Controversy in Human Genetics

Most geneticists believe that genetic factors are involved in susceptibility and resistance to many "non-Mendelizing" human diseases. It seems, therefore, reasonable to look for disease associations among genetic polymorphisms, and a great deal of work has already been done with blood groups in this field. Dr. Vogel summarizes his extensive experience with this approach in the first annotation. Dr. Wiener has been an outspoken critic of such approaches and points out various fallacies in a second annotation. The juxtaposition of contrasting assessments may help readers to form their own opinion. Hopefully, publication of such annotations might lead to more conculsive research studies in the future.

ABO Blood Groups and Disease

F. VOGEL[1]

Aird et al. (1953) discovered a slight but significant association between blood group A and cancer of the stomach. Their paper has stimulated an immense amount of research, which has met with unusually severe criticism. The discussion in recent years has exposed the deficiencies of information flow in medicine: usually, authors examining a special problem or criticizing the whole direction of research were conversant only with a small part of the available information. Consequently, the same problems were examined over and over again, whereas some related topics were not attacked at all. Vogel and Krüger (1968) tried to summarize the information available to the end of 1966 dealing with the associations between ABO blood groups and noninfectious disease. Their results will be mentioned in the first part of the survey; in the second part, the data on infectious disease will be discussed.*

BLOOD GROUPS AND NONINFECTIOUS DISEASE

Table 1 contains a selection of those diseases for which a significant association was found in a reasonably large sample. Woolf's (1955) method was used for the statistical analysis. X is the weighted average of the values for "relative incidences" x in the samples examined. For the comparison A:O, this means: $x = (A_{Pat} \cdot O_{Contr})/(O_{Pat} \cdot A_{Contr})$ (Pat = patient; Contr = control). When blood group A is more frequent in the patient group, then $x > 1$. Table 1 contains only the most informative compari-

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* The number of papers on blood groups and disease runs into thousands. The references cited in this paper are representative. A fairly complete bibliography will be published in Vogel and Helmbold (1970).

TABLE 1

SIGNIFICANT ASSOCIATIONS BETWEEN BLOOD GROUPS AND (NONINFECTIOUS) DISEASE

DIAGNOSIS	NO. OF SERIES	NO. OF		COMPARISON	X	χ^2 FOR x (df = 1)	SIGNIFICANCE	χ^2 FOR HETEROGENEITY	df	SIGNIFICANCE
		Patients	Controls							
Neoplasias of the intestinal tract:										
Cancer, ventriculi	101	55,434	1,852,288	A:O	1.2238	386.267	***	2,178.127	100	***
Carcinoma of colon and rectum	17	7,435	183,286	A:O	1.1099	13.790	***	10.163	16	.....
Malignant tumors of salivary glands	2	285	12,968	A:O	1.6432	13.008	***	14.515	1	***
Cancer, pancreas	13	817	108,408	A:O	1.2359	7.549	**	15.048	12	.....
Cancer, mouth and pharynx	2	757	41,098	A:O	1.2478	7.703	**	1.084	1	.....
Other neoplasias:										
Cancer, colli uteri	19	11,927	197,577	A:O	1.1334	30.959	***	29.362	18	*
Cancer, corporis uteri	14	2,598	160,602	A:O	1.1515	10.163	***	17.511	13	.....
Cancer, ovarii	17	2,326	243,914	A:O	1.2789	26.630	***	19.362	15	.....
Cancer, mammae	24	9,503	355,281	A:O	1.0827	11.183	***	31.042	23	.....
Multiple primary cancer	2	433	7,823	A:O	1.4340	10.401	***	1.396	1	.....
Nonmalignant tumors:										
Nonmalignant salivary tumors	2	581	12,968	A:O	2.0153	54.874	***	23.183	1	**
Other internal diseases:										
Ulcus duodeni	44	26,039	407,518	O:A	1.3492	394.710	***	80.977	43	**
				O:A+B+AB	1.3344	447.196	***	84.415	43	**

* $P \leq .05$. ** $P \leq .01$. *** $P \leq .0027$.

TABLE 1—*Continued*

Diagnosis	No. of Series	No. of		Comparison	X	χ^2 for x (df = 1)	Significance	χ^2 for Heterogeneity	df	Significance
		Patients	Controls							
Other internal diseases—*Cont.:*										
Ulcus ventriculi	41	22,052	448,354	O:A	1.1694	95.933	***	78.964	40	**
				O:A+B+AB	1.1774	125.107	***	62.978	40	*
Ulcus ventriculi et duodeni	6	957	120,544	O:A	1.5291	26.973	***	19.453	5	**
				O:A+B+AB	1.3561	18.722	***	24.120	5	**
Ulcus, without differentiation between stomach and duodenum	11	4,199	88,239	O:A	1.1462	14.864	***	8.833	10	.....
				O:A+B+AB	1.1765	24.988	***	16.828	10	.....
Bleeding ulcera (ventriculi et duodeni)	2	1,869	28,325	O:A	1.4640	52.973	***	0.457	1	.....
				O:A+B+AB	1.5076	72.879	***	0.567	1	.....
Rheumatic diseases	17	6,589	179,385	A:O	1.2350	49.765	***	28.575	16	.....
				A+B+AB:O	1.2341	57.402	***	32.850	16	**
Pernicious anemia	13	2,077	119,989	A:O	1.2453	20.149	***	11.904	12	.....
Diabetes mellitus	20	15,778	612,819	A:O	1.0710	13.719	***	37.543	19	**
				A+B+AB:O	1.0721	16.243	***	42.198	19	**
Ischemic heart disease	12	2,763	218,727	A:O	1.1817	13.906	***	22.808	11	*
				A+B+AB:O	1.1743	15.033	***	29.183	11	**
Cholecystitis and cholelithiasis	10	5,950	112,928	A:O	1.1734	25.746	***	9.637	9	.....
Eosinophilia	3	730	1,096	A:O	2.3792	45.757	***	0.597	2	.....
				A+B+AB:O	2.1315	48.920	***	0.961	2	.....

* $P \leq .05$. ** $P \leq .01$. *** $P \leq .0027$.

sons. For cancer of the stomach, an additional very slight but significant association with blood group B as compared with O was found. This finding, however, could be due to the fact that blood donors, who represented the control population, show a slight increase of blood group O when compared with the population average (see Jörgensen and Schwarz [1968] for references). A more complete set of comparisons is documented by Vogel and Krüger (1968), who also cite most of the studies which so far have given negative or doubtful results for blood group and disease associations. It is likely that some of these negative or doubtful results will become positive as soon as more data are available.

A relatively high degree of heterogeneity in some associations (table 1, last col.) has been noted. In some cases, this finding is evidently due to minor inconsistencies in the control series used, whereas in others (diabetes, rheumatic diseases) differences among the patient series probably explain the heterogeneity. A full discussion of this problem (Vogel and Helmbold 1970) also provides complete tables of all series so far evaluated, summarizing all positive and negative results.

No less than 101 series were examined for cancer of the stomach; the χ^2 (df = 1) for the main effect approaches 400. Some critics have asserted that associations can be simulated by selective publication of series which confirm, by chance, the results published so far, whereas negative results remain unpublished. Figure 1 (Vogel and Krüger 1968) shows the distribution of χ values calculated from the 101 χ^2 values for x (A:O). If there is no association, χ should show a normal distribution with a mean of zero and a variance of one. If a normal distribution is drawn into figure 1, with a mean of zero and with the right section equalling the slope of the distribution curve in figure 1, its surface would be about three to four times this distribution curve. This means that about 200–300 unpublished series would have to rest in the files of research workers because they showed no significant association between cancer of the stomach and blood group A. Still more important, the variance would be much higher than the expected value of one. Hence, these considerations make the argument of selective publication quite unlikely.

Another line of criticism is based on the possibility that the control series used are biased in favor of one blood group, for example, blood group O. To a certain extent this is true, since blood donors sometimes were used as controls. However, the order of magnitude of this bias is much too small. Besides, as research workers became increasingly aware of the intricacies of the problem of appropriate controls, due consideration was given to this point in many of the series analyzed. Even if true, however, this argument would not dispose of all associations described. In stomach and duodenal ulcers, the association found is with blood group O. If, with this exception, all diseases examined so far would show an association with group A, the argument would have to be regarded very seriously. However, it could be refuted if various groups of diseases showed no association with blood groups in spite of the fact that controls were selected in the same way. Fortunately, there are data consistent with this premise. The entire group of congenital malformations, which includes congenital heart disease, harelip and cleft palate, malformation of kidney and urinary tract,

hydrocephalus, and others, did not show any association even though 4,762 patients and 156,716 controls were examined (table 2).

If, as table 1 seems to suggest, group A is associated with many serious diseases, especially cancers, then it has to be expected that, on the average, persons of blood group O will generally be healthier and will reach a higher age (gastro-duodenal ulcers are rarely fatal). This problem was examined by Jörgensen and Schwarz (1968) (see table 3). Healthy subjects above the age of 75, active athletes above 40, and volunteer

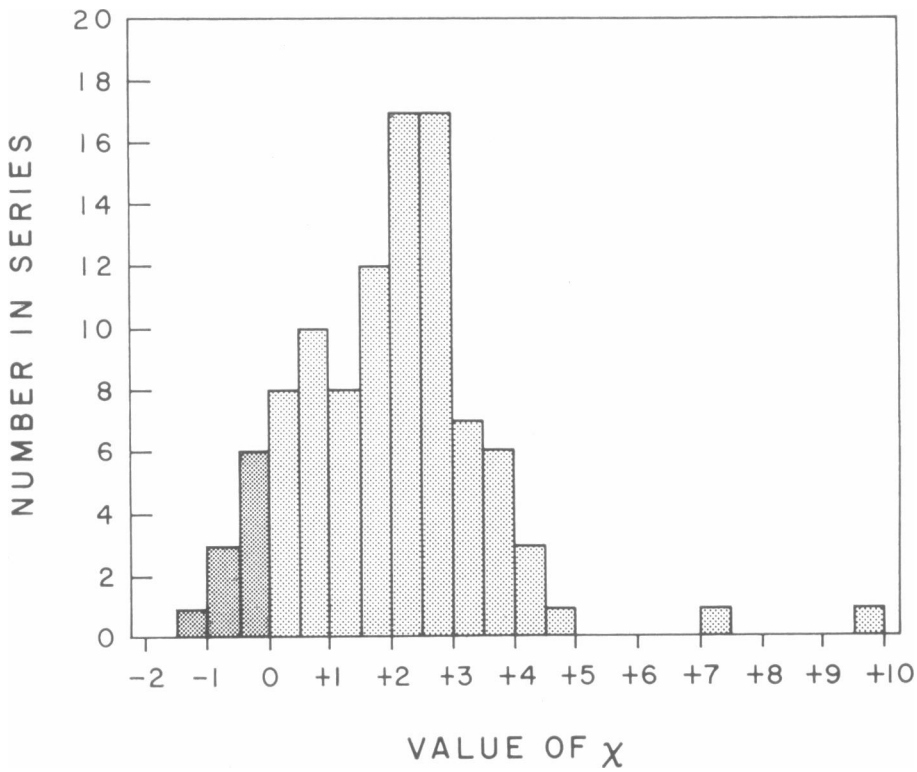

FIG. 1.—Distribution of values of χ for 101 series in which the association between cancer of the stomach and ABO blood groups was examined (Vogel and Krüger 1968).

soldiers were compared with the general population, and all of them showed a higher frequency of blood group O. The comparison between healthy aged subjects and aged patients who had undergone major surgery indicated an especially high difference (table 3). In Germany, volunteer soldiers are selected for good health and bodily fitness and have to serve a much longer time in the army than draftees. Among the aged patients with major surgery, the majority had suffered from neoplasia (for details see Jörgensen and Schwarz 1968).

All the evidence points to a higher fitness of group O as compared with A, at least under modern living conditions. As to group B, the information available is equivocal and will not be discussed here (Vogel and Krüger 1968; Vogel and Helmbold 1970).

TABLE 2

NEGATIVE RESULTS IN CONGENITAL MALFORMATIONS

DIAGNOSIS	NO. OF SERIES	NO. OF		COMPARISON	X	χ^2 FOR x (df = 1)	SIGNIFICANCE	χ^2 FOR HETEROGENEITY	df	SIGNIFICANCE
		Patients	Controls							
Congenital malformations without specification	2	818	27,514	A:O	0.9849	0.035m	.....	0.014	1	.....
				B:O	0.8056	3.619	.....	0.342	1	.....
				AB:O	1.0975	0.407	.....	0.475	1	.....
				A+B+AB:O	0.9465	0.554	.....	0.060	1	.....
Congenital malformations of the heart	4	2,836	124,654	A:O	1.0323	0.444	.....	5.880	3	.....
				B:O	1.0418	0.299	.....	1.528	3	.....
				AB:O	0.9712	0.066	.....	4.105	3	.....
				A+B+AB:O	1.0291	0.420	.....	4.872	3	.....
Hydrocephalus	1	145	1,508	A:O	1.2741	1.714	.....	.....	0	.....
				B:O	0.8759	0.151	.....	.....	0	.....
				AB:O	1.0424	0.007	.....	.....	0	.....
				A+B+AB:O	1.1886	0.960	.....	.....	0	.....
Hare lip and cleft palate	1	493	694	A:O	0.9433	0.207	.....	.....	0	.....
				B:O	0.9756	0.014	.....	.....	0	.....
				AB:O	0.8706	0.258	.....	.....	0	.....
				A+B+AB:O	0.9420	0.247	.....	.....	0	.....
Malformations of kidney, ureter, and bladder	1	470	2,346	A:O	1.0158	0.021	.....	.....	0	.....
				B:O	0.8115	1.246	.....	.....	0	.....
				AB:O	0.3845	8.028	**	.....	0	.....
				A+B+AB:O	0.9215	0.646	.....	.....	0	.....

SOURCE.—Vogel and Krüger (1968).

** $P \leq .01$.

Further statistical analysis of blood group associations included (1) comparisons of the same associations in populations of different origin and under different living conditions, (2) different subtypes of the same disease, and (3) interactions with other polymorphic systems, especially the ABO secretor system. In diabetes, for example, an association with blood group A is only found in aged patients, and in cardiac infarction the same association seems to be restricted to populations in which the incidence of myocardial infarction is low. The material available will be discussed elsewhere (Vogel and Helmbold 1970).

BLOOD GROUPS AND INFECTIOUS DISEASES

So far, nothing has been mentioned about possible physiological causes of the associations described. The interaction between ABO and secretor system hints that the

TABLE 3

BLOOD GROUPS, HEALTH, AND AGE

DIAGNOSIS	NO. OF SERIES	NO. OF		COMPARISON	X	χ^2 FOR X (df = 1)	SIGNIFICANCE
		Patients	Controls				
Healthy aged subjects (above 75)[1] compared with German controls	1	521	81,985	O:A	1.597	23.219	***
Healthy aged subjects (above 75)[1] compared with surgically treated aged patients	1	521	614	O:A	1.935	25.055	***
Athletes above 40 compared with German controls	1	340	81,985	O:A	1.34	9.937	***
Volunteer soldiers compared with draftees	1	484	1,005	O:A	1.29	4.437	*

SOURCE.—Data are from Jörgensen and Schwarz (1968).

[1] Partially unpublished data.

* $P \leq .05$.

*** $P \leq .0027$.

blood group determinants themselves could be involved rather than a completely unknown pleiotropic gene effect (see Clarke [1961] for discussion). The suggestion of Helmbold (1959) that the association of cancers with blood group A as well as the association of ulcer disease with group O could possibly be explained by immunological processes has helped to direct attention toward infectious diseases. For some of these, the evidence for blood group associations is now available. Table 1 refers to rheumatic diseases. The data for tuberculosis, sarcoidosis, leprosy, and syphilis are tabulated in table 4. This table also has information about some virus diseases.

For most of these associations, there exists only a general immunological advantage of group O, but no specific hypothesis has been brought forward. On the other hand, a specific hypothesis was discussed for infant diarrhea* (Kircher 1961, 1964; Vogel et al. 1964), smallpox (Vogel et al. 1960), and rheumatic fever (Zih and

* Recently, an association of group B with infant diarrhea has been described by Socha et al. (1969).

TABLE 4

BLOOD GROUPS AND INFECTIOUS DISEASES

DIAGNOSIS	NO. OF SERIES	NO. OF		COMPARISON	X	χ^2 FOR x (df = 1)	SIGNIFICANCE	χ^2 FOR HETEROGENEITY	df	SIGNIFICANCE
		Patients	Controls							
Leprosy:[1]										
Patients against healthy controls	33	12,687	394,278	A:O	1.0887	12.108	***	106.203	32	***
Lepromatous against nonlepromatous patients	10	4,477	3,065	A:O	1.1831	7.709	**	19.904	9	.....
Tuberculosis[2]	17	9,284	82,526	A:O	1.0592	4.084	*	68.869	16	***
				B:O	1.1010	7.211	**	95.279	16	***
				A+B+AB:O	1.0629	5.651	*	94.412	16	***
Boeck's sarcoid[3]	1	518	81,985	A:O	1.142	15.22	***	.....	.....	.....
Syphilis:[2]										
Tertiary syphilis against normal controls	9	2,186	54,097	B:O	1.51	39.664	***	27.893	8	***
				A+B+AB:O	1.1654	10.130	***	23.61	8	**

[1] Vogel (1968*a*); Vogel et al. (1969).

[2] Vogel and Helmbold (1970).

[3] Jörgensen; see Vogel and Helmbold (1970).

* $P \leq .05$.

** $P \leq .01$.

*** $P \leq .0027$.

TABLE 4—*Continued*

Diagnosis	No. of Series	No. of Patients	No. of Controls	Comparison	X	χ^2 for x (df = 1)	Significance	χ^2 for Heterogeneity	df	Significance
Syphilis—*Cont.*:										
WaR− after salvarsan treatment against WaR+	3	1,632 (WaR+)	1,951 (WaR−)	A:O	1.65	34.651	***	5.318	2	*
				B:O	1.63	28.210	***	8.419	2	*
				A+B+AB:O	1.67	45.514	***	9.542	2	**
Hepatitis and sequelae:[2,4]										
Acute hepatitis against controls	2	532	66,266	A:O	1.272	6.359	**	0.683	1	.....
Cirrhosis of the liver against controls	4	974	47,843	A:O	1.495	27.858	***	12.117	3	**
Smallpox:[5]										
Patients against healthy controls (siblings)	2	437	428	A+AB:B+O	6.09	128.92	***	6.09	1	*
Severe cases against mild cases	2	300 (severe)	137 (mild)	A+AB:B+O	2.70	19.52	***	0.83	1	.....
Dying cases against surviving cases	2	210 (died)	227 (survived)	A+AB:B+O	3.975	38.66	***	5.59	1	*
Influenza A_2 virus infection[6]	3	701	47,108	O:A	1.4892	22.87	***	2.136	2	.....
Adenovirus infection[6]	3	667	47,108	A:O	1.2687	8.027	**	0.084	2	.....

[4] Zuckerman and McDonald (1963).
[5] Vogel and Chakravartti (1966).
[6] McDonald and Zuckerman (1962).

* $P \leq .05$.
** $P \leq .01$.
*** $P \leq .0027$.

Thoma 1967). This hypothesis was based on the well-known fact that some microbial organisms have blood-group-like antigens in common with human beings (see Springer [1967] for references). These blood-group-like antigens are undisputed in some pathogenic *Escherichia coli* strains. Examination of blood group associations in *E. coli* enteritis of infants gave significant results not only with incidence but also with severity of the disease. However, these associations differed in relation to the subspecies of the germs involved (see also Vogel 1965). Eichner et al. (1963) described a blood-group-dependent difference of antibody titers against *E. coli* 0-86 in normal adults. Rheumatic fever, which shows a definite advantage of group O compared with the other blood groups (table 1), is due to an allergy against *Streptococcus pyogenes;* the more intensive the immunological response, the higher the probability of sensitization. Now, the C substance of *St. pyogenes* has a component (β-N-acetyl-D-glucosamin) in common with the human H substance, whereas this component is present in much lower concentration in the other blood groups. This finding would reduce the chance of sensitization for patients with blood group O (Zih and Thoma 1967). A lower rate of carriers with streptococci in the saliva of persons excreting high amounts of H substance was described by Haverkorn and Goslings (1969).

For smallpox, an A antigen in one vaccinia virus strain was found by Pettenkofer and Bickerich (1960). Harris et al. (1963) asserted that this result was due to an experimental error. This problem seems to be unsolved to date.

From Pettenkofer's result, it was concluded that smallpox might take a milder course in groups B and O, since the virus could be partially neutralized by the anti-A isoantibodies (Vogel et al. 1960). This was confirmed by Vogel and Chakravartti (1966) in an unvaccinated Indian population living under primitive conditions (table 4). In vaccinated patients and under hospital conditions, on the other hand, the association was not found (Downie et al. 1965; Sukumaran et al. 1966). In these series, mortality was also very much reduced.*

In contrast with the associations with internal diseases which mainly affect persons of postreproductive age, associations of blood groups with infectious, and especially with epidemic, diseases are bound to influence gene frequencies. It was postulated that the differences in ABO gene frequencies of the aboriginal populations of the world are partly due to different exposure to these epidemics. For the aboriginal population of India and Pakistan, Bernhard (1966) found a significant negative rank correlation ($\rho = -0.643$, $P < .01$) for frequency of phenotype A and smallpox mortality. A similar correlation ($\rho = -0.499$, $P < .01$) was found by Vogel (1968*b*) for phenotype A frequency and smallpox morbidity in Africa. Otten (1967) published some interesting suggestions of other possible interactions with blood group substances which may influence natural selection via nutrition and infections.

In conclusion, associations between ABO blood groups and disease have been established beyond any reasonable doubt. They seem to influence fitness in higher age groups under modern living conditions. Under primitive conditions, a relationship of the ABO blood groups with resistance to infectious diseases, and hence an influence

* Recently, Krieger (1969) has published a relatively small, but unbiased series from Brazil. The results were negative, but the epidemic must have been unusually mild, as no patients died.

on natural selection, is very likely. However, the physiological basis of the associations is not yet clearly understood. The hypotheses available to date have not found general acceptance. In view of the ubiquitous occurrence of blood group determinants and their obvious importance for human health, this problem provides a challenge for experimental immunologists.

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