Blood Donor Controls for Blood Group Disease Researches

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INTRODUCTION

SINCE THE REPORT BY AIRD *ET AL* (1953), increasing numbers of communications have appeared suggesting an association between the ABO blood groups and certain diseases. The evidence for such associations is the finding of statistically significant differences between the blood type frequencies of patients, and those of "healthy" persons (controls). Blood donors have most often been used as the controls. It has been assumed that blood donors provide reliable "normal" blood type frequencies as they are "healthy" persons not having the disorder being studied.

In our investigations, Buckwalter *et al*, (1956), the controls were random samples from consecutive voluntary blood donors seen at the Methodist Hospital, Des Moines and the University Hospitals during 1952 through 1954 (Controls I). The blood type frequencies agreed closely with those quoted for Iowa and the United States, with those observed in a University Hospital patient group (excluding patients with gastric carcinoma and duodenal ulcer), and with those of blood donors seen at other Iowa hospitals. It was therefore assumed that a satisfactory control sample had been obtained. However, as our investigations progressed, questions arose indicating a need for a more exhaustive study of the blood donor controls. Some of the questions were: (1) Was the number of blood donors large enough to provide statistically satisfactory control data? (2) Were the donors seen during three years representative of the population which provided patients during a 17 year period? (3) Were we correct in assuming that the "normal" blood type frequency of the population does not change with age? (4) Were the blood type frequencies of the sexes the same; if so, does it remain so at different ages? (5) Did unsuspected factors such as the season influence the observed blood type frequencies? (6) What effect did inadvertent inclusion of professional donors have? (7) Are blood donors reliable controls for these investigations? Are there better controls? The results of the investigations designed to answer these questions follow.

MATERIALS AND METHODS

Data were obtained from the records of the University Hospitals' blood bank, 1940–1956 (Controls II). All the blood typing during the 17 years was performed by

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blood bank personnel under the supervision of Dr. E. L. DeGowin who established the blood bank in 1938. A slide technique has been employed. The only significant technical change during this interval was the use of progressively higher titer antisera.

Only voluntary blood donors, friends or relatives of the patients who came to the University Hospital to replace blood given, were included. No donors were selected because of their blood type. The only prospective donors rejected were those failing to meet health requirements. Professional donors were excluded except as stated. The race of the blood donors was not recorded. About two per cent of the donors and about two per cent of the patients were Negroes. The number of donors or patients of other non-white racial groups was negligible. No attempt was made to exclude the infrequent repetitious voluntary donor because there is no apparent cause for a higher incidence of repetitious donors of one blood type than another.

The age, sex, and ABO blood type of consecutive voluntary donors during January, February, May, June, July, August, November and December of each year were recorded. The number of voluntary blood donors in each year is given in table 3.

The statistical significance of the observed differences in blood type frequencies between the several years, was determined by the Chi Square (χ^2) method. Differences occurring in the O:A frequencies, and those occurring simultaneously for the four blood types, O:A:B:AB, were examined. This method of examining the data was described in detail in an earlier communication, Buckwalter *et al* (1956).

RESULTS AND DISCUSSION

The original control data (Controls I), and the later control data (Controls II) with which this report is primarily concerned, are recorded in table 1. Notice that the differences considering, (1) only those of blood types O and A, and (2) those occurring simultaneously in the four blood types, are not statistically significant. Of interest is the higher frequency of blood type O, lower frequency of blood type A, in the original controls. As noted before, Controls I consisted of random samples of blood donors from the years 1952 through 1954. In contrast, Controls II consist of about three thousand donors from each of 17 years, 1940 through 1956. Possibly, the original "random" sample selected higher O and lower A frequency donors. More care was exercised in excluding professional donors from Controls II than from Controls I. The effect of including professional donors is shown in table 2. These data were obtained from blood donors (voluntary and professional) seen during July and August of each of the 17 years. They reflect the clinical needs dictated by the relatively high demand for blood type O (universal donor blood). Notice that the inclusion of professional donors raised the frequency of blood type O at the expense of the three other blood types. The differences between the two groups of data, including and excluding the professional donors, are statistically significant.

The blood type data for each of the 17 years are recorded in table 3. A Chi Square test of the data given in table 3 resulted in $\chi^2 = 86.66$ with 48 degrees of freedom; a result which is significant at the 1 per cent level. Further investigation revealed that the greatest differences of the observed from the expected occurred during 1951 (AB blood type), 1941 (B blood type), and 1954 (AB blood type), with somewhat

TABLE 1. COMPARISON OF BLOOD TYPE FREQUENCIES OF CONTROLS I (1952–54 BLOOD DONORS) AND CONTROLS II. WHEN THE 4,690 UNIVERSITY HOSPITAL 1952–54 BLOOD DONORS COMMON TO CONTROLS I AND CONTROLS II ARE EXCLUDED, $P > .10$ FOR O:A AND O:A:B:AB COMPARISONS.

Controls		Blood Type				Total	O:A		O:A:B:AB	
		O	A	B	AB		χ^2	Prob.	χ^2	Prob.
I	No.	2,892	2,625	570	226	6,313				
	%	45.8	41.6	9.0	3.6	100.0				
							1.908	$P > .10$	2.848	$P > .10$
II	No.	22,392	21,144	4,695	1,748	49,979				
	%	44.8	42.3	9.4	3.5	100.0				

TABLE 2. EFFECT OF PROFESSIONAL DONORS ON BLOOD TYPE FREQUENCIES. NOTE THE HIGHLY SIGNIFICANT DIFFERENCES BETWEEN THE PROFESSIONAL AND VOLUNTARY DONORS ARE REFLECTED IN SIGNIFICANT DIFFERENCES OBSERVED BETWEEN TWO BLOOD DONOR SAMPLES (WITH AND WITHOUT PROFESSIONAL DONORS).

Blood Donors		Blood Type				Total Donors	Statistical Analysis			
							O:A		O:A:B:AB	
		O	A	B	AB		χ^2	Prob.	χ^2	Prob.
Professional	No.	2,609	2,075	446	157	5,287				
	%	49.35	39.25	8.43	2.97					
							29.41	$.001 > P$	36.38	$.001 > P$
Voluntary	No.	5,462	5,257	1,168	408	12,295				
	%	44.42	42.76	9.50	3.32					
							5.27	$.05 > P > .02$	6.45	$.10 > P > .05$
Professional and Voluntary	No.	8,071	7,332	1,614	565	17,582				
	%	45.90	41.70	9.18	3.21					

smaller differences during 1947 (O and A blood types). A supplementary investigation of the data during these years indicated that the differences referred to above were somewhat inflated; for example, in a second sample of 1001 in 1941 the per cent in the B blood type was 8.49 instead of 7.79 as given in table 3; in a second sample of 1001 in 1951 the per cent in the AB blood type was 2.70 instead of 2.49 as given in table 3; and in a second sample of 1028 in 1954 the per cent in the AB blood type was 3.79 instead of 4.41 as given in table 3. A second sample of 1026 in 1947 revealed a similar situation with respect to the O and A blood types (47.27 compared to 47.35 and 40.16 compared to 39.76). It is interesting to observe that in each of the second samples, including 1947, the percentages approach the percentages given in the subtotal, table 3. No significant difference was found in the data which make up the subtotal.

No satisfactory explanation for the findings in 1941 (type B), 1951 (type AB), and 1954 (type AB) which are responsible for the heterogeneity of this data can be suggested. As indicated above, when these three years are excluded, the data appear homogeneous. Note the close agreement of the blood type frequencies recorded in the subtotal and total.

TABLE 3. NUMBER AND PERCENTAGE OF VOLUNTARY BLOOD DONORS OF EACH ABO BLOOD TYPE, UNIVERSITY HOSPITALS BLOOD BANK, 1940 THROUGH 1956

Year	Blood Type								Total No. Donors
	O		A		B		AB		
	No.	%	No.	%	No.	%	No.	%	
1940	938	43.79	898	41.92	227	10.60	79	3.69	2,142
1941	1,254	46.76	1,142	42.58	209	7.79	77	2.87	2,682
1942	1,279	43.76	1,265	43.28	280	9.58	99	3.39	2,923
1943	1,357	44.51	1,310	42.96	280	9.18	102	3.35	3,049
1944	1,462	45.08	1,384	42.68	280	8.63	117	3.61	3,243
1945	1,367	44.11	1,317	42.50	304	9.81	111	3.58	3,099
1946	1,420	43.39	1,438	43.94	299	9.13	116	3.54	3,273
1947	1,484	47.35	1,246	39.76	288	9.19	116	3.70	3,134
1948	1,313	42.89	1,323	43.22	306	10.00	119	3.89	3,061
1949	1,435	45.61	1,280	40.69	313	9.95	118	3.75	3,146
1950	1,515	47.05	1,343	41.71	267	8.29	95	2.95	3,220
1951	1,337	44.45	1,321	43.92	275	9.14	75	2.49	3,008
1952	1,234	44.87	1,146	41.67	273	9.93	97	3.53	2,754
1953	1,242	45.73	1,116	41.09	266	9.79	92	3.39	2,716
1954	1,276	42.62	1,281	42.78	305	10.19	132	4.41	2,994
1955	1,284	45.10	1,204	42.29	267	9.38	92	3.23	2,847
1956	1,195	44.39	1,130	41.98	256	9.51	111	4.12	2,692
Sub Total*	18,525	44.86	17,400	42.14	3,906	9.46	1,464	3.55	41,295
Total	22,392	44.80	21,144	42.31	4,695	9.39	1,748	3.50	49,979

* Excludes 1941, 1951, and 1954.

TABLE 4. COMPARISON OF THE BLOOD TYPE FREQUENCIES OF 1940–1948 AND 1949–1956 BLOOD DONORS

Year		Blood Type				Total	O:A		O:A:B:AB	
		O	A	B	AB		χ^2	Prob.	χ^2	Prob.
1940–1948	No.	11,874	11,323	2,473	936	26,606				
	%	44.63	42.56	9.29	3.52	100.00				
							1.199	P > .10	1.868	P > .10
1949–1956	No.	10,518	9,821	2,222	812	23,373				
	%	45.00	42.02	9.51	3.47	100.00				

The use of higher titer antisera might be expected to lower the blood type O frequency. Note that there is a slight increase in blood type O frequency (the difference is not statistically significant) when the data from the first and last half of the 17 years are compared (table 4). The higher titer antisera may not have resulted in the expected detection of more persons with blood types A, B, and AB and fewer with type O, or, more A, B, and AB, and fewer O blood types may have been detected, but this was offset by a simultaneous increase in blood type O frequency in the population during the later years. The answer to this question is not provided by the data; the first explanation seems more plausible.

TABLE 5. NUMBER AND PERCENTAGE OF VOLUNTARY BLOOD DONORS OF EACH ABO BLOOD TYPE, BY AGE GROUP AND SEX

Age in Years	Sex	Blood Type								Total No. Donors
		O		A		B		AB		
		No.	%	No.	%	No.	%	No.	%	
	Males	1,959	43.04	1,998	43.89	432	9.49	163	3.58	4,552
<25	Females	964	46.32	846	40.65	197	9.47	74	3.56	2,081
	Sex Unknown	2,042	44.30	1,941	42.11	453	9.83	173	3.75	4,609
	Males	1,648	44.50	1,618	43.69	307	8.29	130	3.51	3,703
25–29	Females	601	44.45	582	43.05	125	9.25	44	3.25	1,352
	Sex Unknown	1,532	45.05	1,433	42.13	334	9.82	102	3.00	3,401
<30	Total	8,746	44.40	8,418	42.74	1,848	9.38	686	3.48	19,698
	Males	1,615	45.42	1,479	41.59	345	9.70	117	3.29	3,556
30–34	Females	599	46.08	545	41.92	108	8.31	48	3.69	1,300
	Sex Unknown	1,474	47.17	1,252	40.06	281	8.99	118	3.78	3,125
	Males	1,433	43.88	1,414	43.29	311	9.52	108	3.31	3,266
35–39	Females	610	45.80	539	40.46	124	9.31	59	4.43	1,332
	Sex Unknown	1,353	45.10	1,265	42.17	274	9.13	108	3.60	3,000
30–39	Total	7,084	45.47	6,494	41.69	1,443	9.26	558	3.58	15,579
	Males	1,191	45.18	1,086	41.20	254	9.64	105	3.98	2,636
40–44	Females	474	41.98	523	46.32	96	8.50	36	3.19	1,129
	Sex Unknown	947	43.94	912	42.32	208	9.65	88	4.08	2,155
	Males	840	45.65	775	42.12	171	9.29	54	2.93	1,840
45–49	Females	366	44.91	346	42.45	77	9.45	26	3.19	815
	Sex Unknown	797	44.95	757	42.70	156	8.80	63	3.55	1,773
40–49	Total	4,615	44.60	4,399	42.51	962	9.30	372	3.59	10,348
	Males	499	42.65	510	43.59	131	11.20	30	2.56	1,170
50–54	Females	246	41.77	263	44.65	59	10.02	21	3.56	589
	Sex Unknown	425	45.45	388	41.50	90	9.63	32	3.42	935
	Males	353	48.49	281	38.60	73	10.03	21	2.88	728
>54	Females	137	45.21	124	40.92	33	10.89	9	2.97	303
	Sex Unknown	287	45.63	267	42.45	56	8.90	19	3.02	629
>49	Total	1,947	44.72	1,833	42.10	442	10.15	132	3.03	4,354
Totals	Males	9,538	44.46	9,161	42.71	2,024	9.44	728	3.39	21,451
	Females	3,997	44.91	3,768	42.33	819	9.20	317	3.56	8,901
	Sex Unknown	8,857	45.13	8,215	41.86	1,852	9.43	703	3.58	19,627
Grand Total.....		22,392	44.80	21,144	42.31	4,695	9.39	1,748	3.50	49,979

TABLE 6. COMPARISON OF BLOOD TYPE FREQUENCIES OF DONORS GIVING BLOOD DURING WINTER AND SUMMER

Season		Blood Type				Total Donors	Statistical Analysis			
							O:A		O:A:B:AB	
		O	A	B	AB		χ^2	Prob.	χ^2	Prob.
Winter	No.	3,751	3,582	832	335	8,500				
	%	44.13	42.14	9.79	3.94					
							.06	P > .10	4.83	P > .10
Summer	No.	3,777	3,635	800	288	8,500				
	%	44.43	42.77	9.41	3.39					

Any shift in the blood type frequencies related to ageing, would have important implications. A higher incidence of certain diseases in persons of a specific blood type would act to reduce the number of those with this blood type in the older age groups. For example, carcinoma of the stomach, a highly lethal disease with a significantly higher incidence in persons with blood type A, would cause a reduction in the frequency of this blood type with advancing age. However, if, as seems possible and perhaps probable, equally lethal diseases have an increased incidence in persons of the other blood types, the effect of carcinoma of the stomach and other diseases might balance one another. Thus diseases may act as dynamic selective factors helping to determine the blood type frequencies of any population. Reduction in fertility rates related to disease contracted before or during the reproductive years, affects blood type frequencies by reducing the expected number of progeny of these patients. In carcinoma of the stomach this effect is minimal as compared with peptic ulcer which occurs in higher incidence at an earlier age. It is apparent that knowlege of the blood type frequencies of the "healthy" population at different ages is essential if valid conclusions are to be drawn from comparisons of blood type frequencies of blood donors from such a population, and patients with diseases having varying age incidences

The blood types of the donors by sex and age groups are recorded in table 5. No statistically significant differences in the blood type frequencies between the various age groups were found. This was true when the data were divided into four groups (10 year intervals: 4 x 4 table, d. f. = 9 χ^2 = 11.06) or eight groups (5 year intervals: 8 x 4 table, d. f. = 21 χ^2 = 27.63). Since most of the blood donors were from younger age groups, the older age groups are smaller in numbers and therefore, are of less significance. More data for older persons of the "healthy" population will be necessary to provide a convincing answer to this question.

As anticipated, the blood type frequencies of men and women did not differ significantly. The possibility that the blood type frequencies of the sexes might differ by age groups was examined and no differences of significance were found (table 5).

There may be other unknown factors acting to influence the blood type frequency of the blood donors. Season of the year when the blood was obtained might be one. Farmers make up a higher proportion of the blood donors in the winter than summer. An excess or dearth of such donors, strong vigorous men, might influence the blood

type frequencies of the blood donors. The data from winter and summer donors seen during the 17 year period are recorded in table 6. No evidence of heterogeneity between the two groups of data is observed. It is essential that investigators continue to search for such factors which may significantly affect the control data.

In many of the researches in this field the bulk of the control data were obtained from blood banks located in the same city as the hospital residence of the patients. Since the blood bank and hospital, although in the same city, were usually independent organizations often in different areas of the city, the donors were rarely relatives of the patients. As the metropolitan areas which have been the sites of the various investigations are ethnologically heterogeneous, it is unlikely that the blood donors and patients would be homogeneous, ethnologically or by blood groups. The use of such blood donor samples as controls, then, is subject to criticism since differences from the blood type frequencies of the patients may be ethnological ones, not indicating a causal relationship between the patients' blood group and their diseases. To avoid this pitfall, it would be necessary to have precise information concerning the racial, national and geographical origins of all persons, donors and patients alike. Appreciation of the possible contribution that racial stratification has made to the observed differences was one factor prompting the researches of Clark *et al* (1956), in which the relatives of patients with duodenal ulcer were used as controls, rather than other patients or blood donors.

The blood donor controls for our investigations have been relatives or friends of the patients. They have come from the same geographic areas and have similar ethnologic origins. The population of the state of Iowa is relatively stable. There are no large metropolitan areas and few transient residents. These facts reduce the chance of heterogeneity between our blood donors and patients.

Although the blood type frequencies of Controls I (Buckwalter *et al* 1956) and Controls II are similar with no statistically significant differences between them, there are reasons for believing the latter are more representative of the population from which the patients came, and are therefore better controls. Among these are: (1) Controls II were obtained from donors from each of the 17 years from which the patient material was obtained. Ethnological and other changes in the population which might affect the blood type frequencies of the patients should be reflected in the blood donor data. (2) No significant differences with respect to age, sex, or season of year when the blood was collected were noted in the data for Controls II. (3) The effect of including professional donors was observed. (4) The eight-fold larger number in the sample enables the finding of significant differences when otherwise such differences might not be discovered.

Because of the differences in the blood type frequencies of Controls II from Controls I, table 1 (differences not statistically significant), the statistical significance of the findings for several diseases is altered. Chi Square values and probability for the O:A and O:A:B:AB comparisons using the original and new controls, are recorded in table 7. For example, notice that the differences between the controls and patients with stomach carcinoma, pernicious anemia and hip fractures appear less significant, while the findings in lung carcinoma and gastric ulcer appear more significant.

TABLE 7. RESULTS OF THE STATISTICAL EVALUATION OF THE PATIENT DATA USING THE ORIGINAL AND NEW CONTROLS

Patients		Blood Types				Patients: Controls I			Patients: Controls II	
		O	A	B	AB		O:A	O:A:B:AB	O:A	O:A:B:AB
Peptic Ulcer, 1839	No.	983	679	134	43	χ^2	23.258	37.049	38.133	56.777
	%	53.5	36.9	7.3	2.3	Prob.	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Duodenal Ulcer, 1301	No.	698	472	102	29	χ^2	20.340	29.573	30.864	41.943
	%	53.7	36.3	7.8	2.2	Prob.	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Gastric Ulcer, 469	No.	248	183	26	12	χ^2	4.206	12.905	6.373	19.950
	%	52.9	39.0	5.5	2.6	Prob.	$.02 < P < .05$	$.001 < P < .01$	$.01 < P < .02$	$P < .001$
Gastric Carcinoma, 908	No.	383	416	84	25	χ^2	5.623	7.607	3.844	5.439
	%	42.2	45.8	9.2	2.8	Prob.	$.01 < P < .02$	$.05 < P < .10$	$.02 < P < .05$	$P > .10$
Pernicious Anemia, 158	No.	59	76	14	9	χ^2	4.012	6.722	3.219	4.819
	%	37.3	48.1	8.9	5.7	Prob.	$.02 < P < .05$	$.05 < P < .10$	$.05 < P < .10$	$P > .10$
Breast Carcinoma, 866	No.	370	383	81	32	χ^2	2.861	2.877	1.567	1.085
	%	42.7	44.2	9.4	3.7	Prob.	$.05 < P < .10$	$P > .10$	$P > .10$	$P > .10$
Lung Carcinoma, 395	No.	202	144	33	16	χ^2	4.643	5.259	6.635	7.475
	%	51.1	36.5	8.4	4.0	Prob.	$.02 < P < .05$	$P > .10$	$.01 < P < .02$	$.05 < P < .10$
Rheumatic Disease, 254	No.	100	113	26	15	χ^2	2.461	7.339	1.707	6.255
	%	39.4	44.5	10.2	5.9	Prob.	$P > .10$	$.05 < P < .10$	$P > .10$	$.05 < P < .10$
Hip Fractures, 981	No.	410	441	95	35	χ^2	5.312	5.687	3.539	3.616
	%	41.8	45.0	9.7	3.5	Prob.	$.02 < P < .05$	$P > .10$	$.05 < P < .10$	$P > .10$

The question has been asked, and has not been finally answered, whether blood donors do, in fact, provide the best controls for these investigations. Each of the alternatives which have thus far been brought forward has disadvantages which make it less attractive than blood donors. Other patients in the hospital population receiving transfusions, usually have serious disorders themselves which may have an association with blood type. Evidence of associations of varying statistical significance has been found in patients with gastric carcinoma, Aird *et al* (1953), Hollander (1953), Køster *et al* (1955), Jennings *et al* (1956), Billington (1956), Buckwalter *et al* (1957); peptic ulceration, Aird *et al* (1954), Clarke *et al* (1955), Brown *et al* (1956), Clarke *et al* (1956), Billington (1956), Buckwalter *et al* (1956); pernicious anemia, Creger and Sortor (1956), Collective series (Great Britain 1956), Buckwalter *et al* (1956); diabetes mellitus, McConnell *et al* (1956); rheumatic fever, Buckwalter (1957); hip fractures, Buckwalter *et al* (1956); and, pituitary adenomas, Mayr *et al* (1956). It is probable that investigations now in progress will disclose associations for additional diseases. Unaffected siblings, parents, and children of patients provide controls which eliminate population stratification as a possible explanation for the blood group disease associations. However, the accumulation of sufficient data may be impossible and is always difficult. It is unlikely that samples of the population such as hospital visitors, voters, tax payers, or a sample obtained by door to door canvass, would be superior to that provided by blood donors. These sources might provide a better answer to the question concerning the relationship of age to blood type frequencies.

All of these controls are subject to a common criticism tending to invalidate their use. The so-called "healthy" population is so only in the sense that all persons included are free of disease at a given time. However, from this time on, increasingly larger numbers of this so-called "healthy" population develop disease processes, including those diseases being studied. If there is a causal relationship between diseases and blood types, not as yet to be accepted as fact, the disease predisposition exists undetected in "healthy" controls. If this concept is correct, supported by the evidence of associations between the blood groups and a variety of disorders, blood type frequencies of any "healthy" population sample reflect mean frequencies determined by multiple selective factors related to disease and blood types. Therefore, there would be no "healthy" population in this sense, not predisposed to diseases related to blood types, to use as controls.

The patients themselves, may provide the best controls. Observe the striking differences in the blood type frequencies, gastric carcinoma and peptic ulcer, or lung carcinoma and pernicious anemia, table 7. By contrast, note the lesser differences from the blood donor controls. This would be expected, if blood type frequencies observed in blood donors or other heterogeneous samples of the population such as patients with other diagnoses, are means resulting from selection related to diseases and the blood groups. Direct comparison of homogeneous patient groups reveals differences not apparent when patient and blood donor groups are compared.

To establish that differences in blood type frequency unrelated to ethnological factors do exist in patients with various disorders, large numbers of cases must be collected. For example, 395 patients with lung carcinoma showing an increase in

blood type O (table 7), suggests only a need for the collection of more data. It is of the first importance for these patient groups to be homogeneous. Only patients with unequivocal diagnoses should be included.

SUMMARY

The controls are of vital importance to investigations concerned with the association of the ABO blood groups to disease. Data obtained from 49,979 voluntary blood donors have been reported. Use of these data as controls has been discussed. The authors suggest the findings warrant the following tentative conclusions: (1) Large (49,979) numbers of blood donors provided better controls than smaller numbers (6,313). (2) Controls more representative of the population from which the patients came were obtained when the blood donors came from the same time interval as the patients. (3) There was no evidence of a change in the blood type frequencies related to age (18 to 60 years). (4) The blood type frequencies of men and women were similar over-all and in the different age groups. (5) Blood type frequencies did not differ significantly when winter and summer donors were compared. (6) Inclusion of professional donors significantly increased the frequency of blood type O. (7) Homogeneous patient groups may well be better controls than blood donors.

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