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Part I.—Original Articles.

MATERNAL AGE, ORDER OF BIRTH AND DEVELOPMENTAL ABNORMALITIES.

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1. INTRODUCTION.

SINCE early times interest has centred round the problem of whether special virtue or taint is attached to the first-born child. Some recent workers, like Pearson (1914), have believed the first-born child to be liable to physical and mental handicaps. Still (1927) focuses attention on certain diseases which appeared to be more frequently manifested in the first child in a family than in children born later in that family. He also realized that maternal age might be a significant factor in other conditions. A summary of a good deal of the work done on these problems was published by Thurstone and Jenkins (1931). These writers drew attention also to parallel studies in animal genetics. Wright (1926 and 1936), by his analysis of polydactyly and coat colour in guinea-pigs, laid a foundation for genetical work on maternal age. The effects he observed were due to alterations of characters in early offspring. Unfortunately, experimental animals rarely live long enough to make possible the corresponding study of maternal age effects at the end of the reproductive period. Evidence that birth order of itself is of significance in animal genetics has been scanty. Recently, however, Goetsch (1937) reported that the first eggs of the queen ant (*Pheidole pallidula*) give rise to small and physically feeble workers. In the present communication the results of some of the writer's recent researches on the effects of maternal age and birth order in human genetics are discussed. A multitude of human malformations are relevant to this study. Investigations of their respective ætiologies is of interest from the point of view of elucidating the effects of natural selection in man as well as from the standpoint of preventive medicine.

2. Maternal Age and Mongolism.

The relationship of the incidence of mongolism to maternal age has been intensively studied by Orel (1926), van der Scheer (1927), Schultz (1931), Penrose (1932, 1933, 1934), Thomsen (1932), Jenkins (1933,, and Bleyer (1937). The usual method of approach to the problem has been to compare the maternal ages at the births of a series of cases of mongolism with an estimate of the standard distribution of maternal ages for births in the general population. This standard distribution can be inferred from official statistics in countries where age of the mother is recorded on birth certificates. In England such material has not been hitherto available and, in these circumstances, the standard for comparison can only be inferred from the maternal ages at the births of the patients' sibs, or a control series of cases. The avoidance of using official figures has certain advantages in that ages in each family can be carefully checked by personal investigation and the order of birth of each child accurately ascertained. A disadvantage of using the patient's own sibs as controls is that the presence of the abnormality in the propositus may tend sometimes to cause artificial family limitation ; this factor might tend to make the ætiological effect of birth order or maternal age appear greater than it really is. In the case of mongolism, however, the difference between mean maternal ages for births of mongols and for births of normals is so great that even a crude method suffices to demonstrate its significance. The mean maternal age for 224 mongol births investigated by the present writer was 37·4 years. For a control series of 1,132 non-mongolian mentally defective patients (Penrose, 1938*a*) the mean maternal age was 29·4 years, with a standard deviation of 6·6 years. The incidence of mongolism in the general population changes rapidly if succeeding maternal age groups are separated ; indeed, the probability that a mother will have a mongol child is more than doubled for every increase of five years after the age of 25.

3. Maternal Age and Congenital Deformity of the Nervous System.

The commonest congenital deformities in man are those which affect the central nervous system. Anencephaly, hydrocephaly and spina bifida, either as separate or combined abnormalities, account for about half the cases of fœtal deformity which can be noticed at birth ; they occur in 1% of all births (Malpas, 1937). Both Malpas (1937) and Murphy (1936) have shown that there is a positive relationship between the incidence of the births of children with malformed nervous systems and maternal age increase. The relationship is of the same type as that found in mongolism, but is less marked (see Tables I and II). In 144 cases investigated by the present writer, the mean maternal age was 31·7 years. Since the expected mean maternal age, calculated from

the data on normal sibs in these families, was 29·8 ± 5·9, the increase over the normal is significant: for 144 cases the error of the difference, 1·9 years, is 0·5 years. According to Malpas the cases of spina bifida showed less maternal age effect than the cases of anencephaly, but, in the writer's own data, the spina bifida cases had a higher mean maternal age than the cases without spina bifida. The three lesions specified, however, are intimately connected embryologically, and it seems satisfactory to discuss them together.

TABLE I.—*Percentage Distribution of Cases according to Maternal Age.*

Data and source.		Births in maternity hospital (Malpas).	Mongolism (Penrose.)	Deformities of nervous system. (Malpas.)	Deformities of nervous system. (Penrose.)	Central placenta prævia. (Penrose.)
Number of cases		13,964	224	140	144	35
Maternal age group	16–20	7·6	1·8	2·1	2·1	0·0
	21–25	30·0	5·3	24·3	24·2	8·6
	26–30	29·0	7·2	25·7	19·5	17·1
	31–35	19·0	16·9	19·3	24·9	34·3
	36–40	11·0	30·8	19·3	19·5	22·9
	41–45	3·0	31·3	7·1	9·0	14·2
	46–50	0·34	15·9	2·1	0·7	2·9

TABLE II.—*Incidence Compared with Standard Maternal Age Groupings.*

Data.		Births in maternity hospital.	Mongolism.	Deformities of nervous system (*a*).	Deformities of nervous system (*b*).	Central placenta prævia.
Maternal age group	16–20	1·0	0·3	0·3	0·3	0·0
	21–25	1·0	0·2	0·8	0·8	0·3
	26–30	1·0	0·4	0·9	0·7	0·6
	31–35	1·0	0·9	1·0	1·3	1·8
	36–40	1·0	2·8	1·8	1·8	2·1
	41–45	1·0	10·4	2·4	3·0	4·7
	46–50	1·0	43·9	6·2	2·1	8·5

4. MATERNAL AGE AND CENTRAL PLACENTA PRÆVIA.

The placenta is chiefly a fœtal structure and its abnormalities can be classed with fœtal deformities. When the site of attachment to the uterine wall encroaches upon the lower segment or covers the os, the condition is known as placenta prævia. There is, according to some authorities, an embryological distinction between the central type, which covers the os, and other types. In a recent paper by the present writer (Penrose, 1939) it was shown

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to be probable that maternal age is a specially important ætiological factor in cases of central placenta prævia. In 35 cases the mean maternal age was found to be significantly raised (33·8 years) and the distribution of the cases showed a relationship to maternal age more marked than in the congenital abnormalities of the nervous system, but less marked than in mongolism. In the non-central types of placenta prævia, the mean maternal age was only 31·4 years for 112 cases, and there was evidence here that multiparity was an important predisposing cause.

5. Multiparity as an Ætiological Factor.

The earlier investigators of the causes of mental defect often attributed mongolism to maternal exhaustion due to repeated pregnancies. It can be shown that the basis for this assumption is apparent and not real, and is due to the fact that the mothers' age and the order of birth are correlated. Indeed, the product moment correlation, in a random sample of families, between age and birth order varies from + 0·50 to + 0·60. For similar reasons the age of the father has sometimes been erroneously supposed to play a part in the ætiology of mongolism. As far as the present writer's data are concerned no evidence of a separate paternal age influence could be detected either in mongolism or in other congenital malformations.

The exact treatment of the question whether birth order has an effect which is independent of maternal age is difficult and laborious. The assumption that maternal age was the significant factor in mongolism was found to be in agreement with the data in 224 families (Penrose, 1934). The residual effect attributable to birth order was too slight to be detected with any certainty, but a very small excess of mongol births in first births and in ranks above the seventh was found. It might be that if a series of 1,000 cases were studied in the same way a residual effect of birth order would be observed. The writers' data on 144 cases of congenital deformity of the nervous system were also analysed in detail to discover whether the effect of birth order was likely of itself to be ætiologically important. The observed mean birth rank for these 144 cases was 3·56, and the expected mean rank based upon the sibships reconstructed by a method previously described (Penrose, 1933), which is a modification of the method of Yule and Greenwood (1914), was 3·04 ± 2·44. The increase in mean birth rank above expectation is apparently significant. Expressed in another way, the biserial correlation of incidence with birth rank was + 0·218 ± 0·082. Incidence here means the observed number of cases divided by the expected number in each rank. This correlation, though apparently significant, was lower than the corresponding value obtained for incidence and maternal age, + 0·266 ± 0·081. Since the correlation of expected maternal age and expected rank is 0·584, the partial correlation of incidence with rank for constant maternal age is only 0·078 ± 0·84, which is insignificant.

In the converse comparison, the partial correlation of incidence with maternal age for constant birth rank is still significant, i.e. 0·171 ± 0·83.

A similar line of reasoning, applied to the cases of central placenta prævia indicated that in this condition birth rank was relatively unimportant. With respect to the other types of placenta prævia, however, birth rank was shown to be at least as important as maternal age, and probably more so.

Recent statistical work on the nature of the distribution of still-births in the general population according to birth rank and maternal age suggests that both factors are important in determining "pregnancy wastage". Table III which was calculated by Gould (1938) from American statistics, shows independent effects of both variables, though the rise of incidence with maternal age is the more marked. Not improbably many still-births are caused by fœtal malformation and, though the incidence of some types may be dependent upon maternal age, the incidence of other types may depend upon birth order or upon both factors.

TABLE III.—*Percentage of Still-births among White Women of the U.S.A.*, 1932.

Birth rank.	Maternal age group.								All ages.
	Under 15.	15–19.	20–24.	25–29.	30–34.	35–39.	40–44.	45+.	
1st	5·3	3·1	2·8	3·0	4·2	5·9	8·2	8·6	3·2
2nd	—	2·2	1·5	1·7	2·0	2·9	4·8	6·9	1·9
3rd	—	3·0	2·0	1·9	2·2	3·1	4·2	6·0	2·2
4th	—	5·9	2·1	2·0	2·5	3·3	4·5	5·7	2·5
5th	—	9·1	3·0	2·1	2·6	3·5	5·1	6·1	2·8
6th	—	—	4·5	2·7	2·7	3·6	4·7	5·9	3·2
7th	—	—	5·2	3·6	2·8	3·4	4·5	9·2	3·4
8th	—	—	5·1	4·3	2·9	3·4	5·1	5·8	3·7
9th	—	—	6·3	5·3	3·6	3·7	4·8	5·1	4·1
10th and over	—	—	2·2	4·8	4·9	4·7	5·4	6·9	5·1
All ranks	5·3	3·0	2·3	2·3	2·8	3·7	5·1	6·9	2·8

6. PRIMOGENITURE.

Some of the conclusions of Pearson (1914) concerning the effects of primogeniture have been doubted because his analytical methods have been criticized. The proof that a disease occurs more frequently in the first-born than in later births is more difficult than was formerly supposed. Still (1927) showed that nearly half the cases of congenital deformity occurred in first-born children. In order to be sure that this proportion is significantly high the number of expected first-born children in families selected in the same way from the same kind of

population must be known. The small size of human families in civilized countries makes the investigations of this problem particularly difficult. Moreover, if primogeniture and raised maternal age should both be ætiologically important in the same disease, the two effects might mask one another. Again, the assumption that the regression of incidence on birth rank is linear, which is implied in the use of partial correlation, is not necessarily correct. In Table III, for example, neither the regression of still-births on age or on rank is linear. In this way the full effect of either variable may be concealed by relying on arithmetical averages.

The application of the x-value technique (used in the 224 cases of mongolism by the writer) to the data on 144 cases of fœtal abnormality showed how a hidden excess of first-born could be revealed. After fitting probability values for the incidence so that the maternal age effect was fully accounted for, a marked residual effect of primogeniture and a slight residual effect of multiparity after the seventh-born was observed (see Table IV). As in mongolism and in still-births generally, the incidence first decreases with maternal age, and then increases rapidly after the age of 30 years is passed. The residual relationship of the incidence to birth order also had the same general character as in Table III. Though it is very doubtful whether primogeniture has any significance in the ætiology of mongolism, it probably is a significant factor in the nervous system malformations. Analysis of cases of

TABLE IV.—*Deformities of the Nervous System.*

Maternal age group.	Observed number of cases.	Probability of incidence (x-value).	Calculated number of cases.
16–19	3	1·43	3·3
20–34	90	0·72	88·7
35–44	48	3·01	49·0
45–49	3	15·82	3·03
Total	144	1·00	144·0

Birth rank.	(*a*) Observed number of cases.	(*b*) Expected number of cases.*	(*c*) Expected number of cases.†	Difference (*a*–*c*).
1	49	46·2	31·2	+ 7·8‡
2, 3	38	54·1	48·4	— 10·4
4, 5, 6	31	29·0	30·8	— 0·2
7–15	26	13·7	22·4	+ 3·6
Total	144	143·0	133·0	0·0

* (*b*) Modified Yule-Greenwood reconstruction.

† (*c*) x-value reconstruction; on the assumption that the whole of the effect is due to maternal age.

‡ The standard error is approximately 3·5.

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placenta prævia did not indicate that primogeniture was an ætiological factor in that disease.

7. Primogeniture in Congenital Pyloric Stenosis.

Although there may be doubts as to what part is played by primogeniture in the production of some congenital abnormalities, nearly all authorities agree that pyloric stenosis is more often found in first-born children than is to be expected by chance. Thus, in 221 cases whose family histories were studied by the staff of the Royal Eastern Counties' Institution Research Department, 109 were found to be the results of first pregnancies. In 222 cases studied by Cockayne (1939) 126 were first in the family. The proportions of first-born cases in these two sets, 49% and 58% respectively, are much higher than are found for control patients selected by the presence of any other disease. The proportion of first-born children in the population from which a sample of mentally defective cases was drawn was close to 28% (Penrose, 1938*a*). A higher estimate for primogeniture in the general population (46%) was given by Malpas (1937), but it was conceded that this estimate was exceptional and due to the special conditions of a maternity hospital survey. The simple comparison of observed and expected proportions of first-born is liable to certain errors. For example, if the disease studied has a high familial incidence and sibships come under observation immediately after the birth of the first case in that sibship, the proportion of cases in the early part of the family appears unduly high. Pyloric stenosis, for instance, is usually recognized by the infant's vomiting and loss of weight in the first two months of life. To obviate the errors due to inclusion of unfinished families, the investigation of 221 cases was carried out many years after their identification. In the families investigated seven or more years after the birth of the propositus we found an excess of first-born patients as compared with their own sibs, though it would need a much more extensive investigation to prove conclusively that this excess was not due to chance (see Table V). Maternal age may also have a slight effect, but it was too small to be significant in these data.

Table V.—*Congenital Pyloric Stenosis.*

Number of years since birth of propositus.	Number of cases.	Number of cases which are the result of first pregnancies.	
		Observed.	Expected.
0–6	90	48	54·62
7	58	26	25·96
8–13	73	35	30·76
0–13	221	109	111·34

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8. The Genetic Mechanisms.

All the abnormal conditions discussed in this communication are to some extent familial. They all have a low familial incidence. As pointed out by Malpas (1937) and by Murphy (1937), there is a tendency for the same type of abnormality to be repeated in the same family. There may also be heterogeneous cases in the same sibship, but these are less frequent. In Table VI the nature of the specificity of the familial incidence can be studied. It is fairly evident that the group of nervous system deformities, mongolism, placenta prævia and pyloric stenosis are different entities. The specificity is seen both in sibs and in other relatives. There are, moreover, some important differences in the biology of these various conditions. Congenital pyloric stenosis is nearly five times more common in males than in females. Mongolism is slightly more commonly found in males than in females. The same possibly applies to placenta prævia. Spina bifida and congenital hydrocephaly are found with equal frequency in males and females, and anencephalics are nearly always females.

Table VI.—*Specific Familial Incidence.*

Propositi.		Affected sibs.						Sibs not thus affected.
Number.	Abnormality.	M.	A.	H.	S.	P.P.	P.S.	
63	M.	4	—	—	1	—	—	266
19	A.	—	1	—	1	—	—	40
43	H.	—	—	—	—	1	—	182
75	S.	1	1	—	4	1	—	222
69	P.P.	—	1	1	—	3	—	194
212	P.S.	—	—	—	—	—	9	307

M. = Mongolism. A. = Anencephaly. H. = Congenital hydrocephaly. S. = Spina bifida or meningocele. P.P. = Placenta prævia. P.S. = Congenital pyloric stenosis.

In searching for a genetic hypothesis to explain the epidemiology of these malformations it is obviously useless to look for Mendelian ratios unless the effects of maternal age or primogeniture are first taken into consideration. Actually, even after making due allowance for prenatal environmental factors, it is difficult to believe that the average proportion of susceptible children in sibships is even as high as one-quarter (Penrose, 1932), because the familial incidence generally is so low. The chance of finding a second case of mongolism in a sibship of a propositus is only about one in sixty. The chance of finding a second case of pyloric stenosis, however, is somewhat greater—about one in thirty.

Consanguineous parentage is more frequent for children with pyloric stenosis than for normal children, or for any of these kinds of congenital deformity discussed here. Thus, in a series of cases investigated (221 by the present writer, and 222 by Cockayne) there were, altogether, 6 examples of

first cousin and 3 examples of second cousin parents—that is, double the number expected for the general population. A slight excess of consanguineous parentage has been found in mongolism by some observers, but it is doubtful if this excess is significant (Thomsen, 1932). The preponderance of males in pyloric stenosis does not suggest the influence of a sex-linked factor (Cockayne, 1938) because the proportion of males to females in normal sibs is as in the general population. The underlying cause of congenital pyloric stenosis is quite likely to be a recessive factor ; males are constitutionally more liable to develop the condition than are females, and the first-born is much more likely to be affected than others in the sibship.

The other congenital deformities—mongolism, anencephaly, etc.—do not fall easily into line with any simple genetic hypothesis. The type of inheritance in mongolism, for instance, can be described as irregularly dominant (Fantham, 1925 ; Doxiades and Portius, 1938) with a very low familial incidence. Parents are always unaffected, though they may show some mild features of the disease and transmission can occur through both male and female lines. The same type of inheritance seems to apply to spina bifida (Penrose, 1938*b*) and possibly also to the other related neurological malformations.

Anencephaly in mice has been studied by Snell and others (1935). The abnormality was attributed to the effects of X-rays, which had caused chromosome translocation in a parent. Individuals with unbalanced chromosomes can occur among the offspring of a parent with translocation in proportions which are not Mendelian ratios. These unbalanced offspring are usually non-viable. It was pointed out, moreover, that the unbalanced condition is not always lethal to the zygote however, and, in favourable environmental conditions, some unbalanced embryos may develop normally. There may also be genetic modifying factors, favourable or unfavourable, carried by the female transmitter, so that some stocks may be more susceptible than others.

If one of the environmental modifying factors in man is maternal age, the parallel of anencephaly in man and in mice is very close. Another interesting point is that many kinds of translocation produce the same type of deformity in mice. Possibly in this group of human neurological abnormalities we have examples of the effects of many different chromosome derangements. The peculiar sex incidence of anencephaly suggests that, in this malformation, the sex chromosomes may be deranged. In mongolism the consistency of the clinical picture suggests that a specific duplication or deletion may be the cause. Such an abnormal chromosome could be transmitted from parent to a small proportion of the offspring and some of the offspring who possessed it would develop normally.

9. Summary.

A positive association is demonstrable between maternal age and the incidence of mongolian imbecility, gross malformation of the nervous system, and

central placenta prævia. The independent effect of birth order is not easy to demonstrate conclusively. Primogeniture, however, is likely to be a significant factor in determining the incidence of gross malformation of the nervous system and of congenital pyloric stenosis. The study of maternal age and birth order usefully precedes the investigation of the genetical backgrounds of these conditions. The underlying cause of congenital pyloric stenosis seems to be a recessive diathesis. Mongolism and some other malformations may have their origin in chromosome anomalies.

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