Diaphragmatic activity dropped to a minimum during the first second of expiration. With loud trumpet-playing, the recorded activity with diaphragmatic leads slowly increased again towards the end of expiration, but activity was always much less than that recorded during inspiration.

In view of the anatomical relationships of the oesophagus as it passes through the diaphragm, it seems unlikely that these action potentials can be ascribed to any other muscles. The activity in the external obliques increased steadily throughout expiration. The late re-entry of diaphragmatic activity in these extreme conditions is puzzling and no adequate explanation is available. This combination of contraction of abdominal muscles and diaphragm was also seen during efforts at "bearing down."

Summary

Methods are described for estimating the tracheal pressure during speech and of recording activity in the diaphragm and a variety of thoracic and abdominal muscles.

During a steady level of loudness of speech the mean tracheal pressure is kept remarkably steady. The pressure needed varies from 2 cm. of water for very quiet speech to 30 cm. for parade-ground shouting.

To attain a steady level of 2 cm. of water throughout an expiration the inspiratory muscles—the external intercostals—at first oppose the relaxation pressure (there is usually a short period when all muscles are inactive and the relaxation pressure acts alone); then expiratory muscles, beginning with the internal intercostals and later involving other muscles, such as the rectus abdominis, reinforce the diminishing relaxation pressure.

In paraplegics the maximal expiratory pressure that can be exerted is lower the higher the level of transection between T 12 and C 6.

The shortest reaction time when a subject was instructed to say "ma" as soon as possible after a sound was 140 msec. to the start of internal intercostal muscle activity. The first sound started consistently about 50 msec. later.

We are indebted to Dr. Ludwig Guttman for permission to examine some of his paraplegic patients. We thank Mr. C. Shepley, department of medical illustration, University of Edinburgh, for his assistance with Fig. 1, and Mr. W. T. S. Austin for his technical assistance throughout this study.

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MATERNAL HEALTH AND MONGOLISM

BY

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The genetical basis of mongolism has been established by the recent discovery of an extra chromosome in the cells of affected individuals. The cause of this abnormality, however, remains unknown, but there are reports of associated effects, often connected with maternal status, which may be of aetiological significance.

For this reason much attention has been paid to maternal health and, in particular, to endocrinological, gynaecological, and obstetric abnormalities. With respect to endocrinological changes, early reports were for the most part contradictory and were not supported by objective findings. Thus Dollinger (1921), Myers (1938), and Benda (1949) had reported a high incidence of thyroid abnormalities in the mothers of mongols, but this was not confirmed by Øster (1953).

No objective findings were reported until Ek (1959) and Ek and Jensen (1959) published the results of their investigations into thyroid and adrenocortical function in the mothers of mongols. Ek investigated 41 mothers of mongols and reported that their serum protein-bound iodine (P.B.I.) was significantly raised (mean value 7.1 $\mu\text{g.}/100\text{ ml.}$) compared with that of a control group (mean value 5.9 $\mu\text{g.}/100\text{ ml.}$). Ek and Jensen also studied the corticoid output in the urine of 20 of these mothers, and found that, though the 17-ketosteroids and 17-ketogenic steroids were normal, certain fractions containing dehydroepiandrosterone and an ether-extractable tetrazolium-salt-reducing ketocorticoid were double the value found in a control group.

Ek also reported that 20 of the 41 patients had marked psychoneurotic symptoms and that the increase in P.B.I. was most marked in these women. This is in keeping with observations of Benda (1949) and Øster (1953, 1956) that there is an increased incidence of nervousness and neurosis in the mothers of mongols.

The present study was designed primarily to investigate further these factors, which may be of possible aetiological significance in mongolism.

The Investigation

The present series consists of 55 mothers of mongols. Their ages ranged from 28 to 61, with a mean of 44.1 years. The mean number of years between the birth of the mongol and the interview in the present investigation was 10.6 years. In each case every effort was made to obtain accurate information from the mother regarding past events, but it was fully realized that distortion of memory occurs with the passage of time, and this is especially so in connexion with the circumstances surrounding the birth of a defective child. None of the mothers had any family history of consanguinity among their forebears. All had borne only one mongol, except one who had borne two mongol daughters.

Medical, gynaecological, and obstetric histories were taken from each mother. A clinical examination was then carried out in each case, special attention being paid to evidence of thyroid dysfunction. In addition, anthropometric measurements were made, the serum P.B.I. was estimated, and a personality questionnaire was undertaken.

Assessment of Thyroid Function

No clinical evidence of past history of thyrotoxicosis was found in any of the subjects.

The serum P.B.I. is the nearest approach to an estimation of the circulating thyroid hormone at present available. This estimation was carried out in 54 cases. One mother refused to have a venepuncture.

The P.B.I. was estimated according to the method of Grossmann and Grossman (1955). None of the subjects had at the time been taking any drug known to affect the level of P.B.I., and none had had an x-ray examination during the previous year. The normal range of values for P.B.I. according to various techniques used is 3–8 $\mu\text{g.}/100\text{ ml.}$ From a control series of 30 mothers who had not borne mongol children blood was obtained for the estimation of P.B.I. The mean age of this control group was 39.9 years.

TABLE I.—Protein-bound Iodine

	Mothers of Mongols (n=54)		Controls (n=39)		Comparison Between Groups	
	Mean	S.D.	Mean	S.D.	t	P
P.B.I. ($\mu\text{g.}/100\text{ ml.}$)	4.7	1.0	4.8	0.7	0.7	Not significant
Age (years)	45.6	6.6	39.9	10.8	1.92	"

The group of mothers of mongols did not differ from the control group with respect to the P.B.I. (Table I). Only one of the former group had an abnormally high P.B.I.—8.9 $\mu\text{g.}/100\text{ ml.}$ There was no thyroid enlargement in her case or any clinical sign of thyroid dysfunction. One mother with a very low normal P.B.I. level of 3.2 $\mu\text{g.}/100\text{ ml.}$ had a sister who had been diagnosed as a cretin.

Moderate enlargement of the thyroid was found in 9 of the 55 subjects. Ek (1959) found thyroid enlargement in 12 of his series of 41 mothers of mongols.

Psychological Factors

A psychiatric history was taken from each of the mothers, and the incidence of any nervous or mental illness requiring treatment at home or in hospital was noted.

The Maudsley Personality Inventory was applied to each of the mothers. This is a questionnaire of 48 items devised by Eysenck to measure two personality factors—extraversion and neuroticism. Extraversion refers to the outgoing sociable qualities of the personality. Neuroticism is defined as the general emotional lability of a person and his liability to neurotic breakdown under stress. Neurotic groups of patients have been shown to score consistently higher on the neurotic rating of the inventory (Eysenck, 1959).

None of the subjects in the present series had a history of psychiatric illness. Two had been admitted to hospital for a reactive depression after the birth of the mongol. In each case the shock of having borne a

mongol child, coupled with associated stress factors in the environment, was considered by psychiatrists at the time of the breakdown to have been the immediate cause of the depressive illness.

Seven subjects had suffered from mild neurotic symptoms for which they had been treated at home by their general practitioners.

Scores obtained on the Maudsley Personality Inventory (Table II) for both neuroticism and extraversion did not differ significantly from those

TABLE II.—Maudsley Personality Inventory

	No. of Subjects	Neuroticism Score		Extraversion Score	
		Mean	S.D.	Mean	S.D.
Mothers of mongols	55	20.8	9.5	26.8	6.1
Controls (present series)	31	20.2	10.2	23.8	8.9
Controls (Eysenck, 1959)	1,800	19.9	11.0	24.9	9.7

Comparison between controls (present series) and mothers of mongols: neuroticism: $t=0.273$ (not significant); extraversion: $t=1.82$ (not significant).

obtained from the control group and were in accordance with those obtained by Eysenck (1959) for normal subjects. The results are in agreement with the clinical impression that these subjects showed no marked psychiatric disturbance or personality deviation. Seven of them reported that they had suffered from anxiety during their pregnancy with the mongol. Of these, five were living in environmental circumstances likely to provoke anxiety in the most stable of temperaments.

Physique

The discriminant androgyny score (Tanner, 1951, 1955) was obtained for each patient by measuring the biacromial and bi-iliac diameters and applying the following formula:

$$3 \times \text{biacromial diameter (cm.)} - 1 \times \text{bi-iliac diameter (cm.)}$$

All measurements were made by the same observer, using a Martin anthropometer.

The term androgyny may be defined as the presence of masculine features in women and feminine features in men. Each sex has a characteristic score (90.1 with S.D. 4.7 for men; 78.9 with S.D. 4.6 for women), and only 12% of a normal population of men and women were misclassified by this score (Tanner, 1951). This feature of physique arises at puberty, probably under the influence of the sex hormones, and recent investigations suggest that the androgyny score is associated with other sexual characteristics and abnormalities. Thus Ferriman *et al.* (1957) found that women with hirsuties had an increased urinary 17-ketosteroid output, a tendency to oligomenorrhoea, and an increased biacromial diameter. Raboch (1957) found small biacromial diameters in hypogonadal men with female sex chromatin. Coppen (1958) reported that patients with pre-eclamptic toxæmia have considerably more masculine scores than a control group of normal pregnant women. Thus it is possible that women with a constitutional predisposition to endocrine overactivity, as has been postulated in the case of mothers of mongols, would show abnormalities in their androgyny score. The control group of Coppen (1958), which was practically identical with that of Tanner (1951), was used in the present study.

Height, biacromial and bi-iliac diameters, together with the androgyny scores, are shown in Table III. The

subjects of the present series did not differ significantly from the normal controls (Coppen, 1958) with respect to any of these values.

TABLE III.—*Physique*

	Mongol Mothers (n = 55)		Controls (n = 50)		Comparison Between Groups	
	Mean	S.D.	Mean	S.D.	t	P
Height (cm.)	160.8	5.7	160.0	4.8	0.98	N.S.
Biacromial diameter (cm.)	36.3	1.3	35.9	1.2	1.78	..
Bi-iliac diameter (cm.)	29.4	1.7	28.9	1.6	1.52	..
Androgyny score	79.7	3.7	78.9	3.3	1.12	..

A suggestion has been made by Penrose (1951, 1954) that mothers who have borne mongols at a relatively early maternal age may include individuals of specific genetical constitution who may lack the protection afforded by younger maternal age against the conception of a mongol child.

With this in mind, the entire group of mothers in the present series was divided according to age at the mongol birth. The division was made at a point one standard deviation below the mean—that is, at 27 years of age. It was found (Table IV) that the younger group

TABLE IV.—*Maternal Age at Birth of Mongol and Physique*

	Mothers Over 27 (n = 38)		Mothers Under 27 (n = 16)		t	P
	Mean	S.D.	Mean	S.D.		
Androgyny score	78.9	3.8	81.4	3.0	2.32	0.05
Biacromial diameter (cm.)	36.1	1.3	36.9	1.3	2.05	0.05
Bi-iliac diameter (cm.)	29.3	1.6	29.4	1.8	0.03	N.S.

had a significantly higher mean androgyny score and mean biacromial diameter than did the older group. Other measurements made during the investigation, including the P.B.I., however, showed no significant differences between the groups.

A further trend appeared which suggested a possible association between the number of miscarriages and the androgyny score, though the numbers are too small for statistical evaluation. This is shown in Table V. The

TABLE V.—*Mean Androgyny Score and Number of Miscarriages*

Group	No. in Group	Mean Androgyny Score
Mothers with no miscarriages	29	79.2
.. .. one miscarriage	15	78.9
.. .. two miscarriages	7	79.9
.. .. three or more miscarriages	3	83.5

mean androgyny score was found to be raised in groups of mothers who had had two or more miscarriages, but this effect was not seen in groups of mothers who had had one or no miscarriage.

Medical History of the Mother

Øster (1953), in his extensive survey of mongolism in Denmark, observed that illnesses in the mother, with the exception of abdominal tumours, showed a marked tendency to accumulate around the time of birth of the mongol. This has not been observed in the present small series.

Of the mothers with illnesses occurring in the year preceding the mongol's birth, one had a threatened mastoid, one had a perineal abscess, and two had miscarriages. One mother suffered from arterial

hypertension, but this had been a constant finding for years before and after the birth of her mongol child. Another mother suffered from mitral stenosis as a sequel to rheumatic fever in childhood.

Of mothers with physical complaints immediately after the birth of the mongol, one had a severe perineal rash, another had an outbreak of carbuncles in various parts of the body, a third suffered from epigastric pain and suspected but unconfirmed peptic ulceration, and a fourth had an operation for displacement of the uterus.

Menstrual and Obstetric History of the Mother

All of the 55 subjects were able to give their age at menarche. The mean age of the series is 14.4, based on the completed year of age, ignoring fractions, with a range of 10 to 19 years.

Øster (1953) found a mean age of menarche of 413 mongol mothers in his series to be 14.48 years, based on the completed year of age, which he found slightly younger than average ages of menarche in Danish urban and rural control groups.

Only two mothers had suffered from irregularity of periods throughout their menstrual histories. A third mother gave the history of one month's amenorrhoea at the age of 26, prior to her miscarriage, when she became obese but had no other complaints. She did not seek medical advice, and the obesity disappeared on a slimming diet. Another, who had a regular but three-weekly menstrual cycle, described greatly diminished menstrual flow for three periods immediately before the conception of the mongol at the age of 39. The effect was so marked that she believed she was menopausal, but after the birth of the mongol she reverted to her normal menstrual pattern, which has continued unchanged, she now being 43 years of age.

The remainder of the subjects gave histories of a regular menstrual cycle of constant duration and amount of flow, up to the onset of the menopause where this had been reached.

Twenty-four mothers had become menopausal by the time of the investigation, taking the time of menopause to be the time when menstrual periods previously regular became irregular. The mean age at the menopause was 47.6, with a range of 36 to 55 years. Øster (1953) found the mother's age at menopause to be remarkably high, in 50% of his cases it not having occurred until after the age of 50. In the present series the mean length of time that had elapsed between the birth of the mongol and the first signs of the menopause was 10.6 years, with a range of 6 months to 19 years. Only two mothers in the series were menopausal at the time of the birth of the mongol. One had been having hot flushes for a year before the conception of the mongol, her periods being regular until that date, but she had no further periods after the birth of the mongol; another had no menopausal signs before the conception of the mongol, but had no further menstruation after the period that terminated the flow of lochia after the mongol's birth. The mother who became menopausal six months after the birth of her mongol child was only 36 when her periods finally stopped.

The mean maternal age at the time of birth of the mongol was 33.5 years, based on the completed year of age, ignoring fractions (range of 22 to 44 years). This figure is comparable to that reported by Øster (1956),

who in 518 mothers found a mean maternal age of 35.1 years at the time of the birth of the mongol. Penrose (1951) found in a pooled sample of 1,038 mongols from widely different sources that the maternal age was 36.6 years (S.D. 7.1). He compared this with the mean maternal age for all births in England and Wales in 1939, which was 28.6 years (S.D. 6.0). The mean ordinal position of the mongol in the conception order was $0.74 (= \frac{\sum m-1}{n-1} / N, \text{ according to Slater, 1958})$, with a standard deviation of 0.38 and a standard error of mean of 0.05. This indicates that the mongol tends to appear late in the conception order, the expected mean ordinal position being 0.50.

Forty-five of the mothers had already been pregnant prior to the pregnancy with the mongol. Of these, 15 had had miscarriages or stillbirths in the pregnancy immediately preceding that with the mongol. The mean time between the conception of the mongol and the immediately preceding miscarriage or stillbirth was 45.9 months (range, 11 to 196 months). The mean time between the conception of the mongol and the immediately preceding live birth was 48.3 months (range, 13–171 months).

Of the total number of conceptions, 93 in all, prior to the conceptions of the mongols, 28 pregnancies (of which one was counted twice, having preceded the birth of two mongols), or 31%, had ended in abortion or stillbirth. Four of these had been artificially procured.

This figure of 31% is nearly double that obtained by Ingalls *et al.* (1957), who found that of total pregnancies prior to the birth of the mongols the 52 mothers in their series had had 15.5% of such mishaps in past pregnancies, which was much greater than the incidence of 9.4% in their control group. It greatly exceeds that of Øster (1953), who reported 148 stillbirths and abortions, or 9.7%, in 1,523 pregnancies prior to that of the mongol in a series of 515 mothers. The miscarriage rate in the present series is extremely high compared with that estimated by the Biological and Medical Committee of the Royal Commission on Population (1950), who considered that the incidence of spontaneous abortion in the general population lay between 7 and 11% of all pregnancies, and that perhaps 2 to 5% of pregnancies were terminated by induced abortion.

Ingalls *et al.* (1957) has drawn attention to the incidence of vaginal bleeding or spotting in the first three months of pregnancy with a mongol child. In their series about 10% of mothers gave a history of such haemorrhage, and the effect was seen more often in the older mothers of the series. Øster (1953) reports 25 cases of vaginal bleeding or spotting in the first three months of pregnancy with a mongol child, out of 429 cases, or about 5.8%. In the present series, in 9 of the 56 mongol pregnancies, or in 16.1%, the mothers had vaginal bleeding within the first three months. Of these mothers, four were 25 years or under and three were 40 years or older.

Other incidents during the pregnancies with the mongols which were noted were psychological trauma or marked anxiety in nine cases; raised blood-pressure and/or marked swelling of the ankles in eight cases; severe or prolonged periods of vomiting in five cases; and infection of the urinary tract requiring medical treatment in two cases, at nine weeks and eight months respectively.

Discussion

The mean P.B.I. level of the present series of mothers of mongols was $4.8 \mu\text{g./100 ml.}$, which was almost identical with that of the control group, and is well within the limits of normal for the method of estimation used. Thus the present findings differ greatly from those of Ek (1959), who found a mean value of $7.1 \mu\text{g./100 ml.}$ for the P.B.I. level in his series of 41 mothers of mongols. Moreover, no fewer than 12 subjects in Ek's series had P.B.I. levels of $7.9 \mu\text{g./100 ml.}$ or over.

Ek (1959) reported that no fewer than 20 out of his 41 subjects complained of neurotic symptoms. It was this group that had the higher P.B.I. levels in his series, with a mean of $7.8 \mu\text{g./100 ml.}$ as compared with a mean of $6.4 \mu\text{g./100 ml.}$ for the remainder of his subjects, who were classified as less neurotic. Øster (1956) was also impressed by the excess of cases of nervous illness among the relatives of mongols, and that this effect was especially pronounced among the mothers. In the present series, however, there was no evidence of an excessive incidence of neurosis when this is based on the criterion of the necessity for treatment at home or in hospital, and the scores obtained on the Maudsley Personality Inventory were not compatible with increased neuroticism in the group of mongol mothers.

The constitutional difference, as shown by differences in body-build between the younger and older groups of mothers in the present series, is compatible with the view expressed by Penrose (1951, 1954) that some mothers are especially likely to have mongol children by virtue of their genetical constitution. Penrose suggests that their increased susceptibility might be due to a partial suspension of the protective effect of young maternal age.

The main findings in the present series all seem to suggest that an endocrinological imbalance may be commonly present in the mothers of mongols, and the younger group of mothers have a body-build suggestive of constitutional endocrinological imbalance. The high miscarriage rate for the group of mothers as a whole may also be related to endocrinological factors which in the older mothers may be connected with the normal process of ageing and the approach of the menopause.

As the androgyny score and the biacromial diameter appear to be most influenced by the sex hormones and in particular by the androgens, it would be most interesting to have confirmation of the findings by Ek and Jensen (1959) of increased dehydroepiandrosterone output in the mothers of mongols.

A striking finding was the very high rate of miscarriages and stillbirths prior to the birth of the mongol. Attention has been focused on the pregnancies prior to the birth of the affected child, as these are clearly of greater biological significance than those after the mongol, which may have been intentionally restricted by the parents. This seems to indicate that at the time of the conception of the mongol the mother was already susceptible to increased obstetric risks. The connexion between this and the production of a mongol child is not clear, and the relationship may be an indirect one involving perhaps several factors, including increased maternal age and possibly related degenerative changes in the reproductive system of the mother. In view of the most recent finding of chromosomal variation in mongolism, it seems not unreasonable to consider also the possibility of mutation in the germ cells

of the mother leading to the production of a non-viable foetus. Such an idea would be supported if it were found that the miscarriages and stillbirths prior to the pregnancy with the mongol tended to accumulate close to this event. With this in mind, the present material was examined to find whether or not there were an unexpectedly large number of conceptions ending in miscarriage in the conception order immediately prior to the mongol. The results are shown in Tables VI and VII. The difference between the observation of 15 and the expectation of 12.72 is clearly not significant.

TABLE VI.—*Positions of Normal Births and Miscarriages in Relation to Mongol in Conception Order*

Position of Conception in Relation to Mongol	No. of Normal Births	No. of Miscarriages
-5	2	1
-4	5	1
-3	8	5
-2	22	7
-1	29	15
+1	18	2
+2	9	1
+3	1	4
+4	0	3
+5	1	1
+6	0	1
+7	1	0
	96	41

N.B.—One miscarriage was counted twice owing to two mongols occurring in one sibship.

TABLE VII.—*Incidence of Miscarriage Immediately Prior to Mongol in Conception Order*

Conception Order of Mongol	Observed Incidence of Miscarriage in Immediately Preceding Conception	Expected
2	5	3.49
3	4	4.57
4	2	1.83
5	2	0.83
6	2	2.00
Total ..	15	12.72

$$\chi^2 = \frac{(2.28)^2}{12.72} = 0.41. \text{ D.F. 1. } P = 0.5.$$

Moreover, when all other possible relationships between the conception order of a miscarriage and the conception of a mongol are considered (see Table VII), it is found that no single relationship is favoured at the expense of others: thus there is approximately the same expectation of a miscarriage before as after the birth of a mongol.

Summary

Fifty-five mothers of mongols were examined. The findings failed to confirm earlier reports of thyroid abnormality, including raised serum P.B.I. The body-build of the group as a whole did not differ from normal. When the group, however, was examined according to maternal age at the time of the mongol birth, it was found that the group of mothers bearing a mongol at 27 years of age or younger had a significantly raised mean androgyny score and mean biacromial diameter. A tendency was also observed for the mothers with multiple miscarriages to have a raised androgyny score. Psychological testing and general medical history failed to show deviations from normal. The obstetric histories, however, showed an extremely high rate of miscarriage irrespective of conception order and unrelated to birth order of the mongol.

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INFLUENZAL ENCEPHALOPATHY AND POST-INFLUENZAL ENCEPHALITIS HISTOLOGICAL AND OTHER OBSERVATIONS

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Cases of neurological disorder associated with influenza have been reported for many years; perhaps it is merely because laboratory investigation has become so much more widely available that more cases have been reported associated with Asian influenza than with previous epidemics or pandemics. We (Flewett and Houl, 1958) reported 12 such cases. Six of these presented neurological symptoms after the acute attack of clinical influenza had subsided, and all but one recovered; the others were cases of clinical "encephalitis" with convulsions or "fits" proceeding to coma and death, which occurred during the acute phase of an attack of influenza, and which showed a very congested brain at necropsy; we found no obvious histological lesions in a few sections of paraffin-embedded material. This paper describes the results of detailed histological examinations of the brains of five of these patients. The first were children, aged between 5 and 13, who died at intervals of seven to nine days after the onset. The fifth patient was a man aged 44 who died 11 days after the onset.

Methods

Large blocks were taken from the following sites and embedded in celloidin: spinal cord (in some cases only),