the abo blood groups and disease

martin anthony - williams
final year medical student

The discovery of definite associations between the ABO blood groups and disease, apart from certain antigenic phenomena, has only been made in the last two decades. In a few conditions an association has been very well established. *Aird, Bentall and Roberts* (1953) were the first to produce strong evidence to show the disadvantage of group A in cancer of the stomach, and *Aird et al* (1954) that of group O for peptic ulcer.

The advantages and disadvantages of belonging to one or other ABO blood group are being slowly established but the cause of the association between blood groups and certain diseases is still unknown, although, in the case of peptic ulcer it has been suggested that group-specific substances (A, B or H) in the gastrointestinal secretions may exert a protective influence.

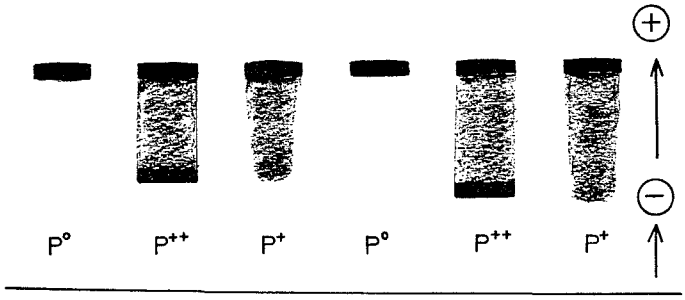
Secretor Character

Some individuals not only have the ABO blood group antigens on their red cells but also in their body fluids, and when this is the case they are termed "secretors". Secretion and non-secretion are inherited characters, the former being dominant to the latter. In Britain about 78% of the population are secretors and 22% are non-secretors. Saliva, gastrointestinal juice and semen have particularly high concentrations of the antigens.

Group O secretors secrete H substance only. Secretors of other blood groups secrete not only their group-specific substance i.e. A, B, or AB, but H substance as well. Non-secretors of ABH do not however have "nothing" on their red cells but usually possess the equivalent amount of the Lewis blood group antigens, i.e. the non-secretors of ABH are generally secretors of Lewis (Le^a).

Alkaline Phosphatase, diet and the ABO blood groups

Using starchgel electrophoresis two different patterns of alkaline phosphatese (both under genetic control) have been discovered, although the method of inheritance is not clear *(Arfors et al., 1963)*. All human sera show one alkaline phosphatase band, but sera from some individuals show also a second slowly moving band. This double band is found much more commonly in those subjects who are group A or AB. Furthermore double band persons are nearly always secretors of their particular ABO blood group substances.



Some electrophoretic patterns of serum alkaline phospatase. (adapted from **Bamford** *(1965), Lancet* **I**, *530.)*

Bamford et al (1965), using a more delicate technique showed on electrophoresis of the serum of 468 British blood donors that about 33% had a weak second band which had not been previously detected (FIG. 1). The population could therefore be divided into three groups — those with no second band (P°, about 50%), those with a weak second (P+, about 33%), and those with a strong second band (P++, about 17%). This second band is found much more commonly in individuals of blood group O or B than those of A or AB, and people of these blood groups had on the average much higher serum level of alkaline phosphase than those who were group A. Furthermore, double band individuals whether P+ or P++were nearly always secretors of ABH substances.

Following earlier observations that serum alkaline phosphatase levels may vary with time in the same individual, the effect of a fatty diet was studied by *Langmen et al* (1966). In 24 secretors of blood groups O or B, one individual was graded as P++ in the fasting sample, five were P++ four and a half hours after a fatty breakfast, and 18 P++ seven and a half hours after, having also eaten lunch. In five secretors of blood groups AB the changes were similar but less marked. In 14 secretors of blood group A there was very little change — as was also seen in the non-secretors.

These findings suggest that there may be differences in the physiological behaviour of the epithelial cells of the small bowel in people with differing ABO blood groups and that the blood group antigen has something to do with the formation of an enzyme. If this is true of alkaline phosphatase it might be equally well be so of other enzymes of the gastrointestinal tract and its appendages.

The enzymes responsible for the first band P° originates principally in the liver and it is probable that the second band (P+ and P++) is quantitatively different and derives from the jejunal mucosa (*Clark*, 1969).

It seems likely that this may provide a clue to the cause of the association between blood groups, secretor status, and certain gastro-intestinal diseases, such as duo-

denal ulcer with group O, cancer of the stomach and pernicious anaemia with group A.

ABO blood groups and disorders of the gastrointestinal cancer of the stomach

In a search to pin-point the mechanism by which certain genes can influence the susceptability of an organ for cancer, *Aird et al* (1953) investigated the relationship between ABO blood group and cancer of the stomach. This disease is more prevalent in northern parts of England than in the South, as is blood group O. The expected association between cancer of the stomach and blood group O was not found. It was found however, that both in the North and South blood group A was more common among patients with cancer of the stomach than among the general population or than hospital controls (see Table 1). Individuals who are group A are 20% more liable to the disease than those of other blood groups. The association with pernicious anaemia, which is also high in group A, is of interest.

TABLE 1

Total of	Cancer cases %				Controls %			
	O	A	B	AB	O	A	B	AB
North of England; (1406 cases)	42.9	46.4	7.6	3.1	50.7	39.3	6.8	3.2
London (478 cases)	43.1	46.0	7.9	7.9	45.8	42.2	8.9	3.1

Percentage distribution of blood groups in cases of carcinoma of the stomach compared with that in equal number of controls. (Aird et al, B.M.J., 1953)

Working on an immunological basis *Barber and Dunsford* (1959) demonstrated a very high concentration of A substance in the serum of a patient dying of carcinoma of the stomach. However more recently a "normal" non-secretor frequency has been found in carcinoma of the stomach (*McConnell* 1966).

Several other associations with blood group A have been suggested particularly for diabetes mellitus, pernicious anaemia already mentioned above, cholelithiasis and portal cirrhosis. A moderately significant excess of blood group A has been observed in carcinoma of the pancreas. (*Aird et al*, 1960). *Cameron* (1958) has also found a high incidence of blood group A in patients with salivary gland tumour. A slight increase of blood group A in 610 patients has been noticed in patients with cancer of the oesophagus.

Peptic Ulcer

The relationship between blood group O and duodenal ulcer is well documented. It is complicated however, and not yet fully understood.

It is known that there are more peptic ulcers in relatives of patients with gastric and duodenal ulcer than would be expected in a study of the general population. If a gene or genes were responsible, no known mechanism of selection or inheritance could have caused such a rapid increase in frequency.

TABLE 2
PERCENTAGE GROUP FREQUENCY

Group	Peptic Ulcer (3011 Cases)		
	Control	Disease	Increase or Decrease on Control
	%	%	%
O	47.00	55.40	+17.9
A	40.99	34.67	−15.4
B	8.98	7.44	−17.1
AB	3.03	2.49	−17.9

adapted from Aird et al.

In duodenal ulcer two genetic components are of importance; those at the ABO blood group, and the secretor status of the patients. Thus blood group O individuals are about 40% more liable to duodenal ulcer than are those of group A, B, or AB (Table 2), and non-secretors are about 50% more prone than are secretors.

TABLE 3

% of non-secretors in 1014 cases of Duodenal ulcer and 851 controls

	Group O	Group A, B, & AB
	%	%
Male ulcer	37.20	35.10
control	21.10	24.90
Female ulcer	40.00	36.20
control	24.20	26.20

adapted from Clarke et al.

If the characters are considered together, it is evident that individuals who are both group O and non-secretors are about two and a half times more prone than the least susceptable groups, i.e. groups A, B, or AB. (Table 3). Stomal ulcer has the highest association of all with group O, and also shows an excess of non-secretors (*Doll et al*, 1960) Table 4.

TABLE 4

Distribution of ABO Blood group among stomal ulcer, duodenal ulcer, and control subjects.

Disease Category	Blood groups of subjects				Total number of subjects
	O	A	B	AB	
Stomach ulcer	298	214	39	13	564
Duodenal ulcer	181	96	18	5	300
Control subjects	4,578	4,219	890	313	10,000

Adapted from Doll et al.

The way in which the blood group genes influence susceptability to duodenal ulcer was not previously known but recently *Hanley* (1964) has produced evidence to show that blood group O patients have a higher serum pepsinogen level and a greater gastric acid secretion than average, besides a larger secretory cell mass. It has also been suggested that Lea substance or its degeneration products may be absorbed from the stomach and stimulate hyperplasia of the parietal cell mass.

Various large series indicate that blood group O is associated with severe or complicated duodenal ulcers,

TABLE 5

BLOOD GROUP ASSOCIATIONS WITH DISORDERS OF THE G.I. TRACT

Condition	*Blood Group*	Remarks
Cancer of the stomach	A	*Firm association.*
Duodenal ulcer	O	*Firm association but more marked in non-secretors.*
Gastric ulcer	O	*Firm association but less marked than in duodenal ulcer.*
Stomach ulcer	O	*Firm association. The highest association of all with blood group O.*
Pernicious Anaemia	A	*Marked increase of group A, but number very small.*
Diabetes Mellitus	A	*Evidence equivocal.*
Salivary gland tumour	A	*Evidence fairly strong.*
Cholelithiasis	A	*Fairly firm association.*
Carcinoma of pancreas	A	*Moderately significant excess of group A.*
Portal Cirrhosis	A	*Marked increase of A, but numbers very small.*
Chromophobe adenoma of the pituitary (derivative of the foregut)	O	*Not proven.*
	A	*Not proven.*

Adapted from Genetics for the Clinician — C.A. Clark.

that is to say duodenal ulcers that bleed, giving rise to haematemesis and/or melaena, or perforate. Some workers doubt this relationship but they appear to be in the minority.

Other associations with blood group O have been noticed. *Mayr et al* (1965) found a large excess of blood group O in chromophobe adenoma of the pituitary gland (a derivative of the foregut) but *Damon* (1957) in a smaller series, and *Aird et al* (1960), in the largest series, found no such excess.

Rheumatic fever and rheumatic heart disease

Host susceptability obviously plays a significant role and evidence is now strongly in favour of there being a genetic constitution which favours the rheumatic response to streptococcal infection. *Glynn* and his collegues (1956) pointed out that the growth of streptococci in the throat might be modified by the secretor status of the patient. The features of the rheumatic constitution show a significant excess of ABH saliva non-secretors and also an excess of group A.

The most susceptible individuals seem to be females who possess blood group A or B with non-secretor status.

Antibodies and Resistance to infection

It has been shown that antibody levels vary between the blood groups. Antibody to strain 086B7 of E. coli is universally present in man. However, the serum levels of the antibody have shown to be highest in individuals of blood group AB and lowest in group O.

This may be because group O is less able to produce the antibody or less susceptible to infections by E. coli. It has been suggested that if there were cross antigenicity, individuals of a particular ABO blood group might be at a selective advantage in combatting infection due to an organism carrying a cross-reaction antigens.

It is well established that some strains of micro-organisms have heterophile antigens, e.g. some strains of E. coli. 086 have a powerful group B-like blood antigen and following infection with this organism, greatly elevated levels of anti-B may be found in the sera of the patients.

Susceptibility to infectious diseases

One study has shown that children of blood group A in the west of Scotland are at a greater risk of death from bronchopneumonia than those of other blood groups. An excess of group O and a deficiency of group A have been demonstrated among sufferers from A2 influenza virus infections, and an opposite trend has been shown in the case of adenovirus infections. An excess of group A has also been shown in sufferers from infectious hepatitis.

Helmbold, in India (L960) pointed out that smallpox scars appear to be more severe in group A and there is a slight excess of smallpox cases with blood group A. He also pointed out that vaccination induced-encephalitis is two times more common in group A individuals.

Vogel et al (1960) have shown that individuals of blood group O are much more likely to develop plague, as geographic evidence in areas such as India and Outer Mongolia bears out.

Susceptibilty to Chronic Diseases

Lewis and Wood (1961) found that there was a significant difference in blood group distribution between patients with sarcoidosis and with tuberculosis, seen at the Brompton Hospital. The 164 sarcoid patients showed an excess of blood group A and a deficit of group O, 40% belong to group O and 51% to group A, as compared with 48.8% and 38.9% respectively for 894 tuberculous patients.

Fergeusen and Wurm (1964) studied the ABO blood groups in 518 sarcoid patients in Germany. They found that the percentage of group A was 4.81% higher than was found in the unspecified German control groups, this excess was at the expense, principally, of group B, and to a less extent of group O. From these figures it was

estimated that group A subjects were 14.2% more likely to have sarcoidosis than group O. Unlike *Lewis and Wood*, they found a slight predominance of group A in tuberculosis as well as in sarcoidosis.

The other association mentioned in Vogel's paper is a possible relationship between syphilis and the ABO blood group. He pointed out that people with A, B, or AB group have a 67% higher chance to stay seropositive after treatment than group O. As treatment is increased, this proportion increases further. This shows that syphilites with blood group O are more likely to develop a milder disease and therefore there would be more group O in areas of epidemic syphilis.

Conclusion

Finally, conclusive evidence of an association between the blood groups and disease has been shown. Most of the diseases which show an association with a particular ABO blood group appear to be *diseases of the upper part of the gastro-intestinal tract and its appendages*. Carcinoma of the stomach and pernicious anaemia, occur more frequently in persons with blood group A than in those with other blood groups; peptic ulcer more frequently in those of group O. In addition to the association for gastric cancer and pernicious anaemia, there is evidence of the association between *rheumatic heart disease* and blood group A.

The relationship between the ABO blood groups and susceptibility to virus infection and chronic infection is not a very specific one, but there is enough evidence to show that the blood groups are not genetically neutral but may actually have a bearing on disease suscepitibility in general.

Similar interrelationships between other blood groups and disease may also exist and need to be studied further.

REFERENCES

Aird et al B.M.J .1, 1953. A relationship between cancer of the stomach and the ABO blood group.

Bourke G.J., Clarke N. & Thornton E.H. (1965). Smallpox vaccination and ABO blood groups J. Medical Genetics 2, 122-125.

Clarke C., Selected topics in Medical Genetics (1969), 29-34, 62-65, 254-255 and 262.

Clarke C., Genetics for the Clinician, 115-119 and 181.

D. Evans: Gastroenterology Vol. 40.3 March 1961.

McDonald J.C., ABO Blood group and acute respiratory virus disease, B.M.J. 1962, 89-90.

Scadding J.G., Sarcoidosis and ABO Blood group, 473.

Vogel F., 1966, ABO Blood group and smallpox in a rural population of West Bengal and Bihar (India), Humangenetik 3, 166-180.

Walker C., Rheumatic heart disease and blood group A, Practitioner, Feb. 1970.

I am grateful to Prof. Kenneth Hill, Head of the Department of Pathology, Royal Free Hospital School of Medicine, who stimulated my interest in this subject while clerking in his Department, and also to Dr. Rizzo Naudi, Consultant in Medicine at St. Luke's Hospital, who so kindly read the manuscript, for useful criticism. My thanks are also extended to my colleagues Messrs Ben Anazodo and Arthur Felice for their kind help.