ANIMAL MODEL OF HUMAN DISEASE

Autosomal Trisomy, Developmental Impairment and Fetal Death

Animal Model: Autosomal Trisomies in Fetal Mice, Exencephaly in Mice with Trisomy 12

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The experimental system in the mouse described in this report is based on the observation that structural heterozygosity of the Robertsonian type may enhance irregular meiotic segregation and thus produce chromosomally unbalanced gametes and aneuploidy of the embryo.[1,2]

Robertsonian changes (Rb) involve centric fusion which unite the arms of two acrocentric chromosomes to form one metacentric. In the mouse, whose normal karyotype contains 40 acrocentric chromosomes, a series of metacentrics with known composition of the chromosome arms (designated Rb1 to 10Bnr) has been introduced in laboratory strains.[3,4] In metacentric heterozygotes, meiotic anaphase I nondisjunction[5,6] may occur. This rate is high (25 to 42% aneuploid metaphase II figures) in double metacentric heterozygotes with monobrachial homology, because under this condition a tetravalent is formed in meiosis I, which promotes nondisjunction.

Experimental Design

Figure 1 visualizes the types of segregants resulting from irregular anaphase I distribution in cases with two partially homologous metacentrics. Fertilization in backcross mating with normal laboratory strain mice may then lead to monosomy or trisomy or combined monosomy/trisomy of zygotes. Simple trisomy (number of chromosome arms = 41) is the only unbalanced combination viable after 8 or 9 days gestation, even though in the mouse, trisomics are eventually eliminated by the time of birth. This condition presupposes the presence of both metacen-

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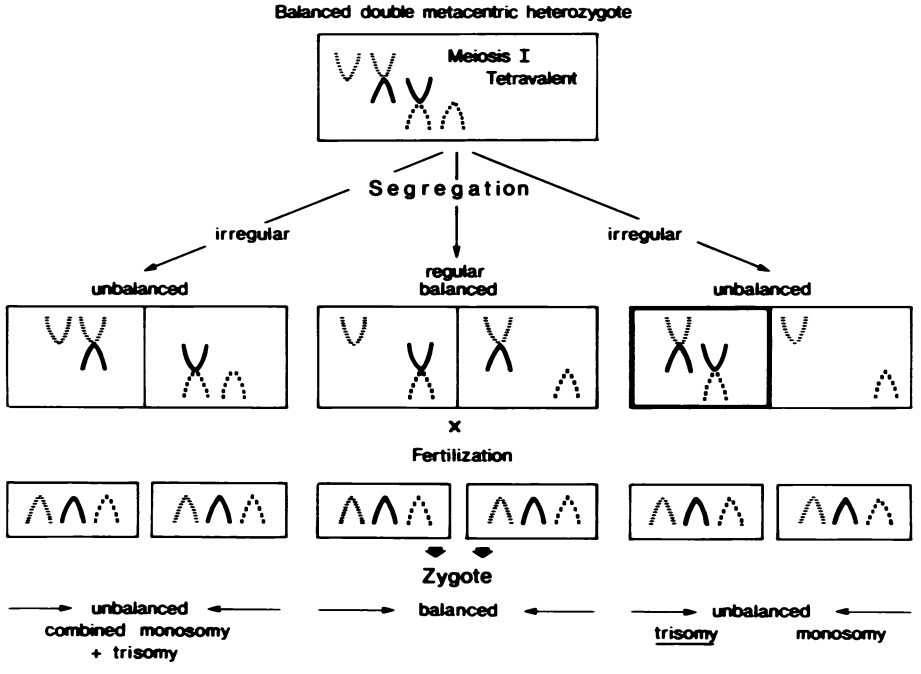


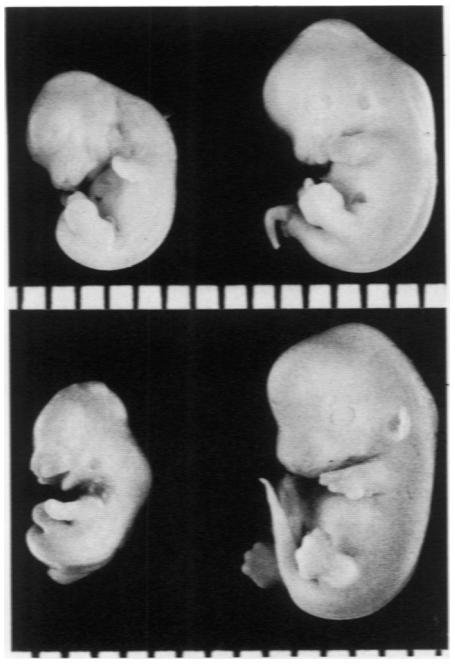
Fig 1—Experimental design used to obtain specific trisomic conditions. (Darkly bordered rectangle, simple trisomy recognizable by the presence of both metacentrics.)

trics and is therefore easy to ascertain by chromosome analysis using the fetal membranes.

The specific nature of the trisomy may be determined by use of the special double heterozygote combination. Thus, the Rb1/Rb10Bnr heterozygote is used for the study of trisomy of chromosome 1 because the two metacentrics Rb(*1*, 3)1 and Rb(*1*. 10)10 share a chromosome arm corresponding to mouse chromosome 1. The Rb(8, *12*)5/Rb(4, *12*)9Bnr heterozygote is suitable for the induction of trisomy 12.[6] Other combinations are available.

Biologic Features

In the Rb1/Rb10 system, trisomy 1 has been observed in 23% of 188 live embryos from 22 females killed at day 10 to 14. At these stages probably all other chromosome aberrations were already dead or resorbed. The phenotypic expression of trisomy 1 (Figure 2) is developmental retardation and marked smallness (hypoplasia, runting); death occurs around day 15. In some instances more conspicuous hypoplasia of the mandible is present. The same features characterize the fetal trisomy 1 syndrome by histologic study.



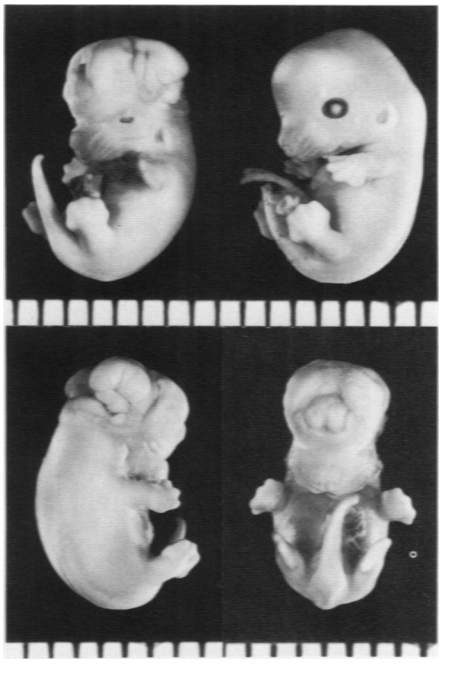


Fig 2 (left)—Normal embryos (right) and littermates affected with trisomy 1, day 13 (left). **Fig 3 (right)**—Normal embryo (top right) and littermate affected by trisomy 12, day 13½ (three views).

Trisomy 12 has an incidence of 19% in a study comprising 253 live embryos of days 10 to 14 backcrosses of Rb5/Rb9 double heterozygotes.[7] All embryos with trisomy 12 exhibit a complete defect of the cranial vault and exencephaly, usually with fairly well-developed cerebral lobes (Figure 3) and with microphthalmia. The affected embryos are only slightly retarded, if at all, and display slight reduction of their size. Apparently all embryos with trisomy 12 die by day 16 to 17.

Comparison with Human Disease

In 1,457 karyotyped human abortuses,[8] chromosomal aberrations have been detected in 61%. It has been calculated that in man about 50% of all conceptuses may be chromosomally unbalanced and prone to earlier or later fetal death and abortion.[8] Autosomal trisomies represent the largest group of chromosomal errors in recognized abortuses, though the relative frequencies of the individual autosomes involved differ markedly (from 0.7% for B group trisomies to about 14% for trisomy 16).

Only incomplete data are available on the teratologic profiles and the developmental capacity of the individual autosomal trisomic conditions in man.[9,10] Furthermore reliable data elucidating the causal relationships

of malsegregation are scarce, except those underlining the importance of maternal age.

Usefulness of the Model

The teratologic profiles and biochemical properties of trisomic embryos and placentas can be studied experimentally under optimal conditions of preservation. In the case of trisomy 12, the changes of the skull base and of the eyes accompanying the morphogenesis of exencephaly can be investigated. Other trisomic conditions (*eg*, trisomy 1) are suitable for elucidating the causal relationship between fetal hypoplasia (runting) and eventual fetal death.

In the mouse model the interrelationships between meiotic malsegregation, embryonic death and impairment of fertility are susceptible to direct study. Differences exist in this respect between the offspring of male and female heterozygous progenitors[2,11] which may provide clues of similar but so far unexplained observations in man.

Availability

The single metacentric homozygous mice used for breeding the double heterozygotes cited in this report are kept by the author in the Abteilung für Pathologie der Medizinischen Hochschule Lübeck, Germany.

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