E (16-18) TRISOMY SYNDROME: ANALYSIS OF 13 CASES

BY

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The syndrome of multiple congenital abnormalities associated with an additional autosome in the Denver Group 16-18 (E) was first described by Edwards, Harnden, Cameron, Crosse, and Wolff (1960). Its documentation has gradually been accumulated since, notably by Smith, Patau, Therman, and Inhorn (1960), Smith, Patau, Therman, and Inhorn (1962), Smith (1963), and Hecht, Bryant, Motulsky, and Giblett (1963). Morphological evidence is cited to show that the additional autosome is unequivocally No. 18 in all cases of our series, with one exception, where a possible small duplication in the long arms of the additional chromosome is postulated.

The data on all 13 cases are presented in tabular form, and the individual anomalies discussed in order that their over-all pattern may be appreciated. Case 13 has been reported by Sinclair (1963).

Analysis of Anomalies in 13 Cases

(i) Anomalies Evident on Clinical Examination (Table 1).

Cranio-facial.—In 6 cases the skull circumference was less than the normal range. The bifrontal diameter was reduced in all cases, and in the most marked examples this gave a false impression of widening of the parietal region. Although some degree of microcephaly was present in 6 cases, this was not immediately obvious on inspection because of the considerable relative retardation of facial growth and variable degree of hypoplasia of both maxillae and mandible. The supra-orbital ridges were poorly developed in most cases, and the orbits were shallow. Abnormal occipital prominence is reported as being common (Finley, Finley, and Carte, 1963; Voorhess, Vaharu, and Gardner, 1962; Smith et al., 1962; Smith, 1963). None of the present series showed this finding. It is probable that the marked retardation of facial growth is responsible for this impression. The occipito-frontal circumference was below the lowest limits of normality in relation to birth weight in 6 of the 11 cases in which it was ascertained and in no case was it greater than the mean. In the extreme instances (Fig. 1a) there appeared to be complete continuity of frontal and nasal bones, a so-called Grecian nose, while in others nasal bridge development was normal (Fig. 1b). Where no true bridge exists, the association of this with the other cranio-facial features constitutes an unmistakable face. Radiography of

FIG. 1a.—Case 5. Face in profile to demonstrate the ‘Grecian nose’, micrognathia, and flattened ‘stretched-out’ upper segment of pinna.

FIG. 1b.—Case 7. Elfin appearance of the second of two facial categories.
### Table 1

**Clinical Findings**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>11</th>
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<td>Sex</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>Gestation (wk.)</td>
<td>36</td>
<td>42</td>
<td>40</td>
<td>36</td>
<td>37</td>
<td>2607</td>
<td>&lt;2267</td>
<td>3402</td>
<td>2097</td>
<td>2295</td>
<td>1756</td>
<td>2239</td>
<td>2182</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g.)</td>
<td>1332</td>
<td>2097</td>
<td>1998</td>
<td>1445</td>
<td>1700</td>
<td>2607</td>
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<td>1669</td>
<td>1750</td>
<td>1756</td>
<td>2239</td>
<td>2182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resuscitation difficulty</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>13/13</td>
<td></td>
</tr>
<tr>
<td>Age at death (days)</td>
<td>9</td>
<td>66</td>
<td>31</td>
<td>SB</td>
<td>18</td>
<td>9</td>
<td>60</td>
<td>31</td>
<td>49</td>
<td>22</td>
<td>21</td>
<td>29</td>
<td>8</td>
<td>9/13</td>
</tr>
</tbody>
</table>

**Craniofacial**

- Narrow bifrontal diameter: +
- Small face: +
- Micronathia: +
- Hypoplasia of orbital ridges: +
- Epicanthic folds: +
- Narrow palpebral fissures: +
- Ocular defect: +
- Low-set ears: +
- Cartilaginous deficiency ears: +
- Atretic auditory meatus: +
- Abnormally situated auditory meatus: +
- Small mouth: +
- High arched palate: +
- Neck webbing: +
- Facial palsy: +
- Thalassemia: +
- Paraplegia of meatus: +
- Congenital iridial hernia: +
- Imperforate anus: +
- Abnormal genitalia: +
- Limbs:
  - Flexion deformity of fingers: +
  - Flexion deformity of wrists: +
  - Flexion deformity of elbows: +
  - Flexion deformity of hips: +
  - Aplasia radius: +
  - Aplasia or hypoplastic radius: +
  - Short hallux: +
  - Syndactyly 2nd and 3rd toes: +
  - Lobster claw deformity: +
  - Phenomenon of nails: +
  - Hypertonia of nails: +
  - Hypertonia: +

The skull (Fig. 2) showed no typical defect, apart from poor facial growth; the occiput seems prominent, but this was not apparent clinically. All but one case had narrow palpebral fissures. The impression of 'ptosis' derived from an inability to separate completely the eyelids. In some cases, the impression of proptosis, contributed to by shallowness of the orbits, was exaggerated by the hypoplasia of the supra-orbital ridges. Case 5 had microphthalmus on the left, and Case 6 had bilateral hazy corneal opacities. Case 12 showed a coloboma of the choroid involving the optic disc on the right, while the coloboma was confined to the disc on the left. Optic abnormalities do not appear to be common in Group E trisomy, though optic atrophy and glaucoma (Townes, Manning, and DeHart, 1962), corneal opacity (Smith, 1963), and lens opacity (Smith et al., 1960) have been described. The ears were considered to be low set in 9 cases where the uppermost point of the pinna lay below the outer canthus of the eye. Deficiencies in cartilaginous formation of the external ear varied from a rudimentary skin ridge (Fig. 3), to being paper thin and rather elephantine (Fig. 1a), to flattening of the pinna superiorly with primitive helical development. In Case 1 the skin of the scalp was directly reflected over the pinna which could not be pulled forward. Abnormalities of the external auditory meatus were found in 7 cases, ranging from complete atresia (Fig. 3), or an extremely low location, to small size and excessive anterior direction. Unilateral meatal atresia was present in 2 cases, and...
was associated with a rudimentary external ear. Fig. 2 illustrates absence of canalization of the petrous temporal bone on radiography. In only two cases were the ears normal. The mouth was small in all our cases and tended to be triangular in some. In Cases 4 and 10 the palate was high and arched, but there were no cases of cleft lip or palate. Peripherally right-sided facial palsy was seen in 3 cases. Seventh nerve palsy has been noted previously (Smith et al., 1962; Holman, Erkman, Zacharias, and Kock, 1963), and has invariably been right-sided. In 2 cases there was associated atresia of the right external auditory meatus, and it is possible that this could affect the course of the 7th nerve, as sometimes seen in the first visceral arch syndrome. Neck webbing was bilateral in 6 cases and unilateral in 1; a recent review (Finley et al., 1963) revealed this in 6 of 8 cases where sought.

Thorax. The most common clinical anomaly in this series was hypermobility of the shoulders which could be unduly approximated. The sternum was short, with a 'shield like' thorax and wide subcostal angle in half the cases; Finley et al. (1963) noted these features in the records of 13 of 15 cases where sought, while Smith (1963) found them in 14 out of 16. In 2 (Cases 2 and 13) the medial third of both clavicles was absent and the lateral portions were extremely thin. Unusually thin clavicles have been noted previously (German, Rankin, Harrison, Donovan, Hogan, and Bearn, 1962). One or both nipples were displaced well outside the mid-clavicular line in half of our cases, and showed varying degrees of hypoplasia.

Cardiovascular System. A systolic murmur was noted in the 12 born alive, in all but one appearing within the first three days of life.

Abdomen. Inguinal herniae were noted in 11 of 16 cases in Smith's review (1963). No inguinal hernia was found in this series, but two examples of paraumbilical hernia occurred and were associated with marked diastasis recti and gross bulging of the epigastric area on crying. Clinical evidence of pyloric stenosis emerged in 2, Cases 3 and 12, with post-mortem confirmation in Case 3.

Limbs. Hypertonia was extremely marked in some infants, and was present in 11 of 12 cases. It is a constant feature in the reviews, but in one case (Finley et al., 1963) there was striking hypotonia. Anomalies of the limbs, particularly of distal segments, are consistent in this syndrome and emphasized in all the published reviews. A curiously frequent posture adopted by 6 cases was created by abduction of the arms at the shoulder and flexion at the elbow, the so-called 'surrender position'. Flexion deformities of the fingers with abduction of the thumb across the palm and the index finger overriding one or more of the other fingers are extremely common (Smith et al., 1962; Finley et al., 1963; Gottlieb, Hirschhorn, Cooper, Lusskin, Moloshok, and Hodes, 1962) and were found in most of our
cases. The fifth finger often overrides the fourth (Fig. 4). The fingers of these cases could only be straightened with great difficulty, and in one case barely at all. Characteristically this forcible extension of the fingers was attended by their gross ulnar deviation (Fig. 5) and instability of the interphalangeal and metacarpophalangeal joints. The flexion deformities were associated with varying degrees of apparent hypoplasia of the long flexor muscles and tendons to the fingers, as seen in arthrogryposis, and often with hypoplasia of thenar and hypothenar muscles. Aplasia and hypoplasia of thenar musculature has been the subject of comment by Smith et al. (1962), who also noted a decrease of muscle mass generally in these patients. The thumb was hypoplastic in 8 cases and completely absent in one (Case 9): this was associated with shortening of the first metacarpal, and in 2 infants with aplasia (Cases 9 and 13). Hypoplasia or aplasia of the first metacarpal was invariably associated with hypoplasia of thenar musculature. There was considerable splaying of the metacarpal heads on forcible extension in most cases.

Hypoplasia of the hallux (Fig. 6) was invariable, and intermittent dorsiflexion found in 10 instances was not associated with hypoplasia of the long extensor muscles. In some shortening of the first metatarsal was noted (Fig. 7). Varying degrees of syndactyly of the second and third toes were seen (Fig. 6), a common enough anomaly in otherwise
normal people, presumably because these toes derive from a single developmental bud. Protuberance of the heels was present in 9 infants, but not in association with a vertical talus in the 5 where radiographs were available. In Case 8 (Fig. 8) there was a bizarre cleft between the right hallux and toes 4 and 5 with absence of the second and third toes. A similar smaller cleft was present on the left foot. In Case 12 this defect was present to a mild degree also, but was not associated with aplasia of any toes. A vertical skin crease between the first and second toes was found in 4 other infants but no skin cleft was present. Hypoplasia of the nails was found in 4 but aplasia was not observed.

The dermal ridges characteristically show a predominance of the simple arch pattern. Uchida and Soltan (1963) found that in 20 patients, 18 had 6 or more simple arches, and in 8 arches were present on all 10 digits. In the present series prints were obtained only from Cases 10, 11, and 12, and examined by Professor L. S. Penrose. These conformed to the criteria of Uchida and Soltan (1963), and in Cases 11 and 12 this pattern was found on all 20 digits. Hallucal and palmar patterns are so far non-contributory. A single flexion crease on the fifth finger is also a frequent finding (11 out of 18 in Uchida’s series), 2 of our series showing this feature. Obtaining prints during life is technically extremely difficult in these cases owing to the flexion deformities.

Flexion deformities of the large joints of the upper limbs were progressively less frequent the more proximal the joint and did not appear to be secondary to hypertonia since complete extension could not be obtained passively. In Cases 11 and 12 the hips could not be fully abducted. This did not seem to be associated with skeletal muscle hypoplasia but was related to curiously tight skin folds and hypertonia. In both cases there was some clitoral hypertrophy similar to that illustrated by Hecht et al. (1963). No other abnormalities of the external genitalia were found.

Defective ossification of the skull was noted in 3 of 5 cases where radiography was performed; the knee epiphyses were present in all 5. In one (Fig. 7) there was lack of ossification of the middle phalanges of the 3rd and 4th toes bilaterally and of the distal phalanges of the 5th toes. In the longest-lived cases of the series, osseous development remained at birth level.

(ii) Anomalies Found at Necropsy (Table 2).

Cardiovascular System. The most consistent anomaly was wide patency of the ductus arteriosus usually associated with a high ventricular septal defect. In Case 2 a second ventricular septal defect was present below and posterior to the higher defect, while in 3 the aortic valve was partially transposed. Only minor defects of valves were found: in 2 instances both aortic and pulmonary valves were bicuspid and in 3 others there was one bicuspid semilunar valve. A single umbilical artery was associated with low rectal atresia in Case 1, and Case 8 showed a left superior vena cava draining into a dilated coronary sinus.

Changes in the pulmonary vessels were noted histologically in Cases 2 and 7 (Fig. 9). In arteries of 3-400 μ external diameter, there were scattered eccentric patches of intimal thickening due to relatively acellular fibroelastic tissue. In arteries of
80-200 μ diameter marked cellular intimal proliferation of both concentric and nodular type severely reduced the size of the lumen and sometimes totally occluded the vessel. These changes were often prominent where a small artery was given off from a medium-sized vessel. The cellular lesions consisted of fairly large cells with vesicular nuclei and clear cytoplasm. The media was of normal thickness for the age and well defined in vessels as small as 40 μ external diameter. Only in some vessels was the internal elastic lamina lacking or interrupted.

Rubin and Strauss (1961) described similar obliterative changes of small pulmonary arteries in 5 infants who died during the perinatal period with multiple anomalies. Though no chromosomal studies were made, the anomalies present in their Cases 1, 3, and 4 are suggestive of trisomy 13-15 and include many features found in trisomy 18.
Urogenital. Two infants had horseshoe kidneys, both being associated with a number of microscopical cysts in the renal cortex. The lower pole of the left kidney in Case 11 extended to the midline but was not fused with the right kidney. In 7 cases the ovaries were examined microscopically, and 2 showed considerable reduction in the number of primordial follicles associated with marked proliferation of granulosa cells to form irregular small masses of deeply staining cells (Fig. 10). Similar 'granulosaballen' were seen in Cases 5 and 11, but in these infants primordial follicles were present in normal numbers.

Neurological. Only the stillborn infant (Case 4) showed gross abnormalities of the central nervous system. The whole brain weighed only 136 g. and showed incomplete separation into two cerebral hemispheres; the frontal lobes were separate for a distance of about 3 cm., but, more posteriorly, there was an area of fusion 4-5 cm. long with divergence of the hemispheres posteriorly; the frontal and occipital lobes were underdeveloped with relatively large temporal and parietal lobes, and the gyral pattern was abnormal with rather stout convolutions. The olfactory nerves and grooves were lacking but all other cranial nerves appeared to be present. The tuber cinereum was unusually prominent and the cerebellum appeared normal.

Diaphragmatic. There was partial fibrosis of the left dome of the diaphragm in 2 infants. It was almost completely absent in Case 4 where the left pleural sac contained the greater part of small and large intestines together with the stomach, spleen, and left lobe of liver; the left lung was hypoplastic.

Obstetric Factors

Family History. The mean maternal age in this series (32-2 years) was higher than in the general population (Table 3). It was less than in the review of 37 cases (34-4 years) by Hecht et al. (1963), but was greater than that reported by Weiss, Di George, and Baird (1962) in their 4 cases (22-4 years). The mean maternal age is considerably less than that for trisomy 21 (Penrose, 1961). The mean paternal age of this series (37 years) is comparable with the figure of 36 years quoted by Hecht et al. (1963). As they noted, there are two peaks of maternal age incidence, one in the mid-twenties, and one in the mid-thirties. More significantly, the mean of the sum of the ages of the parents is increased. In our series this mean value was greater than 30 years in 8 of 11 cases, a figure that agrees with the findings of Hecht et al. (1963).

In only 3 instances was any kind of congenital anomaly traceable in the family history. A maternal aunt of Case 2 died at the age of 3 days from renal agenesis, and a female sib of Case 7 had a haeman-
gioma of the lower lip. The father of Case 10 had been married previously, and the second child by his first wife, who died in the neonatal period, had a cleft palate and hare-lip. In previously reported series the incidence of familial congenital abnormality was also not above the normal.

Previous Obstetric History. Maternal parity did not appear to be significant in this series. There were 3 primigravidae, 2 under 25 years of age: 2 (Cases 3 and 5) have since given birth to normal children. There was no evidence of relative subfertility. Where the interval between any two pregnancies was high, the maternal and paternal ages were also high. This can be taken as the normal decline in fertility related to age. Abnormalities of previous pregnancies were few. In contrast to Smith's series (1963) the incidence of abortion in our cases was low, and was confined to the eldest mothers. Placenta praevia occurred in previous pregnancies of Cases 1 and 9.

Present Pregnancy and Delivery. There was a high incidence of severe pre-eclamptic toxæmia, and three instances of persistent breech presentation requiring external version. Drainage of blood-stained liquor was relatively common, but only two cases of foetal distress occurred. Placenta praevia was present in two cases. Polyhydramnios occurred in 4, and was acute in onset in 2 of them. The association of this condition, coupled with an extremely small placenta, was noted by Smith et al. (1960) and Smith (1963). Apart from iron, no drugs were taken except in Case 11 in which antihistamines and phenobarbitone were presented because of hyperemesis. In no case was either parent exposed to ionizing radiation or X rays. Intrauterine growth retardation was marked, and even before delivery 10 out of 13 infants were said to be small for the period of gestation. The birth weights were low, and in only 3 were they greater than 5 lb. (2,267 g.). Gestation was prolonged in 6 instances, and labour was induced at term in 3.

Delivery was normal in 10 cases, by caesarean section in one (Case 1), and by the breech in one (Case 10).

This report agrees with the predominance of females noted by most authors (Ferguson-Smith, 1962). 2 of the 3 males were the shortest lived of the series, but the proportion of males is not sufficient to draw comparisons as to survival in the sexes; Ferguson-Smith (1962) states that there is no difference. Studies on spontaneous abortions and stillbirths may provide the ultimate answer to this question.

Clinical Progress

Resuscitation difficulties were experienced in 9 infants, in all of whom endotracheal intubation was required following failure of spontaneous respirations at 5 minutes.

All except Case 4 required continuous tube feeding from the first few days of life, and all but one of the live-born infants (Case 8) developed respiratory distress or cardiac failure in the first 3 days of life. None gained more than 1 lb. (453 g.) in weight throughout life. All but Case 11 underwent progressive cardiopulmonary failure before death. It is of interest that 3 infants were very sensitive to digoxin (Cases 2, 6, and 7) in a digitalizing dose of 0·02 mg./lb. body weight, all developing varying
degrees of atrioventricular heart block. This seems a high incidence (20%), and considering the relative tolerance of newborn infants to the drug, might suggest a specific defect in these cases. In a number of instances the cardiac condition did not seem to be severe enough to account for early death. Death was sudden and unexplained, even after necropsy data were available. Compared with trisomy 13-15 and trisomy 21, this condition appears to carry a poor prognosis. Of the series reported by Smith et al. (1962), only one survived the age of 6 months, ultimately succumbing at 16 months; this is the longest lived case so far recorded, excluding mosaic forms. Smith (1963) comments that the failure to thrive and death seem to be due to a summation of anomalies, rather than to any specific one.

In 5 cases chromatography of the urine was performed, and no abnormality was found. Electrolyte, calcium, and phosphorus estimations were normal in 9 cases on which they were performed. No specific biochemical abnormality has yet been found in this condition. Case 2 had a transient glucose tolerance of diabetic type, but was the only case tested.

**Cytogenetic Findings**

Preparations of chromosomes were obtained by using cultures of leucocytes from peripheral blood and tissue cultures of skin fibroblasts. The methods were based on those of Moorhead, Nowell, Mellman, Battips, and Hungerford (1960), of Tjio and Puck (1958), Rothfels and Siminovitch (1958), and Harn- den (1960), but with some important modifications which are the subject of a separate publication.

The results of chromosome studies are summarized in Table 4. The chromosome count in all cases was consistently 47 in the tissues sampled, all cells with a count less than the modal number being broken during preparation. Most of the cells with 46 chromosomes contained 7 in Group E. Those cells from skin cultures with a count greater than 48 were tetraploid with 94 chromosomes. Other excess counts were due to chromosome breakage.

At least 6 complete karyotypes were prepared for each tissue, the Group E chromosomes identified in photographs of the remainder, and arranged in order. Despite the variation in the degrees of contraction between homologous chromosomes, which is sometimes encountered and which can be quite marked in Group E, especially in the case of No. 16, the majority could be matched satisfactorily so that a trisomic condition for No. 18 resulted. Measurements on photographs magnified to \( \times 8,000 \) were made as a standard procedure to check the visual arrangement. Because of the variations referred to above, they could not be arranged in order by reference to over-all length. There is considerable overlap in the range of relative lengths in normal karyotypes as shown in Table 5. These figures have been derived from a study of a series of 50 normal karyotypes, mostly from clinically normal subjects, and the results compare with the lower limits of those published in Table 2 of the Denver Report (1960), being closely similar to those of Fraccaro and Lindsten (1960) and Buckton, Jacobs, and Harnden (1960).

It has been found much more reliable to consider both the relative length of the short arms (i.e. the centromeric index), and the arm ratio. Chromosome 16, having the longest short arms, has a greater centromeric index and smaller arm ratio than chromosome 18 which has the shortest short arms of the Group. Using these criteria, a consistent pattern has emerged and all patients with one exception showed a regular trisomy for 18. Occasional cells in some patients could be interpreted, both visually and by measurement, as trisomy 17, while other cells contained an extra chromosome which could not be matched accurately. In assessing their probable identity, the average of several cells is taken into consideration.

Case 9, however, could not be interpreted as a straightforward trisomy 18. The measurements of
Group E chromosomes from 26 cells from Case 9 are shown in Table 5, and their appearance in Fig. 11. The relative length of the extra chromosome was similar to that of No. 16 but with significantly different arm ratio and centromeric index values, the long arm length exceeding that of both 17 and 18. It is possible that in this case the long arm of the extra chromosome contains extra chromatids which could be of homologous or non-homologous origin. The anomaly might exist in one of the parents or could have arisen during gametogenesis and could be a factor in non-disjunction. Muldal (1961) has suggested an explanation for the origins of apparent trisomy 17 and of deletion of 18, by considering a duplication of the short arms of a No. 18. He further suggests that this would explain how, at that time, trisomy for 17 and 18 had been reported with equal frequency. From this series, however, there has been no indication that half of the patients could be interpreted as trisomy 17. In fact, since 1961, most reported cases have been interpreted as either trisomy 18 or, less dogmatically, trisomy 17-18 pointing to the fact that duplications are of rare occurrence. Recent autoradiographic studies (Yunis, Hook, and Mayer, 1964) have pinpointed 18 as a late DNA-replicating chromosome compared with 17 which replicates early. This behaviour pattern is a valuable one, but the distinction between the two still hinges on morphological differences.

Comment

Clinical recognition of the syndrome is not difficult. There appears to be a gradation of facial

![Fig. 11.—Case 9. Group E from 10 cells showing the abnormal additional chromosome 18. (Approximately × 2,500.)](http://adc.bmj.com/)

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**THE E (16-18) TRISOMY SYNDROME**

**TABLE 5**

MEASUREMENT OF GROUP E CHROMOSOMES

<table>
<thead>
<tr>
<th>Chromosome number</th>
<th>Normal Karyotype Measurements (50 cells)</th>
<th>Karyotype Measurements of Case 9 (26 cells)</th>
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<td></td>
<td>16</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Relative length</td>
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<td></td>
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</tr>
<tr>
<td>Arm ratio</td>
<td>33 (± 4)</td>
<td>30 (± 4-5)</td>
<td>29 (± 5-5)</td>
</tr>
<tr>
<td>Centromeric index</td>
<td>1.3 (± 0.3)</td>
<td>1.7 (± 0.4)</td>
<td>2.2 (± 0.4)</td>
</tr>
</tbody>
</table>

Note: Most values were, in fact, close to the mean, and when a value for one particular chromosome was at the extreme end of the range, then other chromosomes in the group had a value at the same extreme, depending on the relative degree of contraction. The mean figures, therefore, represent a true guide as to the relationship of one chromosome to another, and thus statistically the extra chromosome in Case 9 is significantly different from both '17' and '18'.
types with those at each end of the range being quite distinct. At one extreme the facies is unmistakable with the 'Grecian' nose, round face, and extreme narrowing of the palpebral fissures (Fig. 1a). At the other end there is a well-developed nasal bridge, with an upturned nose and only slight narrowing of the palpebral fissures, giving rise to a rather elfin appearance (Fig. 1b). None of the cases of this type (Cases 6, 7, and 10) had microcephaly, and 2 of them were the largest infants in the series. Good examples of this type are seen in the series of Smith et al. (1962, Fig. 3) and the paper of German et al. (1962, Fig. 1). There was no specific combination of anomalies that correlated with either facial type.

The aural and facial abnormalities have many features of the first arch syndrome (McKenzie, 1958), and it is possible that insufficiency of the blood supply between the third and fifth weeks of intrauterine life may be responsible. McKenzie (1958) states that during this phase, following the disappearance of the first aortic arch, the first visceral arch depends on only the stapedial artery, and the developing external carotid artery. If this delicate balance is disturbed then the typical spectrum of cranio-facial anomalies of the syndrome will occur.

As can be seen from Table 1, the clinically obvious anomalies occur in the limbs and cranio-facial areas. Limb anomalies are progressively more frequent from the proximal to distal direction. A combination of the above anomalies should raise the suspicion of trisomy E as a clinical diagnosis.

The chromosome studies produced a consistent pattern despite variation in the clinical appearance.

Summary

The clinical features of 13 cases of 'E' trisomy are presented, and the pattern of anomalies is discussed. Consideration of the facies together with the other anomalies permits a reasonably accurate clinical diagnosis.

The major necropsy findings are presented and analysed. The most consistent anomaly on internal examination was wide patency of the ductus arteriosus, usually associated with a high ventricular septal defect. In two cases there was intimal proliferation of small pulmonary arteries.

No specific antenatal factor could be held responsible in any case. Dysmaturity was common, and associated with small placental size.

Apparent hypersensitivity to the standard dose of digoxin was encountered in two cases, with resulting atriocentric heart block.

The only biochemical abnormality discovered was that of a transient glucose intolerance, with glycosuria, in one case.

Morphologically the extra chromosome is considered to be No. 18 in all but one. The exception shows an extra chromosome with increased length of the long arms.

This investigation required the co-operation and encouragement of many individuals. We wish to thank the following physicians for permission to publish clinical details of cases under their care: Dr. I. M. Anderson (Cases 10 and 13), Dr. R. J. K. Brown (Cases 1, 4, and 11), Dr. R. H. Dobbs (Cases 7 and 12), Dr. C. G. Fagg (Case 6), Dr. N. F. O'Reilly (Case 8), and Dr. M. J. Wilmers (Cases 3 and 9).

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References


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