ABO BLOOD GROUPS AND CANCER OF OESOPHAGUS, CANCER OF PANCREAS, AND PITUITARY ADENOMA

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It is a striking fact that up to the present time the diseases for which really strong evidence of associations with the ABO blood groups have emerged are, with one exception, conditions of, or associated with, the upper part of the gastro-intestinal tract. The one exception is Helmbold's (1958) finding of a highly significant excess of group A among women suffering from uterine cancers. Hence diseases of the gastro-intestinal tract not hitherto studied are of particular interest. Cancer of the pancreas and cancer of the oesophagus are diseases for which serious operation is often required, hence blood-grouping is frequently carried out and retrospective studies become possible. Neither condition is, however, common enough to make it easy to secure adequate numbers. The series reported in this paper are distinctly small, but it is hoped that other workers may be able to add further samples in due course.

The third disease, chromophobe adenoma of the pituitary, is also of particular interest because of the finding by Mayr, Diamond, Levine, and Mayr (1956) of a very marked excess of group O, which contrasted with the absence of any apparent blood-group association in other intracranial tumours. The further findings published by Damon (1957) weakened the evidence, but clearly a problem remained in regard to which the collection of further data was highly desirable.

We were further encouraged to investigate chromophobe adenoma of the pituitary gland when we recollected that this is not, strictly speaking, a brain tumour; the anterior pituitary from which chromophobe tumour grows develops from what is really pharyngeal epithelium, and the anterior pituitary is much more closely related to the epithelium of the salivary glands, whose tumours have shown an extremely strong ABO blood-group association (Cameron, 1958), than to the nerve cells of the brain.

Control Series

The control series used in the present paper are listed in Table I. The London sample is that of Discombe and Meyer (1952), which we have used before (Aird, Bentall, Mehigan, and Roberts, 1954). The Oxford sample was provided by the Nuffield Blood Group Centre of the Royal Anthropological Institute, and has also been used before (McConnell, Pyke, and Roberts, 1956). All the other series have kindly been provided by the Nuffield Blood Group Centre and are based on consecutive registrations of new donors by the National Blood Transfusion Service. Those for Birmingham, Cardiff, Liverpool, and Sheffield are enlarged samples which include the smaller numbers used on previous occasions. At five centres, however—namely, Bristol, Manchester, Newcastle, Glasgow, and Leeds—entirely new samples have been substituted for those previously used. We have done this deliberately, as it serves to emphasize an important point in the selection of population controls.

Some writers have been concerned over the choice of population controls and the supposed errors or discrepancies to which they might lead. Manuila (1958) is especially critical in this respect. Some detailed comments on his contentions have been made in a recent paper (Roberts, 1959a). One important point is that successive rationally selected samples from the same areas show no more fluctuation of frequencies from one to another than would be expected by chance, and this is allowed for in estimating significance. At the Nuffield Blood Group Centre some hundreds of thousands of consecutively registered blood donors have been counted and successive samples from the same areas repeatedly compared. The differences have turned out to be extremely close to those theoretically expected (A. C. Kopec, 1959, personal communication). Essentially the same conclusions are reached by Buckwalter and Knowler (1958), who have carried out a detailed analysis on control samples in Iowa amounting to 50,000 individuals. The one series which did yield significant discrepancies was the professional blood donors, who differed from the others in being higher in group O. This is not surprising, as usefulness is likely to be a factor in such a specially selected or self-selected group.

At the five centres specially mentioned above, the new samples are totally different from the old, and a comparison of the figures is given in Table II. The percentage frequencies are closely similar in each instance. The only differences which even approach significance at the 5% level are the distributions for the AB's at Bristol

TABLE I.—*Control Samples*

Centre	O	A	B	AB	Total
London ..	4,578	4,219	890	313	10,000
Oxford ..	2,888	2,839	557	208	6,492
Birmingham ..	4,559	4,038	751	242	9,590
Bristol	861	905	164	59	1,989
Cardiff ..	403	357	86	28	874
Liverpool ..	4,124	3,131	736	211	8,202
Manchester ..	2,570	2,221	490	150	5,431
Sheffield ..	1,837	1,709	324	132	4,002
Leeds	2,966	2,582	515	197	6,260
Newcastle ..	1,971	1,532	388	141	4,032
Glasgow ..	3,150	1,911	667	200	5,928

TABLE II.—*Comparison of Alternative Control Samples from the Same Centres*

Centre	Sample	No.	Percentage Frequencies			
			O	A	B	A
Bristol	Present	1,989	43·3	45·5	8·2	3·0
	Previous	*40,740*	*44·0*	*44·1*	*8·2*	*3·6*
Manchester	Present	5,431	47·3	40·9	9·0	2·8
	Previous	*9,370*	*48·4*	*40·3*	*8·4*	*2·9*
Newcastle	Present	4,032	48·9	38·0	9·6	3·5
	Previous	*13,572*	*48·6*	*38·8*	*9·7*	*2·9*
Glasgow	Present	5,928	53·1	32·2	11·3	3·4
	Previous	*5,898*	*53·9*	*32·3*	*10·8*	*3·0*
Leeds*	Present	5,548	53·5	46·5	—	—
	Previous	*21,164*	*53·7*	*46·3*	—	—

*O and A only

and Newcastle. AB's are essentially irrelevant to the comparisons in this paper, and, in any event, the previous figure for Bristol was somewhat suspect. As already mentioned, all the new samples were provided by the Nuffield Blood Group Centre. The previous ones were obtained very differently. At Bristol the original count was made on blood donors during the early part of the war (Roberts, 1948). Similarity to the Nuffield Centre frequencies is all the more remarkable because the previous groupings were known to include a not inappreciable proportion of errors, as described in the paper quoted. At that time it was the practice to group donors, often in the field, on registration, and to correct these as necessary when donations of blood were made. This practice was soon afterwards abandoned. At Manchester the previous series is a very good one given by Stratton (1953), but it refers to the Manchester hospital area instead of the city, as is the case with the new series. At Glasgow and Leeds the samples were different, and at Leeds, as at Bristol, the first samples were based on wartime groupings, and so were obtained many years before the new sample.

We have emphasized the correspondences because they indicate very clearly that rationally selected control population samples for given areas turn out to give closely similar results. The differences between them are trivial in comparison with those found in connexion with proved blood-group and disease associations; for, of course, it is only relatively very large associations that can be detected with samples of practicable size.

Carcinoma of the Pancreas

At the various centres listed all cases of cancer of the pancreas that had been blood-grouped were included. It is possible that some of these may have been carcinomas of the ampulla of Vater or of the lower end of the common bile-duct, for when these are advanced and have spread into the pancreas it is not always possible to distinguish their precise anatomical origin. The basic data are given in Table III.

With such small numbers it does not seem worth while complicating the table with subdivisions by age and sex. These have been recorded, however, and may be used on a further occasion. Table IV shows the findings in briefest summary. The control frequencies are simply weighted according to the number of patients at each centre. The comparison is given for illustration only, and, of course, no statistical tests can be carried out on these figures.

TABLE III.—*Cancer of Pancreas. Basic Data*

Centre	O	A	B	AB	Total
London	39	56	10	4	109
Birmingham	24	22	6	1	53
Bristol	21	26	5	2	54
Cardiff	17	21	4	1	43
Liverpool	58	67	4	4	133
Manchester	43	30	2	3	78
Sheffield	5	18	3	0	26
Leeds	11	8	3	0	22
Newcastle	17	18	5	0	40
Glasgow	37	19	5	1	62
Total	272	285	47	16	620

TABLE IV.—*Cancer of Pancreas. Brief Summary*

Blood Group	Cancer of Pancreas	Controls*	Increase or Decrease on Controls
O	43·9%	47·9%	−8·4%
A	46·0%	40·1%	+14·7%
B	7·6%	9·1%	−16·5%
AB	2·6%	3·0%	—

* Controls weighted according to number of patients at each centre.

The method we now use for the combination of data from different centres is that of Woolf (1955), which is particularly appropriate for the purpose. This method has the advantage that the results appear in a form with a simple and direct physical meaning, with the further advantage that centres with distinctly different ABO frequencies in their populations can be combined without introducing bias.

In Table V the figures shown in the columns giving relative incidences are obtained by simple cross-multiplication. Thus, for example, the results for

TABLE V.—*Cancer of Pancreas. Incidence in Group A Relative to Incidence in Group O and in Groups (O+B)*

Centre	Relative Incidence A:O	χ^2	Relative Incidence A:(O+B)	χ^2
London	1·56	4·47	1·48	3·99
Birmingham	1·03	0·01	0·96	0·02
Bristol	1·18	0·30	1·13	0·20
Cardiff	1·39	0·99	1·37	0·99
Liverpool	1·52	5·38	1·68	8·47
Manchester	0·81	0·80	0·92	0·13
Sheffield	3·87	7·13	2·85	6·02
Leeds	0·84	0·15	0·77	0·35
Newcastle	1·36	0·83	1·26	0·52
Glasgow	0·85	0·35	0·90	0·13
Mean weighted relative incidence	1·25		1·27	
χ^2 Total		20·41		20·82
χ^2 Diff. from unity. D. of F.=1		6·57		8·36
χ^2 Heterogeneity. D. of F.=9		13·84		12·46
P Heterogeneity		0·13		0·2

London show 39 O's and 56 A's among patients with cancer of the pancreas, as against 4,578 O's and 4,219 A's amongst the controls.

$$\frac{(56 \times 4{,}578)}{(39 \times 4{,}219)} = 1.56$$

So we can say that this sample indicates an incidence of the disease of 1.56 in persons of group A as compared with 1.0 in persons of group O. As regards the O and A comparison, it will be seen that at three centres—London, Liverpool, and Sheffield—the departure from unity is significant at the 5% level. At four centres there is a non-significant excess of A, but at three—Manchester, Leeds, and Glasgow—group O is in excess. The combination of these data yields an average weighted relative incidence of 1.25 in group A as against 1.0 in group O. χ^2 for the deviation from unity, with 1 degree of freedom, is 6.57, corresponding to a probability of a little more than 1 in 100. Table IV shows that the reduction in group B as against the controls is even greater than that on group O. Accordingly the last two columns of Table V give a comparison of the incidence in group A relative to that in groups O and B combined. The significance of the difference from unity is somewhat increased, the χ^2 of 8.36 corresponding to a probability of about 1 in 250. For both comparisons the differences between centres do not exceed those to be expected by chance.

There is evidence of some strength that cancer of the pancreas is commoner in persons of group A than in persons of groups O or B. But we should not like to attach too much weight to this result, and hope that other series will be forthcoming, which will disprove, or prove beyond reasonable doubt, the reality of this association. But at least the present evidence is rather

more than suggestive. If it is ultimately confirmed, this is a highly interesting finding because of the known relationship between diabetes and carcinoma of the pancreas. It has long been known that carcinoma of the pancreas is commoner in diabetics than in non-diabetics, and it has appeared that blood group A is possibly commoner in diabetics than in the general population. The association between group A, diabetes, and carcinoma of the pancreas strongly suggests an analogy with the association of blood group A with pernicious anaemia and with carcinoma of the stomach, for it is known that carcinoma of the stomach is commoner in patients who suffer from pernicious anaemia than in population controls.

In this connexion Buchanan and Higley (1921) reported an examination of the ABO blood groups of patients with jaundice at the Mayo clinic. This group of jaundiced patients showed an excess of A, which Buchanan and Higley regarded as unimportant but which, when statistically analysed, shows a significant excess of group A. Buchanan and Higley separated from the figures for jaundice a series of patients who suffered from gall-stones, so that the jaundice series would in all probability include a greater number of carcinoma of the pancreas. The excess of A in the jaundice group may have reflected a number of cases of carcinoma of the pancreas in the jaundice series.

Carcinoma of the Oesophagus

This series was restricted to carcinomas of the oesophagus which were known to have been squamous in type: it was thought that this restriction would prevent the inclusion of any carcinomas of the stomach spreading up to the lower part of the oesophagus. These would presumably be glandular.

TABLE VI.—*Cancer of Oesophagus. Basic Data*

Centre	O	A	B	AB	Total
London	58	61	15	3	137
Birmingham	28	33	7	1	69
Bristol	10	13	2	1	26
Cardiff	24	17	5	2	48
Liverpool	68	64	10	3	145
Manchester	27	20	3	1	51
Sheffield	7	10	4	0	21
Leeds	15	16	3	3	37
Newcastle	12	8	3	1	24
Glasgow	25	18	8	1	52
Total	274	260	60	16	610

TABLE VII.—*Cancer of Oesophagus. Brief Summary*

Blood Group	Cancer of Oesophagus	Controls*	Increase or Decrease on Controls
O	44·9%	47·9%	−6·3%
A	42·6%	40·1%	+6·2%
B	9·8%	9·0%	+8·9%
AB	2·6%	2·9%	—

* Controls weighted according to number of patients at each centre.

The basic data are shown in Table VI, and a brief summary is given in Table VII. The detailed comparison which is shown in Table VIII indicates an average relative incidence of the disease of 1.14 in persons of group A as compared with 1.0 in persons of group O. χ^2 for the difference from unity is only 2.17, so it is not significant at the 5% level. Actually the observed figure is compatible with the null hypothesis that there is no association; but it is equally compatible with a true incidence of 1.2, which represents the very highly significant excess on the large numbers of cancer of the stomach so far published.

TABLE VIII.—*Cancer of Oesophagus. Incidence in Group A Relative to Incidence in Group O*

Centre	Relative Incidence A:O	χ^2
London	1·14	0·51
Birmingham	1·33	1·23
Bristol	1·24	0·25
Cardiff	0·80	0·47
Liverpool	1·24	1·49
Manchester	0·86	0·27
Sheffield	1·54	0·75
Leeds	1·23	0·32
Newcastle	0·86	0·11
Glasgow	1·19	0·30
Mean weighted relative incidence	1·14	
χ^2 Total		5·70
χ^2 Diff. from unity. D. of F. = 1		2·17
χ^2 Heterogeneity. D. of F. = 9		3·53
P Heterogeneity		0·9

One other series has been recorded. Billington (1957) reports the following series from Sydney: O, 50; A, 54; B, 12; AB, 3, against control frequencies of O, 14,672; A, 11,514; B, 2,912; AB, 902. χ^2 for the O:A comparison is 2.64. If his figures are added to those of Table VIII the total χ^2 for the deviation from unity becomes 4.03, and so is just significant at the 5% level. The areas, adding his material, are still perfectly homogeneous. Hence there is already some slight indication that cancer of the oesophagus may ultimately prove similar to cancer of the stomach in showing an increased incidence in persons belonging to group A. It is also emphasized once again how large numbers must be in studies of this kind. A series of 600 patients is quite inadequate for detecting even a moderately large association; the counts needed are to be numbered in thousands rather than hundreds, and we trust that further results will be forthcoming.

Adenoma of the Pituitary

Mayr *et al.* (1956) recorded the ABO blood-group frequencies of 367 patients with brain tumours of various kinds. With the exception of 123 with pituitary adenomata, the figures were unremarkable. But for the pituitary tumours the figures were O, 74; A, 24; B, 19; AB, 6. The excess of group O and deficiency of group A were thus truly striking and very highly significant. Later, Damon (1957) published a further series from New York, but, though he still found some excess of O, the association was very much smaller (151 whites gave an O:A ratio of 1.33 and 34 negroes 1.35). Our own series consists of 408 patients with pituitary adenomata drawn from seven centres. The basic data are shown in Table IX; a brief summary is given in Table X and a detailed analysis in Table XI.

It will be seen from Table X that the overall differences between the patients and the control series are

TABLE IX.—*Chromophobe Adenoma of Pituitary. Basic Data*

Centre	O	A	B	AB	Total
London	80	67	18	6	171
Oxford	36	40	4	2	82
Birmingham	15	9	1	0	25
Bristol	10	11	3	0	24
Cardiff	11	10	3	1	25
Liverpool	15	19	3	0	37
Manchester	26	12	6	0	44
Total	193	168	38	9	408

TABLE X.—*Chromophobe Adenoma of Pituitary. Brief Summary*

Blood Group	Adenoma	Controls*
O	47·3%	46·1%
A	41·2%	42·1%
B	9·3%	8·8%
AB	2·2%	3·0%

* Controls weighted according to number of patients at each centre.

TABLE XI.—*Chromophobe Adenoma of Pituitary. Incidence in Group O Relative to Incidence in Group A*

Centre	Relative Incidence O : A	χ^2
London	1·10	0·33
Oxford	0·88	0·28
Birmingham	1·48	0·85
Bristol	0·96	0·01
Cardiff	0·97	0·00
Liverpool	0·60	2·19
Manchester	1·87	3·21
Mean weighted relative incidence	1·04	
χ^2 Total		6·87
χ^2 Diff. from unity. D. of F. = 1		0·17
χ^2 Heterogeneity. D. of F. = 6		6·70
P Heterogeneity		0·4

negligible. The weighted mean relative incidence in group O as compared with group A is only 1.04, as shown in Table XI. Nor is there significant heterogeneity between centres. At an earlier stage, when figures were briefly reported (Roberts, 1959b), patients at Manchester gave the rather unusual figures—O, 22; A, 6—which led to a significant χ^2 at this centre. Further figures from Manchester, however, included 4 O's and 6 A's, so this suggestion of an excess of O at one centre, similar to that found by Mayr *et al.*, has been reduced to non-significance.

Rhesus Groupings

Fairly adequate numbers of groupings (positive and negative) are available for patients with carcinoma of the pancreas and carcinoma of the oesophagus. The results are shown in Table XII. With both diseases the proportion of rhesus-negatives is within the range to be expected in the general population of Great Britain.

TABLE XII.—*Rhesus Groupings*

	Rh+	Rh−	Total	% Rh−
Cancer of pancreas	416	82	498	16·5
,, ,, oesophagus	418	93	511	18·2

Summary

620 patients suffering from cancer of the pancreas show an excess of group A and a deficiency of groups O and B. The differences are moderately significant. The increased incidence in group A relative to group O corresponds to a probability of about 1 in 100, and in group A relative to groups O and B combined about 1 in 250.

610 patients suffering from cancer of the oesophagus show some excess of group A, but this is non-significant. On these numbers, however, the figures are not incompatible with an incidence in group A as high as that found in cancer of the stomach.

408 patients with adenomata of the pituitary gave ABO frequencies closely similar to those of the controls.

The proportion of rhesus-negatives among those with cancer of the pancreas and of the oesophagus is within the range expected in Great Britain.

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