A RELATIONSHIP BETWEEN CANCER OF STOMACH AND THE ABO BLOOD GROUPS

BY

IAN AIRD, Ch.M., F.R.C.S.*
Professor of Surgery, University of London

AND

H. H. BENTALL, M.B., F.R.C.S.
Senior Surgical Registrar, Postgraduate Medical School of London

With statistical analysis by J. A. FRASER ROBERTS, M.D., D.Sc., F.R.C.P.†
Lecturer in Medical Genetics, London School of Hygiene and Tropical Medicine

It was shown by Stocks (1950) that the standardized mortality of cancer of the stomach tended to be greater in northern than in southern towns in England. Stocks considered this to be consistent with the hypothesis that gastric cancer depends on an irritant. The only environmental factor which appeared to correlate in any way with the varying incidence of cancer of the stomach was hardness of water, towns with a water supply of moderate hardness tending to have lower rates than towns with soft or very hard water. This correlation was not a very close one. He showed also that the standardized mortality of cancer of the stomach was greater in towns with a low proportion of people of advanced age and in towns with a high proportion of men in unskilled and partly skilled occupations. Stocks did not explore, and apparently did not take into account, any possible genetic difference in the populations which he examined, nor was this possibility mentioned by Legon (1951, 1952) in attempts to correlate the geographical variations in the mortality from gastric cancer with variations in the organic content of the soil.

It occurred to one of us that there might be a correlation between the high northern incidence of cancer of the stomach and the genetic differences which are reflected in the ABO blood groups, the frequency of blood group O being greater, that of A less, in northern than in southern populations, B and AB being similar in all geographical areas in England and Scotland.

Previous published work on the association of the ABO blood groups with cancer has been on very small series of cases without adequate controls. The results have been diverse and without statistical significance (Alexander, 1921; Johannsen, 1925; Goldfeder and Fershing, 1937).

Method

A collection was made of cases of cancer of the stomach from a number of hospitals in England and Scotland, and the distribution of the ABO blood groups in patients with stomach cancer from each hospital was compared with the distribution of ABO blood groups in an equal number of patients chosen at random from the same hospital. The criterion of diagnosis has in most cases been a histological report on material obtained at operation or post-mortem examination, but in a few cases we have been dependent upon "a cast-iron clinical diagnosis based on radiological findings, operative findings, and clinical follow-up." Our survey concerns only cases treated in the past five years, for in most hospitals blood grouping has been dependable and accurately recorded only during this period. In most cases the blood groups have been determined by hospital laboratories, though in a very few cases the determinations have been made in the laboratory facilities of a clinical unit. Wherever possible, cross-checks against the case records were obtained from the hospital transfusion service.

For controls we have selected, where possible, a cross-section of the patients of the hospital concerned rather than data from the regional transfusion organization, since the hinterland of a hospital has not necessarily the same population as that served by the transfusion service. This type of control has been used in all the provincial and Scottish hospitals which we have approached, with two exceptions. In these two exceptions controls were not easily obtainable from the hospital population, and in the case of these, affecting 566 of our controls, the blood groups of an equal control number were estimated from their frequencies in very large numbers of the local population obtained from the local transfusion centre. In the London area we have used as controls the blood-group frequencies in a series of 10,000 from North-west London collected and published by Discombe and Meyer (1952). These frequencies are very close to those given by Fisher and Taylor (1940) for Southern England.

Results

Our results are presented in simple form in Table I, and are analysed statistically by Dr. Fraser Roberts in Table II. It is clear that throughout England the distribution of blood groups in cancer of the stomach is different from their

TABLE I.—*Percentage Distribution of Blood Groups in Cases of Stomach Cancer Compared with that in Equal Numbers of Controls*

	Cancer Cases				Controls			
	O	A	B	AB	O	A	B	AB
Newcastle (101 cases)	43·6	43·6	11·9	1·0	52·5	37·4	7·6	2·5
Leeds (217 cases)	42·4	47·9	7·4	2·3	46·5	40·3	7·1	6·2
Manchester (771 cases)	44·7	44·5	6·4	3·8	52·1	38·4	7·0	2·5
Liverpool (217 cases)	39·2	44·7	12·4	3·7	49·7	39·6	7·8	2·7
Birmingham (100 cases)	37·0	57·0	3·0	3·0	49·6	44·4	3·0	3·0
Total of Northern England (1,406 cases)	42·9	46·4	7·6	3·1	50·7	39·3	6·8	3·2
London (1,340 cases)	43·1	46·0	7·9	2·9	45·8	42·2	8·9	3·1
Scotland (478 cases)	51·2	36·4	9·6	2·7	52·6	32·5	11·7	3·1
Overall* figures (3,632 cases)	44·5	44·8	7·8	2·9	48·6	39·8	8·3	3·2

Gene Frequencies†

London		Northern England		Overall English + Scottish*	
Cancer	Control	Cancer	Control	Cancer	Control
p=0·287	0·261	0·290	0·236	0·278	0·243
q=0·058	0·064	0·056	0·047	0·056	0·058
r=0·657	0·678	0·655	0·713	0·668	0·698
1·002	1·003	1·001	0·996	1·002	0·999

* The overall figures are the sum of Northern England, London, Scotland, and four other scattered hospitals in the south of England (the latter individually too small for deductions but included for completeness).

† Calculated from nomograms published by Boyd (1937-8).

*From the Department of Surgery, Postgraduate Medical School of London.

†From the Burden Mental Research Department, Stoke Park Colony, Bristol, and the London School of Hygiene and Tropical Medicine.

distribution in the general population in England, and this difference is highly significant. Blood group A is more frequent, blood group O less frequent in patients suffering from cancer of the stomach than in the general population of the same locality. In every hospital from which data were obtained this same difference was observed. There thus seems to be a direct or indirect correlation between the A and O groups and susceptibility to cancer of the stomach in this country.

Discussion

Since cancer of the stomach is commoner in the North of England than in the South, while group A is less common in the North of England than in the South, it follows that this correlation with the blood groups is not responsible for the geographical differences in the incidence of cancer of the stomach demonstrated by Stocks. We must postulate that there are at least two influences operating in the cause of cancer of the stomach in England. One is an inherited influence with a relation to the A and O blood groups. The other, presumably environmental, must be assumed to be responsible for the high northern frequency of carcinoma of the stomach which Stocks showed. Since group A is commoner in the South of England than in the North and is more frequent in the cancer of stomach patients, it follows that the inherited factor operates in a direction opposite to the environmental factor of Stocks with regard to the geographical distribution of cancer of the stomach in England. Because of the low frequency of group A in the North of England, cancer of the stomach should be less common there than it is in the South, while Stocks has shown that it is in fact more common. Our figures thus add weight to the importance of the environmental factor which Stocks has postulated.

Any explanation of the apparent susceptibility to cancer of the stomach with which blood group A is invested, or protection against cancer of the stomach which is afforded by the possession of blood group O, is exceedingly difficult. It is clear that the susceptibility to cancer of the stomach or the protection against cancer of the stomach which our figures suggest must be inherited, since blood groups A and O are inherited. Our preliminary interpretation of the data was that they revealed high-incidence and low-incidence strains in the population of England with respect to cancer of the stomach. Such a hypothesis, however, would be difficult to substantiate in the light of the known facts of Britain's genetic history. The essential difference between patients with cancer of the stomach and controls affects blood groups O and A in a reciprocal fashion, B and AB retaining an equal level in both groups throughout. This reciprocity between O and A, and the constancy of B and AB, which are characteristic of the ethnological pattern of the population in this country, do perhaps strengthen an anthropological (i.e., ethnological) hypothesis. It would still be difficult, however, to devise a genetic explanation for the correlation of the blood groups with cancer of the stomach based on the known ethnological origins of the population of this country.

The alternative explanation would in its turn offer difficulty to the pathologist. It is hard to conceive any mechanism whereby the antigen A could offer a slight but definite susceptibility to, or the antigen O offer a slight but definite protection against, such a disease as cancer of the stomach. Further speculation would appear to be unprofitable at this stage. Extension of the data to cover other forms of malignant disease and other populations ethnologically alien to ours might make it clear whether an ethnological or a serological hypothesis is more tenable.

Some other conclusions may be drawn from our figures. It is generally assumed that the ABO blood groups have no selective value, at least in adults, the possession of any one of the groups conferring neither advantage nor disadvantage on its possessor with respect of survival. Our figures would seem to show that blood group A has in England at least a negative selective value, blood group O a positive selective value because of the greater and lesser risk of cancer of the stomach which they respectively offer. Admittedly cancer of the stomach most often affects individuals after their most active reproductive period, and the transmission of the gene for group A is in most cases not prevented. Nevertheless, cancer of the stomach does affect younger people on occasion, and blood group A must therefore be regarded as having some negative, and blood group O some positive, selective value, however slight.

It is possible that there is some intermediate influence affording an indirect rather than a direct correlation between these blood groups and cancer of the stomach. Achlorhydria and pernicious anaemia, for example, come to mind as possible links.

Cancer of the stomach is commoner among the unskilled and semi-skilled than among the professional and clerical orders. We have attempted, but failed, to find a method to correlate blood groups with social class. It seems unlikely that in this country there should be differences of blood-group distribution in the various social orders, and Fraser Roberts (1953) has informed us that no such class difference appears to exist in at least one English locality.

The inheritance of cancer of the stomach has been previously suspected. One need only mention the Bonaparte family in this connexion.

Further evidence could be obtained from studies on the incidence of cancer of the stomach in twins. Gorer (1937–8) reviewed the literature on cases of cancer of all sites occurring in twins. He recorded four pairs of monozygotic twins and one pair of dizygotic twins of which each pair developed cancers of the stomach either simultaneously or within a year of each other. He concluded : (1) that heredity and environment should not be regarded as alternative causes of cancer, and that genetic factors must be regarded as influencing the sensitivity of individuals to stimuli capable of giving rise to malignancy ; (2) that evidence obtained from studies with pure lines of mice shows that such genetic factors can be of great importance but do not fix the time at which the tumour will appear ; (3) the likelihood of obtaining simultaneous development of identical tumours in man is probably much lower ; and (4) that tumours of the alimentary canal, and especially the stomach, appear to be influenced by genetic factors.

Our findings would seem to substantiate that inheritance plays some part in the susceptibility to or protection against cancer of the stomach. The data respecting twins suggest that susceptibility is more important in this connexion than resistance.

We have explored a little the geographical and ethnological aspects of the correlation between blood groups and cancer of the stomach beyond the British Isles, but the collection of data is difficult. We have, however, obtained with the help of Dr. Holländer and his Swiss colleagues the most striking figures from Basle, where the incidence of blood groups in 704 cases of cancer of the stomach is O 36.22%, A 53.12%, B 7.53%, AB 3.13%, while in 4,518 controls from the general population the frequencies are O 41.65%, A 45.06%, B 9.03%, AB 4.26%. These differences are highly significant.

Certain North American Indian tribes have a very high incidence of group A indeed. If it could have been shown that they had also a high incidence of cancer of the stomach the hypothesis that predisposition to or protection against cancer of the stomach depended directly on an antigenic or a serological factor would be greatly strengthened. The American Bureau of Indian Affairs has assisted us in this matter, but the Indian tribes with high incidence of group A are so small, and their expectation of life is so low, that figures about cancer of the stomach are not available.

This technique of examining the distribution of blood groups in a disease is capable of further extension. It could be applied most conveniently to those diseases which require blood grouping for their treatment by transfusion, or which are commonly submitted to an operation which requires transfusion. We propose to examine cancer of the rectum, cancer of the colon, cancer of the lung, brain

tumours, and the blood dyscrasias with particular reference to pernicious anaemia, and peptic ulceration for other possible relationships with the blood groups. In view of the virus work of Bittner it would be desirable to apply the method also to cancer of the breast, though transfusion is seldom required for a patient submitted to radical amputation of the breast, and a large enough series might be difficult to collect.

Statistical Analysis

It is clear that there is practically no difference in the proportions of those with gene B for England and Scotland : $\frac{(B + AB)}{(O + A + B + AB)}$ = 11.08% and 11.57% respectively. The Swiss data do show a difference—10.65% and 13.28%—but this is not significant : χ^2 (with Yates's correction) = 3.504. What the British data do show is a reciprocal difference in the relative proportions of O and A. Hence the simplest and most straightforward analysis is to examine the ratio $\frac{A}{(A + O)}$. This is done in Table II. The conclusions are clear. The total χ^2 for the difference in A/(A + O) between cancer patients and controls is enormously significant, P<1/10,000, and the seven separate areas are perfectly homogeneous in this respect.

TABLE II.—*Analysis of Differences in Relative Proportions of Groups O and A in Cancer Patients and Controls*

1	2	3	4	5	6	7	8	9
	Cancer Cases		Controls		A/(A+O)%			
	O	A	O	A	Cancer	Control	Diff. Cancer-Control	χ^2
Manchester ..	343	349	402	295	50·43	42·32	+8·11	9·183
Liverpool ..	85	97	108	86	53·30	44·33	+8·97	3·022
Leeds ..	92	104	102	87	53·06	46·03	+7·03	1·902
Birmingham ..	37	57	50	44	60·64	46·81	+13·83	3·616
Newcastle ..	44	44	53	37	50·00	41·11	+8·89	1·418
London ..	578	617	614	565	51·63	47·92	+3·71	3·267
Scotland ..	245	174	252	155	41·53	38·08	+3·45	1·022
Total ..	1,424	1,442	1,581	1,269	50·31	44·53	+5·78	19·198

Col. 9: χ^2 separately from the eight 2 × 2 tables.

Analysis	D. of F.	χ^2
Sums of χ^2 for seven areas separately ..	7 ..	23·430
Total for England and Scotland	1 ..	19·198
Difference attributable to heterogeneity ..	6 ..	4·232

As might be expected, weighting makes practically no difference. The mean difference becomes +5.80 instead of +5.78, and the χ^2 for heterogeneity 4.121 instead of 4.232.

The frequencies in the controls correspond reasonably with what would be expected in the regions concerned. Fisher and Taylor's (1940) figure for $\frac{A}{(A + O)}$ for the South-east of England is 48.8, against that given for London in the present paper of 47.9. A figure of 45.5 would very fairly represent England east of the Pennines over an area stretching from Leeds, Bradford, and Hull to Newcastle-upon-Tyne. The northern area controls give 43.4. Thus the ratios for controls are lower than expectation, though only slightly so; in any event the ratios for the cancer series are far higher than those for the corresponding general populations.

Conclusions

The frequency of blood group A is greater and the frequency of blood group O less in patients suffering from cancer of the stomach than in the general population of the locality in which they live.

From this correlation of blood groups and cancer of the stomach it follows that there is an inherited element in the susceptibility or to protection against cancer of the stomach.

This inherited element is not responsible for the known geographical differences in the incidence of cancer of the stomach in England.

The environmental element which Stocks has postulated in the aetiology of cancer of the stomach is more potent than would appear from the geographical incidence of the disease in England.

It is not possible from our present data to deduce whether the relationship between blood groups A and O and cancer of the stomach is dependent upon high- and low-incidence strains of cancer of the stomach in the general population of Great Britain or upon some specific effect of the antigens A and O.

In view of the relationship with cancer of the stomach in Great Britain it is no longer possible to regard blood groups A and O (in adults) as being devoid of selective value.

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Ciba Laboratories have recently presented a film on senile obliterative arteritis of the legs to the B.M.A. Film Library. The course, diagnosis, and management of the condition are demonstrated by members of the university surgical unit, Manchester Royal Infirmary. The film is a 16-mm. colour film with commentary, and it runs for about 55 minutes. It is divided into three parts : the first deals with the pathological anatomy, the second with clinical examination, and the last with the general and local management of intermittent claudication and severe ischaemia. The producer was Dr. Brian Stanford.