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Chromosomal control of early embryonic development in mice

II. Experiments on embryos with structural aberrations of autosomes 7, 9, 14 and 17

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SUMMARY

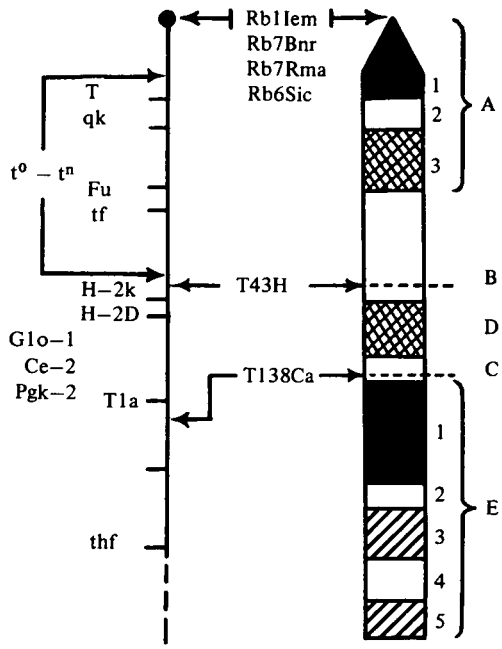
Perculiarities of preimplantation and early postimplantation development were studied in embryos with partial deletions and duplications of chromosomes 7, 9, 14 and 17, in the progeny of mice heterozygous for the unequal reciprocal translocations T(7; 14)2Iem, T(16; 17)43H and T(9; 17)138Ca. Deficiencies for any part of autosomes 9 or 14 combined with duplications of the corresponding segments of autosomes 7 or 17 do not affect preimplantation development, though they are lethal soon after implantation. Deficiency for the distal part of chromosome 7 (Df7F4) induces embryonic death by the early blastocyst stage. Deficiencies for the distal part of chromosome 17 (Df17E1–E5), as well as for its proximal region (Df17AB) carrying all genes of the *T-t* complex, have no detrimental effects on cleavage, blastulation and implantation, but are lethal after implantation, mostly during early neurulation. Deficiency for the middle part of chromosome 17 (Df17CD) is expressed just after a few cleavage divisions, and these embryos all die by the morula stage. It is suggested that the genes of the CD region of chromosome 17 and of the F4 region of chromosome 7 are of major significance for genetic control of early development in the laboratory mouse.

1. INTRODUCTION

Since the classical works pioneered by G. Snell (Snell, Bodeman & Hollander, 1934; Snell, 1941, 1946) mice heterozygous for chromosomal translocations have been considered as favourable tools in experiments on developmental genetics and cytogenetics (Ford & Clegg, 1969). Such mice regularly produce a definite proportion of chromosomally unbalanced gametes. Fertilization of unblanced gametes results in zygotes with monosomy or trisomy of whole chromosomes involved in centric fusion (Robertsonian type of translocations), or in zygotes with duplications and deficiences of both chromosomes involved in reciprocal translocations (Baranov & Dyban, 1968, 1971; White *et al.* 1972; Gropp, Tettenborn & Lehmann, 1970; Oshimura & Takagi, 1975; de Boer & Groen, 1974).

It was recently found that chromosome 17, though comparatively small in size, plays a major role in genetic control of the initial stages of embryogenesis in mice.

Trisomy of 17 is lethal during major organogenesis (Baranov & Dyban, 1970; Baranov & Udalova, 1975; Gropp, Putz & Zimmerman, 1976), while monosomy of 17 affects cleavage and blocks embryonic development by the morula stage (Baranov, Dyban & Chetobar, 1980). However, it is not known what genes in chromosome 17 produce these affects. Mice heterozygous for the reciprocal translocations T(16; 17)43H (hereafter T43) and T(9; 17)138Ca (hereafter T138), which divide chromosome 17 into three almost equal parts (see Text-fig. 1), were used to study this problem.



Text-fig. 1. Regional assignments of genetic map (left) to G-bands of chromosome 17 (right) by means of T43H and T138Ca translocation breakpoints (arrowed). Gene symbols in normal chromosomes 17 are brachyury, *T*; quaking, *qk*; fused, *Fu*; tufted, *tf*: *H-2K*, *H-2D*; glyoxalase, *Glo-1*: catalase, *Ce-2*; phosphoglycerate kinase, *Pgk-2*; Thymus leukaemia antigen, *Tla*; thin fur, *thf*. (See the text for detailed explanations.)

One breakpoint in translocation T43 disrupts the centromeric heterochromatin of chromosome 16 while the other break is situated in the distal end of band 17B (Searle *et al.* 1978). Breakpoints in translocation T138 are located in the D segment of chromosome 17 and B segment of chromosome 9 (Miller & Miller, 1975).

In contrast to chromosome 17, our knowledge on developmental effects of aneuploidy for chromosome 7 is very scarce. Some preliminary observations indicate early death after implantation of embryos with trisomy 7 (Gropp, 1981*a*, *b*), but nothing is known about the expression of monosomy 7. Some data on paternal gene Gpi-I expression (Brinster, 1973) and the effects of the lethal albino deletion mutations (Gluecksohn-Waelsch, 1979) suggest that chromosome 7 plays a major role in the control of morphogenetic and biochemical differentiation in early

development. This hypothesis can be tested on mice with the unequal reciprocal translocation T(7; 14)2Iem (hereafter T2), which has one of its breakpoints in the distal part of chromosome 7 (presumably in bands 7F3–4) and the other in the centromeric region of chromosome 14 (band 14B). Both translocation products are easily identified in metaphase plates without differential staining (Baranov, 1979).

Neither trisomy nor monosomy for chromosomes 9, 14 or 16, involved in translocations T138, T2 and T43, respectively, interferes with preimplantation development (Dyban & Baranov, 1978; Baranov, 1980). Therefore it was of special interest to study early developmental profiles of mouse embryos with partial deletions of chromosomes 7 and 17. The results of the present communication indicate that both the middle part of chromosome 17, primarily the CD region, and the distal part of chromosome 7 are involved in the genetic control of preimplantation development.

2. MATERIALS AND METHODS

(i) *Mice*

Breeding nuclei of mice homozygous for translocation T43 and for translocation T138 were obtained through the courtesy of Dr J. Forejt, Institute of Molecular Genetics, Prague, CSSR, and Dr A. Malaschenko, Laboratory of Biological Models, Yurlovo, Moscow, USSR. Translocation T2 arose spontaneously in an outbred stock of mice kept in the Institute for Experimental Medicine, Leningrad, USSR (Baranov, 1979). Translocation heterozygotes T43/+, T138/+ and T2/+ were obtained from the mating of corresponding homozygotes to CBA/Lac mice of normal karyotype.

(ii) *Embryological methods*

Mice, heterozygous for the translocations, were crossed either to F_1 (CBA × C57BL) (hereafter F_1) or to mice with the Robertsonian translocation Rb(2.6)4Iem (Baranov, 1981). Embryos were examined before implantation (days 3 or 4) (the day of vaginal plug was always considered as day 1 of pregnancy) or after implantation (days 8–10). Preimplantation embryos were obtained by flushing the female reproductive tract with TC199 prewarmed to 37 °C. After stereomicroscopic inspection they were air-dried and studied microscopically. The numbers of blastomeres, pyknoses, mitoses and micronuclei were registered. Postimplantation embryos were recovered from total implants and, after dissection from foetal membranes and external examination under the stereomicroscope, were used for chromosomal preparations.

(iii) *Cytogenetic methods*

Direct chromosomal preparations from preimplantation embryos, made according to the original technique of double fixation and softening (Dyban & Baranov,

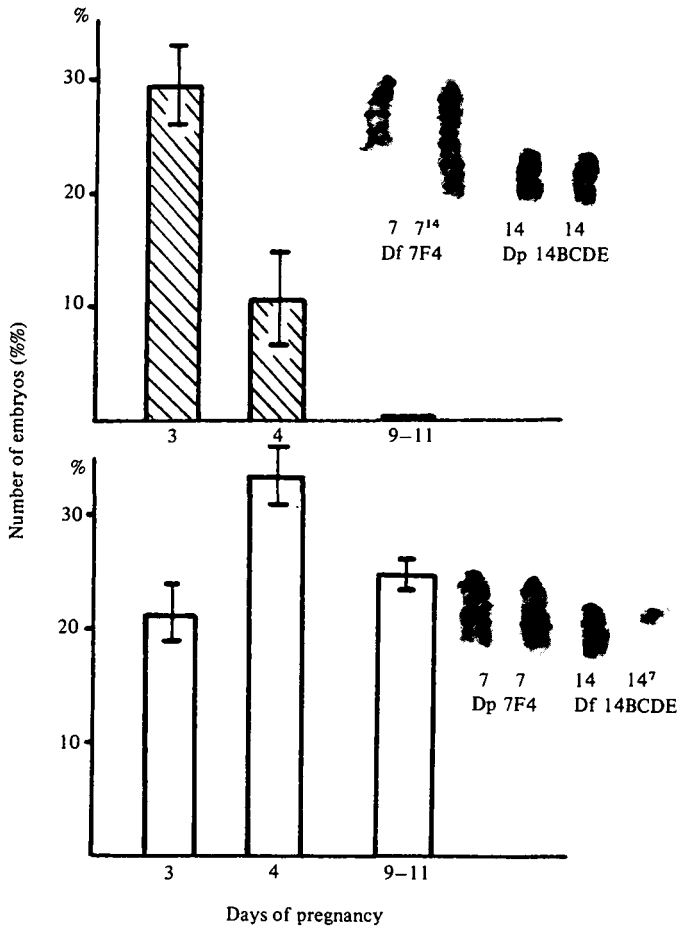
1978), were stained with Giemsa solution and used for exact counts of total chromosome number in all available metaphase plates. At the next step the preparations were destained with pure methyl alcohol and processed for G-bands according to the conventional trypsin–Giemsa method (Wurster, 1972) with some modifications. Chromosome preparations from postimplantation embryos were

Table 1. *Frequencies of embryos with structural aberrations of autosomes 7 and 14 before and after implantation in the progeny of mice heterozygous for translocation T2*

	Day of pregnancy			Total examined
	3	14	9–11	
Total no. of embryos ...	336	208	93	637
No. scored†	109	97	78	284
Karyotype analysis*				
Genetically balanced				
No.	51	49	54	154
%	46·7	50·5	69·2	—
M^+m^+	34	27	26	87
M^+m^-	17	22	28	67
Genetically unbalanced				
No.	58	48	24	130
%	53·3	49·5	30·7	—
Euploid				
No.	49	41	19	109
%	44·9	44·2	24·3	—
M^+m^-	29	10	0	39
M^-m^+	20	31	19	70
Aneuploid				
No.	9	7	5	21
%	8·2	7·2	6·4	—
Trisomy				
M^+m^+	2	2	2	6
M^+m^-	1	1	0	2
M^-m^+	1	0	2	3
Monosomy				
M^-m^-	5	2	1	8
M^+m^-	0	0	0	0
M^-m^+	0	2	0	2

* M, A major marker 7^{14}; m, a minute marker 14^7.
† Karyotype determination possible.

made according to the modified Wroblewska–Dyban technique (Dyban & Baranov, 1978). Chromosome counts were made on 10–15 metaphase plates, stained for G bands. Translocation products and normal homologues were identified in each embryo. Karyotypes were constructed according to the Committee on Standardized Genetic Nomenclature for Mice (Committee, 1972). A total of 568 embryos (343 before and 225 after implantation) were analysed both morphologically and cytogenetically.



Text-fig. 2. Percentage frequencies of the embryos with structural aberrations of chromosomes 7 and 14 on 3, 4 and 9–11 days of pregnancy in mice heterozygous for T2Iem translocation (*T2Iem*/+ ♂ × +/+ ♀).

3. RESULTS

(i) *Translocation T2Iem*

Table 1 shows that the overwhelming majority of all the embryos with known karyotype in the progeny of T2/+ mice on the 3rd day (100 out of 109) and on the 4th day (90 out of 97) had a normal diploid chromosome number. However, in at least half of them only one translocation product can be identified – either a large marker, 7^{14}, or a small one, 14^{7}. So these embryos had structural aberrations of the translocated chromosome. It should be pointed out that the small chromosome 14^{7} always combined with two chromosomes 7 and one chromosome 14. Vice versa, a large marker 7^{14} combined with two chromosomes 14 and only one chromosome 7. Taking into account the positions of the exchange points, this means that the embryos of the first group had duplication for a small distal part of chromosome 7 and deletion of practically the whole chromosome 14 except for its small centromere region (Dp7F4; Df14BCDE), while the embryos of the second group

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had duplication of chromosome 14 and deletion of a distal segment in chromosome 7 (Dp14BCDE; Df7F4).

The frequencies of chromosomally unbalanced embryos of both groups were similar on the 3rd day (29 and 20, respectively, $P > 0{\cdot}05$) (Text-fig. 2); while on the 4th day the number of embryos with a small marker (group 1) was at least three times the number with a large marker (group 2) (31·9% and 10·3%, respectively, $P < 0{\cdot}01$). Not a single embryo of group 2 was recovered after implantation (9–10th days), but there were 19 embryos of group 1 among 78 embryos with known karyotype. A few of the embryos studied before and after implantation were aneuploids (see Table 1). Aneuploidy was due to the imbalance of non-translocated chromosomes in 14 of 21 embryos, while 7 embryos had an excess or deficiency of translocated marker chromosomes.

Morphologically, all the chromosomally unbalanced embryos resembled quite normal morulae in the process of compaction on the 3rd day (mean cell count $10{\cdot}2 \pm 2{\cdot}3$ compared to $13{\cdot}1 \pm 1{\cdot}8$ in the control litter-mates) and normal early blastocysts on the 4th day (mean cell count $34{\cdot}1 \pm 2{\cdot}9$ and $39{\cdot}5 \pm 4{\cdot}3$, respectively). It is worth mentioning, however, that numerous pyknoses and micronuclei, indicating progressive degeneration, were present in 6 out of 10 embryos of group 2. Taking into account the greatly reduced proportion of group 2 embryos on the 4th day, these observations indicate that chromosomal unbalance due to Df7F4; Dp14BCDE affects blastulation and is always lethal by the early blastocyst stage. Group 1 embryos (Dp7F4; Df14BCDE) were recovered both before and after implantation in about equal proportions, though at later stages they looked abnormal.

Of the embryos of group 1, 10 of 19 were represented by small empty yolk sacs without traces of embryoblast derivatives, and 9 had remnants of neural folds. Maternal blood in the implantation chamber and the absence of allantois proved progressive resorption of these embryos. Two aneuploid embryos with partial trisomy of a small marker chromosome (Ts14[7] T2Iem) looked morphologically quite normal on the 10th day.

(ii) *Translocation T43H*

Table 2 shows structural chromosomal aberrations in almost half of all karyotyped embryos (75 out of 163) in the progeny of T43/+ female mice. The number of chromosomally abnormal embryos was somewhat higher before than after implantation (47% and 44%, respectively). All four main groups of chromosomal aberrations expected from non-disjunction of translocated products were registered before implantation and only three of them were found after it (Table 2). The proportion of the embryos for each unbalanced group varied. Before implantation embryos with Df17AB prevailed, but at later stages embryos with Dp17AB represented the most numerous group. Deletion of the CDE region of chromosome 17 combined with trisomy of chromosome 16 (Df17CDE; Ts16) was found exceptionally on the 4th day, that is before implantation but not after it. Morphologically these rare embryos looked abnormal and demonstrated a conspicuous lag in growth by the morula stage (Plate 1*a*). The mean cell number

per embryo with Df17CDE was 2–3 times less than in the embryos of genetically balanced karyotype of the same cross (12·1 ± 2·6 and 31·2 ± 1·8, respectively). Numerous micronuclei, pyknoses, unusually large and light nuclei, combined with metaphase chromosomes separated prematurely into paired chromatids, indicated advanced degeneration and the death of these embryos by the morula stage.

Table 2. *Frequencies of embryos with structural aberrations of chromosomes 17 and 16 before and after implantation, in the progeny of T43/+ females crossed to +/+ or Rb4Iem/+ males*

Day of pregnancy ...	4	8–10
No. of ♀♀	37	20
Total no. of implants	217	147
Karyotype possible	82	81
Karyotype genetically balanced	43	45
Karyotype genetically unbalanced		
Total no.	39	36
Type of aberration (nos.)		
Df17CDEDp16	7	—
Dp17CDEDf16	12	10
Dp17AB	7	14
Df17AB	13	12

The deficiency for the proximal part of autosome 17 (Df17AB) or the duplication of any region of chromosome 17 (Dp17AB or Dp17CDE) had no harmful effect on preimplantation development. Mean cell count per embryo in these groups was 28–32 (Plate 1*b*) and was equal to that in the control group. Some embryos with Df17AB remained alive after implantation, though all of them looked abnormal. Nine of these were represented by very small trophoblastic vesicles without embryoblast derivatives visible under the stereomicroscope, and three looked like an abnormal neurula (Plate 2*a*). Meanwhile, the complete absence of the embryo remnants in at least half of all implantation sites on the 9–10th days proved that embryonic death occured soon after implantation.

Out of 14 embryos with Dp17AB, 11 looked quite normal and were registered only at chromosomal preparation, 2 embryos were slightly retarded and 1 was malformed.

(iii) *Translocation T138Ca*

A total 216 viable embryos were obtained from 38 females, and 125 embryos were successfully karyotyped: 55 before and 70 after implantation (Table 3). The frequency of chromosomally unbalanced embryos on the 4th day was almost twice that on days 8–10 (47·3% and 25·7%, respectively), indicating that embryonic selection was operative by implantation. Actually, at least one main group of chromosomally unbalanced embryos deficient for the proximal segment of chromosome 17 (Df17ABCD + Dp9AB) was registered exclusively before implantation. All 6 embryos of that group on the 4th day were composed of 6–12 blastomeres (mean cell count 8·7 ± 3·6 compared to 31·5 ± 1·8 in controls) some of which were pyknotic or abnormally large with very light transparent nucleoplasm (Plate 2*b*).

These embryos are dead by the morula stage. Out of 18 chromosomally unbalanced embryos on the 8–10th days, 9 were deficient for the distal part of chromosome 17 (Df17E) and had in excess most of chromosome 9 (Dp9CDEF). These aberrations did not interfere with cleavage, blastulation and implantation but were selected soon thereafter. The development of chromosomally unbalanced embryos of two other groups (see Table 3) Dp17E; Df9CDEF and Dp17ABCD; Df9AB, was morphologically similar to that of the former group (Df17E; Dp9CDEF).

Table 3. *Frequencies of embryos with structural aberrations of chromosomes 17 and 9 before and after implantation, in the progeny of T138/+ males crossed to +/+ females*

Day of pregnancy ...	4	8–10
No. of ♀♀	13	25
Total no. of implants	96	120
Karyotype possible	55	70
Karyotype genetically balanced	29	52
Karyotype genetically unbalanced		
Total no.	26	18
Type of aberration (nos.)		
Df17E + Dp9CDEF	10	9
Dp17E + Df9CDEF	4	3
Df17ABCD + Dp9AB	6	0
Dp17ABCD + Df9AB	6	6

4. DISCUSSION

It should be pointed out first that structural aberrations of chromosomes 7 and 17 in the present work always combined with genetic unbalance of the other chromosomes involved in the reciprocal translocations, namely no. 16 (T43), no. 9 (T138) or no. 14 (T2). It should also be remembered that monosomy for any of the latter autosomes does not affect cleavage or blastulation and is often compatible with implantation (Dyban & Baranov, 1978; Baranov *et al.* 1980; Baranov, 1981) while their trisomy is lethal during organogenesis (11–12 days for Ts9), or in the foetal period (16–18 days for Ts16 and 14) (Baranov & Udalova, 1975; Gropp *et al.* 1976). Therefore the genetic unbalance of these chromosomes is morphologically evident at relatively late stages of embryogenesis, and so the detrimental effects of structural aberrations of these chromosomes might be at least partly neglected when the preimplantation development is considered.

(i) *Deletion for the distal segment F4 of chromosome 7*

This aberration though rather common on the 3rd day, was registered in quite a few degenerating early blastocysts. Such an early lethal effect of a very small deletion requires special consideration.

Chromosome 7 is one of the most thoroughly studied genetically, with at least 30 structural genes mapped on it (Eicher & Washburn, 1978). Some of these genes are known to be expressed as early as the 8-blastomere stage (McLaren, 1976). c^{25H} deletion in the middle of chromosome 7 (Miller *et al.* 1974) is already lethal during

cleavage (Gluecksohn-Waelsch, 1979). The breakpoint T2Iem in chromosome 7 is located in the most distal region, probably in segments 7F3–F4, so it presumably shares no common region with the c^{25H} deletion. The genetic map of segment 7F4 is almost completely unknown (Eicher & Washburn, 1978; Womack, 1978). Meanwhile, the results of the present work indicate the great significance of the genes in the distal segment of chromosome 7 for the control of early development in mice. Whether that effect is due to the expression of certain structural genes or is caused by the disbalance of genes with regulatory functions is still unknown.

(ii) *Deletions for the different parts of chromosome 17*

The present study of T43 and T138 heterozygotes provided evidence that deficiencies for different parts of chromosome 17 impaired development potentials of mouse embryos to different extents. The absence of the distal part (17E-1 to E-5) or of the proximal region (A1–A3; B) of this chromosome (Fig. 1) does not affect cleavage, blastulation or implantation, and some of these embryos might be recovered from implants during neurulation, though all of them look abnormal. Contrary to these observations the effects of deletions 17ABCD and 17CDE are already evident during cleavage and they completely block embryonic survival by the morula stage. So the damaging effect of these deletions is almost identical and is expressed at almost the same stage of development as in monosomy for the whole autosome 17 (Baranov *et al.* 1980). Both deletions studied (17ABCD and 17CDE) have in common the region of chromosome 17 enclosed between the breaks T43 and T138 (Text-fig. 1). As it may be inferred from the present data the deletions for the proximal (AB) or the distal (E) segments of chromosome 17 do not affect preimplantation development. There is, therefore, sufficient evidence for the assumption that the absence of the middle segment encompassed between exchange points of T43 and T138 is actually responsible for the early lethal effects of both partial deletions 17CDE and 17ABCD as well as monosomy of chromosome 17. If this suggestion is really true it might be inferred that region CD of this chromosome contains the genes controlling the initial stages of mouse embryogenesis. Therefore, the genetic content of the middle part of chromosome 17 is of special interest and should be discussed in more detail.

The genetic map, related more or less precisely to the cytological map, of chromosome 17 is drawn schematically in Text-fig. 1. The breakpoint of translocation T43H is located to band 17B just distally to tf (Lyon *et al.* 1979) and the following linkage relationship of three gene markers to the breakpoint was established *T-tf*-T43H-*H2* (Forejt, Capkova & Gregorova, 1980). It means that the T43 breakpoint separates physically the two major genetic complexes *T-t* and *H2*, with the *T-t* located in the large translocated product 17^{16}, and *H-2* in 16^{17}. Genes of the complex *T-t* system are known to be intimately involved in embryonic development and spermatogenic differentiation (Bennett, 1975, 1981; Sherman & Wudl, 1977; Lyon *et al.* 1979). Nevertheless, duplication of the AB segment, e.g. trisomy for the whole set of *T-t* genes, does not interfere with embryonic survival (Gregorova, Baranov & Forejt, 1981; Baranov, Gregorva & Forejt, 1981). Moreover, this trisomy is compatible with normal postnatal development and normal

fertility in both sexes (Forejt *et al.* 1980). Even more unexpected are the data of the present work which demonstrate normal preimplantation development of embryos with deficiency for all maternal genes of the *T-t* locus though they die during neurulation. Embryos deficient for a large distal segment, E1–E5, show normal development before implantation and perish soon after it. Unfortunately, the genetic content of this segment is still almost unknown.

The genetic map of the central part of chromosome 17 encompassed by the breakpoints T43 and T138 is known in more detail. Besides the genes of the complex *H-2* locus it carries DNA for a number of other structural genes such as catalase (*Ce-2*), phosphoglycerate kinase (*Pgk-2*), glyoxalase (*Glo-1*), etc. (Womack, 1978). Expression of some *H-2* genes from the early blastocyst stage can be reliably demonstrated by immunofluorescent methods (Searle *et al.* 1976; Magnusson & Epstein, 1981). Therefore the disbalance for these genes does not seem to be responsible for the death of CD-deficient embryos by the morula stage. On the other hand, according to more recent data at least some *H-2* associated genes, named *Ped* (preimplantation embryonic development) do affect the time of the first cleavage division and the rate of subsequent development (Goldbard, Verbanac & Warner, 1982*a*, *b*). Though the real nature of *Ped* genes as well as their gene products remains unknown they might be considered as main candidates for so-called 'early genes' (Dyban, 1974) controlling initial stages of embryogenesis in mammals.

It should be mentioned, however, that the lethal effect of the CD deletion is already expressed in heterozygotes and this differs from the other early lethal mutations such as t^{12} or c^{25H} (Bennett, 1975, 1981; Gluecksohn-Waelsch, 1979) which are lethal only in homozygotes. One might suggest therefore that deficiency 17CD in some still unknown way influences the function of the relevant segment of the normal homologous chromosome 17. So at the cellular level deficiency CD expresses as a nullisomy of corresponding segment 17CD. These results therefore might be considered as additional arguments in favour of a recent suggestion on mutual activation of homologous chromosomes and their segments at initial stages of embryogenesis (Baranov, 1982). The latter suggestion is also supported in part by the remarkable phenomenon discovered by D. R. Johnson (1974, 1975) that postulates the existence of a special activation centre in the segment of chromosome 17, proximal to the T138 breakpoint, which is probably necessary for activation of the normal homologous chromosome 17 during embryogenesis (Lyon & Glenister, 1977).

Whatever the extact mechanism of early embryo lethality caused by the partial deletions studied in the present work, it seems clear that chromosomes 7 and 17 actually control initial embryogenesis in mice, and that most probably the regions 17CD and 7E4 are especially concerned with early genetic activity of these chromosomes.

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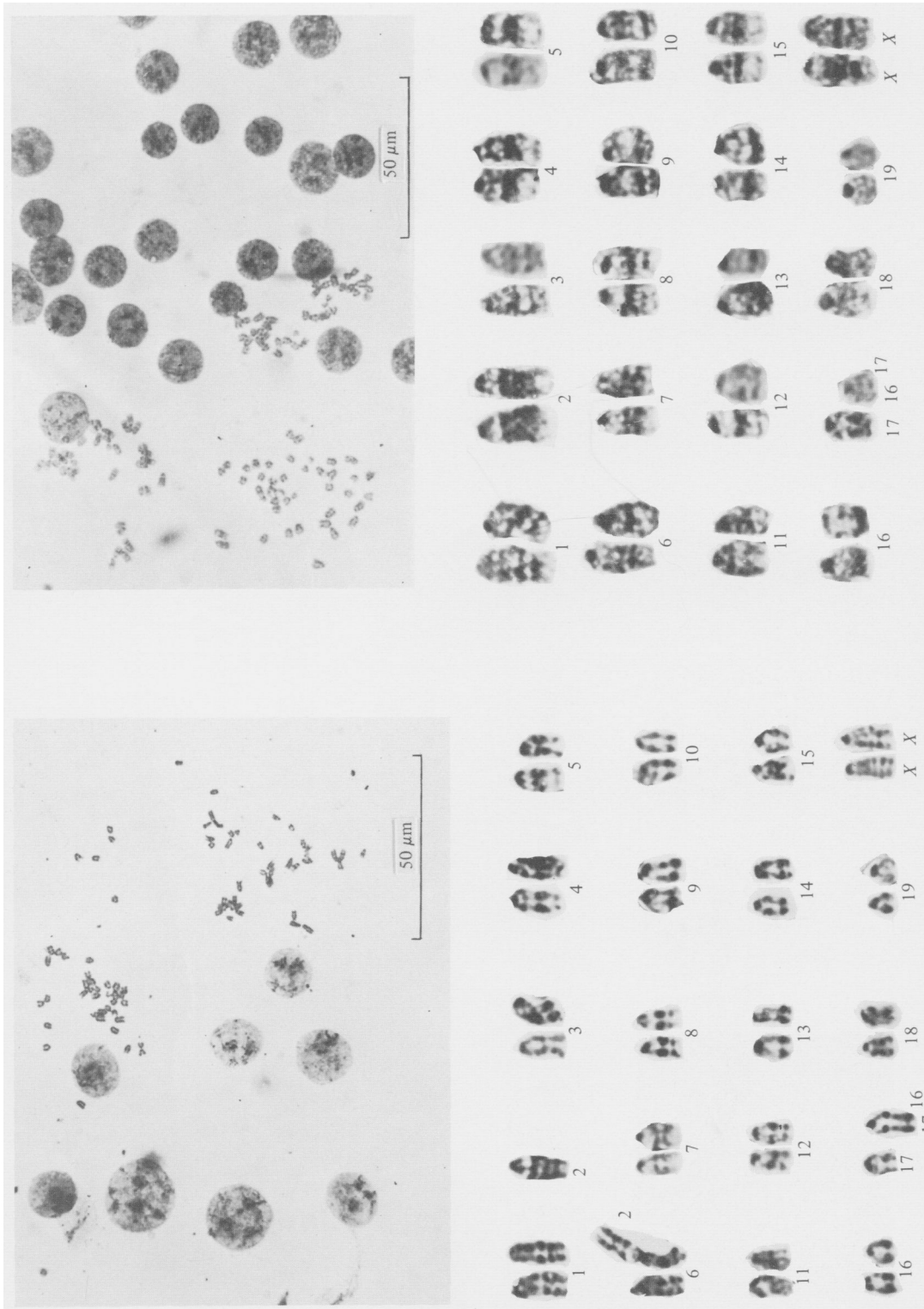

1*b*

1*a*

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EXPLANATION OF PLATES

PLATE 1

(*a*) Deletion 17CDE + Trisomy 16. Total preparation and trypsin–Giemsa banded karyotype of the 4th day embryo (Rb4Iem/+♂ × T43/+♀). Double fixation method. Greatly reduced blastomere number.

(*b*) Deletion 17AB. Total preparation and trypsin-Giemsa banded karyotype of the 4th day embryo (+/+♂ × T43/+♀). Double fixation method. Normal cell count, no sign of degeneration.

PLATE 2

(*a*) Deletion 17AB. External view under stereomicroscope, metaphase plate and trypsin-Giemsa banded karyotype of the 9th day embryo (+/+♂ × T43/+♀). 1, Neurula folds; 2, allantois. Greatly reduced in size malformed neurula.

(*b*) Deletion 17ABCD + Duplication 9AB. Total preparation and trypsin-Giemsa banded karyotype of the 4th day embryo (T138/+♂ × +/+♀). Double fixation method. Reduced blastomere number. 1, Pyknotic nuclei; 2, abnormally large nuclei with transparent nucleoplasm.