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Interaction between ABO and Rhesus blood groups, the site of origin of gastric cancers, and the age and sex of the patient

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SUMMARY ABO and Rhesus blood group data have been examined for 1,680 patients treated for gastric cancer in four London hospitals.

The risk of developing gastric cancer was estimated to be 16% higher for group A subjects than for group O subjects, in close agreement with many previous reports throughout the world. More detailed analysis failed to support the suggestion that there was any special correlation between either ABO or Rhesus blood groups and the site of origin of the tumour within the stomach or the sex or age of the patient.

Male predominance among the patients was noted to be greater at ages 40-69 years than at other ages and greater for tumours of the upper two thirds of the stomach than for tumours that arose distally.

The relevance of genetic factors to the aetiology of gastric carcinoma is widely accepted and is derived from familial and blood group studies (McConnell, 1966). The precise contribution of these genetic factors, however, is unknown.

Aird, Bentall, and Roberts (1953) were the first to study ABO blood groups in a large number of patients with gastric cancer and found an excess of group A and a deficiency of group O in comparison with control patients. Subsequently, at least 71 controlled series have been published; in 55 of these the cancer patients showed an excess of group A, in 14 a slight predominance of group A, and in only two a deficiency of group A (McConnell, 1966). These world-wide studies show that group A increases the risk of gastric malignancy by about 20%, and that this proportional increase is approximately the same irrespective of whether the overall incidence is low, intermediate, or high.

To define more exactly the contribution of this genetic effect to the pathogenesis of gastric cancer, workers have examined blood groups in relation to such variables as tumour site, histology, gastric acidity, and age and sex of the patient. Among these studies was that of Doll, Swynnerton, and Newell (1960) who found a decreasing ratio of group A to O from the proximal to the distal end of the stomach. The differences, however, were not statistically significant. The purpose of the present study was to obtain additional material and to make a more detailed examination of the interrelationship between the blood group, sex, and age of the subject and the occurrence of cancer in different parts of the stomach.

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Material

Data on ABO and Rhesus blood groups were obtained for 823 gastric cancer patients seen in the years 1950-63 at three London hospitals (Central Middlesex, University College, and St. Bartholomew's) and were added to the previous data for 857 patients seen at the Central Middlesex and St. James's hospitals in the years 1950-58 (Doll *et al*, 1960).

The criterion of diagnosis was, in the majority of cases, a histological diagnosis of adenocarcinoma by biopsy, operation, or postmortem examination. In the remaining cases the diagnosis was based on definitive radiological findings, operative observations, and clinical course. Care was taken to exclude cases of oesophageal carcinoma extending into the cardia.

Tumour sites were determined by reviewing

operative notes, *x*-ray findings, or postmortem examinations. Tumours were classified as arising in the proximal, middle, or distal thirds of the stomach, including tumours of the cardia and fundus in the proximal third and tumours of the pylorus and antrum in the distal. Tumours that could be classified only as arising in the upper or lower half of the stomach, and diffuse or multicentric tumours were excluded from the analysis by site.

The distribution of blood groups was examined in relation to the site of the tumour, the age and sex of the patient, and the hospital in which the patient was treated, except for the St. James's cases for which data on sex and age were not available.

Interactions between the four variables—age, sex, site, and hospital—could have produced a spurious correlation or masked a genuine relationship between any one variable and the patient's blood group. Tables of observed and expected numbers were, therefore, constructed which enabled a comparison to be made between the observed proportions of patients belonging to groups O and A in each category of each variable and the numbers that would be expected after adjusting for the effect of the other variables. In fact, none of the four variables introduced much bias into the association between the other variables and the blood groups and so only the uncorrected expectations are given in Tables III, IV, and V.

Two sets of data were used for controls: blood group data on 10,000 pregnant women attending the antenatal clinic of the Central Middlesex Hospital during the years 1947-1951 (Discombe and Meyer, 1952) and on 33,062 blood donors of both sexes, resident in London, and aged 18-60 years, which were collected during 1952-1960 (Kopeć, 1970). The percentage distributions of the ABO groups in these two control series were identical to one decimal place, and the series were, therefore, combined. Pregnant women and blood donors have frequently been used in the past to provide an estimate of the distribution of blood groups in the general population and the similarity of the results in these two series strengthens the belief that neither source is likely to be materially biased.

Results

The age range of the 1,237 patients seen at the three of the four hospitals for which data on sex and age were available was 19 to 92 years, with a mean of 61·7 years. Male predominance was more marked at ages 40-69 years than at other ages. The decrease in the sex ratio after 60 years of age could be accounted for only in part by the decrease in the proportion of men in the population at older ages (Table I), as was observed previously by Griffith (1968) in a survey of gastric cancer throughout the world. The male predominance was significantly greater for cancers of the proximal and middle thirds (2·48:1 and 2·43:1 respectively) than for those arising in the distal third of the stomach (1·46:1).

Table II summarizes the blood group data for the gastric cancer patients and the two control series. The frequency of group A is greater and that of group O is less in gastric cancer patients than in the controls ($P < 0.01$). The relative risk of cancer in group A subjects compared with the other groups was calculated by Woolf's method (1955) to be 1·16:1.

This excess risk of developing gastric carcinoma in

Age (in years)	*No. of Cases*	*Ratio of Males to Females*	
		No. of Cases	*Corrected for Populations at Risk*
Less than 40	50	1·78:1	1·73:1
40-49	133	2·50:1	2·57:1
50-59	345	2·75:1	3·03:1
60-69	400	1·99:1	2·66:1
70 or over	309	1·01:1	1·65:1
All ages	1,237	1·84:1	1·96:1

Table I *Variation of sex ratio in gastric cancer with age*[1]

[1]Data not available for St. James's Hospital patients.

Subject	*Series*	*Number of Subjects Belonging to Blood Group*				*Total Subjects*	*Relative Risk A : O + B + AB*
		O	*A*	*B*	*AB*		
Gastric cancer	Central Middlesex	267 (42·7%)	280 (44·8%)	55 (8·8%)	23 (3·7%)	625	1.11:1
	St. Bartholomew's	128 (40·5%)	146 (46·2%)	30 (9·5%)	12 (3·8%)	316	1.17:1
	St. James's	190 (42·8%)	202 (45·6%)	38 (8·6%)	13 (2·9%)	443	1.14:1
	University College	121 (40·9%)	143 (48·3%)	20 (6·6%)	12 (4·1%)	296	1.28:1
	All hospitals	706 (42·0%)	771 (45·9%)	143 (8·5%)	60 (3·6%)	1,680	1.16:1
Control	Discombe and Meyer (1952)	4,578 (45·8%)	4,219 (42·2%)	890 (8·9%)	313 (3·1%)	10,000	—
	Kopeć (1970)	15,121 (45·8%)	13,937 (42·2%)	2,951 (8·9%)	1,017 (3·1%)	33,026	—
	Combined series	19,699 (45·8%)	18,156 (42·2%)	3,841 (8·9%)	1,330 (3·1%)	43,026	—

Table II *Distribution of ABO blood groups in gastric cancer patients attending different hospitals and in control subjects*

persons of group A is in close agreement with previous studies (McConnell, 1966). Several investigators (for example, Hoskins, Loux, Britten, and Zamcheck, 1965) have suggested that this group A excess may be due to the high risk of developing gastric cancer in patients with pernicious anaemia and to the fact that pernicious anaemia is more common in group A subjects. This, however, could not be the explanation as only a small minority of patients with gastric cancer develop the disease against a background of pernicious anaemia and the proportion of patients with pernicious anaemia who belong to blood group A is not appreciably greater than the proportion in patients with gastric cancer alone. The data of Hoskins *et al* (1965) was limited to 32 patients with both diseases and 337 patients with gastric cancer alone and with these numbers the difference between the proportions belonging to blood group A was not statistically significant. That these findings were, in fact, due to chance is suggested by new data collected by Langman, Callender, and MacLeod (personal communication). Of 46 patients who suffered from both diseases, only 19 belonged to blood group A whereas 20 belonged to blood group O.

No significant association was found between blood group and the sex (Table III) or the age of the gastric cancer patients, irrespective of whether age was examined in three broad groups (Table IV) or by five-, 10-, or 15-year groups. This conforms with the results of previous investigations (Aird, Bentall, Mehigan, and Roberts, 1954; Haddock and McConnell, 1956; Buckwalter, Wohlend, Colter, Tidrick, and Knowler, 1957; and Mosbech, 1958). The lack of evidence of a trend in the ratio of blood groups with age is of particular interest as it implies that genetic factors play their part throughout life and do not simply define a high risk group in whom the induction period is grossly shortened.

The distribution of intragastric cancer sites is shown in Table V. Tumours known to arise in the

Series	*Total Patients*	*Site of Lesion*	*No. of Patients Belonging to Group*		*Ratio A:O*
			O	*A*	
Jennings *et al* (1956)	129	Cardia	6	10	1·67:1
		Body	23	18	0·78:1
		Pylorus + antrum	20	42	2·10:1
Billington (1956)	483	Cardia	24	50	2·08:1
		Body	154	47	0·31:1
		Prepyloric	53	96	1·81:1
Haddock and McConnell (1956)	443	Cardia + body	85	109	1·28:1
		Pylorus + antrum	118	87	0·74:1
Mosbech (1958)	1,739	Cardia	83	105	1·27:1
		Body	203	271	1·33:1
		Prepyloric	311	387	1·24:1
Beasley (1960)	920	Cardia	34	46	1·35:1
		Body	142	154	1·08:1
		Pylorus	144	149	1·03:1
Doll *et al* (1960)	857	Cardia	49	65	1·33:1
		Middle third	50	53	1·06:1
		Pylprus + antrum	132	125	0·95:1
Present series	823	Proximal	70	76	1·09:1
		Middle	102	89	0·87:1
		Distal	108	108	1·00:1

Table V *Distribution of O and A blood groups in gastric cancer patients by site of lesion (collected series)*

Difference between O and A in different sites (present series) $\chi^2 = 0{\cdot}814$, n = 2, $0{\cdot}6 < P < 0{\cdot}7$

Sex	*Number of Subjects Belonging to Blood Group*				*Total Subjects*	*Ratio A:O*
	O	*A*	*B*	*AB*		
Male	326 (40·7%)	370 (46·2%)	75 (9·4%)	30 (3·7%)	801	1·13:1
Female	190 (43·6%)	199 (45·6%)	30 (6·9%)	17 (3·9%)	436	1·05:1
Both sexes	516 (41·7%)	569 (46·0%)	105 (8·5%)	47 (3·8%)	1,237	1·10:1

Table III *Distribution of ABO blood groups in gastric cancer patients by sex*[1]

Difference between proportions of O and A, male versus female: $\chi^2 = 0{\cdot}33$, n = 1, $0{\cdot}5 < P < 0{\cdot}6$
[1]Data not available for St. James' Hospital patients

Age (in years)	*Number of Subjects Belonging to Blood Groups*				*Total Subjects*	*Ratio A:O*
	O	*A*	*B*	*AB*		
Less than 50	79 (43·2%)	77 (42·1%)	18 (9·8%)	9 (4·9%)	183	0·97:1
50-69	293 (39·3%)	362 (48·6%)	65 (8·7%)	25 (3·4%)	745	1·24:1
70 or over	144 (46·6%)	130 (42·1%)	22 (7·1%)	13 (4·2%)	309	0·90:1
All ages	516 (41·7%)	569 (46·0%)	105 (8·5%)	47 (3·8%)	1,237	1·10:1

Table IV *Distribution of ABO blood groups in gastric cancer patients by age*[1]

Difference between proportions of O and A at different ages: $\chi^2 = 5{\cdot}01$, n = 2, $0{\cdot}05 < P < 0{\cdot}10$
[1]Data not available for St. James's Hospital patients

proximal, middle, or distal thirds of the stomach represent 74% of the total (3,998 out of 5,394). No significant predilection appears for any one gastric site to be associated with group A compared with the others.

The results of previous studies relating the ABO blood group to the site of origin of the tumour within the stomach are summarized in Table V. Jennings, Balme, and Richardson (1956), who studied 129 patients at another hospital in London, and Billington (1956), who studied 483 patients in Sydney, found a higher frequency of group A compared with the other groups in patients with cancers in the cardia and antrum while group O predominated in patients with cancers in the body of the stomach. In contrast, Haddock and McConnell (1956) found an excess of group A in the cardia and midzone cases combined and an excess of group O in the antral cases.

Studies based on larger numbers of cases have failed to show such marked differences. Beasley (1960) reported on 920 patients from Wales, Mosbech (1958) reported on 1,739 cases from Denmark, and Doll *et al* (1960) reported on 857 cases from London. The present series adds a further 823 cases from London. Taken individually none of these series provides evidence of any significant difference in blood group distribution between the three principal intragastric sites. We may note, however, that three of the series show a relatively greater proportion of group A cases in cancers of the cardia than in cases of the body, while none show any appreciable or consistent differences between cancers of the body and of the antrum. When combined by Woolf's technique (1955) these four series show an excess risk for group A compared to group O of 27% for cancers of the cardia, 16% for cancers of the middle zone, and 11% for cancers of the antrum. The diminishing excess of group A from cardia to antrum is, however, not statistically significant, neither when the trend is examined ($\chi_1^2 = 1{\cdot}89$) nor when the tumours in the cardia and fundus are compared with tumours in the pylorus and antrum ($\chi_1^2 = 1{\cdot}85$).

The frequency with which the Rhesus factor was found in the cancer cases did not differ significantly from that in the controls and was not related to the tumour site or the sex or age of the patient.

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References

Aird, I., Bentall, H. H., and Roberts, J. A. F. (1953). A relationship between cancer of the stomach and the ABO blood groups. *Brit. med. J.*, **1**, 799-801.

Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. F. (1954). The blood groups in relation to peptic ulceration and carcinoma of colon, rectum, breast, and bronchus. *Brit. med. J.*, **2**, 315-321.

Beasley, W. H. (1960). Blood groups of gastric ulcer and carcinoma. *Brit. med. J.*, **1**, 1167-1172.

Billington, B. P. (1956). Gastric cancer: Relationships between ABO blood groups, site, and epidemiology. *Lancet*, **2**, 859-862.

Buckwalter, J. A., Wohlwend, C. B., Colter, D. C., Tidrick, R. T., and Knowler, L. Q. (1957). The association of the ABO blood groups to gastric carcinoma. *Surg. Gynec. Obstet.*, **104**, 176-179.

Discombe, G., and Meyer, H. (1952). The capillary-tube method of rhesus testing. *Amer. J. clin. Path.*, **22**, 543-548.

Doll, R., Swynnerton, B. F., and Newell, A. C. (1960). Observations on blood group distribution in peptic ulcer and gastric cancer. *Gut*, **1**, 31-35.

Griffith, G. W. (1968). The sex ratio in gastric cancer and hypothetical considerations relative to aetiology. *Brit. J. Cancer*, **22**, 163-172.

Haddock, D. R., and McConnell, R. B. (1956). Carcinoma of stomach and ABO blood groups. *Lancet*, **2**, 146-147.

Hoskins, L. C., Loux, H. A., Britten, A., and Zamcheck, N. (1965). Distribution of ABO blood groups in patients with pernicious anaemia, gastric carcinoma, and gastric carcinoma associated with pernicious anaemia. *New Engl. J. Med.*, **273**, 633-637.

Jennings, D., Balme, R. H., and Richardson, J. E. (1956). Carcinoma of stomach in relation to ABO blood groups. *Lancet*, **2**, 11-12.

Kopeć, A. C. (1970). *The Distribution of the Blood Groups in the United Kingdom*. Oxford University Press, London.

McConnell, R. B. (1966). *The Genetics of Gastro-intestinal Disorders*. Oxford University Press, London.

Mosbech, J. (1958). ABO blood groups in stomach cancer. *Acta genet. (Basel)*, **8**, 219-227.

Woolf, B. (1955). On estimating the relation between blood group and disease. *Ann. hum. Genet.*, **19**, 2551-253.