MONGOLISM: THE EFFECT OF TRENDS IN AGE AT CHILDBIRTH ON INCIDENCE AND CHROMOSOMAL TYPE

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Incidence:

Since mongolism was described by Langdon Down (1866) a number of estimates of incidence have been made. These have varied from about 1 in 600 to 1 in 800 consecutive births.

Differences between one estimate and another may partly be due to biased sampling or to real differences in incidence in different countries or in the same countries in different years. The most important factor influencing incidence is maternal age at childbirth. It was noted by Shuttleworth as long ago as 1909 that mongols tended to be last born children. It was not until much later, however, (Penrose, 1933; Jenkins, 1933) that statistical proof was provided that late age of the mother, not of the father, was relevant, and that the number of previous pregnancies was not a factor (Penrose, 1934).

The most extensive survey yet undertaken (Collmann and Stoller, 1962) yields an incidence of 1 mongol for every 2,300 babies born to mothers under 20, rising to 1 in 46 born to mothers over 45, a fiftyfold increase in incidence (Table 1). The consequence of this is that the number of mongols born in the community in any year will be strongly influenced by the ages at which mothers tend to have their babies. To take an extreme case: If, in one year, 2,300 babies were born, all to mothers under 20, using estimates derived from the survey of Collman and Stoller (Table 1), one mongol birth would be expected that year. If, in some other year, the

TABLE 1

Maternal Age Distribution of Total and Mongol Births and Incidence of Mongol Births. (Victoria, Australia, 1942-1957, from Collmann and Stoller, 1962).

M.A. Group	Total Births	Mongol Births	Mongol Incidence
10—	122	0	0
15—	35,433	15	1/2,300
20—	207,931	128	1/1,600
25—	253,450	208	1/1,200
30—	170,970	194	1/870
35—	86,046	297	1/300
40—	24,498	240	1/100
45—	1,707	37	1/46
Not stated	11	-	
Total	780,168	1,119	
Mean	27.9	33.7	1/690

same number of 2,300 babies were born, but this time, all to mothers in the 45-49 age range, then 50 mongol babies would be expected. Naturally, no such extreme change of maternal habits in respect of childbearing age is likely to occur, but the example emphasises the enormous influence of childbearing age on incidence, so that a reduction in the average age at childbirth of a few years could have an appreciable effect in reducing the incidence of mongolism. It is therefore of interest to examine the actual trends in childbearing age in England and Wales. Since 1939, the Registrar General has published the total number of births to mothers of each quinquennial age group. Owing to population change and changes in family size, the total number of babies born varies from year to year. To compare different years it is therefore necessary to convert the numbers into a proportionate or percentage distribution. Table 2 gives the proportionate distribution for 1939 and every

TABLE 2

Maternal Age Expectations derived from Registrar-General's Reports for England and Wales

Table AA

	Maternal age (years)							
Year	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages
To 1939	0.043	0.230	0.322	0.234	0.126	0.041	0.004	1.000
1939	0.046	0.226	0.323	0.234	0.127	0.040	0.004	1.000
1940	0.045	0.238	0.323	0.226	0.124	0.041	0.003	1.000
1944	0.033	0.257	0.267	0.249	0.148	0.043	0.003	1.000
1948	0.039	0.271	0.321	0.201	0.126	0.039	0.003	1.000
1952	0.044	0.281	0.317	0.214	0.108	0.034	0.002	1.000
1956	0.054	0.291	0.317	0.204	0.102	0.030	0.002	1.000
1960	0.066	0.306	0.308	0.192	0.099	0.027	0.002	1.000
1964	0.087	0.314	0.309	0.176	0.087	0.026	0.001	1.000

fourth year from 1940 to 1964 (which may be converted to a percentage distribution by moving the decimal point two places to the right). It shows, for instance, that whereas, in 1939, about 4½ percent of all babies were born to mothers under 20 years of age, in 1964, over 8½ percent were born to mothers of this age group. At the other extreme, 0.4 percent of babies were born to mothers over 45 in 1939, but only 0.1 percent in 1964. Since 1948, there has been a general trend for mothers to have babies at younger ages. The mean maternal age at childbirth has fallen from about 28.5 years to just over 26 years. Using the Registrar General's reports and applying the incidence figures of Collmann and Stoller, we can estimate the effect of this change on the numbers of mongols born. The method is set out in Table 3. Column (b) gives the actual numbers of babies born in 1939 to mothers of each maternal age group. Column (c) is the result of converting these numbers into a proportionate distribution. Column (d) is the proportionate distribution of babies born in 1964. As observed above, mothers tended to bear children younger in 1964 than in 1939, which is apparent from a comparison of these columns.

The actual number of babies born in 1964 was considerably greater than the number born in 1939 owing to population increase and increase in family size, that is to say, there was a larger population of mothers available to have babies and the number of babies born per mother was also greater, in 1964. The population of babies born was therefore greater and this cause, alone, would increase the *number*

TABLE 3

Effects of trends in the incidence of Mongolism: 1939 and 1964 compared

M.A. Group	No. of births 1939	Proportionate distribution of births		1939 births distributed as in 1964	Mongolism incidence per 1,000 births, Collmann & Stoller, 1962	Estimated mongol births 1939 (b x f) / 1,000	Estimated mongol births 1964 (e x f) / 1,000
		1939	1964				
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
15—	29,384	0.046	0.087	55,575	0.43	13	24
20—	144,367	0.226	0.314	200,580	0.61	88	120
25—	206,324	0.323	0.309	197,380	0.82	169	162
30—	149,477	0.234	0.176	112,427	1.13	169	127
35—	81,126	0.127	0.087	55,575	3.45	280	191
40—	25,552	0.040	0.026	16,608	10.00	256	166
45—	2,555	0.004	0.001	638	21.76	56	14
Total	638,790	1.000	1.000	638,790		1,031	804
Mean M.A.	28.5			26.7		1/620	1/795

of mongols born without any increase in *incidence* (which is a ratio of mongol to non-mongol babies). As we wish to examine the effect on incidence of the tendency to have babies at younger maternal ages, we shall eliminate the effect of population increase by assuming the same number of babies to have been born in 1964 as in 1939, thus examining the effect of changing trends in maternal age at childbirth alone, and will consider separately, below, the effect of population change. Column (e) therefore shows how the babies that were born in 1939 (638,790) would have been distributed in relation to maternal age at birth, if born in 1964. This is obtained by multiplying 0.087, at the top of column (d), by 638,790 to obtain 55,575, born to mothers in the 15-19 maternal age group, and performing the same calculation with the appropriate figure in column (d) for every other age group. Comparison of columns (b) and (e) clearly shows that many more babies were born to younger mothers and less to older mothers in 1964, with a drop in the mean maternal age at birth of over two years. It is now a simple matter to estimate the number of mongols expected by applying the incidence figures of Collmann and Stoller to the numbers of babies born in each maternal age group. The results appear in columns (g) and (h). There is a reduction in the number of mongols born of about 22% and the overall incidence falls from 1 in 620 births to 1 in 795 births.

Table 4 shows the results of making the same calculation for alternate years from 1946-64 inclusive. For this purpose, however, the birth population has been fixed at the 1946 level (843,634), which was considerably greater than that of 1939. The table reveals the continuous trend towards younger maternal age at childbirth. The mean M.A. for all births drops from 28.8 years to 26.7 years. The effect is, both to reduce the incidence of mongolism and to reduce the mean M.A. of mongol births, which drops from 34.8 to 32.5. The total number of mongols born is considerably reduced, but the *proportion* of mongols born to younger mothers is increased. The consequences of this are discussed below.

As mentioned above, the actual population of babies born varies from year to year and this change has been eliminated in the tables in order to examine the maternal age effect independently. Table 5 demonstrates the effect of population

TABLE 4

Effect of Trends in Age at Childbirth on the Incidence of Mongolism. Birth Population Fixed at 1946 Level (843,634)

M.A. Group	Year 1946	1948	1950	1952	1954	1956	1958	1960	1962	1964
15—	11	14	16	16	17	20	21	24	29	32
20—	122	139	140	145	148	150	154	157	160	162
25—	208	222	226	220	217	219	217	213	211	214
30—	235	192	188	204	211	194	185	183	174	168
35—	413	367	349	314	279	297	306	288	265	253
40—	337	329	304	287	278	253	211	228	228	219
45—	55	55	55	37	37	37	37	37	37	18
TOTAL	1,381	1,293	1,278	1,223	1,187	1,170	1,131	1,130	1,104	1,066
Mean MA.	34.77	34.3	34.22	33.80	33.61	33.43	33.14	33.13	32.96	32.52
Mongol incidence	1/611	1/640	1/660	1/690	1/711	1/721	1/746	1/746	1/764	1/791
Mean MA. Total Births	28.8									26.72

TABLE 5

Effect of Change in Birth Rate on Incidence of Mongolism, 1946-64. Maternal Age fixed at 1946 Distribution

Maternal Age Group	Year 1946	1948	1950	1952	1954	1956	1958	1960	1962	1964
15—	11	10	9	9	9	9	10	10	11	11
20—	122	115	103	97	100	104	109	116	123	129
25—	208	196	176	170	170	177	187	198	211	220
30—	235	222	198	192	193	200	211	224	238	249
35—	413	389	349	338	338	351	371	392	418	436
40—	337	317	285	276	276	287	303	320	342	356
45—	55	52	47	44	45	46	49	52	56	58
All Ages	1,381	1,301	1,167	1,126	1,131	1,174	1,240	1,312	1,399	1,459
Incidence	1/611	1/611	1/611	1/611	1/611	1/611	1/611	1/611	1/611	1/611
Total Births	843,634	793,705	713,181	688,971	689,851	716,740	757,003	800,824	854,200	890,518

Mean M.A. at birth of mongols, 34.8 years, of total births, 28.8 years. (1946 Distribution)

change on the numbers of mongols born. The maternal age at birth distribution has been fixed at the 1946 level. That is to say, we have assumed the same distribution for all subsequent years examined and thereby eliminated the effect of the trend towards younger childbirth. Any change in the number of mongols is thus the result of population change alone. In fact, the birthrate fell until 1952 and has risen steadily again until 1964, in which year the population of babies born was about 47,000 more than in 1946. Fixing the maternal age distribution fixes the incidence at the 1946 level of 1 mongol per 611 births. The number of mongols born in 1964 in excess of 1946 resulting from population increase will therefore be an excess amounting to approximately 47,000 divided by 611, giving an increase of 78 mongols. Thus, population increase slightly increases the number of mongols born and the trend towards younger childbirth greatly reduces it.

Table 6 combines the effects of population change and the changing maternal age distribution, and the net result, which is an estimate of what has actually happened to the incidence of mongolism in the community, discloses an appreciable reduction in numbers of 256, or over 20%.

TABLE 6

Estimated birth incidence of mongolism, 1946-1964

M.A. Group	1946	1948	1950	1952	1954	1956	1958	1960	1962	1964
15—	11	13	13	13	14	17	19	23	30	33
20—	122	131	119	118	121	127	138	150	162	171
25—	208	209	191	179	177	186	195	202	214	226
30—	235	180	159	167	172	165	167	174	177	177
35—	413	345	295	257	229	252	274	274	268	267
40—	337	310	257	234	228	215	189	216	231	232
45—	55	52	47	30	30	31	33	35	37	19
Total	1,381	1,240	1,081	998	971	993	1,015	1,074	1,119	1,125
Mean M.A. Incidence	34.8 1/611	34.3 1/640	34.2 1/660	33.8 1/690	33.6 1/711	33.4 1/721	33.1 1/746	33.1 1/746	32.9 1/764	32.5 1/791
Mean of all births	28.8									26.7

Penrose (1967) has estimated the effect of changing trends in maternal age at childbirth by a different technique, obtaining relative incidence of mongol to control births for each maternal age group, using data from a large sample of mongols in England to obtain a maternal age distribution. The overall estimate he employed is also derived from English data. The resulting estimates show similar considerable reduction in the estimated numbers of mongols born, comparing 1939 and 1964, but the reduction is somewhat greater than that obtained by the present method. The difference may be due to local influences, to incomplete ascertainment in the Australian survey (although this was very thorough) or to bias in the maternal age distribution of the English data.

Prevalence:

At this point, it is worth noting that the prevalence of mongolism (the number, alive at any one time, in the community) is determined by birth incidence and survival. There is evidence that between 1929 and 1957 the mortality of mongolism in childhood fell greatly, so that the resulting prevalence at the age of 10 years may be four times what it was in 1929 (Carter, 1958). Reduction in mortality, therefore, has caused an increase in the number of mongols in the community by far outweighing the reduction in birth incidence; less mongols are born, but more are alive at the age of 10 years, than in 1946, probably many more. There is less information available about changes in survival after the age of 10 years, but this may also have increased. A Swedish investigation (Forssman and Akesson, 1965) indicates that between the ages of 5 and 45, the mortality of mongolism is only slightly higher than in the general population,but is significantly higher after that age. Even so, it may be less now than formerly, but there is little evidence available to confirm this. Table 7 gives the numbers and age distribution of mongols resident at St.

TABLE 7

Age Distribution of Mongols
Resident at St. Lawrence's Hospital in 1941 and 1965

Age Group	Age in 1941		Age in 1965	
	No.	%	No.	%
0— 4	—	—	—	—
5— 9	2	2.7	12	6.4
10—14	9	12.3	14	7.4
15—19	27	37.0	34	18.1
20—24	17	23.3	18	9.6
25—29	6	8.2	26	13.8
30—34	6	8.2	25	13.3
35—39	2	2.7	28	14.9
40—44	4	5.5	12	6.4
45—49	—	—	8	4.3
50—54	—	—	4	2.1
55—59	—	—	5	2.7
60—64	—	—	2	1.1
Total	73	99.9	188	100.1
Mean		21.3		28.9

Lawrence's hospital in 1941, for which the data is fortunately available, and 1965. No mongols resident in 1941 had reached the age of 45 years whereas over 10% were older than this in the 1965 population. It is also notable that the total number of mongols resident in 1965 is much greater, although the total hospital population has changed little. Table 8 shows that non-mongols tend to live to later ages than mongols. In interpreting these tables, it has not been possible to obtain reliable data about changing trends in admission and discharge that might have influenced findings, but it appears likely that increased prevalence and survival are at least partly responsible for them.

TABLE 8

Age Distribution of Non-Mongol and Mongol Subjects, St. Lawrence's Hospital, 1965

Age Group	Severely Subnormal Non-Mongols		Mongols	
	No.	%	No.	%
0— 4	2	0.1	—	—
5— 9	35	2.0	12	6.4
10—14	96	5.3	14	7.4
15—19	177	10.1	34	18.1
20—24	150	8.6	18	9.6
25—29	168	9.6	26	13.8
30—34	166	9.5	25	13.3
35—39	203	11.6	28	14.9
40—44	150	8.6	12	6.4
45—49	135	7.7	8	4.3
50—54	128	7.3	4	2.1
55—59	122	6.9	5	2.7
60—64	95	5.3	2	1.1
65—69	43	2.5	—	—
70—74	43	2.5	—	—
75—79	22	1.2	—	—
80—84	9	0.5	—	—
85—89	7	0.4	—	—
90—94	2	0.1	—	—
Total	1753	99.8	188	100.1
Mean		37.9		28.9

Chromosomal Type:

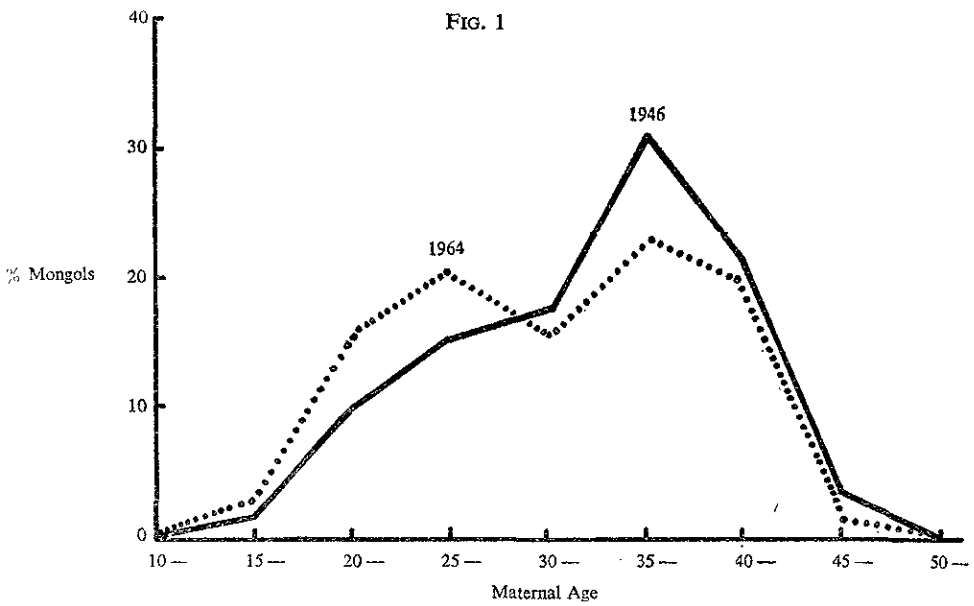
Although late maternal age is a potent influence in the occurrence of mongolism, it has long been evident that it is not the only one. Not all mongols are born to elderly mothers. Examination of a maternal age distribution curve shows a bimodal tendency, that is to say, it tends to have two peaks, a smaller one at the 25-29 and a larger one at the 35-39 maternal age group. The former is the age group at which the largest percentage of normal babies are born, and the maternal age distribution curve for normal babies shows a single peak here.

The usual explanation of the bimodal tendency is that mongols may be divided into two groups, the maternal age independent group, or Group A (Penrose, 1967) and the maternal age dependent group, or Group B. Group A mongols are due to causes independent of maternal age, and therefore they are born at the same maternal age, as non-mongol babies. Group B, the larger one, consists of mongols born

to older mothers, forming the higher peak on the curve, whose occurrence is influenced by maternal age. There are techniques for estimating how many mongols belong to Group A and Group B (Penrose and Smith, 1966; Penrose 1967).

One interesting consequence of the general tendency for mothers to have babies younger is the effect this has on the relative incidence of Groups A and B. Penrose (1967) comparing the years 1939 and 1964 estimated that the percentage of mongols belonging to Group A increased from 28.7 to 37.8, Group B mongols being correspondingly reduced. Table 9 compares numbers and percentages of mongols born in 1946 and 1964, estimates having been obtained by the method described above. Figure 1 expresses the percentage distribution graphically. It is clearly evident that the mild bimodal tendency of the 1946 curve is more emphatic in the 1964 curve, due to the increase in Group A or maternal age independent mongols. In actual numbers (see Table 9) there is a moderate increase in the number of mongols born to young mothers, but a very big reduction in the numbers born to elderly mothers.

FIG. 1



Maternal Age Distribution of Mongols born in 1946 and 1964 compared. Note that the curves represent *percentage* distributions, and therefore demonstrate the more pronounced bimodal tendancy of the maternal age distribution of 1964 mongol births, but *not* the reduction in numbers of mongols born, which is recorded in Table 9.

Since the proportion of mongols that are maternal age independent, on the assumptions and estimates we have made, has increased, it is of some interest to examine briefly the causes of mongolism in this group. It is not proposed to discuss all the possible causes of M.A. independent mongolism that have been mooted. These include a genetical tendency to chromosomal anomalies in some families (Penrose & Smith, 1966), and such environmental factors as an infective agent affecting oogenesis, particularly viral hepatitis (although this, too, may be maternal age related, according to Collmann and Stoller, 1962) and parental radiation (Sigler, Lilienfeld, Cohen and Westlake, 1965).

TABLE 9

Maternal Age Distribution of Mongol Births: 1946 and 1964.

M.A.	1946		1964		1946		1964	
	No.	%	No.	%	No.	%	No.	%
15—	11	0.8	33	2.9	341	24.6	430	38.2
20—	122	8.8	171	15.2				
25—	208	15.0	226	20.1				
30—	235	17.0	177	15.7	1040	75.4	695	61.8
35—	413	30.0	267	23.7				
40—	337	24.4	232	20.6				
45—	55	4.0	19	1.8				
Total	1381	100	1125	100	1381	100	1125	100

Of particular interest is the relationship of chromosomal anomalies to maternal age at birth. With rare exceptions, mongols are of the following chromosomal types:

1. Trisomy 21 ("regular mongols").
2. 13-15/21 reciprocal translocation (D/G translocation).
3. 21-22/21 reciprocal translocation (G/G translocation).
4. Mosaic mongols (usually, 46/47 mosaicism).

The first is by far the commonest and denotes an extra chromosome, there being three, instead of a pair, of chromosome No. 21. In translocations, there is also an extra chromosome No. 21, but this is fused to another chromosome. In nearly all reported instances, this is either a chromosome of the 13-15 group, or of the 21-22 group. In mosaicism, the extra chromosome is present in some cells only, in others, the chromosome complement is normal.

By combining data from cytogenetic surveys of mongolism that have been undertaken in different countries, a sufficiently large sample can be obtained to examine the relationship of the different chromosomal types to maternal age at birth (Table 10). It is apparent that, at all maternal ages the usual type of trisomy 21 is the commonest. However, whereas about 85% of all mongols born to mothers under 20 have trisomy-21, over 98% born to mothers over 45 are of this type. The rarer anomalies are less obviously maternal age influenced. In particular, D/G translocations appear to be independent of maternal age. The other two anomalies, although maternal age at birth tends to be somewhat higher than for normal babies, are less often maternal age influenced than the regular mongols. It is beyond the scope of this paper to discuss mosaic mongolism in greater detail, but this is more complicated as there are theoretically two different ways in which this anomaly may originate, one of which may usually be maternal age dependent, the other, maternal age independent. Analysis of approximately 140 mosaic mongols the author has collected from various sources, leads to an estimate of about 70% maternal age independent cases, which is about double that for the ordinary trisomy mongols.

The main point of these observations is to suggest that the rarer chromosomal anomalies form an appreciably higher proportion of mongols born to younger mothers, as indicated by Table 10. The consequence of the prevailing tendency for mothers to have babies younger, as noted above, is that the proportion of mongols

born to younger mothers has increased, and this should lead to an increased proportion of mongols with the rarer chromosomal anomalies, at the expense of the regular, trisomy mongols.

TABLE 10

Distribution of different chromosomal types by maternal age: data from surveys

M.A.	Trisomy		D/G Trans.		G/G Trans.		Mosaicism		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
15—	23	85.2	2	7.4	1	3.7	1	3.7	27	100
20—	96	87.3	7	6.4	3	2.7	4	3.6	110	100
25—	147	94.8	3	1.9	0.0	0.0	5	3.2	155	100
30—	177	92.2	3	1.6	5	2.6	7	3.6	192	100
35—	263	95.6	4	1.5	3	1.1	5	1.8	275	100
40—	280	97.2	0	0.0	3	1.0	5	1.7	288	100
45—	55	98.2	0	0.0	0	0.0	1	1.8	56	100
Total	1041	94.4	19	1.7	15	1.4	28	2.5	1103	

The Future:

It is not possible to predict trends in prevalence and incidence with accuracy. It seems unlikely that such major changes in mortality, and therefore in prevalence, will occur in the next few decades as have occurred in the last as a result of advances in medical treatment. Nor can the trend towards younger maternal age at childbirth continue indefinitely. Changes in prevalence and incidence will probably be smaller and will fluctuate in so far as age at marriage and family size are subject to the influence of social and economic conditions.

Summary:

The birth incidence of mongolism is strongly influenced by maternal age at childbirth. The known trend towards younger age at childbirth should reduce the incidence of mongolism. By applying incidence figures for mongolism at different maternal ages obtained from the survey of Collmann and Stoller to the numbers of babies born annually to mothers of each group published by the Registrar General, an estimate of numbers and incidence of mongols born in different years is calculated. The results demonstrate an appreciable reduction in the incidence of mongolism. Reduced mortality over the same period of years, however, has increased prevalence.

The effect of the trend on the proportion of maternal age independent mongols and on chromosomal type is discussed.

Acknowledgements

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