BLOOD GROUPS IN HEALTH AND IN MENTAL DISEASE.

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THE distribution of the blood-groups in persons suffering from mental disease has been widely investigated, but the literature is full of conflicting statements. It may fairly be taken that no one has yet demonstrated any statistically significant alteration of the blood-group distribution in any other disease, but there have been many claims for variation in mental diseases.

The present investigation consists of the comparison of the group distribution (*A–B–O*, *M–N* and *O–*A_1*–*A_2*–B* systems) in a series of 526 mental patients in Shenley Hospital with that obtaining in a parallel series of 374 normal persons. The mental patients have been classified into disease groups, and the group distribution in each of these categories is compared statistically. In the result, we found no deviation from the normal in our mental series, and the data for the combined series of 900 persons is analysed as a sample of the population at large.

SURVEY OF LITERATURE.

The literature upon this subject is fairly extensive, and we have summarized the more important investigations in Table I. The larger series generally show a normal group distribution, the anomalous distribution of others being due, we believe, to two causes. Firstly, there is the question of technique, and it is significant that the most divergent results are the oldest. Those of Feldman and Elmanowitsch (1925), who found a third of their patients belonging to Group *AB*, are capable of no other interpretation than that they failed to distinguish between pseudo- and true iso-agglutination. Secondly, there is the fact that practically none of the earlier investigations were subjected to any statistical test, and that inferences were drawn from an analysis of fifty persons, which were given equal weight to those drawn from 500.

In general, the majority of workers have found no alteration in the group distribution in mental disease as a whole (Gundel, 1928; Herman and Derby, 1937; Ohnsorge, 1927; Pilcz, 1927; Saleck, 1929; Shusterov, 1927; Snyder,

1926; Vuori, 1929). In particular, Bunker and Myers (1927), Jacobsohn (1926) and Saleck (1932) found a normal distribution in general paresis, the disease which has been most widely investigated. An increase in Group *A* was reported in this disease by Myer (1928) and by Kasevarov (1928); an increase in Group *B* by Wilczowski (1927), and an increase in both Groups *B* and *AB* by Gundel, Guttierrez Angel (1932) and by Perkel and Israelson (1928). Fattovitch (1928) found an apparent increase in Group *O* in a small series of cases. Hermann and Derby found a normal distribution in schizophrenia, manic-depressive insanity, general paresis and the involutional psychoses. Martial (1935) could find no relationship between the blood-group, psychological make-up and physical characteristics of any of his patients.

Amsel and Halber (1925), Straszynski (1925) and Poehlmann (1934) investigated the relationship between blood-groups and a positive Wassermann reaction in diseases of luetic origin. Straszynski showed an apparent but not significant increase in Groups *B* and *AB*, but Poehlmann's (300) and Amsel and Halber's (1736) cases gave a normal distribution.

In schizophrenia the literature is again confusing. Chominskij and Sustova (1927) state that the distribution is normal in a large series, but suggest that the *A*/*B* ratio is higher, especially in male schizophrenics. Meyer also found a normal distribution in his series of over 500 cases, but with small numbers of manic-depressives and idiots there were apparent variations. Proescher and Arkush (1927) found a normal distribution in more than 2,000 cases of the disease, but their figures for all psychotics are difficult to interpret, the proportion of *O* bloods being excessively high for the mixed American population. Similar results have been obtained by Kruse (1929), Pankratov (1929), Raphael, Searle and Scholten (1927), Sola (1931), Somogyi and Angyal (1931), and by Toulouse, Schiff and Weiseman-Netter (1926).

The most common claim for variation in schizophrenia is that there is an increase in Group *B* (Canuto, 1928; Palmieri, 1929; Pannachi, 1928; Rubaschin and Lieserman, etc.). Würz (1928), however, made the opposite claim from the examination of a fairly large series—that the Group *B* incidence was low. His results are not actually significant, and are probably due to the use of too weak anti-*B* test sera. We have analysed the reported Group *B* frequencies in schizophrenia for significance by the D/σ_c test (*vide infra*) and the results are shown in Table II. In no case is the apparent deviation from normal of any statistical significance.

Yorshis and Gottlieb (1934) have suggested that there is an increased tendency in schizophrenia for the mother's group to be transmitted to the daughter and for the son to inherit his father's group. The number of their cases is too small to warrant any such deduction, and it is now well established that the blood-group genes are not in any way sex-linked. Their total distribution figures, being based upon family material, are not to be taken as true frequencies.

In this country the only investigation appears to be that of Penrose (1932), who examined two series of mongolian imbeciles and of non-mongolian mental defectives at Colchester. In each series the group distribution was normal.

The only investigations upon the *M*–*N* distribution which we can find are those of Hilgerman and Birnbaum (1934), whose data appear unreliable, and those of Herman and Derby, who found no departure from the normal in a series of 1,800 patients.*

The general consensus of opinion is that the blood-group distribution is normal in any large series of mental patients taken as a whole. The discrepancies which have been reported, and to which undue importance has been attached, are due, apart from questions of personal technique, to the interpretation of figures obtained from a small series of patients as significant, without subjecting them to any statistical test.

* Recent papers which we have been unable to obtain are those of Bianchini (1937), Imber (1934), Makowiecz (1936), Prokop and Skalickova (1936), Sogliani (1937) and Spagnoli (1936).

TABLE I.—*Blood-groups in Mental Disease.*

All types.

Author.	Country.	Total cases.	*O.*	*A.*	*B.*	*AB.*
Herman and Derby	U.S.A.	1,849	43·7	37·8	14·0	4·5
Proescher and Arkush	,,	1,525	53·8	28·2	16·5	1·5
Fattovitch	Italy	300	56·3	30·0	9·7	4·0
Leischner (1)	Prague	1,331	32·6	40·7	20·0	6·7
,, (2)	,,	..	32·3	42·8	19·1	5·8
Vuori	Finland	274	35·4	42·7	15·3	6·6

Schizophrenia.

Herman and Derby (3)	U.S.A.	218	42·7	38·5	15·6	3·2
,, ,, (4)	,,	209	44·0	37·3	12·0	6·7
Raphael *et al.*	,,	800	41·0	41·4	11·5	6·1
Snyder	,,	200	45·0	42·0	9·0	4·0
Yorshis and Gottlieb (5)	,,	121	35·0	32·0	26·0	7·0
Toulouse *et al.* (6)	France	..	31·0	50·0	13·4	5·6
Fattovitch	Italy	134	53·7	28·9	13·4	6·0
Chominskij and Schustova	Germany	276	28·5	44·3	17·4	9·8
Meyer	,,	526	38·7	42·3	14·5	4·5
Saleck	,,	2,380	43·2	41·8	10·3	4·7
Somogyi and Angyal	,,	411	32·6	42·6	18·1	6·8
Wilczowski	,,	227	30·4	41·4	20·3	7·9
Leischner	Prague	312	34·3	38·5	21·8	5·4
Pilcz	Vienna	96	36·5	42·7	12·5	8·3
Würz	Basle	334	41·0	50·9	4·5	3·6

Manic-depressive Psychosis.

Herman and Derby	U.S.A.	188	42·0	37·8	14·9	5·3
Raphael *et al.*	,,	300	43·7	40·3	8·3	7·7
Fattovitch	Italy	47	72·0	19·0	7·0	2·0
Chominskij and Schustova	Germany	27	33·3	33·3	18·4	15·0
Meyer	,,	32	28·1	31·2	34·4	6·3
Saleck	,,	298	42·0	40·3	12·7	5·0
Somogyi and Angyal	,,	35	37·1	40·0	20·0	2·9
Leischner	Prague	98	34·7	36·7	22·5	6·1
Pilcz	Vienna	61	37·7	32·8	16·4	13·1

General Paresis.

Author.	Country.	Total cases.	O.	A.	B.	AB.
Bunker and Myers	U.S.A.	91	39·5	41·5	14·5	4·5
Herman and Derby	,,	273	45·4	37·7	11·4	5·5
Toulouse *et al.* (6)	France	..	42·8	34·6	14·3	8·3
Fattovitch	Italy	14	50·0	28·6	7·1	14·3
Jacobsohn	Germany	100	33·0	47·0	17·0	3·0
Meyer	,,	20	27·8	50·0	11·1	11·1
Ohnsorge	,,	100	28·0	44·0	18·0	10·0
Saleck	,,	202	43·6	45·0	9·4	2·0
Wilczowski	,,	119	31·1	36·2	18·4	14·3
Chominskij and Schustova	,,	37	59·4	18·9	16·3	5·4
Leischner	Prague	218	30·3	40·0	20·6	8·7
Perkel and Israelson	Odessa	100	33·0	47·0	17·0	3·0
Pilcz	Vienna	226	36·7	42·9	15·9	4·4
Poehlmann (7)	Germany	300	41·7	42·3	13·0	3·0
Amsel and Halber (7)	Warsaw	1,736	31·2	38·4	21·3	8·3

Epilepsy.

Kaunauchova	Germany	355	29·0	29·0	31·0	11·0
Somogyi and Angyal	,,	46	36·9	45·7	15·2	2·2
Chominskij and Schustova	,,	52	34·6	40·4	15·4	9·6
Meyer	,,	127	34·6	37·8	18·1	9·4
Saleck	,,	181	40·9	44·2	11·0	3·9
Pilcz	Vienna	46	32·6	41·3	21·7	4·4
Leischner	Prague	76	26·3	55·2	11·8	6·5
Snyder	U.S.A.	150	48·0	40·0	10·0	2·0

Miscellaneous.

Penrose (8)	England	158	41·1	49·4	7·6	1·9
,, (9)	,,	225	42·5	47·3	6·7	3·5

(1) Psychotics.
(2) Neurological cases.
(3) Paranoid type.
(4) Catatonic type.
(5) Family material.
(6) Total number not stated.
(7) All syphilitics.
(8) Mongolian imbeciles.
(9) Non-mongolian mental defectives.

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TABLE II.—*Significance of Variations in Group B Frequencies in Schizophrenia.*

Author.	Cases.	p_B.	σ_B.	D.	σ_c.	D/σ_c.
*Normal (U.S.A.)**	20,000	·100	·002	..	..	..
Herman and Derby (1)	218	·156	·025	·056	·163	·34
,, ,, (2)	209	·120	·002	·020	·157	·13
Raphael *et al.*	800	·115	·011	·015	·116	·13
Snyder	200	·090	·020	·010	·149	·07
Yorshis and Gottlieb	121	·260	·040	·160	·230	·70
*Normal (Italy)**	17,157	·140	·003	..	..	..
Fattovitch	134	·134	·029	·006	·179	·03
*Normal (Germany)**	16,750	·158	·003	..	..	..
Chominskij and Schustova	276	·174	·023	·016	·160	·10
Meyer	526	·145	·015	·013	·134	·10
Saleck	2,380	·103	·006	·054	·084	·66
Somogyi and Angyal	411	·181	·019	·023	·148	·16
Wilczowski	227	·203	·025	·045	·168	·27
Leischner	312	·218	·023	·060	·162	·37
*Normal (Austria)**	1,000	·201	·013	..	..	..
Pilcz	96	·125	·032	·076	·211	·36
*Normal (Switzerland)**	2,500	·123	·007	..	..	..
Würz	334	·045	·011	·078	·134	·58

* From Wiener, A. S., *Blood Groups and Blood Transfusion*, Baltimore, 1935, first edition.
(1) Paranoid cases.
(2) Catatonic cases.

MATERIAL.

Our normal group is composed of 374 persons who have been examined during the past three years. They consist of a heterogeneous mixture of student and master, policeman and criminal, mother and father, nurse and doctor, and the many other persons whom we have grouped for one purpose or another during this time. Throughout we have excluded family material, and when a family was grouped, only the parents were included in the final analysis.

The mental group consists of 526 patients in this hospital. We have grouped every new admission to the hospital and every Wassermann blood for six months, and have made up the numbers from some of the chronic patients. Of the 526 bloods, 301 came from the reception wards, 175 from the infirmary wards and 50 from the chronic blocks. At the same time the iso-agglutinin, heterophile agglutinin and heterophile hæmolysin titres of the Wassermann sera were determined, the results of these investigations being discussed in a subsequent paper (Thomas and Hewitt, 1939).

The mental cases are further divided into six disease groups: I. Manic-depressive psychosis, II. Schizophrenia, III. Epilepsy, IV. Senile and Organic Dementias, V. Delusional Insanity, and VI. Miscellaneous mental disorders.

METHODS.

The methods which we have used for grouping the bloods are essentially the same as those described by one of us (Thomas, 1937), and by Taylor and Prior (1938*a*, *b*). We have modified the method in certain minor particulars, such as the size of the tubes and the elimination of sodium citrate.

Collection of Blood Samples.

Blood was taken from the finger-tip into 0·85% saline to form an approximately 2% suspension. This was adjusted before use to a 1/100 blood (1/200 cell) suspension by eye. With Wassermann bloods the cells were washed from the clot by gentle agitation with saline, and the resulting suspension allowed to stand for 15 minutes. The upper part was then pipetted off into a clean tube. By this means any small cell aggregates which have been separated from the clot are removed, leaving a microscopically particulate cell suspension. The cells were always examined on the day on which they were taken.

Test Sera.

I. *Anti*-A *and* -B *sera* (*normal*).—These sera were prepared in the usual manner, and were stored in the refrigerator (2° C.) after heat sterilization or preservation with merthiolate, the latter being found to be an excellent method for serum storage. Five or six sera of each type were available, and we insisted on a titre of not less than 256 for each.

II. *Anti*-A *and* -B *sera* (*rabbit immune*).—Each of the mental cases, and approximately 100 of the normal cases were tested with immune anti-*A* and -*B* sera; these were prepared by a modification of the method described by Boyd and Boyd (1937*a*).

Rabbits were immunized with a 30% suspension of washed cells of the appropriate group, the dose being 1 ml. on alternate days. Usually seven injections were given in the first course, and the majority of the animals gave a good serum a week or ten days after the seventh injection. If a preliminary test showed the anti-human titre to be sufficiently high (10,000 or more) the animal was bled out on the tenth day. We found the most satisfactory method of bleeding was under intravenous nembutal anæsthesia with a fine glass cannula in the carotid artery. By this means we were able completely to exsanguinate the animal with the loss of but two or three drops of blood, the final yield being in the region of 1/20th to 1/25th of the body-weight. The blood was collected in sterile tubes, the serum separated, inactivated and stored frozen either in ampoules or in serum bottles.

For absorption the sera were diluted from 1/10 to 1/20 according to their titre and absorbed with washed cells of the heterologous group (type *MN* cells were invariably used). As for *M* and *N* sera, the ideal fluid for absorption is that dilution of the crude serum which is exactly absorbed by one-half its volume of packed cells in half-an-hour at room temperature. Taylor and Prior have commented upon this, and we agree that the preparation of all immune blood-grouping sera is a matter of "playing about" to find the optimum serum dilution for absorption; each serum is different, and it is impossible to guarantee that a given serum will repeat its behaviour in a subsequent absorption. It is, however, easier to prepare immune *A* and *B* sera than to make *M* and *N* sera, and the titre of the former is considerably higher. None of our immune sera of this type had a titre of less than 256.

It is a curious feature of immune sera, and one which we have not seen commented upon elsewhere, that even with relatively low titres, the final aggregate of cells in the test proper is more firm, compact and plaque-like than with iso-sera. Moreover, shaking breaks it up less easily.

The use of these immune sera serves as an added check upon the iso-sera, and we have never found even the weakest A_2 blood not to be agglutinated by such sera.

III. *Anti*-M *and* -N *sera*.—The *M* and *N* blood groups were demonstrated by

Landsteiner and Levine (1928) by the use of rabbit immune sera. There are many methods of preparing these sera, and the one which we have employed in no way differs from that described by Taylor and Prior (one of us—J. C. T.—is greatly indebted to Dr. G. L. Taylor for allowing him to work in his laboratory some years ago, and there learn the method of preparation of these sera).

The method consists of the daily injection of 1 ml. of either *OM* or *ON* cells by the intravenous route for a week, followed by a week's rest; the whole course is then repeated as necessary. If a rabbit did not yield a good serum after three courses it was rejected. When an animal produced a good serum it was bled out and the serum stored frozen after inactivation.

For absorption we have constantly used A_1M and A_1N cells; for a number of sera we used pooled *O*, A_1 and *B* cells, and for others A_1B cells of the appropriate *M–N* type.. By this means we ensured the complete removal of any naturally occurring anti-*A* or -*B* agglutinins in the rabbit serum (Clausen, 1934). The use of A_1B cells is not to be recommended, for the content of the A_1 receptor is lower than with cells containing that agglutinogen alone. That volume of A_1 cells which is required to remove the anti-*A* agglutinin from a crude serum will be insufficient if A_1B cells are substituted. Again, the aim is to arrive at the optimum dilution which is exactly absorbed by a half volume of packed cells in half-an-hour, as repeated absorptions tend to lower the titre of the homologous agglutinin. We have not used sera unless they gave a definite macroscopic agglutination in a *final* dilution of 1/32. Taylor and Prior require a positive agglutination in a *serum* dilution of 1/8. Throughout we have used three sera of each type.

IV. *Anti-*A_1 *sera.*—Anti-A_1 sera were prepared by absorbing anti-*A* sera with A_2 cells. Originally the absorbing cells which we used were from one of us (Group A_2B). This group has been confirmed by a number of workers, but absorption even with an excess of cells does not result in an entirely specific anti-A_1 serum; it still agglutinates some, but not all A_2 bloods. This fact was pointed out by Dr. Taylor some years ago, and since then we have used a pooled sediment of A_2 cells for absorption. The resulting sera are always weak, but we have succeeded in keeping them within the titre range of the *M* and *N* sera. Attempts to prepare a specific immune anti-A_1 serum have failed.

In certain cases of difficulty we have titrated the cells against anti-*A* and -A_1 sera, A_2 and A_2B cells being markedly less sensitive than those containing the A_1 factor (Friedenreich and Zaccho, 1931).

The Test Proper.

The tests were set up in rimless tubes (2 in. × ⅜ in.) in a wooden block rack. The unit which we adopted throughout was 0·1 ml., and equal volumes of serum and cell suspension were mixed. To avoid pseudo-agglutination the iso-sera were diluted 1/2 or 1/4 before use. Several sera of each type were used. With each batch of tests we put up a series of control bloods of known groups to ensure the potency and specificity of the sera.*

The tubes were read after two hours at room temperature, first by the naked eye, and if apparently negative, microscopically. By the use of the larger bore tubes, and by reading down as well as through the tubes against a fairly bright background, we found that the microscopic readings agreed with the macroscopic in practically every case. The larger tubes have the advantage that they fit the racks more closely and that they are easier to clean.

Our system of recording was ++++ (one large clump), +++ (several clumps with a clear substrate after shaking), ++ (small clumps with a turbid substrate), + (just visible macroscopic agglutination, definite microscopically), and ± (faint microscopic agglutination). The ± readings were usually anomalous, and repetition with different sera gave negative results.

* We were fortunate in having A_1BN and A_2BM cells available as controls among the staff; our usual series consisted of A_1M, A_1BN, A_2BM, OMN and A_1MN cells, the *N* factor in the last blood being weak.

Blood-Group Distribution in Normal Persons.

Among the 374 normal persons which we examined, the blood-group distribution which we observed was—

Group.	*O.*	*A.*	*B.*	*AB.*	Total.
Frequency (f)	156	162	38	18	374
Proportion (p)	·417112	·433156	·101604	·048128	1·000000
σ_p*	±·025497	±·025622	±·015623	±·011068	..

* For statistical purposes our results are expressed in *proportions* rather than *percentages*; a proportion of ·417112 corresponds to 41·7112%.

The probable error of any observed proportion, p, is given by—

$$\text{P.E.}_p = \cdot 6745\sqrt{\frac{p(1-p)}{P}},$$

where P is the number of persons observed.

The standard error of p (σ_p) which is more commonly used in this country is obtained by substituting—

$$p = \frac{\text{P.E.}_p}{\cdot 6745},$$

or—

$$\sigma_p = \sqrt{\frac{p(1-p)}{P}}.$$

In view of the fact that there is a close correlation between the normal and mental series, and that we have taken the combined totals as representative of the group distribution among 900 of the population, a statistical analysis of this separate series is redundant. We have therefore fitted our combined totals alone to the accepted theories of blood-group heredity.

The distribution of the *M–N* groups was—

Group.	*M.*	*N.*	*MN.*
f	116	77	181
p	·310161	·205882	·483957
σ_p	±·023920	±·020908	±·025841

To ensure that our *M–N* sera were not contaminated with either of the anti-*A* or -*B* agglutinins, the *M–N* distribution in each of the four primary groups was determined.

Group.		*O.*	*A.*	*B.*	*AB.*
M	f	47	52	12	5
	p	·310282	·320988	·315789	·277778
	σ_p	±·036734	±·033069	±·075405	±·105570
N	f	32	33	9	3
	p	·205128	·203703	·236842	·166667
	σ_p	±·032329	±·031643	±·068975	±·087841
MN	f	77	77	17	10
	p	·493590	·475309	·447369	·555555
	σ_p	±·040029	±·039691	±·080660	±·117121

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There being no significant deviation in the proportions of the M–N types in the four groups (the differences in group AB being adequately accounted for by the smallness of the numbers), our sera were not contaminated.

The A_1–A_2 proportions were—

$$\begin{array}{rl} A_1 + A_1B = 147 & (\ \cdot 816667 \\ A_2 + A_2B = \ 33 & (\ \cdot 183333 \end{array} \pm \cdot 028841)$$

$$180\ (1 \cdot 000000)$$

Blood-Group Distribution in Mental Patients.

The observed distribution for the whole series of 526 mental patients was—

Group.	*O.*	*A.*	*B.*	*AB.*	Total.
f	223	232	53	18	526
p	·423955	·441065	·100760	·034220	1·000000
σ_p	±·021547	±·021649	±·013125	±·007927	..

Group.	*M.*	*N.*	*MN.*	Total.
f	163	108	255	526
p	·309886	·205323	·484791	1·000000
σ_p	±·020164	±·017612	±·122043	..

The test for contamination gave—

Group.		*O.*	*A.*	*B.*	*AB.*
M	f	68	71	18	6
	p	·304933	·306035	·339622	·333333
	σ_p	±·030900	±·030255	±·065052	±·110856
N	f	46	46	13	3
	p	·206278	·198275	·245283	·166667
	σ_p	±·027096	±·026176	±·059100	±·087841
MN	f	109	115	22	9
	p	·488789	·495690	·415095	·500000
	σ_p	±·033474	±·032825	±·067688	±·117851

Again, therefore, there was no contamination.

The A_1/A_2 ratio was

$$\begin{array}{rl} A_1 + A_1B = 203 & (\ \cdot 812000 \\ A_2 + A_2B = \ 47 & (\ \cdot 188000 \end{array} \pm \cdot 024710)$$

$$250\ (1 \cdot 000000)$$

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Comparison of Normal and Mental Series.

In comparing any two series of blood-grouping data to determine whether or not there is any significant difference between them, use is made of the D/σ_c ratio, D being the observed difference between the proportions of the two groups, and σ_c being given by—

$$\sigma_c = \sqrt{\sigma_1 + \sigma_2},$$

where σ_1 and σ_2 are the standard errors of the two frequencies under comparison. A difference is not significant unless it is more than three times the combined standard error (σ_c), i.e., with a value of D/σ_c of less than 3, D is not significant.

With our two series of normal (n) and mental (m) patients, the D/σ_c test gives—

Group.	*O.*	*A.*	*B.*	*AB.*
p_m	·423955	·441065	·100760	·034220
p_n	·417112	·433156	·101604	·048128
D	·006843	·008909	·000844	·005908
σ_c	·214579	·217419	·169553	·137822
D/σ_c	·031890	·040976	·004977	·042866

Group.	*M.*	*N.*	*MN.*
p_m	·309886	·205323	·484791
p_n	·310161	·205882	·483957
D	·000275	·000559	·000834
σ_c	·209962	·196265	·218824
D/σ	·001309	·002838	·003811

There is, therefore, no significant difference between the two series of persons, and in mental disease taken as a whole, both the *A–B–O* and the *M–N* blood-group distributions are normal.

Distribution in Individual Disease Groups.

The mental patients were divided into six disease groups, the majority falling into the manic-depressive class. With such a restricted classification as this, some of the patients were difficult to place; when such difficulty arose, the primary state of the patient on admission to hospital was used for this analysis in preference to the state of the patient at the time of

examination. The distribution of the patients among the various groups was as follows :

Disease category.	Frequency.	Percentage.
Manic-depressive psychosis	257	48·83
Schizophrenia	67	12·73
Epilepsy	9	1·80
Organic and senile dementia	94	17·85
Delusional insanity	65	12·34
Miscellaneous mental disorders	34	6·45
Total	526	100·00

The manic-depressive psychoses, schizophrenias, dementias and delusional insanities form large enough groups to allow of statistical analysis, and each of these groups has been treated in detail. The epileptic and miscellaneous groups are too small and have not been so examined. For simplicity we have adjusted the data for comparison to four significant figures, and the distribution in each group is compared with that in the combined series of 900 persons.

A. *Manic-depressive Psychosis.*

The observed distribution and the D/σ_c test in this class was—

$$P = 257.$$

Group.	*O.*	*A.*	*B.*	*AB.*	*M.*	*N.*	*MN.*
f	107	117	26	7	78	53	126
p	·4163	·4553	·1011	·0273	·3035	·2062	·4903
σ_p	±·0307	±·0311	±·0181	±·0080	±·0287	±·0252	±·0336
D/σ_c	·0222	·0802	·0000	·1050	·0302	·0030	·0263

There is thus no significant deviation from the normal group distribution in this series of 257 manic-depressives.

B. *Schizophrenia.*

$$P = 67.$$

Group.	*O.*	*A.*	*B.*	*AB.*	*M.*	*N.*	*MN.*
f	27	28	8	4	23	12	32
p	·4030	·4179	·1194	·0597	·3433	·1791	·4776
σ_p	±·0599	±·0585	±·0395	±·0060	·0580	±·0452	±·0610
D/σ_c	·0654	·0727	·0823	·1762	·1229	·1094	·2044

Although this series is small, there is no statistical evidence of any deviation from the normal distribution, and in particular there is no increase in

Group *B*. We have not had the opportunity of checking the statement of Yorshis and Gottlieb that in this disease there is a sex linkage of the groups, but on *a priori* grounds this is extremely improbable.

c. *Epilepsy*.

This group consisted of nine patients only, and is not susceptible of statistical analysis. The observed groups were *OM*, *AM*, *AN*, *AMN* and *BN* (once each), and *OMN* (four times).

d. *Organic and Senile Dementias*.

$P = 94$.

Group.	*O.*	*A.*	*B.*	*AB.*	*M.*	*N.*	*MN.*
f	44	38	7	5	32	21	41
p	·4681	·4042	·0745	·0532	·3404	·2234	·4362
σ_p	±·0514	±·0495	±·0271	±·0230	±·0478	±·0452	±·0515
D/σ_c	·1813	·1323	·1381	·0767	·1209	·0734	·1847

Thus the small apparent deviations in this group are not statistically significant, and are accounted for by the smallness of the sample.

e. *Delusional Insanity*.

$P = 65$.

Group.	*O.*	*A.*	*B.*	*AB.*	*M.*	*N.*	*MN.*
f	24	31	8	2	20	14	31
p	·3692	·4769	·1231	·0308	·3077	·2154	·4769
σ_p	±·0600	±·0619	±·0407	±·0214	±·0572	±·0510	±·0619
D/σ_c	·1845	·1396	·0977	·0551	·0085	·0386	·0268

Here again the observed variations in group distribution are only of a minor degree without statistical significance.

f. *Miscellaneous Mental Disorders*.

The smallness of the numbers in this group does not allow of statistical treatment. The observed distribution among these 36 patients was—

Group.	*O.*	*A.*	*B.*	*AB.*	*M.*	*N.*	*MN.*
f	16	15	3	0	8	6	20
p	·4706	·4412	·0082	·0000	·2353	·1765	·5882

The deviation in these proportions is due to the smallness of the sample and is of no significance.

Blood-Group Distribution in the Combined Series of 900 Persons.

The A–B–O System.

There being no significant difference between the two groups of normal persons and mental patients, we may combine the two and take the combined totals as representative of the group distribution in a sample of 900 persons from the population at large. This is the largest series which has been investigated in this country.

The distribution of the four primary blood-groups in the combined series is—

Group.	*O*.	*A*.	*B*.	*AB*.	Total.
f	379	394	91	36	900
p	·421111	·437778	·101111	·040000	1·000000
σ_p	±·016420	±·016537	±·010049	±·006532	..

Bernstein (1924, 1925) first formulated the theory of inheritance of the blood-groups which is accepted to-day. He showed that the four groups are inherited by two of three allelomorphic genes, *A*, *B* and *O* (or, as he called the last gene at the time, *R*, this gene being a Mendelian recessive).

If p, q and r represent the frequencies of the three genes, *A*, *B* and *O* respectively, the frequency with which one would expect to find the various phenotypes is given by—

Phenotype.	Genotype.	Frequency.
O	*OO*	r^2
A	*AA*	p^2
	AO	$2pr$ } $p^2 + 2pr$
B	*BB*	q^2
	BO	$2qr$ } $q^2 + 2qr$
AB	*AB*	$2pq$

From this it can be shown that—

$$p = 1 - \sqrt{\overline{O} + \overline{B}}$$
$$q = 1 - \sqrt{\overline{O} + \overline{A}}$$
$$r = \sqrt{\overline{O}}$$

where $\overline{O}$, $\overline{A}$ and $\overline{B}$ represent the observed proportions of the phenotypes.

By definition, $p + q + r = 1$, but as Bernstein (1930*b*) has shown, this relation is never exact with any observed set of frequencies. He has produced, and Stevens (1938) has elaborated a method for increasing the exactness of this relationship by considering the amount by which the original sum differs from unity (D).

From the above equation—

$$D = 1 - (p + q + r)$$
$$= \sqrt{\overline{A} + \overline{O}} + \sqrt{\overline{B} + \overline{O}} - \sqrt{\overline{O}} - 1$$

and the applied corrections are given by—

$$p' = (1 + \frac{D}{2})\,(1 - \sqrt{\overline{O} + \overline{B}})$$

$$q' = (1 + \frac{D}{2})\,(1 - \sqrt{\overline{O} + \overline{A}})$$

$$r' = (1 + \frac{D}{2})\,(\sqrt{\overline{O}} + \frac{D}{2})$$

where p', q' and r' are the improved gene frequencies.

With the frequencies which we observed, the initial equation becomes—

$$p = 1 - \sqrt{\overline{O} + \overline{B}} = \cdot 27735 1$$
$$q = 1 - \sqrt{\overline{O} + \overline{A}} = \cdot 073237$$
$$r = \sqrt{\overline{O}} = \cdot 648931$$
$$\text{Sum} = \cdot 999519$$
$$D = \cdot 000481$$

Thus
$$p' = \cdot 277418$$
$$q' = \cdot 073245$$
$$r' = \cdot 649327$$
$$\cdot 999990$$

and the original postulate of $p + q + r = 1$ is, to all intents, fulfilled. Our results are therefore in good agreement with Bernstein's original theory of blood-group inheritance.

Bernstein (1930*a*) has shown that the probable error of D is given by—

$$\text{P.E.}_D = \frac{\cdot 6745}{P}\sqrt{\frac{pq}{2\,(1-p)(1-q)}}$$

where P is the number of persons examined. The value of σ_D is again given by ubstitution of $\sigma_D = \frac{\text{P.E.}_D}{\cdot 6745}$.

From the values of p, q and r calculated from the initial equation—

$$D = \cdot 000481$$
$$\sigma_D = \cdot 004105$$
$$D/\sigma_D = \cdot 117$$

Thus the observed deviation, D, is less than the standard error for the series and the statistical fit is good.

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Recently Boyd (1938) has produced a workable nomogram for the rapid determination of p, q and r for any set of observed figures, together with one for calculating σ_D. Applied to our figures the nomogram gave—

$$\begin{aligned} p &= \cdot 277 \\ q &= \cdot 073 \\ r &= \cdot 649 \\ \hline & \cdot 999 \\ D &= \cdot 001 \\ \sigma_D &= \cdot 0041 \\ D/\sigma_D &= \cdot 244 \end{aligned}$$

It is interesting to note that the same figures are given for σ_D by both the nomogram and logarithms.

A further check upon our figures is provided by a re-calculation of the expected phenotype frequencies from the improved p', q' and r' values.

$$\begin{aligned} \overline{O} &= r'^2 &&= \cdot 421626 \\ \overline{A} &= p'^2 + 2p'r' &&= \cdot 437230 \\ \overline{B} &= q'^2 + 2q'r' &&= \cdot 100499 \\ \overline{AB} &= 2p'q' &&= \cdot 040644 \end{aligned}$$

Our observed frequencies approximate very closely to these expected frequencies.

The M–N System.

Our combined figures for the M–N distribution are in excellent agreement with the theory of inheritance of these groups defined by Landsteiner and Levine, who showed that they are inherited by two allelomorphic genes, M and N, each of equal dominance.

The observed distribution was—

Group.	*M.*	*N.*	*MN.*	Total.
f	279	185	436	900
p	·310000	·205556	·484444	1·000000
σ_p	±·015416	±·013470	±·016659	..

If m and n represent the frequencies of the two genes M and N, then

$$m = \sqrt{\overline{M}} \qquad \text{and} \qquad n = \sqrt{\overline{N}},$$

and by definition—

$$m + n = 1.$$

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With our observed figures,

$$m = \sqrt{\cdot 310000} = \cdot 556778 \quad \text{and} \quad n = \sqrt{\cdot 205556} = \cdot 453383$$

$$m + n = 1 \cdot 010161$$

$$\text{and} \quad D = 1 - (m + n) = \cdot 010161.$$

Wiener (1931, 1935) has shown that the probable error of D is given by—

$$\text{P.E.}_D = \frac{\cdot 6745}{2\sqrt{P}},$$

where P is the number of persons tested. By the same substitution as before one obtains σ_D, and for our figures—

$$\sigma_D = \cdot 016667$$
$$D/\sigma_D = \cdot 61$$

Boyd's nomogram also gave a value for D/σ_D of approximately ·6, which is nsignificant. Thus our observed frequencies are in good agreement with the theory of Landsteiner and Levine.

The gene frequencies may be calculated by an alternative equality. If a, b and c represent the observed *frequencies* of the persons in groups M, MN and N respectively, and P is the number of persons examined, then—

$$m = \frac{2a + b}{2P} \quad \text{and} \quad n = \frac{2c + b}{2P}.$$

Using these formulæ, the calculated gene frequencies for our series are—

$$m = \cdot 552222 \quad \text{and} \quad n = \cdot 447778.$$

These frequencies approximate closely to the totals for all observers in this country calculated by Stevens, his figures being ·554062 and ·445937 respectively.

A test for contamination of the sera upon the combined data is unnecessary, as its absence has already been demonstrated in the individual series.

The O–A_1–A_2–B System.

The demonstration of the subdivision of the A factor by von Dungern and Hirschfeld (1911), and the proof that these subdivisions are inherited by an additional allelomorphic gene by Thomsen, Friedenreich and Worsaae (1930, *a*, *b*), necessitates a further analysis of our figures.

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Group.	O.	A_1.	A_2.	B.	A_1B.	A_2B.	Total.
f	379	322	72	91	28	8	900
p	·421111	·357778	·080000	·101111	·031111	·008889	1·000000
σ_p	±·016420	±·015978	±·009043	±·010049	±·005787	±·003129	..

$$\begin{aligned} A_1 + A_1B &= 350\ (\ \cdot 814000 \\ A_2 + A_2B &= \ 80\ (\ \cdot 186000 \end{aligned} \pm \cdot 018764)$$

$$430\ (1 \cdot 000000)$$

Thomsen showed that with the introduction of the fourth gene, the gene frequencies could be calculated by a simple extension of Bernstein's original formula. If p_1, p_2, q and r represent the frequencies of the A_1, A_2, B and O genes, the expected frequencies of the phenotypes are given by—

Phenotype.	Genotype.	Frequency.	
O	OO	r^2	
A_1	A_1A_1	p_1^2	$= p_1^2 + 2p_1p_2 + 2p_1r$
	A_1A_2	$2p_1p_2$	
	A_1O	$2p_1r$	
A_2	A_2A_2	p_2^2	$= p_2^2 + 2p_2r$
	A_2O	$2p_2r$	
B	BB	q^2	$= q^2 + 2qr$
	BO	$2qr$	
A_1B	A_1B	$2p_1q$	
A_2B	A_2B	$2p_2q$	

From this it can be shown that—

$$\begin{aligned} p_1 &= \sqrt{\overline{O} + \overline{A}_1 + \overline{A}_2} - \sqrt{\overline{O} + \overline{A}_2} \\ p_2 &= \sqrt{\overline{O} + \overline{A}_2} - \sqrt{\overline{O}} \\ q &= \sqrt{\overline{O} + \overline{B}} - \sqrt{\overline{O}} \\ r &= \sqrt{\overline{O}} \end{aligned}$$

With our observed frequencies—

$$\begin{aligned} p_1 &= \cdot 218909 \\ p_2 &= \cdot 058961 \\ q &= \cdot 073718 \\ r &= \cdot 648931 \end{aligned}$$

$$1 \cdot 000519$$

Thus the theoretical equation $p_1 + p_2 + q + r = 1$ is fulfilled in this case, and our observed figures support Thomsen's four-gene theory of inheritance.*

* Stevens, using Fisher's method of maximum likelihood, has produced a slightly improved series of gene frequencies for this system.

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Recalculation of the expected phenotype frequencies from the values of p_1, p_2, q and r gives—

$$\begin{aligned} \overline{O} &= \cdot 421111 \\ \overline{A_1} &= \cdot 357849 \\ \overline{A_2} &= \cdot 079999 \\ \overline{B} &= \cdot 101109 \\ \overline{A_1B} &= \cdot 032275 \\ \overline{A_2B} &= \cdot 008693 \end{aligned}$$

which approximate very closely to our observed values.

Blood-Group Distribution in England.

In our series of 526 mental patients we have failed to find, not only any difference in the group distribution among them as a whole, but any deviation from the normal in the various component disease groups. Our results are therefore in agreement with those of Herman and Derby, who have made the most careful study of the blood-groups in mental disease to date.

By combining the two series of normal persons and mental patients we have formed a composite group of 900 persons. The group distribution among these closely approximates to that found by other workers in this country, and is that to be expected from a consideration of the genetic principles underlying the blood-groups.

Taylor and Prior have collected the data of other observers working on English people, and we have reproduced their table in a somewhat modified form for the purpose of comparison. We have included Penrose's observations upon mental defectives, but for certain reasons we have omitted some of the figures which they included. With the exception of L. and H. Hirschfeld's original investigation upon British soldiers on the Macedonian front in 1919, we have excluded all the investigations prior to the publication of Bernstein's hypothesis. The majority of these are upon family material, and the theory of von Dungern and Hirschfeld, which was accepted at that time, allowed certain parent-child combinations which we know to-day cannot occur. When such a combination was found it was accepted as normal, and the groups which were probably incorrect were not re-examined. One at least of Dyke and Budge's families (1923) showed an *A–B–O* combination which is to-day accepted as a genetic impossibility. For these and similar reasons we have excluded the results of Learmonth (1920), Alexander (1921), and Buchanan and Higley (1921), the last-named having examined English patients in the Mayo Clinic. The data of Jones and Glynn (1926) has been excluded for the reason given by Taylor and Prior—that they examined only 40 cases instead of the 1,600 usually attributed to them. We have also excluded the Australian

figures of Tebbutt (1923) and Shipton (1935, 1936). The data is expressed in direct percentages corrected to four significant figures.

I. *A–B–O System.*

Observers.	Date.	Number.	Percentage. *O.*	*A.*	*B.*	*AB.*
Thomas and Hewitt	1939	900	42·11	43·78	10·11	4·00
Taylor and Prior	1938	422	47·87	42·42	8·29	1·42
Boyd and Boyd: Welsh	1937	192	47·92	32·81	16·15	3·12
Irish	1937	399	55·14	31·08	12·03	1·75
Matta	1937	400	48·75	36·00	10·00	5·25
Kirwan-Taylor	1930	500	40·40	46·80	9·60	3·20
L. and H. Hirschfeld	1919	500	46·40	43·40	7·20	3·00
Penrose: Mongols	1932	158	41·10	49·40	7·60	1·90
Defectives	1932	225	42·50	47·30	6·60	3·50

By taking the figures of those workers who have examined the *English* population since 1930, this table may be further simplified (Kirwan-Taylor, Taylor and Prior, Matta, Penrose and the present series). This gives a sample of 2,606 persons with the following distribution of groups:

Group.	*O.*	*A.*	*B.*	*AB.*
f	1,139	1,136	241	90
Percentage	43·71	43·60	9·25	3·44

Our own figures approximate very closely to these totals, and for general purposes we suggest that these percentages should be taken as representing the group distribution in England. In round figures they may be taken as $O = 44\%$, $A = 44\%$, $B = 9\%$, and $AB = 3\%$.

II. *M–N System.*

Observers.	Date.	Number.	Percentage. *M.*	*N.*	*MN.*
Thomas and Hewitt	1939	900	31·00	20·56	48·44
Taylor and Prior	1938	422	28·67	23·94	47·39
Matta	1937	456	35·09	17·10	47·81
Boyd and Boyd: Welsh	1937	192	30·73	14·06	55·21*
Irish	1937	399	30·07	23·31	46·62
Harley	1936	200	32·00	19·50	48·50

* By inspection, these figures cannot be a good sample, the percentage of *MN* bloods being over 50. The frequency of *MN* bloods is given by $MN = 2mn$, and is maximal when $m = n = 0{\cdot}5$ ($MN = 2(\cdot5 \times \cdot5) = \cdot5$). In actual fact the difference between the Boyd's observed figures and 50% is not significant, the D/σ_c value being ·656.

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Again combining the English figures, we get a general group distribution among 1,968 persons of—

Group.	*M*.	*N*.	*MN*.
f . . .	624	403	951
Percentage . .	31·71	20·48	47·81

Thus, in round figures, the distribution of the *M–N* groups in this country may be taken as $M = 32\%$, $N = 20\%$, and $MN = 48\%$.

Investigations upon the distribution of the A_1–A_2 groups in this country have only been made by Taylor and Prior. For the purposes of comparison we have been forced, as they were, to include the observations of Thomsen in Denmark (quoted Wellisch and Thomsen, 1936) and of Wolff and Jonsson in Sweden (1935).

III. *O–A*$_1$*–A*$_2$*–B System.*

Observer.	Date.	Number.	Percentages.					
			O.	A_1.	A_2.	*B*.	A_1B.	A_2B.
Thomas and Hewitt	1939	900	42·11	35·78	8·00	10·11	3·11	0·89
Taylor and Prior	1938	345	46·38	35·94	7·54	8·40	1·16	0·58
Thomsen *et al.*	1930	390	41·54	35·64	10·77	8·21	2·56	1·28
Wolff and Jonsson	1935	1200	37·92	36·92	9·75	10·33	3·92	1·16

For these figures, the respective percentages of A_1 and A_2 bloods are—

Observer.	Percentage.	
	A_1.	A_2.
Thomas and Hewitt	81·40	18·60
Taylor and Prior	82·05	17·95
Thomsen *et al.*	76·02	23·98
Wolff and Jonson	78·91	21·09

The A_1/A_2 distribution in this country is, therefore, in round figures $A_1 = 80\%$, and $A_2 = 20\%$ of all bloods containing the *A* factor. The figures for England appear to show a slightly lower percentage of A_2 bloods than do those for Scandinavia.*

Summary.

1. The blood-group distribution (*A–B–O*, *M–N* and *O–A*$_1$*–A*$_2$*–B*) among 526 mental patients has been compared with that of a normal series of 374 persons. No differences between the two have been found.

2. No significant deviation from the normal proportions was found in manic-depressive psychosis, dementia præcox, organic or senile dementia or delusional insanity.

* Stevens, working with Taylor and Prior's data, has shown that there is a difference in gene frequencies between the two countries, and that the heterogeneity of the Danish, Swedish and English figures is adequately accounted for by variations in the proportion of the *O* gene.

3. The two series combined form a sample of 900 persons from among the population, and the group distribution in this series is discussed in detail.

4. It is shown that the observed figures support Bernstein's theory of the inheritance of the *A–B–O* system, Landsteiner and Levine's theory of the inheritance of the *M–N* system and Thomsen's theory of the inheritance of the subdivisions of the *A* factor.

5. The results of other workers in this country are discussed, and it is shown that our figures are in general agreement.

6. From an analysis of the results of other workers, in combination with our own, we have defined the normal blood-group distribution of this country as Group $O = 44\%$; Group $A = 44\%$ (Group $A_1 = 80\%$); Group $B = 9\%$; Group $AB = 3\%$; Group $M = 32\%$; Group $N = 20\%$; Group $MN = 48\%$.

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