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Relationship of blood groups to disease: do blood group antigens have a biological role?

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Relationship of blood groups to disease: do blood group antigens have a biological role?

Statistical associations of abh blood groups and disease

Table I shows some of the more important associations of blood groups with disease. Some of these are early statistical associations, some are more recent associations based on scientific findings (see later). Prokop and Uhlenbruck give an excellent review of the early literature of associations of blood groups and disease in their book.[1] Some of these are rather strange: In 1927, Warnkowsky reported that hangover was worse in individuals of group A and that group B's defecate the most. In 1930, Suk reported that group O's have the best teeth. Bohmer found an increased incidence of group B amongst criminals There have been several papers relating ABO blood groups to personality characteristics. In his book, "Character, Blood Groups and Constitution", Schaer found that military personnel who were group O had less satisfactory strength of character and personality, and group B's were more impulsive. Reports of such strange associations continue to the present day; a book entitled "You are Your Blood Type-The Biochemical Key to Unlocking the Secrets of Your Personality" was published in 1988.[2] The book gives examples of how large companies in Japan still use blood types when advertising for, or evaluating, job applicants.

Other unusual associations appear to this day in respectable scientific journals. In 1973, the highly respected scientific journal Nature published a paper by Gibson et al on a relationship between ABO groups and intelligence.[3] Group A2 were found to have the highest IQ; A2 and O were found to have a higher IQ than group A1.[3] In 1984, Nature published a paper entitled "Blood group and socioeconomic class", which purported to show that, in the British population, group A is significantly more common among members of the higher socioeconomic groups.[4] This generated a wealth of correspondence in response; these letters, with responses from the authors, make entertaining reading.[5] From 1997 to 2003, four books were published relating ABO blood groups to the ideal diet.[7-9] There is very little, if any, scientific data to support this premise.

Having said that, there are some undeniable associations of blood groups with disease. Blood group antibodies can cause hemolytic transfusion reactions, hemolytic disease of the newborn and autoimmune hemolytic anemia, graft re-

Table I
Associations of blood groups with disease

Disease	Blood group association
Cancer	A, "A-like" Le^x, Le^y, Sialyl-Le^x, T, Tn P Fy
Peptic Ulcer	O ABH secretion Le^b
Coagulation bleeding clotting	 O A
Infection	A, B, O, P, Dr, Fy, AnWj
Renal Disease	Raph (MER2)

Palabras clave
✓ grupos sanguíneos
✓ antígenos sanguíneos

Key words
✓ blood groups
✓ blood antigens

jection, and spontaneous abortion. What is more open to debate is whether the many statistical associations mean anything, and whether blood group antigens have a biological role. This author is now convinced that, whether the statistical associations are valid or not, there is increasing evidence that some blood groups may play a biological role (see later).[10,11]

It is important to realize that blood group antigens are rather simple chemical moieties on the red blood cell (RBC) surface whose structure is gradually being elucidated. Some of these antigens (e.g., A, B, H, I, i, P, Lewis) are widely distributed throughout the body (e.g., on other cells and sometimes in body fluids). Their function may not be related directly to the RBC; we may have coincidentally labelled these chemical moieties as blood groups (i.e., RBC) antigens because they caused problems in blood transfusion (e.g., incompatible crossmatches). It should also be remembered that "naturally occurring" anti-A and anti-B are bacterial antibodies that coincidentally cross-react with RBCs (see later). The early statistical associations with disease, that are of the most interest, are those with malignancy, peptic ulcers, coagulation, infection. Many of these early statistical associations now have some associated scientific findings suggesting a rationale for the statistical associations. Some authors have suggested that the ABO blood group antigens should be termed ABH histo-blood group antigens to emphasize that they are primarily tissue antigens.[12,13] ABH antigens appear earlier in evolution in ectodermal or endodermal tissue than in mesenchymal hematopoietic tissue and cells, including RBCs.[12] Clausen and Hakomori[13] state that ABH antigens are the major allogeneic antigens on most epithelial cell types and are also found in primary sensory neurons.

Blood group antigens and malignancy

The literature is replete with publications of an association of a certain ABO blood type with a certain malignancy. Many of the reports before 1950 are not too reliable because of the lack of appreciation of the large numbers needed for studies (usually studies on less than 300 patients is uninformative), and the inadequate controls used (e.g., blood donors usually are not representative of the general population).[14] In addition, at the time many of the studies were performed it was not known that such wide variation of ABO could occur over short geographical distances, even within a population that was thought to be ethnically homogeneous.[14] The report that most investigators seem to accept as the first reliable report is that of Aird and Bentall[15] who, in 1953, showed that 20 % more group A had cancer of the stomach than group O. This was a large study and the findings have been confirmed in more than more than 100 separate studies in different parts of the world. It seems hard to dispute that cancer of the stomach occurs more frequently in group A compared to group O. If one reviews all the published work of associations of ABO groups and malignancy, one is impressed that overall group A predominates over group O, especially if one reviews data from the largest studies, or when smaller studies, on a particular malignancy, have given similar results when reported by many different investigators.

In the last 25 years, there has been a tremendous amount of work published on the chemistry of blood group antigens and tumor immunology.[10,11] Some of this may be pertinent to the suggested increase of group A over O in many malignancies. As cells (e.g., in tissue) become malignant, they tend to lose normal antigens and acquire new antigens; these are the so-called tumor antigens. It has been proven that ABO antigens diminish on malignant cells as the malignancy progresses; the loss of A, B, and H antigens is proportional to the metastatic potential of the tumor.[10,11] Some tumor antigens have been shown to have A or "A-like" properties [i.e., some of these antigens appear to be true A antigens, others have properties very close to the A antigen ("A-like")]; others (e.g., Tn) can cross-react with anti-A). Such A or "A-like" antigens can be detected on tumors of patients who are not group A (so-called "illegitimate" antigens). Hakomori has suggested that if the immune surveillance theory is correct and we recognize tumor antigens as foreign, leading to attack of the tumor, then the "A-like" properties of tumor antigens may not be recognized by group A patients as foreign as readily as group O patients.[16]

Springer's group have produced some fascinating work associating the presence of the blood group antigens, T and Tn, in the tissues, with malignancy.[17-19] They found several interesting facts: 1) T and Tn were not present on normal breast tissue but were present on malignant cells from breast cancer; this was later extended to other malignancies; 2) anti-T and anti-Tn were present in smaller amounts in patients with cancer; 3) delayed hypersensitivity tests where T and Tn antigens were used in skin tests showed no reactions in normal subjects; small numbers of positives in patients with benign tumors, high numbers of positive reactions in patients with cancer. This suggested that the T and Tn blood group antigens were involved in a cellular immune response in cancer. Many other investigators have confirmed Springer's findings. T and Tn blood group antigens (natural and synthetic) have been used in diagnosing cancer and in immunotherapy trials.[19]

The Lewis genes are closely associated with the genetical and biochemical pathways involving the expression of ABH in addition to Lewis antigens on RBCs and in body fluids. There have been hundreds of papers published suggesting that certain Lewis antigens (e.g., Lex) appear on malignant cells and are very useful tumor markers. These antigens may be very important for the malignant cell to move through the tissue (i.e., metastasize); this is discussed in a later section on adhesion molecules.

Blood group antigens, peptic ulcers and coagulation

In 1954, Aird and Bentall reported that group O individuals were 20 % more likely than group A's to have peptic (gastric and duodenal) ulcers.[21] The increase was mainly associated with duodenal ulcers. Duodenal ulcer was found to be 35 % more likely to develop in group O compared to group A, B and AB, and 50 % more likely to develop in nonsecretors of ABH blood group substances (i.e., 20 % of the population). Taking the ABO group and secretor status into account yielded the relative liability of O secretors as 1:35, A and B nonsecretors as 1:6, and O nonsecretors as 2:5. The finding that the latter group are 2½ times more likely to have a duodenal ulcer compared with A, B or AB secretors is a most impressive statistic. These are some of the most acceptable associations of blood groups with disease; they have reproduced in hundreds of other studies in many different countries. There has been much discussion about why these associations occur, but the data by Borén et al[22] is the most exciting. In 1993, Borén et al[22] reported that the Lewis blood group antigen, Leb (which has close associations with the ABO system), was the receptor for Helicobacter pylori. H. pylori is associated with gastritis, adenocarcinoma, and is thought to be a major cause of gastric ulcers. Some of the data (i.e., in group A, less Leb sites are available for bacterial attachment) provided a strong scientific rationale for the report of Aird et al in 1954,[21] and many others since, that gastric ulcers are much more common in group O than in group A.

There are many reports showing that thrombosis, serum cholesterol levels and myocardial infarction are more common in group A than group O.[10-11]

Thus, there is a tendency for group A to bleed and group O to thrombose. Mourant[23] make the interesting point that group A individuals have a higher average level of the coagulation factor, antihemophilic globulin (factor VIII), present in their plasma than do group O individuals.[24,25] He suggested that the differ-ence in factor VIII in the plasma, even within the physiological range, may determine whether clinically detectable bleeding may occur from a deep ulcer or, on the other hand, in an atheromatous blood vessel, whether clotting time will ensure. Kingsbury[25] conjectured that the higher frequency of group O in the atherosclerotic patients with increased mural atheroma (as opposed to the lower ratio of group O in the occlusion group) could be due to a tendency of the group O patients to hemorrhage (rather than thrombose) into the arterial walls, thus sustaining more tissue damage. Several other workers had confirmed the association of group A with a higher factor VIII level,[24,25] and there have also been associations with other coagulation factors.[10,11,26] There are interesting associations with von Willebrand factor; 75 % of type 1 von Willebrand disease are group O.[26]

Blood group antigens and infectious diseases

Anti-A and anti-B are not RBC antibodies but bacterial antibodies cross-reacting with RBCs. Individuals lacking A or B antigens make either anti-A or anti-B at about 3-6 months of age when they make their own bacterial antibodies. Springer showed that many gram negative organisms (e.g., E. coli) have chemical moieties on their membranes resembling A and B blood group antigens,[27] and this is the stimulus for anti-A and anti-B production by human infants. Anti-B has been shown to kill E. coli in vitro, so the obvious question is do anti-A and anti-B play a role in destroying bacteria in vivo? There are many reports associating different infections with a particular ABO group.[10,28,29] Table II shows some of these correlations.

Mourant et al[30,31] discuss suggestions that the major differences seen in ABO blood groups in different parts of the world may be due to epidemics that have occurred in the past. It was suggested that some major differences were due to the presence of an "A-like" antigen on the smallpox virus, and an "H-like" antigen on the plague bacillus (and cholera). This would make individuals who have anti-A (group B and O) more resistant to smallpox, and individuals who can make anti-H (A1 and B) more resistant to the plague and cholera. The work showing the presence of an "A-like" antigen on the smallpox virus was criticized. There is interesting correspondence on this controversy in Nature;[32,33] other authors have also expressed their opinions on the controversy.[1,34]

Blood group antigens as receptors for parasites, bacteria, and viruses

During the last twenty years, there have been increasing reports suggesting that blood group antigens may act as receptors for parasites, bacteria and viruses. In 1975, Miller et al[35] showed that malarial parasites [P. knowlesi, and later[36] P. vivax] would not enter RBCs that lacked both of the Duffy blood group antigens Fya and Fyb [i.e., Fy(a–b–) phenotype]. It has been known since the 1930's that many black people are resistant to infection by P. vivax. It is also known

Table II
Association of blood groups with Infectious disease

	Increased incidence of blood group
Bacterial	antigen/antibody or secretor status
Plague	O
Cholera	O
Leprosy	A,B (lepromatous form) O (tuberculoid form)
Yaws	M
Tuberculosis	O, B
Gonorrhoea	B
Streptococcus pneumoniae infection	B
Neisseria meningitidis infection	non-secretor
Haemophilus influenzae infection	non-secretor
Escherichia coli infection	B, AB
Salmonella infection	B, AB
Viral	
Epstein Barr Virus (EBV) infection	anti-i
Smallpox	A, AB
Mumps	O
Fungal	
Candida albicans	non-secretor

that 65-70 % of the African-Americans population and over 95 % of the black population of Africa are Fy(a–b–). The more severe form of malaria caused by P. falciparum is not influenced by the Duffy phenotype. P. falciparum parasites will not adhere to RBCs lacking other blood group antigens; glycophorin A and sialic acid seem to be important in these interactions.

To colonize and infect the urinary tract efficiently, E. coli have to attach firmly to the uroepithelium. They do this through nonflagellar surface structures on their surface called pili or fimbriae. These pili have been shown to bind specifically to glycoproteins and glycolipids on the endothelial cells lining the urinary tract. The E. coli causing childhood pyelonephritis were shown to attach to glycolipids identical to the P blood group antigen.[37-39] Other *E. coli* were found to attach to receptors identical to the Dr blood group antigen.[39] Haemophilus influenzae has been shown to attach to RBCs through a specific interaction with the AnWj high frequency blood group antigen.[40,41] As mentioned previously, Borén et al[22] showed that the receptor to Helicobacter pylori is the Leb blood group antigen. Brown et al[42,43] showed that the receptor for Parvovirus B,[19] a virus that replicates only in erythroid progenitor cells, was the P blood group antigen. In a further publication, the authors showed that individuals with the rare p phenotype were resistant to Parvovirus B19 infection.[43]

Associations of blood group antigens with immunologically important proteins

There have been an increasing number of reports of an association of blood group antigens with immunologically important proteins (Table III). Some of these recent observations support the concepts that blood group antigens may indeed have a biological role.

There have been several relationships of blood group antigens to adhesion molecules described.[10,11,44-48] To get to a site of injury, leukocytes must get from the circulation into the tissue. To do this they must first adhere to the endothelium. An important family of adhesion molecules, the selectins, are responsible for the initial tethering of the leukocytes to the endothelium. Selectins are ideally suited for this role because they have a long molecular structure that extends above the surrounding glycocalyx and allows them to capture passing leukocytes that express the appropriate receptor. The tethering is a loose bond as the leukocytes must next roll along the endothelium. This rolling is essential for the leukocyte to search the endothelium for appropriate trigger factors (e.g., the IL-8 cytokine) that activate leukocyte integrins. The integrins mediate strong adhesion of the leukocyte to the endothelium. After this stage, the leukocytes change shape and migrate through the endothelium. A form of the Lewis blood group antigen (Lex), sialyl-Lex, has been found to be the ligand for the E, P and L selectins. Sialyl-Lex is needed for the very first interaction of white cells with endothelial cells which leads to the subsequent movement from the blood stream to the site where they are needed. Recent data suggests that malignant cells move through the body in a similar way and may well relate to the association of Lex with the metastatic potential of tumors mentioned earlier.[20]

The LW antigen (the original Rh antigen described by Landsteiner and Weiner) is known to immunologists as intracellular adhesion molecule (ICAM-4), a member of another family

Table III
Association of blood group antigens with immunologically important proteins

Protein	Blood Group
HLA (B7, B17, A28)	Bg^a, Bg^b, Bg^c
C4 (C4d)	Ch, Rg
Complement (C3b/C4b) receptor (CR1)	Kn/McC/Yk
Decay accelerating factor (DAF)	Cromer
CD44 (adhesion molecule)	Indian (In^b)
Selectins (adhesion molecules)	Lewis (sialyl-Le^x)
Integrins (adhesion molecules)	Landsteiner-Wiener (LW)
CD108 (?adhesion molecule)	JMH
CD99 (?adhesion molecule)	Xg
Laminin	Lutheran (Lu)
Cytokines	Duffy (Fy6)
CD147	Ok^a

of adhesion molecules, the integrins.[44,45,48] It appears that LW is only present on RBCs; LW may play a role in erythropoiesis. Another adhesion molecule, CD44 (homing-associated cell adhesion molecule), is a widely distributed cell surface proteoglycan that has been implicated in a wide range of biologic functions. The molecule has been found to mediate recirculation of lymphocytes between blood and lymphoid organs, from which it derived its original name of lymphocyte homing receptor. CD44 has also been implicated in lymphocyte (T-cell) activation, hematopoietic development, and tumor metastasis. There has been an increasing stream of publications implicating CD44 in tumor progression; studies of non-Hodgkins lymphoma are particularly impressive. CD44 has been found to be identical to the blood group antigen Inb, and is suppressed on 21-61 % of RBCs from some individuals with the Lutheran null [Lu(a–b–)] genotype.[44,45,48] The Lutheran (Lu) glycoprotein is known as BCAM to immunologists, and is a ligand for laminin; there are a number of interesting papers relating this to sickle cell disease.[44-48]

Table IV
Abnormalities associated with depressed or lack of common blood group antigens

Phenotype	Abnormality
Rhmod/Rhnull	Stomatocytosis of RBCs; hemolytic anemia
McLeod	Acanthocytosis of RBCs; muscle abnormalities
Lunull (InLu type)	Acanthocytosis of RBCs; suppressed CD44
Genull (Leach type)	Elliptocytosis
Crnull (Inab type)	Protein-losing enteropathy; RBCs have increased sensitivity to complement-mediated lysis
i (Asians)	Cataracts

Chemokines are members of a superfamily of small secreted proteins, numbering over 20, that recruit leukocytes to sites of inflammation. This superfamily has 2 major branches, the C-X-C family and the C-C family. RBCs contain a receptor that binds selected members of both families (e.g., IL-8). The chemokine receptor on RBCs was shown to be the Duffy blood group glycoprotein.49 Anti-Fy6 was found to block binding of chemokines to the RBC. The Duffy antigen receptor for chemokines (DARC) was shown to be present also on endothelial cells (e.g., littoral cells in the spleen and endothelials cells lining bone marrow sinusoids and postcapillary venules, but not those lining capillaries, venules, veins, arterioles, or arteries). It is unclear what the function of DARC is on RBCs, but it has been suggested that RBCs may act as a "sink" for chemokines.[49] In 2002 Lentsch suggested that DARC may be associated with angiogenesis and cancer of the prostate in African Americans.[50] African American males have a 60 % increased incidence of cancer of the prostate. Angiogenic CXC chemokines are implicated in prostate cancer and bind to DARC (angiostatic cytokines do not bind). It was suggested that DARC+ RBCs clear angiogenic cytokines from the system, and as almost 70 % of African Americans lack Fya and Fyb, they may be more susceptible to cancer of the prostate.[50]

Associations of disease with increased, decreased, missing, or acquired blood group antigens

The i antigen is usually present in large amounts on fetal RBCs but is present in very small amounts on adult RBCs. The i antigen is increased on the RBCs of patients with many hematological conditions (e.g., thalassemia). The most marked increase of RBC i antigen is seen in dyserythropoietic anemia type II [hereditary erythroblast multinuclearity with a positive acid serum test (HEMPAS)], a rare congenital anemia. The amount of i antigen on HEMPAS RBCs is at least as high as encountered on fetal RBCs but, in contrast, I antigen is also present in normal or increased quantities.

It is quite common to see A and B antigens decrease, until they are not detectable with routine methods, in patients with acute leukemia. As the patient responds to treatment, the antigens increase to their former status. It is thought that this is associated with a general defect of enzyme systems in leukemia, thus the glycosyl transferases, responsible for putting on the A and B determinant sugars, become defective during the disease. Rare individuals are en-

countered who have depressed Kell system antigens, the McLeod phenotype. Such individuals have abnormal (acanthocytic) shaped RBCs and have a compensated hemolytic anemia.

Some rare individuals are encountered who lack all the blood group antigens, from a particular system, on their RBCs. Many of these patients have been found to have associated RBC abnormalities (Table IV).[46] Rhnull individuals, who lack all Rh antigens, have stomatocytic (cup-shaped) RBCs, instead of biconcave discs, and a compensated hemolytic anemia. Individuals lacking antigens of the Gerbich system, of the Leach type, have elliptocytic RBCs. The rare individuals who lack all Cromer system antigens may have severe protein-losing enteropathy, and their RBCs have an increased sensitivity to complement-mediated lysis. The findings that RBCs have abnormal shapes when all antigens of a particular system are missing (i.e., rare null phenotypes) suggest that these antigens have a function in maintaining membrane integrity. Recent work has shown that some blood group antigens are intimately associated with important functions of the red cell (see Table V).[44-46]

Sometimes, blood group antigens, that are not supposed to be there (i.e., not genetically determined), are detected on RBCs. The mechanism is understood in most cases (e.g., changes to the RBC membrane induced by bacterial enzymes). Table VI shows antigens that can be acquired by RBCs in vivo, and the associations with various diseases.

Conclusions

We have come a long way since the early reports of statistical associations of ABO blood groups and various diseases, and the ensuing vitriolic debates. In the last 20 years there has been increasing evidence that blood groups have a function and play a biological role. This biological role often does not relate to the red cell, but to the presence of chemical moities on other cells that were initially identified as red cell antigens. Antigens, first identified on RBCs, are now known to be important as receptors and ligands for bacteria, parasites and immunologically important proteins (e.g., those associated with movement of normal and malignant cells throughout the body).[10,11] Some blood group antigens also appear to be important in the function of the red cell itself.[4-7]

Although most RBC antigens and antibodies were discovered in the process of trying to successfully transfuse blood from one human to another, common sense should dictate that blood group antigens and antibodies are not there only to give us problems in this artificial exercise.

Table V
Blood group antigens associated with functional properties of the RBC membrane

Blood group antigens	*Functional property*
	Membrane Transport Proteins
Colton	Aquaporin 1 (Water channel)
GIL	Aquaporin 3 (Water channel)
Diego/Wright	Anion exchange
Kidd	Urea transport
Rh	Amonia transport
	Enzymes
Cartwright	Acetylcholinesterase
Kell	Zinc-binding neutral endopeptidases
Dombrock	ADP-ribosyltransferase

Table VI
Acquired blood group antigens

Antigen	Acquired by Group	Associated with
B	A_1	Colon cancer
T	All ABO groups	Neuraminidase-producing acteria
Tn	All ABO groups	Thrombocytopenia Hemolytic anemia preleukemia
Tk, Tx, Th, VA	All ABO groups	? infection (sometimes)

References

1. Prokop O, Uhlenbruck G . Human blood and serum groups. New York: Wiley Interscience; 1969. p. 390-722.
2. Nomi T, Besher A. You are your blood type. New York: Pocket Books; 1988.
3. Gibson JR, Harrison GA, Clarke VA, Hiorns RW. IQ and ABO blood groups. Nature1973;246:498-500.
4. Beardmore JA, Karimi-Booshehri F. ABO genes are differentially distributed in socio-economic groups in England. Nature 1983;303:522-524.
5. Correspondence. Blood groups and socio-economic class. Nature 1984;309:395-399.
6. D'Adamo PJ. Eat right 4 your type. New York: GP Putnam's Sons; 1997.
7. D'Adamo PJ, Whitney C. Live right 4 your type. New York: Putnam; 2001.
8. D'Adamo PJ. Whitney C. Eat right 4 your type. Complete blood type encyclopedia. New York: Berkley Publishing Group; 2002.
9. D'Adamo PJ, Whitney C. Eat right 4 your baby. New York: Putnam; 2003.
10. Garratty G. Do Blood Groups have a biological role? En: Garratty G, ed. Immunobiology of transfusion Medicine. New York: Dekker 1994:201-55.
11. Garratty G. Blood groups and disease: a historical perspective. Transfus Med Rev 2000;14:291-301.
12. Oriol R, LePendu J, Mollicone R. Genetics of ABO, H, Lewis, X and related antigens. Vox Sang 1986;51: 161-71.
13. Clausen H, Hakomori S. ABH and related histo-blood group antigens; immunochemical differences in carrier isotypes and their distribution. Vox Sang 1989;56:1-20.
14. McConnell RB. Blood groups and disease. En: Seligson D, ed. CRC Handbook Series in clinical Laboratory Science, Section D: Blood Banking. Volume 1, 19:519-531.
15. Aird I, Bentall HH, Roberts JAF. A Relationship between cancer of the stomach and the ABO blood groups. Brit M J 1953;I:799.
16. Hakomori S. Fucolipids and blood group lipids in normal and tumor tissue. Prog Biochem Pharmacol 1975;10:167-96.
17. Springer GF. T and Tn, general carcinoma auto-antigens. Science 1984;224:1198-1206.
18. Springer GF, Desai PR, Tegtmeyer H, Carlstedt SC, Scanlon EF. T/Tn antigen vaccine is effective and safe in preventing recurrence of advanced human breast carcinoma.Cancer Biotherapy 1994;9:7-15.
19. Desai PR. Immunoreactive T and Tn antigens in malignancy: role in carcinoma diagnosis, prognosis, and immunotherapy. Tranfus Med Rev 2000;14:312-25.
20. Kannagi R, Izawa M, Koike T, Miyazaki K, Kimura N. Carbohydrate-mediated cell adhesion in cancer metastasis and angiogenesis. Cancer Sci 2004;95:377-84.
21. Aird I, Bentall HH, Mehigan JA, Roberts JAF. The blood groups in relation to peptic ulceration and carcinoma of colon, rectum, breast, and bronchus. Brit M J 1954;315.
22. Borén T, Falk P, Roth KA, Larson G, Normark S. Attachment of helicobacter pylori to human gastric epithelium mediated by blood group antigens. Science 1993;62:1892-1825.
23. Mourant AE, Kopec AC, Domainiewska-Sobczak K. Blood-groups and blood-clotting. Lancet 1973;1: 223-228.
24. Preston AE, Barr A. The plasma concentration of factor VIII in the normal population. II. The effects of age, sex and blood group. Br J Haematol 1964; 10:238-45.
25. Kingsbury KJ. Relation of ABO blood groups to atherosclerosis. Lancet 1971;1:199-203.
26. O'Donnell J, Laffan MA. The relationship between ABO histo-blood group, factor VIII and von Willebrand factor. Transfus Med 2001;11:343-351.
27. Springer GF, Williamson P, Brandes WC. Blood group activity of gram-negative bacteria. J Exp Med 1961;113:1077-1093.
28. Berger SA, Young NA, Edberg SC. Relationship between infectious diseases and human blood type. Eur J Clin Microbiol Infect Dis 1989;8:681-689.
29. Moulds JM, Moulds JJ. Blood group associations with parasites, bacteria, and viruses. Transfus Med Rev 2000;14:302-311.
30. Mourant AE, Kopéc AC, Domaniewska-Sobczak K. The Distribution of the Human Blood Groups and Other Biochemical Polymorphisms. 2nd edition, Oxford: Oxford University Press, 1976.
31. Mourant AE, Kopéc AC, Domaniewska-Sobczak K. Blood Groups and Diseases. London: Oxford University Press, 1978.
32. Springer GF, Wiener AS. Alleged causes of the present-day world distribution of the human ABO blood groups. Nature 1962;193:44 (letter).
33. Pettenkofer HJ, Stöss B, Helmbold W, Vogel F. Alleged causes of the present-day world distribution of the human ABO blood groups. Nature 1962; 1993;445-446.
34. Muschel LH. Blood groups, disease, and selection. Bacteriological Reviews 1966;30:427-441.
35. Miller LH, Mason SJ, Dvorak JA, McGinniss MH, Rothman IK et al. Erythrocyte receptors for Plasmodium knowlesi malaria: Duffy blood group determinants. Science 1975;189:561-3.
36. Miller LH, Mason SJ, Clyde DF, McGinniss HH. The resistance factor to Plasmodium vivax in Blacks. N Eng J Med 1976;295:302-4.
37. Väisänen V, Elo J, Tallgren LG, Siitonen A, Makela PH, Svanborg-Eden C et al. Mannose-resistant haemagglutination and P antigen recognition are characteristic of Esherichia coli causing primary Pyelonephritis. Lancet 1981;2:1366-9.
38. Källenius G, Möllby R, Svenson SB, Helin I, Hulthberg H, Cedergren B, Winberg J. Occurrence

of P-Fimbriated Escherichia coli in urinary tract fnfections. Lancet 1981;2:1369-72.
39. Moulds JM, Nowicki S, Moulds JJ, Nowicki BJ. Human blood groups: incidental receptors for viruses and bacteria. Transfusion1996;36:362-74.
40. van Alphen L, Poole J, Overbeek J. The Anton blood group antigen is the erythrocyte receptor for Haemophilus influenza. FEMS Microbiol Lett 1986; 37:69.
41. Poole J, van Alphen L. Haemophilus influenaze receptor and the AnWj antigen. Transfusion 1988; 28:289.
42. Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 Parvovirus. Science 1993;262:114-17.
43. Brown KE, Hibbs JR, Gallinella G, Anderson SM, Lehman ED, McCarthy P, Young WS. Resistance to parvovirus B19 infection due to lack of virus receptor (erythrocyte P antigen). N Eng J Med 1994;330:1192-6.
44. Cartron JP, Bailly P, Le Van Kim C, Cherif-Zahar B, Matassi G, Bertrand O, Colin Y. Insights into the structure and function of membrane polypeptides carrying blood group antigens. Vox Sang 1998; 74(S2):29-64.
45. Cartron JP. Molecular basis of red cell protein antigen deficiencies. Vox Sang 2000;78(Suppl 2):007-023
46. Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol 2004;41:93-117.
47. Telen MJ. Red blood cell surface adhesion molecules: their possible roles in normal human physiology and disease. Semin Hematol 2000;37:130-142.
48. Spring FA, Parsons SF. Erythroid cell adhesion molecules. Transfus Med Rev 2000;14:351-363.
49. Hadley TJ, Peiper SC. From malaria to chemokine receptor: the emerging physiologic role fo the Duffy blood group antigen. Blood 1997;89:3077-3091.
50. Lentsh AB. The Duffy antigen/receptor for chemokines (DARC) and prostate cancer. A role as clear as black and white? FASEB J 2002;16:1093-1095. rm