Haptoglobin is one of the acute phase plasma proteins that are responsible for the inflammatory response (Baumann & Gauldie, 1994). Haptoglobin binds free haemoglobin forming haptoglobin-haemoglobin complex (Hp-Hb complex), which is metabolized by the liver (Bowman, 1993); thereby preventing iron loss and preventing kidney damage by free haemoglobin (Hb) during hemolysis (Giblet, 1968). The Hp-Hb complex is soluble and stable (McCormick & Atassi, 1990). The haemoglobin binding capacity of haptoglobin is attributed to the haptoglobin β-chain (Bowman & Kurosky, 1982).

Haptoglobin has been demonstrated to inhibit neutrophils respiratory burst by specifically binding them to glycoproteins (Oh et al., 1990). Recent observations showed that Hp is concentrated within granulocytes and monocytes and is exocytosed after neutrophil activation, suggesting that Hp concentrations may be enhanced locally at sites of inflammation to modulate granulocyte activity (Wagner et al., 1996). Also the β-chain of Hp has been demonstrated to bind to the B cell adhesion glycoprotein (CD22) (Barclay et al., 1993; Hanasaki et al., 1995).

CD22 mediates B cell interactions with erythrocytes, monocytes, T lymphocytes, neutrophils, and endothelial cells by specific binding to glycoproteins with α-2-6-linked sialic acid residues (Powell et al., 1993). Additionally, CD22 has a function in T cell activation via binding to the leukocyte common antigen (CD45RO), this antigen is expressed by the activated or memory T cells (Law et al., 1994). Haptoglobin inhibits the CD22 binding to TNF-α-activated endothelial cells of human umbilical veins by selectively binding CD22 (Hanasaki et al., 1995). The three major haptoglobin phenotypes can bind to the cell surface of human B-lymphocytes with equal affinity (Oh et al., 1990). However, the saturation of CD22 molecules depends on Hp type because of differences in molar Hp concentrations required (Langlois & Delanghe, 1996).
Haptoglobin exhibits an inhibitory effect on the activity of cathepsin B, a lysosomal protease (Snellman & Sylvén, 1967). In inflammatory processes and tissue injury where cathepsin B is liberated, increased Hp concentrations in plasma protect against active proteolysis.

Striking similarities are evident between the primary structure of the haptoglobin β-chain and the serine proteases, a group of proteolytic enzymes that includes trypsin, chymotrypsin, thrombin, plasmin, elastase, and some complement factors (Arcoleo & Greer, 1982). Lectins are sugar-binding proteins that agglutinate cells or precipitate glycoconjugates. Remarkably, the Hp β-chain has 53.6% homology with the plant lectin concanavalin A (Dobryszynka & Przysiecki, 1984).

A homology has been demonstrated in the Hpα domain with both the activation peptides of the serine proteases and a domain found in thrombin, tissue plasminogen activator, and plasmin (Bowman & Yang, 1987). There is also a homology between the primary structure of the Hpα-chain and the light chains of the gamma globulins (Black & Dixon, 1968).

Apparently, Hp1-1 is a ligand for the beta2-integrin dimmers CD11b/CD18 (Mac-1) on granulocytes and monocytes (El-Ghmati et al., 1996). CD11b/CD18 is involved in transducing signals generating inflammatory mediators in monocytes (Palmer & Paulson, 1997). The beta2-integrin dimmers CD11b/CD18 are involved in cell-cell and cell-matrix interactions, including binding to fibrinogen and to the cell surface molecule ICAM-1 (CD54) (Barclay et al., 1993). Moreover, haptoglobin binds specifically to human mast cells via a receptor different from CD22 and CD11b/CD18, and may play a role in the modulation of mast cell functions (El-Ghmati et al., 2002).

Infectious diseases are numerous. Diseases once thought to have been nearly eradicated from the developed world (e.g., TB, cholera, rheumatic fever...etc) have rebounded with renewed ferocity. Newly discovered and emerging infectious agents, worldwide, appear to have been brought into contact with humans by changes in the environment and movements of populations (Fauci et al., 1998). Many infectious diseases are
present in Sudan, such as tuberculosis (Elsony et al., 2000), schistosomiasis (Chitsulo et al., 2000), leishmaniasis (Osman et al., 2000), trypanosomiasis (El Rayah et al., 1999), onchocerciasis (Mukhtar et al., 1998).

Haptoglobin polymorphism is associated with the prevalence and clinical evolution of many inflammatory diseases. It is also related to the prevalence and outcome of various pathological conditions with altered iron metabolism such as hemochromatosis, and infections (Delanghe & Langlois, 2002). These effects are explained by a phenotype-dependent modulation of oxidative stress and prostaglandin synthesis (Lange, 1992; Langlois & Delanghe, 1996).

The Hp2a allele is estimated to have originated from India ~2 million years ago (Schultze & Heremans, 1966) and has since spread over the world under a strong genetic pressure, gradually displacing the monopoly of the Hp1 allele. This suggests a selective advantage provided by the Hp2 allele (Schultze & Heremans, 1966). Recent evidence is growing that Hp is involved in the immune response as well. The strong genetic pressure favoring the Hp2-2 phenotype suggests an important role of haptoglobin in human patholgy (Langlois & Delanghe, 1996).

Research in haptoglobin phenotypes, levels, and their role in immune system, worldwide, is extensive. Hp1-1 was found to be associated with an increased risk for chronic Hepatitis C (Louagie et al., 1996) and with sickle cell disease in USA blacks (Ostrowski et al., 1987). Hp2-1 was found to be associated with ovarian carcinoma in patients with family history of this tumor (Frohlander & Stendahl, 1988), and Hp2-2 was found to be associated with autoimmune diseases (Lange, 1992), bladder cancer (Beckman et al., 1986), antituberculosis immune suppression in TB patients (Platonova & Sakhelashvili, 2001), lung cancer (Benkmann et al., 1987) and retinal detachment (Padma & Murty, 1983).

In Sudan, a study was conducted by Elagib et al. (1998), who assessed the haptoglobin phenotypes of Sudanese patients with complicated and uncomplicated falciparum
They reported an increased incidence of haptoglobin phenotype (1-1) among malaria patients in Sudan.

As the association between haptoglobin and certain infectious diseases is not known in Sudan, and because of the importance of knowing such information in predicting whether a subject is susceptible to get an infection or not, therefore the present study was designed to gain knowledge on the role of haptoglobin phenotypes and their relation to the susceptibility to some of the major infectious diseases in Sudan and to fill the gap in this field of research.

In this study, the distribution of haptoglobin phenotypes among various infectious diseases was assessed. Phenotype (1-1) was found to be the commonest among Sudanese subjects infected with parasitic diseases (i.e. leishmaniasis, trypanosomiasis, and schistosomiasis). An increased frequency in clinical symptoms of falciparum malaria was associated with haptoglobin phenotype (1-1) (Elagib et al., 1998). Singh et al., (1986) studied the association of haptoglobin phenotypes with the susceptibility to *Plasmodium vivax* malaria in India. They concluded that Hp1 variant had greater susceptibility to *P. vivax* malaria infection whereas Hp2-1 had some protection against it. Quaye et al., (2000) studied the association between haptoglobin phenotypes and the susceptibility to severe *P. falciparum* malaria in Ghana. They found that Hp1-1 was significantly more prevalent among the patients than among the healthy controls and that Hp1-1 was also more prevalent among patients with the complications of cerebral malaria and severe anaemia.

This study showed no significant difference in the haptoglobin phenotypes distribution between onchocerciasis patients and the healthy control. This might be attributed to the difficulty in obtaining control samples from endemic areas or to factors associated with the parasite strains survival that is independent of the Hp phenotype.

In the present study, the haptoglobin phenotype (2-1) was found to be the commonest type among the healthy control group. Such findings are consistent with the findings reported earlier by Elagib (1999).
Yang et al., (2001) suggested that an elevated level of haptoglobin promotes haemoglobin scavenging by alveolar macrophages. This is most likely mediated by the recently identified receptor CD163 for Hp-Hb complexes (Kristiansen et al., 2001). After endocytosis, iron can be released from Hb catalysed by haem oxygenase, and is either sequestered in ferritin or mobilized to extracellular space. Both haem oxygenase and ferritin are known to be produced at high levels in alveolar macrophages and are up regulated during inflammation. Interestingly, Yang et al., (2001) found that a key iron export protein (ferroprotein1) is expressed in alveolar macrophages. Ferroprotein1 (also known as MTP-1 or Ireg 1) is responsible for exporting iron taken up by the intestine to the circulation in a transferrin-bound form. Since macrophages are known to have a high turnover of iron, ferroprotein1 could be involved in mobilizing iron out of alveolar macrophages in a stable protein-bound form. Haptoglobin in conjunction with proteins involved in iron mobilization may play important role(s) in lung defence (Yang et al., 2001). Hp1-1 was shown to be associated with lower iron saturation, lower ferritin concentration and lower transferrin saturation (Delanghe & Langlois, 2002). Iron is vital for bacterial growth, Lounis et al., (2001) suggested that an excess of iron may enhance the growth of *M. tuberculosis* and worsen the outcome of human tuberculosis; therefore the haptoglobin phenotype (1-1) will not be suitable for bacterial flourishing among such patients. Interestingly, the present results showed that the common haptoglobin phenotype among TB patients was Hp2-1. Since this phenotype was similar to the healthy controls, therefore the risk of TB infection is higher among people with Hp2-1. This result is comparable to that obtained by Kaminskaia et al., (1997) in Russian subjects and Kasvosve et al., (2000) in Zimbabwean subjects with pulmonary tuberculosis.

Results comparing subjects infected with schistosomiasis, African trypanosomiasis and visceral leishmaniasis and the healthy controls showed significant difference in the distribution of haptoglobin phenotypes. While Hp1-1 was more common among patients, Hp2-1 and Hp2-2 were more common among the healthy control group. The biological functions of haptoglobin are related to its ability to bind haemoglobin and to modulate immune response (Yang et al., 2001) (Appendix I, Table 1). Hp1-1 has no agglutination effect (Köhler & Prokop, 1978) and is a strong prostaglandin synthesis
inhibitor (Langlois & Delanghe, 1996) these functions may explain the association of such parasitic infections to the haptoglobin phenotype (1-1).

In comparing patients with parasitic infections (whether protozoal or schistosomal) and those with mycobacterial infection, haptoglobin phenotypes were found to be significantly different. While Hp1-1 was more common in the parasitic infections, Hp2-1 and Hp2-2 were more common among those infected with tuberculosis.

As expected, there was no significant difference in haptoglobin distribution among males and females. Haptoglobin gene is located on chromosome 16q22 and is inherited as a somatic characteristic (Bowman, 1993).

Since haptoglobin is capable of binding free haemoglobin, it has been detected by polyacrylamide gel electrophoresis of Hb-supplemented serum or plasma/benzidine staining method, which was sensitive and simple.

Conclusions and recommendations:

1. The present study indicates that there may be an association between Hp1-1 and certain infectious diseases (schistosomiasis, visceral leishmaniasis, and trypanosomiasis).

2. There is a highly significant difference ($\chi^2$-test, $P=0.000$) in the distribution of haptoglobin phenotypes between subjects with parasitic infections on one side and those with $M. tuberculosis$ on the other side.

3. Haptoglobin phenotyping can be used as an indicator for some endemic diseases infection.

Further immunological studies to assess the role of haptoglobin in modulating the immune response are needed, and a haptoglobin phenotyping survey is warranted for determining haptoglobin phenotypes distribution among Sudanese ethnic groups.