for multiple additive factors, taken together with the high values of sib-sib, uncle-nephew, aunt-niece etc., co-efficients suggest strongly that some of the multiple factors are recessive genes" and in the next paragraph, concerning the differences between the co-efficients for paternal and maternal uncles and aunts and nephews and nieces, that "These findings are in keeping with what would be expected if one or more of the genetic factors which modify age of onset were sex-linked...".

The suggestions that sex-linked and recessive genes are responsible for aspects of psychosis are amongst the reasons why it seems that the data collected and analysed by Penrose ought to be more widely known.

References

Crow TJ (1988) Sex chromosomes and psychosis: the case for a pseudoautosomal locus. Br J Psychiatry 153:675–683

Crow TJ (1990) The nature of the genetic contribution to psychosis: a continuum viewpoint. Acta Psychiatr Scand 81:401–408

Harris H (1973) Lionel Sharples Penrose. Biographical Memoirs of The Royal Society. 19:521–561

Mott FW (1910) Hereditary aspects of nervous and mental disease. Br Med J II:1013–1020

Penrose (1942a) Auxiliary genes for determining sex as contributory causes of mental illness. J Ment Sci 88:308–316

Penrose LS (1942b) Mental disease and natural selection. Am J Ment Defic 46:453–458

Penrose LS (1968) Critical survey of schizophrenia genetics. In: Howells JG (ed) Modern perspectives in world psychiatry. Oliver and Boyd, Edinburgh, pp 3–19

Rosenthal D (1962) Familial concordance by sex with respect to schizophrenia. Psychol Bull 59:401–421

Survey of Cases of Familial Mental Illness[1]

L. S. Penrose, July 1945

Division of Psychiatric Research, Ontario Department of Health

1 Introduction

The material presented here summarizes an investigation undertaken by the Division of Psychiatric Research. There were two main objects in view, both connected with the study of the constitutional background of mental illness. First, the nature of familial mental illness was examined with respect to psychiatric diagnosis; that is to say, the question was asked: if a close relative of a patient breaks down into mental illness, how far will this illness in the relative resemble that of the patient clinically? The information of this kind obtained by examining records of patients admitted to the Ontario Hospitals gives clues as to how far certain mental illnesses are or are not genetic entities. Secondly, in consequence of the unreliability of clinical diagnosis, a complete analysis was made of the ages of onset of patients compared with those of their mentally ill relatives without reference to the type of illness. The age of onset was measured by taking the date of first admission to any mental hospital. Though it was, of course, realised that the admission date only approximately represents the age at onset of illness, this date is highly correlated with the beginning of acute symptoms and has the advantage of being an exact measurement. As will be shown in Sect. 3, the age

at first admission is a characteristic feature of each separate type of illness diagnosed. Furthermore, because it is an arithmetic criterion, the age at first admission can be used in calculations to estimate the likeness of type of illness in different relatives. From these measurements, information can be obtained about the mode of inheritance of the factors that determine either the mental illness itself or of the constitution which predisposes to such illness.

The survey, which was begun in 1943 at the Ontario Hospital, London, was continued first at Queen Street and then further extended to cover all the Ontario Hospitals. The families in which more than one relative had been admitted were traced through the patients' statistical cards. These records go back to 1926, and thus, a period of at least 18 years was covered. Files of all cases selected in this manner were searched, and a great many special enquiries were made. Only those instances where at least one member of the family was diagnosed as mentally ill were included; that is to say, cases of uncomplicated mental defect did not come into the survey unless a relative had mental disorder. The survey, moreover, was limited to patients who had actually been resident in mental hospital at some time during their lives, with one exception, namely, cases where a relative had committed suicide were also included in the survey. In such instances, the data of suicide of a subject who had not been admitted to a mental hospital was taken as being equiva-

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[1] Stylistic amendments to the original Penrose text have been made where necessary for further clarity

lent to a first admission date in the other cases. In justification for this procedure it may be remembered how frequently cases are first admitted to hospital after an unsuccessful or threatened suicidal attempt.

The material collected is very extensive. In all, 5456 pairs of affected relatives were counted, and this number of pairs represents a much greater number of individuals investigated. The number of individuals is not quite twice as great as the number of pairs, because families with more than two affected members can contribute more than one pair for every two individuals. However, for simplicity in analysis, the *pairs* of relatives were treated as the units of the data. This implies a potential number of persons equivalent to 5461 males and 5451 females, though we know that this potential number includes certain individuals who have been counted more than once. The effect of this is to exaggerate the number of cases in which there is a high familial incidence. so that the data, as tabulated, actually are weighted to give more information about cases of familial mental illness (where many are affected in one family) than about cases where only one pair is affected; consequently, any conclusions drawn cannot be necessarily held to apply to sporadic cases. Actually, the data cover about one-tenth of the total volume of the patient population.

Complete analysis of this material cannot be provided at present, but a great number of the tables have been drawn up. Summaries of such tables are included with this report. They show many features of interest. There has been no previous investigation on quite the same lines as the present one, and it was fortunate that in the Ontario Hospitals the records are kept in such a manner as to be easily available for this study. It will be some years before any such survey can be repeated on so great a scale. All the relevant material collected is filed at the office of the Division of Medical Statistics so that it can be used as a basis for further analysis or subsequent inquiries if desired. A general indication of the main points of significance that arise out of the survey will now be

Table 1. Diagnoses recorded in members of pairs of relatives

Diagnosis group	Familial survey		First admissions 1953	
	Number	%	Number	%
1 Schizophrenic	3350	32.9	546	28.3
2 & 3 Affective	3345	32.9	419	21.7
4 Arteriosclerotic	414	4.1	195	10.1
5 Senile	440	4.3	224	11.6
6A Paretic	201	2.0	83	4.3
6B Huntington's chorea	132	1.3	5	0.3
6C Organic	268	2.6	150	7.8
7 Epileptic	201	2.0	98	5.1
8 Defective	786	7.7	–	–
9 Psychopathic or psychoneurotic	408	4.0	103	5.3
10 Undiagnosed	626	6.2	105	5.5
Total	10171	100.0	1928	100.0
11 Suicide	741	–	–	–

Table 2. Classification of diagnoses

1	*Schizophrenic*	Simple schizophrenic
		Paranoid schizophrenic
		Catatonic schizophrenic
		Hebephrenic schizophrenic
		Paranoid: involutional or senile paranoid
		Dementia praecox
		Schizophrenic defective
		Arteriosclerotic paranoid
		Alcoholic paranoid
2	*Schizophrenic affective*	1 and 3 combined
		Schizophrenic and manic or depressive
		Paranoid depression
3	*Affective*	Manic
		Manic depressive
		Depressive: reactive or psychoneurotic depressive
		Involutional depressive or melancholic
		Involutional psychosis
		Manic alcoholic
		Manic psychosis with mental defect
		Senile manic or depressive
		Arteriosclerotic manic or depressive
4	*Arteriosclerotic*	Psychosis with cerebral arteriosclerosis
5	*Senile*	Organic senile
		Senile dementia
		Senile with mental defect
6A	*Paresis*	General paretic
		Paretic
		Juvenile paretic
		Tabetic
6B	*Huntington's chorea*	Huntington's chorea
6C	*Other organic*	Exhaustion delirium
		Post-encephalitic
		Post-infective
		Toxic or toxic confusional
		Disseminated sclerosis
		Alcoholic delirium
		Psychosis with somatic disease
		Psychosis with tuberculosis
		Psychosis with syphilis
		Traumatic psychosis
7	*Epileptic*	Psychotic epileptic
		Epileptic defective, imbecile or idiot
		Psychopathic epileptic
8	*Defective*	Borderline defective without psychosis
		Moron, imbecile or idiot
		Microcephalic idiot
		Mongolian idiot
		Hemiplegic idiot
		Phenylketonuric idiot
9	*Psychoneurotic and psychopathic*	Psychopathic defective
		Court case
		Alcoholic or drug addict
		Neurasthenic
		Hysteria
10	*Undiagnosed*	Unknown diagnosis
		Psychotic
		Psychotic defective
		Chronic mental illness
		Pre-senile psychosis
11	*Suicide*	(Not hospitalised)

given, but no attempt to draw profound conclusions will be made here. Some speculations on the deeper meanings of the findings were presented in a paper read to the American Psychiatric Association, 1944.

2 Analysis of Clinical Diagnosis in Familial Cases

The diagnoses given by the hospital staffs in the cases who were members of the pairs of relatives were grouped into 11 classes, as shown in Table 1. In Table 2, the composition of the diagnosis classes is given in detail. Comparison with first admissions for 1943 shows that the group in the familial survey contained every type of case. A first indication as to whether or not any given disease has a familial incidence is given by comparing the percentages in the survey and the 1943 first admission control group. Naturally, the cases of suicide, who were not in hospital, are excluded for purposes of this comparison. Defectives are also excluded from the control group, because they came only secondarily into the investigation. We find that, in the schizophrenic group and, especially, the affective group, there is an excess of cases in the familial survey. This indicates that these conditions tend to be familial rather than sporadic. The same tendency, as was to be expected, is also very marked in the cases of Huntington's chorea, which accounts for 1.3% of the survey diagnoses and for only 0.3% of first admissions in 1943.

The diagnoses in males and females in the survey sample are shown in Table 3, where cases are also classified by the type of relationship. In general, the diagnoses follow similar lines for males and for females, though certain conditions, such as general paresis (6A) and suicide (11), are definitely more frequent in males. Important differences are found when the types of relatives are examined. Schizophrenia (1), though common in broth-

ers, sons, nephews and grandsons, is relatively rarely found in grandfathers or fathers. Conversely, schizophrenia is quite frequently diagnosed in grandmothers and mothers though, in the sisters and daughters, it is less frequent than affective psychosis. Relative rarity of schizophrenia in male parents is an important feature which permeates the whole survey. The same feature shows itself clearly, when age on first admission to hospital is analysed, in the fact that mental illness of early onset is rare in fathers. The demonstration of this peculiarity, with respect to diagnosis, is given in Table 4. Schizophrenic diagnosis is altogether rarer in parents than in offspring but male schizophrenic parents are especially uncommon.

The percentage frequencies of types of mental illness found in all relatives of all subjects are shown in Table 5, column (b). Compared with this is the frequency distribution of relatives, who have the same diagnosis as that of any chosen subject, column (a). Table 5 gives an idea of how true to type is the diagnosis within family groups. For instance, for all cases, the likelihood of the diagnosis of schizophrenia in a psychotic relative is 30.70% whereas, for a schizophrenic subject, the likelihood of the diagnosis of schizophrenia in a psychotic relative is 44.36%. The tendency for any diagnosis to remain true to type in relatives can be measured by the correlation coefficient, r, and this calculation shows that Huntington's chorea is the only diagnosis which stays strongly true to type. Other diagnoses, which are significantly, if not so strongly, true to type, probably represent genetical entities also; these include schizophrenia, affective psychosis, senile psychosis and mental defect without psychosis. Nevertheless, it can be shown that some diagnoses, although they differ from one another, are more closely akin than others. Thus, for example, given that the psychotic relative of a schizophrenic patient is not a schizophrenic, he is more likely to be diagnosed as manic

Table 3. Diagnoses of cases in sample

Type of relative	Diagnosis group													
	1	2	3	4	5	6A	6B	6C	7	8	9	10	11	Total
Grandfather	12	–	53	4	23	–	2	1	5	1	1	7	19	125
Father	72	4	279	60	96	22	6	16	8	4	19	61	190	837
Uncle	172	1	194	31	36	25	8	10	14	18	17	53	39	617
Brother	743	8	590	94	55	76	21	42	33	192	110	137	206	2307
Son	315	–	213	29	13	26	10	18	20	106	44	40	42	876
Nephew	236	1	118	9	4	20	5	10	23	65	47	22	17	577
Grandson	53	1	18	–	–	3	5	–	3	27	7	3	2	122
Total Male	1603	15	1462	227	226	172	57	97	106	413	245	323	515	5461
Grandmother	24	1	37	5	20	–	3	1	3	–	2	6	11	113
Mother	222	2	339	36	64	8	12	28	9	18	19	66	68	891
Aunt	150	3	200	22	34	2	7	30	6	16	8	48	14	540
Sister	796	10	798	87	76	13	35	54	42	159	61	124	104	2359
Daughter	275	3	277	27	16	6	12	29	20	100	35	37	15	852
Niece	234	3	169	9	4	–	5	24	11	56	32	20	13	580
Granddaughter	46	–	26	1	–	–	1	5	4	24	6	2	1	116
Total Female	1747	22	1846	187	214	29	75	171	95	373	163	303	226	5451

or depressive than anything else. In Table 6, where these cases of unlike diagnosis in relatives are classified, critical ratios of partial correlation coefficients give an interesting indication as to how far different types can be reasonably assumed either to have something in com-

mon genetically or to be essentially different from one another. Positive values show that schizophrenia and affective psychoses are slightly genetically interrelated (+1.1), as also (but more strongly) are the arteriosclerotic and senile types (+2.9). Schizoaffective states and suicides are shown to have affinity for the affective group rather than for the schizophrenic group. Suicides, moreover, are common in relatives of subjects with Huntington's chorea and psychopathy. The undiagnosed group evidently contains an excess of schizophrenics and defectives. Relatives of paretics tend to have the diagnosis of senile psychosis or epilepsy.

The analysis of the different types of relationships, fathers and sons, brothers and sisters, etc., with respect to diagnosis, is summarised in Table 7, where pairs with concordant diagnosis are listed. In the first place, the totals show that psychosis in mother and son (M S) is the

Table 4. Relatives with schizophrenia

Type of relative	Total diagnoses	Schizophrenic diagnosis	
		Number	Percentage
Grandfathers and fathers	962	84	8.7
Grandmothers and mothers	1004	246	24.5
Sons and grandsons	998	368	36.9
Daughters and granddaughters	968	319	33.0

Table 5. Percentage frequencies of types of mental illness found in all relatives of all subjects

	Subject's diagnosis	Percentage frequency of same diagnosis in subject's relatives	Percentage frequency of same diagnosis in relatives of all patients	Degree of likeness of diagnosis in relatives (r)	Clinical ratio of r[a]
		(a)	(b)	$(a - b)/(100 - b)$	$r \sqrt{b \times 10912/100}$
1	Schizophrenia	44.36	30.70	+0.197	11.4
2	Schizo-affective	0.00	0.34	−0.034	0.2
3	Affective	42.99	30.32	+0.183	10.5
4	Arteriosclerotic	5.80	3.79	+0.021	0.4
5	Senile	15.91	4.03	+0.155	3.3
6A	Paretic	12.94	1.84	+0.112	1.6
6B	Huntington	83.33	1.21	+0.831	9.5
6C	Other organic	3.73	2.46	+0.013	0.2
7	Epileptic	7.96	1.84	+0.062	0.9
8	Defective	34.61	7.20	+0.295	8.3
9	Psychopathic	11.27	3.74	+0.078	1.6
10	Undiagnosed	10.46	5.74	+0.050	1.3
11	Suicide	7.83	6.79	+0.012	0.3

[a] Values greater than 2.5 are significant

Table 6. Degree of inter-relationship of different diagnoses

Diagnosis type		Diagnosis type												
		1	2	3	4	5	6A	6B	6C	7	8	9	10	11
Suicide	11	−	−	−	−	−	−	−	−	−	−	−	−	0.0
Undiagnosed	10	−	−	−	−	−	−	−	−	−	−	−	0.0	−4.0
Psychopathic	9	−	−	−	−	−	−	−	−	−	−	0.0	0.0	+3.0
Defective	8	−	−	−	−	−	−	−	−	−	0.0	+1.0	+3.7	−1.0
Epileptic	7	−	−	−	−	−	−	−	−	0.0	+3.3	−1.1	−1.2	−2.0
Other organic	6C	−	−	−	−	−	−	−	0.0	0.0	+0.8	−1.0	−0.2	−0.0
Huntington	6B	−	−	−	−	−	−	0.0	0.0	0.0	0.0	0.0	+2.0	+5.0
Paretic	6A	−	−	−	−	−	0.0	0.0	+1.3	0.0	+2.7	−1.1	−1.4	−0.0
Senile	5	−	−	−	−	0.0	+5.3	−1.0	0.0	0.0	−0.6	+1.0	+0.2	−1.0
Arteriosclerotic	4	−	−	−	0.0	+2.9	−0.4	−1.0	−0.9	+1.7	0.0	−1.0	−0.4	+0.0
Affective	3	−	−	0.0	+0.3	−0.7	−2.2	−1.9	−1.9	+0.4	−3.9	−1.5	−0.7	+4.0
Schizo-affective	2	−	0.0	+1.5	−0.7	+1.4	−1.0	0.0	0.0	0.0	−0.7	+1.4	−1.4	−1.0
Schizophrenic	1	0.0	−0.9	+1.1	−1.4	−2.2	0.0	−1.3	+1.6	−0.7	+1.1	−0.2	+2.3	−3.0

The figures in the table represent the critical ratios of partial correlation co-efficients of the diagnoses with one another in pairs of relatives which have no tendency towards concordant diagnosis

Table 7. Breakdown of different types of relationship with respect to diagnosis

Type of pair	Number of pairs of relatives				Total pairs
	Both schizophrenic	Both affective	Both same diagnosis	Unlike diagnosis	
Father–son	28	48	20	319	415
Father–daughter	16	68	19	319	422
Mother–son	51	59	20	331	461
Mother–daughter	55	67	16	292	430
Brother–brother	106	69	75	372	622
Brother–sister or sister–brother	192	140	92	639	1063
Sister–sister	124	118	58	348	648
Paternal uncle–nephew	17	15	9	112	153
Maternal uncle–nephew	22	11	9	120	162
Paternal aunt–nephew	13	14	2	86	115
Maternal aunt–nephew	22	11	4	110	147
Paternal uncle–niece	22	24	6	102	154
Maternal uncle–niece	20	19	6	103	148
Paternal aunt–niece	15	18	3	93	129
Maternal aunt–niece	24	27	5	93	149
Paternal grandfather–grandson	3	2	1	28	34
Maternal grandfather–grandson	1	3	3	29	36
Paternal grandmother–grandson	2	3	2	20	27
Maternal grandmother–grandson	2	–	–	23	25
Paternal grandfather–granddaughter	–	7	–	25	32
Maternal grandfather–granddaughter	3	1	–	19	23
Paternal grandmother–granddaughter	2	–	–	26	28
Maternal grandmother–granddaughter	3	3	–	27	33
Total	743	727	350	3636	5456

most frequent type of parent-child combination (461 pairs) and father and son (F S), the least frequent (415 pairs). Brother and sister (B S) pairs, which ought to be approximately equal in number to the combined total of brother-brother (B B) and sister-sister (S S) pairs, are some 200 short of this number, i.e. 1063 as against 1270. The most frequent type of affected sib-pair is made up of two sisters. In the uncle and nephew degree of relationship, we find maternal uncle and nephew the commonest combination (162 pairs), paternal aunt and nephew the least common (115 pairs). Among the types of grandparental pairs, maternal grandfathers and their grandsons figure most frequently. Table 7 also shows, in general, that discordance of diagnosis in related pairs of patients is much commoner than concordance; especially is this so in the parent-child and grandparent-grandchild pairs.

Turning to the specific diagnoses we note that, for parent and child pairs, both schizophrenic, the like-sexed pairs (F S) and (M D) are more frequently represented than the unlike-sexed pairs (F D and M S), in the proportion 83:67. Similarly, with schizophrenic sibs, the like-sexed pairs (B B) and (S S) are more frequent than unlike-sexed pairs (B S), in the proportion 230:192. Where an affective diagnosis applies to both members of the pair, the same phenomenon is shown in the sibs, (B B) and (S S), together numbering 187 as opposed to 140 (B S). Parent and child pairs with affective diagnosis,

however, show the opposite tendency and here the like-sexed pairs, (F S) and (M D), are fewer than the unlike-sexed, (F D) and (M S), in the ratio 115:127.

Further details concerning the diagnosis of closely related cases are given in Table 8. As might be expected, schizophrenic parents have fewer children with an affective diagnosis than with a schizophrenic diagnosis, and the reverse is true of parents with affective diagnosis. Moreover, schizophrenic fathers have altogether fewer psychotic children than have schizophrenic mothers, 72 as compared with 222, partly, no doubt, because of the exceptional infertility of schizophrenic males. However, an extra peculiarity is shown in that whereas schizophrenic fathers have more psychotic sons than psychotic daughters (41:31), schizophrenic mothers have fewer psychotic sons than psychotic daughters (109:113). The counterpart of this, for parents with affective psychosis, is that fathers diagnosed as affective have fewer psychotic sons than psychotic daughters, (136:146), whereas mothers diagnosed as affective have more psychotic sons than psychotic daugthers, (191:148). For sibs the picture, as given in Table 8 (B), is similar for both schizophrenic and affective subjects. Thus, for either schizophrenic or affective male subjects, more psychotic brothers than psychotic sisters appear in the sample and, for either schizophrenic or the affective female subjects, there are fewer psychotic brothers than psychotic sisters.

Table 8. Psychotic offspring and sibs of schizophrenic and affective subjects

(A) Psychotic offspring

Type of parent	Type of offspring	Diagnosis of offspring			Total
		Schizo-phrenic	Affec-tive	Other	
Father (schizophrenic)	Son	28	2	10	41
	Daughter	16	3	12	31
Mother (schizophrenic)	Son	51	10	48	109
	Daughter	55	19	39	113
Father (affective)	Son	44	48	44	136
	Daughter	42	68	36	146
Mother (affective)	Son	74	59	58	191
	Daughter	45	67	36	148

(B) Psychotic sibs

Type of subject	Type of sib	Diagnosis of sib			Total
		Schizo-phrenic	Affec-tive	Other	
Brother (schizophrenic)	Brother	212	74	97	383
	Sister	192	93	75	360
Sister (schizophrenic)	Brother	192	58	97	347
	Sister	248	59	142	449
Brother (affective)	Brother	74	138	117	329
	Sister	58	140	71	269
Sister (affective)	Brother	93	140	128	361
	Sister	59	236	129	424

3 Age at First Admission in the Different Diagnosis Groups

The fact that each diagnosis has its own characteristic range for age at first admission can be ascertained from the Annual Reports of the Ontario Hospitals. The New York and Massachusetts state hospital returns, respectively analysed by Malzberg (1935) and by Dayton (1940), have allowed the same conclusion. The present material differs from that collected in annual reports in that it only deals with familial cases. However, the correspon-

dence between first admission age and diagnosis agrees fairly well with that shown in random samples of first admissions. The means for various diagnosis groups are given in Table 9 and are compared with figures for unselected first admissions. The general agreement in mean values tend to show that the diseases studied in the present survey are essentially similar to those which seem to occur sporadically in the majority of cases, that is without any definitely recorded familial background. Mental defect has the earliest mean first admission age and schizophrenia, affective and organic psychosis, in ascending order, have later characteristic means.

Differences between the sexes are found in the mean first admission ages for various groups; these sex differences can be shown to be as characteristic, though not as great in degree, as differences between the diagnosis groups themselves. Table 10 compares the mean first admission ages for males and females. Allowance can be made, if desired, for the fact that, in the Ontario population from which the survey patients were almost exclusively drawn, the mean age of males is slightly lower than the mean age of females. In either event, on average, male schizophrenics have a lower first admission age than female schizophrenics and, conversely, the males with affective diagnosis are admitted later on average, than the corresponding female cases. These differences are significant. Some diagnoses, notably mental defect and psychopathic states, follow the same rule as schizophrenia in this respect, whereas organic psychosis, epilepsy and suicide resemble the affective diagnoses in that they appear to be of later onset in males than in females.

4 Analysis of Age on First Admission in Familial Cases

The analysis of the ages of onset of severe symptoms, judged by first admission ages, while it neglects clinical differences, has the advantage of being suitable for mathematical treatment, because we are dealing here with a measurable characteristic of the subjects concerned. In tabulating material classified by first admision ages, cases with every type of diagnosis within the orbit of the investigation could be pooled, including the suicides and defectives. In Table 11, the mean ages (and standard deviations) of the various subjects making up the related pairs are shown. The mean first admission ages for all males

Table 9. Mean ages on first admission

Diagnosis group		Family survey		Ontario hospitals 1943		New York State hospitals 1928–1931	
		Males	Females	Males	Females	Males	Females
4, 5, 6B & 6C	Organic	61.8	58.2	64.2	65.1	63.4	64.2
6A	Paretic	44.1	41.1	46.6	42.7	44.7	43.0
2 & 3	Affective	43.9	42.2	47.2	45.2	40.8	39.2
9	Psychopathic	38.1	41.3	37.5	38.6	42.3	38.5
1	Schizophrenic	31.6	35.3	33.4	35.9	32.4	37.1
7	Epileptic	32.4	26.6	24.5	30.7	–	–
8	Defective	17.6	21.6	18.2	18.4	–	–

Table 10. Mean chronological ages in years on first admission

Population and Definition of Age		Males	Females	(i) Diff.	S. E. Diff.	(ii) Diff.
	Ontario, Census 1941	32.25	32.64	−0.39	0.02	0.00
1	Schizophrenic, on 1st admission	31.64	35.33	−3.69	0.43	−3.30
2 and 3	Affective, on 1st admission	43.87	42.20	+1.67	0.49	+2.06
4, 5 and 6	Organic, on 1st admission	57.88	57.27	+0.61	0.89	+1.00
7	Epileptic, on 1st admission	32.43	26.58	+5.85	2.04	+6.24
8	Defective, on 1st admission	17.64	21.62	−3.98	0.88	−3.59
9	Psychopathic, on 1st admission	38.06	41.33	−3.27	1.22	−2.88
10	Undiagnosed, on 1st admission	37.99	36.80	+1.19	1.18	+1.68
11	Suicide, at death	46.80	42.62	+4.18	1.13	+4.57
	All diagnosis types	39.74	39.88	−0.14	0.10	+0.25

(i) Diff., Difference uncorrected; S.E. Diff., standard error of difference; (ii) Diff., difference corrected for census population age distribution

Table 11. Mean ages on first admission

Type of relative	Number of cases	Mean age in years	Standard deviation of age
Grandfather	125	55.16	11.80
Father	837	53.96	14.00
Uncle	617	44.87	16.63
Brother	2307	37.96	16.59
Son	876	33.06	16.06
Nephew	577	30.76	13.54
Grandson	122	24.58	11.63
Total males	5461	39.74	17.51
Grandmother	113	55.23	14.31
Mother	891	47.18	14.54
Aunt	540	44.72	15.49
Sister	2359	39.46	15.79
Daughter	852	35.43	15.40
Niece	580	32.34	13.16
Granddaughter	116	25.23	11.57
Total females	5451	39.88	16.16

and all females are very similar, 39.74 and 39.88 years, respectively, but the standard deviation, i.e. the measure of the scatter of age, is significantly greater in the males than in the females, i.e. ± 17.51 and ± 16.16 years, respectively; the difference between these two standard deviations is 1.35 ± 0.23 years.

It will be observed, moreover, that the mean age on first admission is much later in parents and, especially in grandparents than it is in children and, especially, in grandchildren. For instance, the mean age for fathers is 53.96 years and that for mothers 47.18 years, whereas the mean first admission age for sons is 33.06 years and that for daughters 35.43 years. This finding, which, in one form or another, is very characteristic of mental hospital data, has in the past been attributed to a tendency for progressive degeneration or anticipation of diseases in succeeding generations. Such an explanation, which is

not in accordance with the concepts of modern genetics, is unnecessary, because more likely explanations are close at hand. In the first place, early onset of mental illness is a factor that tends to prevent parenthood. In the second place, children, and especially grandchildren, whose parents or whose grandparents have already been mental patients, can only be known to be psychotic (and, consequently, can only enter the sample) if they become mentally ill in early life. An imbecile grandson and a grandfather with senile psychosis can enter hospital for the first time in the same year although they may be 60 years apart in age, but we must wait 60 years for a grandchild of a senile patient to become a senile psychotic. For these reasons, the parents, grandparents, children, grandchildren and, to a lesser extent, the uncles, aunts, nephews and nieces represent a restricted sample. The restriction is clearly shown by the diminished standard deviations in many of these groups, particularly in grandparents and grandchildren.

The distribution of first admission ages is given in Table 12. Figure 1 shows clearly how the scatter for male cases is wider than the scatter for female cases. The males have their peak of highest frequency between the ages of 20 and 25 years and the females have their peak between 30 and 35 years. The curves for both sexes show something of a dip near the mean value between 35 and 40 years. The two parts of the distribution, on either side of this dip, correspond very roughly to the subjects in the two main diagnosis groups, i.e. schizophrenics, whose onset age is usually below 35 years, and cases with affective reaction, whose onset is usually after the age of 35 years.

Analysis of first admission age can be carried out in a manner parallel to the analysis made of diagnosis. Thus, in Table 13, the subjects are grouped according to whether the age on first admission was less than 35 (early onset) or greater than 35 years (late onset). The result is similar to that obtained in Table 8. For parents with early onset and for both types of sibs (early and late onset), like-sexed pairs are more frequently represented than the unlike-sexed pairs. That is to say, a father with early onset has more psychotic sons than daughters (39:23), whereas a similarly classified mother has few-

Table 12. Distribution of age on first admission for all subjects

|	0	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	Total
Grandfather	–	–	–	3	1	–	10	14	12	18	20	17	11	13	4	1	1	–	125
Father	–	–	4	13	21	24	70	86	91	119	119	97	78	56	28	23	6	2	837
Uncle	1	9	11	37	72	68	60	58	68	60	40	42	32	29	21	8	1	–	617
Brother	36	62	155	313	287	254	228	215	181	164	122	101	82	67	26	13	1	–	2307
Son	32	40	94	155	125	92	66	63	49	57	42	17	18	17	8	1	–	–	876
Nephew	29	10	53	123	96	85	45	55	19	24	13	13	8	2	1	1	–	–	577
Grandson	14	8	18	26	23	12	8	5	3	4	1	–	–	–	–	–	–	–	122
All males	112	129	335	670	625	535	487	496	423	446	357	287	229	184	88	47	9	2	5461
Grandmother	–	–	–	–	–	7	14	10	13	9	17	11	7	14	8	1	2	–	113
Mother	–	–	12	24	45	99	112	122	133	88	76	44	61	39	22	9	3	2	891
Aunt	–	1	16	31	60	52	59	48	67	60	49	33	29	17	11	7	–	–	540
Sister	27	37	153	215	271	306	265	254	235	171	136	99	80	56	28	21	5	–	2359
Daughter	14	33	74	113	101	118	87	91	67	50	44	18	19	11	5	5	2	–	852
Niece	18	16	51	97	91	77	59	61	50	30	15	6	4	3	2	–	–	–	580
Granddaughter	11	10	20	18	13	19	14	6	2	1	1	1	–	–	–	–	–	–	116
All females	70	97	326	498	581	678	610	592	567	409	338	212	200	140	76	43	12	2	5451
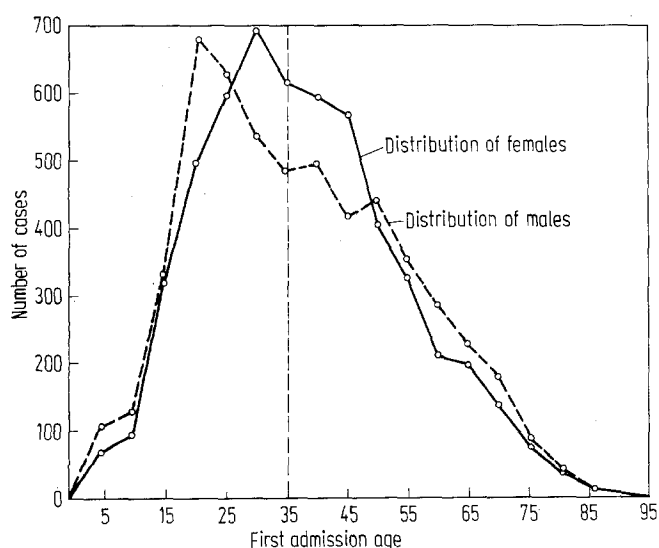
Fig. 1. Age at first hospital admission in relation to sex

er psychotic sons than daughters (79:101). For parents with late onset, the reverse is true in that the psychotic father-daughter and mother-son relationships predominate.

A more precise understanding of the nature of the association between first admission age and degree of relationship is obtained by use of the correlation coefficient. In Table 14, the results of analysing different types of related pairs of cases by this method are given. These coefficients are calculated from tables in which the ages at first admission were classified by 5-yearly age groups. They show the degree of likeness of psychotic type, as measured by first admission age, in the various types of pairs. The general likeness between parent and child is

given by the coefficient +0.385, which is definitely lower than that for sibs, +0.537. The coefficient for uncles and aunts with their respective nephews and nieces is +0.335, a high value in relation to the other coefficients; that for grandparent and grandchild is very low, +0.104. These coefficients, which are accurate measurements in consequence of the large number of pairs involved, tell us something about the mode of inheritance of genetic factors that may be responsible for determining age of onset in mental illness. This is not the place to go into a detailed discussion of the subject, but it may be stated that the correlations are consistent with the view that modification of age of onset is, to a large extent, genetically determined. Also, the genetic factors involved must be multiple. The relatively low values of the parent-child and grandparent-grandchild coefficients, as opposed to expected values of 0.500 and 0.250, respectively, for multiple additive factors, taken together with the high values of sib-sib, uncle-nephew, aunt-niece, etc., coefficients suggest strongly that some of the multiple factors are recessive genes. Such genes might, in certain cases, be responsible for specific diseases.

Further information of great interest is obtained from the detailed analysis of each type of pair by means of the same correlation technique as shown in Table 15. The association between mother and son, +0.440, is higher than that between other types of parental pairs and the father-son association, +0.302, is the lowest in this group. Among the three sib-sib coefficients, brother-sister pairs have the lowest value. For uncles, aunts, nephews and nieces, the coefficient with the highest value, +0.480, belongs to the maternal uncle and nephew relationship and the lowest coefficient, +0.144, belongs to paternal aunt and nephew. These findings are in keeping with what would be expected if one or more of the genetic factors which modify age of onset were sex-linked, that is to say, carried on the X-chromosome.

Table 13. Psychotic offspring and sibs of early and of late-onset subjects

(A) Psychotic offspring

Type of parent	Type of offspring	First admission age of offspring		Total
		Below 35 years	35 years and over	
Father	Son	31	8	39
(Adm. below 35 years)	Daughter	17	6	23
Mother	Son	66	13	79
(Adm. below 35 years)	Daughter	79	22	101
Father	Son	212	164	376
(Adm. 35 years and over)	Daughter	174	225	399
Mother	Son	229	153	382
(Adm. 35 years and over)	Daughter	183	146	329

(B) Psychotic sibs[a]

Type of sib	Type of sib	First admission age of sib		Total
		Below 35 years	35 years and over	
Brother	Brother	428	173	601
(Adm. below 35 years)	Sister	320	186	506
Sister	Brother	320	142	462
(Adm. below 35 years)	Sister	360	187	547
Brother	Brother	173	470	643
(Adm. 35 years and over)	Sister	142	415	557
Sister	Brother	186	415	601
(Adm. 35 years and over)	Sister	187	562	749

[a] The numbers in Table (B) are doubled

Table 14. Summary of correlations of first admission ages

Type of pair	Number	Correlation	Expected values for multiple modifiers
Parent–child	1728	0.385	0.500
Brother or sister–brother or sister	2333	0.537	0.500
Uncle or aunt–Nephew or niece	1157	0.335	0.250
Grandparent – grandchild	238	0.104	0.250

In a discussion previously published (1942), the writer drew attention to the possibility that the sex differences in age of onset of mental disease, described here in Sect. 3, might be due to the action of natural selection. Selection would favour genetic modifying factors, which tended

Table 15. Correlation co-efficients of first admission ages

Type of relationship	Number of pairs	Correlation	Standard error
Father–son	415	0.302	0.045
Father–daughter	422	0.327	0.043
Mother–son	461	0.440	0.038
Mother–daughter	430	0.386	0.041
Parent–child	1728	0.385	0.021
Brother–brother	622	0.588	0.026
Brother–sister or sister–brother	1063	0.498	0.023
Sister–sister	648	0.541	0.028
Sib	2333	0.537	0.015
Paternal uncle–nephew	153	0.293	0.074
Maternal uncle–nephew	162	0.480	0.061
Paternal aunt–nephew	115	0.144	0.092
Maternal aunt–nephew	147	0.284	0.076
Paternal uncle–niece	154	0.232	0.076
Maternal uncle–niece	148	0.414	0.068
Paternal aunt–niece	129	0.316	0.079
Maternal aunt–niece	149	0.387	0.070
Uncle, nephew, etc.	1157	0.335	0.026
Grandparent–grandchild	238	0.104	0.064

to delay the onset for males especially in the later age groups and for females in the earlier age groups. The search for evidence of sex-linked modifying factors in the present survey is justfied by the consideration that such modifying factors as are favoured by natural selection, could reasonably be supposed to be carried on the sex chromosomes.

5 Summary

An investigation was made of all known cases of mental illness where more than one member of the family entered one of the Ontario Mental Hospitals. The materials is fairly complete for a period of 18 years. Analysis of the resulting data, on pairs of relatives, gave rise to the following conclusions of particular interest.

(i) Schizophrenia, affective psychosis, senile psychosis, Huntington's chorea and mental defect are shown to be conditions which remain siginficantly true to type when mental disease occurs in different members of a family. As a rider to this, however, it is found that schizophrenia and affective psychosis are not very distinct entities and groups of closely related familial cases frequently include both diagnoses.

(ii) Schizophrenia is a rare diagnosis in the fathers of patients and occurs in only 8.7% of fathers, as opposed to the 30.7% in the whole sample of relatives: it is not so rare in mothers (24.5%).

(iii) The most frequent type of relationship in pairs of patients is sister and sister: next in frequency is the type brother and brother, then brother and sister. Mother and son, mother and daughter, father and daughter and then father and son come next in order. Less frequent are uncle and nephew or uncle and niece and, again less frequent, aunt and nephew or niece; grandparents and grandchildren were rarely found.

(iv) Fathers, diagnosed schizophrenic or first admitted below the age of 35, have more psychotic sons than psychotic daughters, but the reverse is true for mothers in the same categories.

(v) Fathers diagnosed as having affective illness or first admitted at the age of 35 or over have more psychotic daughters than psychotic sons, but the reverse is true for mothers in the same categories.

(vi) Male subjects with either schizophrenic or affective diagnosis and in early- or late-onset age groups, have more psychotic brothers than psychotic sisters. Similarly, female subjects have more psychotic sisters than psychotic brothers.

(vii) Each main diagnosis group has its characteristic first admission age.

(viii) The first admission age is earlier in males than in females for schizophrenics, and later in males than in females for affective disorders.

(ix) Study of first admission ages in families indicates that parents and, particularly, grandparents are much older than children and, particularly, grandchildren at first admission. This effect is not attributed to progressive degeneration.

(x) Male subjects show a significantly wider scatter of first admission ages than do female subjects.

(xi) Correlation coefficients calculated for first admission ages show that mother and son are significantly more alike in respect of this character than are father and son.

(xii) The likeness of first admission age measured by the correlation coefficient shows that brother-brother and sister-sister pairs are significantly closer in respect of this character than brother-sister pairs.

(xiii) Psychotic nephews are significantly more like their maternal uncles with respect to age on first admission than they are like their paternal aunts.

(xiv) The magnitudes of he correlation coefficients can be interpreted in genetical terms and indicate that (a) multiple modifying factors and (b) some sex-linked factors play a significant part in influencing age of onset of psychosis as measured by first admission age.

References

Dayton NA (1940) New facts on mental disease. Thomas, Baltimore

Malzberg B (1935) A statistical study of age in relation to mental disease. Mental Hygiene 19:449

Penrose LS (1942) Mental disease and natural selection. Amer J Ment Def 46:453