Localization of Genes on Chromosome 13:
Analysis of Two Kindreds

GERALD E. BLOOM[1,2] AND PARK S. GERALD[2]

The D_1 trisomy syndrome is characterized by severe mental retardation and multiple congenital malformations, including polydactyly, cleft lip, cleft palate, ocular anomalies, and congenital heart disease (Patau et al., 1960). In addition, severe hematologic changes that have been attributed to a maturational delay of normal physiologic events are commonly associated with this syndrome. These changes include an elevated level of fetal hemoglobin (Huehns, Hecht, et al., 1964; Powars et al., 1964), persistence of embryonic hemoglobin into the neonatal period (Huehns, Hecht, et al., 1964), an increased number of neutrophil nuclear projections (Huehns, Lutzner, and Hecht, 1964), a decreased level of hemoglobin A_2, and a decreased concentration of carbonic anhydrase (Lee et al., 1966; Walzer et al., 1966).

Yunis and Hook (1966) have studied three patients believed to have partial trisomy of different portions of the D_1 (13) chromosome. Their findings suggested that it might be possible to dissect this chromosome with respect to those chromosome segments* responsible in the trisomic condition for the increased neutrophil nuclear projections and the elevated level of fetal hemoglobin. They tentatively concluded that these segments were located on the long arm of chromosome 13 (identified by autoradiography) near the centromere. Their observations were supported in part by Walzer et al. (1966), who reported a patient with a D/D translocation "trisomy" with an elevated fetal hemoglobin level but a nearly normal nuclear projection count.

It is apparent from these studies that the partial trisomic state provides a unique opportunity for determining the relative positions of various genetic determinants known to be present on a given chromosome. If it were possible to establish with reasonable certainty the topographic relationship of those chromosomal segments responsible for the various clinical and hematologic findings in the D_1 trisomy syndrome, the information could then be used to improve our understanding of more complicated chromosome lesions. The two patients† who are the subjects of the pres-

* Since it is not known if morphologic features are controlled by single genes, as compared to gene complexes or even regions of chromosomes, the noncommittal phrases "chromosome segment" and "genetic determinant" have been used throughout.

† A preliminary description of these two patients has been previously presented (Gerald et al., 1964).

[1] Hematology Division, Children's Hospital Medical Center, Boston, Massachusetts 02115.

[2] Clinical Genetics Division, Children's Hospital Medical Center, and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115.

ent report furnish further evidence bearing on the localization of the genes on the D_1 (13) chromosome which govern the neutrophil projection abnormality, the elevated fetal hemoglobin level, and possibly some of the congenital malformations in the D_1 trisomy syndrome. In addition, an attempt is made to show how the use of this information combined with DNA replication analysis may help to clarify an otherwise enigmatic cytogenetic problem.

METHODS

Fetal hemoglobin values were determined quantitatively by a minor modification of the method of Singer *et al.* (1951). Normal adult values with this technique are less than 1.5% in this laboratory. For confirmation, a visual estimation of the fetal hemoglobin level was obtained by starch-gel electrophoresis of whole hemolyzate using the tris–EDTA–borate buffer of Smithies (1965). The fetal hemoglobin band can easily be seen when values greater than 1.5% are present.

Neutrophil projections were classified in the manner previously described (Walzer *et al.*, 1966). The proportion of cells with two or more projections was used to determine the projection count. Normally, the percentage of such cells is slightly elevated in newborns and gradually decreases during the first two years of life. Beyond the age of two years, more than 4% of neutrophils with two or more nuclear projections is considered abnormal.

Chromosome analyses of peripheral leukocytes were done according to a modification of the technique of Moorhead *et al.* (1960). DNA replication analysis was performed according to modifications of previously described methods (Schmid, 1963; German, 1964). Briefly, tritiated thymidine (New England Nuclear Corporation, specific activity 2.0 c/millimole) was added to a 72-hour culture of phytohemagglutinin-stimulated peripheral lymphocytes to a final concentration of 1 μc/ml. Three and one-half hours later, colchicine was added to arrest the cells in metaphase, and in two more hours the culture was harvested. Slides containing the specimens were then coated with a photosensitive emulsion (Kodak A.R. 10), exposed in the dark for four days at 4° C and then developed. Appropriately labeled cells were photographed and their positions recorded. The grains were then removed from the photographic emulsion with a solution of potassium ferricyanide (7% w/v) and sodium thiosulfate (20% w/v). The degrained cells were relocated and a second set of photographs was taken for comparison.

PATIENT MATERIAL

Patient 1 (Family A87)

This nine-year-old female was the 6 lb. 7 oz. product of a full-term pregnancy. She was initially referred for genetic evaluation at age six years because of mental retardation and a peculiar facies. The mother was 20 and the father 19 years old at the time of the child's birth. Two male sibs are living and well. There is no family history of mental retardation, congenital malformations, or frequent miscarriages. The family pedigree is presented in Figure 1. The child first smiled at 10 months, sat alone at 15 months, began to creep at 18 months, and started talking at 21 months of age.

Physical examination at age six years revealed a small, microcephalic child with

an alternating strabismus, generalized hypotonia, short incurved fifth fingers, a right metatarsus valgus, and a systolic murmur along the left sternal border interpreted as indicating a small ventricular septal defect. There was no cleft palate, coloboma, cataract, or extra digit.

Buccal smear examination showed a normal female sex chromatin pattern. Dermatoglyphic studies revealed the axial triradii to be distally located. An ulnar loop was present on all fingers except the left index finger, which contained an arch.

Patient 2 (Family A29)

This six-year-old female was first seen for genetic evaluation at age three and one-half years because of mental retardation and multiple congenital malformations.
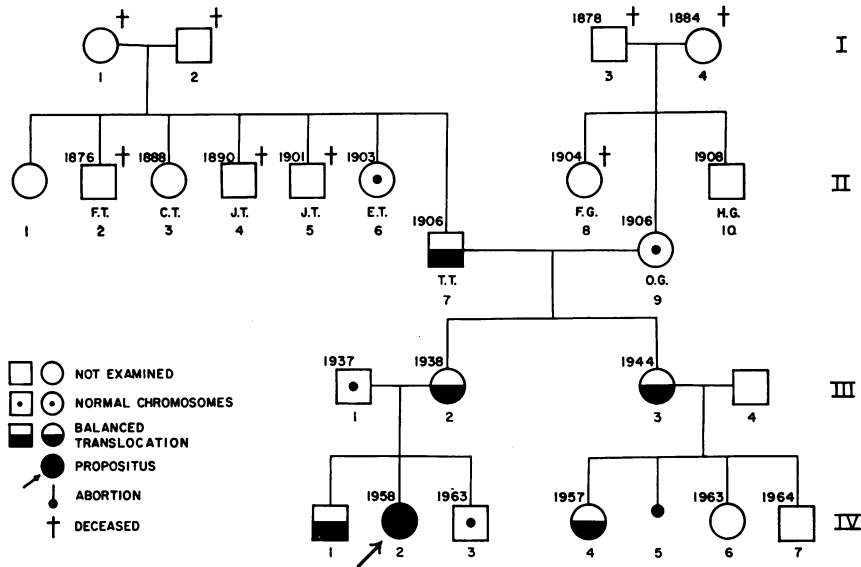

FIG. 1.—Pedigree of family A87

The child's birth weight was 9 lb. 12 oz. The mother was 26 years old and the father 28 years old at the time of the child's birth. The family pedigree is presented in Figure 2.

At birth the child was noted to be microcephalic, with a broad nasal bridge, high arched palate, bilateral lenticular opacities, low-set ears, and a cleft soft palate. An extra digit, which was subsequently excised, was present on the ulnar side of the left hand. There were six complete toes on each foot. No cardiac murmurs were present. An intravenous pyelogram and chest X ray were normal. Roentgenograms of the hands showed hypoplasia of the middle phalanges of the second and fifth digits. When seen at six years of age, she was severely retarded and unable to sit, walk, or talk. Fingerprint patterns showed a radial loop on the first and second digits of both hands and on the fourth finger of the right hand, a whorl on the left third and fourth fingers and the right third finger, and an ulnar loop on the right and left fifth fingers. The triradii

were normal in their position. An arch tibial pattern was present in both hallucal areas.

The mother's first, third, fourth, and fifth pregnancies ended in abortions at three, three, four, and six months of gestation, respectively. Another child, the product of the second pregnancy, was born with multiple congenital abnormalities and died at 18 hours of age. These anomalies included microcephaly, cleft palate, cleft lip, a sixth finger on the ulnar side of both hands, extra complete digits on both feet, coarctation of the aorta, and a large patent ductus arteriosus. At postmortem examination, the brain was described as showing prominence of the major convolutions, indicating relative immaturity.
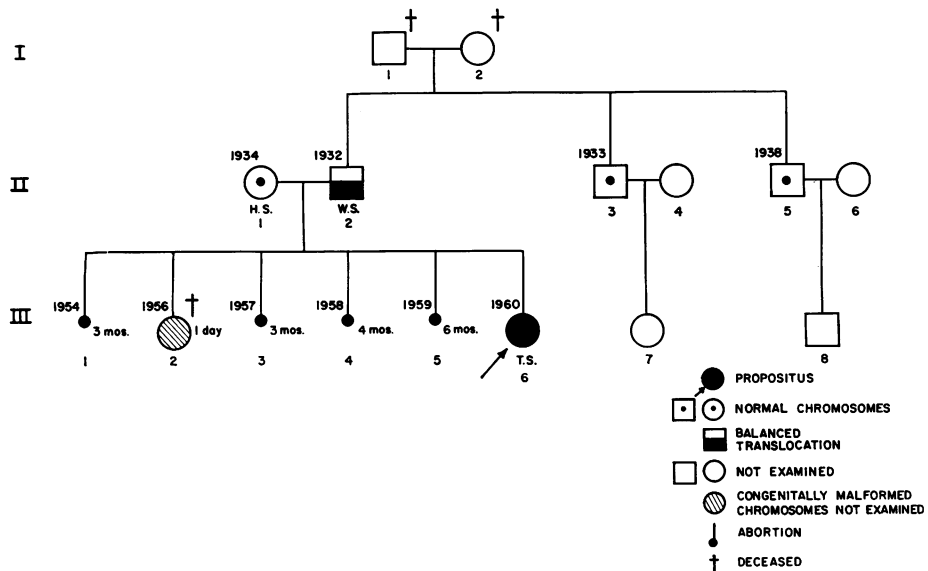

FIG. 2.—Pedigree of family A29

RESULTS

The fetal hemoglobin values and nuclear projection counts from both patients are shown in Table 1. Patient 1 showed a moderate elevation of both parameters. The findings on patient 2 were normal.

Extensive blood grouping and serum protein studies in the families of both patients failed to demonstrate either an anomalous inheritance pattern or linkage of a blood group with the chromosome abnormality (Table 2).

Chromosome Studies

Patient 1 had a modal number of 47 chromosomes. The extra chromosome was approximately the size of the E group; however, it was acrocentric and satellites could frequently be seen on the short arms. It resembled a D-group chromosome with deletion of a portion of the long arms (Fig. 3). Chromosome studies were done on all available family members. The father's karyotype was normal. The mother, who was

TABLE 1

HEMATOLOGIC AND DNA REPLICATION STUDIES

| SUBJECT | HEMATOLOGIC STUDIES | | | | DNA REPLICATION STUDIES | | | |
| | Fetal Hemoglobin Values | | Neutrophilic Projection Counts* | | Total Number Cells Examined | Number of Cells Satisfactory for Use | Number of Cells with Consistent Labeling Pattern† | Number of Nonconforming Cells |
	%	Age (years)	%	Age (years)				
Mother of patient 1.....	....	....	....	....	104	64	62	2
Patient 1.....	{2.5 {3.5	6 7	13 7	6} 7}	....	....	....	....
Father of patient 2.....	0.7	26	1	26	74	48	46	2
Patient 2.....	{1.5 {0.4	3½ 4	3 0	3½} 5½}	80	52	51	1
Normal......	0–1.5	3	0–4	4	....	....	....	....

* Cells with two or more projections.

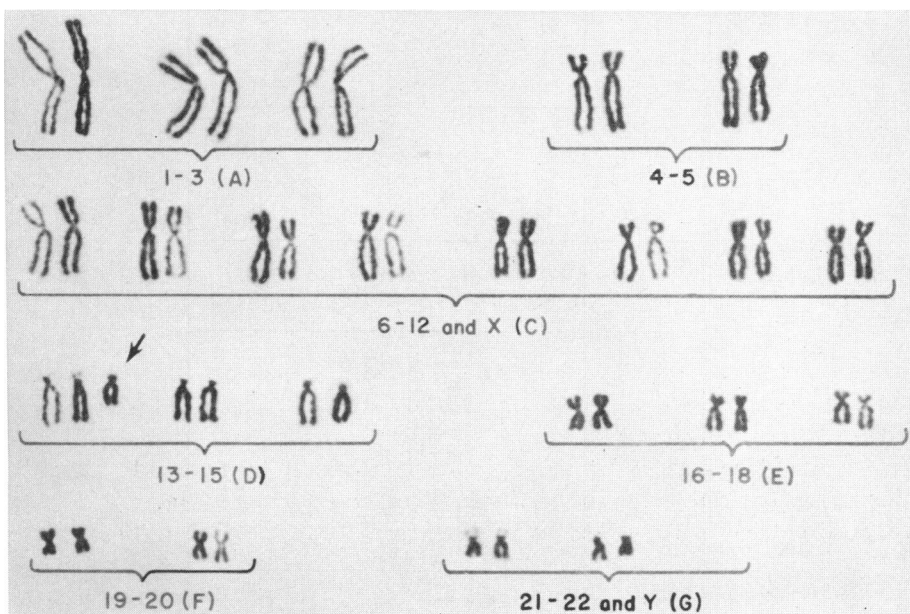† In all three persons examined the abnormal D chromosome was identified as a chromosome 13.

FIG. 3.—Karyotype of patient 1

TABLE 2

BLOOD GROUPS AND SERUM TYPES

Individual	Karyotype	ABO	Probable Rh Genotype	MNSs	P_1	Kell			Fya	Jk		Lua	Gm			Inv(1)	Hp	Tp
						K	Kpa	Kpb		a	b		1	2	5			
Family 1:																		
II-6	Normal	A_1	CDe/cde	++0+	0	0	0	+	0	+	+	0	+	+	+++	0	2-1	C
II-7	Translocation carrier	A_2	CDe/cde	+0++	+	0	0	+	0	+	+	0	+	+	++	0	2-2	C
II-9	Normal	A_2	cD^{u}E/cde	++0+	+	0	0	+	0	+	+	0	0	0	·	0	2-1	C
III-1	Normal	B	CDe/cde	++0+	+	0	0	+	+	+	0	0	·	·	·	·	2-2	C
III-2	Translocation carrier	A_2	CDe/cde	++++	+	0	0	+	0	+	0	0	+	+	++	0	2-2	C
III-3	Translocation carrier	A_2B	cde/cde	0+0+	+	0	0	+	0	0	+	0	0	0	·	0	2-1	C
IV-1	Propositus	A_2	CDe/CDe	+0++	+	0	0	+	0	+	0	0	++	+	·	·	2-2	C
IV-2	Translocation carrier	A_2	CDe/cde	+0++	+	0	0	+	+	0	+	0	·	·	+	0	2-2	C
Family 2:																		
II-1	Normal	A_1B	CDe/CDe	++++	+	0	0	+	0	+	+	0	0	0	++	0	2-2	C
II-2	Translocation carrier	A_1	CDe/CDe	++++	+	0	0	+	+	+	0	0	0	0	·	0	2-1	C
II-3	Normal	A_1	CDe/cde	++++	+	0	0	+	+	+	+	0	·	·	·	·	2-1	C
II-4	Normal	A_1	CDe/cde	+0+0	+	0	0	+	+	+	+	0	0	0	+	0	2-2	C
III-6	Proposita	AB*	CDe/CDe	++++	+	0	0	+	+	+	+	0	·	·	·	·	2-2	C

* Subgroup typing not done.

phenotypically normal, had only five normal D-group chromosomes (Fig. 4). The sixth D chromosome was replaced by an abnormal acrocentric chromosome of the propositus. In addition, one of the mother's chromosomes in the C group consistently had a median centromere in all cells examined. Linear measurements of the deleted D and its homologue (as identified by autoradiography) from 25 of the mother's cells revealed that about 35% of the total length of the chromosome was missing. These changes were interpreted as evidence for a translocation involving the long arm of a D and the short arm of a C chromosome (46,XX,t [Dq-;Cp+]).* This is presumed to be a reciprocal translocation, in the absence of evidence to the contrary, since it is currently assumed that a two-break process is more likely to occur than one involving
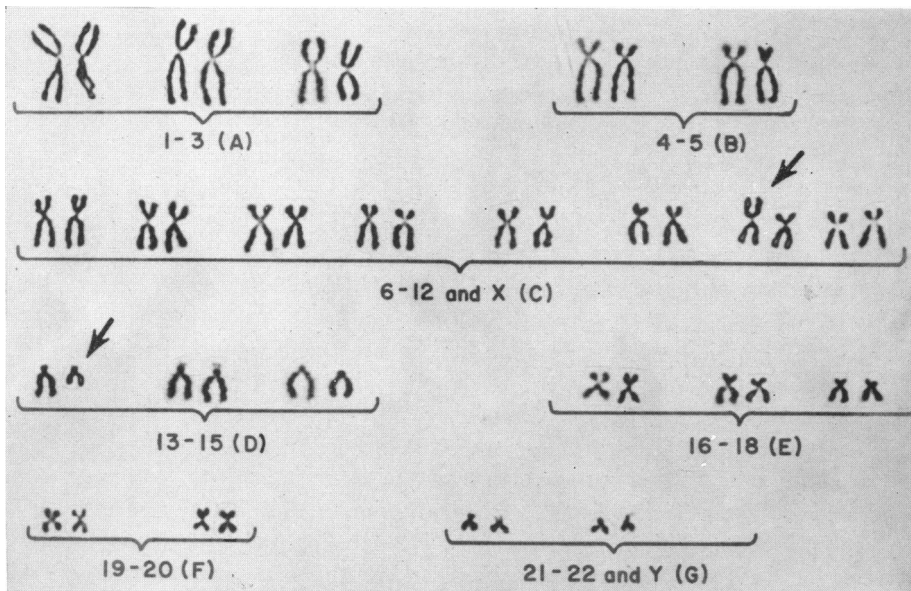

FIG. 4.—Karyotype of mother of patient 1

three or more breaks. One of the patient's brothers, a maternal aunt, the maternal grandfather, and a cousin were also found to be carriers of this same C/D translocation (Fig. 1). The propositus' karyotype (47,XX,[Dq—]+mat) was considered to represent trisomy for the short arms, centromere, and proximal portion of the long arms of a D chromosome, as well as trisomy for an undetermined amount of the short arm of a C chromosome.

The members of the second family who were available for study included the propositus, her parents, and two paternal uncles (Fig. 2). The patient and her phenotypically normal father had morphologically identical chromosome abnormalities. The modal number of their chromosomes was 46. Only five normal D-group members were present; the long arms of the sixth D chromosome were abnormally short. Linear

* This nomenclature conforms to the recommendations of the *Chicago Conference: Standardization in Human Cytogenetics* (1966).

measurements of the abnormal D and its homologue (as identified by autoradiography) revealed that about 50% of the total chromosome was missing in both the patient and her father (25 cells from each were measured). In addition, in both the child and the father, one arm of a chromosome 1 was longer than its homologue by an amount approximately equal to that missing from the D-group members. Superficially, the karyotype in the father (Fig. 5, *top*) appeared to represent a balanced reciprocal translocation (but see the Discussion) between the long arm of a D-group chromosome and one arm of chromosome 1 (46,XX,t[Dq−;1?+]). The same morphologic abnormality was present in the patient (Fig. 5, *bottom*). No abnormalities were found in any of the other family members studied (Fig. 2).

Autoradiographic Studies

The D-group chromosomes can be divided into three pairs based on their characteristic autoradiographic labeling pattern during the latter part of the DNA synthetic period (German *et al.*, 1966). One pair (D_1 or 13) is labeled intensely on the distal portion of the long arms. A second pair (D_2 or 14) is characteristically labeled over the short arms and centromere. The third pair (D_3 or 15) is unlabeled except for the occasional presence of a few scattered grains. The D_1 (13) chromosome identified in this manner has been given this designation because it is the member which is trisomic in the D_1 trisomy syndrome (Yunis *et al.*, 1964; G. E. Bloom and P. S. Gerald, unpublished).

Autoradiographic studies were done for the mother of patient 1 with the D/C translocation. Sixty-four cells were adequately labeled and could be analyzed. In these cells, only one distally labeled member (D_1 or 13) was regularly present. Two D_2 (14) and two D_3 (15) chromosomes could be distinguished (Table 1, Fig. 6). Occasionally, a few grains were present over the distal ends of the long arms of the shortened D. These findings indicated that the shortened D was derived from a D_1 (13) chromosome and that a portion of the late labeling region of this chromosome was missing. It is assumed that this is the distal portion of the chromosome, since, if the intermediate portion were involved, more than one break would be required. The median C-group chromosome was labeled primarily at one end. The intensity of the terminally labeled portion was approximately equal to that of the normal 13 chromosome in the same cell. This terminal portion was, therefore, thought to represent the segment deleted from the shortened chromosome 13. A normal late-replicating X chromosome was present. The propositus who possessed the abnormal D chromosome, in addition to the normal complement, was interpreted as being trisomic for the short arm, centromere, and proximal two-thirds of the long arms of chromosome 13.

DNA replication studies were done for both patient 2 and her father. Only one normal D_1 (13) chromosome was consistently present in the father, while two D_2 (14) and two D_3 (15) chromosomes could be identified (Table 1, Fig. 7). The deleted D was therefore derived from a D_1 (13) chromosome. This was confirmed by the labeling pattern of the abnormally long arm of chromosome 1. The end of this long arm contained a heavy concentration of label, in contrast to the normal chromosome 1 (Fig.
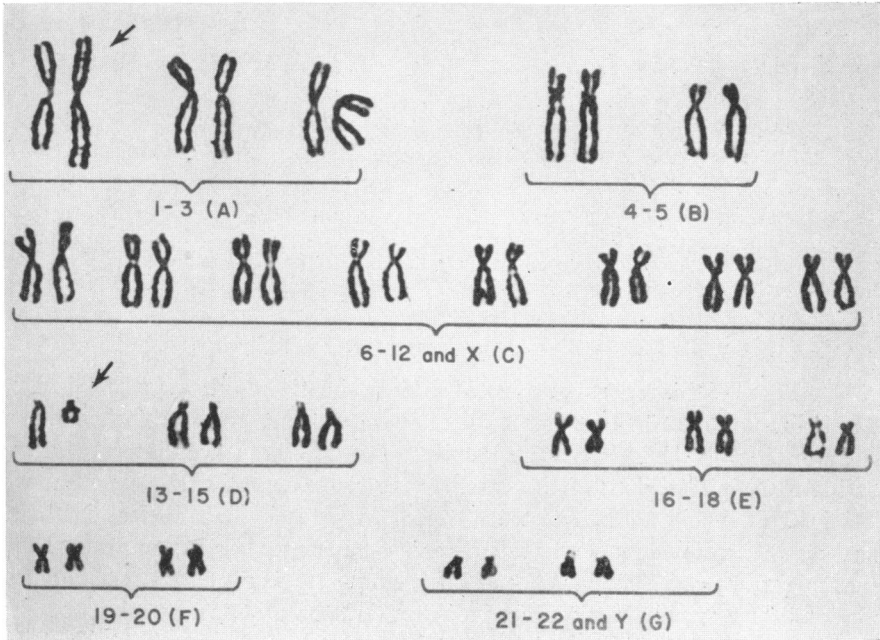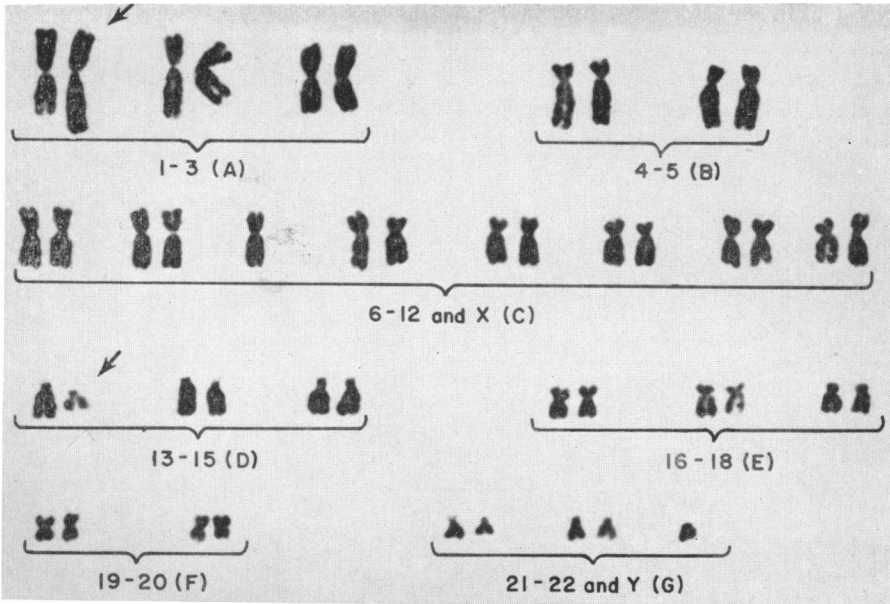
FIG. 5.—*Top*, Karyotype of father of patient 2. *Bottom*, Karyotype of patient 2

7). The intensity of label at the end of the long arm correlated well with the intensity of label at the distal portion of the normal D_1 (13) chromosome. It was not possible to identify whether the secondary constriction found at times on chromosome 1 was present on the abnormally long arm. The autoradiographic findings in patient 2 appeared to be identical to those in her father.
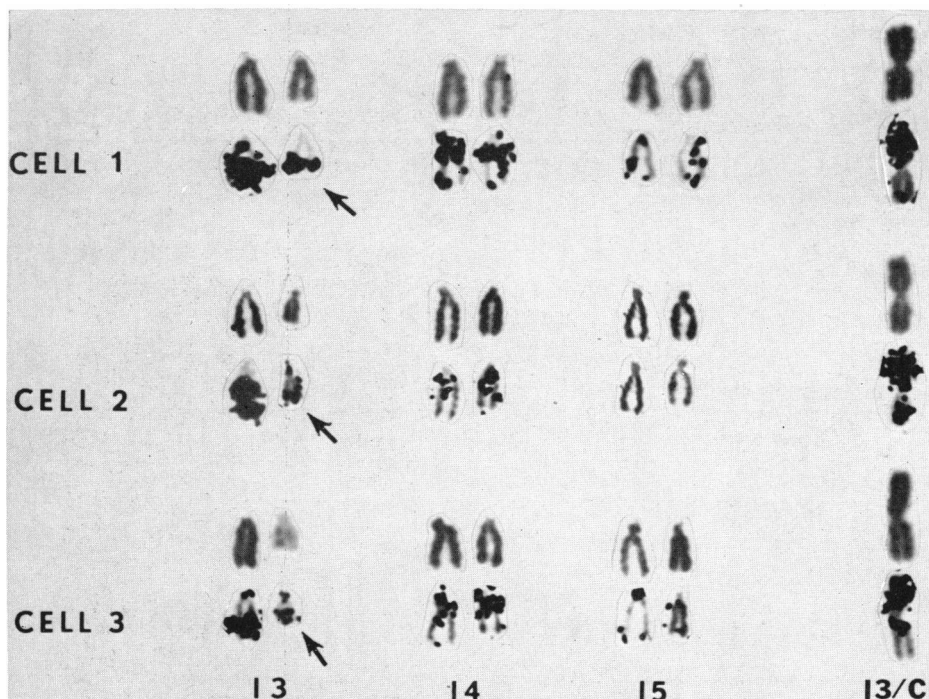

FIG. 6.—Autoradiographic study in three cells from the mother of patient 1. The 13–15 group and the 13/C translocation chromosome from each cell are shown. The labeled chromosomes are located directly beneath the corresponding unlabeled ones. The arrows point to the shortened 13 chromosome.

DISCUSSION

The purpose of this report is to present evidence bearing on the topographical mapping of chromosome 13 with respect to certain of the hematologic, biochemical, and clinical findings in the D_1 trisomy syndrome. The data have been interpreted as indicating that finite regions of the chromosome cause a *specific* clinical effect when trisomic. This should not be construed to mean that each clinical effect can be produced by only a single region on this chromosome or that regions on other chromosomes might not cause similar effects. For example, the similarity of phenotypes in different chromosomal abnormalities indicates that the genetic determinants responsible for some malformations, such as mental retardation and congenital heart disease, may be widely spread through the chromosome complement. With the limited information available, it seems reasonable to postulate that the development of certain complex structures such as the eye, heart, and brain may be controlled by genetic

determinants present on many chromosomes. Imbalance in any one of several genetic determinants on different chromosomes could then lead to similar results. It is within this context that the present study was done.

Yunis and Hook (1966) have suggested a localization of genes (*sic*) governing the polymorphonuclear leukocyte projection abnormality and fetal hemoglobin elevation found in the D_1 trisomy syndrome. They studied three patients who were considered (on the basis of autoradiography) to be partially trisomic for various portions of the D_1 (13) chromosome. Their first patient, with 46 chromosomes, had an abnormal

FIG. 7.—Autoradiographic study of three cells from both the father and proposita of family 2. Only chromosome 1 and the 13–15 group are shown. For each cell, the labeled chromosomes are located directly beneath the corresponding unlabeled ones. The arrows point to the shortened 13 and elongated 1 in each group.

chromosome which was interpreted as a translocation between a D and a G chromosome and hence was believed to be partially trisomic for the distal four-fifths of chromosome 13. This child had a normal projection count but an elevated fetal hemoglobin level. The second patient had 47 chromosomes, including an extra G-sized member with satellites at both ends, and an abnormal projection count but a normal fetal hemoglobin level. This child was considered trisomic for the short arms and the centromeric portion of the long arms of chromosome 13 (47,XX,[Dq−]+). The final patient, with 47 chromosomes, had an extra G-like chromosome and was thought to be trisomic for the short arm and proximal long arms of chromosome 13 (47,X?, [Dq−]+). This patient had both an elevated fetal hemoglobin level and an abnormal projection count. On the basis of these observations, Yunis and Hook (1966) concluded that trisomy for the pericentric portion of 13 resulted in increased nuclear projections and an elevated fetal hemoglobin level. (A fourth patient, only partially studied by Yunis and Hook, suggested that the short arms of 13 had no effect on the hematologic features.)

The findings in patient 1 of the present report provide further evidence concerning the positioning of the chromosome segments determining nuclear projections and fetal hemoglobin levels on the D_1 chromosome. This child was trisomic for the short arms and proximal portion of the long arms of a D-group chromosome and had both an abnormal neutrophil projection count and an elevated level of fetal hemoglobin. DNA replication studies on the mother, who had a balanced D/C translocation, clearly showed that the trisomic state involved chromosome 13. Patient 1 is only moderately retarded and lacks the characteristic congenital malformations of the D_1 syndrome (ocular defects, cleft palate, and polydactyly). These findings suggest that the chromosomal segments controlling these characteristic malformations of the D_1 trisomy syndrome may be located on the distal end of the D_1 chromosome and that those controlling fetal hemoglobin values and nuclear projections are probably situated on the proximal portion of chromosome 13. These conclusions are consistent with those of Yunis and Hook (1966).

Patient 2 provided an opportunity to utilize the information derived from the study of DNA replication, fetal hemoglobin, and nuclear projections to help interpret a complicated cytogenetic problem. The patient was a severely retarded child with multiple congenital anomalies. Her father was phenotypically normal, yet both had the same morphologic chromosome abnormality, which superficially appeared to be a reciprocal translocation between the long arms of a D and a chromosome 1. If both father and child did, in fact, have identical chromosome changes, then the abnormal features of the child could not be explained on the basis of the cytogenetic disturbance, since the father was phenotypically normal. (This argument assumes that neither the father nor the daughter is a mosaic and that the peripheral blood leukocyte cultures reflect the karyotypic findings in other tissues. Unfortunately, we have not been able to examine other tissues.) The congenital malformations in the proposita and her severely affected sib, however, are highly characteristic of the D_1 trisomy syndrome. This suggests that, although the chromosomes in both father and child are morphologically indistinguishable, there may have been some chromosomal rearrangement during paternal meiosis, so that the two are actually genetically dissimilar.

Lejeune and Berger (1965) recently described two families in which a phenotypically normal parent and malformed child both had the same morphologic chromosome abnormality. Grouchy (1965) and Grouchy *et al.* (1966) have also reported several instances in which a parent and child appeared to have the same chromosome disturbance; however, again, the parent was phenotypically normal and the child severely affected. As a balanced reciprocal translocation could not explain the observed difference in phenotype in these families, the authors suggested a complex chromosomal rearrangement followed by crossing over during meisois, a process referred to as "aneusomy by recombination," to account for the observed differences. This mechanism required that the original translocation arose not as the result of a simple two-break event but from at least three breaks with the insertion of a chromosomal segment. During meiosis, crossing over between the inserted segment and its homologue produces some gametes which are genetically unbalanced but which may not be grossly altered in their morphology.

The cytologic events of aneusomy by recombination that could have occurred during meiosis in the father of patient 2, with alteration of the genome but not the chromosome morphology, are depicted in Figure 8. The initial chromosome event requires three breaks with insertion of the middle portion of chromosome 13 into the distal portion of chromosome 1. If one crossover within the inserted segment occurs at meiosis, then a zygote may be formed with chromosome morphology resembling that of the father but which nonetheless is trisomic for the distal end of chromosome 13 and partially monosomic for the tip of chromosome 1.

It was hoped that DNA replication analysis of the chromosomes from both father and child would reveal a difference between the two. According to the hypothesis of aneusomy by recombination, the tip of the long arm of the translocated chromosome 1 in the child is actually the distal portion of chromosome 13, which is late labeling. In the father, this region should be derived from chromosome 1 and should complete DNA replication early and should, therefore, be unlabeled. No difference in the labeling pattern of the abnormal chromosome 1 in the father compared to the child, however, could be demonstrated. This might indicate that the original break in chromosome 1 occurred very near the tip and that the portion distal to the inserted segment is too small to be distinguished by autoradiography. If this interpretation is correct, then patient 2, who has many of the characteristic congenital malformations of the D_1 trisomy syndrome, is trisomic for only a small portion of the distal end of chromosome 13. This suggests that those chromosomal segments responsible for these malformations may be situated close together on the end of the long arm of chromosome 13.

No abnormalities in either the fetal hemoglobin value or neutrophil nuclear projection count were found in patient 2, as would be expected if the chromosomal segments governing these characters are situated close to the centromere and are not trisomic in this patient. Previous evidence (Bloom *et al.*, 1967; Gerald *et al.*, 1967) has suggested that the locus for the a chain of haptoglobin is situated on the tip of one arm, presumably the long arm (Bias and Migeon, 1967), of chromosome 13. Since patient 2 is thought to have inherited two distal 13 segments from the father, she could have inherited both of the father's haptoglobin genes (the father has Hp 2-1;
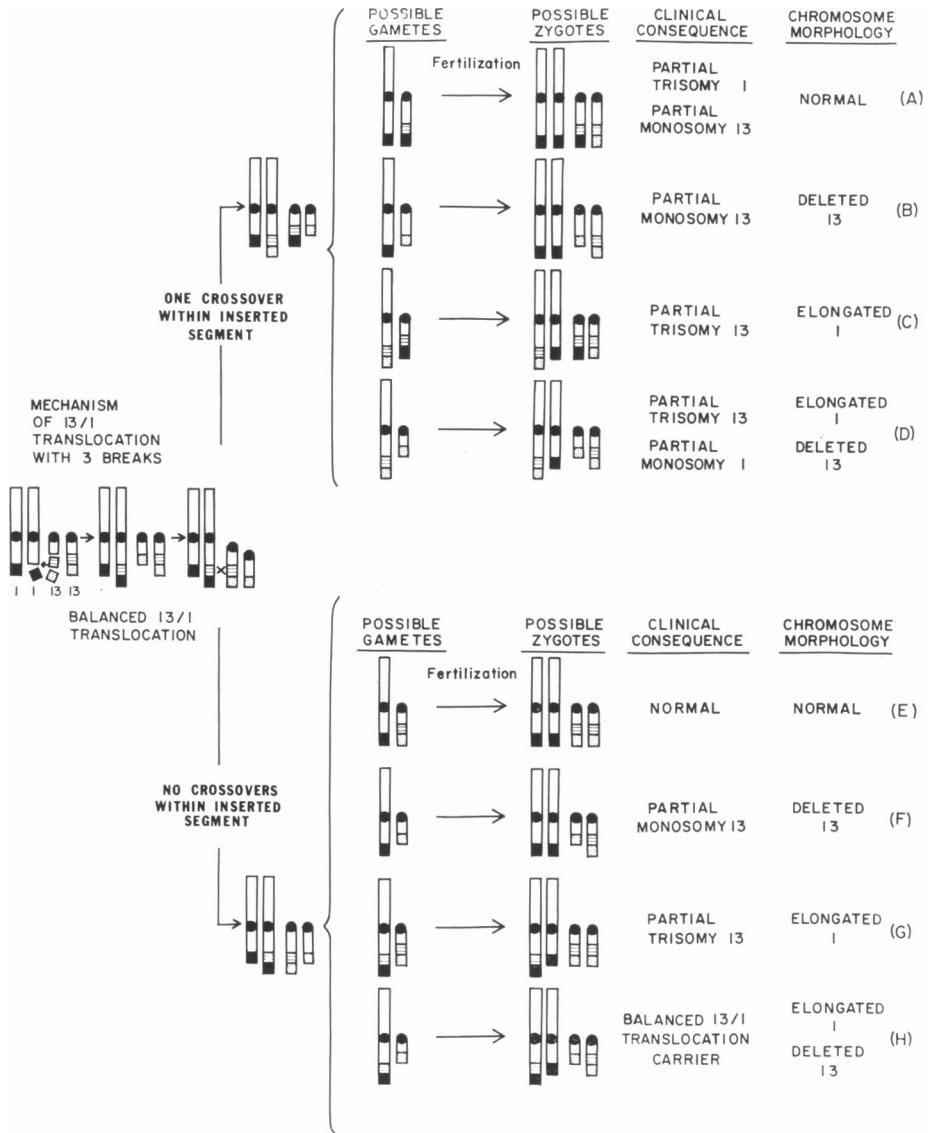
FIG. 8.—Schematic representation of possible meiotic events in the father of patient 2. It is postulated he has a balanced 13/1 translocation due to three breaks with insertion of a chromosomal segment. The possible zygotes formed after a crossover within the inserted segment are shown in the upper portion of the figure. In the lower portion, the possible zygotes formed after a two-strand double crossover or no crossovers are represented. Only zygotes (D) and (H) have the same chromosome morphology as the father. Zygote (H) is balanced like the father, whereas (D) is unbalanced. It is believed that the proposita represents zygote (D). It should be noted that only the gametes and zygotes found by the crossover strands are represented here, although at any chiasma point there are two noncrossover strands which are equally likely to be recovered.

the mother, Hp 2-2; the patient, Hp 2-2). Since the child does not have two different paternal haptoglobin genes, this suggests that, if the haptoglobin locus is at the distal end of the long arms of chromosome 13, then the trisomic portion in the child, which is thought to be small in size relative to the entire chromosome, perhaps does not include the haptoglobin locus. Alternatively, it is possible that the haptoglobin locus is included in the trisomic portion of the D_1 chromosome but that a further crossover event may have occurred which prevented the child from receiving both of the father's haptoglobin alleles (Fig. 9). The haptoglobin typings in family 1 showed no unusual inheritance patterns.

Grouchy *et al.* (1966) have discussed the genetic implications of complex multi-break chromosomal events. In the case of a two-break event, such as a reciprocal translocation between nonhomologous chromosomes, four types of gametes can be
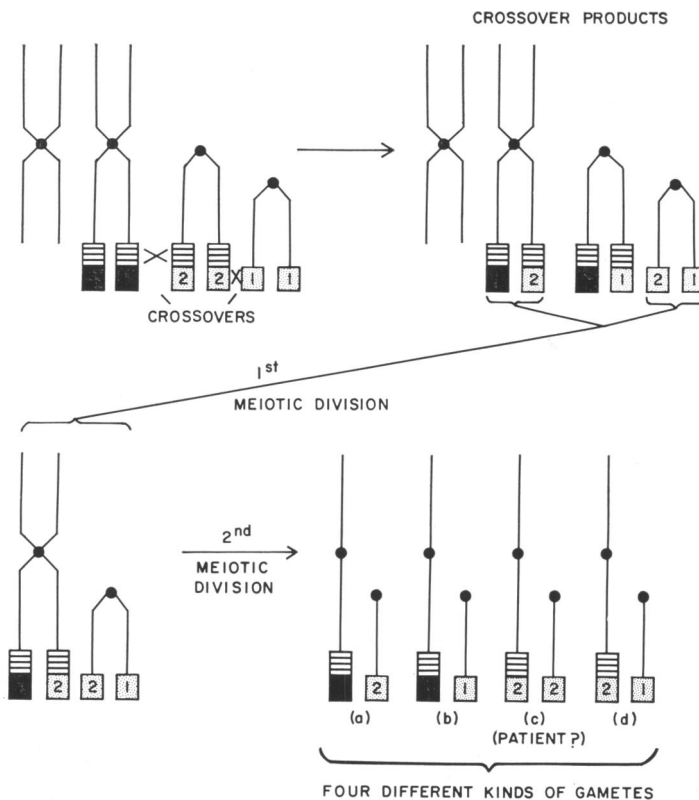

FIG. 9.—Schematic representation of meiotic events in the father of patient 2. Two crossover events are shown, which could lead to four different kinds of gametes with the same chromosome morphology as the father (if only crossover strands are considered). Gametes (a) and (b) are balanced and gametes (c) and (d) are unbalanced. The numbers in the boxes refer to haptoglobin types. The haptoglobin locus is depicted on the distal end of the long arms of chromosome 13 and is included within the triplicated segment. The proposita could have originated from either gamete (c) or gamete (d). Origination from gamete (c) could explain why the proposita did not receive both of the paternal haptoglobin alleles (see text).

expected. Two are genetically balanced and two are genetically unbalanced. This assumes that adjacent and alternate segregation are equally likely. If more than two breaks occur, however, followed by an insertion of a chromosomal segment (without inversion of the inserted segment) and with crossing over during meiosis, it is possible that the genetic risk in affected families may be greater than that expected with simple translocation. The increased frequency of miscarriages observed in families where aneusomy by recombination was postulated is consistent with this argument (Grouchy, 1965; Grouchy et al., 1966; Lejeune and Berger, 1965). If in family 2 an insertion has occurred and if one crossover occurs in the inserted segment with significant frequency, then an increased number of abnormal progeny will occur (Fig. 8, zygotes A, B, C, and D). Alternatively, the high miscarriage rate in this family could be due to segregation of the reciprocal translocation elements, although, as pointed out, this would not explain the findings in the propositus.

SUMMARY

Two patients with D (13-15) group chromosomal abnormalities are described. One patient was trisomic for the short arms, centromere, and proximal portion of the long arms of chromosome 13. Studies of the nuclear projection counts and fetal hemoglobin levels in this child were interpreted as evidence that genetic determinants controlling the levels of these hematologic parameters were located on the trisomic segment.

The second patient with multiple congenital abnormalities was found to have a translocation between chromosomes 13 and 1. Her phenotypically normal father had the same morphologic chromosomal disturbance. A complex chromosomal mechanism (insertion followed by crossing over) was invoked, and the findings were interpreted as showing that the proposita was trisomic for the tip of the long arms of chromosome 13. The normal nuclear projection count and fetal hemoglobin level in this patient were consistent with this hypothesis.

The findings in both patients were consistent with the hypothesis that the chromosomal segments responsible for the elevated fetal hemoglobin levels and increased neutrophil projection counts in trisomy 13 are located near the centromere of chromosome 13—and that the chromosomal segments producing the characteristic congenital malformations (ocular defects, cleft palate, and polydactyly) are near the distal end of the long arm. It must be emphasized that this is only a hypothesis at the present time.

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