Brit. J. prev. soc. Med. (1957), **11**, 107–125

BLOOD GROUPS AND SUSCEPTIBILITY TO DISEASE: A REVIEW

BY

J. A. FRASER ROBERTS

Clinical Genetics Research Unit, Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London.

(1) Introduction and Historical Survey

When the Rhesus blood-group system was discovered it was almost immediately established that maternal-foetal incompatibility was the cause of haemolytic disease of the foetus and the newborn. There has also been much work on maternal-foetal incompatibility in relation to possible differential elimination at a very early stage of life. These important subjects are not dealt with in this paper, which is concerned with another question, which, though it was posed earlier, has only received a clear positive answer during the past few years. This is whether persons belonging to different blood groups may differ in their susceptibility to certain diseases.

In the early days of work on the ABO system it was natural to ask two questions: first, whether the frequencies of the groups are different in people belonging to different races; and secondly, whether the frequencies of the groups are different in persons suffering from different diseases. Both questions were asked, and at about the same time, but the fate of the two lines of inquiry was strangely different. In 1919 Hirschfeld and Hirschfeld published their classical paper. Making use of the special opportunity offered by the very varied racial composition of the Allied army in Macedonia, they selected 8,000 soldiers belonging to sixteen ethnic groups and showed conclusively that there were indeed large differences in blood-group frequencies. Their paper, in fact, foreshadowed in broad outline the pattern which has become steadily more detailed from that time to the present day. The first important paper on blood groups and disease was that of Buchanan and Higley (1921). Their plan was the same as that of the Hirschfelds; they examined at the Mayo Clinic the blood-group frequencies of some 2,400 patients suffering from a variety of diseases. The discovery that in all probability there were differences in their material was only narrowly missed. During subsequent years a large literature accumulated, but it would probably be true to say that during nearly 30 years only one positive association emerged, and that not very clearly, for the numbers were relatively small and the result was obscured in the growing volume of negative and conflicting findings. It is instructive to look back in the light of our present knowledge and to consider what the difficulties were that delayed for 30 years the discovery of associations that now seem so obvious and for which overwhelming evidence had rapidly been forthcoming.

The principal difficulties may be listed as follows:

(*A*) *Numbers*

Even when an association is relatively large, the numbers needed for establishing it are to be counted in thousands rather than in hundreds, and rarely indeed were anything like the necessary numbers forthcoming. Furthermore, a lack of appreciation of the limitations of small series and what they can reveal served to complicate and confuse the literature. Unless and until it is known that there is something definite to look for it is expensive and difficult to carry out *ad hoc* inquiries. With anthropological investigations, normal blood donors have been counted in millions and have provided ready-made data. It is only within the last 8 or 10 years that routine blood-grouping has become general for hospital patients suffering from certain diseases during the course of which a transfusion will probably or possibly be needed. We now have the advantage of being able to analyse existing hospital records, though at most hospitals this will only apply to a few diseases. Most series counted before 1953 were small and could yield results only if combined with others. This leads us to the difficulties described under (*B*) and (*C*).

(*B*) *Reliable and Comparable Techniques*

Much of the earlier grouping was reasonably reliable and consistent, but this was not universally true. Until more recent times, most workers would have rightly thought it dangerous to add together and compare frequencies obtained by different workers at different centres. If this is to be done the figures must be reliable within a small margin, which is generally true to-day for the ABO system. With Rhesus, however, the position is still rather like it used to be with ABO. There appear to be discrepancies between centres which make special precautions necessary if fine comparisons are attempted between series obtained from different laboratories. We have to recall, therefore, that the earlier investigators were faced with problems which with ABO do not now trouble us seriously.

(*C*) *Controls*

To-day, in many countries, reliable figures for blood-group frequencies are available for the general population. These are based on counts of blood-donors or on unselected series of pregnant women. Within single countries and sometimes over quite short distances, there may be apppreciable differences in blood-group frequencies. These are constantly being more efficiently mapped, and control data of increasing value are becoming available to those who would study disease associations. This advantage was largely denied to the earlier workers, who, as will be mentioned later, were often in difficulty over the selection of suitable control series against which to match their patients. It added greatly to the laboriousness of the task if the investigator had to group his own controls. On the other hand, if figures for different diseases were compared, other difficulties obviously arose.

(*D*) *Classification of Diseases*

In searching for blood-group associations races classify themselves, but it is by no means so obvious what groupings of disease entities should be made. Fine subdivisions mean smaller numbers, and it was very natural to look at, say, carcinoma taken as a whole. It is only in the light of after knowledge that we can see that the broad groupings often selected in the past were not happily chosen and could not have revealed anything.

(*E*) *Statistical Methods*

Hirschfeld and Hirschfeld (1919) did not use any special statistical techniques, nor were these needed for the establishment of the racial differences they found to exist; the figures were large enough to speak for themselves. If Buchanan and Higley (1921) had counted twice the number they did count, they would probably have discovered one association, and perhaps two. If they had counted three times as many, they would certainly have done so, and without the use of any statistics other than the calculation of percentage group frequencies. Statistical techniques do, of course, improve the analysis; more is extracted from the data. Sometimes, however, a discovery may be made by their use that would otherwise be missed. This happened with Buchanan and Higley, for a simple analysis would have shown that the group frequencies for the different diseases were suspiciously heterogeneous, and that there was at least a problem for further investigation. To-day, the use of efficient statistical techniques is so universal that it is unlikely that much will be missed through their neglect.

In spite of the difficulties, the discovery that there were associations between blood groups and particular diseases might well have been made by Buchanan and Higley. They did not fail by very much where, working on similar lines, the Hirschfelds had succeeded. Apart from the interest of contemplating the years that the locust has eaten, and of reflecting on the possible consequences had the discovery of associations been firmly established 30 years earlier than it was, a closer examination of their data is of value from the point of view of the planning of future work, and not only in this particular field.

Buchanan and Higley were stimulated to make their count by a paper published by Alexander (1921), one of the first, or perhaps the first, in this field. Alexander gave the following frequencies for fifty patients suffering from various forms of carcinoma: O, 14; A, 14; B, 16; AB, 6. He contrasted these with 175 results from fifty normal subjects, fifty suffering from tuberculosis, fifty with syphilis, and 25 with tetanus, the totals being: O, 84; A, 62; B, 22; AB, 7. Alexander concluded that persons of Groups B and AB were especially susceptible to carcinoma. Stimulated by this paper, Buchanan and Higley analysed the results for 2,446 patients grouped at the Mayo Clinic from

January 1917 to May 1921. They classified the patients into seventeen diseases or groups of diseases, with a residual miscellaneous group. A summary of the figures is presented in Table I (combining the three small series of leukaemias), together with a test for homogeneity in regard to Groups O and A.

TABLE I

DATA OF BUCHANAN AND HIGLEY (1921)

	Disease	O	A	B	AB	Total	O, A
1	Carcinoma ..	140	119	22	11	292	0·01
2	Pernicious Anaemia..	189	202	46	20	457	4·53
3	Leukaemia ..	35	22	16	1	74	1·36
4	Splenic Anaemia	23	17	1	—	41	0·23
5	Haemophilia and Purpura	19	16	4	1	40	0·01
6	Acute and Chronic Kidney Disease ..	37	21	4	—	62	2·38
7	Cardiac, Valvular, and Myocardial Disease	10	7	3	—	20	0·18
8	Diseases of the Thyroid ..	23	12	2	—	37	2·03
9	Tumours other than Cancer ..	33	21	10	1	65	1·19
10	Calculi (Nearly All Cholelithiasis)	63	55	12	4	134	0·00
11	Fibroid Uterus	54	64	13	6	137	2·99
12	Secondary Anaemia (All Causes) ..	82	82	21	9	194	0·90
13	Acute and Chronic Gallbladder Disease	95	62	13	6	176	2·93
14	Chronic Ulcers (Nearly All Peptic) ..	102	55	8	7	172	8·02
15	Jaundice (All Causes) ..	64	83	20	6	173	6·11
16	Miscellaneous	177	150	26	19	372	0·02
Total		1,146	988	221	91	2,446	
Per cent. Frequencies Degrees of Freedom 15; $P=0·005$ ..		46·85	40·39	9·04	3·72	$\chi^2 = 32·89$	

Looking at the percentage frequencies for the larger groups, Buchanan and Higley came to the following conclusions:

"(1) There is no relationship between blood groups and malignancy as suggested by Alexander.

(2) There is no relationship between blood groups and any disease in which sufficient data are available to justify a conclusion.

(3) The percentages originally presented by Moss are approximate and capable of considerable variation, without special significance.

(4) Nationality should be taken into consideration in the presentation of statistical studies of blood-grouping."

Applying a test for homogeneity, however, as shown in Table I, it can be seen that the material is suspiciously heterogeneous. If indeed there are no associations, the probability of getting such a divergence by chance is about 1 in 200. It can be further seen that this is nearly all due to three disease groups, namely, chronic ulcers, jaundice, and pernicious anaemia. Two of these divergencies we now know to be real.

Internal evidence suggests that the technique of grouping was very good. The overall percentage frequencies would do very well for the frequencies now well established in those parts of the United States. Fisher's test for reasonableness of group proportions (Dobson and Ikin, 1946) yields a non-significant χ^2.

Buchanan and Higley did not have the advantage of outside controls for comparison, and they had been struck by the discrepancies in the series so far published. They were thus confined to comparisons within the material, but, as has just been mentioned, these could have led them, if only tentatively, to the right conclusion. There was a special difficulty, however. They were also very conscious of the big racial differences recently demonstrated by the Hirschfelds. They showed patients of different origins separately, and indeed, if those not native to the United States are omitted (and it is difficult to see what else they could have done), the evidence for heterogeneity is considerably weakened. Nevertheless, it is a pity that after looking at the figures they did not conclude that Group O was in excess with ulcers and Group A with jaundice and pernicious anaemia. Had they done so, others would probably at once have made further studies on these particular diseases and two associations would then have been discovered.

The subsequent literature is voluminous and for the most part unrevealing. In many studies the numbers were far too small. Where they were fairly large the disease groups chosen (as we know now, though it could not have been known then) were too broad, for example, carcinoma, or mental diseases. Furthermore, the inquiries tended to be diverted by the idea that diseases could change the blood group, a conception which was not finally disposed of until the mid-1930s. In fact the next positive indication of any weight did not appear till 1936, when Ugelli discovered, or re-discovered, the association between Group O and gastroduodenal ulcer.

Ugelli (1936) chose peptic ulceration for a special reason. Impressed by the known anthropological associations, he felt that studies should be made on blood-group frequencies in relation to constitutional type; and so he chose peptic ulcer as a disease in which it was strongly suspected that psychoconstitutional factors are important. His series showed: Group O, 127; Group A, 81; Group B, 29; Group AB, 7. The percentage frequencies are respectively: 52·0; 33·2; 11·9; 2·9. He quoted five series of Italian frequencies. Unfortunately they showed wide discrepancies. He preferred the series of Viola (1934), both on account of its relatively large numbers and because it corresponded well with a small series of his own, based on healthy subjects. Actually, Viola's sample seems rather high in A and low in O. In any event, Ugelli came to the correct conclusion; he stated in his summary that there was an excess of Group O.

In 1949, Lessa and Alarcao published a valuable review of the literature, but the only indication of an association which could be regarded as reasonably probable was peptic ulcer, as previously indicated by the results of Buchanan and Higley and of Ugelli. Their own series of some 500 confirmed the excess of O. By this time, however, so much had been written, there had been so much discussion about non-significant differences, so much was negative, and so many conflicting views had been expressed, that Ugelli's undoubted discovery, supported by this later result, seems to have been generally overlooked. Something more was needed, a result based on really large numbers, a significance so overwhelming that it could not be ignored, before it was likely to be generally realized that there are indeed large and important associations between blood groups and some common chronic diseases of adult life. Before proceeding with the story, however, one striking and so far isolated result must be mentioned.

In 1951 new ground was explored by Struthers. He examined the ABO groups in 400 consecutive infants coming to *post-mortem* examination at a children's hospital in Glasgow. He found an excess of children of Group A. Further analysis showed that the excess was due to those exhibiting bronchopneumonia. This work is mentioned more fully in a later section.

The long-postponed general realization that there are indeed large and important associations between ABO blood groups and disease came in 1953. It was due to the initiative and persistence of Professor Ian Aird. Like Ugelli, Aird selected one particular disease, namely cancer of the stomach, and again, like Ugelli, had a particular reason for doing so. The incidence of cancer of the stomach shows very large differences in different parts of the British Isles. In particular, this disease is about twice as frequent in the north of England as in the south. Could some racial or constitutional factor be responsible? If so, it would be a good plan to look at ABO blood group frequencies, which also show considerable and regular differences in the British Isles. Aird was determined to collect large numbers, and thanks to the growing practice of routine blood-grouping of patients, was able to do so from the existing records of a large number of hospitals. The hypothesis proved irrelevant, as in fact the association was with Group A, which is commoner in the south of England, where cancer of the stomach is less common. But that did not matter, for what emerged was that patients with cancer of the stomach have a higher frequency of Group A than do corresponding controls. On a total of some 3,500, the result was overwhelmingly significant. A series contributed by Dr. L. P. Holländer of Basel showed the same excess of Group A. The results were published by Aird, Bentall, and Roberts (1953).

Stimulated by this positive finding, these workers carried out a further study of those diseases in which routine hospital groupings are commonly made (Aird, Bentall, Mehigan, and Roberts, 1954). The association between Group O and peptic ulcer was rediscovered, and this time at three separate centres and on numbers large enough to dispel any doubt. Three cancers, those of the colon and rectum, lung, and breast, gave negative results.

During the short time that has since elapsed, much progress has been made, and results have been published from a number of different countries. There is now strong evidence that the association between Group O and duodenal ulcer is closer than that between Group O and gastric ulcer, a finding that the figures of Aird and others (1954) were insufficient to establish. Pernicious anaemia shows an association with Group A. There is fairly strong evidence for a similar association in diabetes mellitus. It has also been discovered, by Clarke, Edwards, Haddock, Howel-Evans, McConnell, and Sheppard (1956), that duodenal ulcer is commoner in non-secretors of substances with ABO specificity than it is in secretors. A considerable body of data has been collected on Rhesus, though so far this is almost entirely confined to the simple categories positive and negative. With the subdivisions of Group A and with some of the other blood-group systems a beginning has been made, but numbers are as yet much too small for any conclusions to

emerge. Most of this paper presents an analysis of the evidence, under the heading of each separate disease, for the ABO system. As a preliminary, however, it is necessary to say a word about the methods of calculation used.

(2) Methods of Calculation

Nothing need be said about the use of standard statistical procedures, but there is one special problem of great importance in this work which requires a short description, as the methods for dealing with it are fundamental to the analyses made in this paper. It is essential to combine data from different countries, and different centres within countries, all with different group frequencies in their populations. In the first place, the numbers available at any one centre must often be individually too small, and so they have to be combined with others. In the second place, it is necessary to arrive at a combined weighted estimate of the strength of an association, pooling all available data, and then to test its significance. Thirdly, it is necessary to see whether the different centres are or are not homogeneous in respect of the existence and of the magnitude of an association. In general, simple addition of the frequencies will not yield a correct combined estimate, or lead to valid tests of significance. To take an unweighted average of the differences or incidences, as between disease and control series at the different centres, is inefficient, as it does not allow for differences in the accuracy with which these proportions have been determined. What is required is to give the difference in proportion, or in relative incidence, for each area a weight which is inversely proportional to its estimated variance.

The method originally described by Aird and others (1954) is due to R. A. Fisher and was used for analysis of the somewhat similar problem of possible associations between blood groups and sex (Fisher and Roberts, 1943). Although the second method, which is described below, is the one employed in this paper, the first is also given because it has been used in a number of other papers.

Let us take as an illustration the comparison of Group O and Group A in a disease series and in the corresponding controls. In each area let n_1 be the number of Os and As in the disease series, giving a proportion of A/(A + O) of p_1;

n_2 and p_2 are the corresponding figures for the controls;

$p_1 + q_1 = 1$, and $p_2 + q_2 = 1$;

$p_1 - p_2 = d$;

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

the combined weighted mean difference for all areas $= Swd/Sw$;

χ^2 for the difference, with one degree of freedom $= (Swd)^2/Sw$;

χ^2 for the homogeneity of areas $= Swd^2 - (Swd)^2/Sw$, with degrees of freedom one less than the number of areas.

The second method is that of Woolf (1955). It is very similar in principle, but starts with relative incidences instead of differences. In each area let the number of Os and As in the disease series be h and k, and in the corresponding control series H and K, then the incidence of the disease in persons of Group O is hK/Hk compared to 1 in persons of Group A.

$x = hK/Hk$;

$y = \log_e x$;

$$w = 1/\left(\frac{1}{h} + \frac{1}{k} + \frac{1}{H} + \frac{1}{K}\right);$$

$Y = Swy/Sw$;

χ^2 for the difference from unity, with one degree of freedom $= (Swy)^2/Sw$;

χ^2 for the homogeneity of areas $= Swy^2 - (Swy)^2/Sw$, with degrees of freedom one less than the number of areas;

estimated mean relative incidence = antilog Y $= X$;

standard deviation of $Y = 1/\sqrt{(Sw)}$;

approximate 95 per cent. fiducial limits $= Y \pm 1{\cdot}96$ S.D.;

antilogs give fiducial limits of X.

Woolf's method has the advantage that the results come out in a form with a simple and direct physical meaning; it is natural to think of diseases in terms of incidence. For example, we can say that the relative incidence of duodenal ulcer is 1·38 in persons of Group O as compared with 1 in persons of the other groups. The second advantage is that Woolf's method can be used for combining and comparing populations with widely differing blood-group frequencies. When, however, the populations considered do not show any wide divergences, for example, throughout Western Europe, the two methods give closely similar results.

(3) Duodenal Ulcer

Relatively large series have now been published for London, Manchester, Newcastle-upon -Tyne, Liverpool, Glasgow, Copenhagen, Oslo, Vienna, and Iowa. Table II gives a brief summary of the findings. These figures cannot be used for statistical tests, but they do bring out some of the essential features of the association.

TABLE II

DUODENAL ULCER

Brief Summary of results from Nine Centres shown separately in Table III

Blood Group	Duodenal Ulcer		Controls* Percentages	Per cent. Increase or Decrease on Controls
	Numbers	Percentages		
O	4,424	53·48	45·78	+16·8
A	2,902	35·08	40·43	−13·2
B	694	8·39	10·13	−17·2
AB	252	3·05	3·66	−16·7
Total	8,272			

Approximate Relative Incidences:

O : A, 1·35; O : B, 1·41; O : AB, 1·40;
O : (A+B+AB), 1·36; A : B, 1·05; A : AB, 1·04;
AB : B, 1·01.

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

In duodenal ulceration, the proportion of Group O is substantially increased, all the other groups being correspondingly diminished, and to much the same extent. Actually, the approximate relative incidences, simply calculated from the percentage group frequencies, are very similar to the values accurately calculated, as shown in Table III. It will be seen that the incidence of the disease in persons of Groups A, B, and AB is closely similar, the whole difference being between Group O and the remainder.

Table III gives an analysis of the results from the various centres. It will be seen that the higher incidence in Group O as against both Group A and Group B is enormously significant; even Group AB, with its relatively small numbers, differs highly significantly from Group O.

It will be noted, however, that the areas show significant heterogeneity. Each one separately shows the increased incidence in Group O, the χ^2's being over 20 at each of six of the areas taken separately. The heterogeneity is due to lower figures at Manchester, Glasgow, and Vienna, though the Manchester series is rather small.

TABLE III

DUODENAL ULCER

Analysis of Incidence of Disease in Persons of Group O Relative to its Incidence in Persons of the Other Groups

	Centre†	No. in Disease Series	Relative Incidence O : A	χ^2	Relative Incidence O : B	χ^2	Relative Incidence O : AB	χ^2	Relative Incidence O : (A+B+AB)	χ^2
1	London	946	1·59	38·33	1·41	6·93	1·41	2·66	1·54	39·83
2	Manchester	423	1·27	4·77	1·06	0·09	*	*	1·21	3·76
3	Newcastle	482	1·46	14·20	1·92	11·32	*	*	1·57	22·75
4	Liverpool	1,059	1·64	47·89	1·41	8·53	0·92	0·20	1·54	44·26
5	Glasgow	1,642	1·10	2·32	1·31	7·39	1·61	6·05	1·17	7·51
6	Copenhagen	680	1·42	17·50	1·53	8·84	2·23	10·16	1·48	25·06
7	Oslo	579	1·49	19·78	2·03	13·39	1·76	4·83	1·56	26·77
8	Vienna	1,160	1·21	7·76	1·35	8·51	1·06	0·17	1·22	9·95
9	Iowa	1,301	1·34	20·26	1·35	6·71	1·88	9·81	1·37	26·49
10	Boston	144	—	—	—	—	—	—	1·86	13·16
Total		8,416								
Mean Weighted Relative Incidence			1·36		1·41		1·35		1·38	
χ^2	Total			172·82		71·71		33·88		219·53
	Difference from Unity, D. of F. = 1			144·53		61·93		17·38		192·06
	Heterogeneity, D. of F. = 9									27·48
	Heterogeneity, D. of F. = 8			28·28		9·78				
	Heterogeneity, D. of F. = 6							16·50		
P	Heterogeneity			·004		·3		·01		·001

* Numbers too small.

†(1–3) Aird, Bentall, Mehigan, and Roberts (1954);
(4) Clarke, Cowan, Edwards, Howel-Evans, McConnell, Woodrow, and Sheppard (1955);
(5) Brown, Melrose, and Wallace, (1956);
(6) Køster, Sindrup, and Seele (1955);
(7) Heistø (1956);
(8) Speiser (1956);
(9) Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956 b).
(10) Mayr, Diamond, Levine, and Mayr (1956).

To the results of Table III may be added the findings from three other centres. The figures for Italy (Ugelli, 1936) have been quoted, and also those of Lessa and Alarcao (1949) from Portugal. They are not included in the Tables because gastric and duodenal ulcers are treated together, and with Ugelli's series it is difficult to choose a suitable control series. The third country is Australia, where, at Sydney, Billington (1956b) finds a very high excess of Group O in a relatively small series. His further findings are, however, so remarkable that his series has not been included in the foregoing comparisons. There is also a small series from Boston in a paper by Mayr, Diamond, Levine, and Mayr (1956) which is mentioned later. They simply give the number of Os and the total number for duodenal ulcer; small though the series is, the excess of Group O is highly significant.

It may be concluded, therefore, that, in all the countries where studies have so far been carried out, duodenal ulcer is considerably more common in persons of Group O than in persons belonging to the other groups, and that there are good indications that differences between the other three groups are small or non-existent. But, though the excess in persons of Group O appears in all series, it is significantly variable in amount, Glasgow and Vienna showing lower figures than other centres. There seems to be no obvious reason for this variation; as regards population blood-group frequencies at least, these two cities are at opposite ends of the scale in the material so far published. It is not surprising perhaps that when numbers become sufficiently large differences should be revealed; no doubt they will in time furnish valuable clues to the meaning of the associations.

The search for differences when subdivisions are made is of great potential value. But of course with subdivision the numbers become progressively smaller and truly vast series are required. Some of the authors quoted have looked at sex and age differences in considerable detail, but so far there is nothing substantial to contradict the hypothesis that the difference between persons of Group O and the other groups is true of both sexes and over all ages.

Attempts have been made to look for differences in relation to the severity of the disease, notably by Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956b) and Brown, Melrose, and Wallace (1956) but with two possible exceptions nothing has yet emerged. Thus, Brown and others (1956) found no appreciable difference between those having bleeding or perforated ulcers and the remainder. Nor was there any difference between those macroscopically diagnosed, that is, largely surgical cases, and those radiologically diagnosed, who included many medically treated cases. At Liverpool, Clarke, Cowan, Edwards, Howel-Evans, McConnell, Woodrow, and Sheppard (1955) actually found a greater excess of Group O in those radiologically diagnosed. Buckwalter and others found no difference between medically and surgically treated cases. Køster, Sindrup, and Seele (1955) suggested that the blood group association in peptic ulcer and in cancer of the stomach might be related to level of output of hydrochloric acid. But Buckwalter and others found no difference between those respectively high and low in free hydrochloric acid.

One of the exceptions mentioned above is of much potential interest, should it be confirmed on larger numbers. Brown and others (1956) noted that the excess of O was particularly high in those suffering from anastomotic or stomal ulcer, which may be regarded as the most extreme form of the ulcer diathesis. A re-examination of the data of Aird and others (1954) lends some corroboration. The results are shown in Table IV.

TABLE IV

COMPARISON OF STOMAL ULCER WITH DUODENAL ULCER

	Centre*	Stomal Ulcer		Duodenal Ulcer		Relative Incidence Stomal *v.* Duodenal O : (A+B+AB)	χ^2
		O	A+B+AB	O	A+B+AB		
1	Glasgow	55	24	947	695	1·68	4·34
2	London	35	18	506	394	1·51	1·94
3	Newcastle	16	11	281	186	0·96	0·01
Total		106	53	1,734	1,275		6·29
Mean Weighted Relative Incidence						1·46	
χ^2	Difference from Unity, D. of F. = 1						4·88
	Heterogeneity, D. of F. = 2						1·41
P	Heterogeneity						0·5

*(1) Brown, Melrose, and Wallace (1956); (2–3) From data of Aird, Bentall, Mehigan, and Roberts (1954).

The relative incidence of stomal ulcer in persons of Group O is about double the figure for persons of the other groups. The most useful comparison, however, is with those suffering from duodenal ulcer at the same centres. Measuring the relative incidence against the already high figure shown by patients with duodenal ulcer, the incidence in Group O is further raised by an indicated figure of 1·47. The χ^2 for the difference even on these small numbers is 4·88 for one degree of freedom and so is significant at the 5 per cent. level. Of course, it would be unwise to accept this result as more than a suggestive indication, and it is to be hoped that further results will soon be forthcoming.

The other exception was noted by Buckwalter and others (1956b). Those whose free hydrochloric acid was increased after histamine were higher in Group O than those in whom no increase was produced. Comparing Groups O and A, χ^2 was 4·44 for one degree of freedom and so significant at the 5 per cent. level. This finding also is an indication for further work.

A major discovery, already briefly mentioned, has been made by Clarke and others (1956). As is well known, some persons secrete in their body-fluids substances having ABO specificity, whereas others do not. It is a simply inherited difference, secretion being dominant to non-secretion. The saliva of a secretor of Group A contains group-specific substance A; a secretor of Group B, substance B; a secretor of Group AB, both substances. A secretor of Group O secretes H substance, which is not group-specific, being secreted by secretors of the other groups also. The H substance in the saliva of persons of Group O was detected by using extracts of Ulex, a technique which has proved very reliable. In brief summary, 514 patients with duodenal ulcer included 180 non-secretors (35·0 per cent.), while 491 controls included 119 (24·2 per cent.), a figure close to that accepted as the usual frequency of non-secretors in Great Britain. There was no significant difference as between the sexes, nor as between persons of the different groups, including Group O. The overall difference between ulcer patients and controls gave a χ^2 of 13·97 for one degree of freedom, and so is very highly significant.

To sum up, there is overwhelming evidence that duodenal ulcer is commoner in persons of Group O than in those belonging to the other groups. Differences as between the other groups are very small and are non-significant. The overall incidence in persons of Group O is 1·38 compared to 1 in those belonging to the other groups, this result being based on more than 8,000 cases collected at a number of centres in various different countries. While, however, the excess is found at all centres so far studied, there is significant variation in the level of the excess as between the different centres. Subdivision of the material by sex, age, severity, etc. has not so far shown any differences, except for two possibly suggestive findings on which there is some evidence: that the excess of Group O is particularly marked in those with stomal or anastomotic ulcers; and that the excess is higher in those who respond to histamine by a rise in free hydrochloric acid. There is extremely strong evidence that duodenal ulcer is commoner in those who do not secrete the ABO substances in their body-fluids.

(4) Gastric Ulcer

In the earlier studies, gastric and duodenal ulceration were considered together. In the series of Aird and others (1954) patients with gastric ulcer differed with high significance from the controls. The excess of Group O was lower than in duodenal ulcer, but the difference was not significant. With the appearance of further series, however, it became clear that the difference between the two kinds of ulceration was real. As before, a simple way of looking at the overall findings up to the present time is to add all the figures for gastric ulcer and compare the percentage frequencies with control frequencies obtained by weighting the controls according to the number of patients with gastric ulcer at each centre (Table V).

TABLE V

GASTRIC ULCER

Brief Summary of Results from Nine Areas shown separately in Tables VI and VII

Blood Group	Gastric Ulcer		Control* Percentages	Corresponding Duodenal Ulcer* Percentages	Per cent. Increase or Decrease	
	Numbers	Percentages			Of Gastric Ulcer on Controls	Of Gastric Ulcer on Duodenal Ulcer
O	1,903	47·59	43·33	51·26	+ 9·8	−7·2
A	1,597	39·93	42·25	36·54	− 5·5	+9·3
B	351	8·78	10·38	8·59	−15·4	+2·2
AB	148	3·70	4·04	3·61	− 8·4	+2·5
Total	3,999					

* Weighted according to number of patients with gastric ulcer at each centre.

The nine centres shown in Table V are the same for both kinds of ulceration, so that corresponding weighted percentages, calculated in the same way, can be shown for duodenal ulcer.

The result is quite clear. With gastric ulcer the proportion of persons belonging to Group O is increased and all the other groups are diminished. The numbers are smaller, however, than for duodenal ulcer and in addition the differences are proportionately less. Hence the figures are rather more irregular than those for duodenal ulcer given in the preceding section. The comparison with duodenal ulcer shows a lower proportion of Group O and a higher proportion of all the other groups. In fact, the figures for gastric ulcer are about intermediate between duodenal ulcer and the controls.

The analysis for gastric ulcer and controls is shown in Table VI. The comparisons are O : A and O : (A + B + AB). Though the evidence for a greater incidence in Group O is not so overwhelming as in duodenal ulcer, it is overwhelming enough. The mean weighted relative incidence of gastric ulcer in persons of Group O, taken over all the centres, is 1·16 as against persons of Group A, and 1·19 as against persons of the other three groups added together. The areas are perfectly homogeneous.

An analysis of the difference between the two kinds of ulceration is shown in Table VII.

TABLE VI*

GASTRIC ULCER

Analysis of Incidence of Disease in Persons of Group O Relative to its Incidence in Persons of the Other Groups

	Centre	No. in Disease Series	Relative Incidence O : A	χ^2	Relative Incidence O : (A+B+AB)	χ^2
1	London	599	1·27	7·08	1·30	9·98
2	Manchester	232	1·13	0·77	1·18	1·61
3	Newcastle	184	1·40	4·23	1·31	3·36
4	Liverpool	438	0·96	0·16	1·01	0·00
5	Glasgow	300	1·16	1·24	1·18	1·96
6	Copenhagen	337	1·22	2·79	1·26	3·66
7	Oslo	412	1·25	4·45	1·26	5·27
8	Vienna	1,028	1·09	1·26	1·09	1·48
9	Iowa	469	1·23	4·19	1·33	8·73
Total		3,999				
Mean Weighted Relative Incidence			1·16		1·19	
χ^2	Total			26·18		36·05
	Difference from Unity, D. of F.=1			18·54		27·65
	Heterogeneity, D. of F.=8			7·64		8·40
P	Heterogeneity			0·5		0·4

TABLE VII*

COMPARISON OF GASTRIC AND DUODENAL ULCER

Relative Incidence of Duodenal Ulcer in Patients of Group O as against the Incidences shown for Gastric Ulcer

	Centre	No. of Patients with Duodenal Ulcer	No. of Patients with Gastric Ulcer	Relative Incidence O : (A+B+AB)	χ^2
1	London	946	599	1·18	2·53
2	Manchester	423	232	1·02	0·02
3	Newcastle	482	184	1·19	1·02
4	Liverpool	1,059	438	1·53	13·82
5	Glasgow	1,642	300	0·99	0·01
6	Copenhagen	680	337	1·17	1·44
7	Oslo	579	412	1·24	2·67
8	Vienna	1,160	1,028	1·12	1·79
9	Iowa	1,301	469	1·03	0·08
Total		8,272	3,999		
Mean Weighted Relative Incidence				1·17	
χ^2	Total				21·60
	Difference from Unity, D. of F.=1				12·09
	Heterogeneity, D. of F.=8				9·51
P	Heterogeneity				0·3

* Sources of material as in Table III.

The comparison is in terms of O : (A+B+AB), and what is shown this time is the relative incidence of duodenal ulcer in patients of Group O, not as against the controls, but as against patients at the same centres with gastric ulcer. There is strong evidence that the difference between the two types of ulceration is real, and, once again, on these numbers, the nine centres give no indication at all of significant heterogeneity.

The results of this section are instructive in the clear indications they give for the need for large numbers. Some of the writers have been concerned by the apparent variation shown by the different series. Thus, with 438 patients at Liverpool, the figures for gastric ulcer are almost identical with those for the controls. At Manchester, Glasgow, and Iowa, the excess of Group O is fully as great as in duodenal ulcer. Nevertheless, when all the series are combined, there is no indication of any significant heterogeneity. This kind of variation is only to be expected with series of these orders of magnitude. It is fortunate that ABO blood-grouping is now so uniformly reliable, and that the requirements for obtaining suitable controls are so well understood, that series from different centres, collected by different workers, can be safely compared and combined. It is the larger figures for duodenal ulcer that are significantly heterogeneous, though, because the excess of Group O appears in some degree at all centres, this is not immediately obvious and has invited little or no discussion. It may well be that, when much larger numbers are available for gastric ulcer, significant heterogeneity will duly appear, but that time is not yet.

It is far from easy to classify ulcers situated near the pylorus and it might be suggested that the apparent excess of Group O in gastric ulcer is due to some degree of misclassification of ulcers which should have been called duodenal, or omitted altogether for safety. It would seem, however, that the excess of Group O in gastric ulcer is altogether too large for this; a 50 per cent. misclassification would be needed to account for the findings.

As with duodenal ulcer, no subdivision of the material has as yet revealed differences in blood group proportions, apart from the quite remarkable findings of Billington (1956b). In a series of 237 patients at Sydney, he had these results:

Type of Ulcer	Group			
	O	A	B	AB
Prepyloric	22	52	7	2
Non-prepyloric	94	47	11	2
Total Gastric Ulcers ..	116	99	18	4

Turning these figures into percentages and comparing with the control series, the figures are:

Type of Ulcer	Group Percentages			
	O	A	B	AB
Prepyloric	26·5	62·7	8·4	2·4
Non-prepyloric	61·1	30·5	7·1	1·3
Total Gastric Ulcers ..	48·9	41·8	7·6	1·7
Controls	48·9	38·4	9·7	3·0

The total frequencies are close to those of the controls, but the enormous excess of Group A in prepyloric ulcers and of Group O in the remainder are both very highly significant. It is greatly to be hoped that further studies will soon be forthcoming, but in the meantime it is desirable to suspend judgment, as indeed Billington himself rather suggests. He was faced with the difficulties of classifying the ulcers retrospectively from hospital notes and many doubtful cases had to be omitted. It should also be said that the cases of Clarke and others (1955) which were classified as juxtapyloric, though not very numerous, are fully as high in Group O as their cases of duodenal ulcer, and that a small series of ulcers classified as prepyloric in the material of Aird and others (1954) gave nineteen Os, eleven As, and two Bs. Both these findings are entirely at variance with Billington's extraordinary excess of Group A, both differences being highly significant.

(5) Cancer of the Stomach

A summary of results is given in Table VIII (opposite). Amongst patients the proportion of Group A is increased, the proportions of Groups O and B both being decreased. On these numbers nothing definite can be said about Group AB.

The analysis is shown in Table IX (opposite). The results are unequivocal; the relative incidence of the disease is greater, with very high significance, in

TABLE VIII

CANCER OF THE STOMACH

Brief Summary of Results from Thirteen Centres shown separately in Table IX

Blood Group	Cancer of Stomach		Control* Percentages	Per cent. Increase or Decrease on Controls
	Numbers	Percentages		
O	2,795	41·13	44·43	− 7·4
A	3,127	46·02	41·86	+10·0
B	606	8·92	9·88	− 9·7
AB	267	3·93	3·83	+ 2·6
Total	6,795			

Approximate Relative Incidences:

A : O, 1·19; A : B, 1·22; O : B, 1·03;

* Weighted according to number of patients with cancer of the stomach at each centre.

persons of Group A as against persons both of Group O and Group B. The centres are not significantly heterogeneous. Once again we can conclude that there is no evidence to suggest that the thirteen centres are not uniform for the increase in Group A.

A point of interpretation arises here. Speiser (1956) concludes that his large series from Vienna does not confirm the findings at other centres. This is entirely correct; Vienna would certainly differ with fairly high significance from all the other areas taken together. But if there is no reason for choosing one particular result out of the thirteen, it is equally legitimate to say that a series, even of this size, may differ from the rest by chance, when the comparison is one arbitrarily selected from many that could be made. A mere inspection of the relative incidences reveals a very reasonable uniformity, and out of thirteen results there is not one that, for the more reliable A : O comparision, shows a higher proportion of O than of A in the disease series as against the controls. It would be interesting to know whether the incidence of the disease is raised in persons of Group AB, but much larger numbers will be required before this point can be decided.

With one exception, no evidence has yet appeared that subdivision of the material yields significant differences. The exception is once again the site of the lesion. Jennings, Balme, and Richardson (1956) analysed results for 254 patients treated by partial or total gastrectomy, and found a large excess of Group A in those in whom the tumour was situated at the pylorus, a moderate excess of Group A when the tumour was at the cardia, and equality of Groups O and A when the site was the body of the stomach. Billington (1956c) also found an excess of Group A in prepyloric and cardiac cancers and a very large

TABLE IX

CANCER OF STOMACH

Analysis of Incidence of Disease in Persons of Group A Relative to the Incidence in Persons of Group O and Group B

	Centre	No. in Disease Series	Relative Incidence A : O	χ^2	Relative Incidence A : B	χ^2
1	London	1,340	1·16	5·67	1·23	3·39
2	London	97	1·80	6·70	*	*
3	Manchester	770	1·22	6·39	1·49	6·34
4	Newcastle	101	1·25	1·12	*	*
5	Liverpool	217	1·31	2·75	0·87	0·34
6	Birmingham	100	1·60	4·46	*	*
7	Leeds	217	1·31	3·52	1·22	0·50
8	Glasgow	299	1·09	0·45	1·16	0·48
9	Basel	704	1·36	12·16	1·41	4·90
10	Copenhagen	413	1·39	8·75	1·19	1·08
11	Vienna	1,146	1·00	0·00	1·07	0·49
12	Iowa	908	1·20	5·61	1·08	0·32
13	Sydney	483	1·06	0·41	1·39	3·24
Total		6,795				
Mean Weighted Relative Incidence			1·19		1·19	
χ^2	Total			57·99		21·09
	Difference from Unity, D. of F. =1			39·64		13·66
	Heterogeneity, D. of F.=12			18·36		
	Heterogeneity, D. of F.=9					7·43
P	Heterogeneity			0·1		0·6

* Numbers too small.

Note: Control figures for Glasgow are from a new and improved series subsequently published by Brown, Melrose and Wallace (1956).

(1, 3–7) Aird, Bentall, and Roberts (1953); (10) Køster, Sindrup, and Seele (1955);
(2) Walther, Raeburn, and Case (1956); (11) Speiser (1956);
(8) Wallace (1954); (12) Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956a);
(9) Dr. L. P. Holländer of Basel, *cited by* Aird and others (1953); (13) Billington (1956c)

excess of Group O in cancers of the body of the stomach. The results for O and A in the two investigations are as follows:

Site of Cancer	Authors and Date			
	Jennings and others (1956)		Billington (1956c)	
	O	A	O	A
Pylorus and Antrum ..	33	64	53	96
Body of the Stomach ..	41	42	154	47
Cardia	15	22	24	50

With differences of this magnitude, moderate differences in control frequencies are of little moment. The percentages of Groups O and A may be taken as 46 and 42 for London, and 49 and 38 for Sydney. The two series are in close agreement for prepyloric cancers and not significantly different for cancers of the cardia. The figures for cancer of the body of the stomach are, however, utterly discrepant. The total result is that in Billington's series there is little difference from the controls, whereas in that of Jennings and others there is a large excess of Group A. Incidentally, the figures of Jennings and others cannot be included in Tables VII and IX, as some of the cases have already been included in the figures for London published by Aird and others (1953). In this instance, too, it would be unsafe to come to any conclusion, and it is greatly to be hoped that further data bearing on the point will be forthcoming. The partial agreement of these two independent studies lends considerable weight to the findings, but the failure of the series of Jennings and others to confirm the extraordinary excess of Group O in cancer of the body of the stomach in the Sydney series makes caution desirable.

(6) Pernicious Anaemia

With a relatively rare disease, and one for which routine blood-grouping may often not be carried out, it is difficult to secure the numbers required. Nevertheless, the evidence has now accumulated to the point at which it may be said with considerable confidence that patients suffering from this disease are unduly high in Group A. Table X gives, as before, a brief summary of results set out in more detail later.

Group A is increased, Groups O and B being correspondingly diminished, and to very much the same extent. The figures for Group AB are, of course, far too small to reveal anything.

Table XI gives the analysis for the comparision of Groups O and A. It will be noted that in London and Glasgow certain hospitals are left separate. This was because discrepant results seemed to be emerging and it seemed desirable not to risk masking a real heterogeneity that might be present. Actually, however, there is no significant heterogeneity. The χ^2 for the difference from unity of 16·54 for one degree of freedom leaves little doubt about the reality of the association. The comparison of Groups A and B has not been made; with these very small series special methods would have to be used. But the close similarity of the relative incidences

TABLE X

PERNICIOUS ANAEMIA

Brief Summary of Results shown separately in Table XI

Blood Group	Pernicious Anaemia		Control* Percentages	Per cent. Increase or Decrease on Controls
	Numbers	Percentages		
O	636	42·46	47·00	− 9·7
A	685	45·73	40·30	+13·5
B	126	8·41	9·36	−10·1
AB	51	3·40	3·34	+ 1·8
Total	1,498			

Approximate Relative Incidences:

A : O, 1·26; A : B, 1·26; O : B, 1·01;

* Weighted according to number of patients at each centre.

TABLE XI

PERNICIOUS ANAEMIA

Analysis of Incidence of Disease in Persons of Group A Relative to its Incidence in Persons of Group O

	Centre*	No. in Disease Series	Relative Incidence A : O	χ^2
1	London — Hammersmith ..	134	1·70	8·05
2	London — Kingston	68	1·98	6·90
3	London — Others	42	1·03	0·01
4	Oxford	258	1·09	0·41
5	Cambridge	110	1·01	0·00
6	Sheffield	123	1·36	2·35
7	Newcastle	109	1·03	0·02
8	Glasgow — Southern General	110	0·93	0·13
9	Glasgow — Royal Infirmary ..	160	1·41	3·83
10	Copenhagen	111	0·98	0·01
11	Iowa	158	1·42	3·97
12	San Francisco	115	1·70	6·96
Total		1,498		
Mean Weighted Relative Incidence ..			1·26	
χ^2	Total			32·64
	Difference from Unity, D. of F. = 1			16·54
	Heterogeneity, D. of F. = 11			16·10
P	Heterogeneity			0·14

*(1–9) *British Medical Journal* (1956);
(10) Køster, Sindrup, and Seele (1955);
(11) Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956 a);
(12) Creger and Sortor (1956).

makes it fairly certain that Groups O and B go together. A comparison of Group A against Groups O and B combined raises the χ^2 for the difference from unity to 18·5 and still leaves the areas homogeneous. The figures of Buchanan and Higley (1921) as shown in Table I, cannot be included, as there are no controls, but they undoubtedly support the conclusion.

The difficulties and dangers of small numbers are even more clearly shown than by the larger series of the preceding sections. With numbers of this order there is nothing unexpected in getting individual incidences ranging from practically two to one down to an actual excess of Group O. Thus Creger and Sortor (1956) are concerned about the difference between their findings and those of Buchanan and Higley. Actually, the results agree as well as could reasonably be expected. Only when series are added together can clear conclusions be expected, and at the moment there is nothing to contradict at the conventional 5 per cent. level the hypothesis that all centres agree. But of course real discrepancies may emerge later; it will be time enough then to attempt to account for them.

(7) Diabetes Mellitus

We now come to conditions for which the evidence is less strong, justifying no more than a provisional conclusion which may serve as a pointer to profitable work in the future. With diabetes mellitus, however, the evidence is fairly strong. The usual summary is given in Table XII.

TABLE XII

DIABETES MELLITUS

Brief Summary of Results from Centres shown separately in Table XIII

Blood Group	Diabetes Mellitus		Control* Percentages	Per cent. Increase or Decrease on Controls
	Numbers	Percentages		
O	990	46·05	49·12	− 6·3
A	892	41·49	38·31	+ 8·3
B	183	8·51	9·58	−11·2
AB	85	3·95	2·99	+32·1
Total	2,150			

Approximate Relative Incidences:
A : O, 1·16; A : B, 1·22; O : B, 1·06

* Weighted according to number of patients at each centre.

Once again Group A is increased and Groups O and B both diminished and in very nearly the same proportion. On such numbers nothing can be said about the apparently high figure for AB in the disease series.

The detailed analysis is shown in Table XIII for Groups A and O. It will be seen that the χ^2 for the difference from unity is 9·2 and the four areas are perfectly homogeneous. The addition of Group B to Group O would increase the figure appreciably, so it may be concluded that there is strong, though by no means overwhelming, evidence, that diabetes mellitus is indeed commoner in those belonging to Group A. The evidence is less strong than for pernicious anaemia, although the numbers are considerably larger. This is because the excess in Group A is a good deal less.

TABLE XIII

DIABETES MELLITUS

Analysis of Incidence of Disease in Persons of Group A Relative to its Incidence in Persons of Group O

	Centre*	No. in Disease Series	Relative Incidence A : O	χ^2
1	S.W. Lancashire ..	634	1·12	1·71
2	W. Cheshire	199	1·19	1·39
3	Oxford	500	1·11	1·49
4	Glasgow	817	1·20	5·02
Total		2,150		
Mean Weighted Relative Incidence ..			1·16	
χ^2	Total			9·61
	Difference from Unity, D. of F. = 1			9·20
	Heterogeneity, D. of F. = 3 ..			0·41
P	Heterogeneity			0·9

**Note:* Control figures for Glasgow are from a new and improved series published by Brown, Melrose, and Wallace (1956).

(1–3) McConnell, Pyke, and Roberts (1956).
(4) Craig ahd Wang (1955).

McConnell, Pyke, and Roberts (1956) provide a useful warning of the dangers inherent in this type of work at the stage when differences are only moderately significant. They found in the first three areas of Table XIII that the excess of Group A was entirely confined to men. A direct comparison of the sexes was moderately significant and these matters were discussed at length. The results of Craig and Wang (1955) for Glasgow showed the same excess of Group A, but in that instance it occurred in women only. Combining the figures from the four centres, the sex difference became non-significant. In these 2,000 observations there is nothing appreciable to contradict the hypothesis that the excess occurs in both men and women, and also that it is present, and to an equal degree, over all ages at onset of the disease.

(8) Bronchopneumonia in Infants

Struthers (1951) determined the ABO blood group frequencies in 400 consecutive cases coming to *post-mortem* examination at the Royal Hospital for Sick Children, Glasgow. 320 were under the age of 2 years. In 148 the diagnosis of bronchopneumonia was confirmed histologically, 55 having no other apparent abnormality. These children showed a very low frequency of Group O and a high frequency of the other groups. The remaining 252 gave frequencies very similar to a control series of blood donors. The results are summarized in Table XIV.

TABLE XIV

BRONCHOPNEUMONIA IN INFANTS

Data on 400 Consecutive *post-mortem* Examinations (Struthers, 1951)

Blood Group	Controls		Bronchopneumonia			
			Present		Not Present	
	Numbers	Percentages	Numbers	Percentages	Numbers	Percentages
O	3,063	50·9	47	31·8	126	50·0
A	2,115	35·2	68	45·9	90	35·7
B	654	10·9	21	14·2	29	11·5
AB	179	3·0	12	8·1	7	2·8
Total	6,011		148		252	

The difference between the controls and the bronchopneumonia series is highly significant. Comparing Os and non-Os in a four-fold table, χ^2 is 20·54 for one degree of freedom. It will be noted that, small though the numbers are, there is an indication that, in addition to Group A, Groups B and AB are also increased.

This work has been repeated by Carter and Heslop (1957) on a somewhat larger series from London. Owing to the great reduction in deaths of infants from bronchopneumonia, however, the new sample corresponds only to that part of Struthers' material in which bronchopneumonia was an associated finding. The London series shows no significant difference from the controls. Using all Struthers' 148 cases, the difference between the two series is significant, but this is not so if the 55 dying of bronchopneumonia are omitted. While it seems likely that the London and Glasgow series are in definite disagreement, it would be premature to conclude that there is not a real phenomenon to be investigated and it is to be hoped that further studies will be carried out.

(9) Pituitary Adenoma

Mayr, Diamond, Levine, and Mayr (1956) have studied the blood-group frequencies in patients suffering from brain tumours and pituitary adenomata. With 637 brain tumours of various kinds the frequencies were closely similar to those of a large control series for Boston. 123 pituitary adenomata, however, gave a very different result, the frequencies being: O, 74; A, 24; B, 19; AB, 6. The excess of Group O and deficiency of Group A are very highly significant. As some patients came from places remote from Boston, and two New York Hospitals were also added, the authors have preferred to compare the pituitary adenomata with the other patients with brain tumours, who were selected in the same way. Even these limited figures yield a χ^2 of 9·97 when Group O is compared with the sum of the other groups, and 18·45 when Group A is similarly compared with the sum of the other groups (both for one degree of freedom).

Much weight is added to the result by the correspondence between the figures from the six different hospitals, four at Boston and two at New York. Apart from one hospital which contributed only four cases, the other five were in complete agreement in showing very high numbers of Group O and very low numbers of Group A. The authors are cautious and say that it is advisable to consider the findings as tentative, but they have certainly put forward a strong case, and it is greatly to be hoped that confirmation will be sought at other centres.

(10) Portal Cirrhosis

Billington (1956a) examined the records of 111 cases, mostly blood-grouped because they had bleeding oesophageal varices. There was a marked excess of Group A, the figures being: O, 37; A, 65; B, 7; AB, 2. Control frequencies were: O, 14,672; A, 11,514; B, 2,912; AB, 902. χ^2 for the comparison of Groups O and A, with one degree of freedom, was 17·12. A series of 149 patients with bronchiectasis gave entirely normal frequencies. There might possibly be some connexion here with Buchanan and Higley's figures for "Jaundice, All Causes" as shown in Table I; these indicate a large number of Group A. Nevertheless, as Mayr and others (1956) remarked about their findings with pituitary adenoma, it is well to regard such results, whatever their apparent significance, as tentative until they are confirmed at other centres and on larger numbers.

(11) Rheumatic Fever

Glynn, Glynn, and Holborow (1956) found 124 non-secretors amongst 450 children with rheumatic fever (27·6 per cent.). In 460 healthy schoolchildren 100 (21·7 per cent.) were non-secretors. The difference just attains the 5 per cent. level of significance.

(12) Three Negative Results

Cancer of the Colon and Rectum, Lung, and Breast

It would be disturbing and suspicious if almost all diseases were to show blood-group associations. When positive findings appear it is reassuring to get completely negative results for other diseases. This is especially true when positive and negative results are found by the same workers at the same hospitals. The negative series of patients from the same hospitals also serve as second-line controls, confirming the results obtained by using control series of blood donors. The three conditions described in this section have all been studied at several centres and on fairly large numbers of patients. The results are shown in Table XV, which gives incidences in persons of Group A relative to that in persons of Group O.

The χ^2's for the difference from unity are all non-significant and the centres are perfectly homogeneous in all three instances. It will be noted, however, that there is one result individually significant at the 5 per cent. level. This is an excess of O in cancer of the breast at Iowa. But, of course, one such result out of eighteen is close to expectation at this level of significance.

It will be further noted that even with numbers ranging from 2,000 to 3,000 the approximate 95 per cent. fiducial limits are still fairly wide. The three results are certainly negative on these numbers, but a rather small association is not excluded. Negative results, too, need large numbers if they are to be established with confidence. It is permissible, perhaps, as an illustration, to combine all three diseases. If this is done, χ^2 for the difference from unity is 1·24 for one degree of freedom and χ^2 for heterogeneity is 3·91 for five degrees of freedom. The mean weighted relative incidence is 1·03, and with 7,600 in the disease series the 95 per cent. fiducial limits are down to the fairly close bracket 0·98–1·09.

(13) Further Negative Results

Pike and Dickins (1954) studied a series of women suffering from toxaemia of pregnancy and found a significant excess of Group O. Further work at the same hospital, however (Dickins, Richardson, Pike, and Roberts, 1956) did not confirm the previous findings, the combined data now yielding a negative result. Pearson and Pinker (1956) also obtained a negative result. The combined series comprised 1,385 patients and following the methods of this paper χ^2 for the difference from unity is 0·07. The two series, however, are just significantly heterogeneous, χ^2 being 5·36 for one degree of freedom. Actually, one series gives an excess of O, the other of A, but these cancel out when the figures

TABLE XV

CANCER OF COLON AND RECTUM, OF LUNG, AND OF BREAST

Analysis of Incidence of Disease in Persons of Group A Relative to the Incidence in Persons of Group O

	Centre*	Cancer of Colon and Rectum			Cancer of Lung			Cancer of Breast		
		No. in Disease Series	Relative Incidence A : O	χ^2	No. in Disease Series	Relative Incidence A : O	χ^2	No. in Disease Series	Relative Incidence A : O	χ^2
1	London	1,514	1·10	2·80	384	1·06	0·26	85	1·12	0·21
2	Manchester	359	1·12	0·97	340	1·05	0·17	325	0·96	0·11
3	Birmingham	520	0·99	0·00	274	0·89	0·63	502	0·98	0·04
4	Newcastle	206	1·00	0·00	—	—	—	105	1·02	0·01
5	Liverpool	—	—	—	939	0·95	0·44	—	—	—
6	Iowa	256	0·95	0·12	395	0·79	4·62	866	1·14	2·86
7	London (2)	185	1·03	0·04	184	1·15	0·77	137	1·24	1·28
Total		3,040			2,516			2,020		
Mean Weighted Relative Incidence			1·06			0·96			1·07	
95 per cent. Fiducial Limits			0·98–1·15			0·88–1·05			0·97–1·18	
χ^2	Total			3·93			6·89			4·50
	Difference from Unity, D. of F.=1			2·15			0·80			1·65
	Heterogeneity, D. of F.=5			1·78			6·09			2·85
P	Heterogeneity			0·9			0·3			0·7

*(1–4) Aird, Bentall, Mehigan, and Roberts (1954)
(5) McConnell, Clarke, and Downton (1954)
(6) Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956 a);
(7) Walther, Raeburn, and Case (1956).

are combined. The individual χ^2's for the two series do not attain significance.

Maxwell and Maxwell (1955) published results for 2,147 patients with hypertension. The O : A ratio was almost identical in patients and controls. It was pointed out, however, by Aird, Bentall, and Roberts (1955) that there is a curious and indeed significant deficiency of AB's amongst the men, which might just possibly be meaningful. Trobridge (1956) obtained a negative result in 1,400 patients with tuberculosis. His findings for Rhesus are mentioned later.

Smaller series have appeared for a number of other diseases, showing no significant differences from controls. They will be very useful when further results appear and can be added, for though the findings are negative at present, quite sizeable associations cannot be ruled out when numbers are small.

(14) The Rhesus System

The only results available up to the present refer to the simple division into Rh positive and Rh negative. Results for relatively large series of patients with gastro-duodenal ulcer, cancer of the stomach, cancer of the colon and rectum, cancer of the lung, and cancer of the breast, have been published by Aird and others (1954), Clarke and others (1955), Buckwalter and others (1956a, b), Speiser (1956), and others. These results are all negative. The frequencies observed either agree with those in control series or are in reasonable agreement with the frequencies to be expected in the population concerned. With Rhesus, unlike ABO, there are difficulties about contrasting the results of workers at different laboratories, and suitable controls are not so easily obtained.

Apart from the negative results for relatively large numbers there are one or two papers in which claims for association are made. In view, however, of some uncertainties as to how the data were collected, and of the fact that there are discrepancies in population results from different centres, with the doubt this raises about possible small differences in technique, it seems better to suspend judgment for the present. These findings are not dealt with, as it would require much space to elaborate objections, and it would be ungracious to criticize work without setting out objections in detail.

One finding, however, requires special mention. Trobridge (1956) examined ABO and Rhesus frequencies (positive and negative) in patients suffering from tuberculosis. As already mentioned, the results for ABO were negative, but the Rhesus findings are suggestive. The patients were drawn from the five south-western counties of England, and Trobridge used as controls blood donors grouped by the National Blood Transfusion Service. He was careful to check his technique against theirs and a sample of patients was grouped by both, without any discrepancy appearing. In 1,362 patients the percentage who were Rh negative was 22·54 against 18·69 in 9,066 controls. The figures for the controls, however, show significant heterogeneity as between the five counties. So applying the method used throughout this paper and treating the counties separately, it is found that the mean weighted relative incidence of tuberculosis in persons who are Rh negative is 1·25. χ^2 for the difference from unity is 9·84 for one degree of freedom; and for heterogeneity 3·80 for four degrees of freedom. So there is at least a strong suggestion that tuberculosis may be commoner in those who are Rhesus negative.

(15) Subdivisions and the Other Blood-Group Systems

It would be very interesting to discover whether, for example, the excess of Group A in patients suffering from cancer of the stomach or pernicious anaemia applied both to A_1 and A_2. A search for disease associations with the subdivisions of Rhesus and also with all the other blood-group systems is of great potential interest. No result on adequate numbers are yet available, however. Nevertheless, a beginning has been made. Data are being recorded, and in due course we may look forward to a substantial extension of the subject. For example, Walther, Raeburn and Case (1956) have published results for 1,000 patients suffering from malignant disease of various kinds, showing groupings for ABO, including the subdivision of A into A_1 and A_2, Rh+ and Rh−, MN, and secretor status. In due course numbers will become adequate, and in view of past experience no one can foretell what discoveries may not be made.

(16) Comment

Some associations between blood groups and disease are now known to exist, and others are probable. In considering what they imply there are, broadly, three possibilities. In the first place, the associations might in a sense not be real at all; they might be secondary to stratifications within the population. Secondly, the differing susceptibilities might be pleiotropic effects of the blood-group genes, that is, some other and different effect from that of their role in determining the presence of the antigens. Thirdly, the associations might depend upon the

physical presence of the blood-group substances, though this action need not necessarily be antigenic.

To take the first possibility, suppose we had a mixed population of Eastern Europeans with dark hair and of largely fair-haired Northern Europeans, then if blood-grouping were carried out it would be found that dark hair was associated with Group B. But, of course, this would merely be secondary to the racial difference. The associations with disease cannot be explained on a racial basis, but, it could be asked, might there not be within populations strains who were at the same time high in Group O and unduly susceptible to duodenal ulceration, and other strains relatively high in A and especially resistant to that disease? There are a number of considerations which seem to make this stratification hypothesis unlikely. First of all, it would be very curious if the same kind of stratifications existed in the very different populations of the various countries in which the associations have been found. In the second place, there is no evidence that stratifications for blood-group frequencies do in fact exist. On the contrary, such evidence as there is points to homogeneity of populations. Moreover, the differences in blood-group frequencies between the hypothetical strata would have to be relatively enormous to account for associations of the magnitude of that found, for example, with duodenal ulcer. Nevertheless, a more direct test of the stratification hypothesis is very desirable, and this is what Clarke and others (1956) have carried out by comparing duodenal ulcer patients with their own brothers and sisters.

Clarke and others (1956) grouped 293 sibships of brothers and sisters, each starting with a patient, a propositus, with duodenal ulcer. Unfortunately, the many sibships in which all the members belong to the same blood group cannot give any information. But those which contain both Os and non-Os can be analysed. The method used is due to C. A. B. Smith. It is simple and efficient; for full details the paper of Clarke and his co-workers may be consulted. Briefly, if we think of a sibship of two, one O, one non-O, then on the null hypothesis that there is no association within sibships between blood group and ulcer, the propositus with the ulcer who brings this segregating sibship into the record has an equal chance of being O or non-O. Probabilities are computed in the same way for different sizes and compositions of sibships. There were 112 segregating sibships and the propositus was of Group O in 59 instances. The expected number, on the null hypothesis of no association, was 54·9095, the difference being only 0·804 times its standard error. It was therefore concluded that there was no evidence that persons of Group O are any more likely to develop ulcer than their own non-O sibs. Actually, however, while this is true, the numbers are insufficient for any conclusion either way. As pointed out by Roberts (1957), the calculation may be repeated using probabilities calculated on the basis of a relative incidence of ulcer in Os of 1·54, which is the figure indicated for Liverpool by the previous survey of Clarke and others (1955). The expected number is now 65·989; the difference from the observed 59 is 1·39 times its standard error and so non-significant at the 5 per cent. level. In fact, the data do not contradict at this level of significance any figure for relative incidence in Os which does not exceed 1·71, which is far higher than the mean figure of 1·38 shown in Table III, and considerably higher than the figure at any single centre.

Hence in regard to ABO blood groups the data of Clarke and others (1956), though an admirable beginning, will have to be supplemented by further observations before it can be decided whether the association observed in the general population also holds or does not hold within sibships of brothers and sisters.

With secretion, however, the result is conclusive. In 89 sibships segregating for secretion, the propositus was a non-secretor in 52 instances against an expectation of 42·464 on the null hypothesis of no association within sibships. The difference is 2·13 times its standard error. Roberts (1957) has pointed out, however, that sex should not be ignored. In England duodenal ulceration is about six times commoner in men than women. Thus if we consider a mixed sibship of two, one secretor and one non-secretor, one with ulcer and one normal, the propositus with the ulcer will nearly always be the man, whatever his secretor status. The simple plan is to consider only sibs of the same sex as the propositus. When this is done with Clarke's data 53 segregating sibships are left. The propositus is a non-secretor in 38 instances against an expectation of 24·900, The difference is now 3·72 times its standard error, corresponding to a probability of 1 in 5,000. There is thus extremely strong evidence that the association between ulcer and non-secretion holds within sibships of brothers and sisters as well as in the general population, and the hypothesis of stratification can be ruled out.

Incidentally, using sibships of one sex only for the ABO comparison, the result is still in doubt; the observed figure lies between that expected on the null hypothesis and that on the hypothesis of a relative incidence of 1·54 in persons of Group O, and does not differ significantly from either.

To call the effect pleiotropic means no more than that the blood-group genes may have other functions, unsuspected hitherto. It seems quite possible, however, that the presence of the blood-group substances may be involved in some way. It is certainly true that nearly all the diseases with which associations have been found are diseases of, or closely associated with, the upper part of the gastro-intestinal tract, a region in which, in secretors, group specific substances are present in large amounts. There has been a considerable amount of speculation, which should serve to stimulate work in the future, but for the moment there is little more to say.

This paper has concentrated on the biometrical aspects of the problem. Here we see biometry performing its classical function of uncovering problems for study, and sometimes furnishing pointers to lines of investigation which may prove profitable. Clearly there is still much to be done on these lines. It would be very useful to have many more bodies of data from many more centres, both for diseases already investigated and for others. When sub divisions are thought of the numbers can hardly be too large; it will be difficult indeed to secure enough. Standard subdivisions by sex, age, and many other factors should always be made. Above all, there is subdivision by type of disease, by its severity, and by its site. Anything that shows a difference may be a pointer to researches which may elucidate the associations and may be useful in the study of disease.

Finally, the biological implications are considerable. Following Fisher (1930), a neutral gene is almost unthinkable. Most of the blood-group genes have seemed to some almost devoid of selective value. Yet they show a polymorphism which must be as old as the species. For the ABO groups are found in the anthropoid apes. A long continued polymorphism must be dynamic, not static. It must depend on an interplay of selective advantages and disadvantages. Here, for the ABO system is a possible mechanism, for if the associations are truly causal, they are very large associations indeed. They fit in with the ideas of Mourant (1954), who has noted that while most of the blood group systems show variations in frequency which are continental, or sub-continental, the ABO system shows variation over much smaller areas. This suggests the operation of powerful selective factors. The balance is likely to be a nice one, however. All the evidence points to relative stability of frequencies over relatively short periods, and there seems to be every likelihood that the ABO system, to say nothing of the others, will maintain its usefulness in throwing light on the movements and inter-relationships of populations. But how far back it will be safe to go seems rather more uncertain than it did. It may be necessary to think in hundreds rather than in thousands of years.

(17) Summary

There is overwhelming evidence that duodenal ulceration is about 40 per cent. commoner in persons of Group O than in persons of the other groups. This is the average figure for a number of centres in several different countries. Duodenal ulcer is also commoner in non-secretors of the ABO substances than in secretors. Gastric ulceration shows a higher relative incidence in persons of Group O, though it is not as high as with duodenal ulcer.

Cancer of the stomach and pernicious anaemia have a higher relative incidence in persons of Group A. Again, the evidence is exceedingly strong. There is fairly strong evidence for an association between Group A and diabetes mellitus. There is some evidence for further associations, but more investigations are needed before they can safely be accepted.

Negative results have been obtained for a number of other diseases, and for Rhesus with some of those mentioned.

It seems unlikely that the associations are secondary to stratifications in the populations studied. With duodenal ulcer and non-secretion stratification has been disproved. It may be that differing susceptibility to certain diseases is a pleiotropic effect of the blood-group genes. It seems even more probable that some direct physiological effect of the blood-group substances may be involved.

References

Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. Fraser (1954). *Brit. med. J.*, **2**, 315.
——, ——, and Roberts, J. A. Fraser (1953). *Ibid.*, **1**, 799.
——, ——, —— (1955). *Ibid.*, **2**, 321.
Alexander, W. (1921). *Brit. J. exp. Path.*, **2**, 66.
British Medical Journal (1956). "Association between Blood Group A and Pernicious Anaemia. Collective Series from a Number of Centres", **2**, 723.
Billington, B. P. (1956a). *Austral. Ann. Med.*, **5**, 20.
—— (1956b). *Ibid.*, **5**, 141.
—— (1956c). *Lancet*, **2**, 859.
Brown, D. A. P., Melrose, A. G., and Wallace, J. (1956). *Brit. med. J.*, **2**, 135.
Buchanan, J. A., and Higley, E. T. (1921). *Brit. J. exp. Path.*, **2**, 247.
Buckwalter, J. A., Wohlwend, E. B., Colter, D. C., Tidrick, R. T., and Knowler, L. A. (1956a). *J. Amer. med. Ass.*, **162**, 1210.
——, ——, ——, ——, —— (1956b). *Ibid.*, **162**, 1215.
Carter, C. O., and Heslop, B. (1957). *British Journal of Preventive and Social Medicine*, **11** (in the press).
Clarke, C. A., Cowan, W. K., Edwards, J. W., Howel-Evans, A. W., McConnell, R. B., Woodrow, J. C., and Sheppard, P. M. (1955). *Brit. med. J.*, **2**, 643.
——, Edwards, J. W., Haddock, D. R. W., Howel-Evans, A. W., McConnell, R. B., and Sheppard, P. M. (1956). *Ibid.*, **2**, 725.
Craig, J., and Wang, I. (1955). *Glasg. med. J.*, **36**, 261.
Creger, W. P., and Sortor, A. T. (1956). *A.M.A. Arch. intern. Med.*, **98**, 136.

Dickins, A. M., Richardson, J. R. E., Pike, L. A., and Roberts, J. A. Fraser (1956). *Brit. med. J.*, **1**, 776.
Dobson, A. M., and Ikin, E. W. (1946). *J. Path. Bact.*, **58**, 221.
Fisher, R. A. (1930). "The Genetical Theory of Natural Selection". Clarendon Press, Oxford.
Fisher, R. A. and Roberts, J. A. Fraser (1943). *Nature (Lond.)*, **151**, 640.
Glynn, A. A., Glynn, L. E., and Holborow, E. J. (1956). *Lancet*, **2**, 759.
Heist, H. (1956). *T. norske Laegeforen.*, **76**, 10.
Hirschfeld, L., and Hirschfeld, H. (1919). *Lancet*, **2**, 675.
Holländer, L. P. *Cited by* Aird, Bentall, and Roberts (1953).
Jennings, D., Balme, R. H., and Richardson, J. E. (1956). *Lancet*, **2**, 11.
Køster, K. H., Sindrup, E., and Seele, V. (1955). *Ibid*, **2**, 52.
Lessa, A., and Alarcao, J. (1949). *Hema*, **2**, 1.
McConnell, R. B., Clarke, C. A., and Downton, F. (1954). *Brit. med. J.*, **2**, 323.
——, Pyke, D. A., and Roberts, J. A. Fraser (1956). *Ibid*, **1**, 772.
Maxwell, R. D. H., and Maxwell, K. N. (1955). *Ibid.*, **2**, 179.
Mayr, E., Diamond, L. K., Levine, R. P., and Mayr, M. (1956). *Science*, **124**, 932.
Mourant, A. E. (1954). "The Distribution of the Human Blood Groups". Blackwell, Oxford.
Pearson, M. G., and Pinker, G. D. (1956). *Brit. med. J.*, **1**, 777.
Pike, L. A., and Dickins, A. M. (1954). *Ibid.*, **2**, 321.
Roberts, J. A. Fraser (1957). *Ibid.*, **1**, 758.
Smith, C. A. B. *See* Clarke and others (1956).
Speiser, P. (1956). *Krebsarzt*, **6**, 344.
Struthers, D. (1951). *British Journal of Social Medicine*, **5**, 223.
Trobridge, G. F. (1956). "Blood-Groups in Tuberculosis". Thesis, Univ. Birmingham.
Ugelli, L. (1936). *Policlinico (sez. prat.)*, **43**, 1591.
Viola, D. (1934). *G. Med. milit.*, **82**, 253.
Wallace, J. (1954). *Brit. med. J.*, **2**, 254.
Walther, W. W., Raeburn, C., and Case, J. (1956). *Lancet.*, **2**, 970.
Woolf, B. (1955). *Ann. hum. Genet.*, **19**, 251.