PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

The Incidence of Down's Syndrome and Progress Towards Its Reduction [and Discussion]

Margareta Mikkelsen, Ursula Mittwoch and A. E. H. Emery

Phil. Trans. R. Soc. Lond. B 1988 **319**, 315-324
doi: 10.1098/rstb.1988.0053

Phil. Trans. R. Soc. Lond. B **319**, 315–324 (1988)
Printed in Great Britain

The incidence of Down's syndrome and progress towards its reduction

By Margareta Mikkelsen

Department of Medical Genetics, John F. Kennedy Institute, 7 Gl. Landevej, DK 2600 Glostrup, Copenhagen, Denmark

Down's syndrome is the most common autosomal aberration and single cause of mental retardation in man. There is a close relation between advanced maternal age and Down's syndrome. The limitation of family size has made a considerable impact on the incidence of Down's syndrome. In Denmark in the 1950s, 50% of Down's syndrome cases were born to mothers over the age of 35. The percentage went down to 25% in the 1970s and was reduced by prenatal diagnosis to 8% in the 1980s.

For the period 1980–85 we followed the birth prevalence closely for the different maternal age groups. The birth prevalence was lowered for the age group over 35, but there was a steady rise for the age groups below 35. Early diagnosis, high rate of survival of light-for-date babies and babies with congenital heart defect, and, possibly, exogenous factors working on gametogenesis might be an explanation. To achieve a reduction in incidence, maternal α-fetoprotein (AFP)-serum screening for low values may be a possibility. So far, avoidance, but not primary prevention, of Down's syndrome is available.

Introduction

Down's syndrome is the most common single cause of mental retardation and thus it is a major health problem and a burden to families and society. It has been known as a clinical entity since Langdon Down described the syndrome in 1866, and since then research workers have looked for exogenous factors (Down 1866).

Generally, the clinical diagnosis is easy and well-known to all medical workers. In premature babies, however, the diagnosis may be difficult, but a chromosome study can give the final diagnosis with few exceptions.

In Scandinavia, about 90% of the cases are regular trisomies, in about 3% mosaicism is found and in about 6% translocations are observed. Double trisomies and rare aberrations are found in less than 1% (Mikkelsen *et al.* 1976; Iselius & Lindsten 1986; Nielsen *et al.* 1987). The distribution is different in countries with a different age distribution of child-bearing women as, for example, in Northern Ireland, where translocations count for 3% only as they are maternal-age independent and prenatal diagnosis is rarely done (Elwood & Darragh 1981).

Point incidences of Down's syndrome

Incidences at birth and at week 16 of pregnancy (amniocentesis) have been well studied and risk figures for maternal ages have been established (Trimble & Baird 1978; Hook 1981; Lindsjø 1974; Lindsten *et al.* 1981; Stene & Mikkelsen 1984; Iselius & Lindsten 1986; Ferguson-Smith & Yates 1984). Of the cases diagnosed at the 16th week, 20–30% end as a spontaneous abortion or a miscarriage later in pregnancy (Hook 1983*a*). Figures from first trimester chorionic villi sampling show an incidence of trisomy 21 at week 8–10 nearly double

that at week 16 (Mikkelsen & Aymé 1987). Spontaneous abortions in the first trimester have a ten times higher incidence than birth incidence (Hassold *et al.* 1980). These figures indicate an unknown, but certainly high, mutation rate at conception and a continuous fetal loss throughout gestation.

Factors increasing the incidence of Down's syndrome

Factors include advanced maternal age, earlier diagnosis, survival of small-for-date infants and an increased mutation rate.

Advanced maternal age

Advanced maternal age as an important factor in Down's syndrome has been known for more than 50 years (Jenkins 1933; Penrose 1933).

We followed the incidence of Down's syndrome in Denmark throughout the period 1980–1985 and compared these data with the incidence found in Copenhagen from 1960–1971 in a study with nearly complete ascertainment (Mikkelsen *et al.* 1976). In table 1 the differences in the maternal-age distributions between the two studies are shown. More than half of the births were given by mothers of 24 years and younger in the first period, whereas there was a decrease for this age group in the 1980s, a considerable increase in the number of mothers in the age groups between 25 and 35, and only a slight increase for the over 35 years old. In the same periods, the percentage of Down's syndrome mothers decreased for the youngest age group and increased for the age group 25–35 (table 2). For those over 35 there was a considerable decrease in Down's syndrome cases, reflecting the high degree of utilization of prenatal diagnosis in Denmark.

Table 1. Maternal-age distribution in Denmark

	normal population		Down's syndrome	
age	1960–71	1980–85	1960–71	1980–85
< 25	51.7	34.3	34.5	26.2
25–29	29.2	38.9	18.7	37.8
30–34	12.6	20.0	18.7	27.4
> 34	6.5	6.8	28.1	8.6

Age-related incidences for the two study periods are given in table 3. There were no significant differences between the two periods for ages below 30, but a considerable decrease for the age over 30 was found, as expected, reflecting the effect of the prenatal test.

Many hypotheses have been put forward to explain the association between advanced maternal age and Down's syndrome. Age-deterioration of the ovum was an accepted explanation for a long time. Delayed fertilization due to decreased frequency of coitus (German 1968) has also been discussed for 20 years. Ingalls (1972) proposed that delayed fertilization could be the consequence of endocrine function failures or of infections of the mother. Matsunaga (1967) proposed relaxed uterine selection in elderly mothers as a possible cause of the age effect. Advanced maternal age is also observed in cases of paternal failure (Mattei *et al.* 1980). Aymé & Lippmann-Hand (1982) found on abortion data that relaxed selection may play a role in the age effect. This could not be confirmed by Hook (1983*b*). Recently, Stein *et al.* (1986) suggested that the association of trisomy 21 with maternal age is based on

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

TABLE 2. LIVE-BORNS WITH DOWN'S SYNDROME (DS) AND TOTAL NUMBER OF LIVE-BIRTHS (LB) IN DENMARK, 1980–1985

maternal age distribution...	< 25	25–29	30–34	> 34	unknown	liveborns total
1980						
no. of						
DS	13	16	9	7	—	45
LB	21614	21498	10830	3351	—	57293
1981						
no. of						
DS	13	10	10	2	—	35
LB	19498	20199	10040	3352	—	53089
1982						
no. of						
DS	11	19	10	5	—	45
LB	18376	20546	10205	3531	—	52658
1983						
no. of						
DS	15	15	14	4	—	48
LB	16860	20236	10214	3531	—	50821
1984						
no. of						
DS	9	20	17	3	1	50
LB	16601	20473	10783	3943	—	51800
1985						
no. of						
DS	12	25	16	2	—	55
LB	16579	21369	11630	4171	—	53749
total						
DS	73	105	76	23	1	278
LB	109528	124321	63702	21859	—	319410

TABLE 3. DOWN'S SYNDROME: AGE RELATED INCIDENCES PER 1000 LIVE-BIRTHS

maternal age	1960–71	1980–85
< 25	0.77	0.67
25–29	0.73	0.85
30–34	1.71	1.19
> 34	5.13	1.05

a failure of the screening process between fertilization and recognition of pregnancy. The difference in prevalence rates of trisomy 21 in spontaneous abortion from young and old mothers indicates the amount of attrition that takes place in the pre-recognition phase at young maternal age. In women of age 40, trisomy 21 constitutes as much as 10% of all miscarriages (Stein *et al.* 1986). As the incidence of Down's syndrome strongly depends on the age distribution of child-bearing women in a population, the restriction of family size observed in developed countries and the decreasing number of women giving birth at higher maternal ages should have produced a decrease in the birth incidence of Down's syndrome. However, the same incidence as reported earlier before family size restriction was observed in several studies from Canada, Denmark, Great Britain and Finland (Lowry *et al.* 1976; Mikkelsen *et al.* 1976; Holloway & Emery 1977; Evans *et al.* 1978; Leisti *et al.* 1985) and a certain increase in incidence was observed in Sweden and in studies of the 25–34 age group (Iselius & Lindsten 1986; Nielsen *et al.* 1987).

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Earlier diagnosis

Most likely, the unchanged total incidence figures reflect a better ascertainment throughout the 1970 and 1980s, where most Down's syndrome infants were diagnosed in the first week of life. Previously, a number of Down's syndrome infants will have died before the diagnosis was registered, or sometimes the diagnosis was deliberately not given on the birth certificate. Iselius & Lindsten (1986) followed the Down's syndrome incidence from 1967 to 1982 and found a slight increase throughout the period in both sexes, but also a possible cyclical variation limited to boys. They considered the degree of ascertainment to be high and unchanged throughout the period, and also the perinatal mortality to be unchanged.

Survival of small-for-date infants

There was a rise in total incidence throughout the period 1980–1985 (table 4). This increase was observed in newborns as well as in amniocentesis data. In the same period, the number of newborns with Down's syndrome born prematurely or light-for-date increased from 26.7 % to 43.6 %. A comparison between the figures from the normal population and Down's syndrome figures for birth weight below 2500 g, preterm births and Caesarian section showed considerably higher figures for the Down's syndrome population (table 5). A slight increase in the survival of low weight infants or premature babies will show as an increase in the incidence of Down's syndrome and is an important factor concerning morbidity and mortality in Down's syndrome.

TABLE 4. INCIDENCES OF DOWN'S SYNDROME, DENMARK 1980–1985

period	no. of live-borns with Down's syndrome	no./1000	no. of fetuses with Down's syndrome	total incidence
1980–81	80	0.72	36	1.05
1982–83	93	0.90	63	1.51
1984–85	105	0.99	54	1.51
1980–85	278	0.87	153	1.35

TABLE 5. PERCENTAGES OF BIRTH WEIGHT BELOW 2500 g, PREMATURITY AND CAESARIAN SECTION

	normal population	Down's syndrome population
birth weight below 2500 g	5.6 %	19.4 %
pre-term	4.4 %	10.1 %
Caesarean section	11.0 %	18.1 %

Infant mortality

Mortality in Down's syndrome throughout the first two years is still very high. In the early 1970s 22 % of newborns with Down's syndrome died in their first year (Mikkelsen & Nielsen 1976). In the period 1980–85 15 % died before one year of life and 22 % were dead before the end of the second year. An early diagnosis will be reflected in higher incidences at birth as 4.7 % of the Down's syndrome cases in the 1980–1985 period died perinatally (Nielsen *et al.* 1987).

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Mutation rate

Finally, there might be a real rise in the mutation rate of Down's syndrome. One way to follow mutation rates is to compare *de novo* translocation incidences with free trisomy rates (Hook 1981). When 1970 data were compared with the findings in the 1980s a slight increase was observed: 16/252 = 0.063 compared with 5/160 = 0.031 in the 1960–1971 period.

Paternal factors

That paternal non-disjunction can occur in Down's syndrome was shown in 1973 simultaneously by Uchida (1973) and Sasaki & Hara (1973). Larger studies have shown that 20% of the meiotic failures are of paternal origin (Mazo *et al.* 1982; Mikkelsen 1982).

A possible paternal-age effect has been disputed for a long time. Stene *et al.* (1977) proposed a paternal-age effect for the age group over 55 on data from Copenhagen, and for paternal age over 41 on German amniocentesis data (Stene *et al.* 1981). A few studies confirmed a weak paternal-age effect (Matsunaga *et al.* 1978; Stene & Mikkelsen 1984), but most studies could not demonstrate a paternal-age effect (Hook & Cross 1982; Ferguson-Smith & Yates 1984). To elucidate the question further a European collaborative effort was made to compare maternal and paternal meiotic failures and age distribution of the parents (Aymé *et al.* 1986). In paternal failures a maternal-age effect was observed, as also previously shown by Mattei *et al.* (1980). This finding is unexplained so far but possibly related to relaxed selection in the pre-recognition phase of pregnancy in elderly women carrying a trisomic fetus (Stein *et al.* 1986). When paternal cases were matched for maternal age, a weak paternal-age effect could be shown for first meiotic division error in the father. Second division failure in the father was negatively associated with paternal age (Aymé *et al.* 1986) and mean maternal age was lower than in the three other division failure groups.

Sex ratio in Down's syndrome

It has previously been shown that more males with Down's syndrome are born than females (Hug 1951; Bernhein *et al.* 1979; Nielsen *et al.* 1981, Iselius & Lindsten 1986). Also, in spontaneous abortuses more males than females with trisomy 21 are observed (Hassold *et al.* 1983).

The increased male:female sex ratio was also observed in our 1980–1985 study: 156 males and 117 females with trisomy 21. A positive sex ratio was also observed in translocation Down's syndrome, with 17 males and 3 females. This is different from the findings by Iselius & Lindsten (1986) and Lindsten *et al.* (1981). They did not find a deviation from the expected sex ratio in translocation trisomies. When correlated to meiotic failure a sex ratio of 3.40 was found when the meiotic failure had occurred in the first meiotic division of the father. However, the sex ratio was positive in all types of failure, with the exception of paternal meiosis II, when it was 1:1 (table 6), but figures are small. No difference was observed between first and second division failures. The collaborative European study, where part of this study was included, did not show an increased sex ratio for paternal meiosis I failures. The excess of males in Down's syndrome newborns, prenatally diagnosed fetuses, and spontaneous abortions is still not understood. A similar sex ratio was observed in children of carriers of hepatitis associated antigen (Drew *et al.* 1978).

Other factors studied, which might influence mutation rates, were infectious diseases,

Table 6. Sex ratio and meiotic failure

type of division	male	female	male:female ratio
maternal I	63	59	1.07
maternal II	16	11	1.45
paternal I	17	5	3.40
paternal II	8	8	1.00
total	104	83	1.25

thyroid disease, type of contraception, gonadal irradiation, medication, place of residence, or social class. A possible association between maternal gonadal irradiation and maternal meiotic I and II division failures was observed. Obviously this association should be studied further as low-dose irradiation was shown to be associated with Down's syndrome by Uchida *et al.* (1968). The reactor accident in Chernobyl might elucidate the question about Down's syndrome and low-dose irradiation. The incidence of Down's syndrome should be followed in areas with large and small doses of fallout, and the type of failure of division studied with the sex ratio and last menstrual period of the mother.

Factors decreasing the birth prevalence of Down's syndrome

Factors were: concentration of births at maternal ages 20–30; voluntary abortions; and prenatal diagnosis.

The limitation of family size and reduction of births in the maternal age-groups over 35 has made the greatest impact on the incidence of Down's syndrome in developed countries. Compared with the 1960s and the early 1970s, in 1979–1980 birth rates for those aged 35–39 fell by 58.8% and for those aged 40–44 by 78% (Mikkelsen *et al.* 1983).

Voluntary abortions accounted for 52% of the pregnancies in the age group 35–39, and 79% of the pregnancies in women over 40 ended with an induced abortion (Mikkelsen *et al.* 1983). More cases were avoided by induced abortion than by prenatal diagnosis. However, the prenatal test has made a great impact on the incidence of Down's syndrome in the age groups over 35 in Denmark.

Prenatal diagnosis

In the period 1980–1985 in Denmark, 15333 pregnancies in women 35 and older have been screened for Down's syndrome and 123 fetuses with Down's syndrome aborted. The total number of cases found by the prenatal test were 147, more than one third of 425 Down's syndrome cases (prenatally and postnatally diagnosed) (table 7). All prenatally detected cases were voluntarily aborted. A utilization rate of 70% for prenatal diagnoses for the whole country and 75–85% for the Copenhagen area and certain areas in Jutland are the highest utilization rates reported; they are much higher than data reported by Luthy *et al.* (1980) or data from New York State (Hook *et al.* 1981) or Australia (Mulcahy & Michael 1983). A much higher utilization rate than the Danish one for advanced maternal age cannot be expected, and the percentage has also kept nearly constant for the past 3 years.

With the main indication groups for the prenatal test used in Denmark (maternal age over 35, recurrence risk and recurrent miscarriages), 35% of the affected fetuses can be detected.

The causes of non-disjunction leading to Down's syndrome are still unknown. The large

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

TABLE 7. FETUSES WITH DOWN'S SYNDROME (DS) PRENATALLY DIAGNOSED, AND TOTAL NUMBER OF LIVE-BIRTHS (LB) IN DENMARK, 1980–1985

maternal age distribution...	> 34	< 35	total
1980			
no. of			
DS	11	3	14
LB	3351	53942	57293
1981			
no. of			
DS	16	4	20
LB	3352	49737	53089
1982			
no. of			
DS	28	1	29
LB	3531	49127	52658
1983			
no. of			
DS	25	6	31
LB	3511	47310	50821
1984			
no. of			
DS	22	5	27
LB	3943	47857	51800
1985			
no. of			
DS	21	5	26
LB	4171	49578	53749
total			
DS	123	24	147
LB	21859	297551	319410

maternal-age effect is still a riddle. The European collaborative pilot study looking for causal factors in non-disjunction has not given clear results (Aymé *et al.* 1986). We are far from the prevention of Down's syndrome but have been able to avoid a certain number of cases.

Maternal serum AFP and Down's syndrome

Screening for low AFP values in serum of pregnant women might be a possibility for a further reduction in the number of Down's syndrome cases.

Merkatz *et al.* (1984) demonstrated a significant association between low serum AFP and the finding of trisomy 21 and trisomy 18 in the fetus. Since then several studies (Cuckle *et al.* 1984; Murday & Slack 1985) have shown the association of low AFP and trisomy 21. It has been proposed that a combination of maternal age and AFP values could reduce the number of amniocenteses in the higher maternal age group, so reducing the number of miscarriages by amniocenteses and, in addition, defining a risk group among younger pregnant women (Tabor *et al.* 1984, 1987; Davis *et al.* 1985; Hershey *et al.* 1986). In many countries women are already screened for high serum AFP in programmes for detection of neural-tube defects (Brock 1984).

Ashwood *et al.* (1987), in a retrospective study, found decreased AFP levels in maternal serum and amniotic fluid in pregnancies with a trisomy 21 fetus. They constructed a risk table for maternal ages 14–45 based on age risk and serum AFP level, under the assumption that serum AFP levels are similar in women over and under 35 years of age carrying a fetus with trisomy

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

21. Also, Tabor *et al.* (1987) constructed an iso-risk curve for pregnant women based on age and serum AFP level in 1980–1985 data from Denmark.

Before major screening programmes for low AFP for the population of pregnant women are implemented, prospective evaluation of low serum AFP values in well-established programmes is absolutely necessary. It has to be considered that many women have to be offered amniocentesis at week 17–19 of pregnancy, with considerable stress on the women (and possibly the fetus) and the necessity of a late pregnancy interruption in cases of Down's syndrome, with a risk of miscarriage because of the procedure. A screening programme for low and high serum-AFP levels has to be debated in public when enough prospective data are available and risks can be evaluated.

Brambati *et al.* (1986) showed an association between low maternal serum AFP levels and fetuses with trisomy 21 in the first trimester of pregnancy. It is possible that more sensitive assays in the low range and in early pregnancy will be available in the future. Research along that line would be worthwhile.

In conclusion, the avoidance of several Down's syndrome cases is possible by prenatal diagnosis, restriction of family size and voluntary abortion, but primary prevention is still not possible.

References

Aymé, S. & Lippmann-Hand, A. 1982 Maternal age effect in aneuploidy: does altered embryonic selection play a role? *Am. J. hum. Genet.* **34**, 558–565.

Aymé, S., Baccichetti, C., Bricarelli, F. D., Dallapiccola, B., Lungarotti, D., Mikkelsen, M. & Nevin, N. 1986 Factors involved in chromosomal non-disjunction. In *Seventh International Congress of human genetics, Berlin 1986, Abstracts*, part 1, p. 167.

Ashwood, E. R., Cheng, E. & Luthy, D. A. 1987 Maternal serum α-fetoprotein and fetal trisomy-21 in women 35 years and older: implications for α-fetoprotein screening programs. *Am. J. med. Genet.* **26**, 531–539.

Bernheim, A., Chastang, Cl., de Heaulme, M. & Grouchy, J. de 1979 Excès de garçons dans la trisomie 21. *Annls Génét.* **22**, 112–114.

Brambati, B., Simoni, G., Bonacchi, I. & Piceni, L. 1986 Fetal chromosomal aneuploidies and maternal serum α-fetoprotein levels in first trimester. *Lancet* ii, 165–166.

Brock, D. J. H. 1984 Maternal serum α-fetoprotein as screening test for Down syndrome. *Lancet* i, 1292.

Cuckle, H. S., Wald, N. J. & Lindenbaum, R. H. 1984 Maternal serum α-fetoprotein measurement: a screening test for Down syndrome. *Lancet* i, 926–929.

Davis, R. O., Cosper, P., Huddleston, J. F., Bradley, E. L., Finley, S. C., Finley, W. H. & Milunsky, A. 1985 Decreased levels of amniotic fluid α-fetoprotein associated with Down syndrome. *Am. J. Obstet. Gynec.* **153**, 541–544.

Down, J. L. H. 1866 Observations on an ethnic classification of idiots. *Clin. Lect. Rep. Lond. Hosp.* **3**, 259–262.

Drew, J. S., London, T., Lustbader, E. D., Hesser, J. E. & Blumberg, B. S. 1978 Hepatitis B virus and sex ratio of offspring. *Science, Wash.* **201**, 687–692.

Elwood, J. H. & Darragh, P. M. 1981 Prevalence of mongolism in Northern Ireland. *J. ment. Defic. Res.* **25**, 157–160.

Evans, J. A., Hunter, A. G. W. & Hamerton, J. L. 1978 Down syndrome and recent demographic trends in Manitoba. *J. med. Genet.* **15**, 43–47.

Ferguson-Smith, M. A. & Yates, J. R. W. 1984 Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative European study on 52,965 amniocenteses. *Prenat. Diagn.* **4**, (spec. iss.), 5–44.

German, J. 1968 Mongolism, delayed fertilization and human sexual behavior. *Nature, Lond.* **217**, 516.

Hassold, T., Chen, N., Funkhouser, J., Jooss, T., Manuel, B., Matsuura, J., Matsuyama, A., Wilson, C., Yamane, J. A. & Jacobs, P. A. 1980 A cytogenetic study of 1000 spontaneous abortions. *Ann. hum. Genet.* **44**, 151–178.

Hassold, T., Quillen, S. D. & Yamane, J. A. 1983 Sex ratio in spontaneous abortions. *Ann. hum. Genet.* **47**, 39–47.

Hershey, D. W., Crandall, B. F. & Perdue, S. 1986 Combining maternal age and serum α-fetoprotein to predict the risk of Down syndrome. *Obstet. Gynec.* **68**, 177–180.

Holloway, S. & Emery, A. E. H. 1977 Factors affecting the incidence of Down syndrome in Scotland. *J. biosoc. Sci.* **9**, 453–465.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Hook, E. B. 1981*a* Rates of chromosome abnormalities at different maternal ages. *Obstet. Gynec.* **58**, 282–285.
Hook, E. B. 1981*b* Interchange trisomic Down's syndrome and Patau's syndrome: general approaches to estimating mutation rates and epidemiological advantages for monitoring. In *Population and biological aspects of human mutation* (ed. E. B. Hook & J. H. Porter), pp. 167–190. New York: Academic Press.
Hook, E. B. 1983*a* Chromosome abnormalities and spontaneous fetal death following amniocentesis: further data and associations with maternal age. *Am. J. hum. Genet.* **35**, 110–116.
Hook, E. B. 1983*b* Down syndrome rates and relaxed selection at older maternal ages. *Am. J. hum. Genet.* **35**, 1307–1313.
Hook, E. B. & Cross, P. K. 1982 Interpretation of recent data pertinent to genetic counseling for Down syndrome: maternal-age-specific rates, temporal trends, adjustments for paternal age, recurrence risks, risks after other cytogenetic abnormalities, recurrence risk after remarriage. In *Clinical genetics: problems in diagnosis and counseling* (ed. A. W. Willey, T. Carter, S. Kelly & I. H. Porter), pp. 119–145. New York: Academic Press.
Hug, E. 1951 Das Geschlechtsverhältnis beim Mongolismus. *Annls paediat.* **177**, 31–54.
Ingalls, T. H. 1972 Maternal health and mongolism. *Lancet* ii, 213.
Iselius, L. & Lindsten, J. 1986 Changes in the incidence of Down syndrome in Sweden during 1968–1982. *Hum. Genet.* **72**, 133–139.
Jenkins, R. L. 1933 Etiology of mongolism. *Am. J. dis. Child.* **45**, 506–519.
Leisti, J., Vahtola, L., Linna, S.-L., Herva, R., Koskela, S.-L. & Vitali, M. 1985 The incidence of Down syndrome in northern Finland with special reference to maternal age. *Clin. Genet.* **27**, 252–257.
Lindsjø, A. 1974 Down's syndrome in Sweden. *Acta paediat., Stockh.* **63**, 571–576.
Lindsten, J., Marsk, L., Berglund, K., Iselius, L., Ryman, N., Annerén, G., Kjessler, B., Mitelman, F., Nordenson, I., Wahlström, J. & Vejens, L. 1981 Incidence of Down's syndrome in Sweden during the years 1968–1977. In *Trisomy* 21 (ed. G. R. Burgio, M. Fraccaro, L. Tiepolo & U. Wolf), pp. 195–210. Berlin & Heidelberg: Springer-Verlag.
Lowry, R. B., Jones, D. C., Renwick, D. H. G. & Trimble, B. K. 1976 Down syndrome in British Columbia, 1952–73: incidence and mean maternal age. *Teratology* **14**, 29–34.
Luthy, D. A., Emanuel, I., Hoehn, H., Hall, J. G. & Powers, E. K. 1980 Prenatal genetic diagnosis and elective abortion in women over 35: utilization and relative impact on the birth prevalence of Down syndrome in Washington State. *Am. J. med. Genet.* **7**, 375–381.
Matsunaga, E. 1967 Parental age, live-birth order and pregnancy-free interval in Down's syndrome in Japan. Mongolism–Ciba Foundation Study Group no. 25, p. 6. London: J. & A. Churchill.
Matsunaga, E., Tonomura, A., Oishi, H. & Kikuchi, T. 1978 Re-examination of paternal age effect in Down's syndrome. *Hum. Genet.* **40**, 259–268.
Mattei, J. F., Ayme, S., Mattei, M. G. & Giraud, F. 1980 Maternal age and origin of non-disjunction in trisomy 21. *J. med. Genet.* **17**, 368–372.
Mazo, J. del, Castillo, A. P. & Abrisqueta, J. A. 1982 Trisomy 21: origin of non-disjunction. *Hum. Genet.* **62**, 316–320.
Merkatz, I. R., Nitowsky, H. M., Macri, J. N. & Johnson, W. E. 1984 An association between low maternal serum α-fetoprotein and fetal chromosomal abnormalities. *Am. J. Obstet. Gynec.* **7**, 886–894.
Mikkelsen, M. & Aymé, S. 1987 Chromosomal findings in chorionic villi. A collaborative study. In *Human genetics. Proceedings of the Seventh International Congress, Berlin 1986* (ed. F. Vogel & K. Sperling), pp. 597–606. Berlin & Heidelberg: Springer–Verlag.
Mikkelsen, M., Fischer, G., Hansen, J., Pilgaard, B. & Nielsen, J. 1983 The impact of legal termination of pregnancy and of prenatal diagnosis on the birth prevalence of Down syndrome in Denmark. *Ann. hum. Genet.* **47**, 123–131.
Mikkelsen, M. 1982 Parental origin of the extra chromosome in Down's syndrome. *J. ment. Defic. Res.* **26**, 143–151.
Mikkelsen, M., Fischer, G., Stene, J., Stene, E. & Petersen, E. 1976 Incidence study of Down's syndrome in Copenhagen, 1960–1971: with chromosome investigation. *Ann. hum. Genet.* **40**, 117–182.
Mikkelsen, M. & Nielsen, G. 1976 Cost–benefit analysis of prevention of Down's syndrome. In *Prenatal diagnosis* (ed. A. Boué) INSERM **61**, 283–289.
Mulcahy, M. T. & Michael, C. A. 1983 The utilization of prenatal cytogenetic diagnosis in Western Australia. *Aust. N. Z. J. Obstet. Gynaec.* **23**, 8–10.
Murday, V. & Slack, J. 1985 Screening for Down's syndrome in the North East Thames Region. *Br. med. J.* **291**, 1315–1318.
Nielsen, J., Jacobsen, P., Mikkelsen, M., Niebuhr, E. & Sorensen, K. 1981 Sex ratio in Down syndrome. *Annls Génét.* **24**, 212–215.
Nielsen, K. G., Pilgaard, B. & Mikkelsen, M. 1987 Incidence and survival of newborns with Down's syndrome in Denmark 1980–85. *Ugeskr. Læg.* **149**, 2170–2173.
Penrose, L. S. 1933 The relative effects of paternal and maternal age in mongolism. *J. Genet.* **27**, 219–224.
Sasaki, M. & Hara, Y. 1973 Paternal origin of the extra chromosome in Down's syndrome. *Lancet* ii, 1258.
Stein, Z., Stein, W. & Susser, M. 1986 Attrition of trisomies as a maternal screening device. An explanation of the association of trisomy 21 with maternal age. *Lancet* i, 944–946.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Stene, J., Fischer, G., Stene, E., Mikkelsen, M. & Petersen, E. 1977 Paternal age effect in Down's syndrome. *Ann. hum. Genet.* **40**, 299–306.
Stene, J., Stene, E., Stengel-Rutkowski, S. & Murken, J. D. 1981 Paternal age and Down's syndrome. Data from prenatal diagnoses (DFD). *Hum. Genet.* **59**, 119–124.
Stene, J. & Mikkelsen, M. 1984 Down syndrome and other chromosome disorders. In *Antenatal and neonatal* (ed. N. J. Wald), pp. 74–105. Oxford University Press.
Tabor, A., Nørgaard-Pedersen, B. & Jacobsen, J. C. 1984 Low maternal serum AFP and Down syndrome. *Lancet* ii, 161.
Tabor, A., Larsen, S. O., Nielsen, N., Nielsen, J., Philip, J., Pilgaard, B., Therkelsen, Aa. Videbech, P. & Nørgaard-Pedersen, B. 1987 Screening for Down's syndrome using an isorisk curve based on maternal age and serum α-fetoprotein level. *Br. J. Obstet. Gynec.* **94**, 630–642.
Trimble, B. K. & Baird, P. A. 1978 Maternal age and Down syndrome: Age-specific incidence rates by single-year intervals. *Am. J. med. Genet.* **2**, 1–5.
Uchida, I. A. 1973 Paternal origin of the extra chromosome in Down's syndrome. *Lancet* ii, 1258.
Uchida, I. A., Holunga, R. & Lawler, C. 1968 Maternal radiation and chromosomal aberrations. *Lancet* ii, 1045–1049.

Discussion

URSULA MITTWOCH (*University College London, U.K.*). One factor that Professor Mikkelsen did not mention as a cause of Down's syndrome is the inheritance of the extra chromosome from an affected mother by secondary non-disjunction. Would she give us the reason for this low frequency? Are women with Down's syndrome very infertile, or are they otherwise being prevented from having children?

MARGARETA MIKKELSEN. I did not mention secondary non-disjunction because Down's syndrome women giving birth are extremely rare. I have never seen a case myself. There are 32 cases of Down's syndrome women giving birth in the literature, and studies of the ovaries of Down's syndrome females have shown that there are follicles, but the frequency is considerably reduced. The fertility of Down's syndrome women is certainly reduced, but not completely inhibited.

A. E. H. EMERY (*The Medical School, University of Edinburgh, U.K.*). The problem of Down's syndrome points up the distinction between prevention and avoidance. True prevention would be the ideal whereby prenatal diagnosis would no longer be the entire answer. One solution might be to encourage mothers to have their children at an earlier age, yet in some studies the relation with maternal age is J-shaped, indicating that there may be an increased risk at younger maternal ages also. Would Professor Mikkelsen comment on this, in particular in relation to J. German's theory of delayed fertilization as a result of sexual behaviour?

MARGARETA MIKKELSEN. I fully agree that prenatal diagnosis and voluntary abortion are measures to avoid Down's syndrome and not true prevention. True prevention would be possible if environmental factors could be identified with certainty. There is also a risk of Down's syndrome in young mothers and an even higher risk in the very young. In our 1960–1971 study the risk of the age group 19 years and younger was higher than the risk in the age group 20–30 (Mikkelsen *et al.* 1976). This could depend on the sexual habits of the teenagers, with a risk of delayed fertilization, or be the result of hormonal disturbance in the very young females. We had very few pregnancies in females younger than 18 years in our 1980–1985 study because of free abortion. The J-shaped curve for maternal ages was not refound in the later study.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES