BLOOD GROUPS AND DISEASES

N Saha

Department of Physiology
National University of Singapore
Kent Ridge
Singapore 0511

N Saha, BSc, MBBS, MD, PhD (Med)
Association Professor

This is a review of the work carried out by the author and his colleagues.

SYNOPSIS

The literature on the association of blood groups, abnormal haemoglobins, serum proteins and red cell enzymes in some common diseases is critically reviewed. The scope of the article has been limited only to the studies of diseases in which the author has been actively involved. An attempt is made to examine the significance of some of the associations observed as for example i) Pulmonary tuberculosis and ABO-Lewis[a] blood groups; ii) Diabetes mellitus and red cell G6PD deficiency; iii) Lack of association of blood groups with coronary heart disease and risk factors; iv) Malaria and haemoglobin E; v) Interrelationship of haemoglobin, haptoglobin, transferrin, red cell G6PD and acid phosphatase phenotypes.

It is now generally believed that susceptibility of most of the diseases in man is influenced by genetic characteristics of man. The evolutionary significance of diseases in man has been suggested by Haldane (1, 2). Even prior to that, immediately after the discovery of ABO blood groups by Landsteiner, the geneticists were looking for the significance of the occurrence of different blood groups by studying the association of certain blood groups in diseases.

The present paper focuses on studies on the association of blood groups with some of the common diseases in man. The progress in the area had been phenomenal, but in most of the studies only the ABO blood groups were used as marker. There has been very limited work done on the association of other blood groups such as Rhesus (D), MN and HLA types. The literature available on the subject had been reviewed in a book form by Mourant and colleagues (3). It is beyond the scope of the present paper to deal with the hundreds of papers published on the topic. I would therefore like to restrict the discussion pertaining to our own studies, and bringing in others' work occasionally, only in the studies of diseases, in which we had been actively involved.

1. Pulmonary Tuberculosis

The results of twin studies in pulmonary tuberculosis are suggestive of a strong genetic factor involved in the aetiology of the disease (4). Studies on the association of blood groups in pulmonary tuberculosis date back to 1926 when Hilber and Hirzfeld (5) first reported their negative finding on the association of ABO blood groups in the disease. Since then conflicting reports have appeared in the literature published on work in different population groups. We have observed a significant association of the B-antigen in pulmonary tuberculosis with a higher incidence of B and AB groups persons ($P<0.005$) in the Chinese in Singapore (6, 7). Since then the same association has been reported in diverse groups of populations: Indians (8); Japanese (9); Eskimos (10). Inspite of the other conflicting reports published, there seems to be a presence of a true association of ABO blood groups in pulmonary tuberculosis. The study of genetic association is complicated by the selection of a proper healthy control. Singapore had the unique advantage of being served by only one Blood Bank for the whole country at the time of investigation. The Japanese study was based on a sample of 21,365 patiens in the whole nation whose blood groups were known. This association fits well with the antigenicity of tubercle bacillus having B-like antigen (11). The observed excess of B group people in the pulmonary tuberculosis series may be attributed to the lack of protection in persons of groups B and AB who lack anti-B to neutralise the tubercle bacilli by reacting with antigen on the bacilli when a person is infected with the tubercle bacilli. This is similar to the hypothesis put forward by Vogel (12, 13) for small-pox and blood group A (A-like antigens of vaccinia virus). In order to explore further the possible mechanism of action a study on the secretor status of 354 Chinese patients suffering from the disease showed a trend indicating involvement of secretor locus in the association of B-antigen in pulmonary tuberculosis. No significant association of red cell G6PD deficiency was observed in pulmonary tuberculosis (14). However an excess of abnormal haemoglobin was observed in Chinese patients, compared to the normal control (15). This significant association of ABO blood groups in pulmonary tuberculosis should be explored further. Pulmonary tuberculosis is one of the oldest diseases of mankind, documented by the presence of bone tuberculosis in Egyptian mummies. It may have a great evolutionary significance in man.

2. Leprosy

The extensive literature on the association of ABO blood groups in leprosy has been reviewed by Vogel (13) and on the basis of 33 published papers an association of O:A has been suggested ($P\leq 0.0027$). However there is wide degree of variation of the association in these series even in the same population group (Japanese). We failed to observe any deviation of the distribution ABO, Rhesus (D), abnormal haemoglobins and G6PD deficiency in lepers and the healthy control series (16). In a study in Thailand Vogel et al (17) reported the relative incidence of 0.8551 for A/O and 1.1345 for B/O in 335 leprosy patients. The similar relative risk was observed in our series of Chinese patients (16). There was also no significant different in the frequency distribution of ABO blood groups between lepromatous and non-lepromatous patients. The reported positive association of red cell G6PD deficiency in leprosy (18) may be a chance finding unless it is observed in some other populations.

3. Syphilis

No association of ABO, Rh (D) blood groups, red cell G6PD deficiency and abnormal haemoglobins was noted in 1041 patients suffering from syphilis (19). Schofield (20) also failed to detect any association of ABO and Rh (D) blood groups with syphilis. There is very limited data on the distribution of genetic markers in this common condition. More work needs to be carried out in future to look into the genetic susceptibility in the development and prognosis of veneral diseases in man.

4. Malaria

It has been postulated that the heterozygous form of haemoglobin S, and probably also haemoglobin E and G6PD deficiency offer protection against *Plasmodium falciparum* infection. Allison (21) demonstrated that 13 out of 15 subjects with the sickle-cell trait were resistant to the induced *Plasmodium falciparum* infection whereas 14 out of 15 control subjects showed no such resistance. Subsequent studies confirmed that the presence of sickle-cell trait offers protection against *P. falciparum* but no *P. malirae*. Ray, *et al* (22) observed that E-thalassaemia also offers protection against *P. vivax* infection. In general, the geographical distribution of the sickle cell gene and the red cell G6PD deficiency gene run parallel with the past incidence of malaria. However wide variations of abnormal haemoglobins and G6PD deficiency in different populations in same geographical areas cannot be adequately explained and is contrary to the hypothesis. Only when more data will be available on the population genetics of these genetic markers, will it be possible to examine the malarial hypothesis adequately. The incidence of the E haemoglobin and red cell G6PD deficiency in East and South-East Asia in relation to past malarial endemicity is more conflicting. In a study of the incidence of red cell G6PD deficiency and abnormal haemoglobins among the ethnic groups of Singapore, we could not evidently support the malarial hypothesis in conferring resistance in the presence of E haemoglobin or G6PD deficiency (23). Similar lack of association of these genes with malaria was observed

in Thailand. Miller (24) had reported evidence that Duffy blood group offers protection against *Plasmodium Knowlesi*. However, more extensive work is warranted to confirm this observation.

5. Coronary Heart Disease

From the study of the concordance in twins it is evident that there is a strong genetic component in the development of coronary heart disease (25). The genetic and cultural inheritance have been worked out by a computer model on the basis of the distribution of the most important risk factor (serum total cholesterol) in families by several authors. In recent years an association with ABO blood groups with higher incidence of Coronary Heart Disease, has been observed among A group persons in most of the populations studied and the literature has been reviewed by Mourant *et al* (3). The incidence and mortality from coronary heart disease in the Chinese of Singapore has been reported to be very low compared with that in the Indians of Singapore (1:4) and Caucasians in the west (26, 27). The multiracial population of Singapore with differential mortality of coronary heart disease provided a unique opportunity to study the genetic association in myocardial infarction. Several series of studies have been published on the association of ABO blood groups in myocardial infarction (27, 28). The average relative risk has been estimated as 1.29 for A/O and 1.19 for B/O in the ranges from .78 to 3.0 and .77 to 2.37 respectively. In a study of the incidence of ABO, Rh, Le^a, Xg^a blood groups, G6PD deficiency and haemoglobin types in myocardial infarction patients of Chinese, Indian and Malay origin we failed to establish genetic association with any of these markers in myocardial infarction (Saha *et al*, 1973; Saha, 1974). However a marginal association of A blood group was observed only in Indian patients ($P < 0.05$). It seems that the question of association in a disease may be influenced by the ethnic composition — probably it is different in Mongoloid and Caucasoid subjects. This is also true of the association of O blood group in duodenal ulcer with lack of association in Negro patients. Serum cholesterol and triglycerides are known to be important risk factors for myocardial infarction (29, 30). In another study, a higher level of serum cholesterol ester was observed in A group persons in Indian subject ($P = 0.02$) which fits well with the higher incidence of myocardial infarction in A groups Indians (31, 32). The influence of blood groups in the control of serum cholesterol level is probably expressed in the post-natal period resulting from the interactions of genes and environment (33). In an extensive study to examine the genetic markers association in the regulation of serum cholesterol, we have investigated more than 5000 subjects of Caucasian, Mongoloid and African origins. The results are being processed. X-linked genes (Xg^a blood group and G6PD) did not have any influence on serum cholesterols (34, 35). The higher incidence of myocardial infarction in Indians confirmed the earlier reports from Singapore and India (26, 36), however it failed to elucidate further as to the reasons for these striking ethnic differences in the incidence and mortality of coronary heart disease. Though some epistatic genetic factors may be involved — it seems, environmental factors may be playing a more important role in the expression of the genetic predisposition in the causation of coronary heart disease. There was highly significant correlation of both serum total and esterified cholestrols levels with body- weight ($r = 0.78$ and 0.84) and calculated body-fat content ($r = 0.73$ and 0.84) (31). The socio-economic status of Indians and Chinese in Singapore is very comparable excepting the differences in their traditional dietary habits. In a nutritional survey we have recorded an intake of about 30% of calories from fat in Chinese (37-40). In an earlier study in Indian medical students, similar intake of fat was recorded (41). However the sources of dietary fat in Chinese and Indians in Singapore are different — coconut oil is the main cooking medium in the former while lard in case of Chinese food. In another study of dietary intakes in Singapore populations we observed no difference of the intakes of energy, fat (saturated and unsaturated), protein and cholesterol though Chinese took significantly higher amount of nicotic acid and thiamine (39). Customary higher intake of these two vitamins by Chinese may have some protective effect against the development of coronary heart disease in a population. The hypocholesterolemic effect of therapeutic doses of nicotinic acid is well-established. It appears that the appropriate environmental factors are required for the expression of genetic predisposition resulting in disease.

6. Diabetes Mellitus

The genetic association of diabetes mellitus has been studied in the past mainly by studying the rate of concordance in twins, family materials and calculating the relative incidence of blood groups and serum proteins (3). The results are rather conflicting. In a series of six hundred male Chinese patients suffering from maturity-onset-diabetes mellitus we could not establish the reported association of ABO blood groups. However, a significant positive association of red cell G6PD deficiency was observed with higher relative risk of diabetes in G6PD deficient subjects. (Relative risk 2.2 in Chinese and 3.39 in Indians ($P < 0.002$ and 03 respectively). The relative risk of G6PD deficient subjects was higher even in prediabetics (42, 43). The observed association of G6PD deficiency in diabetes mellitus supports the hypothesis put forward by Kessler (44) — suggesting a negative association of G6PD deficiency in cancer and a positive relationship in diabetes mellitus. Naik and Anderson (45) observed a negative association of G6PD deficiency in cancer in American Negro patients, but only in females. In our series we observed a positive correlation of G6PD deficiency in diabetes mellitus in two ethnic groups of Singapore. It will be interesting to look into the phenotypic expression of red cells G6PD in diabetes mellitus in different populations of the world as there are many populations with a high incidence of diabetes, but with a low or no red cell G6PD deficiency. The underlying significance of the association of G6PD deficiency in diabetes mellitus is not clear at the moment.

7. Vitiligo

The etiology of vitiligo is not known, however the genetic factors are probably involved. There have been many studies in the past to examine the association of ABO blood groups and the secretory status in vitiligo patients (46-51). The results are far from being definitive. We investigated the distribution of A_1A_2BO, MNSs, Rhesus (C, D, E, c, e), Kell and Duffy blood groups; haptoglobins and transferrins; and red cell enzymes (acid phosphatase, 6-phosphogluconate dehydrogenase, phosphoglucomutase and glucose-6-phosphate dehydrogenase); and haemoglobins in a series of 170 Sudanese patients suffering from vitiligo, and compared them with those in a control series of

random subjects (52, 53) and another series of blood donors. No significant association was observed with ABO, Ss, Rhesus , Kell and Duffy blood groups in vitiligo. However, a significant association was observed for the MN system with an excess of homozygotes and of the M gene in vitiligo for homozygote excess and 6.6 for M gene excess (X^2_1 — 29.87, 21.91; $P<0.001$; (54). There was no association with the serum protein markers or red cell enzyme markers excepting glucose-6-phosphate dehydrogenase deficiency. An excess of G6PD deficiency was present in this patient group ($P<0.05$). However there was no association with any specific phenotype (Gd^A or Gd^B) of the enzyme (53).

8. Infertility

Differential fertility and mortality are two of the important selective factors in the maintenance of the genetic characteristics of a population. Infertility is at the lowest end of the scale of the former and is expected to exert a selective influence on a population. There have been many studies on differential fertility in relation to ABO blood groups in different population groups. The mot commonly cited series with positive associations are those of Waterhouse and Hogben (55); Allan (56); Kirk *et al* (57, 58); Matsungaga and Itoh (59). At the same time many authors have failed to confirm this association of fertility with ABO blood groups (60-62). There have been relatively limited studies on the association of ABO blood groups in infertility (63-65) with conflicting observations. Morgan *et al* (66) had suggested the involvement of the secretor locus in infertility on the basis of sperm-antibody and antigenicity of uterine secretion. Cohen (67) had suggested an interaction of ABO and Rhesus genes in fertility. With the above in view we studied the distribution of ABO, Le^a, Rhesus (C, D, E, c, e) blood groups, red cell G6PD deficiency and abnormal haemoglobins in a group of 308 Chinese and 70 Indian infertile women in Singapore and compared them with those in controls. There was a relative excess of blood groups A among the Chinese infertile women, which probably worked through the secretor locus (relative excess of Le^a negative; $X^2_1 = 5.12$). R_1R_1 gene complex of the Rhesus system was deficient in infertile groups ($X^2_1 = 9.55$). There was no significant difference in the distribution of red cell G6PD deficiency and haemoglobin types infertility (68).

9. Schizophrenia

It is one of the commonest mental illnesses which may disturb the balance in a population due to lower fertility among schizophrenics. The family studies had conclusively established the importance of genetic involvement in the disease though the extent of heritability had not yet been ascertained. The concordance rate in twins was inconclusive due to the small size of the sample (25). There has been a very limited amount of work done on the genetic association in this common disease and the scanty studies have been limited to only ABO blood groups and some serum proteins (3). We have studied the distribution of ABO (AA_1, B); Rhesus (C, D, E, c, e); Le^a; MN Blood groups; some serum protein (Gc, Hp, Tf) and red cell enzyme markers in a group of Chinese Schizophrenics. An interesting new association with an excess of Le^a+ had been observed in Schizophrenics (69). Other blood groups did not reveal any association. The results of other markers are being processed.

10. Goitre

It is generally believed that goitre is prevalent in areas of iodine deficiency. However, not everyone living in the area developes goitre. It seems that some genetic factors may be involved in the genetic predisposition for the development of goitre. There have been many studies carried out on the distribution of ABO blood groups among various population groups of the world (3) with inconclusive diverse results. However another aspect of the studies on the genetic association in goitre had been more promising — that is its association with PTC (Phenyl thiocarbamide) tasting system with lower incidence of taster among the goitrous patients particularly in female patients (3). In a study of genetic association in endemic goitre in goitrous areas of Jabal Merah in the Sudan a similar association of PTC sensitivity has been observed while no other association was identified with the other blood genetic markers studied (Hb, Hp, G6PD, GPGD, PGM, AP, Tf, etc). Further in the same study a strong genetic component in the aetiology of the disease was observed by studying the relative incidence of the disease (age and sex-matched) among the offsprings of the consanguineous (sharing more similar genes) than those of non-consanguineous matings (70).

11. Interrelatioships of haemoglobin, serum haptoglobin, transferrin; red cell G6PD and acid phosphatase phenotypes

These polymorphisms have been suggested to have some selective importance in having common interacting ecological backgrounds (e.g. malaria, temperature, humidity etc (71-75). The phenotypic and quantitative expression of red cell acid phosphatase was examined in relation to various haemoglobin, haptoglobin and G6PD phenotypes in three populations of the Sudan and Nilgiris, India. No consistent association of red cell acid phosphatase types was observed in different haemoglobin, haptoglobin and G6PD phenotypes excepting a lack of AB phenotype of acid phosphatase in G6PD deficient subjects of Nilgiris. However the G6PD deficient subjects had a lower level of red cell acid phosphatase activity compared with those with normal G6PD activity and β-thalassaemia carriers in Sudanese patients (76).

12. G6PD Deficiency

Distribution of ABO and Le^a blood groups in G6PD-deficient persons was similar to that in non-deficient subjects. There was a significant lack of the R_1 gene in G6PD-deficient subjects (77-79; 23).

13. Serum Uric Acid

Gout and hypeuricemia is generally a familial disorder, so one would expect some genetic control of this parameter. There have been several studies in the past to examine the influence of blood groups on serum uric levels with inconsistent results (80-81). In another study we examined the genetic association of serum uric acid using several genetic markers (ABO, Rhesus, Le^a blood groups; haptoglobin, transferrin, C^3 and transferrin subtypes; red cell acid phosphatase, phosphoglucomutase (PGM), esterase D, G6PD phenotypes and PGM subtypes). No association of serum uric acid was observed with any genetic marker. However a marginal association was revealed with PGM subtypes — PGM^{1+}_1 phenotype tends to be associated with higher serum uric acid than the other

phenotypes (82). However a stronger influence of environmental components on serum uric acid was observed in most of our studes (83).

14. Miscellaneous

Several interrelated findings were observed in the course of the genetic association studies. Sickle cell trait was associated with hepatic dysfunction (84) and at the same time had some selective advantage in stimulation of haemopoiesis (85). β-thalassaemia trait also had similar selective advantage. Red cell G6PD deficiency was associated with lowered red cell acid phosphatase (76), increased haemopoiesis (85), isoelectric variations (86). Total iron-binding capacity of serum is influenced by Tf subtypes, haemoglobin types and G6PD deficiency (87, 88).

ACKNOWLEDGMENT

The author is thankful to Miss Fannie Chan for typing this article.

REFERENCES

1. Haldane J B S: Selection against heterozygosis in man. Ann Eugen 1942; 11:333-42.
2. Haldane J B S: Natural selection in man. Acta Genet (Basel) 1957; 6:321-33.
3. Mourant A E, Kopeć A C, Domaniewska-Sobezak K: Blood groups and diseases. Oxford Press 1978.
4. Carter C O: An ABC of medical genetics. I. Genetics in the aetiology of disease. Lancet 1969; 1:1014-6.
5. Hilber W, Hirszfeld L: Studien uber die konstitutions serologie. Z Immun-Forsch 1926; 48:34-68.
6. Saha N, Banerjee B: Incidence of ABO and Rh blood groups in pulmonary tuberculosis in three ethnic groups. J Med Genet 1968; 5:306-7.
7. Saha N: Distribution of ABO and Le^a blood groups in pulmonary tuberculosis in Chinese. Clin Genet 1973; 4:288-90.
8. Jain R C: ABO blood groups and pulmonary tuberculosis. Tubercle (Lond) 1970; 151:322-3.
9. Hirano I: Association between ABO blood groups and tuberculosis in Japanese. Jap J hum Genet 1972; 16:222-56.
10. Overfield T, Klauber M R: Prevalence of tuberculosis of Eskimos having blood group B gene. Hum Biol 1980; 52:87-92.
11. Nunome T, Akai T: On the blood group substance in tuberculin liquid. Proc Jap Acad 1951; 27:309-12.
12. Vogel F: Anthropological implications of the relationship between ABO blood groups and infections. Proc 8th Int Congr Anthropol & Ethnol Sci, 1968; 1:365-70.
13. Vogel F: ABO blood groups and disease. Am J Hum Genet 1970; 22:464-75.
14. Saha N: Incidence of G6PD deficiency in patients of three ethnic groups suffering from pulmonary tuberculosis. J Med Genet 1969; 6:292-3.
15. Saha N: Prevalence of abnormal haemoglobins in pulmonary tuberculosis in three ethnic groups. J Med Genet 1970; 7:44-6.
16. Saha N, Wong H B, Banerjee B, Wong M O: Distribution of ABO blood groups, G6PD deficiency and abnormal haemoglobins in leprosy. J Med Genet 1871; 8:315-6.
17. Vogel F, Kruger J, Song, Y K, Flatz, G: ABO blood groups, leprosy, and serum proteins. Humangenetik 1969; 149-62.
18. Kher M, Grover S: Glucose-6-phosphate dehydrogenase deficiency in leprosy. Lancet 1969; i:1318-9.
19. Saha N, Banerjee B: ABO blood groups, G6PD deficiency and abnormal haemoglobins in syphilis patients of three ethnic groups. Acta Genet Med Gemell 1971; 20:260-3.
20. Schofield C B S: ABO and Rhesus blood group distribution among patients attending Veneral Diseases Clinic. J Med Genet 1966; 3:101-3.
21. Allison A C: Polymorphism and natural selection in human populations. Quant Biol 1954; 29:137-49.
22. Ray R N, Chatterjea J B, Chaudhuri R N: Bull Wld 41th Org 1964; 30:51-6.
23. Saha N, Banerjee B: Erythrocyte G6PD deficiency among Chinese and Malays of Singapore. Trop Geogr Med 1971; 23:141-4.
24. Miller L H, Masoh S J, Dvorak J A, MeGinnos M H, Rothman J K: Erythrocyte receptors for Plasmodium knowlesi malaria: Duffy blood groups determinants. Science 1975; 189:561-3.
25. Hauge M: Quoted by Carter C O in ABC of Medical Genetics: Genetics in the aetiology of disease. Lancet 1969; i:1014-6.
26. Danaraj T J, Acker M S, Danaraj W, Wong H O, Tan B Y: Ethnic group differences in coronary heart disease in Singapore — an analysis of necropsy records. Am Heart J 1959; 58:516-26.
27. Saha N, Toh C C S, Ghosh M B: Genetic association in myocardial infarction. Ethnicity, ABO, Rh, Le^a, Xg^a blood groups; G6PD deficiency and abnormal haemoglobins. J Med Genet 1973; 10:340-5.
28. Saha N: Genetic marker association with myocardial infarction and serum cholesterols. Proc 5th Asia Ocean Congr Endocr, Chandigarh 1974.
29. Kannel W B, Castelli W P, McNamera P M: The coronary profile: 12 year follow-up in the Framingham Study. J Occup Med 1967; 9:611-9.
30. Carlson L A, Bottiger L E: Ischaemic heart disease in relation to fasting values of plasma triglycerides and cholesterol. Lancet 1972; 1:865-8.
31. Banerjee B, Saha N: Interrelation of serum cholesterols. ABO-Rh blood groups and body fat. Med J Malaya 1969; 24:41-4.
32. Banerjee B, Saha N: Blood-groups and serum cholesterols. Lancet 1969; ii:961.
33. Saha N, Banerjee B: Blood-groups and serum cholesterols. Lancet 1971; i:969.
34. Saha N, Banerjee B: X-Chromosome and serum cholesterols. Abs 4th Int Congr Hum Genet, Paris 1971.
35. Saha N, Banerjee B: Xg^a blood groups in Chinese, Malays and Indians in Singapore. Vox Sang 1973; 24:542-4.
36. Padmavati S, Gupta S, Pantulu G V: Dietary fat, serum cholesterol levels and incidence of atherosclerosis in Delhi. Circulation 1959; 19:849-55.
37. Banerjee B, Saha N: Engery cost of some common daily activities of active tropical male and female subjects. J Appl Physiol 1970; 29:200-3.
38. Banerjee B, Tan P Y, Saha N: Calories and nutrient intake of pregnant Asian women. Trop Geogr Med 1972; 24:249-52.
39. Tan P Y, Ng T B, Saha N: Dietary intakes of three ethnic groups in Singapore. Proc Soc Nutr 1984; 43:135A.
40. Saha N, Tan P Y, Banerjee B: Energy balance study in Singapore medical students. Ann Nutr Metabol. 1985; 29:216-22.
41. Banerjee B, Lal D C, Saha N: Calories intake of male and

female adult healthy middle-class Indians in summer and winter months. Calcutta Med J 1965; 65:119-22.

42. Saha N: Diabetes and glucose-6-phosphate dehydrogenase deficiency. Abstr 4th Int Congr Hum Genet, Paris, 1971.

43. Saha N: Association of G6PD deficiency with diabetes mellitus in ethnic groups of Singapore. J Med Genet 1979; 16:431-4.

44. Kessler I I: A genetic relationship between diabetes and cancer. Lancet 1970; i:218-20.

45. Naik S N, Anderson D E: The association between glucose-6-phosphate dehydrogenase deficiency and cancer in American Negroes. Oncology 1971; 25:356-64.

46. El-Hefnawi H O, Mohieddin O, Rasheed A: ABO blood groups in various skin disorders. J Egypt Med Ass 1953; 47:1097-101.

47. Srivastara G N, Shukla R C: ABO blood groups in vtiligo. Indian J Med Res 1965; 53:221-5.

48. Singh G, Shanker P: Vitiligo and blood groups. A preliminary report. Brit J Derm 1966; 78:91-2.

49. Sehgal V N, Dube B: Secretion of blood group specific substances in saliva of vitiligo patients. Brit J Derm 1967; 79:704-5.

50. Sehgal V N, Dube B: ABO blood groups and vitiligo. J Med Genet 1968; 5:308-9.

51. Kareemullah L V, Taneja V, Begum S, Sarma P K M, Baig H A: Association of ABO blood groups and vitiligo. J Med Genet 1977; 14:211-3.

52. Saha N, Samuel A P W, Omer A, Ahmed M A, Husseln A A, El Nour G: A study of some genetic characteristics of the population of the Sudan. Ann Hum Biol 1978; 5:569-75.

53. Saha N, Ahmed M A, Wasfi A I, El Munshid H A: Distribution of serum proteins, red cell enzymes and haemoglobins in vitiligo. Hum Hered 1982; 32:46-8.

54. Wasfi A I, Saha N, El Munshid H A, Sheikh H A, Ahmed M A: Genetic association in vitiligo: ABO, MNSs, Rhesus, Kell and Duffy blood groups. Clin Genet 1980; 17:415-7.

55. Waterhouse J A H, Hogben L: Incompatibility of mother an foetus with respect to iso-agglutinogen A and its antibody. Brit J Prev Soc Med 1947; 1:1-17.

56. Allan T M: ABO blood groups and human fertility. Brit J Prev Soc Med 1953; 7:220-6.

57. Kirk R L, Kirk M, Stenhouse N S: Differential fertility between women of blood group O and A. Brit J Prev Soc Med 1953; 7:1-8.

58. Kirk R L, Shield J W, Stenhouse N S, Bryce L M, Kakobowicz R: A further study of ABO blood groups and differential fertility among women in two Australian maternity hospitals. Brit J Prev Soc Med 1955; 9:104-11.

59. Matsunaga E, Itoh S: Blood groups and fertility in a Japanese population, with special reference to intrauterine selection due to maternal-fetal incompatibility. Ann Hum Genet 1958; 22:111-31.

60. Johnstone J N: Heterospecific pregnancy. Brit J Prev Soc Med 1954; 8:117-23.

61. Haga H: Studies on the natural selection in ABO blood groups with special reference to the influence of environmental changes upon the selective pressure due to maternal-fetal incompatibility. Jap J Hum Genet 1959; 4:1-20.

62. Reed T E, Gershowitz H, Soni A, Napier J: A search for natural selection in six blood group system and ABH secretion. Am J Hum Genet 1964; 16:161-79.

63. Behrman S J, Buettner-Janusch J, Hegler R, Gershowitz H, Tew W L: ABO (H) blood incompatibility as a cause of infertility: a new concept. Am J Obstet Gyn 1960; 79:847-55.

64. Solish G I, Gershowitz H: Distribution of ABO blood types among fertile and infertile women. Am J Hum Genet 1969; 21:23-35.

65. Nag R N, Banerjee A R: ABO and Rh blood groups among the primary infertile and fertile females. J Obstet Gyn India 1970; 20:795-801.

66. Morgan H, Stedronske J, Hendry W E, Chamberlain G V P, Dewhurst C J: Sperm-cervical-mucus crossed hostility testing and antisperm antibodies in the husbands. Lancet 1977; i:1228-30.

67. Cohen B H: ABO and Rh incompatibility. II, is there a dual interaction in combined ABO and Rh incompatibility? Am J Hum Genet 1970; 22:441-52.

68. Saha N, Ratnam S S: Genetic association in infertility: ABO, Rh (subtypes), Le^a blood groups; G6PD deficiency and haemoglobin types. Singapore Med J 1981; 22:16-9.

69. Saha N, Tsoi W F, Kua E H: Distribution of ABO, Rhesus, MN and Duffy blood groups in Schizophrenia. Ann Acad Med 1984; 14:110-2.

70. Bayoumi R, Saha N: Genetic association in goitre. IN PREPRATION.

71. Modiano G, Filippi G, Brunelli F et al: Red cell acid phosphatase activity in carriers of thalassaemia and glucose-6-phosphate dehydrogenase deficiency. Isr J Med Sci 1968; 4:856-66.

72. Choremis C, Kyriakides V, Papadakis E: Studies on the blood lipids and lipoproteins in thalassaemia and sickle cell anaemia. J Clin Path 1961; 14:361-4.

73. Bottini E, Lucarelli P, Bastianon V, Gloria F: Erythrocyte acid phosphatase polymorphism and haemolysis. J Med Genet 1972; 9:434-5.

74. Bottini E, Lucarelli P, Agostino R *et al*: Favism: Association with erythrocyte acid phosphatase phenotypes. Science 1971; 171:409-11.

75. Palmarino R, Agostino R, Gloria F *et al*: Red cell acid phosphatase: another polymorphism correlated with malaria? Am J Phys Anthrop 1975; 43;177-86.

76. Saha N, Patgunarajah N: Phenotypic and Quantitative relationship of red cell acid phosphatase with haemoglobin, haptoglobin and G6PD phenotypes. J Med Genet 1981; 18:271-5.

76. Adam A, Dressler L, Sheba C, Szceinberg A: A comparative study of blood group distribution among normal and G-6-PD deficient subjects in Israel. 11th Int Congr of Genet. The Hague, 1963.

78. Saha N, Banerjee B: Incidence of erythrocyte G6PD deficiency among different ethnic groups of Indians. Hum Hered 1971d; 21:78-82.

79. Saha N, Hawkins B R, Wong H B: Distribution of ABO and Rhesus blood groups in G6PD deficient Chinese and Malay newborns. Acta Genet Med Gemell 1975; 24:131-5.

80. Saha N, Banerjee B: Genetic influences on serum-uric-acid. Lancet 1969; ii:911.

81. Saha N: Genetic association of serum uric acid among the ethnic groups of Singapore. Proc 6th Int Congr Hum Genet, Israel, 1981.

82. Tan P Y, Ng T B, Saha N: Blood genetic marker association of serum uric acid in Singapore Chinese. Abstr Am J Hum Genet 1983.

83. Banerjee B, Saha N: Social Class and serum cholesterols. Lancet 1970; i:1113.

84. Saha N, Samuel A P W: Sickle cell gene and liver functions in a Sudanese population. Acta Haemat 1982; 68-65-7.

85. Saha N: Haematological parameters in relation to haemoglobin and G6PD phenotypes. Proc 3rd Int Congr

Inborn Err of Metabol in Man, Munchen; 1984.

86. Samuel A P W, Saha N, Omer A, Hoffbrand A V: Quantitative expression of G6PD activity in different G6PD and haemoglobin phenotypes. Hum Hered 1981; 31:110-5.

87. Wong C T, Saha N: Serum transferrin concentrations and total iron-binding capacities in relation to different haemoglobin types. Ann Acad Med, 1984; 13:491-3.

88. Wong C T, Saha N: Total iron-binding capacity in relation to transferrin phenotypes. In Structure and Function of Iron Storage and Transport Proteins. Eds I Urushizaki et al, Elsevier, Amsterdam, 1983; pp 397-8.