Brit. J. Psychiat. (1967), **113**, 1309–1315

The Distribution of Blood Groups in Psychiatric Illness

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There is evidence that the susceptibility to certain diseases varies in people of different blood groups. Associations have been claimed to exist between the ABO blood groups and diseases such as duodenal ulcer, carcinoma of the stomach, pernicious anaemia, diabetes mellitus, and rheumatic fever. The most convincing evidence for an association between a blood group and a disease is that of the increased frequency of group O in patients with duodenal ulcer (Aird *et al.*, 1954), and also an increased frequency of non-secretion in the same disorder (Clarke *et al.*, 1956).

What these apparent associations may mean is a matter for speculation and for further research. In most cases a direct causal effect is unlikely, but racial stratification, pleiotropic effects of blood group genes, or a maternal effect (Clarke *et al.*, 1956) are all possible explanations. Pleiotropism, where a single gene controls more than one character, has recently been demonstrated at the biochemical level (Evans, 1965). Individuals whose sera show a second alkaline phosphatase band on electrophoresis are found to be much more often of blood group O or B. People with these blood groups also have on average higher serum levels of alkaline phosphatase than those who are group A1 or A2. It is, therefore, not inconceivable that some forms of mental illness, especially those where heredity and/or biochemical factors are thought to play a part, might show an association with a particular blood group.

Thomas and Hewitt (1939) found no difference from normal in the distribution of the ABO and MN blood groups in 526 patients with a variety of psychiatric disorders. In the absence of any description of diagnostic criteria it is not possible to comment adequately on their results. A short paper by Lafferty, Knox and Malone (1957) came to the conclusion that no clear-cut correlations could be demonstrated between schizophrenia and ABO, Rhesus, and MN groups. They did, however, find that there was a trend towards a larger number of group A rhesus positives in their schizophrenic population than in the corresponding control group. Little value can be placed on their results, as they gave no adequate description of methods used, no actual figures on which they based their calculations, and no hint of diagnostic criteria used in the selection of cases.

Parker, Theilie, and Spielberger (1961) assessed the distribution of the ABO, MN, Rhesus, Duffy, and Kell blood groups in a strictly defined homogeneous group of manic-depressives and also in a group of psychoneurotic depressive patients. They found a significantly higher incidence of group O in their manic-depressives compared with the distribution in the general Caucasian population ($p < 0{\cdot}001$). As blood group frequencies are available for the distribution of ABO in the North Carolina population from which their manic-depressives were drawn, a more accurate analysis of their results can be made. Using the ABO distribution for 5,080 white North Carolina donors (Hervey *et al.*, 1951), there is still an increased incidence of group O in the manic-depressives, but the value of p is now only $< 0{\cdot}05$. Parker and his colleagues also found a higher incidence of E-positives in their psychoneurotic group compared with the manic-depressive group ($p < 0{\cdot}05$) and with the available population norms ($p < 0{\cdot}001$). Their Kell-positive figures for both types of depressive illness were also higher than expected ($p < 0{\cdot}05$). Their study was prompted by a previous finding (Parker *et al.*, 1959) that there was a relatively high incidence of duodenal ulceration in manic-depressive patients compared with the normal population. The known apparent association of blood group O with duodenal ulceration suggested the possibility of an altered blood

group distribution in manic-depressive illness.

The purpose of the present paper is to report the findings of an investigation into the blood group distribution in a series of 500 new admissions to Whittingham Hospital and the associated psychiatric unit at Sharoe Green Hospital, Preston.

Methods

Collection of Data

All the patients were admitted from Preston and the surrounding county area, which included the towns of Chorley and Leyland. They were considered to be fairly representative of the psychiatric admissions from that part of Lancashire. No attempt was made to select cases, and every new patient seen by the author was automatically included in the analysis of blood groups. It had been decided to exclude any case in which a recent blood transfusion might interfere with the grouping (Clark *et al.*, 1962), but nobody fell into this category. The author personally interviewed every patient at least once, and on more than one occasion when there was any difficulty in reaching a diagnosis. In addition to diagnosis, a total of 59 factors and symptoms commonly found in psychiatric disorders were looked for and recorded when unequivocally present. The Maudsley Personality Inventory was personally administered and scored for the 312 patients who were able to understand and complete the questionnaire satisfactorily.

Diagnostic Criteria

The weakest point in the whole project was considered to be that of diagnosis, as this handicaps most psychiatric research by virtue of the conceptual problems involved. Two ways of partially overcoming this difficulty were envisaged. One was to adopt very strict and consistent diagnostic definitions for each disease category under investigation. It seemed preferable to do this even at the expense of having to exclude many cases which would normally be included in a specific diagnostic group. This meant that smaller numbers were obtained for each diagnostic category, but those included formed a more homogeneous group to which statistical analysis could be more meaningfully applied. The second method was to record individual symptoms and factors, such as: well organized auditory hallucinations; suicidal feelings, intentions or serious attempts; somatic passivity experiences. The following criteria were adopted and adhered to throughout:

(i) Manic-depressive psychosis. All patients who showed periodicity of acute self-limiting mood swings, and no progressive or residual personality deterioration before or after psychotic episodes of elation or depression (Kallmann, 1953). All had had at least one period of hypomania or mania, and most had had at least one period of severe depression accompanied by such symptoms as retardation, diurnal variation, early morning wakening, and impaired concentration. No patient was included who showed more than one of the signs found to be pathognomic of schizophrenia by Lewis and Piotrowski (1954) in their follow-up of patients previously diagnosed as manic-depressive.

(ii) Schizophrenia. All "definite" cases conformed to a definition based on that given by Fish (1964): "Schizophrenia is a group of mental disorders in which there is no coarse brain disease and in which many different clinical pictures can occur. The form and content of some of the symptoms cannot be understood as arising emotionally or rationally from the affective state, the previous personality, or the current situation; with the proviso that if delusional notions and delusion-like ideas are present, the diagnosis cannot be made in the absence of other 'non-understandable' symptoms." It was also decided to extract from this group of "definite" schizophrenics a smaller and more rigidly defined group of cases who unequivocally possessed at least one of Schneider's "first rank symptoms" (Schneider, 1959), i.e. audible thoughts, voices heard arguing, voices heard commenting on one's actions; the experience of influences playing on the body (somatic passivity experience); thought withdrawal and other interferences with thought; diffusion of thought; delusional perceptions of significance or self-reference; and all feelings, impulses and volitional acts that are experienced by the patient as the work or influence of others.

(iii) Involutional and senile depression. This included all severe cases of depression arising for the first time in these periods of life, with the exception of those cases conforming to the criteria for manic-depressive psychosis. The group consisted of truly endogenous depressions, depression arising in life-long neurotic personalities, depression arising in life-long obsessional (anankastic) personalities, and depression reactive to the environmental situations commonly occurring at this time of life.

(iv) Organic states included senile and other degenerative dementias, and all cases where psychiatric symptoms were largely caused by known underlying physical disease.

(v) Personality disorder. This label was applied to all patients whose basic disorder appeared to be an abnormal personality as defined by Schneider (1959). Included were anxiety states, neurotic depressives, obsessional neuroses, inadequates, attention-seeking personalities, and sociopathic personalities.

Serology

The blood samples were taken by the author, venous blood being collected in sterile disposable syringes and placed in standard oxalate bottles. Eight samples were obtained by finger prick. The typing was carried out

TABLE I

Blood Group Distribution for Main Diagnostic Categories

	Blood Groups																						
	A1	A2	A	O	B	AB	MM	MN	NN	KK	Kk	K+ve	kk	CC	Cc	C+ve	cc	D+ve	D−ve	EE	Ee	E+ve	ee
Controls			243	334	58	17																	
Total 500 Patients	134	61	195	266	30	9	171	226	103	2	30	32	468	81	239	320	180	403	97	18	121	139	361
Personality Disorder	54	33	87	118	14	7	82	99	45	1	12	13	213	41	106	147	79	190	36	10	59	69	157
Neurotic Depression	34	23	57	79	12	5	57	63	33	1	7	8	145	27	81	108	45	132	21	5	39	44	109
Organic..	16	4	20	26	3	1	16	23	11	0	3	3	47	7	24	31	19	36	14	1	8	9	41
Involutional-Senile Depression	18	5	23	31	1	1	22	21	13	0	2	2	54	5	27	32	24	39	17	1	12	13	43
Definite Schizophrenia ..	29	12	41	41	5	0	24	47	16	0	7	7	80	14	40	54	33	74	13	5	21	26	61
1st Rank Schizophrenia ..	18	5	23	24	4	0	11	30	10	0	4	4	47	6	28	34	17	44	7	3	10	13	38
Manic-Depressive	6	1	7	25	3	0	11	17	7	0	3	3	32	6	19	25	10	27	8	0	8	8	27
Duodenal Ulcer	2	1	3	22	0	1	11	11	4	0	1	1	25	4	16	20	6	21	5	0	6	6	20

TABLE II

Blood Group Distribution for Sub-Groups and Personality Dimensions

	Blood Groups																						
	A1	A2	A	O	B	AB	MM	MN	NN	KK	Kk	K+ve	kk	CC	Cc	C+ve	cc	D+ve	D−ve	EE	Ee	E+ve	ee
Controls			243	334	58	17																	
Depression	83	39	122	164	22	6	117	124	73	2	16	18	296	49	156	205	109	254	60	10	80	90	224
Suicidal	36	16	52	74	11	4	52	58	31	1	8	9	132	21	75	96	45	115	26	4	34	38	103
Psychotic	50	23	73	107	12	1	55	93	45	1	15	16	177	29	92	121	72	157	36	7	48	55	138
Auditory Hallucinations ..	18	7	25	18	3	0	10	27	9	0	3	3	43	4	25	29	17	39	7	3	9	12	34
Neuroticism > 1 S.D. ..	42	19	61	96	12	3	58	72	42	1	7	8	164	33	78	111	61	143	29	8	46	54	118
Extraversion > 1 S.D. ..	10	6	16	26	3	0	17	21	7	0	4	4	41	2	23	25	20	36	9	0	17	17	28
Introversion > 1 S.D. ..	25	13	38	51	5	1	30	40	25	0	5	5	90	12	43	55	40	74	21	3	28	31	64
Dysthymia	22	9	31	50	5	2	34	25	29	1	4	5	83	13	40	53	35	72	16	5	25	30	58
Psychopathy-Hysteria ..	6	5	11	26	1	1	11	23	5	0	1	1	38	8	20	28	11	33	6	2	12	14	25

within 18 hours of collection by a fully qualified technician who had had adequate previous experience in blood grouping.

The antisera used were those which detected the following antigens: A, A1, B, M, N, C, c, D, E, e, K, and k. All D-negative bloods were tested for D^u, and only E positive bloods were tested for e. The ABO groups were checked by testing each patients' plasma (except where blood was obtained by finger prick) with known A and B cells. The antisera were checked against known control groups for each of the blood groups whenever a fresh batch of patients was being typed. The typing was carried out by standard methods and strictly according to the instructions of the suppliers of the antisera.

All the blood grouping was done "blind", to avoid bias, i.e. the diagnosis in each case was decided upon before typing was carried out, so that the diagnosis could not be influenced by prior knowledge of the patient's blood group. In the same way, the technician carrying out the typing was kept unaware of the diagnosis arrived at for each patient.

The Controls

There has been some debate and controversy over the choice of a control population for blood group frequency studies. The control most often used has been the blood donor population of the area from which the patients were drawn. Buckwalter and Knowler (1958) have pointed out some of the dangers of relying on donor figures as controls. They suggested that homogeneous patient groups were better controls than blood donors. Clarke and his colleagues (1956) suggested that the sibs of patients under investigation should be used as controls, as this would rule out any question of racial stratification being responsible for apparent blood group-disease associations. This method was not considered to be very practical or reliable for research into blood group frequencies in psychiatric patients.

In this study two sets of figures were available for use as donor controls for the ABO system. A total of 6,344 donors from North-West Lancashire was analysed by Kopeć (1956), and the following distribution found—Group A 2,663 (41·98 per cent.), Group O 2,990 (47·13 per cent.), Group B 520 (8·20 per cent.), and Group AB 171 (2·69 per cent.). An analysis of 652 recent donors from the Preston area showed the following distribution—Group A 243 (37·3 per cent.), Group O 334 (51·2 per cent.), Group B 58 (8·9 per cent.), and Group AB 17 (2·6 per cent.). The ABO distribution of the total 500 patients and also of the largest group (the 226 patients with personality disorder) approximated closest to the figures for the 652 Preston Donors, and this latter group was therefore used as the most satisfactory donor control.

The group of 226 patients classed as suffering from personality disorder was decided upon as the best patient control as their ABO distribution was very similar to that of the 652 Preston donors, and the distribution of their C c, D, E, e, M, N, K, and k types was close to that given for English people by Race and Sanger (1962).

Both the donor control and patient control groups were used in the analysis of the data.

Results

Table I shows the total numbers of each blood group for the main diagnostic categories. In addition, 26 patients had a proven duodenal ulcer, the majority having had a partial gastrectomy. Their blood group distribution is included for interest.

Table II shows the total numbers of each blood group for various symptoms and subcategories of mental illness, together with certain personality dimensions derived from the Maudsley Personality Inventory scores.

Table III shows some of the corresponding percentage distributions for the ABO groups.*

* Copies of the percentage distribution tables for all the blood groups have been duplicated and can be obtained from the author.

Table III

Percentage Distribution of ABO Groups

	Blood Groups					
	A1	A2	A	O	B	AB
Controls	—	—	37·3	51·2	8·9	2·6
Total 500 Patients	26·8	12·2	39·0	53·2	6·0	1·8
Personality Disorder	23·9	14·6	38·5	52·2	6·2	3·1
Neurotic Depression	22·2	15·0	37·2	51·7	7·8	3·3
Auditory Hallucinations	39·1	15·2	54·3	39·1	6·5	0·0
Involutional-Senile Depression	32·1	8·9	41·0	55·4	1·8	1·8
Definite Schizophrenia	33·3	13·8	47·1	47·1	5·7	0·0
1st Rank Schizophrenia	35·3	9·8	45·1	47·1	7·8	0·0
Manic Depressive	17·1	2·9	20·0	71·4	8·6	0·0
Duodenal Ulcer	7·7	3·8	11·5	84·6	0·0	3·8

https://doi.org/10.1192/bjp.113.504.1309 Published online by Cambridge University Press

The figures for A1B and A2B are more conveniently treated together as AB, without influencing the results.

In general, the distribution of all the blood groups is not significantly different from that to be expected for the normal population of North-West Lancashire.

In the 35 patients diagnosed as manic-depressive there are 25 who are group O. If we compare the distribution of the ABO groups in manic-depressive psychosis with that of the 652 Preston donor controls we get the following:

$$\text{Relative incidence O : A} = \frac{25 \times 243}{7 \times 334} = 2 \cdot 598.$$

Using the method of Woolf (1955), $\chi^2 = 4 \cdot 796$, and $p < 0 \cdot 05$.

Comparing manic-depressive psychosis with the 226 patients suffering from personality disorder:

$$\text{Relative incidence O : A} = \frac{25 \times 87}{7 \times 118} = 2 \cdot 632.$$

$$\chi^2 = 4 \cdot 617 \text{ and } p < 0 \cdot 05$$

Comparing manic-depressive psychosis with the 87 patients diagnosed as definite schizophrenics:

$$\text{Relative incidence O : A} = \frac{25 \times 41}{7 \times 41} = 3 \cdot 571.$$

$$\chi^2 = 6 \cdot 992 \text{ and } p < 0 \cdot 01.$$

The highest incidence of group A is found in the group of patients experiencing auditory hallucinations, and also in the two categories of schizophrenia. The figures, however, do not reach any degree of significance. The incidence of D-negative blood appears to be much higher than normal in the group of patients suffering from involutional and senile depressions. When comparison is made with other groups, which are matched for age, this increased incidence of D-negative blood is no longer significant.

The E-positive incidence in neurotic depressives is normal, and the Kell-positive incidence in neurotic depressives and manic-depressives is also normal.

As might be expected, the incidence of group O in the 26 patients with duodenal ulcer is higher than in any other group, reaching a value of 84·6 per cent.

Discussion

The finding of an increased incidence of group O in patients suffering from manic-depressive psychosis is in agreement with the results of Parker, Theilie and Spielberger (1961). However, their increased incidence of E-positive blood in psychoneurotic depressives, and of Kell-positives in all depressives, is not supported by this study. It is possible to explain their increased Kell-positives on the assumption that this is a reflection of the normal incidence of this blood group in North Carolina. Their increased number of E-positives in psychoneurotic depression may be just a chance finding, as they themselves state; but it is also possible that the two psychoneurotic groups are not strictly comparable.

Although these results in manic-depressive psychosis appear to be in agreement, psychiatric diagnosis is so relatively uncertain, that it would be most unwise to combine the data, as has been done for duodenal ulcer series from different centres. Wiener (1962) has criticized this tendency to combine results and claim the total as homogeneous. His criticism would certainly be justified as regards psychiatric diagnoses.

In the same paper, Wiener also suggests that one should not apply the conventional 5 per cent. level as proof of "statistical significance". I would agree with this, and even the 1 per cent. level ($p < 0 \cdot 01$) may not have the same degree of significance in associations between blood groups and disease as it has in other fields. If one does accept the 1 per cent. level as significant, this result is only found in comparing the incidence of group O in 35 manic-depressive patients with that in 87 schizophrenics. However, the numbers are small, and the diagnostic difficulties are so great that I feel these figures only suggest a possible trend, and further work will be necessary to confirm or refute the relationship of group O to manic-depressive psychosis.

If, on the basis of these results and those of Parker, Theilie, and Spielberger (1961), one can accept the probability that there is an association between group O and manic-depressive psychosis, the problem remains as to its meaning.

Parker and his colleagues suggest that their

findings support the impression of a possible genetic factor in manic-depressive illness. They also discuss the possible relationship between type O blood and "the psychodynamic and alimentary problems that are observed in both manic-depressive and peptic ulcer patients". It is of interest to note that most of the 26 peptic ulcer patients in the present study were diagnosed as neurotic depressives, and not one was considered to be suffering from manic-depressive psychosis.

Racial stratification could be the simple explanation of the suggested association. According to this hypothesis there would be a section of the population with a high incidence of group O and also a high incidence of manic-depressive psychosis, the occurrence of both together in the same section being entirely due to chance. Whilst this could apply to manic-depressive illness, it is thought to be unlikely to be applicable to such associations as that existing between group O, secretor status and duodenal ulcer (Clarke *et al.*, 1956).

Clarke and his colleagues (1956), in discussing the increased incidence of group O in duodenal ulceration, postulate that there could be a maternal effect which might depend on a behaviour difference in group O women affecting the upbringing of their children. They say: "Such behaviour differences have never been adequately investigated in man and are by no means an impossible explanation. In more thoroughly studied organisms, however, genes affecting the morphology of an animal are known sometimes to affect its behaviour." The increased incidence of group O in duodenal ulceration might be due entirely to the presence of a large group of ulcer patients in whom emotional factors are predominant in the production of ulceration. It could be that group O is associated with inherited tendencies towards the development of these particular emotional factors, and only indirectly with the presence of an actual ulcer crater. The almost universal acceptance of peptic ulcer as a surgical problem has diverted attention from the psychological aspects. In this hospital, 5 per cent. of all male admissions in the last few years have had a partial gastrectomy, and in this present series of 500 admissions 32 have had definite peptic ulceration (26 being duodenal ulcers, and 22 of these being group O).

As has been previously mentioned, these apparent associations between blood group and disease could also be due to pleiotropic effects of blood group genes, the ABO locus possibly having an effect in controlling certain enzyme systems. The gene modification which produces a group O individual might then modify these enzyme systems sufficiently to make that individual more prone to manic-depressive psychosis. The true illness would only appear in the presence of other genetic and environmental factors, which need not be as prominent as in group A, B, or AB individuals who develop manic-depressive psychosis.

Future research into manic-depressive psychosis might reveal significant metabolic abnormalities which could be related to the production or presence of symptoms. It would then be interesting to assess the distribution of genetic markers such as blood groups in those patients who possessed these abnormalities.

Summary

This paper describes an investigation into the frequency of a wide range of blood groups in a series of 500 patients admitted to hospital with some form of mental illness.

Previous work has suggested a possible association between blood group O and manic-depressive psychosis. An analysis of the present data adds some support for such an association. The numbers are small, but the adoption of strict diagnostic criteria has ensured a more homogeneous group of patients. The possibility of a causal effect is considered to be most unlikely. Racial stratification may be the answer, but further studies from different regions of the world, including the collection of sibship data, will be necessary before any definite conclusions can be reached. Other possibilities considered are a pleiotropic effect of blood group genes, and a maternal effect.

A word of warning is sounded about the over-eager acceptance in this field of the usual 5 per cent. and 1 per cent. levels of significance. Adopting this more cautious approach, the general conclusion is that there is no significant correlation between the ABO, MN, Rhesus and

Kell blood groups and psychiatric disorders. However, there is the suggestion of an increased incidence of group O in manic-depressive psychosis, and further research on this possible association might be worth while.

ACKNOWLEDGMENTS

This work was carried out with a grant from the Manchester Regional Hospital Board.

I am also indebted to Whittingham Hospital Management Committee for their help, to Drs. J. D. Glynn and C. S. Parker for allowing me full access to their patients, and to Mrs. Joan Edwards and Mr. R. Benson who did the blood grouping.

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(*Received 15 November, 1966*)