Correlations of ABO Blood Groups with Peptic Ulcer, Cancer, and Other Diseases

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The particular problem with which this paper is concerned is whether individuals belonging to different ABO blood groups do or do not differ in their susceptibility to certain common "adult" diseases. The question is not a new one. As long ago as 1921 Buchanan and Higley at the Mayo Clinic investigated the matter (4) and came to the conclusion that there was no association between any of the ABO groups and the diseases which they tested—and these included peptic ulcer, pernicious anemia, and various types of malignant disease.

Interest lay almost dormant for 30 years and was only renewed in 1953 when Aird and his colleagues (2) in England published a paper showing that there was a striking relationship between group A and carcinoma of the stomach in all parts of the country. Other authors have since published similar findings, although there is one large series, from Vienna, where the association has not been found. Aird and his colleagues (1) also investigated three other cancers, those of the colon and rectum, lung, and breast, and obtained negative results. In the same paper they described the biggest association of all, that between peptic ulcer and blood group O. They concluded that an individual who was group O was 35 per cent more prone to develop an ulcer than one who was not O.

Since 1954 a great deal of literature has accumulated. The association between group O and peptic ulcer has been found in many parts of the world—Boston, Iowa, Copenhagen, Oslo, and Vienna, to mention some of them, and it has also been found in Chinese, Japanese, and in Negroes. Usually the association has been greater with duodenal than with gastric ulcer, and it seems probable that there is a real difference between the two diseases. Table 1 shows the results we obtained in Liverpool (1955) and it can be seen that in our series the figures for gastric ulcer do not differ significantly from those for the controls. The controls in this and all the other series I have so far mentioned have been obtained either from grouped blood donors or from over-all grouped hospital populations, excluding those suffering from the disease being investigated. I shall refer to this again later.

TABLE 1

LIVERPOOL DATA (1955)

	O	A	B	AB
Duodenal ulcer: 860	505	263	62	30
Percentages	58.72	30.58	7.21	3.49
Gastric ulcer: 377	185	151	31	10
Percentages	49.07	40.05	8.22	2.65
Controls: 15,377	49.0	39.1	9.4	2.5

* Reader in Medicine.

In 1956 a group of workers in England showed that there was a convincing association between pernicious anemia and blood group A (7).

The next part of the story concerns the secretor character in duodenal ulcer. As is well known, some individuals secrete their ABH antigens in their body fluids and some do not. The character is inherited in a simple mendelian way, secretion being dominant to non-secretion. We thought that there might be physiological differences between those who did and those who did not secrete their antigens and that it might not be entirely fortuitous that the saliva and gastric juice

TABLE 2

SECRETION OF ABO BLOOD GROUP ANTIGENS; PERCENTAGES OF NON-SECRETORS (1956)

Duodenal ulcer: 973 patients	36.6 per cent
General population control: 849 patients	24.4 per cent
No heterogeneity for blood group or sex	
Comparison ulcers: Controls χ_1^2	31.64
	$P<0.001$.

of secretors contained particularly large quantities of these blood group substances. We therefore investigated (1956) the character in duodenal ulcer and found a highly significant association between the disease and non-secretion. Table 2 shows the details of this survey, and this part of the work was entirely carried out by Dr. R. B. McConnell. Table 3 shows the range of the diseases which have been tested for secretor character, and it will be seen that the only significantly abnormal finding is that for duodenal ulcer.

Table 4 shows the details of what we may regard as the well established associations between blood groups and adult diseases.

It appeared at first sight as though the various findings could be readily correlated. We surmised that individuals who were group O might be pouring out excess hydrochloric acid in their stomachs and therefore be liable to duodenal ulcer and only rarely develop gastric cancer. On the other hand, with group A, there was the association with gastric carcinoma and pernicious anemia, the latter always and the former often showing achlorhydria. Then there was the knowledge that the secretor substances were mucopolysaccharides and therefore in non-secretors there might be less of the protective mucoid barrier in the stomach.

The first criticism came from Penrose.[1] He thought that the findings might be due to stratification and that it was possible that there might be in the population a strain high in O and high in duodenal ulcer but with no causal connection. He said that before causality could be accepted family studies should be made, and we have investigated up to the present time nearly 400 duodenal ulcer sibships. In all the other series that have been published, the controls have been blood donors or over-all grouped hospital populations, but in our family studies it is the unaffected sibs who

TABLE 3

SECRETOR CHARACTER AND DISEASES

	No. tested	Per cent Nonsecretor
Controls	849	24.4
Duodenal ulcer	973	36.6
Gastric ulcer	132	28.0
Aphthous ulcer	156	23.7
Carc. stomach	167	19.2
Carc. cervix	220	28.3
Diabetes mellitus	318	26.1
Asthma	250	23.6

act as controls, and they cannot be criticized on the ground that they do not come from the same population as the ulcer population.

We have analysed the data by the method of Dr. C. A. B. Smith of the Galton Laboratory, London. The principle of Smith's method is to assess in each segregating family the chance of the propositus being O and then to compare the total observed results with the total expected. It must be emphasized that in this type of analysis it is only families which segregate for blood group—some of the sibs being O and some not O—that can be used, and many families there-

[1] Personal communication, 1953.

fore give no information. If we consider the simplest possible case, that of a duodenal ulcer sibship consisting of four individuals, two of whom are group O and two of group A, clearly the chance of the propositus being group O is an even one, and the expected result is therefore scored as 0.5. If, in fact, the propositus is group O, then the observed score is 1, whereas if he is group A, the observed score is zero.

Table 5 illustrates the results in 134 sibships which segregated for the O blood group. It will be seen that the observed score is slightly higher than the expected, but nowhere near significantly so. Nor is significance obtained if the propositus is paired with a sib of her or his own sex. These findings do not contradict the hypothesis that group O predisposes to ulcer, but they give no support to it.

Table 5 also shows the data analysed for secretion and nonsecretion. Again it will be seen that within families an individual who is a nonsecretor is not significantly more likely to have the ulcer than his secretor sib. If, however, the propositus is paired with a sib of the same sex, significance is obtained, but it seems doubtful from the way the work is going whether this will hold with more material.

Since I spoke about this in Copenhagen, there is some additional evidence of interest. Dr. Richard Doll of the Central Middlesex Hospital, London, has recently started a similar sibship investigation in duodenal ulcer, and he has very kindly allowed me to quote his preliminary results.[2] In 63 propositi with a total of 69 sibs he has found no association within families between group O or nonsecretion with the ulcer.

The explanation of these findings is difficult. We are loath to accept the explanation of stratification, since it seems incredible that the same stratification could occur here in the U.S.A., in England, and also in Denmark, Norway, and Portugal. We are therefore driven to consider the possibility, unlikely though it may seem in a disease such as duodenal ulcer, of a maternal factor. If mothers who are group O are more likely than mothers who are group A, B, or AB to produce children who will develop duodenal ulcer irrespective of *their* blood group, the ulcer population would be being bred from a high O strain and would give you the type of result which we have in fact obtained. Such a maternal effect might operate im-

TABLE 4

WELL ESTABLISHED ASSOCIATIONS WITH ABO BLOOD GROUPS*

	Duodenal ulcer	Gastric carcinoma	Pernicious anemia
Number of centers reporting	9	13	9
Number of patients analysed	8,272	6,795	1,498
Difference from controls	Group O +16.8 per cent	Group A +10.0 per cent	Group A +13.5 per cent

* From J. A. Fraser Roberts (9).

TABLE 5

ANALYSIS OF DUODENAL ULCER SIBSHIPS*

	Propositus Group O	Propositus nonsecretor
Expected	65.326	44.283
Observed	69	48
Difference	+ 3.674	+ 3.717
S.E.	± 5.577	± 4.705
P	> 0.5	> 0.4

* Method of C. A. B. Smith.

TABLE 6

FUCOSE IN SALIVA*

	No. tested	Mean fucose (μg/ml)	Standard error
O Secretor	23	93	±10.9
O Nonsecretor	23	78	± 6.5
A Secretor	23	86	± 7.5
A Nonsecretor	23	77	± 8.4
B Secretor	17	101	±12.1

* D. A. P. Evans' figures.

[2] Personal communication, 1958.

munologically or as a behavior difference between O and non-O women. There is something of a parallel if we consider the ABO blood groups of children with erythroblastosis due to anti-D. If in 1938, knowing nothing about rhesus, someone had investigated the ABO groups of erythroblastotic babies, he would have found that they were higher in O than the general population but that this association would not have held in sibships (see paper by Levine in this symposium).

Whether some antigen-antibody reaction occurring *in utero* could possibly cause predisposition to duodenal ulcer seems highly speculative, but any clue is worth pursuing, and we have continued to investigate the problem from both the biochemical and immunological points of view—in spite of our sibship results. The data may be summarized as follows:

1. Peebles Brown and his colleagues in Glasgow (3) have shown by means of augmented histamine test meals that individuals who are group O do not have potentially more hydrochloric acid in their stomachs than those who are not O.

2. Morgan (8) has pointed out that the nonsecretors of ABH are usually secretors of Lewis, and therefore, in terms of total blood group mucopolysaccharide in the stomach, there will be nothing to choose between the secretors and nonsecretors of ABH. One of our team, Dr. Price Evans, is investigating this matter at the moment. The sugar fucose provides a very good index of blood group activity, and Evans has found in his results thus far that there is no significant difference in the amount of fucose in the saliva of secretors and nonsecretors of ABH—in other words, in the nonsecretors of ABH the fucose is coming from the secretion of Lewis (Table 6). Before leaving this point, I should mention that about 8 per cent of the population are known to be nonsecretors of both ABH and Lewis. We wondered therefore, whether duodenal ulcer patients might show an excess of this type of individual, but we have not found this to be so.

3. If the association between duodenal ulcer and nonsecretion is due to a direct effect of the secretor gene, then there might be quantitative differences in antigen titer in the saliva of individuals who are secretors compared with their unaffected secretor sibs—we might expect a lower titer, i.e., less antigen in those who have the ulcer. As far as we have gone (about 70 sib pairs) there is no significant difference in titer between the saliva of the individual with the ulcer and that of the sib without. If this proves to be our final conclusion it will be strong evidence against the possibility that the association between nonsecretion and duodenal ulcer is due to a direct effect of the secretor gene.

4. Coombs has shown, by means of the mixed agglutination technique, that the ABH antigens are present not only on red cells but on many types of surface epithelium as well. Coombs found that antigens were present regardless of whether the individual was a secretor or nonsecretor. We felt that it would be worth while investigating this matter in relation to suspensions of duodenal cells, and one of our team, Dr. Frances Selsnick, an American citizen, is carrying out this work.[3] She is using fluorescein-labeled antibodies as well as Coombs' technique, and, although the results are only tentative, it rather looks as though in the case of duodenal cells the nonsecretors do *not* have antigens on their striated borders, whereas the secretors do. If this proves to be our final view, it would encourage us to explore further the possibility that there might be immunological factors at work in the production of duodenal ulcer. We did at one time postulate that ABH agglutinins in plants might be playing a part—many of the Leguminosae have anti-H or anti-A substances, and the possibility that substances such as soya beans which are used as improvers could be toxic because of their antibody content crossed our minds—but it has been shown that most of these plant antibodies are destroyed by boiling, and therefore this hypothesis rather deteriorates.

[3] Personal communication, 1958.

CONCLUSION

The whole problem, therefore, of the relationship of duodenal ulcer to blood group O remains unsolved. The association does not show up in families, and the biochemical data do not show how the association, if a true one, is exerting its effects. An immunological reaction remains a possible explanation, and we think the blood groups of mothers who have borne children who develop duodenal ulcer are worth investigating.

Nevertheless, the evidence from all parts of the world regarding the association between group O and ulcer, when blood donors are used as controls, is very strong. It is possible that, for some reason, the effect of the O gene is diluted in families because of other genes which predispose to ulcer, and these may be more in evidence in ulcer sibships than in the general population.

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