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OBSERVATIONS ON BLOOD GROUP DISTRIBUTION IN PEPTIC ULCER AND GASTRIC CANCER

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There is increasing evidence that blood group substances play a rôle in the causation of disease or in the protective mechanism against it. This paper records the special liability for patients of blood group O to develop stomal ulceration. Other data studied failed to confirm previous work suggesting that in gastric ulceration or neoplasm blood group A was a characteristic of an antral lesion.

Observations in many countries have established that there is an association between possession of the various ABO blood groups and susceptibility to certain gastrointestinal diseases (Aird, Bentall, and Roberts, 1953; Roberts, 1957). The associations are, however, not strong and the greatest variation from the normal distribution of blood groups, that is, among persons with a duodenal ulcer, implies a difference between the susceptibility of the various groups of only about 40%. The differences could be explained if the blood group substances played some direct part in producing or protecting against the diseases in question. Alternatively, the associations may be indirect and reflect the existence of a common factor which is both responsible for the promotion of the disease and is associated with an abnormal distribution of groups. The fact that the differences are so small weighs, perhaps, against the causal hypothesis, but it may be that the blood group substance is only one of several different causal factors and that clinical subgroups could be isolated in which the association with the specific substances was more marked. For example, Brown, Melrose, and Wallace (1956) noted that the association with blood group O was more marked for stomal ulcers than for duodenal ulcers, and Billington (1956b) noted that the association with blood group A was more marked when cancer arose in the antrum or in the cardiac region of the stomach than when it arose in the body of the stomach.

If these and other similar findings could be confirmed they would strengthen the evidence for the causal hypothesis and they would also indicate a more fruitful field for the study of intra-family comparisons. At present, such comparisons have failed to show any appreciable difference between the blood group distribution of affected and unaffected members; the expected differences are, however, so small that very large numbers of subjects are required and the absence of a significant difference in the published results may be due to chance (Clarke, Evans, McConnell, and Sheppard, 1959).

TABLE I

NUMBER OF PATIENTS STUDIED AND SOURCE OF DATA

Condition	Hospital	No. of Patients	Description of Patients*	Period
Stomal ulcer	Central Middlesex	123	All patients	1944-58
	St. James's, Balham	148	All patients	1942-57
	St. Mary's, Paddington	19	Surgical unit	1950-57
	West London	10	Surgical in-patients	1947-57
Duodenal ulcer	Central Middlesex	564	Patients treated surgically 1954-57 plus a few new cases examined personally by A.N., 1958	1954-58
Gastric ulcer	Central Middlesex	605	Patients treated surgically or for haemorrhage plus patients under medical care of R.D.	1950-57
Gastric cancer	Central Middlesex	414	All patients	1950-58
	St. James's, Balham	443	All patients	1950-57

* Patients excluded those (i) for whom blood group data were not available in the hospital notes or in the records of the pathological departments, and (ii) for whom the diagnosis was not established by radiographs, gastroscopy, operation, or necropsy.

MATERIAL

In the present study, data have been collected from the records of patients treated at the Central Middlesex Hospital, Acton, supplemented by data for cancer of the stomach from St. James's Hospital, Balham, and by data for stomal ulcer from St. James's Hospital and from St. Mary's Hospital, Paddington, and the West London Hospital, Hammersmith. The numbers of patients for whom data have been collected and the sources of the material are shown in Table I.

RESULTS

STOMAL ULCER.—The distribution of the ABO blood group among patients treated for stomal ulcer is shown in Table II, in comparison with the distribution among a series of duodenal ulcer patients treated at the Central Middlesex Hospital and a control series of 10,000 women attending antenatal clinics in north-west London (Discombe and Meyer, 1952). The proportion of group O subjects is higher among the stomal ulcer patients (60·3%) than among the duodenal ulcer patients (52·8%) or among the control patients (45·8%). In each case the difference is statistically significant (stomal ulcer against duodenal ulcer patients, $\chi^2 = 4{\cdot}25$, n = 1, P = 0·04; stomal ulcer against control patients, $\chi^2 = 24{\cdot}80$, n = 1, P < 0·001). From these data it can be estimated that the risk of developing a stomal ulcer among persons of group O is 1·74 times the risk among persons of group A $\left(\frac{181}{96}\Big/\frac{4578}{4219}\right)$ and the relative risk is 1·35 times greater than the corresponding risk of developing a duodenal ulcer $\left(\frac{181}{96}\Big/\frac{298}{214}\right)$.

A comparison between these results and those recorded at other centres is shown in Table III. In Table III the relative risk is shown for group O in comparison with the combined data for groups A, B, and AB, because of the small numbers in some of the series. Mean relative risks, weighted

TABLE II

DISTRIBUTION OF ABO BLOOD GROUPS AMONG STOMAL ULCER AND DUODENAL ULCER PATIENTS AND CONTROL SUBJECTS

Disease Category	No. of Subjects Belonging to Group				All Subjects
	O	A	B	AB	
Stomal ulcer:					
Central Middlesex	72	38	8	5	123
St. James's	91	49	8	0	148
St. Mary's	11	6	2	0	19
West London	7	3	0	0	10
All hospitals	181 (60·3%)	96 (32·0%)	18 (6·0%)	5 (1·7%)	300 (100·0%)
Duodenal ulcer	298 (52·8%)	214 (37·9%)	39 (6·9%)	13 (2·3%)	564 (99·9%)
Control subjects without disease	4,578 (45·8%)	4,219 (42·2%)	890 (8·9%)	313 (3·1%)	10,000 (100·0%)

TABLE III

ABO BLOOD GROUPS AMONG STOMAL ULCER PATIENTS IN COLLECTED SERIES* COMPARED WITH THE DISTRIBUTION AMONG CORRESPONDING GROUPS OF DUODENAL ULCER AND CONTROL PATIENTS

Centre	No. of Stomal Ulcer Patients		No. of Duodenal Ulcer Patients		No. of Control Patients		Relative Risk O : (A+B+AB)	
	Group O	Groups A+B+AB	Group O	Groups A+B+AB	Group O	Groups A+B+AB	Stomal Ulcer : Duodenal Ulcer	Stomal Ulcer: Controls
London[1]	181	119	298	266	4,578	5,422	1·36 : 1	1·86 : 1
London[2]	9	2	111	86			3·49 : 1	
York[3]	21	15	—	—	983	1,079	—	1·54 : 1
Newcastle[2]	16	11	281	186	6,598	6,974	0·96 : 1	1·54 : 1
Glasgow[4]	55	24	947	695	3,177	2,721	1·68 : 1	1·96 : 1
Mean weighted relative incidence							1·41 : 1	1·82 : 1
χ^2 for difference from unity							8·518	37·397
n = 1, P							< 0·01	< 0·001
χ^2 for homogeneity							2·918	0·559
n = 3, P							0·30 to 0·50	0·90 to 0·95

[1] Present series.
[2] Aird, Bentall, Mehigan, and Roberts (1954) and Roberts (1957 and personal communication). The data from the Central Middlesex Hospital and St. James's Hospital, Balham, are excluded as these are largely included in the present series.
[3] Data for stomal ulcer patients provided by Pulvertaft (personal communication); control data collected from Leeds (Aird *et al.*, 1954).
[4] Brown *et al.* (1956).

* Data reported by Balint, Cooper, Price, Pulvertaft, and Swynnerton (1957) are not shown separately as they are all included in the present series from London and York.

according to the numbers of observations in each series, have been calculated according to Woolf's method (Woolf, 1955; Roberts, 1957). The combined results for all the centres show that the risk of developing a stomal ulcer among group O subjects is approximately 1·82 times the risk among persons of groups A, B, or AB (95% limits of probability, 1·50 to 2·22) and that the relative risk is approximately 1·41 times greater than the corresponding risk of developing a duodenal ulcer (95% limits of probability, 1·12 to 1·79). With both comparisons the variation between the results in the different series can reasonably be regarded as due to random fluctuations.

DUODENAL ULCER.—In several investigations, the data for duodenal ulcer patients have been examined to see whether the extent of the association with group O varied with the severity of the disease. Clarke, Cowan, Edwards, Howel-Evans, McConnell, Woodrow, and Sheppard (1955) and Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956) distinguished medically and surgically treated cases, and Brown *et al.* (1956) examined separately those patients whose ulcers had bled or perforated. No evidence was obtained to suggest that there was likely to be a substantial difference between the different groups. In the present series the patients have been divided according to (1) the age at onset of symptoms, and (2), for those who were treated surgically, the age at operation. The results are shown in Table IV. The greatest proportion of group O subjects (60·6%) is found among the patients who were operated on at ages 55 years or older. There is, however, no evident trend with age either at operation or at onset, and the differences in the proportions of group O subjects are not statistically significant. If the association varied with the severity of the disease it might be expected that the association would be strongest among patients in whom the disease appeared early or necessitated operation at an early age, and it seems, therefore, most likely that the present results are due to random fluctuation.

GASTRIC ULCER AND GASTRIC CANCER.—It has been demonstrated in many independent studies that the risk of developing a gastric ulcer is slightly greater for persons with blood group O than for persons with any of the other groups, while the risk of developing gastric cancer is slightly greater with blood group A. Data reported from 13 centres for nearly 4,000 gastric ulcer patients and over 6,500 gastric cancer patients have been reviewed by Roberts (1957), who estimated that the relative incidences of the two diseases among group O and group A subjects were 1·16 : 1 and 0·84 : 1 respectively. This interpretation of the data has, however, been contested by Billington (1956b) and by Balme and Jennings (1957). They suggest that the important association is between the *site* of the lesion and the blood group, and that the *nature* of the lesion, whether simple ulcer or carcinoma, is irrelevant. In their opinion, the overall association of carcinoma of the stomach with group A and of gastric ulcer with group O results from the fact that most carcinomas occur in the antrum where lesions are associated with group A, whereas most ulcers occur in the body of the stomach where lesions are associated with group O. In their experience, the relatively rare lesions of the cardia are associated with blood group A and are similar in this respect to lesions of the antrum. In the present series, gastric ulcers have been classified into three types according to whether the lesion occurred distal to the angulus or in the middle or upper third of the

TABLE IV

ABO BLOOD GROUPS AMONG DUODENAL PATIENTS DIVIDED ACCORDING TO AGE AT ONSET OF SYMPTOMS AND AGE AT OPERATION

Characteristic	No. of Patients Belonging to Group				All Patients	Relative Risk O : A
	O	A	B	AB		
Age at onset						
Under 25 years	61 (53·0%)	46	4	4	115	1·22 : 1
25-34 years	85 (50·0%)	65	15	5	170	1·21 : 1
35-44 years	62 (49·2%)	51	11	2	126	1·12 : 1
45 years and over	84 (58·7%)	48	9	2	143	1·61 : 1
Age not known	6	4	0	0	10	—
Age at operation						
Under 45 years	102 (51·3%)	76	14	7	199	1·24 : 1
45-54 years	70 (47·9%)	59	17	0	146	1·09 : 1
55 years and over	97 (60·6%)	54	5	4	160	1·66 : 1
Not operated	29 (49·2%)	25	3	2	59	1·07 : 1
All ages	298 (52·8%)	214	39	13	564	1·28 : 1

Age at onset:
Group O against groups A, B, and AB; $\chi^2 = 3{\cdot}21$, n = 3, $0{\cdot}3 < P < 0{\cdot}5$
Age at operation:
Group O against groups A, B, and AB; $\chi^2 = 5{\cdot}76$, n = 2, P = 0·07

stomach. Ulcers at the angulus of the stomach or at the junction of the middle and upper thirds have been classified as occurring in the middle zone. Cancers of the stomach were more difficult to locate, because by the time of diagnosis the disease had often spread beyond the zone in which it had arisen. In these circumstances, cancers were regarded as having arisen in the cardiac region only if the main bulk of the tumour was confined to the upper third of the stomach and in the antral region only if the main bulk was located distal to the angulus.

The distribution of blood groups associated with the two lesions in the different sites is shown in Table V. Despite the large number of cases the numbers in some of the subgroups are small and the differences between them may well be due to chance. The data for gastric ulcer would support the view that the association of this disease with blood group O is characteristic of ulcers of the body, but there is no evidence of a similar association for cancer of the stomach and there is very little evidence to suggest that lesions of the antrum are characteristically associated with group A. Other recent data have also failed to support the idea that the association is characteristic of the site of the lesion. In Johnson's (1957) series of gastric ulcers, the prepyloric ulcers showed the strongest association with group O and in Mosbech's (1958) large series of cases of gastric cancer, the ratios of groups O to A were practically the same irrespective of the site of origin of the disease. The published data for the two principal blood groups are summarized in Table VI. There are clearly wide differences between the results obtained in the different series and it is not possible to detect any consistent relationship between lesions in different parts of the stomach.

TABLE V

ABO BLOOD GROUPS IN GASTRIC ULCER AND GASTRIC CANCER PATIENTS DIVIDED ACCORDING TO SITE OF LESION

Site	No. of Patients Belonging to Group				All Subjects	Relative Risk O : A
	O	A	B	AB		
Gastric ulcer						
Upper third	68 (54·0%)	42 (33·3%)	14	2	126	1·49 : 1
Mid third	180 (49·2%)	150 (41·0%)	25	11	366	1·11 : 1
Antrum	24 (45·3%)	22 (41·5%)	5	2	53	1·01 : 1
Mixed sites or site uncertain	31	26	3	0	60	—
	303 (50·1%)	240 (39·7%)	47	15	605	1·16 : 1
Gastric cancer						
Cardiac region	49 (36·8%)	65 (48·9%)	15	4	133	0·69 : 1
Upper half	45 (42·9%)	53 (50·5%)	7	0	105	0·78 : 1
Mid third	50 (43·1%)	53 (45·7%)	9	4	116	0·87 : 1
Lower half	24 (40·7%)	26 (44·1%)	7	2	59	0·85 : 1
Antrum	132 (43·0%)	125 (41·7%)	30	13	300	0·97 : 1
Whole body or site uncertain	62	70	7	5	144	—
All sites	362 (42·2%)	392 (45·7%)	75	28	857	0·85 : 1
Control subjects without disease	4,578 (45·8%)	4,219 (42·2%)	890	313	10,000	—

Difference between O and A for gastric ulcers in the antrum compared with other parts of stomach $\chi^2 = 0{\cdot}297$, n = 1, $0{\cdot}5 < P < 0{\cdot}7$
Difference between O and A for gastric cancers in the cardiac region, mid-third of stomach and antrum $\chi = 2{\cdot}141$, n = 2, $0{\cdot}3 < P < 0{\cdot}5$

TABLE VI

O AND A BLOOD GROUPS IN GASTRIC ULCER AND GASTRIC CANCER PATIENTS DIVIDED ACCORDING TO SITE OF LESION IN COLLECTED SERIES

Authors	Site of Lesion	Gastric Ulcer			Gastric Cancer		
		No. in Group		O/A	No. in Group		O/A
		O	A		O	A	
Billington (1956a, 1956b)	Cardiac region	94	47	2·00	24	50	0·48
	Mid-body				154	47	3·28
	Antrum	22	52	0·42	53	96	0·55
Balme and Jennings (1957)	Cardiac region	76	67	1·13	15	22	0·68
Jennings, Balme, and Richardson (1956)	Mid-body				41	42	0·98
	Antrum	20	29	0·69	33	64	0·52
Johnson (1957)	Cardiac region	127	111	1·14	—	—	—
	Mid-body						
	Antrum	59	32	1·84	—	—	—
Mosbech (1958)	Cardiac region	—	—	—	83	105	0·79
	Mid-body	—	—	—	203	271	0·75
	Antrum	—	—	—	311	387	0·80
Doll, Newell, and Swynnerton (present data)	Cardiac region	248	192	1·29	49	65	0·75
	Mid-body				50	53	0·94
	Antrum	24	22	1·09	132	125	1·06

Summary and Conclusions

Out of 300 patients with stomal ulcers, 181 (60·3%) belonged to blood group O; among 564 patients with duodenal ulcer, the proportion was 52·8%. From these and other published data, it can be estimated that the risk of developing a stomal ulcer is approximately 1·8 times greater among group O subjects than among subjects belonging to the other three groups (O : A + B + AB) and that the relative risk among group O subjects is approximately 1·4 times greater than the relative risk of developing a duodenal ulcer. The observation of a "biological gradient" between the frequency of blood group O and susceptibility to peptic ulceration may be regarded as support for the hypothesis that the blood group substances play a direct part in the causation of the disease, or in protecting against it.

Data for the duodenal ulcer patients failed to provide any evidence that the age of onset of symptoms or the age at operation was likely to be earlier among group O subjects; such differences as were observed were in the opposite direction and could be attributed to chance.

Data for 605 gastric ulcer patients and 857 gastric cancer patients were examined to see whether the frequency of blood groups O and A varied with the site of the lesion. The observed differences were not statistically significant and did not support the suggestion that the association with blood group A was characteristic of an antral lesion or that the association with blood group O was characteristic of a lesion of the body of the stomach.

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