lymphocyte cell cycle progression (*13*). This is 1000 times the [^{3}H]thymidine radioactivity per culture necessary for the observed radiation effects. The fact that ^3H_2O did not block lymphocytes in G_2+M at the high concentrations used lends further support to the concept that the block was caused primarily by intranuclear tritium. The question of whether the β particles emitted from intranuclear tritium would interfere with PI intercalation into DNA is answered by the results in Table 1. The fact that the amounts of intranuclear tritium were similar for both test groups, namely, cultures exposed to 0.1 μCi of [^{3}H]-thymidine (1.9 Ci/mmole) for 18 hours or to 1.0 μCi of [^{3}H]thymidine (50 Ci/mmole) for 20 minutes before being harvested, whereas the FCM analyses differed, suggests that the incorporated radioisotope does not affect dye intercalation.

Ehmann *et al.* (*14*) have also shown by FCM that radiation from [^{3}H]thymidine causes a G_2+M block in various tissue culture lines. Their results in combination with ours demonstrate the consistency with which the perturbation of cell cycle progression by [^{3}H] thymidine is observed.

A block in G_2+M such as the one we describe is evidence of cellular injury and should be taken into account in the testing of compounds that inhibit proliferating cells. The radiation damage promoted by intranuclear tritium combined with the inhibitory action of another agent (for example, chemotherapeutic drugs, chalones), might promote a synergistic or antagonistic effect, thereby distorting the results. In cell cycle studies and in investigations of agents perturbing cycling cells it might be possible to avoid these radiation effects by exposing the cells to [^{3}H]thymidine for short time periods.

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12. The words block and inhibition of lymphocytes in the G_2+M phases refer to the observed elevation in the G_2+M peak when [^{3}H]thymidine is added. Since the FCM analysis provides only a static representation of the distribution of cells about the cell cycle phases, the elevation in the G_2+M peak might reflect some phenomenon other than a block (for example, cells in G_1 and S could have been accelerated relative to the cells in G_2+M). However, the possibility that the increase in the number of cells traversing G_2+M, when exposed to [^{3}H]thymidine, was not due to a block is remote. For this reason the terms block and inhibition are used in the text to denote the elevation in the G_2+M peak.
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Retinoblastoma with 13q− Chromosomal Deletion Associated with Maternal Paracentric Inversion of 13q

Abstract. *A girl with sporadic unilateral retinoblastoma and mental retardation has an interstitial deletion in the long arm of chromosome 13. Her mother has a paracentric inversion of one chromosome 13; the deleted chromosome 13 in the daughter is derived from the mother's normal chromosome 13.*

Although retinoblastoma is an uncommon eye tumor in humans, it has proved to be of exceptional interest as a model system for understanding possible genetic implications for human tumors (*1*). In some instances the tumor is sporadic, whereas in others it is the result of dominant inheritance. A third small group has been found to have a partial deletion of the long arms of chromosome 13 (13q−). While evaluating a patient who falls into this last group, we found that her mother has a paracentric inversion of the long arm of one chromosome 13. To our knowledge, this is the first instance in which a parent of a child with the 13q− deletion has been found to have a chromosome abnormality affecting a chromosome 13. This inversion of the chromosome in the mother appears to have resulted in the partial deletion of the long arm of chromosome 13 in her

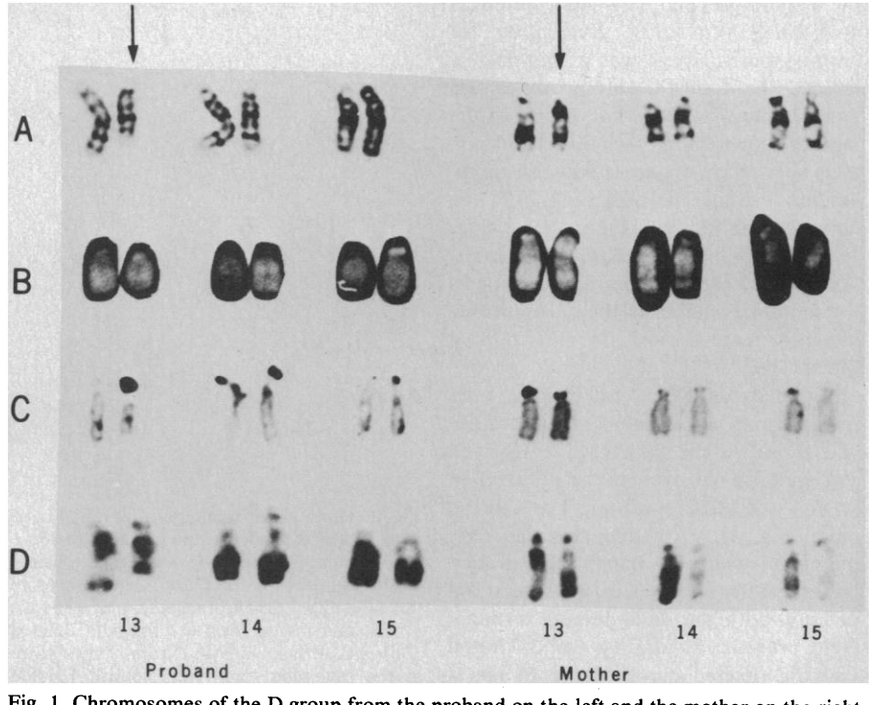

Fig. 1. Chromosomes of the D group from the proband on the left and the mother on the right. Note the deleted chromosome 13 in the proband (arrow) and the inverted chromosome 13 in the mother (arrow). Chromosome stains used are: (A) trypsin-Giemsa banding; (B) quinacrine fluorescence; (C) silver stain; (D) reverse (R) banding. Comparison of the mother's chromosomes 13 with those of the daughter indicates that the daughter's 13q- is derived from the mother's normal chromosome 13 rather than the inverted 13.

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daughter. If this interpretation is correct, it represents a most unusual observation, because paracentric inversions are thought to result in dicentric and acentric chromosomes after meiotic crossing-over within the inverted segment.

The patient was delivered by breech extraction after a 38-week gestation period. Birth weight was 2000 g. Delayed development was noted early but there was no evidence of birth defects. Retinoblastoma was first diagnosed when the patient was 4 years of age, at which time the affected left eye was surgically removed. After surgery the patient received radiation therapy. At about 9 years of age she had a Malherbe's calcifying epithelioma resected from the skin of the face near the external canthus of the left eye. When recently examined she was found to be slightly small for her age. She has expressive aphasia with some poorly developed muscle groups. Dermatoglyphics showed normally placed axial palmar triradii and the digits showed three arches, five ulnar loops, one radial loop, and one whorl. There was no family history of retinoblastoma; the patient has one normal sister and the mother experienced one first-trimester miscarriage.

Chromosome studies showed that all 108 peripheral blood lymphocytes examined and all 22 fibroblast cells from a skin biopsy have an interstitial deletion within the long arm of one chromosome 13; the karyotype (Fig. 1) is interpreted as 46,XX,del(13)(q14q22). Evaluation for chromosome damage was within normal limits. The father's chromosomes are normal. However, the karyotype of the mother shows that in both blood and skin cells she has an apparent paracentric inversion within the long arm of one chromosome 13 giving a karyotype (Fig. 1) of 46,XX,inv(13)(q12q22). The interpretation of the paracentric inversion in the mother is based on the chromosome banding pattern and on her normal phenotype.

To better define the relation between the chromosome changes in the mother and those in the child, we performed some additional cytogenetic studies. In an analysis of chromosome 13q− in the child (Fig. 1), C banding revealed only one centromere; R banding showed a pattern compatible with an interstitial deletion with the dark-staining terminal band present; Q banding demonstrated that the deleted chromosome 13 has a brightly fluorescent centromeric area; and silver staining showed a heavily stained region on the deleted chromosome 13. With both Q banding and silver staining of the mother's chromosomes, the normal chromosome 13 stained heavily whereas the inverted chromosome 13 showed light staining (Fig. 1). The results indicate that the deleted chromosome 13 from the proband has been derived from the normal (noninverted) chromosome 13 of the mother, and that the deleted chromosome 13 in the child is the result of an interstitial rather than a terminal deletion.

Partial deletion of the long arms of a D-group chromosome associated with retinoblastoma has been observed in more than 12 patients; in about six of these patients, banding analysis of the chromosomes has revealed an interstitial deletion within the long arm of chromosome 13 (*2*). There is still some discussion as to whether the primary band affected is band q21 or q14, but the latter is considered more likely (*2*). Since the deletion in our patient appeared to be between bands q14 and q22, our findings do not enable us to distinguish between these possibilities but they are nevertheless consistent with the earlier reports.

The genetic basis of retinoblastoma is not certain. According to the theory proposed by Knudson (*1*) and Knudson *et al.* (*3*), retinoblastoma results from two gene mutations. In the nonchromosomal sporadic occurrences, two somatic mutations are responsible for the tumor. In the inherited form of the tumor, one mutation is already inherited and the other represents a somatic mutation. In keeping with this theory, it is conceivable that the loss of a gene caused by the interstitial chromosome deletion is equivalent to an inherited mutation and then only a single subsequent somatic mutation is required to allow the retinoblastoma to occur. This carries the implication that at least one of the genes responsible for retinoblastoma is located within the deleted portion of the affected chromosome 13. As noted by Knudson *et al.* (*4*), this type of chromosome deletion is the only situation in humans or animals in which a specific chromosome change occurs prezygotically and consistently predisposes the affected subject to a specific tumor. What is of further interest in the family we are reporting is that the patient's mother is a carrier of a chromosome rearrangement which we believe predisposed her daughter to the chromosome deletion.

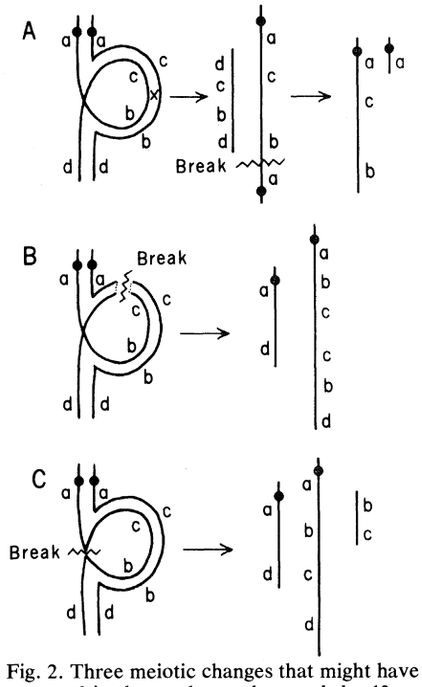

Fig. 2. Three meiotic changes that might have occurred in the mother and caused the 13q− chromosome in the daughter. (A) Crossing-over within the inverted loop; this leads to an unstable dicentric chromosome which breaks at cell division to form a terminally deleted 13q−. (B) Breaks in both chromosomes within the inversion loop; on rejoining (dotted line), the broken chromosomes give rise to an interstitial 13q− abnormality. (C) Two chromosome breaks within the same chromosome; because of the inversion loop the distal ends are next to each other and join, with the interstitial segment being lost.

The appearance of the mother's chromosomes (Fig. 1) is in keeping with the presence of a paracentric inversion within the long arm of one of her chromosomes 13. The inverted segment appears to be larger than the deleted segment in her daughter but it is of interest that the distal end of the inverted segment (band q22) appears to also be at one end of the deleted segment in her daughter. We emphasize that the precise location of the breaks in both the deleted and inverted chromosomes is dependent on the limits of the technique, and that our designations are a best estimate. Figure 2 is a diagrammatic representation of possible explanations for the observed chromosome changes in the patient and her mother. Classically, crossing-over within the inversion loop of a paracentric inversion results in a dicentric chromosome and an acentric fragment; the reason for this is not certain but probably is related to "polarity" of the DNA or the specific mechanism of the crossing-over process. Conceivably, a deleted chromosome with a single centromere could result from the dicentric chromosome, because dicentric chromosomes are unstable (Fig. 2A). This would result in a terminal deletion of the affected chromosome. If our interpretation of the chromosome results is correct, the proband had an interstitial deletion and not a terminal deletion. Hence, this explanation is unlikely.

A second possibility is that a break occurred in both chromosomes involved in the inversion loop, and their rejoining produced an interstitial deletion (Fig. 2B). The possibility of a single dose of radiation or some other similar phenomenon breaking both chromosomes would be enhanced by the homologous pairing occurring in the inversion loop. In this instance the inversion would be important in the production of this deletion, but the inversion would occur by a process separate and different from crossing-over.

A third possibility is that the inversion loop brought two parts of the same chromosome close together and that a single damaging agent, such as radiation, caused two breaks which then united to form an interstitial deletion with loss of the acentric fragment (Fig. 2C). Novitsky (*5*) described an experimental system in which radiation caused restitution of the normal sequence from a paracentric inversion in *Drosophila*. This process could be similar to that observed in the present family, although the inversion here seems larger than the deleted segment; however, the resolution of the current cytogenetic techniques may be misleading and the inverted segment may be the same length as the deletion. Finally, the present findings contrast with those of Novitsky in that we found a deletion rather than restitution of the normal chromosome. But the same phenomenon could account for these observations and it may have been a matter of chance that Novitsky did not observe the deleted products; alternatively, the deletions in *Drosophila* might have been lethal and hence not observed in the progeny. At present we do not know which of these three possibilities applies to our patient, although the second two are favored over the first because they explain the formation of an interstitial deletion which the cytogenetic findings suggest is present.

Only a few paracentric inversions of human chromosomes have been described, but this situation may change with the recent improvements in chromosome banding techniques. To date, no recombinants have been observed in the offspring of the carriers of paracentric inversion carriers, but when such observations are made, it may be possible to determine whether our observation represents a common event in humans or that our explanation is incorrect. However, for the moment we are reluctant to believe that the chromosome changes in the patient and her mother are unrelated.

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On the Nature of Human Interlimb Coordination

Abstract. *Movement time varies as a function of amplitude and requirements for precision, according to Fitts' law, but when subjects perform two-handed movements to targets of widely disparate difficulty they do so simultaneously. The hand moving to an "easy" target moves more slowly to accommodate its "difficult" counterpart, yet both hands reach peak velocity and acceleration synchronously. This result suggests that the brain produces simultaneity of action not by controlling each limb independently, but by organizing functional groupings of muscles that are constrained to act as a single unit.*

Much of human movement involves the coordinative use of both hands, yet, in spite of a resurgence of interest by psychologists and neurophysiologists into problems of motor control (*1*, *2*) little is known about the principles governing interlimb coordination. Perhaps the most important problem facing the development of a theory of coordination is the determination of the significant units with which the nervous system works. One commonly held view is that central command signals specify the states of individual muscles. An alternative is that control decisions are referred to functional groupings of muscles—coordinative structures or linkages (*3*)—that are constrained to act as a single unit (*4*).

The rigorous investigation of muscle collectives has not taken place despite powerful logical arguments that they must be the significant units of control (*5*). Experimentation in motor behavior over the last decade has focused to a considerable degree on issues concerning control by closed-loop feedback or by open-loop programming (*6*). We now report data on a task involving both hands that strongly favors an interpretation based on muscle linkages. We believe this demonstration to be significant since previous evidence for muscle collectives comes from potentially prewired activities such as locomotion (*7*) and respiration (*8*).

How will a person respond when asked to produce movements of the upper limbs to targets each of which varies in amplitude and precision requirements? A relationship between movement duration, movement amplitude, and target demands formulated by Fitts (*9*) allows us to examine this question experimentally:

$$MT = a + b \log_2 2A/W$$

where MT is movement time, a and b are constants, A is the amplitude of the movement, and W is the width of the target. The units of this formula are referred to as "bits" which also serve as units for the index of difficulty of the movement. This fundamental relationship, known as Fitts' law, has been empirically demonstrated in single-limbed movements under a wide variety of environmental conditions including, for example, microscopic (*10*) and underwater (*11*) tasks. The key aspect of the formulation is that movement time depends on the ratio of movement amplitude to movement precision. Thus the movement time for a 3-cm movement to a 0.25-cm target width (a 12:1 ratio) is practically identical to that for a 12-cm movement to a 1-cm target width (*9*).

Consider a one-handed movement condition in which the target size is large and the amplitude is small (termed easy), relative to a condition in which the target size is small and the movement amplitude is large (termed difficult). Movement time in the first case will obviously be shorter in duration. But when these conditions are combined for both hands, does the hand producing a short movement to an easy target arrive much earlier than the more difficult condition, as Fitts' law might predict? We have found that subjects respond virtually simultaneously to targets of various difficulty when asked to respond as quickly and as accurately as possible after an auditory stimulus. In addition to the experiment

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