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# THE BLOOD GROUPS IN RELATION TO PEPTIC ULCERATION AND CARCINOMA OF COLON, RECTUM, BREAST, AND BRONCHUS

## AN ASSOCIATION BETWEEN THE ABO GROUPS AND PEPTIC ULCERATION

BY

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We have previously shown an association between the ABO blood groups and cancer of the stomach, group A being significantly commoner in patients suffering from cancer of the stomach than in controls drawn from the same hospitals (Aird, Bentall, and Roberts, 1953). The further diseases for which fairly large numbers have so far been obtained are peptic ulceration and carcinoma of the colon, rectum, breast, and bronchus. The results are presented in this paper, which also includes some data on Rhesus grouping. In addition, further calculations have been made on the figures for cancer of the stomach already published. A detailed examination of our data follows. The results have proved remarkably clear-cut : blood group O is strikingly high and the other three groups correspondingly low in patients suffering from peptic ulcer. The three cancers now studied, unlike cancer of the stomach, showed no significant blood-group association.

### Collection of Data

The survey was carried out at 12 hospitals in England, and covers cases treated during the years 1948–53. At the first hospital visited, St. Mark's, London, cases from 1946 were included, but, as the blood groups were not often recorded in the earlier years, surveys in hospitals subsequently visited were restricted to 1948–53. It was also felt that during this period blood-grouping techniques were uniform and reliable.

In such a study it was imperative to have rigid criteria of diagnosis in each disease. For the carcinomas, only cases proved by histological report on material obtained by biopsy, operation, or post-mortem examination were accepted. In peptic ulceration the criterion was a macroscopic report (operation or gastroscopy). The majority of these cases were perforated or bleeding ulcers or those submitted to elective surgery, for it is only in these cases that the blood group is often recorded. Thus our series does not include many medically treated cases and therefore is not representative of all patients suffering from peptic ulceration. Similarly, the majority of the carcinoma cases were those surgically treated.

The same system of collection was used throughout the survey. A member of the team (J. A. M.) visited each hospital and extracted the data directly from the patients' case notes. In all, more than 13,000 case records were scrutinized, and, of these, 7,702 were satisfactory as regards diagnosis and record of blood group. In the final analysis a further small number were eliminated because the patient was suffering from more than one disease. This included in particular 27 patients suffering from peptic ulcer and carcinoma of the stomach or other organs.

For each patient the following items were recorded : disease, subdivision of disease, sex, marital status, age, year of diagnosis, ABO and Rh blood group, occupation, social class, and place of residence. All the information was coded and transcribed to punched cards for analysis. The code is too long for publication, but a copy will be supplied on request. Not all these items have been used for the present paper, but it is hoped to make use of them in the future.

### Selection of Controls

Controls against which to match the blood-group frequencies observed in the different diseases can be selected in two ways. Series for the general populations of the areas concerned may be used, these being usually derived from the records of the National Blood Transfusion Service ; or, alternatively, an attempt may be made to secure figures for patients suffering from other diseases at the hospitals concerned. The advantages of the former method are great. Series based on, say, consecutive registrations of blood donors should be unbiased. The numbers available will usually be very much larger than those of the disease groups, so that errors are reduced and smaller differences detected than would otherwise be possible. Moreover, the work has been done already, so that the labour of collecting data is much reduced.

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Nevertheless, circumstances could be conceived in which the blood-group frequencies of patients at a particular hospital might differ from those of the area in which it is situated. Hence, while using population controls for the comparisons, it is advisable to see that the hospital populations do not differ significantly from the general population samples. This, however, is easier said than done. In a retrospective survey the groupings available will be confined to diseases in which blood transfusion may become necessary. Some of these may show associations with the blood groups—for example, the cancer of the stomach of the previous paper, or the peptic ulcer of the present investigation. At a general hospital, patients suffering from peptic ulcer form a relatively high proportion of those grouped. At one general hospital which we have investigated it is more than 30%. This is quite enough to explain why most of the hospital controls used in the previous study were too high in O and too low in the other groups, as was then pointed out. Incidentally, it probably also explains the perennial complaint of transfusion officers in large general hospitals that more group O blood is demanded for patients than the proportion of group O in the general population and in the donor pools would justify; moreover, particularly large amounts of blood are often needed by patients suffering from peptic ulcers.

Clearly, then, consecutive series of hospital groupings irrespective of diagnosis cannot safely be used. Undoubtedly the best second-line control is the discovery that at the same centres and the same hospitals certain of the diseases being studied give negative results, yielding frequencies which do not differ significantly from those of the population controls. This is what has happened for three of the diseases included in the present study.

The population control figures used in this paper are given in Table I. The London series is that of Discombe and Meyer (1952), and is based on 10,000 consecutive groupings of pregnant women in North-west London. The figures for Manchester are given by Stratton (1953). Those for Newcastle-upon-Tyne are taken from Roberts (1953), and refer to a count of the National Blood Transfusion panels for Newcastle and Gateshead, as mentioned in the appendix to that paper. The large series, for O and A only, for Leeds, is that of Fisher (Fisher and Roberts, 1943). The smaller complete series for Leeds, as well as those for Birmingham and Liverpool, were kindly provided by the Nuffield Blood Group Centre of the Royal Anthropological Institute.

TABLE I.—*Population Controls Used*

| Area | Group O | Group A | Group B | Group AB |
|---|---|---|---|---|
| London .. .. | 4,578 | 4,219 | 890 | 313 |
| Birmingham .. | 458 | 442 | 94 | 39 |
| Manchester .. | 4,532 | 3,775 | 788 | 275 |
| Newcastle .. | 6,598 | 5,261 | 1,321 | 392 |
| Leeds .. { | 11,359* | 9,805* | — | — |
| Leeds .. { | 983 | 857 | 161 | 61 |
| Liverpool .. | 462 | 402 | 97 | 28 |

* Used for A/O comparisons.

It is interesting to note that for the relative proportions of O and A the two series for Leeds are closely similar, the difference being far below the level of significance. Similarly, Discombe and Meyer's 10,000 for London do not differ significantly from the very large compilation of Fisher and Taylor (1940) for southern England (O, 48,162; A, 45,958; B, 9,059; AB, 3,298). $\chi^2$ for three degrees of freedom is 4.29, or, for O and A only, 2.32 for one degree of freedom. For most of this country large figures for blood-group frequencies are available, and all the indications are that they are accurate within a very small margin of error. Even more complete and systematic mapping will be available later, when further data have been collected by the Nuffield Blood Group Centre as well as by individual workers. The interest of the variations is primarily anthropological, but in addition those concerned with other aspects of blood-group frequencies are fortunate in having available so excellent a body of data against which to match their own series.

## Results

The main basic data are shown in Table II. The chief findings emerge clearly from the summary given in Table III. The control figures are taken from Table I, being weighted in each instance by the numbers in the corresponding disease group in the various areas. In Table III the figures for cancer of the stomach are repeated from the previous paper, though for England only, omitting Scotland. The Scottish sample was drawn from Glasgow, Aberdeen, Perth, and Dundee, and at the moment adequate population controls are not available for what are probably serologically heterogeneous areas.

TABLE II.—*Basic Data*

| Disease | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | O | A | B | AB | O | A | B | AB |
| Gastric ulcer: | | | | | | | | |
| London .. | 187 | 149 | 30 | 7 | 127 | 79 | 16 | 4 |
| Manchester .. | 84 | 58 | 9 | 2 | 38 | 32 | 6 | 3 |
| Newcastle .. | 71 | 42 | 11 | 6 | 31 | 16 | 5 | 2 |
| Total .. | 342 | 249 | 50 | 15 | 196 | 127 | 27 | 9 |
| Duodenal ulcer: | | | | | | | | |
| London .. | 459 | 264 | 59 | 20 | 76 | 47 | 15 | 6 |
| Manchester .. | 190 | 124 | 32 | 12 | 35 | 24 | 5 | 1 |
| Newcastle .. | 254 | 137 | 26 | 6 | 34 | 20 | 4 | 1 |
| Total .. | 903 | 525 | 117 | 38 | 145 | 91 | 24 | 8 |
| Total peptic ulcers*: | | | | | | | | |
| London .. | 696 | 450 | 93 | 30 | 215 | 129 | 31 | 11 |
| Manchester .. | 283 | 188 | 41 | 14 | 78 | 58 | 13 | 4 |
| Newcastle .. | 329 | 183 | 37 | 12 | 67 | 36 | 9 | 4 |
| Total .. | 1,308 | 821 | 171 | 56 | 360 | 223 | 53 | 19 |
| Cancer of colon and rectum: | | | | | | | | |
| London .. | 406 | 407 | 80 | 26 | 259 | 269 | 48 | 19 |
| Birmingham | 136 | 127 | 21 | 11 | 101 | 100 | 19 | 5 |
| Manchester .. | 90 | 72 | 12 | 5 | 73 | 80 | 25 | 2 |
| Newcastle .. | 57 | 49 | 12 | 6 | 42 | 30 | 8 | 2 |
| Total .. | 689 | 655 | 125 | 48 | 475 | 479 | 100 | 28 |
| Cancer of bronchus: | | | | | | | | |
| London .. | 148 | 157 | 36 | 12 | 18 | 5 | 7 | 1 |
| Birmingham | 118 | 102 | 26 | 5 | 10 | 8 | 4 | 1 |
| Manchester .. | 150 | 134 | 33 | 6 | 10 | 6 | 1 | — |
| Total .. | 416 | 393 | 95 | 23 | 38 | 19 | 12 | 2 |
| Cancer of breast: | | | | | | | | |
| London .. | — | — | — | — | 34 | 35 | 11 | 5 |
| Birmingham | — | — | — | — | 232 | 219 | 40 | 11 |
| Manchester .. | — | — | — | — | 155 | 124 | 34 | 12 |
| Newcastle .. | — | — | — | — | 48 | 39 | 17 | 1 |
| Total .. | — | — | — | — | 469 | 417 | 102 | 29 |

* These totals include in addition to the gastric and duodenal ulcers 113 double ulcers, duodenal and gastric, and 32 classified as "prepyloric."

The proportion of patients of group O is greatly increased in peptic ulcer, all the other groups being reduced, and in very nearly the same proportion. The difference in relative proportions of O and A, of O and B, and even of O and AB are all highly significant. Details of the tests of significance for these and other comparisons are given in the Appendix.

It is perhaps surprising that so marked an association was not generally recognized many years ago. In fact, Buchanan

TABLE III.—*Percentage Group Frequencies*

| Group | Peptic Ulcer (3,011 Cases) | | | Cancer of Stomach (2,745 Cases) | | | Cancer of Colon and Rectum (2,599 Cases) | | Cancer of Bronchus (998 Cases) | | Cancer of Breast (1,017 Cases) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Disease | % Inc. or Dec. on Control | Control | Disease | % Inc. or Dec. on Control | Control | Disease | Control | Disease | Control | Disease |
| O | 47·00 | 55·40 | +17·9 | 46·78 | 42·95 | −8·2 | 46·07 | 44·79 | 46·26 | 45·49 | 46·18 | 46·12 |
| A | 40·99 | 34·67 | −15·4 | 41·38 | 46·19 | +11·6 | 41·78 | 43·63 | 41·70 | 41·28 | 41·52 | 41·00 |
| B | 8·98 | 7·44 | −17·1 | 8·79 | 7·76 | −11·7 | 8·94 | 8·66 | 8·79 | 10·72 | 8·93 | 10·03 |
| AB | 3·03 | 2·49 | −17·9 | 3·05 | 3·10 | +1·6 | 3·21 | 2·92 | 3·25 | 2·51 | 3·36 | 2·85 |

and Higley (1921) did discover it. In a series of patients from the Mayo Clinic, suffering from a variety of diseases, gastro-intestinal ulcer stood out as yielding a big excess of group O. They found 122 O's to 55 A's, as compared with 1,024 O's and 933 A's in the rest of their material. The difference is highly significant, $\chi^2$ being 17.3 for one degree of freedom. It is true that grouping errors may have been present at that early date, but there is no reason why they should not have affected the various disease groups equally. Later, Ugelli (1936) found a marked increase in O in a series of 244 patients, and though there was some difficulty over the choice of suitable controls the difference appears to be a true one. Lessa and Alarcao (1949) published a valuable review of the literature. Their own series yielded 227 O's and 217 A's for peptic ulcer, against 813 O's to 1,021 A's among patients suffering from other diseases ($\chi^2$=6.38). These clear indications have tended to be overlooked, partly because of an understandable omission of adequate statistical analysis in the early work, but mainly, perhaps, because the importance of the real difference which had in fact emerged was obscured by discussion of non-significant fluctuations in large numbers of other diseases.

In carcinoma of the stomach A is increased and both O and B are reduced, the differences in the relative proportions of A and O and also of A and B being highly significant. The reduction in B did not emerge in the comparisons of the previous paper, because the hospital controls then used were unduly low in B, probably because of the inclusion of a high proportion of patients with peptic ulcer. The present finding for B agrees with that of Dr. Hollander in the series from Switzerland we then quoted. The rather remarkable result therefore emerges that, while persons of group O are at an advantage in regard to carcinoma of the stomach and persons of group A at a considerably greater advantage in regard to peptic ulcer, in the two diseases for which associations have so far been established persons of group B enjoy both advantages.

In carcinoma of the colon and rectum, in carcinoma of the bronchus, and in carcinoma of the breast there are no significant differences between the disease series and the controls. A preliminary count at an early stage showed a just significant excess of A in carcinoma of the colon and rectum, $\chi^2$ for one degree of freedom being 5. In the final count the difference has become non-significant.

For those who prefer to look at gene frequencies rather than group frequencies, the results of Table III are repeated in Table IV. The gene frequencies are calculated by Fisher's method (Dobson and Ikin, 1946), and the $\chi^2$ for unreasonableness of group proportions is not significant in any disease.

TABLE IV.—*Percentage Gene Frequencies*

| Group | Peptic Ulcer | | Cancer of Colon and Rectum | | Cancer of Bronchus | | Cancer of Breast | | Cancer of Stomach | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Disease | Control | Disease | Control | Disease | Control | Disease | Control | Disease |
| O | 68·5 | 74·6 | 67·8 | 66·8 | 68·1 | 67·0 | 68·0 | 67·7 | 68·4 | 65·5 |
| A | 25·2 | 20·5 | 25·9 | 27·1 | 25·8 | 25·5 | 25·7 | 25·3 | 25·5 | 28·9 |
| B | 6·3 | 4·9 | 6·3 | 6·2 | 6·1 | 7·5 | 6·3 | 7·0 | 6·1 | 5·7 |

Comparisons by sex can be made for peptic ulcer and for carcinoma of the colon and rectum. The numbers of women suffering from carcinoma of the bronchus and, of course, of men suffering from carcinoma of the breast are so small that no sex comparison is possible. In addition, we can add the group frequencies by sex for 1,000 patients with carcinoma of the stomach, drawn from a number of the hospitals of the previous study at which sex was recorded. The total figures are:—men: O, 275; A, 277; B, 61; AB, 20. Women: O, 178; A, 157; B, 22; AB, 10. That the total number should be exactly 1,000 is a coincidence. The findings are summarized in Table V.

TABLE V.—*Percentage Group Frequencies: Sex Comparisons*

| Group | Peptic Ulcer | | Cancer of Colon and Rectum | | Cancer of Stomach | |
|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| O | 55·5 | 55·0 | 45·4 | 43·9 | 43·4 | 48·5 |
| A | 34·8 | 34·0 | 43·2 | 44·3 | 43·8 | 42·8 |
| B | 7·3 | 8·1 | 8·2 | 9·2 | 9·6 | 6·0 |
| AB | 2·4 | 2·9 | 3·2 | 2·6 | 3·2 | 2·7 |
| No. | 2,356 | 655 | 1,517 | 1,082 | 633 | 367 |

There is no significant difference in group proportion between the sexes in any of the three diseases. Using totals and comparing the four groups simultaneously, $\chi^2$ for three degrees of freedom is 1.17 for peptic ulcer, 1.95 for carcinoma of the colon and rectum, and 5.22 for carcinoma of the stomach. For carcinoma of the stomach, making the comparison likely to give the most significant difference, as judged by inspection of Table V—namely, O versus the three other groups—$\chi^2$ for the sex difference is only 2.20 for one degree of freedom. Some further sex comparisons are shown in Table IX. The errors are relatively large, however. The 1,000 cases of cancer of the stomach are entirely inadequate for discovering even a relatively large sex difference. The figures do not even exclude the possibility (though it seems very unlikely) that the whole of the excess of A in cancer of the stomach occurs in men. It is striking, however, that in peptic ulcer the figures for men and women should prove so closely similar, and here it does seem that, in spite of the very different incidence of the disease in men and women, the excess of persons of group O is substantially the same in both.

We have made many comparisons within the material, subdividing it in a variety of ways, but without finding any clearly significant difference other than those already mentioned. We say "clearly significant" because two or three differences just significant at the 5% level did emerge; but this is to be expected when several scores of comparisons are made. Duodenal ulcer shows a higher frequency of O than does gastric, but the difference is not significant. (We therefore tested gastric ulcer alone, but found that the excess of O as compared with the controls is still highly significant.) Similarly, there is no significant difference between cancer of the colon and cancer of the rectum. Throughout the material the areas have proved homogeneous for each difference or lack of difference. Some of these finer comparisons are dealt with in the Appendix, together with other details of the analysis.

Finally, age comparisons are also given in the Appendix. For the four diseases (we have no particulars of age in respect of cancer of the stomach) the age distributions for persons of the different groups have been compared, both in total and with various subdivisions—for example, by sex,

area, and subdivision of disease. With one exception no significant association between age and blood groups has appeared. The one exception is that in gastric (not duodenal) ulcer the O's tend to be slightly younger than the A's. But once again this is a barely significant difference and one arbitrarily selected out of many. Age differences may appear in the future when larger numbers are forthcoming; for the moment we can only record a negative conclusion for the data we have.

The figures for the *Rhesus group distribution* (when available) in the diseases studied are given in Table VI. It will be seen that the combined material gives a proportion of Rhesus negatives of 17.2%. This figure is similar to the proportion in the general population of this country. For example, Discombe and Meyer (1952) found the same figure —17.2%—and quote Race's figure of 17.1%. It must be recalled, however, that our data collected from various centres and over a considerable period may be somewhat unreliable owing to minor variations in technique of Rhesus grouping. The differences between the individual diseases are not significant, though the $\chi^2$ for heterogeneity approaches the 5% level of significance.

TABLE VI.—*Rhesus Group Frequencies*

| Disease | Rhesus Pos. | Rhesus Neg. | Total | % Rhesus Neg. |
|---|---|---|---|---|
| Peptic ulcer .. .. .. | 2,196 | 422 | 2,618 | 16·12 |
| Cancer of colon and rectum | 910 | 219 | 1,129 | 19·40 |
| ,, ,, bronchus .. | 533 | 103 | 636 | 16·19 |
| ,, ,, breast .. .. | 773 | 172 | 945 | 18·20 |
| All diseases .. .. | 4,412 | 916 | 5,328 | 17·19 |

$\chi^2$ for heterogeneity, 7·09 for three degrees of freedom.

## Comment

Knowledge of associations between diseases and blood-group frequencies is at an early and empirical stage. There is as yet no prior expectation that a particular disease will show an association. There is no question here of converging lines of evidence, insufficient when taken alone but combining to build up a strong presumption in favour of a particular hypothesis. In these circumstances the assumption must be that there is no association until strong evidence is forthcoming which refutes this null hypothesis. It will probably be further agreed that something much stronger than conventional borderline probabilities is needed before results are accepted as more than an indication for the collection of more data. There are several reasons which reinforce this view. For example, there must usually be some doubt about the appropriateness of the control sample used. There may be a small margin of error, which as often as not will inflate the difference. To take another point, when many comparisons are made some must give low probabilities by chance; and if these are singled out without allowing for the fact that they are a few arbitrarily selected from many, the existence of associations will be too readily accepted.

Moreover, it is not only a question of a disease taken as a whole. Subdivisions of the disease may be made, as well as subdivisions by sex, by age, or in other ways. If, taking a disease or disease group as a whole, and taking all patients together, there is no evidence of association, the presumption, unless it is refuted by strong evidence, is that no further subdivision will reveal an association.

The appropriate null hypothesis for subdivisions where a clear association has emerged from the data taken as a whole are not quite so obvious. Presumably, in, say, peptic ulcer, the null hypothesis to be tested is that the increase in O is equal in the two sexes, though here more conventional levels of significance seem appropriate. Again, as both the allied diseases, duodenal and gastric ulcer, show a highly significant rise in O, it is assumed that the rise is the same unless there is a significant difference between them. For age comparisons, the null hypothesis is that there is no difference between patients of the different groups unless there is evidence to the contrary.

The desirability of caution in drawing deductions in this new field of inquiry further emphasizes the numbers needed for the detection even of large differences. If our series is typical, a person of group O is about 35% more likely to develop peptic ulcer (requiring treatment in hospital) than are persons of the other groups. Yet to produce strong evidence that there is an association would require, say, 500 patients if the control series was very large or about 1,000 with a control series of equal numbers. The smaller, though considerable, association in cancer of the stomach could hardly be established with a number substantially less than our 2,700 patients for England. When we turn to subdivisions the difficulties multiply, for not only are the numbers reduced, often into unequal fractions, but they now have to be compared with each other instead of with large population control series.

It is certainly desirable that the relationship between the blood groups and various diseases should be further explored, as indeed it is being explored in many parts of the world. It is also highly desirable to examine subdivisions of various kinds, but very large numbers are required. It is unlikely that any one centre, or even any one country, can furnish sufficient numbers of the rarer diseases or of some of the subdivisions of the commoner ones. There is good reason, therefore, for the publication of series which, though not individually adequate for analysis, can be added to others when sufficient of them are placed on record. It is important that papers published now should avoid the inadequacy of earlier series, an inadequacy which for many years threw this kind of research into disrepute. A survey of the earlier literature shows clearly what these errors are. They include inaccuracy of diagnosis, inadequacy of controls, and the examination of vague clinical or pathological entities, the grouping of unrelated diseases together on the one hand, and the subdivision of diseases into vague and unacceptable groups on the other. If relatively small series are to be collected and reported it would seem important to limit the data to precise pathological entities of a clear-cut kind, whose recognition is likely to be standard throughout the world. Comparison between different series will be possible, and the conclusions based on individual series valid, only if diagnosis is precise and expressed in terms which meet with general acceptance. It is to be hoped, however, that when small series are published restraint will be shown in not complicating the literature with too much discussion of differences which so far are of no significance or of doubtful significance.

Turning to the interest of the present findings in the general field of biology, the outstanding point is the demonstration that the blood groups do in fact have selective value. Following the work of such pioneers as Fisher and Ford, it has long been clear (for the ABO groups in particular) that a polymorphism which is probably as old as the species could have persisted only provided that mechanisms are at work which favour a balance between the allelomorphic genes. With few exceptions all human communities have appreciable amounts of the three genes, O, A, and B; the exceptions, such as the absence of B in the aboriginal population of South America, may well be due to colonization by small groups in whom that gene happened to be lacking or was not perpetuated. No doubt the balance changes, but at least it does not appear that the unconditional advantages or disadvantages are ever such that any of the genes disappear.

While, however, it has been predictable that the different combinations of the blood-group genes would be found to possess balancing advantages and disadvantages, most biologists would probably have expected that these were to be sought in small differences in traits of high survival value, manifested in the selective elimination of foetuses, or in differential death rates before reproductive age is reached. There is, indeed, evidence of such things, for

example, in Hirszfeld and Zborowski's (1926) observation that there are fewer offspring from the mating O mother by A father than in its reciprocal, A mother by O father—a view for which some further evidence has been produced by Waterhouse and Hogben (1947). These and similar ideas have been further developed by Allan (1953). Nor should it be forgotten that in peoples amongst whom Rhesus negatives occur, incompatible ABO matings confer a great advantage in regard to haemolytic disease. After birth there is the observation of Struthers (1951) that an excess of A children, as against O, die of bronchopneumonia during the first two years of life.

What is rather surprising, perhaps, is to find relatively very large associations with diseases of middle and late life, diseases of distinctly low selective value. Nevertheless, even if cancer of the stomach is a disease of late onset, which cannot be expected to have much effect on reproductive rates, peptic ulcer cannot be of negligible import in this respect. Many patients develop their ulcers quite early in life and the mortality is not inappreciable. The extent to which peptic ulcer lessens the likelihood of marriage and a family is more speculative, though it seems likely that reproductive rates are at least somewhat lowered (we reject the hypothesis that marriage and a family are the cause of the ulcers). With so great an association as has emerged in this inquiry, it is clear that even if the selective value of peptic ulcer is no more than moderate it is likely to be a not unimportant factor in the balance.

The two diseases, cancer of the stomach and peptic ulcer, are, however, only two factors out of a number which is likely to be large. An indication of this is seen in the fact that for these two diseases, persons of group B are at an unqualified advantage in both. There may well be other factors of prenatal and early life which redress the balance, as well as associations yet to be discovered with other diseases.

One mechanism for preserving a polymorphism is for the heterozygote to have a selective advantage. It is true that all O's, the group most affected by peptic ulcer, are homozygotes, whereas (in this country) 5 out of 6 A's are heterozygous, together with 29 out of 30 B's and all the AB's. In cancer of the stomach, however, it is the proportion of the mainly heterozygous, the A's, which is increased.

The fact that associations have been found with diseases of adult life—indeed, of middle and old age—brings the blood groups squarely into the general medical field. In the hazards of transfusion and in haemolytic disease of the foetus and newborn the association with the blood groups is dependent upon antigen-antibody reaction; this might also prove to be true of the association between blood group and toxaemia of pregnancy shown by Pike and Dickins (1954) in a paper published elsewhere in this issue. It by no means follows, however, that the association between gastric disease and blood groups, or the association, if it is proved, between blood groups and bronchopneumonia of young children (Struthers, 1951), is due to this antigen-antibody reaction.

Two possibilities may be disposed of at this point. Any explanation inculpating the antibodies themselves as active chemical agents either in the production of peptic ulceration or in carcinogenesis seems unlikely, as the antibodies occurring in groups A and B are both present in group O. The second is the suggestion that blood groups may be changed by cancer. In an annotation in the *British Medical Journal* (1953) the following statement appears: "The validity of this conclusion" (that blood groups have a selective value) "depends on the validity of the assumption that a blood group can never be changed by cancer or extrinsic factors causing cancer. This cannot be regarded as certainly true until it has been properly tested; and if it should prove incorrect an explanation of the statistical relationship might be found in a common cause." There is no known evidence of a change in the blood group of an individual due to cancer or any other cause, and all the known facts contradict the possibility of such an occurrence. During the course of very large numbers of repeated transfusions, and, even more, of repeated donations of blood by millions of donors, surely such a remarkable phenomenon would have come to light. We feel, therefore, that the suggestion that blood groups may change does not merit further consideration.

It is indeed difficult to elaborate any hypothesis which will explain why possession of blood group O should predispose to the development of peptic ulceration while the possession of blood group A should predispose to cancer of the stomach. It is equally difficult to understand why the possession of blood groups A and B should protect against peptic ulceration while possession of blood groups O and B should protect against carcinoma of the stomach. Blood groups A, B, and AB depend upon the presence of relevant A and B substances which are endowed, perhaps fortuitously, with antigenic properties. Chemically these blood-group substances are classified as mucopolysaccharides. These have been distinguished from each other only by their antigenic properties and, more recently, by minor chemical differences. There does not appear to be a specific group substance for the blood group O, as no serum has been proved to react specifically with the product of the O gene. Those who belong to group O are provided with a mucopolysaccharide called H substance, but this appears also to be present to a less extent in people who belong to the other blood groups. These specific mucopolysaccharides are present in small quantities in relation to the red corpuscles of the blood, but they appear in body tissues and fluids in very much larger quantities (Morgan, 1944). In the majority of people they occur in digestive secretions. The stomach wall seems to be rich in these group substances.

The simplest, though not necessarily the most acceptable, explanation of our findings would be the assumption that A substance is carcinogenic with respect to the stomach while both A substance and B substance protect against peptic ulcer. In the light of what is known of chemical carcinogenesis it would be difficult to incriminate the mucopolysaccharides as active agents in the genesis of carcinoma. From what is known of these substances it would be more plausible to think of some kind of protective action exercised by one or other of the polysaccharides against those influences, including hyperacidity, which are known to produce peptic ulceration, and those hypothetical carcinogens which, presumably exerting their action from the lumen of the stomach, may contribute to the environmental factor which Stocks (1950) has postulated. It might be crucial in deciding this question to know whether the secretion of A substance protects against peptic ulceration more effectively than does its mere presence in the blood, and we are collecting data of the incidence of cancer of the stomach and of peptic ulceration in secretors, but the accumulation of data is slow. Further examination of the mechanism of the relationship between the blood groups and these two diseases, peptic ulcer and cancer of the stomach, would be accelerated by direct laboratory experiment, but the separation of the blood-group substances even in tiny amounts is difficult and laborious, and it would perhaps be unwise to draw any conclusions now other than that the blood-group substances might exercise some important gastric function.

## APPENDIX

### 1. Combination of Data from Different Areas

The material analysed in this paper was drawn from several areas having differing blood-group frequencies in their general populations. What is required is a single combined estimate of each difference studied, with a test of its significance, and also a test to show whether the various areas are homogeneous or not in regard to the overall difference. This problem often arises in work on the blood groups, and will no doubt do so even more often in the future, when individual series for various diseases are published, each too small for any conclusion, though adequate for analysis when added together. No doubt, too,

TABLE VII.—*Combination of Areas: Peptic Ulcer, A/(A+O)*

| Centre | Peptic Ulcer | | Population Control | | A/(A+O) | | | Weight (w) |
|---|---|---|---|---|---|---|---|---|
| | O | A | O | A | Ulcer ($p_1$) | Control ($p_2$) | Ulcer-Control ($p_1-p_2=d$) | |
| London .. .. .. | 911 | 579 | 4,578 | 4,219 | 0·388591 | 0·479595 | −0·091004 | 5,324·1 |
| Manchester .. .. | 361 | 246 | 4,532 | 3,775 | 0·405272 | 0·454435 | −0·049164 | 2,342·3 |
| Newcastle .. .. | 396 | 219 | 6,598 | 5,261 | 0·356098 | 0·443629 | −0·087531 | 2,540·4 |

Sw = 10,206·8

it will often be desirable to combine series from different countries, with distinctly different blood-group frequencies. Except for the rather artificial special case in which the numbers in the disease group and the control group are in the same proportion, or practically so, in each area, simple addition of the frequencies will not yield a correct estimate of the combined difference, or lead to valid tests of significance. To take an unweighted average of the differences in proportion between the disease and control series is inefficient because it does not allow for differences in the accuracy of these proportions. What is required is to give the difference in proportion for each area a weight which is inversely proportional to its estimated variance. The procedure is illustrated for the relative proportions of O and A in peptic ulcer as compared with the control series, and the calculations are shown in Table VII.

If in each area $n_1$ is the number of O's and A's in the peptic ulcer series, giving a proportion A/(A+O) of $p_1$; $n_2$ and $p_2$ are the corresponding figures for the controls; then the weight, w, for that area is:

$$1\Big/\left(\frac{p_1q_1}{n_1}+\frac{p_2q_2}{n_2}\right)$$

where $p_1+q_1=1$, and $p_2+q_2=1$. The difference is $p_1-p_2=d$, and the combined weighted mean difference for all areas is Swd/Sw; $\chi^2$ for the difference, with one degree of freedom, is $(Swd)^2/Sw$; $\chi^2$ for the homogeneity of the areas is $Swd^2-(Swd)^2/Sw$, with degrees of freedom one less than the number of areas.

The weight for London, for example, is:

$$1\Big/\left\{\frac{(0.3885906)\ (1-0.3885906)}{(911+579)}+\frac{(0.4795953)\ (1-0.4795953)}{(4{,}478+4{,}219)}\right\}$$
$$=5{,}324.06$$

The weighted mean difference is −0.08054; $\chi^2$ for this difference is 66.21 with one degree of freedom; $\chi^2$ for heterogeneity is 3.01, with two degrees of freedom.

In Table II of the previous paper on cancer of the stomach a simpler procedure was set out, though the results using the method of this section were also stated. We hope that no one will be misled by that table, and would emphasize again that the simpler procedure was applicable only because the disease group and the controls were practically equal in number at each centre.

## 2. Significance of the Differences

With the ABO blood groups it is possible to examine simultaneously the variation in all four group frequencies, or in all three gene frequencies. For a number of practical purposes, however, it seems more appropriate, and is certainly much simpler, to make single comparisons—that is, to examine separately, for example, the relative proportions of groups O and A, or of O and B, or of O against the sum of the other three. In particular, the O and A comparison is often the only one for which the numbers are sufficient, and it may then seem unnecessary to complicate the analysis with groups B and AB. Hence most of the comparisons of this paper have been made in this simple way. Those for each disease taken as a whole, using the method described in the first section of the appendix, are shown in Table VIII. It will be noted that all the areas are homogeneous for each difference, except that for the comparison of A and B for cancer of the stomach the $\chi^2$ just attains the 5% level of significance.

TABLE VIII.—*Significance of Main Comparisons. Weighted Mean Differences and Homogeneity of Areas*

| Disease | Ratio Examined | Weighted Mean Difference (Dis.−Con.) % | $\chi^2$ for Difference (D. of F. =1) | Heterogeneity of Areas | |
|---|---|---|---|---|---|
| | | | | D. of F. | $\chi^2$ |
| Peptic ulcer .. | A/(A+O) | −8·05 | 66·21 | 2 | 3·01 |
| ,, ,, .. | B/(B+O) | −4·31 | 29·06 | 2 | 3·81 |
| ,, ,, .. | AB/(AB+O) | −1·75 | 10·96 | 2 | 0·68 |
| Cancer of colon and rectum .. | A/(A+O) | +1·87 | 2·73 | 3 | 1·03 |
| Cancer of bronchus | A/(A+O) | +0·33 | 0·03 | 2 | 1·03 |
| ,, ,, breast | A/(A+O) | −0·29 | 0·02 | 3 | 0·34 |
| ,, ,, stomach | A/(A+O) | +4·93 | 21·49 | 5 | 2·69 |
| ,, ,, ,, | B/(B+A) | −3·83 | 16·47 | 5 | 11·46 |

Some of the comparisons for subdivisions of the peptic ulcer series are set out in Table IX. No difference is significant, though, as already pointed out in the text, the numbers are distinctly small when subdivisions are made.

TABLE IX.—*Further Tests of Significance for the Ratio A/(A+O) Within the Peptic Ulcer Series*

| Comparison | Weighted Mean Difference % | $\chi^2$ for Difference (D. of F. =1) | $\chi^2$ for Heterogeneity of Areas (D. of F. =2) |
|---|---|---|---|
| (Gastric ulcer)–(duodenal ulcer) | +3·82 | 3·58 | 0·78 |
| (Gastric ulcer ♂)–(gastric ulcer ♀) | +3·13 | 0·85 | 1·66 |
| (Duodenal ulcer ♂)–(duodenal ulcer ♀) .. .. .. | −1·65 | 0·23 | 0·01 |
| (Gastric ulcer)–(controls) .. | −5·63 | 11·49 | 1·02 |

It may be that larger series will show that there is a difference in blood-group frequencies between gastric and duodenal ulcer, and other differences may also emerge, but all that can be done at present is to record negative conclusions on the data available.

## 3. Age

The frequency distributions of ages by disease, sex, and blood group have been analysed for the four diseases treated in this paper, omitting the small number of women with

TABLE X.—*Mean Ages, with Standard Errors, by Blood Group and Sex*

| Group | Gastric Ulcer | | | | Duodenal Ulcer | | | | Cancer of Colon and Rectum | | | | Cancer of Bronchus | | Cancer of Breast | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | Females | | Males | | Females | | Males | | Females | | Males | | Females | |
| | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| O | 52·19 | 0·63 | 55·20 | 0·90 | 47·11 | 0·43 | 49·60 | 1·11 | 61·07 | 0·44 | 59·67 | 0·55 | 54·05 | 0·41 | 54·33 | 0·53 |
| A | 54·15 | 0·69 | 56·48 | 1·16 | 46·78 | 0·56 | 47·66 | 1·31 | 61·03 | 0·48 | 60·32 | 0·54 | 53·82 | 0·41 | 54·92 | 0·60 |
| B | 52·50 | 1·44 | 52·13 | 2·64 | 45·24 | 1·19 | 49·58 | 2·15 | 62·46 | 1·09 | 58·90 | 1·28 | 53·97 | 0·97 | 55·78 | 1·18 |
| AB | 50·50 | 3·80 | 50·28 | 4·09 | 43·42 | 1·77 | 58·13 | 5·21 | 60·00 | 1·40 | 57·32 | 1·85 | 55·33 | 1·60 | 52·50 | 2·34 |

*Note.*—Numbers as in Table II.

cancer of the bronchus. We have no data for cancer of the stomach. Making a number of comparisons, including a variety of further subdivisions, and also of additions, only one barely significant difference emerges. It was noted that in both sexes and in all three areas patients of group A with gastric ulcer were older than patients of group O. Simple addition of the figures gave a difference of 1.64 years, 2.05 times its standard error. Simple addition is not adequate, but, using a method of weighting analogous to that used for the group comparisons, the result was unchanged. This difference, however, is only one arbitrarily selected out of many, and there is no confirmation in the figures for duodenal ulcer, nor in those of groups B and AB. The conclusion is, therefore, that, both in the disease which shows blood-group associations—peptic ulcer—and in the three giving a negative result, there is no evidence on these numbers of any difference in mean age between patients of the four groups. Table X shows mean ages with their standard errors for the most important subdivisions.

## Summary

Data are presented on the ABO blood-group frequencies amongst 3,011 patients with peptic ulcer, mainly those who have required treatment by transfusion and/or operation, 2,599 with cancer of the colon and rectum, 998 with cancer of the bronchus, and 1,017 with cancer of the breast.

Compared with controls from the general population of the areas sampled, patients suffering from peptic ulcer show an increased incidence of group O and a correspondingly lower incidence of the other three groups. The difference is a large one. If our series is typical, persons of group O are about 35% more likely to develop peptic ulceration than are persons of the other groups.

The ABO frequencies shown by the three cancers do not differ significantly from the population controls. These three negative results serve as a test of the appropriateness of using population controls for hospital patients.

On the numbers available, there is no indication of any difference in ABO frequencies between gastric and duodenal ulcer.

In none of the diseases is there any significant difference in sex proportion or in age between patients of the four blood groups.

Patients suffering from the four diseases do not differ significantly in the proportion who are Rhesus negative, the overall value being close to the expectation in the general population.

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# ABO BLOOD GROUPS AND TOXAEMIA OF PREGNANCY

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The advantages and disadvantages of belonging to one or other ABO blood group are being slowly established. Aird, Bentall, and Roberts (1953) have shown the disadvantage of group A in cancer of the stomach, and Aird *et al.* (1954) that of group O for peptic ulcers. There was an excess of group A children dying under 2 years of age from bronchopneumonia (Struthers, 1951); and fertility and abortions (Waterhouse and Hogben, 1947; Allan, 1953) also show differing incidence in the various blood groups. It occurred to one of us (L. A. P.) that toxaemic and non-toxaemic patients could be compared in this respect in relatively large numbers from existing obstetric records.

## Material

The investigation was carried out on 3,813 consecutive admissions to Perivale Maternity Hospital between March, 1951, and April, 1954. Primigravidae are booked in order of their application for admission, to the extent of available beds, and constituted almost half the admissions. Multiparae are admitted on medical, obstetrical, and social grounds only. Dr. J. R. E. Richardson, of the King Edward Memorial Hospital, Ealing, has been responsible for the routine grouping of all patients.

A patient was regarded as toxaemic if she possessed two of the following signs: (1) a blood pressure of 140/90 or