ABO BLOOD GROUPS OF SIBLINGS OF DUODENAL ULCER PATIENTS

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Blood donors, prepartum women, and patients with disorders other than duodenal ulcer have been used as controls for investigations of the association of the ABO blood groups to duodenal ulceration. In a previous communication some of the reasons why the above are not entirely satisfactory controls have been pointed out (Buckwalter and Knowler, 1958). One serious weakness is that such random samples may inadvertently be selected from strata of the population which are not homogeneous with the patients, with skewed blood-type frequencies, thus invalidating their use as controls.

When siblings of duodenal ulcer patients are used as controls the possibility of racial stratification is eliminated. Since environmental and genetic variables are fewer, if a causal basis exists for the observed increased incidence of duodenal ulcer in persons of blood type O, stronger evidence of the association might be expected in families than in the general population. Data obtained from 293 duodenal ulcer sibships have been reported (Clarke *et al.*, 1956). These authors concluded that no evidence to support the hypothesis that a group O person is more likely to have a duodenal ulcer than his A, B, or AB sibs had been found. This is a report of a similar study, the results of which lead to somewhat different conclusions.

Methods

Since 1956 all patients seen at the University Hospitals with duodenal ulcer have become part of a continuing study concerned with the association of this disorder to the ABO and other blood groups (Buckwalter *et al.*, 1958). Patients from the Iowa City Veterans Hospital have been included since July, 1957. In approximately three-quarters of the patients the diagnosis is established at the time of operation; in the remainder there is a

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typical history of ulcer with a positive upper gastrointestinal x-ray study. A blood sample and relevant history is obtained from siblings of the patients (propositi). This is done at the University Hospitals or through the home physician.

In evaluating the data, sibs have been divided into those who have duodenal ulcer disease (affected), those who do not (unaffected), and those whose status is uncertain. There are among the unaffected sibs those with an occult ulcer at the time the information is collected. Information was insufficient in the uncertain group to permit their proper classification. Undoubtedly some of these sibs had duodenal ulcers. It is apparent that with the passage of time some of the at present unaffected siblings in the second and third groups will develop ulcers. These data and the results obtained when they are statistically evaluated, using the χ^2 method, are recorded in Table I. The differences which occur simultaneously in the four blood types were compared.

Results

The propositi (I) had the highest and the controls (V) the lowest blood type O frequencies. Note the high level of significance for the differences between the blood-type frequencies of propositi and controls. The blood-type frequencies of the affected (II), unaffected (III), and uncertain (IV) sibs all fell somewhere between the propositi and controls. When II, III, and IV are combined and compared with the controls, the differences are found to have borderline significance. No statistical significance is found for the differences between the propositi and sibs II and IV. The differences between the propositi and unaffected sibs likewise cannot be regarded as statistically significant. However, $0.05 < P < 0.10$ is interesting, clearly indicating the need for more data.

Clarke *et al.*, in analysing their data, used the method suggested by Dr. C. A. B. Smith, of the Galton Laboratory. Smith's method considers each family separately, thereby controlling the variable of family size. It has the great advantage that data obtained from separate studies may be added together and evaluated. Only families segregating for blood group including an O individual are used in this method; the details of the method has been described by Clarke *et al.* Of 480 sibships, 96 were found to segregate for O. In Table II are recorded the values for four representative segregating families, and the values obtained for all 96 sibships are added.

TABLE I.—Patient (Propositi) and Sibling Data; Results of Statistical Analyses

Blood Type	I Propositi		II Affected Sibs		III Unaffected Sibs		IV Unknown Sibs		V Population Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
O	264	55.0	37	46.3	566	47.2	122	53.2	22,392	44.8
A	163	34.0	32	40.0	469	40.1	81	35.4	21,144	42.3
B	41	8.5	9	11.2	112	9.3	16	7.0	4,695	9.4
AB	12	2.5	2	2.5	39	3.4	10	4.4	1,748	3.5
Total	480	100.0	80	100.0	1,186	100.0	229	100.0	49,979	100.0

V compared with I		χ^2		Probability	
V	II	21.08		P < 0.001	
V	III	1.05		0.10 < P	
V	IV	4.42		0.10 < P	
V	I + II + III + IV	7.87		0.02 < P < 0.05	
V	I + II + III + IV	21.97		P < 0.001	
I	II + III + IV	8.31		0.02 < P < 0.05	
I	II	2.31		0.10 < P	
I	III	7.60		0.05 < P < 0.10	
I	IV	2.39		0.10 < P	

TABLE II.—*Analysis of the Chance of the Propositi Being Group O in the Sibships Segregating for Blood Group O*

Sibship No.	Total Sibs	Sibs Group O	Sibs Not Group O	Group O Propositi		Variance
				Observed	Expected	
608	6	2	4	1	0.3333	0.2222
3,437	3	2	1	0	0.6667	0.2222
6,280	5	3	2	1	0.6000	0.2400
7,383	5	2	3	1	0.4000	0.2400
In the whole series of 96 segregating sibships				56	46.9797	22.0082

From which we obtain $\frac{56 - 46.9797}{\sqrt{22.0082}} = \frac{9.0203}{4.691} = 1.92$. $0.05 < P < 0.10$.

TABLE III.—*Analysis of Combined Clarke and Iowa Data*

	Total Sibships	Group O Propositi		Variance
		Observed	Expected	
Clarke <i>et al.</i>	112	59	54.9095	25.8863
Iowa	96	56	46.9797	22.0082
Total	208	115	101.8892	47.8945

From which we obtain $\frac{115 - 101.8892}{\sqrt{47.8945}} = \frac{13.1108}{6.921} = 1.89$. $0.05 < P < 0.10$.

When these data are combined with those reported by Clarke *et al.* the results indicated in Table III are obtained. The number of proposti observed of blood type O are in excess of those expected in the Clarke and Iowa studies. However, the increased O frequency in the proposti is 1.92 times the standard deviation in the Iowa data, compared with 0.80 in Clarke's data. When the data are combined the difference in the observed and expected O frequencies of the proposti is 1.89 times the standard deviation (1.96, $P < 0.05$). Additional sibship data (C. A. Clarke, 1960, personal communication) collected since 1956 is consistent. When this larger volume of data is combined with our data, $0.02 < P < 0.05$. Another advantage of this method of analysis is that it is not influenced by whether or not the sibs have ulcers. This is a possible source of error as noted before, since some of the siblings in the unaffected and uncertain group undoubtedly had peptic ulcers.

In 15 families there was an affected sib and segregation for group O. In Table IV are recorded sample data from such families, and the results of the analysis of the chance of the affected sib being group O. These data are combined and analysed with Clarke's in

TABLE IV.—*Analysis of the Chance of an Affected Sib Being Group O in Sibships Segregating Group O and Duodenal Ulcer After Proposti have been Excluded*

Sibship No.	Total Sibs	Sibs Group O	Sibs Not Group O	Sibs with Ulcer	Sibs without Ulcer	Group O Ulcer		Variance
						Observed	Expected	
6995	6	3	3	1	5	1	0.5000	0.2500
7616	2	1	1	1	1	0	0.5000	0.2500
8315	4	2	2	2	2	0	1.0000	0.3333
In the whole series of 15 segregating sibships						8	9.9918	3.2832

From which we obtain $\frac{8 - 9.9918}{\sqrt{3.2832}} = \frac{1.9918}{1.812} = 1.10$. $0.10 < P$.

TABLE V.—*Analysis of Clarke and Iowa Data*

	Total Sibships	Group O Ulcer		Variance
		Observed	Expected	
Clarke <i>et al.</i>	14	6	6.9501	3.3594
Iowa	15	8	9.9918	3.2832
Total	29	14	16.9419	6.6426

From which we obtain $\frac{14 - 16.9419}{\sqrt{6.6426}} = \frac{2.9419}{2.577} = 1.14$. $0.10 < P$.

Table V. It will be noted that the observed frequency of blood type O in the Clarke and Iowa affected sibs was less than expected.

Discussion

The data presented provide qualified support for the hypothesis that the well-established increased frequency of blood type O among patients with duodenal ulceration has a causal explanation. Conversely, it makes the population stratification thesis even less tenable. Perhaps the strongest support for a causal hypothesis is provided by the comparison of blood-type frequencies of the proposti (I) and unaffected sibs (III) (Table I). Note that the χ^2 value is almost at the 5% level of significance. Assuming that these findings do indicate a group O ulcer factor, no satisfactory explanation can be offered at this time for the low O frequency of the affected sibs (II) or the high O frequency in the uncertain (IV) sibs. The comparatively small numbers, especially of the affected sibs (II), may be a factor. Another may be improper classification—that is, some affected (II) were really unaffected, while a substantial number of ulcers were actually present in the uncertain group.

The blood type O frequency is higher in all sibs as well as the proposti than in the controls (V). This is to be expected, since the siblings all come from a stratum of the population with a "built-in" high O frequency—namely, a "duodenal ulcer" population. This increased O frequency as compared with a "non-duodenal ulcer" population is dependent on the gene composition of the parents, and is not relevant to the duodenal ulcer group O association.

The findings are inconsistent with a maternal effect characterized by ulcer predisposition of all children whatever their blood type, as suggested by Clarke *et al.* A maternal effect leading to predisposition only or chiefly of O children is possible. It is possible, perhaps probable, that multiple factors which may be anatomical, immunological, biochemical, and/or enzymological, related to the genetic template, are responsible for the observed association of duodenal ulceration to the ABO blood groups.

The findings indicated in Tables IV and V are somewhat disturbing. Assuming a causal relationship, if the data are reliable (II, III) an observed O frequency higher than the expected would be anticipated in the affected sibs. The frequency of O in the affected sibs was actually lower than expected in both the Clarke and the Iowa data. At this time judgment concerning interpretation of these findings must be reserved. A total of 29 sibships provides insufficient data ($0.10 < P$).

Conclusions

The sibship studies reported provide some support for the causative nature of associations between the ABO blood groups and duodenal ulceration. There is an indication for continuing these studies. It is urged that similar studies be undertaken.

REFERENCES

- Buckwalter, J. A., and Knowler, L. A. (1958). *Amer. J. hum. Genet.*, **10**, 164.
 ———, Tidrick, R. T., Wohlwend, E. B., Colter, D. C., Turner, J. H., Raterman, L., Gamber, H. H., Roller, G. J., Pollock, C. B., and Naifeh, V. K. (1958). *J. Iowa St. med. Soc.*, **48**, 76.
 Clarke, C. A., Edwards, J. W., Haddock, D. R. W., Howel-Evans, A. W., McConnell, R. B., and Sheppard, P. M. (1956). *Brit. med. J.*, **2**, 725.