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THE RELATIONSHIP BETWEEN CONGENITAL ANOMALIES AND AUTOSOMAL CHROMOSOME ABNORMALITIES‡

In the three years since convenient methods of human chromosome analysis have been available, three distinct syndromes involving an extra chromosome, other than the X-chromosome, have been described. The clinical findings in mongolism, the first of these three autosomal trisomies to be discovered, are generally known. The features of the syndromes associated with trisomy for a chromosome in the 13-15 group and 17-18 group are outlined in Table 1.

It is the purpose of the present study to delineate the relationship of multiple anomalies to trisomy more closely, to further describe the autosomal trisomic syndromes and to evaluate the clinical usefulness of chromosome determinations in patients with multiple anomalies.

METHODS

Ten children were studied, all of whom were selected on the basis of having multiple anomalies. Nine were from the Yale-New Haven Medical Center and one was from the Hospital of St. Raphael, New Haven, Connecticut. Leukocyte cultures from peripheral blood (5-10 ml.) and chromosome preparations were made by a modification[1] of the procedures described by Moorhead, *et al.*[2]

Of the 10 children studied, four were found to have autosomal trisomy. The clinical findings and their significance are discussed below.

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TABLE 1. ANOMALIES ON TRISOMY 13-15 AND 17-18

Anomaly	*No. of cases with anomaly*	
	Trisomy 13-15	*Trisomy 17-18*
A. *Features characteristic of trisomy 13-15*		
Deafness	6/8	0
Seizures	6/8	0
Capillary hemangiomata	6/7	0
Hyperconvex fingernails	4/6	0
Horizontal palmar creases	5/7	1/15
Polydactyly	8/10	1/15
Cleft lip	6/9	1/15
Cleft palate	7/9	1/15
Eye defect	9/10	2/12
B. *Nonspecific features*		
Mental retardation	9/9	15/15
Congenital heart defect	8/10	13/14
Low-set ears	6/7	14/14
Flexion of fingers and hands	4/6	13/13
Abnormally shaped head*	4/6	10/15
C. *Features characteristic of trisomy 17-18*		
Micrognathia	1/6	12/12
Looseness of neck skin	1/6	5/11
Renal anomaly	2**/10	8/14
Syndactyly	1/10	5/12
Hernia (inguinal and/or umbilical)	1/10	6/12
Dorsiflexion of hallux	0	7/7
Spasticity	0	10/11
Malformed ears	0	14/14
Meckel's diverticulum	0	5/5
Malformed ribs	0	3/3
Malformed sternum	0	9/10
Polyhydramnios	0	5/5

0 No cases reported.

* In trisomy 13-15 the predominant abnormality has been a temporal narrowing and in trisomy 17-18 a prominent occiput has been described in most of the cases.

** One case probable.

TRISOMY 17-18

Thirteen cases of trisomy for 17-18, associated with multiple anomalies, have been previously reported.[8-9] The similarity of the clinical picture suggested that this was a distinct clinical entity.[4] The findings in this syndrome are summarized in Table 1. The following reports describe two additional cases of trisomy 17-18. Cytological observations are presented in Table 2.

TABLE 2. CYTOLOGICAL FINDINGS*

	Number of cells with various chromosome counts						
Case	*<45*	*45*	*46*	*47*	*>47*	*No. of karyotypes*	*Results*
1	1	2	3	44	0	9	Trisomy 17-18
2		2	2	48	1	6	Trisomy 17-18
3	2	2	3	38	2	5	Trisomy 13-15
4	0	1	3	44	3	5	Trisomy 21-22
5	1	2	21	0	1	5	Normal
6	2	1	23	0	1	5	Normal
7	4	2	36	0	0	5	Normal
8	1	1	19	0	0	2	Normal
9	2	1	23	0	0	5	Normal
10	0	3	46	1	0	5	Normal

* Chromosomal complement of leucocytes cultured from the peripheral blood of ten children with multiple congenital anomalies. The sex chromosomes were compatible with the phenotypic sex in each case.

Case 1. N.S. (Y-NH 54-96-90), a 4 lb. 12 oz. girl, was cyanotic at birth. Two siblings were in good health and except for a maternal age of 40 and paternal age of 30 the family history was unremarkable. Because of cardiomegaly, tachycardia and a loud systolic murmur the infant was digitalized. She failed to gain weight, had many choking spells with feeding and was transferred to the Yale-New Haven Medical Center at 2½ months for further evaluation. At this time her weight was 5lb. 3oz., head circumference 35.5 cm., and length 49 cm., all values being well under the 3rd percentile of expected values. Her mental development was also felt to be significantly retarded. Physical findings included a loud systolic murmur and thrill over the precordium with a prominent left chest, micrognathia, high arched palate, low-set, pointed ears with poor cartilage formation, proximal displacement of the thumbs with abnormal abduction, diastasis recti, legs which could not be abducted more than 30°, ulnar deviation of the 3rd, 4th and 5th fingers, small labia and a prominent clitoris. Neurological examination revealed decreased tone in prone and supine positions. When suspended the lower extremities became extended. The head was not pulled up when she was lifted by both arms and tonic neck reflexes were not consistently elicited. An X-ray examination revealed a prominent occiput, with poorly ossified bones over the skull and a small mandible (Fig. 1). An angiocardiogram was suggestive of patent

ductus arteriosus with an interventricular septal defect. Electrocardiography revealed biventricular hypertrophy.

The child continued to do poorly with many bouts of choking and aspiration and periods of apnea, suggestive of Cheynes-Stokes respiration. It was felt that the child was an example of the Pierre Robin Syndrome in that she had unusually shaped ears, high arched palate, micrognathia and that glossoptosis played a significant role in the choking spells. A Douglas tongue-tying procedure was performed in an attempt to alter the choking spells. The spells continued, however, and she died aged three months when ventricular fibrillation followed intubation.

Culture of peripheral white cells revealed 47 chromosomes and trisomy for 17 or 18 (Fig. 2). At autopsy, in addition to the known anomalies, the following were also noted: antimongol slant to eyes, right and left ventricular hypertrophy with a 6 mm. pulmonary artery and a 4 mm. aorta, patent ductus arteriosus, and an aorta slightly juxtaposed to the right, over-riding an interventricular septal defect in the region of the membraneous septum. Many small, grape-like clusters of myxomatous material were seen on the chordae tendineae and valves. The kidney was horseshoe-shaped with fusion occurring at the lower poles and was situated lower in the abdominal cavity than usual. The pelvis of the right kidney was divided in two but joined at a lower point to form one ureter. The ovaries were long, thin string-like structures, 3 cm. in length and 2-3 mm. in width. A section revealed a normal number of follicles and a slight increase in fibrous tissue but the histology was interpreted as being within normal limits. Although the ovaries were somewhat longer than usual, it seemed most likely that the findings represented a normal variant. A buccal smear was not carried out but the mucosal cells of the uterus showed a single chromatous body in over 80 per cent of the cells in the sections prepared at autopsy. The brain was grossly normal, but one of four coronal sections revealed an abnormal, approximately mid-frontal gyrus which showed probable arrested development (Fig. 3). The report of the microscopic examination follows: "At the apex of the gyrus there is a slight protrusion extending to the meninges where there is loss of the usual cortex. This is replaced by an irregular forking mass of primitive-appearing cells, some of which appear to be oligodendria, others astrocytes, and others blastema. These form a central dense core surrounded by other undifferentiated cells. A few of these cells have the appearance of neurons in the Nissl preparation. The immediately adjacent cortex suddenly comes to an end with just a few focal collections of neurons. The deeper portions of this gyrus show the normal configuration of the cortex. This is interpreted as a variant of microgyria."

This case differs from other infants with trisomy 17-18 in that a number of anomalies which have not been previously reported were observed. These included glossoptosis, hypotonia, antimongol slant to the eyes, abnormal thumbs, microgyria, and abnormal genitalia. Other findings, as can be seen in Table 2 were typical of trisomy 17-18. The presence of a localized abnormal development of the cerebral cortex in a trisomic child, and the clinical diagnosis of Pierre Robin Syndrome are of particular interest.

Case 2. S.R. (HSR 5683), a boy, was born at the Hospital of St. Raphael following a pregnancy complicated by polyhydramnios and postmaturity in a 42-year-old mother. The father was also aged 42. Two older siblings were normal and the family history

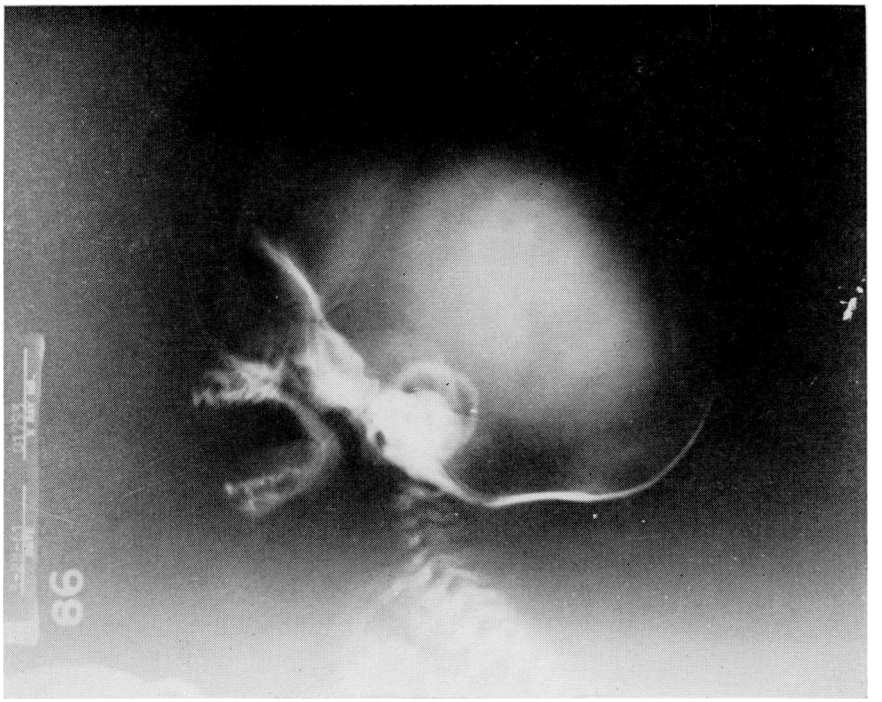

FIG. 1. Skull film showing the characteristic prominent occiput and micrognathia (Case 1).

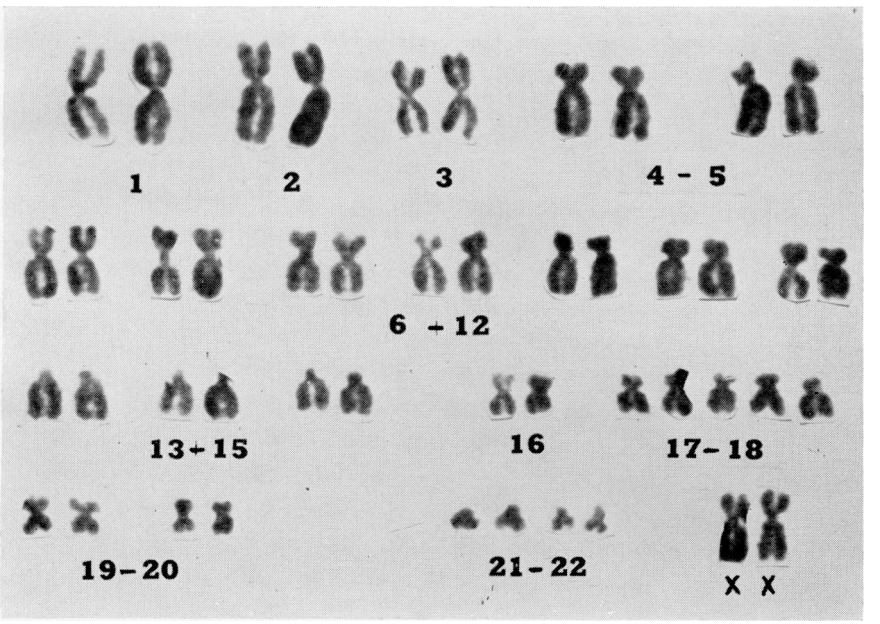

FIG. 2. The karyotype in Case 1. The extra chromosome in the 17-18 group did not consistently resemble chromosome 18 more than 17.

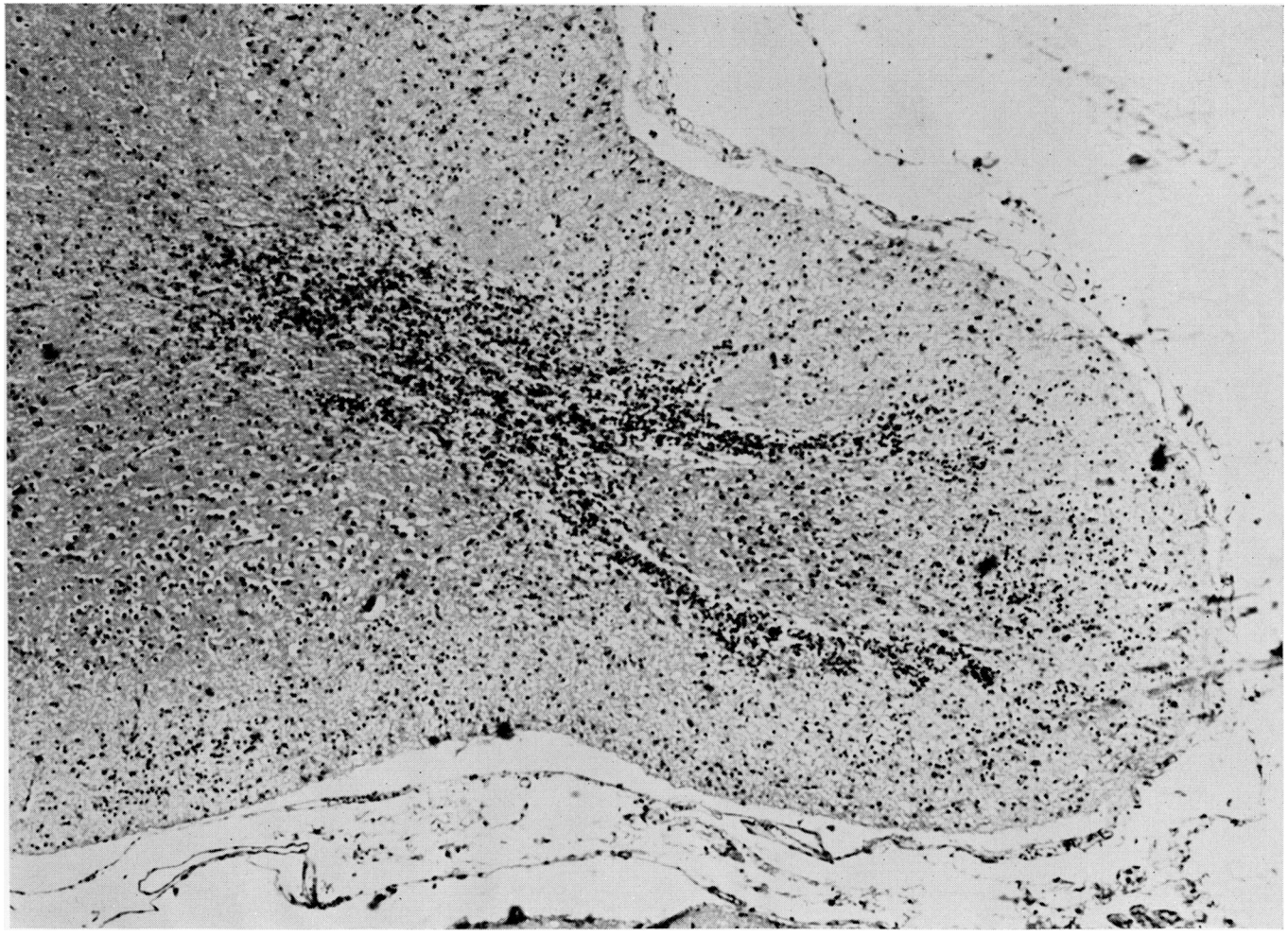

FIG. 3. A transverse section through a mid-frontal gyrus (Case 2, orig. mag. 300X). Note the small size of the gyrus and the primitive appearance of the dark staining cells in the center.

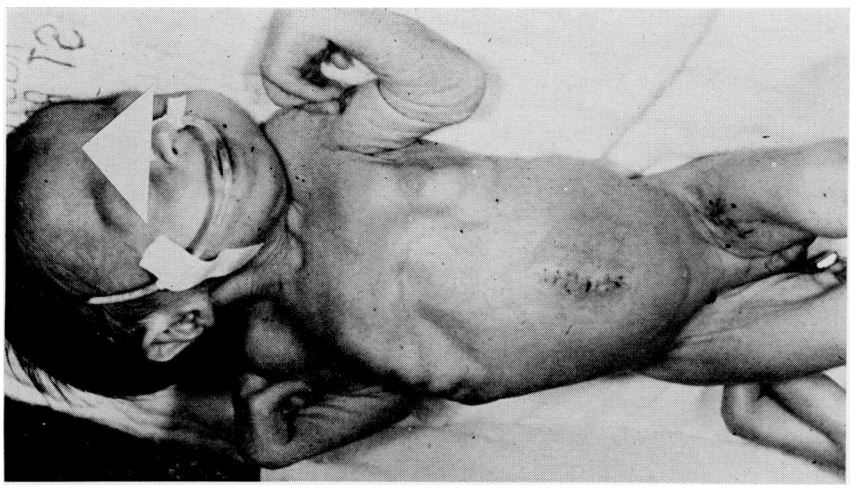

FIG. 4. Photograph of Case 2 showing many of the typical findings in trisomy 17-18, including flexion contractures, overlapping of the 3rd and 4th fingers, abnormal ears, small jaw, abnormal sternum and ribs, and a repaired omphalocele.

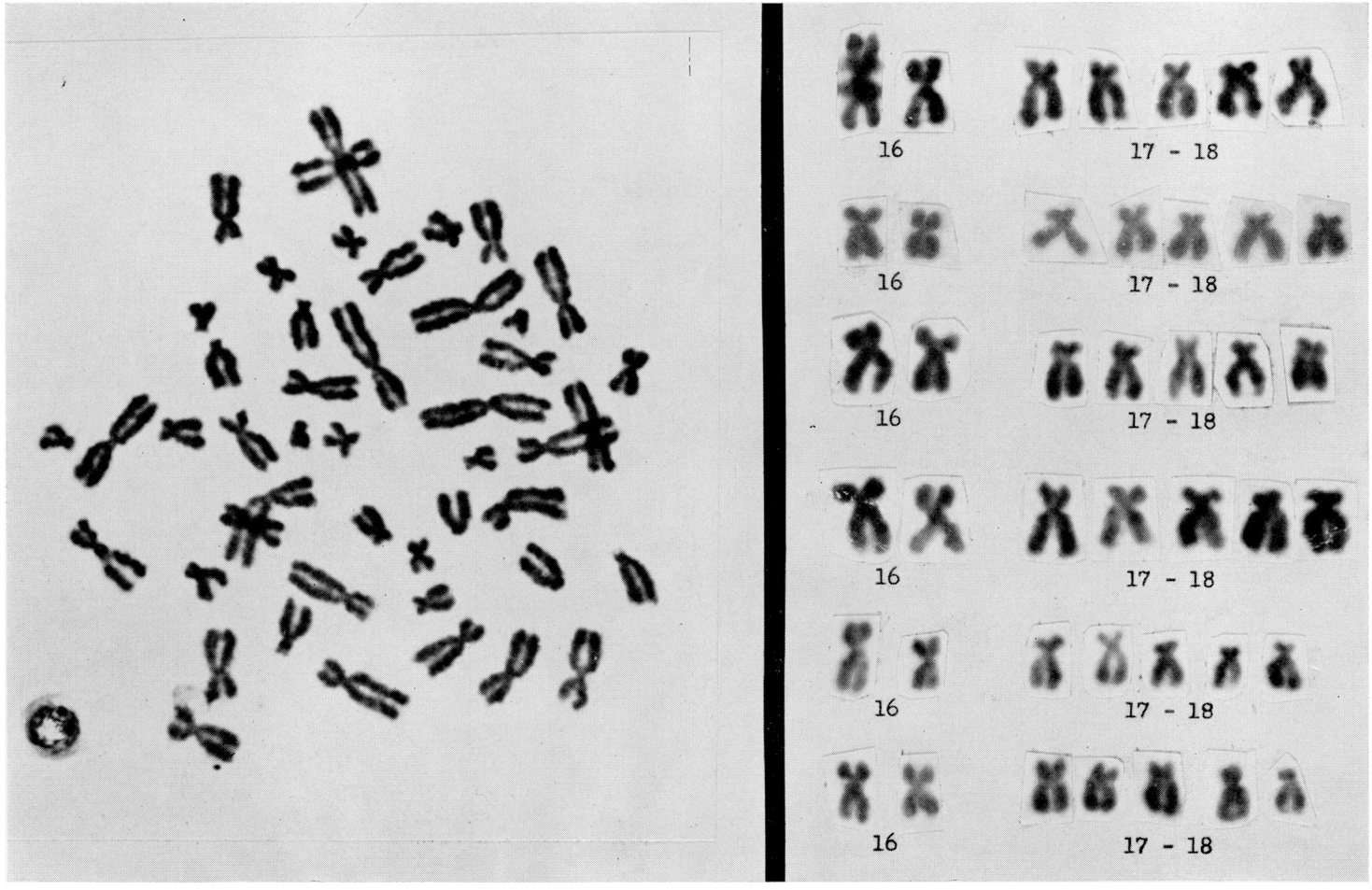

FIG. 5. To the left is a metaphase nucleus from Case 2. At right are chromosomes 16-18 from the six cells studied in detail. An extra chromosome resembling 17 or 18 is present, but the distinction between 17 and 18 cannot consistently be made.

was unremarkable. Multiple anomalies were noted at birth, the most striking of which were contractures and spasticity (Fig. 4). Additional findings included persistent cyanosis, small chin, low-set, abnormally-shaped, pointed ears, high-arched palate, cloudy right cornea, pulmonic systolic ejection murmur over the precordium, omphalocele, flaccid thumbs, and great toes which were set back. A prominent occiput was not noted. An electrocardiogram revealed only low T waves. X-ray studies revealed a slightly enlarged heart and prominent pulmonary vasculature suggestive of a left to right shunt, but no definitive diagnosis of the type of congenital heart disease was made. Fusion of the sternal segments was also noted. His course was marked by choking and apneic spells, aspiration pneumonia, and feeding problems requiring intubation. On the basis of these findings, using an earlier version of Table 1, a clinical diagnosis of trisomy 17-18 was made and was confirmed by chromosomal analysis (Fig. 5). The child did poorly, with a decrease in weight from 5 lbs. 3 ozs. at birth to 3 lbs. 4 oz. and expired 6 weeks after birth. Autopsy permission was refused. Other abnormalities listed in Table 1 were not present.

This infant had the typical findings of trisomy 17-18, and could also be considered an example of the Pierre Robin Syndrome. The degree of flexion and contractures was more marked than in prior cases. It was not possible to determine whether the extra chromosome was 17 or 18 in this case or in Case 1 (Fig. 5). In Case 2 there was a discrepancy in size of the pairs of chromosome 16 (Fig. 5). Whether or not this represents an additional abnormality is difficult to state with certainty, but this variation is greater than usually seen by the authors.

TRISOMY 13-15

Trisomy has also been reported for group 13-15.[10-18] The following is a summary of a case previously reported by the present authors.[17] This was the only child found to have trisomy for a chromosome in group 13-15. Cytological observations are presented in Table 2.

Case 3. B.S. (Y-NH 54-85-30), a girl, was born at the Yale-New Haven Medical Center to a 33-year-old mother and a 32-year-old father. Family history revealed that a maternal grandfather had died of acute leukemia.

At birth bilateral cleft lip and palate, capillary hemangiomata over the suboccipital, lumbar, and pilonidal areas, polydactyly of both hands and the left foot and bilateral horizontal palmar creases were observed. The head was narrowed in the temporal regions. There was marked recession of the mandible, and the skin at the nape of the neck was extremely flabby. The sagittal suture was open (7 cm. wide) from the occiput to the bridge of the nose. The eyes appeared normal, with slight hypertelorism. The ears were low-set and small. Two retroperitoneal masses were suggestive of polycystic kidneys. On the third day of life a harsh pansystolic murmur and faint thrill were noted along the left sternal border with radiation to the apex and to the back in the midline. The muscles were generally hypotonic. At six weeks of life the child showed no interest in her surroundings, and she seemed to be severely retarded. She

did not react to the ringing of a bell, but she did react to light by blinking. No eye defects were noted, and her fundi appeared normal. An intravenous pyelogram revealed enlargement of the right kidney and dilatation of the calyces on the right. Radiographs also showed a lacunar skull and severe hypoplasia of the mandible. On the 50th day of life she had a right-sided seizure—first tonic and then clonic. She was discharged on the 63rd day to a children's convalescent hospital. She died seven weeks later, and necropsy was not performed.

This child is the only instance of trisomy for a chromosome in the 13-15 group in which an abnormality of the eye was not demonstrated. Findings not noted in previous cases include looseness of the skin at the nape of the neck, a wide open sagittal suture and micrognathia. Nevertheless, the many other characteristic anomalies such as polydactyly with capillary hemangioma and cleft palate permit inclusion of this child in this syndrome. Although no single anomaly has been reported in all cases of trisomy 13-15, the high frequency of certain anomalies justifies calling this a definite syndrome[17] as can be seen in section A of Table 1.

MONGOLISM (Trisomy 21-22)

Mongolism (Down's Syndrome) was the first clinical syndrome to be associated with an autosomal chromosome obnormality.[19] The latter was found to consist of the presence of an extra chromosome 21, and was thus called trisomy 21; a number of cases, however, have subsequently been reported to have several types of translocation.[20, 21] In these patients, although the chromosome count is 46, the translocated material is sufficiently large that the patients are effectively trisomic for 21. The following report is a case study of a child exhibiting many features typical of mongolism who had trisomy 21-22. Cytological observations are presented in Table 2.

Case 4. R.T. (Y-NH 54-96-90), a boy, was born at the Yale-New Haven Medical Center to a 25-year-old Negro mother, and a 26-year-old father. Family history failed to reveal any significant disorders.

At seven months of age a diagnosis of mongolism was made in clinic and the following abnormalities noted: nystagmoid movements of the eye, bilateral epicanthic folds, broad base of the nose, high-arched palate, small incurved little fingers, rudimentary 2nd phalanx, increased space between the first and second toes, simian lines bilaterally and a small urethral meatus.

At 19 months hypotonia, mental and physical retardation, a patent anterior fontanelle, cardiomegaly and left spastic hemiplegia of undetermined etiology were noted. The child died suddenly at 26 months of age. Autopsy findings, in addition to the aforementioned congenital abnormalities, included: fatty change in the liver, an extensive right cerebral infarct occurring secondary to complete occlusion of the right internal carotid artery, and a patent anterior fontanelle.

While the initial impression in clinic was that the patient had mongolism, this was not the opinion during a prolonged admission and at the time of autopsy. The cytological findings of trisomy 21-22, however, confirmed the initial impression, and demonstrated the usefulness of such determinations in obscure clinical situations.

DISCUSSION

From Table 1 it can be seen that the 13-15 trisomy syndrome is distinct from that associated with trisomy 17-18. There are, however, several major anomalies which are found quite frequently in both syndromes. These are: mental retardation, congenital heart defects, low-set ears, and flexion deformities of fingers and hands. Mental retardation has also been noted as a frequent finding in many of the other chromosome abnormalities including mongolism, Klinefelter's Syndrome (XXY),[22] triple X[23, 24] and other less common sex chromosome abnormalities. Low-set ears and congenital heart disease are also found commonly in mongolism.[25, 26] It appears therefore that these anomalies are not specifically associated with one type of chromosome abnormality. Why these anomalies should be associated with so many different types of trisomy is not clear. Unless it is a nonspecific effect of trisomy for any chromosome, which seems unlikely, the best explanation probably lies in the complexity of the developmental processes in the heart and brain in particular. This complexity might permit alteration in the normal process at many points, yet still result in a sort of developmental phenocopy. Indeed, the finding of an abnormal mid-frontal gyrus in Case 1 may be one example of a specific abnormality contributing to what is lumped together in ignorance as mental retardation. Similarly, while interventricular septal defects have occurred with both trisomy 13-15 and 17-18, a patent ductus commonly occurs with trisomy 17-18 in contrast to several patients with trisomy 13-15 who have had dextrorotation of the heart.

Other anomalies associated with trisomy 17-18 and 13-15, however, appear to be related to the presence of a specific chromosome abnormality. These anomalies are much more useful diagnostically and are listed in the sections A and C of Table 1. The most unique features of trisomy 17-18 are malformed ears, micrognathia, spasticity, malformed sternum and probably polyhydramnios and dorsiflexion of the hallux. Trisomy 13-15, on the other hand, is best diagnosed on the basis of such findings as polydactylia, capillary hemangiomata, cleft palate and an eye defect. The relationship of individuals with similar anomalies and normal karyotypes to these with trisomy will be discussed in the next section. The anomalies in section B of Table 1 are not defined more precisely in order to reflect the

clinical situation at birth rather than at autopsy or after extensive cardiac evaluation.

Case 2 resembled quite closely, both in clinical course and the congenital anomalies present, cases of the Pierre Robin Syndrome.[27, 28] This syndrome has been variably defined, but the essence seems to be the presence of micrognathia and glossoptosis leading to choking spells, relieved by placing the infant on its stomach, and feeding problems, variably relieved by positioning. Many anomalies which occur in trisomy 17-18 have been described in association with these findings and include: congenital heart defects, anomalies of the hands and feet, low-set, malformed ears, flattened base of the nose, bird-like face, eye defects, mental retardation and failure to thrive. Although Case 3 is the only one in which glossoptosis has specifically been described, most of the reported cases of trisomy 17-18 have mentioned apneic spells and feeding problems. Both of these were of major importance in Case 2. It seems likely, therefore, that many of the cases that have ben termed Pierre Robin syndrome in the past were instances of trisomy 17-18. It is of interest that one of the photographs in Robin's article[27] shows a marked similarity to Case 2, with a short sternum, abnormal ears, and possibly flexion of the fingers. No complete description of the infant was given. Smith, *et al.*[4] have previously commented on the similarity of the facial appearance of these infants to that described by Potter in children with renal agenesis,[29] several of whom had multiple contractures. It will be of interest to study the chromosomes in more infants with both of these syndromes.

Trisomy probably results most commonly from an abnormal first meiotic division, in which a pair of homologous chromosomes fail to disjoin, leading to a gamete with 24, rather than 23 chromsomes. Following fertilization with a normal gamete, three rather than two homologous chromosomes are present in the cells of the resulting individual (trisomy) with a total count of 47 chromosomes. Little is known, however, about the mechanism by which trisomy produces congenital anomalies. Any theory must encompass the two normal patients with trisomy[21, 30] as well as individuals with both severe and borderline stigmata of a particular trisomy. Perhaps simple variation in the genetic content of the homologous chromosomes is the explanation. It is, however, possible that the degree of similarity of the two chromosomes which did not separate during meiosis affects their biological behavior. Two factors are crucial in this regard: whether nondisjunction occurs at first or second meiotic division, and the amount of crossing over at the first meiotic division. In the absence of any crossing over at first meiosis, nondisjunction at first meiosis (where homologous

chromosomes are paired) would lead to a situation in which both chromosomes were genetically different. In contrast, nondisjunction at the second meiotic division (where the two chromatids of a chromosome separate) would result in two identical chromosomes in the gamete. In instances where only one or two crossovers occur the latter condition would be approximated for large portions of the two chromosomes in a gamete following nondisjunction at second meiosis. Following fertilization, two of the three homologous chromosomes would carry identical information over much of their length and it is possible that this might result in a less abnormal condition. If this is correct, then a possible explanation is provided for the occurrence of such widely different manifestations of trisomy 21-22 as the child reported by Zellweger, *et al.*[81] (Case 1) with mental retardation, epicanthic folds and hypotonia, and the child reported by Dunn, *et al.*[82] with hypotonia, but without mental retardation. Neither appeared mongoloid. It is apparent, particularly if one includes the one case of Sturge-Weber Syndrome with trisomy 21-22,[83] that there are more syndromes associated, at least at times, with trisomy of this group than can be accounted for on a "one trisomy—one syndrome" basis. Perhaps the mildly affected cases of Zellweger, *et al.* and Dunn, *et al.* are instances where nondisjunction occurred at the second meiotic division and two of the three homologous chomosomes are quite similar. Future improvements in techniques should provide a means of testing this hypothesis.

CASES WITH NORMAL KARYOTYPES

Six of the ten children selected for study because of their multiple congenital anomalies were found to have normal chomosome counts and karyotypes. Their clinical findings are presented below and the cytological observations in Table 2.

Case 5. T.F. (Y-NH 55-07-22), a boy, was born to a 17-year-old mother. The father was 18 at the time. Family history was unremarkable. Abnormalities observed at birth included: widely set eyes, poorly formed nose, a large bilaterally cleft lip and palate, abnormal genitalia with a 1.5 cm. phallus, a bifid scrotum containing testes and severe hypospadias, bilateral inguinal herniae and an imperforate anus. At three months of age the child's growth and development appeared to be normal for his age.

Lack of mental retardation and a maternal age of 17 were strong points against trisomy in this child (cf. Table 3).

Case 6. D.O. (Y-NH 54-39-07), a girl, was born to a 20-year-old mother. The father was 21 at the time. There was no family history of congenital abnormalities. At birth the baby was noted to have widely set eyes, low-set ears, a small face, nasal deviation, deformed cranium with a meningocele, short extremities, clitoral hypertrophy,

TABLE 3. INCIDENCE OF CONGENITAL ANOMALIES IN SIX CHILDREN WITH NORMAL CHROMOSOME KARYOTYPES

	Case number							*Trisomy*		
Anomaly	*5*	*6*	*7*	*8*	*9*	*10*	*Incidence*	*13-15*	*17-18*	*Mongolism (21-22)*
Mental retardation	—	+	+	+	+	+	5/5	9/9	15/15	++
Palate defect	+	+	+	+	+	+	6/6	7/8	3/15	++
Cleft	+	—	—	+	+	—	3/6			
High-arched	—	+	+	—	+	+	4/4			
Abnormally shaped head	—	+	+	+	+	+	5/6	4/6	10/15	++
Low-set ears	+	+	—	+	—	—	3/6	6/9	14/14	+
Congenital heart defect	+	—	—	—	+	+	3/6	8/10	13/14	++
Micrognathia	+	+	—	+	—	—	3/6	1/6	12/12	—
Hypotonia	—	—	+	—	+	—	2/6	2/5	1/12	++
Renal anomaly							2/6	2/10	8/14	—
Hydronephrosis	+	—	—	—	—	—	1/6		2/5	
Unilat. agenesis	—	—	+	—	—	—	1/6		—	
Broad nose base	—	—	+	—	+	—	2/6	—	2/3	++
Epicanthic folds	+	—	+	—	—	—	2/6	—	—	++
Clitoral hypertrophy		+		+	—		2/3	—	1/12	+
Decreased labia size		+		—	—		1/3	—	1/12	+
Mongol slant to eyes	—	—	+	—	—	—	1/6	—	—	++
Antimongol slant to eyes	—	—	—	—	+	—	1/6	—	1/12	—
Protruding tongue	—	—	+	—	—	—	1/6	—	1/12	++
Horizontal palmar crease	—	+	—	—	—	—	1/6	5/7	1/15	++
Missing phalanx	—	+	—	—	—	—	1/6	—	—	++
Increased gap 1-2 toe	—	+	—	—	—	—	1/6	—	—	++
Syndactyly	—	+	—	—	—	—	1/6	1/10	5/12	+
Talipes equinovarus	—	—	+	—	—	—	1/6		1/2	+
Umbilical and/or inguinal hernia	+	—	—	—	—	—	1/6	1/10	6/12	+
Eye defect (colobomata to micropthalmia)	—	+	—	—	—	—	1/6	9/10	2/12	+
Strabismus	—	—	—	—	—	+	1/6	—	—	+
Ptosis	—	—	—	—	—	+	1/6	—	1/12	+

TABLE 3. Continued

	Case number							*Trisomy*		
Anomaly	*5*	*6*	*7*	*8*	*9*	*10*	*Incidence*	*13-15*	*17-18*	*Mongolism (21-22)*
Short extremities	—	+	—	—	—	+	2/6	—	—	++
Metatarsus varus	—	—	+	—	—	—	1/6	—	—	—
Nose: beak	—	+	—	—	—	—	1/6	—	—	—
poorly formed	+	—	—	—	—	—	1/6	—	—	—
small	—	—	—	—	—	+	1/6	—	—	—
Small face	—	+	—	—	—	—	1/6	—	—	—
Maxillary hypoplasia	—	—	—	—	—	+	1/6	—	—	—
Closely set eyes	—	—	—	—	—	+	1/6	—	—	—
Intrahepatic biliary obstruction	—	—	—	—	—	+	1/6	—	—	—
Imperforate anus	+	—	—	—	—	—	1/6	—	—	—
Port-wine stains	—	—	—	—	—	+	1/6	—	—	—
Bifid scrotum & hypospadias	+		—			—	1/3	—	—	+
							Mean	Mean	Mean	
Maternal age	17	20	23	26	34	24	25.6	32.5	37	36.6[41]
Paternal age	18	21	30	30	35	30	27.3		40.6	

++ = Usually present.
\+ = Present (in reference to mongolism means present infrequently).
— = Absent, rare, or information inadequate.

decreased size of the labia majora and minora, and syndactyly of the toes bilaterally. She had severe craniostenosis with a head circumference of 10¾ inches. Skull films revealed marked deformity of the cranial bones with evidence of hypoplasia and prominence of the convolutional markings in the inner table of the skull. Underdevelopment of the orbits and small palpebral fissures were noted.

At four months of age additional abnormalities were noted: micrognathia, high-arched palate, simian line of the right hand, no apparent proximal interphalangeal joint on the fingers of both hands, and the fifth fingers were very small. The hallux was separated from the other toes by a deep crease with syndactyly between the second and third toes bilaterally. At nine and a half months it was apparent that the patient was mentally retarded, functioning at a five to six month level.

In spite of many features suggestive of each of the three trisomic syndromes the karyotype was normal.

Case 7. L.S. (Y-NH 53-70-96), a boy, was born at the Yale-New Haven Medical Center to a 23-year-old mother. The father was 30 at the time. Family history revealed that a diabetic maternal grandfather was confined in a mental hospital and a maternal uncle had cerebral palsy and a club foot. The mother of the baby appeared to be of limited intelligence.

At birth congenital anomalies noted included: generalized hypotonia, rounded head, epicanthic folds, mongol slant to the eyes, a broadened nose base, a small preauricular tag on the right, a high-arched palate, left talipes equinovarus and metatarsus varus on the right.

At 10 months of age, mental retardation was noted. Intravenous pyelograms failed to reveal any renal function on the left. The pelvis was noted to be unusual with tapering of the ischial pubic rami, flat acetabullar roofs and outward splaying of the iliac wings. The iliac index was 58 (in the range for mongolism). All these findings were thought suggestive of mongolism.

This child had so many features of mongolism that one wonders if he is not a mosaic for 21 or an instance of partial trisomy which is not cytologically detectable. These possibilities are considered further in the discussion.

Case 8. L.H. (Y-NH 54-12-46), a girl, was born to a 26-year-old mother and 30-year-old father. Family history was non-contributory. At seven months of age the following abnormalities were noted: dysostosis of the frontal and parietal bones with a large defect measuring 11 x 20 cm., low-set ears and cleft soft and hard palate.

At 18 months, moderate micrognathia was noted as well as severe growth retardation. At 22 months her height was 27 inches (50th percentile for an 8-month-old child). Her weight was 5750 g. (50th percentile for a 3-month-old child). A moderately enlarged clitoris as well as small palpebral fissures were noted at this time. It was felt that the patient, because of her severe growth retardation, was an example of a primordial dwarf. Mental retardation was also present.

Again, an average maternal age and normal mental development were points against trisomy.

Case 9. D.W. (Y-NH 54-95-69), a girl, was born to a 34-year-old mother. The father was 35 at the time of the child's birth. Family history was non-contributory. At birth flaccidity of both extremities and a cleft palate were noted. At two years of age she was admitted to the Yale-New Haven Medical Center for evaluation of developmental retardation and hypotonia. The following abnormalities were found on physical examination: abnormally shaped head, antimongoloid slant to the eyes, ptosis of the right lid, high-arched, cleft palate and a flat bridge of the nose. A to-and-fro murmur was heard along the left sternal border and chest films revealed left atrial and biventricular enlargement. The findings were thought to suggest an interventricular septal defect.

In addition to the aforementioned abnormalities, neurological examination revealed generalized flaccidity and hypotonia of the lower extremities. A diagnosis of hypotonic diplegia was made and it was felt that the neurologic disorder was the result of lesions involving the cerebellum and cortical-spinal tracts.

None of the features characteristic of trisomy 17-18 or 13-15 were present.

Case 10. R.D. (Y-NH C 29733), a boy, was born at the Yale-New Haven Medical Center to a 24-year-old mother. The patient's father was 30 at the time. Family history was non-contributory. At one week of age increasing jaundice was noted, as well as the following anomalies: prominent frontal and parietal bossing, port-wine stains over the occipito-parietal area of his head and an enlarged liver. Surgical exploration at four months of age revealed a normal extrahepatic ductal system. It was felt that there was biliary obstruction but that it was intrahepatic. The patient, subsequently, has been noted to have peculiar facies with a small nose, closely set eyes, and a hypoplastic maxilla. Other abnormalities include: high-arched palate, small hands and feet, alternating strabismus and mild retardation.

A systolic murmur which radiated to the axilla and back, first noted at four months of age, still persists at age 13, but without clinical symptomatology related to cardiac disease. Electrocardiograms show right axis deviation with incomplete right bundle branch block. The possibility of an interatrial septal defect or anomalous venous return has been suggested.

This boy had a rather unusual set of anomalies, including a peculiar sunken facies and intrahepatic biliary obstruction.

DISCUSSION

Table 3 lists the frequency of anomalies observed in the six cases with normal karyotypes. The incidence is compared with certain anomalies occurring in the three autosomal trisomy syndromes which have been discussed. Anomalies found in the latter, but not found in the children with the normal chromosome karyotypes, are not included in the table.

As can be seen from the table, certain types of congenital anomalies appear to occur frequently not only in the three autosomal trisomy syndromes but also in children with multiple congenital anomalies and normal chromosome karyotypes. Mental retardation, abnormally shaped head, low-set ears, palatal defects, and congenital heart defects were found in all the groups studied. Other congenital anomalies found to be present in at least a few of the children with normal chromosome karyotypes, and also reported in at least one type of autosomal trisomy include: micrognathia, hypotonia, broad base of the nose, renal anomaly, and epicanthic folds.

One child in the group of children with normal chromosomes (Case 7) was considered to be a possible mongoloid. As can be seen from Table 3, he did have many of the stigmata of mongolism, especially hypotonia, epicanthic folds, broad nose base, mongol slant to the eyes, and a protruding tongue. In addition, radiographic findings of the pelvis proved compatible with a diagnosis of mongolism. However, no additional chromosome material was found. It seems possible, however, that trisomy for 21

would have been found if a tissue other than blood had been studied, and that he was a mosaic for 21.

Another possible explanation of the similarity of clinical findings in some children with normal chromosome karyotypes to the clinical findings in children with the autosomal trisomy syndromes is based on the concept of partial trisomy. This possibility was suggested by Patau, *et al.*[34] to explain the recent findings in the Sturge-Weber Syndrome. Hayward and Bower in 1960[38] reported trisomy for chromosome 22 in a patient with the Sturge-Weber Syndrome. In other cases of the Sturge-Weber Sydrome which have been studied trisomy 22 was not found, but normal karyotypes with 46 chromosomes were reported.[34-40] However, Patau, *et al.*[34] did find one Sturge-Weber case in which there was a translocation of a fragment resembling the short arms of 22 onto a chromosome of the 13-15 group. From this finding he postulated the existence of a partial trisomy syndrome for Sturge-Weber in which the extra genetic material present is a fragment of a 22. This fragment could be translocated onto another chromosome, perhaps one of the larger ones, so that by present microscopic techniques it would be undetectable. Patau looked upon this syndrome as the first recognized example of the large class of rare syndromes caused by an inexhaustible variety of chromosome rearrangements. While this possibility is an appealing one, and would explain the similarity of several of the present cases to patients with the trisomic syndromes, it must be regarded as unproven. It is also apparent that more than one tissue must be studied in cases felt clinically to have trisomy if mosaicism is to be ruled out with assurance.

A patient with multiple anomalies who does not fit easily into one of the three trisomic syndromes on the basis of the specific anomalies given in Tables 1 and 3, should, however, be suspected of trisomy if he or she is an infant under three years of age with a great number of anomalies and with an older mother. Trisomies 13-15 and 17-18 have not been found in older children and adults. Although there are many exceptions to these statements they appear useful in deciding whether the possibility of trisomy should be investigated.

CONCLUSIONS

In conclusion, the diagnostic value of chromosome determinations utilizing peripheral blood has been demonstrated, both in confirming clinically borderline cases of trisomy (Case 4) and in ruling out the full trisomic syndromes (Case 7). The latter must be viewed with some caution, however, since mosaicism or partial trisomy may exist but cannot always

be demonstrated by presently available techniques. A clinical diagnosis of a particular trisomic syndrome can usually be made (cf. Table 1). Although the role of chromosome determination in prognosis has not yet been fully evaluated, it seems likely that in view of the marked variability of the clinical findings in all three syndromes the survival and clinical course will still be dependent primarily upon the type and degree of abnormality in certain critical organs such as the brain and heart.

SUMMARY

Four instances of autosomal trisomy have been found in ten children with multiple anomalies. Two new cases of trisomy 17-18 are presented; one is of particular interest in that an abnormal mid-frontal gyrus was present and that the infant was felt to have the Pierre Robin Syndrome, with micrognathia and glossoptosis. Most of the other reported cases of trisomy 17-18 are also compatible with this diagnosis, and it seems likely that many cases termed Pierre Robin Syndrome may have trisomy 17-18.

It is suggested that some minimally abnormal individuals with autosomal trisomy may have resulted from a gamete in which nondisjunction occurred at the second meiotic division following minimal crossing-over. This would result in two of the three homologous chromosomes being identical or at least identical over much of their length. It seems possible that this might represent a more benign condition.

The clinical usefulness of chromosome studies is discussed, and the most important diagnostic features of the trisomic syndromes outlined. In trisomy 17-18 these are: malformed ears, micrognathia, spasticity, malformed sternum, and probably polyhydramnios and dorsiflexion of the hallux. In Trisomy 13-15, they are: polydactyly, capillary hemangioma, cleft palate and eye defect. Such anomalies as congenital heart defect (particularly interventricular septal defect), mental deficiency and low-set ears are found both in the trisomic syndromes and in children with normal chromosomes and multiple anomalies and are therefore not diagnostic.

ADDENDUM

Since this article was submitted for publication two additional cases of trisomy have been reported:

1. Northcutt, R. C.: Multiple congenital anomalies in a Negro infant with 13-15 trisomy. *Sth. med. J. (Bgham, Ala.)*, 1962, *55*, 385-389.

2. Uchida, I., Bowman, J. M., and Wang, H. C.: The 18 trisomy syndrome. *New Engl. J. Med.*, 1962, *266*, 1198.

The finding of greatest interest in these two reports is the absence of the corpus callosum in the report by Northcutt.

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