PRINT: ISSN 0970-9274 ONLINE: 2456-6608
J. Hum. Ecol., 11(2) : 149-160 (2000)
DOI: 10.31901/24566608.2000/11.02.06

Serum Proteins and Diseases

A Qualitative and Quantitative Approach

Swadesh Seth

INTRODUCTION

All human populations are exposed to selective forces where specific alleles confer greater fitness on certain individuals either in the form of increased viability under particular environmental conditions (mainly infection, disease, etc.) or increased fertility. The selective forces, through action upon individuals, tend to bring the population as a whole into equilibrium. The various genetically controlled polymorphisms of blood groups, red cell enzymes, serum proteins etc. are favoured to evaluate these genetic variabilities. The wide variation in the frequencies of genetic markers in different human populations could be attributed to environmental conditions where diseases play a major role. The extent to which variety of polymorphic systems affect fitness and are subject to natural selection, remains a very open question in genetics in general and human genetics in particular (Cavalli-Sforza, 1972).

Genetically determined differential fitness in a population is extremely difficult to observe unless selection co-efficients are very large, *i.e.* sample sizes have to be exceptionally large for selectional changes in gene frequencies to be detected (Cavalli-Sforza and Bodmer, 1971; Hiorns and Harrison, 1970). This indeed is a major limitation in human population genetics. It is probably due to the possible relationship between genetic variability and conditions which affect or are likely to affect fitness.

Genetic markers serve as important tools in investigating the relative influence of genetic factors on the development and progress of diseases. They also help in understanding the pathogenic mechanisms underlying their susceptibility and resistance. Observed associations between a genetic marker and disease may be governed by different underlying mechanisms - a linkage disequilibrium can exist between a marker gene and a disease or through population stratification, rather through linkage or the pleiotropic effects of the gene under investigation (Penrose, 1935; Mayo and Street, 1986). The susceptibility gene, such as an oncogene, or the marker gene product may be functionally involved in disease etiology and or its pathogenesis, or in the modulation of the host defence mechanism. The association of a common disease with genetic polymorphsim can yield important information regarding an individual's risk of developing the disease and provide clues as to its etiology.

The studies of blood groups and diseases (Anand, 1961, 1964 a,b; 1965; Seth, 1969; Seth and Seth, 1972), histocompatibility antigens - HLA (Seth and Seth, 1978), and immunoglobulins (Seth and Seth, 1994) have been dealt with elsewhere. Herein, only serum proteins and diseases have been discussed, in order to understand the biochemical and the pathological mechanisms played by these genetic markers and in delineating their many other facets. This would ultimately help to combat the disease in a more efficient manner.

SERUM PROTEINS AND ALBUMIN

Though easy to describe collectively, plasma proteins present problems for identification, classification and nomenclature because of their vast variation in their constituent components. Since many of the major plasma proteins lack a known genetico-biological activity, their identification throughout the *Animal Kingdom*, is largely based on electrophoresis or their solubility properties and, to a lesser degree, on serological cross-reactivity. Study of such proteins, thus, provides another approach to evolutionary developments and phylogenetic relationships.

The concentration of proteins varies in the embryonic, neonatal and adult stages. Total

proteins in the amniotic fluid have been studied at different gestations in order to know the health status of the developing fetus (Shashi Bala et al., 1986, 1990). The plasma proteins are of great physiological significance for their varying protein contents - both in their major (albumin and immunoglobulin) and their minor (α and β-globulin) components - in different diseases reflect tissue damage and cellular injury. The existence of physiological anomalies in mongolism is well known but the existence of "chemical anomalies" in this condition are not so widely recognised. The belief that hypergammaglobulinemia in mongols compensates for the poor quality of the antibody production amongst them (Appleton and Pritham, 1963) is probably speculative for the γ-concentrations among mongols are either shown to increase with age (Nelson, 1961) or are independent of age (Skanse and Laurell, 1962). Analysis of the protein content of mental retardates revealed varying protein concentrations in patients and the control series. Statistically significant differences have been reported for different age groups of the retardates (Dhiman et al., 1987). The relatively lower protein content in patient series compared to the controls is in conformity with other studies (Rundle et al., 1973; Smith and Berg, 1976).

Decrease in the mean concentration of albumin and an increase in the γ-globulin concentration with α- and γ-concentration within the normal limits has been observed in the cirrhosis patients (Sunderman, 1964; Hilkovitz and Jacobson, 1961). In hepatic cirrhosis and viral hepatitis patients, a low mean concentration of α_1- and α_2- globulins and hypoalbuminemia has been observed. There is a marked decrease in albumin concentration, associated with an increase in the α- and γ-globulin fractions in patients with rheumatic fever (Svartz and Olhagen, 1948; Routh and Paul, 1950). Patients with Reiter's syndrome showed a considerable elevation in the α_1 and α_2 fractions with only a slight elevation of γ-globulins and a moderate decrease in albumin (Svartz and Olhagen, 1948). The quantitative variation of albumin in the retardates is quite irregular due to various pathological conditions involved (Dhiman et al., 1992). Compared to the controls, hypoproteinemia with significant hypoglobulinemia has been reported in patient's suffering from a syndrome comprising of mental retardation, tremors, pigmentation and anemia in infants (Kaul et al., 1973). Significant differences have been observed between γ-globulin concentrations in lymphatic leukemia and lymphomas, and myleogenous and monolytic leukemia (Sunderman and Sunderman, 1957). In both these groups, there occurs significant hypoproteinemia, hypoalbuminemia and hypo-β-globulinemia. The developmental changes of the total proteins and the polymorphic nature of the various fractions of the proteins, namely, α_1- globulin (including α_1-antitrypsin), α_2-globulin (haptoglobin, ceruloplasmin), β-globulin (transferrin and Human Complementary Component C'3), and in relation to diseases have been discussed in the present paper.

Alpha$_1$- antitrypsin

The genetic locus of α_1 - antitrypsin is called P_1 (Protease inhibitor). More than 50 allelic variants, including a null allele, have been recognized at the P_1 locus and the nomenclature has been standardized (Cox et al., 1980; Kamboh, 1985). The P_1 locus is highly polymorphic in human populations showing considerable variations in the allelic frequencies (Kamboh, 1985). There is also marked variation in the distribution of the P_1M subtypes which can be attributed to the genetic composition of the various ethnic/racial groups. A number of investigations indicate that the gene frequency of P_1M_2 allele was increased in patients with obstructive pulmonary diseases. Some others indicate that P_1M_3 is a predisposing genetic factor for some of the chronic liver diseases especially liver cancer (Sizaret et al., 1981). But the frequency of P_1M_3 allele is significantly decreased among patients with bladder carcinoma and haematotogical malignancies suggesting that this gene might have a role in reducing the susceptibility to malignancy (Benkmann et al., 1987; Janardhana and Propert, 1990). A significant increase in the frequency of PIM_1M_1 pheno-

type in pulmonary tuberculosis patients with two radiological subgroups has been reported (Mukerjee, 1993). This is not in agreement with the studies of Fertakis and co-workers (1977). Several studies have suggested that individuals with deficient alleles (PI^z or PI^v), either in heterozygous or homozygous forms, tend to have an increased risk for various diseases. The MS, MZ and SZ phenotypes have been associated with several clinically defined disorders/diseases such as pulmonary tuberculosis (Fagerhol and Huge, 1969; Mukherjee, 1993), liver diseases (Ericksson, 1985), rheumatoid arthiritis (Beckman et al., 1984), and malignancies (Callea et al., 1982; Ericksson et al., 1986). The association between PI deficient types and tuberculosis, particulary in the Indian populations, is an unexpected finding; these genes being rare in this subcontinent (Kamboh, 1984, 1985; Saha, 1990). The lack of PI deficient alleles in the Asian populations, including India, probably limits the use of the PI protein polymorphism in disease association studies among these populations (Saha, 1990).

The normal concentration of α_1-antitrypsin, an acute-phase reactant protein, is about 130 mg/dl, which are generally elevated in response to inflammation and tissue damage. A significant increase in α_1 - antitrypsin concentration has been reported by several researchers (Clarke et al., 1970; Yemul et al., 1983). The mean level of α_1 - antitrypsin in tuberculosis is mostly as high as 487.51 ± 110.70 mg/dl (Yemul et al., 1983) or 405.77 ± 33.56 mg/dl (Mukerjee, 1993). The elevated α_1 - antitrypsin level in these series may be the result of an acute-phase response with an inflammatory process occuring in the lungs. Contrary to these findings, Hunter and coworkers (1968) did not find any significant changes in the α_1 - antitrypsin levels whereas Fertakis and his associates (1977) reported very low values, which might be due to the increased frequency of the deficient alleles in their series. Higher levels have been observed in patients of sarcoidosis (Clarke et al., 1970), leprosy (Celikogu et al., 1976; Agarwal and Saha, 1978), tuberculosis pleural effusion (Sulochana et al., 1988) and carcinoma of the lung (Nash et al., 1980). Increased level of α_1 - antitrypsin neutralises the activated macrophase-derived proteases which probably contribute to the tissue necrosis and cavity formation in tuberculosis and other diseases resulting in tissue damage. It is, thus, necessary to conduct indepth studies of the genetic marker to locate different mutations, and the quantitative disturbances, in order to work out suitable strategies for management and control of the diseases.

Haptoglobin

Haptoglobins are a family of glycoproteins found in the α_2 - globulin fraction of plasma. The discovery of the haptoglobin polymorphism and its easy mass screening by starch gel electrophoresis has led to numerous gene frequency studies among various populations. The total hemoglobin-binding capacity of serum haptoglobin determines the renal threshold for the excretion of hemoglobin. If not scavenged by haptoglobin, the hemoglobin released in the circulation by intravascular hemolysis might be deposited in the renal tubules and produce severe pathological effects. Although the hemoglobin-binding capacity of haptoglobin varies slightly with the genetic type, the difference is small and is of doubtful physiological significance.

The emergence of the Hp^2 allele and of the polymorphic types of haptoglobin is a relatively late evolutionary event, occuring after the separation of the human line from other primates (Javid, 1978). It has been further demonstrated by the distribution of the haptoglobin alleles that individuals carrying the Hp^2 allele enjoy a selective advantage (Javid, 1978). In view of this, several diseases have been studied for their possible association with haptoglobins. Abnormal haptoglobin distribution is seen in individuals with defective immune system (Wendt et al., 1968; Sutton, 1970). It has also been shown that Hp 1-1 individuals have a slightly less immune response, on an average, than Hp 2-2 persons as shown by the low elevation of the antibody titre after immunisation (Nevo and Sutton, 1968). Several reports have suggested an association of Hp 1-1 phenotype with diffrential

susceptibility to various types of leukemias (Latner and Zaki, 1960; Papiha et al., 1974; Nevo and Tatarsky, 1986; Mitchell et al., 1988), breast cancer (Tsamantanis et al., 1980; Kaur et al., 1986), malaria (Singh et al., 1986; Dey, 1988), hyperplastic anaemia (Giblett, 1969), and many other malignant diseases (Sezaki et al., 1973). Tuberculosis patients differ significantly from the controls with respect to hapoglobin phenotype distribution (Mukherjee, 1993). The excess of Hp 2-2 and a corresponding deficit of Hp 2-1 has also been reported. On the other hand, some earlier studies have shown a reverse trend, namely low frequency of Hp 2-2 and a high frequency of Hp 2-1 (Grange et al., 1984; Papiha et al., 1987). In asthmatic patients, no association has been reported (Fröhlander and Stjernberg, 1989). In yet another study of cancer patients, Hp 1-1 phenotype was completely absent (Bakshi et al., 1976). Statistically significant association was found between non-insulin dependent diabetes mellitus and haptoglobin phenotypes. This association shows a dose effect with almost twice the risk of homozygous Hp^1 allele than Hp 2-1(Stern et al., 1986). The higher incidence of Hp 1-1 in the retardates indicates an increased hemoglobin binding capacity than in individuals with Hp 2-2 and 2-1 phenotypes (Dhiman et al., 1984). This difference may be attributed to the faulty stimulation of haptoglobin synthesis in the liver. High frequency of ahaptoglobulinemia (Hp^0) has been reported in many malarial areas (Hill et al., 1987; Trape et al., 1985; Dey, 1988; Giblett et al., 1966).

The normal level of haptoglobin varies from 40-180 mg per 100 ml in healthy adult individuals (Nyman, 1959; Murray et al., 1966). This wide variability in its concentration is based on its hemoglobin binding capacity. Profound changes in the serum haptoglobin levels in various diseases make it a valuable indicator for the diagnosis and prognosis (Owen et al., 1964). Several studies suggest that the haptoglobin concentration is elevated in acute and chronic infections, such as tuberculosis (Wong and Saha, 1989; Caplin et al., 1989), leprosy (Schwantes et al., 1967), rheumatic diseases (Turowska, 1969), progressive and systematic sclerosis (Zlotnik and Rodhan, 1961) and multiple sclerosis (Phillips et al., 1965). A quantitative relationship between infarction size (in acute myocardial infarction) and the increase in the serum haptoglobin levels has also been reported (Chapelle et al., 1981). Recent studies on tuberculosis indicate that levels of haptoglobin were significantly elevated in the patient series (198.36 ± 17.47 mg/dl) than in the controls (88.53 ± 13.20 mg/dl) (Mukerjee, 1993). This high level in the patients can be explained on the basis of involvement of haptoglobin in the regulation of the inflammatory and immunological processes which are of importance in the development of the tuberculosis.

Low levels of serum haptoglobin are observed in severe liver diseases. Since liver is the main site of haptoglobin synthesis, the low level is the result of the faster destruction of the Hp-Hb complex compared to the slower rate of the haptoglobin synthesis (Putnam, 1975; Javid, 1978). Low levels of haptoglobin are observed in numerous haemoglobinopathies, for instance sickle cell anaemia, thalassemia, hereditary spherocytosis and untreated pernicious anaemia (Putnam, 1975). In these patients, the low levels of haptoglobin are due to the high frequency of the Hp 2-2 phenotypes. Individuals with this phenotype have low levels of the protein (Piessen et al., 1984; Surya Prabha et al., 1987).

Ceruloplasmin

Ceruloplasmin, α_2- globulin of human serum, comprises of a single peptide chain having 1050 amino acids. In humans, 70 per cent of the ceruloplasmin is present intravascularly while 30 per cent is present in the extravascular compartments such as amniotic fluids, cerebrospinal fluids, synovial fluids, pleural fluids, ascites fluids and human tears (Wolf, 1982). These glycoproteins form an acute phase reactant part of the organism's defence in inflammation. The first electrophoretic variant of Cp in humans was reported by McAlister and co-workers in 1961. A true genetic polymorphism was not reported until Shreffler and his co-workers (1967) identified various types of Cp variants in American Negroes and

Caucasians using alkaline starch gel electrophoresis (pH 9.0). Later, three main phenotypes (CpA, CpB and CpC) with several other variants were identified (Shokeir and Shreffler, 1970; Fujita et al., 1985).

Very few studies have been conducted to determine the association between ceruloplasmin phenotypes and diseases. Some contradictory findings have been reported towards its association with leprosy. High frequency of phenotypes CpAB and CpBC have been reported in leprosy patients (Walter et al., 1972; Ananthakrishan et al., 1973). Mukherjee's tuberculosis series (1993) and its two subgroups are characterised by an increase in the frequencies of CpAA, CpAB, CpAC and CpBC phenotypes whereas the phenotype CpBB has a lower frequency than in the healthy controls. However, no significant association has been observed between ceruloplasmin and tuberculosis.

Levels of ceruloplasmin are markedly altered in many diseases because this protein is one of the acute phase reactants which is elevated in response to inflammation. A significant increase in its levels is found in patients with acute and chronic viral and bacterial infections such as leprosy, tuberculosis and parasitic diseases (Singhvi and Maitrya, 1971; Emmett et al., 1987; Mukerjee, 1993). In pulmonary tuberculosis, the increased level of ceruloplasmin is correlated with severity of the diseases and may reflect the extent of tissue damage (Caplin et al., 1989; Mukherjee, 1993). Elevated serum concentration of ceruloplasmin has been reported in patients with rheumatoid arthritis (Denko and Gabrial, 1979), acute glomerulonephritis (Wolf, 1982), diabetes and non-diabetic necrobiosis lipoidica (Majewski et al., 1981), liver diseases (Guattery et al., 1981), carcinoma of the breast, and cervix (Schapira, 1972). Increase in the level of ceruloplasmin has also been reported in response to non-pathological conditions, but is non-significant. In patients with Wilson's disease and Menkes Kinky hair syndrome, deficiency of ceruloplasmin is an inherited characteristic (Scheinberg and Sternlieb, 1963; Danks et al., 1973). However, a number of other conditions may at times be associated with a low ceruloplasmin level. There is a lot of inconsistency in the results regarding association between many other diseases (infectious and non-infectious) and ceruloplasmin phenotypes as well as its levels. This definitely needs further detailed study in order to delineate the exact mechanisms involved in genetic variation and quantitative changes in the plasma proteins (ceruloplasmin) in different diseases.

Human Complementary Component (C'3)

Studies of the genetic variability in human proteins with known functions are particularly interesting because they shed light on clinical conditions as well. The genetic polymorphism of C'3 has been established long ago. The complement components constitute a very important biological system of proteins which participate not only in the pathophysiological mechanism of infectious and allergic diseases, but have been shown to play a role in a variety of pathological processes as well. In human pathology, the presence of β_1C - globulin has been established in the arterial walls in hypertension vascular diseases, malignant nephrosclerosis, certain collagenous diseases, lupus erythematosus and cryoglobulinemia (Kunkel and Tann, 1964; Lachman et al., 1962; Paronetto, 1965). The preponderance of FF and FS phenotypes and a deficiency of SS phenotypes in old arteriosclerotic vascular disease patients has been reported (Dissing et al., 1972). The frequency of the $C'_3{}^F$ gene is significantly higher among patients with rheumatoid arthritis and hepatitis (Farhud et al., 1972). Statistically non - significant differences for C'3 phenotypes and various types of leprosy have been reported (Ananthakrishnan et al., 1973; Agarwal et al., 1974). A lower frequency $C'_3{}^S$ gene has been reported in various diseases compared to controls. Most striking of all this is a low frequency of the '*s*' gene in Alzheimer's syndrome (Agarwal et al., 1975). Only in Down's syndrome (Brackenridge et al., 1974; Shobha, 1981), cystic fibrosis (Lederberg and Sackett, 1976), Grave's disease (Pepper and Farid, 1979), chronic uremia (Stofferson and Jorgenson, 1980) and in the mental retardates (Shobha, 1981), the fre-

quency of the '*s*' gene is higher than in the normal controls. These results suggest that the C'3 variants may be important in the mediation of the immune injury in diseases.

Considerable variability, perhaps partly dependent on genetic factors, has been observed in the serum level of the third complement of C'3 in normal healthy individuals (Lundh, 1964). On an average, the concentration of C'3 proteins in normal humans ranges from 50 to 150 mg/100 ml. The allotypes of C'3 differ in net surface charge at pH 8.6 but reveal no significant difference in their hemolytic activity, molecular size, or immune adherence titre. It has been suggested that the concentration of C'3 is the lowest in FF individuals and the highest in the SS individuals; intermediate concentration being in the individuals with FS phenotypes. This indicates that these protein levels are also genetically controlled (Alper and Propp, 1968).

Immunological estimation of C'3 in human serum has proved to be very useful in the diagnosis and prognosis of several diseases. C'3 belongs to the so called acute-phase reactants which have a higher concentration in the inflammatory diseases. Reduced levels of C'3 have been shown to be associated with a number of diseases, such as glomerulonephritis, systemic lupus erythematosus, extra renal diseases, leprosy and fatal acute respiratory infections (Schur and Austin, 1968; Grieco et al., 1971; Schulz, 1971; Agarwal et al., 1974; Aiuti et al., 1980). *In-vitro* conversion rates were identical for $C'_3{}^S$ and $C'_3{}^F$ (Teisberg, 1971; Alper and Propp, 1968; Brönnestam, 1973). A sex difference in C'3 concentration has been described by Lundh (1964). Females are reported to have lower C'3 concentration than males. But these findings are quite contradictory. Hence, it is not clear whether sexual dimorphism exists or not.

Transferrins

These iron-binding β-globulins are monomorhic glycoproteins found in plasma. The main phenotypes, *i.e.* TfC, TfB and TfD, are easily detectable by starch gel electrophoresis. Since the transferrin phenotypes are not supposed to differ in molecular weight and the carbohydrate content, the considerable high frequency of TfCC suggests the necessity to study the selective mechanisms responsible for maintaining this main phenotype in the population. Until 1978, TfC was considered to be a single variant. However, using isoelectric focussing (IEF), a heterogeneity of TfC comprising of two common variants (TfC_1 and TfC_2) was described (Kuhnl and Spielmann, 1978; Thymann, 1978). Later, thirteen more variants were detected. Likewise, D is also controlled by many co-dominant alleles. This heterogeneity of transferrin, detected through isoelectric focussing method, is not caused by its protein moiety, as its amino acid sequence remains the same. It is probably caused by varying amount of iron and/or that of sialic acids and other monosaccharides in the glycon chains (Irie and Tavasoli, 1987). Family studies indicate that these variants are controlled by multiple co-dominant alleles at the Tf locus which has been assigned to the long arm of chromosome 3q21-q26 (Yang et al., 1984).

Transferrins exert bacteriostatic effects on a variety of microbial species and, therefore, play a major role in physiological defence against infection. Thus, a complete understanding of this genetic marker would lead to a greater understanding of the complex interactions between man and his changing environment, and also the health of the future generations. The distribution pattern of transferrin phenotypes among many diseased series does not deviate from that in the normal healthy individuals (controls). Studies have been conducted to determine the association between transferrin, tuberculosis and leprosy (Walter et al., 1970, 1972; Ananthakrishnan et al., 1973; Papiha et al., 1987; Mukerjee, 1993). No significant differences have been observed in the patients and normal individuals. Similarly, no association has been reported with Down's syndrome (Hutton and Smith, 1964; Dhiman et al., 1984), cystic fibrosis of the pancreas (Hsia et al., 1969), breast cancer (Kaur et al., 1986), and malaria (Dey, 1988). In contrast to the findings of Walter and co-workers (1970, 1972), Hitzeroth and co-workers (1978) suggest the possibility of an association between transferrin

and leprosy. An increased frequency of TfD has been found among the leprosy patients indicating that TfD type may be more susceptible to infections by *Mycobacterium laprae* (Hirzeroth et al., 1978). A high frequency of TfC_1 has been reported in populations which live in malaria prone areas. Walter and coworkers (1983) considered only healthy controls. The frequency of *TfC'* in malaria positive Ao Nagas (North-East India) could be attributed to a selection pressure which might be operating in this malaria endemic zone to maintain its gene frequency (Kar et al., 1990). Malaria infection has been found to be associated with significantly raised iron-saturation of transferrin (Oppenheimer et al., 1986). Therefore, it can be suggested that iron may be released equally from all types of transferrins saturated with iron. TfC_1 at this stage may maintain the iron balance between the sites of red cell breakdown to storage sites, *i.e.* liver, in *Plasmodium* induced hemolysis etc. On the other hand, low iron binding of Tf types, i.e. $TfC_{2\text{-}1}$ and $TfC_{2\text{-}2'}$ may put additional burden causing liver dysfunctioning and iron intoxication. Altered liver function, thus, may hamper the life cycle of the *Plasmodium* to the host's advantage. But nothing can be said conclusively as no systematic evaluation of iron binding capacity or *in-vitro* microbial activity of various TfC subvariants has been reported.

The selection at the Tf locus has involved the apparent role of Tf subtypes in reproduction. A high incidence of the C^2 gene has been reported in mothers with a previous history of spontaneous abortion (Beckman et al., 1980) and amongst extremely premature infants (Auconi et al., 1982). An increased frequency of C^3 instead of C^2 has been observed in couples with first trimester recurrent spontaneous abortions (Weitkamp and Schacter, 1985). This may be due to varied immunoregulatory effect of transferrin. The genetic variation of transferrin and its relationship with the immunological system necessitates further studies to delineate the possible environmental and biological factors involved in maintaining the Tf polymorphism.

The level of transferrin in normal human adult varies from 180 to 260 mg/100 ml and remains almost constant throughout life. In a wide variety of pathological and non-pathological conditions, deviation from the normal level of plasma transferrin has been observed. Following tissue injury or infection, transferrin level has been found to be reduced (Kushner and Mackiewicz, 1987). Cancer patients, irrespective of the type of tissue involved, have been found to have a decreased serum concentration (Hughes, 1972). Reduction in the transferrin level is found in patients with acute and chronic infection including tuberculosis (Baynes et al., 1986; Mukerjee, 1993; Immanuel et al., 1990), liver cirrhosis (Teppo and Maury, 1983) and rheumatic diseases (Denko and Gabriel, 1979). The changes in the concentration may be due to the imparied synthesis or enhanced catabolism. Transferrin has been shown to behave as a so-called "negative" acute phase protein (Bornstein, 1982; Kushner and Mackiewicz, 1987). This would imply that the synthesis of transferrin is inhibited in inflammation. There is, however, evidence that decrease in the transferrin concentration is the result of the increased catabolism of the protein (Aisen, 1984).

COMMENTS

The above studies show that associations of common/rare diseases with genetic polymorpisms can yield information about an individual's risk of susceptibility to a disease and provide clues to it's etiology. Susceptibility to infectious diseases, for instance pulmonary tuberculosis, leprosy, malaria etc., is usually influenced by the environment and is determined by the genetic constitution of the host. The extent to which various polymorphic systems affect fitness is an open question *vis-a-vis* population genetics and diseases. Further, it appears that there are considerable quantitative effects of plasma proteins on the inflammatory and immunologic aspects of the host-antigen relationship. Mechanisms by which the level of these proteins can be lowered or increased could be explored for the potential adjuvant effect in altering the host-antigen relationship in the direction of the antigen

(bacterial) control. Many studies on different diseases provide evidence that plasma proteins interact with blood cells having immunologic function that determine the level of cellular immunity expressed. The correlation between genetic markers and immunity may, thus, help in examining the effect of patient's genetic constitution on their immunity. Elucidation of the physiological and biochemical determinants of the potential genetic resistance and susceptibility to mycobacterial infections may provide clues of its pathogenesis, thereby facilitating prevention and treatment. The plasma proteins are a heritable factor tending to promote resistance or susceptibility to many diseases. Some of these genetic markers are significantly associated while others are mildly associated. These findings indicate that the individual's genetic constitution influences the modulation of the disease progression.

KEY WORDS Serum Proteins. Association. Disease. Genetic Markers and Population Genetics.

ABSTRACT The development changes of the total proteins and the polymorphic nature of the various fractions of the proteins have been discussed in order to understand their biochemical and pathological mechanisms. The normal concentration of α_1-antitrypsin (130 mg/dl) is generally elevated in response to inflammation and tissue damage. Higher levels have been observed in patients of sarcoidosis, leprosy, tuberculosis and carcinoma. A quantitative relationship between infarction size and the increase in haptoglobin levels has also been reported. No significant association has been observed between ceruloplasmin and tuberculosis. Reduced levels of C'3 have been shown to be associated with a number of diseases, such as glomerulonephritis, systemic lupus erythemetosus, extra renal diseases, leprosy and fatal acute respiratory infections. The synthesis of transferrin is inhibited in inflammation which is evidence for the decrease in transferrin's concentration and of the increased catabolism of the protein. Elucidation of the physiological and biochemical determinants of the potential genetic resistance and susceptibility of mycobacterial infection may provide clue of its pathogenesis, thereby facilitating its prevention and treatment.

REFERENCES

Agarwal, D.P., Benkmann, H.G., Goedde, H.W., Rohde, R., Delbruck, H. and Rougemont, A.: Level of serum β_{1C-3}/β_{1A} globulin (C'3) and its polymorphism in leprosy patients and healthy controls from Ethiopia and Mali. *Hum. Genet.*, **21**: 355 - 359 (1974).

Agarwal, D.P., Srivastava, L.M., Benkmann H.G., Goedde H.W, and Grunwald, P.: Studies on the polymorphic C'3, Tf and Bg in Down's syndrome and other diseases. *Hum. Genet.*, **29**: 23 - 28 (1975).

Agarwal, S.K. and Saha, K.: Serum α-1-antitrypsin in various forms of leprosy. *Ind. J. Med. Res.*, **68**: 136 - 138 (1978).

Aisen, P.: Transferrin metabolism and the liver. *Sem. Liver Dis.*, **4**: 193 - 206 (1984).

Aiuti, F., Damelio, R., Palmisano, L., Valesini, G., Luzi, G. and Giunchi, G.: Immunoglobulin - a deficiency and circulating immune complexes in Neapoliten (Italy) children with fatal acute respiratory infections. *Lancet*, **i**: 226 - 228 (1980).

Alper, C.A. and Propp, R.P.: Genetic polymorphism of the third component of human complement (C'3). *J. Clin. Invest.*, **47**: 2181 - 2191 (1968).

Anand, S.: ABO blood groups in relation to Eosinophilia. *Anthropologist*, **8**: 33 - 39 (1961).

Anand, S.: Association of ABO blood groups with incidence of renal lithiasis. *Acta Genet. Med. Gemell.*, **13**: 167 - 172 (1964a).

Anand, S.: The relationship of ABO, MN and Rhesus blood groups to Asthma. *Ind. J. Chest Dis.*, **6**: 74 - 79 (1964b).

Anand, S.: Filariasis in its relation to A_1A_2BO, MN, Kell, Duffy and Rhesus blood groups and secretor factor. *Acta Genet. Med. Gemell.*, **14**: 31 - 37 (1965).

Ananthakrishnan, R., Walter, H., Kelleman, G. and Matznetter, Th. : Further studies on association between leprosy and genetic markers in human serum. *Hum. Genet.*, **19**: 183 - 192 (1973).

Appleton, M.D. and Pritham, G.H.: Biochemical studies in mongolism. *Amer. J. Ment. Defic.*, **67**: 521 - 525 (1963).

Auconi, P., Biagini, R., Colarizi, P. and Pascali, V.: Transferrin C subtypes in extremely premature newborn infant. *Paediat. Res.*, **16**: 1022 - 1024 (1982).

Bakshi, S., Sharma, A., Talukdar, G. and Bhattacharya, B.K.: Haptoglobin types in cancer patients in comparison with normal population in the eastern India. *Gann*, **67**: 413 - 416 (1976).

Baynes, R.D., Flax, H., Brothwell, T.H., Bezworda, W.R., MacPhail, A.P., Atkinson, P. and Lewis, D.: Haematological and non-related measurements in active pulmonary tuberculosis. *Scand. J. Ham.*, **36**: 280 - 287 (1986).

Beckman, G., Beckman, L. and Sikström, C.: Transferrin C subtypes and spontaneous abortion. *Hum. Hered.*, **30**: 316 - 319 (1980).

Beckman, G., Beckman, L., Bjelle, A. and Dahlqvist, Rantapa S.: Alpha-1-antitrypsin types and rheumatoid arthritis. *Clin. Genet.*, **25**: 496 - 499 (1984).

Beckmann, H.G., Hanssen, H.P., Ovenbeck, R. and Goedde, H.W.: Distribution of alpha-1-antitrypsin and haptoglobin phenotypes in bladder cancer patients. *Hum. Hered.*, **37**: 290 - 293 (1987).

Börnstein, W.: Leucocytic pyrogen: A major mediator of acute phase reaction. *Ann. N.Y. Acad. Sci.*, **389**: 323 - 337 (1982).

Brackenridge, C.J., Pitt, D.B. and Sheehy, A.J.: The distribution of seven genetic polymorphisms in patients with Down's syndrome. *Clin. Genet.*, **5**: 414 - 419 (1974).

Brönnestam, R.: Studies of the C'3 polymorphsim - Relations between phenotype and quantitative immunochemical measurements. *Hum. Hered.*, **23**: 128 - 134 (1973).

Callea, F., Massi, G., DeWolf-Peeters, C., Lievens, C. and Desmet, V.J.: Alpha-1-antitrypsin phenotypes in malignant lymphoma. *J. Clin. Path.*, **35**: 1213-1215 (1982).

Calpin, M., Grange, J.M. Morley, S., Brown, R.A., Kemp, M., Gibson, J.A., Kardjito, T., Hoeppner, V. and Beck, J.S.: Relationship between radiological classification and the serological and hematological features of untreated pulmonary tuberculosis in Indonesia. *Tubercle*, **70**: 103 - 113 (1989).

Cavalli-Sforza, L.L. : Analytic Review: some current problems of human population genetics. *Amer. J. Hum. Genet.*, **25**: 82 - 104 (1972).

Cavalli-Sforza, L.L. and Bodmer, W.F. : *The Genetics of Human Populations*. W.H. Freeman and Company, San Francisco (1971).

Celikogu, S.I., Goskel, F.M., Salyan, T., Haznedar, S., and Goldberg, J.D.: A prelimnary report on a study of serum alpha-1-antitrypsin and immunoglobulin levels in lepromatous leprosy. *Lepr. Rev.*, **47**: 291-295 (1976).

Chapelle, J.P., Albert, A., Smeets, J.P., Hensghem, C., and Kulbertuo, H.E. : Effect of the haptoglobin phenotypes on the size of a myocardial infarct. *N. Eng. J. Med.*, **307**: 457-463 (1982).

Clark, H.G.M., Freeman, T., Hickman, R., and Pryse-Phillips, W.G.M.: Quantitative immunoelectrophoretic analysis in patients with tuberculosis and sarcoidosis. *Thorax*, **25**: 423-426 (1970).

Cox, D.W., Johnson, A.M., and Fagerhol, M.K. : Report of nomenclature meeting for alpha$_1$ antitrypsin. INSERM Rouen/BOIS-Guilame-1978. *Hum Genet.*, **53**: 429-433 (1980).

Danks, D.M., Cartwright, E., and Stevens, B.J. : Menke's steely-hair (Kinky-hair) disease. *Lancet*, **i**: 891-895 (1973).

Denko, C.W. and Gabriel, P.: Serum proteins - transferring, ceruloplasmin, albumin, α_1 acid glycoprotein and α_1 antitrypsin in rheumatic disorders. *J. Rheumatol.*, **6**: 664-672 (1979).

Dey, Swarupa: *Antigenic and Biochemical Variations in Relation to Malaria Among the Ao Nagas*. Ph. D. thesis Unpublished, University of Delhi, Delhi (1988).

Dhiman, Shobha Rani, Seth, S., and Seth, P.K. : Serum proteins and mental retardation. pp. 205-215. In: *Anthropology in Indian Context*. I.J.S. Bansal (Ed.). Today and Tomorrow's Printers and Publishers, New Delhi (1984).

Dhiman, Shobha Rani, Seth, S. and Seth, P.K.: Total proteins and mental retardation. a quantitative approach. *Disabilities and Impairments*, **1**: 1 - 8 (1987).

Dhiman, Shobha Rani, Seth S. and Seth P.K.: Serum albumins in individuals with mental handicap. *Disabilities and Impairments*, **4**: 72-80 (1992).

Dissing, J., Lund, J. and Sørensen, H.: C'3 polymorphism in a group of old arteriosclerotic patients. *Hum. Hered.*, **22**: 466 - 472 (1972).

Emmett, M., Miller, J.L. and Crowle, A.: Protein abnormalities in adult respiratory distress syndrome, tuberculosis and cystic fibrosis sera. *Proc. Soc. Expt. Biol. Med.*, **184**: 74 - 82 (1987).

Eriksson, S., Carlon, J. and Velez, R. : Risk of cirrhosis and primary liver cancer in α_1-antitrypsin deficiency. *N. Eng. J. Med.*, **314**: 736 - 739 (1986).

Eriksson, S.G.: Liver disease in α_1-antitrypsin deficiency - aspects of incidence and prognosis. *Scand. J. Gasteroenterol.*, **20**: 907 - 911 (1985).

Fagerhol, M.K. and Hauge, H.E.: Serum PI types in patients with pulmonary tuberculosis. *Acta Allergol.*, **24**: 107 - 117 (1969).

Farhud, D.D., Ananthakrishnan R. and Walter, H.: Association between C'3 phenotypes and various diseases. *Hum. Genet.*, **17**: 57 - 60 (1972).

Fertakis, A., Archimandritis, A., Tsourapas, A., Douratsos, D. and Angelopoulous, B.: Serum level and α_1-antitrypsin phenotypes in active pulmonary tuberculosis. *Acta Genet. Med. Gemell.*, **26**: 97 - 99 (1977).

Fröhlander, N. and Stjernberg, N.: Association between haptoglobin groups and hereditary predisposition for bronchial asthma. *Hum. Hered.*, **39**: 7 - 11 (1989).

Fujita, M., Satoh, C., Asakawa, J., Nagahata, Y., Tanaka, Y., Hazama, R. and Gorika, K.: Electrophoretic variants of blood proteins in Japanese. *JPN J. Hum. Genet.*, **30**: 43-50 (1985).

Giblett, E.R.: *Genetic Markers in Human Blood*. Blackwell Scientific Publishers, Oxford (1969).

Giblett, E.R., Motulsky, A.G. and Fraser, G.R.: Population genetic studies in the Congo. IV. Haptoglobin and transferrin serum groups in the Congo and in other African populations. *Amer. J. Hum. Genet.*, **18**: 553-558 (1966).

Grange, J.M., Kardjito, T. and Setibudi, I. : A study of acute phase reactant proteins in Indonesian patients with pulmonary tubrculosis. *Tubercle*, **65**: 23-29 (1984).

Grieco, M.H., Capra, J.D. and Paderson, H.: Reduced serum beta Ic/Ia globulin levels in extra renal disease. *Amer. J. Med.*, **51**: 340-245 (1971).

Guattery, J.M., Aroesty, S., Wilson, H., Rubulins, A., Flood, M.S. and Faloon, W.W.: Copper and ceruloplasmin: Serial studies in viral and alcoholic liver disease. *N.Y. State J. Med.*, **28**: 1603-1612 (1981).

Hilkovitz, G. and Jacobson, A. : Hepatic dysfunction and abnormalities of the serum patients and serum enzymes in sickle cell anemia. *J. Lab. Clin. Med.*, **57**: 856-867 (1961).

Hill, A.V.S., Whitehouse, D.B., Bowden, D.K., Hopkinson, D.A., Draper, C.C., Peto, T.E.A., Clegg, J.B. and Weatherall, D.J.: Ahaptoglobinemia in Melanesia: DNA and malarial antibody studies. *Trans. Roy Soc. Trop Med. Hyg.*, **81**: 573-577 (1987).

Hiorns, R.W. and Harrison, G.A. : Sampling for the detection of natural selection by age group genetic differences. *Hum. Biol.*, **42**: 53-64 (1970).

Hiteroth, H.W., Walter, H. and Hilling, M. : Genetic markers and leprosy in South African Negroes. Part I. Serum protein polymorphisms. *S. Afr. Med. J.*, **54**: 653-658 (1978).

Hsia, D.Y., Ling-Yu, S., Easterberg, S., Farquhar, J., Chong - Bo, K., Yeh, S. and Young, A.: The distribution of genetic polymorphisms among patients with Down's syndrome, phenylketonuria and cystic fibrosis of the pancreas. *Amer. J. Hum. Genet.*, **21**: 285-289 (1969).

Hughes, N.R. : Serum transferrin and ceruloplasmin concentrations in patients with carcinoma, melanoma, sarcoma and cancers of haematopoietic tissue. *Aust. J. Exp. Biol. Med. Sci.*, **50**: 97-107 (1972).

Hunter, C.C. Pierce, J.A. and Laborde, J. : α_1-antitrypsin deficiency - a family study. *JAMA*, **205**: 93-96 (1968).

Hutton, A.C. and Smith, G.F. : Haptoglobins and transferrins in patients with Down's syndrome. *Ann. Hum. Genet.*, **27**: 413-415 (1964).

Immanuel, C., Archaryulu, G.S., Kannapiran, M., Segaran, R. and Sharma, G.R.: Acute phase proteins in tuberculosis patients. *Ind. J. Chest Dis. All Sci.*, **32**: 15-23 (1990).

Irie, S. and Tavassoli, M.: Transferrin-mediated cellular iron uptake. *Amer. J. Med Sci.*, **293**: 103-111 (1987).

Janardhana, V. and Propert, D.N. : α_1-antitrypsin phenotypes in leukemia and lymphoma. *Dis. Markers*, **8**: 93-97 (1990).

Javid, J. : Human haptoglobins. *Curr. Top. Haem.*, **1**: 151-192 (1978).

Kamboh, M.I. : Population genetic studies of PI, Tf, Gc and PGM_1 subtypes among various caste groups in north India. *Acta Anthropogenetica.*, **8**: 159-179 (1984).

Kamboh, M.I.: Biochemical and genetical aspects of human serum α_1-protease inhibitor protein. *Rev. Dis. Markers*, **3**: 135-154 (1985).

Kar S., Seth, S. and Seth, P.K. : Transferrin in relation to malaria among Ao Nagas of Nagaland (India). *Indian Anthropologist*, **20**: 111-115 (1990).

Kaul, K.K., Belapurker, K.M. and Parekh, P.: Syndrome of mental retardation, tremors, pigmentation and anaemia in infants - some biochemical observations. *Ind. J. Med. Res.*, **61**: 86-92 (1973).

Kaur, H., Bhardwaj, D.N., Srivastava, P.K., Sehajpal, P.K., Singh, J.P. and Paul, B.C. : Serum protein polymorphism in breast cancer. *Acta Anthropogenetica.*, **8**: 189-197 (1986).

Kuhnl, P. and Spielmann, W.: Transferrin: Evidence for two common subtypes of the Tf allele. *Hum. Genet.*, 43: 91-95 (1978).

Kunkel, H.G. and Tann, E.M. : Auto-antibodies and diseases. *Adv. Immunol.*, **4**: 351-395 (1964).

Kushner, I. and Mackiewicz, A.: Acute phase proteins as disease markers. *Dis. Marker*, **5**: 1-11 (1987).

Lachmann, P.J., Muller-Eberhard, H.J., Kunkel, H.G. and Paronetto, F.: The localization of *in vivo* bound complement in tissue sections. *J. Expt. Med.*, **115**: 63-82 (1962).

Latner, A.L. and Zaki, A.H.: Clinical uses of starch gel electrophoresis with special reference to leukemia. *Clin. Chim. Acta*, **5**: 22-25 (1960).

Lederberg, S. and Sackett, D. : Distribution of complement C'_3 variants in individuals with cystic fibrosis. *Amer. J. Hum. Genet.*, **28**: 597-601 (1976).

Lundh, B. : A method for quantitative determination of β_1c-globulin, a component of the serum complement system. *Scand. J. Clin. Lab. Invest.*, **16**: 108-114 (1964).

Majewski, B.B.J., Barter, S. and Rhodes, E.L. : Serum α_2-globulin levels in granuloma annulare and necrobiosis lipoidica. *Brit. J. Dermatol.*, **105**: 557-562 (1981).

Mayo, O. and Street, D.J.: Heterogeneity in disease association. *Hum. Hered.*, **36:** 89-92 (1986).

McAlister, R., Martin, G.M. and Benditt, E.P. : Evidence for multiple ceruloplasmin components in human serum. *Nature*, **190**: 927-929 (1961).

Mitchell, R.J. and Carzino, R. : Haptoglobin groups and transferrin subtypes in multiple myeloma. *Hum. Hered.*, **38**: 117-121 (1988).

Mukherjee, P.: *Acute Phase Reactant Protein Profiles in Pulmonary Tuberculosis*. Ph.D. Thesis Unpublished, University of Delhi, Delhi (1993).

Murry, R.F., Robinson, J.C. and Visnich, S.: Observations on the inheritance of hypohaptoglobinemia. *Acta Genet.*, **16**: 113-121 (1966).

Nash, D.R., Mc Larty, J.W. and Fortson, N.G.: Pretreatment prediagnosis immunoglobulins, and alpha-1-antitrypsin levels in patients with bronchial carcinoma. *J. Natl. Cancer Inst.*, **64**: 721-724 (1980).

Nelson, T.L. : Serum protein and lipoprotein fractions in mongolism. *Amer. J. Dis. Child.*, **102**: 369-374 (1961).

Nevo, S.S. and Sutton, H.E. : Association between response to typhoid vaccination and known genetic markers. *Amer. J. Hum. Genet.*, **20**: 461-469 (1968).

Nevo, S.S. and Tatarsky, I.: Serum haptoglobin types and leukemia. *Hum. Genet.*, **73**: 240-244 (1986).

Nyman, M. : Serum haptoblogin : methodological and clinical studies. *Scan. J. Clin. Lab. Invest. Suppl.*, **11**: 39 (1959).

Oppenheimer, S.J., Gibdon, F.D., MacFarlane, S.B., Moody, J.B., Harrison, C., Spencer, A. and Bunari, O. : Iron supplementation increases prevalence and effects of malaria: Report of clinical studies in Papua New Guinea. *Trans. Roy. Soc. Trop. Med. Hyg.*, **80**: 603-612 (1986).

Owen, J.A., Smith, R., Padanyi, R. and Matson, J.: Serum haptoglobin in disease. *Clin. Sci.*, **26**: 3-41 (1964).

Papiha, S.S., Jones, A.L., Thompson, B. and Carr, D.: Haptoglobins in chronic lymphatic leukaemia. *J. Med. Genet.*, **11**: 349-352 (1974).

Papiha, S.S., Singh, B.N., Lanchbury, J.S.S., Roberts, D.F., Parsad, C.E., Wentzel, J. and Murty, K.J.R.: Association of HLA and other genetic markers in South Indian patients with pulmonary tuberculosis. *Tubercle*, **68**: 159-167 (1987).

Paronetto, F. : Immunocytochemical observations on the vascular necrosis and renal glomerular lesions of malignant nephro-sclerosis. *Amer. J. Path.*, **46**: 901-916 (1965).

Penrose, L.S.: The detection of autosomal linkage in data which consists of pairs of brothers and sisters of unspecified parentage. *Ann. Eugen.*, **6**: 133-138 (1935).

Pepper, B. and Farid, N.R. : Polymorphic variants of complement C'_3 in Grave's disease. *Hum. Hered.*, **29**: 279-283 (1979).

Phillips, S.M., Kornguth, S.E. and Thompson, H.G.: Serum haptoglobin changes in multiple sclerosis. *Neurology*, **15**: 415-418 (1965).

Piessens, M.F., Marien, G. and Stevens, E. : Decreased haptoglobin levels in respiratory allergy. *Clin. Allergy*, **14**: 287-293 (1984).

Putnam, F.W.: Haptoglobin. In: *The Plasma Proteins, Structure, Function and Genetic Control.* Vol 2:1-50,

F.W. Putnam (Ed.), Academic Press, New York. (1975).
Routh, J.L. and Paul, W.D. : Electrophoretic analysis of plasma and serum proteins in rheumatoid arthritis. *Arch. Phys. Med.*, **31**: 511-517 (1950).
Rundle, A.T., Atkin, J. and Clothier, B. : Serum proteins in Down's syndrome. Developmental *Medicine and Child Neurology*, **15**: 736-747 (1973).
Saha, N. : α_1-protease inhibitor (PI) subtypes in seven populations of East Asia. *Ann. Hum. Biol.*, **17**: 229-234 (1990).
Schapira, M.: The presence of ceruloplasmin in cancer of the breast and female genital organs. *J. Roy. Coll. Gen. Pract.*, **22**: 383-386 (1972).
Scheinberg, I.M. and Sternlieb, I. : Wilsons disease and the Concentration of ceruloplasmin in serum. *Lancet*, i: 1420-1421 (1963).
Schulz, D.P.: *The Complement System*. Monographs in Allergy S. Karger Basel (1971).
Schur, P.H. and Austin, K.F. : Complement in human disease. *Ann. Rev. Med.*, **19**: 1-24 (1968).
Schwantes, A.R., Salzano, F.M., deCastro, I.V. and Tondo, C.V.: Haptoglobins and leprosy. *Acta Genet. Stat. Med.*, **17**: 127-136 (1967).
Seth, S.: Syphillis in its relation to blood groups. *Anthropologist* (**Special Volume**): 105-115 (1969).
Seth, S. and Seth, P.K. : Blood groups and diseases. In: *Genetics and Our Health*. I.C.M.R. Tech. Report Series **20**: 188-204 (1972).
Seth, S. and Seth P.K. : HLA and diseases - revisited. *Acta Anthropogenetica*, **2**: 61-90 (1978).
Seth, S. and Seth, P.K.: Human immunoglobulins - an overviews. pp 81-117. In: *Human Genetics* P.K. Seth and S. Seth (Eds.). Omega Scientific Publishers, New Delhi (1994).
Sezaki, T., Tanaka, S., Irino, S. and Hirak, A. : A relationship of genetic type in serum haptoglobin with leukaemia, malignant lymphoma and cancer. *Acta Med. Okayama*, **27**: 141-147 (1973).
Shashi Bala, Seth, S. and Seth, P.K. : Total proteins in human amniotic fluid. *Aust. NZ J. Obstet Gynaecol.*, **26**: 141-144, (1986).
Shashi Bala, Seth, S. and Seth, P.K. : Protein fractions in human amniotic fluid. *Ind. Anthropologist*, **20**: 15-24 (1990).
Shobha Rani: *A Study of Genetic Markers in the Human Serum in Mentally Retarded Individuals*. Ph.D. Thesis (Unpublished), University of Delhi, Delhi (1981).
Shokier, M.H.K. and Shreffler, D.C.: Two new ceruloplasmin variants in Negroes - data on three poplations. *Biochem. Genet.*, **4**: 517-528 (1970).
Shreffler, D.C., Brewer, G.J., Gall, J.C. and Honeyman, M.S.: Electrophoretic varation in human serum ceruloplasmin: A new genetic polymorphism. *Biochem. Genet.*, **1**: 101-115 (1967).
Singh, I.P., Walter, H., Bhasin, M.K., Bhardwaj, V. and Sudhakar, K.: Genetic markers and malaria observations in Gujarat, India. *Hum. Hered.*, **36**: 31-36 (1986).
Singhvi, D. and Maitrya, B.B. : Ceruloplasmin activity in pulmonary tuberculosis. *Ind. J. Chest All. Dis.*, **14**: 110-112 (1977).
Sizaret, P., Clerc, M., Esteve, J., Frants, R.R. and Pillot, J.: MZ - alpha-1-antitrypsin phenotype and primary liver cancer. *Brit. J. Cancer*, **43**: 226-228 (1981).
Skanse, B. and Laurell, C.B.: The immunoglobulins in mongolism. *Acta Medica Scand.*, **172**: 63-65 (1962).
Smith, G.F. and Berg, J.M.: *Down Anomaly*, Livingstone London, 2nd Edition (1976).
Stern, M.P., Ferrell, R.E., Rosenthal, M., Haffner, S.M. and Haznda, H.P. : Association between NIDDM, Rh, blood group and haptoglobin phenotype - results from the San Antonia heart study. *Diabetes*, **35**: 387-391 (1986).
Stoffersen, E. and Jørgensen, K.A. : C'3 polymorphism in patients with chronic uremia. *Hum. Hered.*, **30**: 46-49 (1980).
Sulochana, G., Khalifullah, P.A. and Padmanabhan, L. : Adenosine deaminase, alpha-1-antitrypsin, alpha-1-acid glycoprotein, ceruloplasmin and proteins in the diagnosis of tuberculosis pleural effusion. *Ind. J. Chest Dis. All. Sci.*, **30**: 15-18 (1988).
Sunderman, F.W: Studies of the serum proteins. VI. Recent advances in clinical interpretation of electrophoretic fractions. *Amer. J. Clin. Path.*, **42**: 1-21 (1964).
Sunderman, F.W. and Sunderman, F.W. Jr : Clinical applications of the fractionation of serum proteins by paper electrophoresis. *Acta J. Clin. Path.*, **27**: 125-158 (1957).
Surya Prabha, P., Padma, T. and Ramaswamy, M.: Haptoglobin patterns in essential hypertension and associated conditions - increased risk for Hp 2-2. *Hum. Hered.*, **37**: 345-348 (1987).
Sutton, H.E: The haptoglobins. *Prog. Med. Genet.*, **7**: 163-216 (1970).
Svartz, N. and Olhagen, B.: Electrophoretic analysis of proteins in articular rheumatism. *Acta Med. Scand. Suppl.*, **206**: 456-464 (1948).
Tesberg, P.: The conversion rate of human C'3 under different storage conditions. *Vox Sang.*, **20**: 230-238 (1971).
Teppo, A.M. and Maury, C.P.J.: Serum prealbumin, transferrin and immunoglobulin in fatty liver, alcoholic cirrhosis and primary biliary tuberculosis. *Ann Clin. Res.*, **17**: 40-42 (1983).
Thymann, M.: Identification of a new serum protein polymorphism as transferrin. *Hum. Genet.*, **43**: 225-229 (1978).
Trape, J.F., Fribourg-Blanc, A., Bosseno, M.F., Lallemant, M. Engler, R. and Mouchet, J. : Malaria cause of ahaptoglobinemia in Africans. *Trans. Roy. Soc. Trop. Med. Hyg.*, **79**: 430-434 (1985).
Tsamantanis, C., Delinassios, J.G., Kottaridis, S. and Chirstodoulou, C.: Haptoglobin types in breast carcinoma. *Hum. Hered.*, **30**: 44-45 (1980).
Turowska, B. : The value of haptoglobin level determination in synovial exudates in the diagnosis of rheumatic disease. *Rheumatologica*, **7**: 57-61 (1969).
Walter, H., Kellermann, G., Bajatzadeh, M., Kruger, J. and Chakravartti, M.R. : Hp, Gc, Cp, Tf, Bg and Pi phenotypes in leprosy patients and healthy controls from West Bengal (India). *Hum. Genet.*, **14**: 314-325 (1972).
Walter, H., Bajatzadeh, M., Kellermann, G. and Matznetter, Th.: Association between leprosy and serum protein groups. *Hum. Genet.*, **10**: 298-303 (1970).

Walter, H., Stach, M., Singh, I.P. and Bhasin, M.K.: Transferrin subtypes in four northwest Indian tribal populations and some remarks on the anthropological value of this new polymorphism. *Amer. J. Phys. Anthrop.*, **61**: 423-428 (1983).

Weitkamp, L.R. and Schacter, B.Z.: Transferrins and HLA: Spontaneous abortion, neural tube defects and natural selection. *N. Engl. J. Med.*, **313**: 925-932 (1985).

Wendt, G.G., Kruger, J. and Kindermann L. : Serumgruppen und Krankheit. *Hum. Genet.*, **6**: 281-299 (1968).

Wolf, P.L.: Ceruloplasmin methods and clinical use. *CRC Crit. Rev. Clin. Lab. Sci.*, **17**: 229-245 (1982).

Wong, C.T. and Saha, N. : Serum immunoglobulin and acute phase protein concentrations in pulmonary tuberculosis patients in Singapore. *Trop. Geogr. Med.*, **41**: 218-221 (1989).

Yang, F., Lum, J.B., McGill, J.R., Moore, C.M., Waylor, S.L., van Bragt, P.H., Baldwin, W.D. and Bowman B.H.: Human transferrin: cDNA characterization and chromosomal localization. *Proc. Natl. Acad. Sci.*, **81**: 2752-2756 (1984).

Yemul, V.L., Jad C.Y. and Kelkar, S.S. : Serum α_1 antitrypsin levels in pulmonary tuberculosis. *Ind. J. Med. Res.*, **77**: 613-615 (1983).

Zlotnik, A. and Rodhan, C.P.: Immuno-electrophoresis of serum in progressive systemic sclerosis (Diffuse Scleroderma). *Proc. Soc. Exp. Bio. Med.*, **107**: 112-115 (1961).

Author's Address: **Swadesh Seth**, *Professor*, Department of Anthropology, University of Delhi, Delhi 110 007, India.