, Old JM and Weatherall DJ (1991b) Rare  $\beta$ -thalassaemia mutations in Asian Indians. *Br J Haematol* 79: 640
- Varawalla NY, Fitchies AC and Old JM (1992) Analysis of  $\beta$ -globin haplotypes in Asian Indians: origin and spread of  $\beta$ -thalassaemia on the Indian subcontinent. *Hum Genet* 90: 443
- Vogel F and Motulsky AG (1986) Human genetics: problems and approaches. Springer-Verlag, Berlin.
- Wahab A and Ahmad M (1996) Biosocial perspective of consanguineous marriages in rural and urban Swat, Pakistan. *J Biosoc Sci* 28: 305
- Wainscoat JS, Kanavakis E, Wood WG, Letsky EA, Huehns ER, Marsh GW, Higgs DR, Clegg JB, Weatherall DJ (1983) Thalassaemia intermedia in Cyprus: the interaction of  $\alpha$  and  $\beta$  thalassaemia. *Br J Haematol* 53: 411
- Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P, Chard T, Haddow JE, Knight GJ, Palomaki GE, Canick JA (1988) Maternal serum screening for Down's syndrome in early pregnancy. *British Medical Journal* 297: 883
- Wang CH Schilling RF (1995) Myocardial infarction and thalassaemia trait: an example of heterozygote advantage. *Am J Haematol* 49: 73
- Ward RHT, Modell B, Petrou M, Karagozlu F, Douratsos E (1983) Method of sampling chorionic villi in first trimester of pregnancy under guidance of real time ultrasound. *Br Med J* 286: 1542
- Weatherall DJ Clegg JB (1981) The thalassaemia syndromes. Blackwell Scientific Publications, Oxford.
- Weatherall DJ, Clegg JB, Higgs DR, Wood WG (1989) The haemoglobinopathies; In, The metabolic basis of inherited disease, edited by Scriver CR, Beudet AL, Sly WS, Valle D, McGraw-Hill, London.

Weatherall DJ (1996) Disorders of the synthesis or function of haemoglobin; In, Oxford Textbook of Medicine, edited by Weatherall DJ, Ledingham JGG, Warrel DA, Oxford Medical Publications, Oxford.

Weinberg RA (1985) The molecules of life. *Sci Am* 253: 34

Winichagoon P, Fucharone S, Thonglairoam V, Tanapotiwirut V, Wasi P (1990)  $\beta$ -Thalassaemia in Thailand. *Ann NY Acad Sci* 612: 31

WHO working group (1983) Report of WHO working group on hereditary anaemias. Archbishop Makarios Thalassaemia centre, Cyprus 29-31 November (unpublished WHO document HMG/WG/83.9).

WHO working group (1985) Update of the progress of haemoglobinopathies control. (unpublished WHO document HMG/WG/85.8).

WHO working group (1987) Report of the Vth annual meeting on the feasibility study on hereditary disease community control programmes Hereditary anaemias: Alpha thalassaemia.

WHO working group (1993a) 7<sup>th</sup> meeting of the WHO working group on the control of hereditary anaemias. Nicosia, Cyprus, 3-4 April (unpublished WHO document WHO/HDP/TIF/HA/93.1).

WHO working group (1993b) Report on the meeting of the task force on prevention of hereditary disorders. Nicosia, Cyprus, 3-5 April (unpublished WHO document EM/NCD/7-E/R/8.93/91).

Wolpert S (1977) A new history of India. Oxford University Press New York.

Wong C, Antonarakis SE, Goff SC, Orkin SH, Boehm CD, Kazazian HH Jr (1986) On the origin and spread of  $\beta$ -thalassaemia: recurrent observation of four mutations in different ethnic groups. *Proc Natl Acad Sci, USA* 83: 6529

Wong C, Dowling CE, Saiki RK, Higuchi RG, Erlich HA, Kazazian HH Jr (1987) Characterization of  $\beta$ -thalassaemia mutation using direct genomic sequencing of amplified single copy DNA. *Nature* 330: 384

Workman PL and Niswander JD (1970) Population studies on South Western Indian tribes. II Local genetic differentiation in the Papago. *Am J Hum Genet* 22: 24

Yang KG, Kutlar F, George E, Wison JB, Kutlar A, Stoming TA, Gonzalez-Redondo, Huisman THJ (1989) Molecular characterization of  $\beta$ -thalassaemia gene mutations in Malaya patients with Hb-E- $\beta$ -thalassaemia and thalassaemia major. *Br J Haemato* 72: 73

Yaqoob M, Gustavson K-H, Jalil F, Karlberg J, Iselius L (1993) Early child health in Lahore, Pakistan: II. Inbreeding. *Acta Paediatr (suppl)* 390: 17

Yeo GS, Tan KH, Liu TC (1994) Screening for beta thalassaemia and HbE traits with the mean red cell volume in pregnant women. *Ann Acad Med Singapore* 23: 363

Yuen J, Hsia YE, Hall J (1988) Thalassaemia heterozygotes in Hawaii: ethnic attitudes toward screening and prenatal diagnosis. *Haemoglobin* 12: 801

Zuhur-ur-Rehman, Saleem M, Alvi AA, Anwar M, Ahmad PA, Ahmad M (1991)  $\alpha$ -thalassaemia: prevalence and pattern in Northern Pakistan. *J Pak Med Assoc* 41: 246