The 'D' (13-15) Trisomy Syndrome: An Analysis of 7 Examples

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The identification of an additional chromosome in group D (13-15) in a child with multiple congenital anomalies was first made in 1960 by Patau, Smith, Therman, Inhorn, and Wagner (the Wisconsin group). The principal anomalies noted in this case were cleft lip and palate, polydactyly, microphthalmia with hypoplasia of the optic nerves, simian palmar creases, retroflexible thumbs, and ventricular septal defect. The publication of further cases with additional anomalies amply demonstrated that a new, specific, and easily recognizable clinical syndrome had been established (Therman, Patau, Smith, and DeMars, 1961; Ellis and Marwood, 1961; Atkins and Rosenthal, 1961; Lubs, Koenig, and Brandt, 1961). Smith, Patau, Therman, Inhorn, and De-Mars of the Wisconsin group had by 1963 accumulated 7 personal cases, the largest series so far published. The condition seems to be less common than ‘E’ or ‘G’ trisomy syndromes; the authors have been able to find only 33 published examples, almost all in the form of single case reports.

Our clinical, necropsy, and cytogenetic findings in the 7 cases in this report have been analysed to illustrate the spectrum of anomalies which can now be accepted as characteristic. The neuropathological studies of 4 of these cases focus attention upon the failure of prosencephalic (forebrain) cleavage and its possible relationship with the defects of midline cranio-facial development underlying the two main facial categories observed.

Anomalies Evident on External Examination

(Table I)

Cranio-facial. Analysis of the present cases and those in the literature shows that two basic categories of facies occur.

Category 1: Facies associated with defects of prosencephalic cleavage. There is a striking association between certain defects of prosencephalic cleavage, such as characterize some examples of the 'D' trisomy syndrome, and median facial anomalies (DeMyer, Zeman, and Palmer, 1964). The primary embryological defect appears to involve the prechordal mesoderm upon which induction of forebrain development seems to depend, as suggested by Adelmann (1936) in his observations on cyclopia, and from which certain midline facial structures derive.

The facial and even ocular abnormalities occurring in conjunction with the prosencephalic state may be associated rather than primary phenomena, and may thus parallel the severity of the underlying brain defect rather than the trisomic state per se.

Bearing in mind their common embryonic origin, the median facial anomalies should be considered as part of a malformation complex of varying severity, consisting of orbital hypotelorism usually accompanied by severe ocular abnormalities; hypoplasia or aplasia of the crista galli, other components of the ethmoid bone and the nasal septum; and aplasia or hypoplasia of the median philtrum, usually in association with median cleft lip, and palate. Aberrant development of the embryonic median fronto-nasal process forms the basis of this malformation complex.

According to severity, several gradations of this fundamental malformation complex are seen in clinical practice, ranging from the mild to the severe. (1) Orbital hypotelorism associated with bilateral cleft lip and well-developed nasal tip. The philtrum is present. (2) A complex consisting of moderate orbital hypotelorism, absence of the philtrum with median hare-lip, and hypoplasia or aplasia of the nasal septum with a flattened nasal tip. The nasal cavity communicates with the pharynx, and a cleft palate is usual. (3) Cebocephaly, where there is severe orbital hypotelorism and a proboscis in the usual situation of the nose, having a single aperture, which may or may not communicate with the pharynx. (4) Ethmocephaly, where the orbits are just separate and also having a proboscis. (5)
Cyclopia, where there is a single partially divided eye in a single centrally situated orbit, and a proboscis which is usually abnormally situated.

The last four are associated with a holospheric brain; the first is usually associated with arhinencephaly alone.

Cases 2, 4, and 7, all with a prosencephalic cleavage defect, fell into this cranio-facial Category 1. Case 7 showed all the features of the malformation complex with severe microphthalmia (Fig. 1), though surprisingly, in view of the poor frontal lobe development, the forehead did not recede. Case 2 had similar features except that the philtrum was present, though underdeveloped, together with bilateral cleft lip and cleft palate. Case 4 had extremely severe prosencephalic defect with orbital hypotelorism, microphthalmia, and a flattened nasal tip. Unfortunately a detailed description of the nasal structure was not available, though the flattening suggested hypoplasia of the nasal septum. There was no cleft lip or palate, but the latter was high and arched. The mouth was unduly small and
the gums irregular. The pattern of the oral structures corresponded with that found in cebocephaly where, in the almost total absence of the bones derived from the median frontal process, fusion of the lateral maxillary processes occurs without cleft lip or palate. Although the mouth appears intact in cebocephaly and its close relation cyclopia, the philtrum is in fact absent, thus producing the extremely small mouth. The brain defect in Case 4 was similar to that in cebocephaly, but as the nasal septum was present the facies may be considered as transitional between cebocephaly and the malformation complex already described.

Category 2: Facies not associated with a prosencephalic defect. Multiple minor anomalies are a feature of this group. Bilateral cleft lip and palate may be present in addition but are not part of a median facial malformation complex. In these patients prosencephalic cleavage, and usually fusion of maxillary processes with the lateral and medial nasal processes, have proceeded normally. The latter did not occur, however, in Case 6, which had bilateral cleft lip and palate, but following surgical repair closely resembled the other patients in this category (Fig. 2).

Although these patients bore little resemblance to those of Category 1, they closely resembled each other. Their features were coarse, with loose-fitting leathery skin, producing redundant folds in the mandibular and peri-orbital regions (Fig. 3 and 4), and conferring a grotesque appearance, accentuated when crying. The forehead receded (Fig. 5) and mild microcephaly was evident. A striking feature was the large nose with broad well-developed bridge and bulbous fleshy tip (Fig. 6). There was no obvious hypotelorism, though mild diminution of the interpupillary distance was not excluded, and severe optic defects were not present. The upper lip was long and overhung the lower which tended to be slightly everted (Figs. 2 and 3). The mouth was rather large and turned downwards at the corners, in contrast to the small mouth of Category 1. All patients in this category had mild micrognathia and 2 showed minor ear abnormalities.

Ears. The ears were considered low set in 2 patients (Cases 3 and 5), with the upper edge of the pinna lower than the outer canthus of the eye. Primitive helical development was found in 3 patients (Cases 2, 4, and 5), while the remaining 3 had normal ears. These findings contrast with the review of the Wisconsin group (Smith et al., 1963) in which all cases had some ear abnormality where this was specifically mentioned. Atresia of the external auditory meatus, common in ‘E’ trisomy syndrome, has been reported only once (Conen, Phillips, and Maunten, 1962). Indeed, features of the first arch syndrome as delineated by McKenzie (1958) are not usual in this syndrome.

Eyes. Ocular anomalies are frequent. Yanoff, Frayer, and Scheie (1963), who reported one case and reviewed 12 others from the literature, concluded that microphthalmia, coloboma, and cataract
were the most common lesions. In addition, corneal opacities have been noted by Smith et al. (1963), and the presence of intra-ocular cartilage in the severely affected cases has been stressed by Cogan and Kuwabara (1964).

In the present series, 5 patients were examined by the ophthalmologist either during life or at necropsy, and 2 (Cases 1 and 6) were seen by the paediatrician alone. Microphthalmia was bilateral in 2 patients (Cases 4 and 7) and unilateral in one (Case 2). Of the 5 affected eyes, 4 were cystic and 3 had a coloboma of the iris and choroid.

It must be remembered that the cystic eye, microphthalmia, and coloboma are developmental aberrations of differing degrees of severity associated with the formation of the optic cup and fusion of the two lips of the foetal fissure. In one patient (Case 3) the eyes were normal apart from a gross convergent squint, and another developed buphthalmos for which goniotomy was performed. Case 6 was reported to have buphthalmos and colobomata. Case 1 was thought to be normal.

Histological examination was performed in 4 cases. Case 2 showed a coloboma of one eye with a malformed lens adherent to the iridial portion. The other eye was microphthalmic with a detached maldeveloped retina and a cataractous lens. Cases 4 and 7 had small cystic eyes associated with nodules of cartilage in the orbit. Case 5 had buphthalmos with an opaque cornea and a cupped disc on one side. The canal of Schlemm could not be seen in the other eye.

No intra-ocular cartilage was seen in these cases. The most severe ocular abnormalities were confined to those cases with prosencephalic defects (i.e. cranio-facial Category 1), while in the remaining category the ocular development was more nearly normal. This might be expected as the optic vesicle develops at the 2 mm. embryonic stage as an outgrowth from the neural ectoderm which will form the prosencephalon.

**Limbs.** Anomalies of limbs have been a feature of most reported cases (Smith et al., 1963), and, as in the ‘E’ trisomy syndrome, are progressively more frequent in the distal portions. Flexion deformities of the fingers, wrists, and elbows are common (Fig. 6). Retroflexible thumbs were present in 5 patients (Cases 2, 3, 5, 6 and 7), a higher incidence than that reported by the Wisconsin group. Horizontal palmar creases were present in 6 patients and are recorded in the majority of reported cases. Transverse hyperconvexity of the nails was found in all cases where specifically sought, though aplasia of the nails, not uncommon in ‘E’ trisomy syndrome, has never been reported. Polydactyly of the hands or feet is present in the majority of recorded cases and may occur unilaterally or bilaterally. Involvement of three extremities has been described (Lubs, et al., 1961; Townes, DeHart, Hecht, and Manning, 1962; Miller, Picard, Alkan, and Gerald, 1962; Miller, Picard, Alkan, Warner, and Gerald, 1963), but polydactyly of all four limbs has never been reported. Syndactyly was not found in this series and only one instance is known (Warburg and Mikkelson, 1963).

In 5 patients the hands were broad and spade-like with fleshy fingers and dry loose-fitting leathery skin.
They resembled the hands seen in Potter's syndrome of bilateral renal agenesis. Single flexion creases of the fifth finger, common in 'E' trisomy syndrome, were not seen. The soles tended to be unduly fleshy and oblong in most cases. A vertical skin crease between the first and second toes, similar to that found in 'G' trisomy was frequent, while, in addition, a small cleft existed between these toes in three cases. Protuberant heels were common and the hallux was prehensile in 5 cases.

**Abdomen.** The only anomalies noted were midline defects of the upper abdominal wall ranging from devarication of the recti (Case 1) and umbilical herniation (Case 5), to exomphalos in Case 7 and thus conforming with Smith's (1963) findings. The infra-umbilical portion of the abdominal wall derives from a secondary sheet of mesoderm which grows into the anterior portion of the cloacal membrane, and no anomalies of this region have been reported in 'D' trisomy syndrome.

**Genitalia.** External genital anomalies are frequent in published cases and appear to be confined to males. In Cases 1, 2, and 6 the testes were situated in the inguinal canals. Cases 2 and 6 had a hypoplastic scrotum abnormally attached to the ventral surface of a small penis, an anomaly first noted by the Wisconsin group. Both females had normal external genitalia.

**Skin.** Aplasia of the skin of the scalp (Fig. 7) simulating ulceration was present in 2 patients (Cases 1 and 2), and has been noted twice previously (Miller et al., 1963; Warburg and Mikkelsen, 1963). Capillary haemangioma of the neck, glabella region, and lower back, reported as common by Smith (1963), were found only once.

**Dermatoglyphs.** Adequate palm and foot prints were obtained in 2 patients (Cases 3 and 5). Both had markedly distal axial triradii, with an 'atd' angle in excess of 90° and horizontal palmar creases. The arch-fibular-S pattern, said by Uchida and Soltan (1963) to be typical of the plantar pattern, was absent in both.

**Miscellaneous.** Generalized hypertonicity was marked in 3 patients (Cases 3, 4, and 5) and is a feature of the syndrome. Myoclonic attacks, apparent deafness, and severe mental retardation were clinical features of the longest-lived cases but could not be assessed in the remainder. These findings are in accordance with other published reports. Mental retardation is probably invariable for it has been found in all cases old enough to be assessed, while patients dying at an earlier stage have frequently been found to have brain abnormalities incompatible with normal mental development, as in this report. Apnoeic attacks of unknown aetiology occurred in 4 patients.

**Anomalies of Internal Structures** (Table II)

Cardiovascular anomalies were found in 4 of the 5 cases in which necropsy was performed; in each a high ventricular septal defect was associated with wide patency of the ductus arteriosus. A ventricular septal defect was the clinical diagnosis in Case 6. In addition to these lesions in Case 4, the aorta arose entirely from a conspicuously hypertrophied right ventricle, and there was a severely stenosed bicuspid pulmonary valve. Cardiac abnormalities have been a consistent feature of this syndrome, with high ventricular septal defect as the commonest lesion. Dextroposition of the heart was considered to be the next most frequent anomaly by Smith (1963), though this has usually been a clinical interpretation and not a prominent feature at necropsy. Other cardiac lesions reported have been fibroelastosis (Patau et al., 1960), Fallot's tetralogy (Townes et al., 1962), atrial septal defect (Patau, Therman, Smith, and Inhorn, 1961; Neumann, Pierson, Gilgenkrantz, Olive, and Kahn, 1964), and bicuspid aortic valve (Smith et al., 1963). A clinical diagnosis of atrial septal defect and anomalous pulmonary venous drainage was made in one case (Lubs et al., 1961), but no necropsy was performed.
**The ‘D’ (13-15) Trisomy Syndrome**

**TABLE II**

<table>
<thead>
<tr>
<th>Necropsy Findings</th>
<th>Case No.</th>
<th>Observed Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bicuspid pulmonary valve</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dextroposition of aortic valve</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Urogenital system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroencephalus</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Renal hyperlobation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cysts of kidneys</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Septate uterus</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Granulosaballen of hypoplastic ovaries</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Alimentary system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Universal mesentery</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Meckel's diverticulum</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Aberrant splenic tissue</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Skeletal system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar skull</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain weight (g.)</td>
<td>317 429 90 490 176</td>
<td></td>
</tr>
<tr>
<td>Weight of brain-stem and cerebellum (g.)</td>
<td>19 29 29 29 29</td>
<td></td>
</tr>
<tr>
<td>Holospheric brain</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aplasia/hypoplasia of corpus callosum</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Absence of septum pellucidum</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Rhinencephalic dysgenesis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Aplasia/hypoplasia of optic nerves</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Unpaired diencephalon (partial)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Absent or rudimentary third ventricle</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hypoplasia of cerebellar vermis</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

NI = no information.

A single umbilical artery was found only in Case 2; the frequency of this lesion in the syndrome is unknown.

A high incidence of genito-urinary anomalies typifies this syndrome (Smith, 1963). Of our cases, 6 had renal abnormalities of which pathological information was obtained on 5. A hydronephrotic kidney with associated hydroureter was removed at operation from Case 3, and a similar lesion was demonstrated radiologically in Case 6. Bilateral hydronephrosis and hydroureter was found in Case 1, without demonstrable obstruction to the bladder neck or urethra. These particular lesions appear common in this syndrome. Renal microcysts were found in 3 cases; Case 2 showed multiple small cortical cysts of the uncommon variety in which a small glomerular tuft projects into the cavity of each cyst, resembling those noted by Northcutt (1962). Case 4 had small cysts lined by cuboidal or squamous epithelium, some surrounded by increased amounts of connective tissue. This appeared to be an example of cystic dysplasia, as described previously in this syndrome by Mottet and Jensen (1965). Case 5 showed a number of similarly-sized cysts thought to be of tubular origin.

Anomalies of the internal genitalia have been reported in several cases, of which cryptorchidism and septate uterus appear to be frequent. A curious finding in Case 7 was that of hypoplastic ovaries showing collections of granulosa cells (Granulosaballen) and reduced numbers of primordial follicles. A similar observation has been made in this syndrome by Mottet and Jensen (1965) and in the ‘E’ trisomy syndrome by Butler, Snodgrass, France, Sinclair, and Russell (1965).

The commonest gastro-intestinal lesion has been described as a universal mesentery with malrotation of the colon. This was the sole intestinal anomaly in two of the present cases, and one other had a Meckel's diverticulum. Aberrant splenic tissue, a frequent finding in Smith's review (1963), was found in the pancreas of Case 2 only. The gall-bladder was normal at necropsy in all cases, in contrast to the findings of the Wisconsin group (1963). Apart from the cranio-facial region, skeletal anomalies were not found in this series, and appear to be rare.

**Neuropathological findings.** Four cases in this series were subjected to full neuropathological examination.
Case 1. The whole brain weighed 317 g. (normal 388 g.). The brain-stem together with the cerebellum weighed 19 g. The only macroscopical abnormality was underdevelopment of the cerebellar vermis so that the cisterna magna was abnormally large. All cranial nerves were normal. Histologically excessive numbers of ectopic neuronal cells were scattered diffusely and in focal clusters within the white matter of the frontal lobes. Many ectopic collections of granular and Purkinje cells were present in the cerebellar white matter (Fig. 8).

Case 2. The whole brain weighed 429 g. after fixation, the cerebellum and brain-stem accounting for 29 g. The main abnormalities were absence of both olfactory bulbs and tracts, small optic nerves (especially the right), and a short corpus callosum, the splenium of which reached about half-way along the thalamus. The cingulate sulcus was shorter than usual and the precuneus had grown down to fill in the space normally occupied by the posterior part of the corpus callosum. Some distortion of the development of the gyri of the basal surface of the brain had also occurred, the convolutions tending to be drawn inwards towards the retrosplenial region.

Case 4. The whole brain weighed 90 g. and was mushroom-shaped, the stalk consisting of brain-stem prolonged anteriorly by the unpaired diencephalon and the cap being the unpaired cerebrum. The stalk-like structure was inserted into the concave undersurface of the cerebrum near its anterior extremity (Fig. 9). The cerebrum measured 7 cm. in diameter. The only indication that separation into two hemispheres had occurred was a divergence of the posterior poles 2·5 cm. from the posterior margin. The dorsal surface was smooth, sulcus formation being limited to a few grooves radiating for a short distance from the anterior toward the posterior poles. Rudimentary Sylvian fissures were present. On the inferior surface hemispheral pairing was indicated by a shallow midline groove extending from the anterior toward the posterior pole for 2 cm. This abutted on a cystic cavity enclosed by a thick, bluish membrane. Posteriorly a discoid pituitary was adherent to the cyst. Section of the cerebrum revealed a single ventricle (holosphere), with absence of the septum pellucidum, fornices, and corpus callosum. The choroid plexuses were absent. The olfactory and optic nerves were absent, but all other cranial nerves were present. At the inferior margin of the cerebrum, the pallium was reflected upward and inwards ending in a rim encircling the single ventricle. The diencephalon was unpaired and inserted into the pallium by its central portion and two lateral extensions. On its dorsal aspect there was an ependymal surface with a central depression which represented the rudimentary third ventricle. The aqueduct was pinpoint in size. The pons was small but otherwise normal, and cerebellum, medulla, and fourth ventricle were normal.

Case 7. The brain was small (176 g.) and dome-shaped. The two cerebral hemispheres were separated from each other by the longitudinal fissure. This separation was incomplete inferiorly, where the subcallosal areas and posterior parts of the gyri recti were fused across the midline.

The corpus callosum, fornices, and septum pellucidum were absent. A single ventricle was present, normal in size posteriorly but grossly narrowed anteriorly (Fig. 10).
The corpora striata and anterior portions of the thalami were fused in the midline. Posteriorly a small vertical slit indicated rudimentary diencephalic cleavage which was complete at the level of the pulvinaria. The hypothalami were fused and the third ventricle was absent. The corpora mamillaria could not be identified. The hippocampi were well formed and the fimbriae ascended normally to their insertion in the undersurface of the intercerebral mantle. All trace of these formations was lost further anteriorly.

The cerebellum and brain-stem were normal and weighed 15 g.

**Cytogenetic Findings** (Table III)

**Materials and methods.** Using techniques described by Butler (1965; 1966, simplified skin and peripheral blood techniques for use in cytogenetic studies, unpublished observations), chromosome preparations were obtained as far as possible from cultures of both peripheral blood and skin. The relative duration of
Snodgrass, Butler, France, Crome, and Russell

TABLE III

Chromosome Counts and Karyotype Diagnoses

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tissue</th>
<th>Chromosome Count</th>
<th>Photos</th>
<th>Karyotypes Analyzed</th>
<th>Trisomic Category (Based on Visual Arrangement)</th>
<th>Enlarged Satellites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blood</td>
<td>1 1 56</td>
<td>30</td>
<td>25</td>
<td>Trisomy 13</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Blood</td>
<td>2 2 54</td>
<td>22</td>
<td>22</td>
<td>Trisomy 13/14</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>3 2 54</td>
<td>30</td>
<td>25</td>
<td>Trisomy 13/14</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Blood</td>
<td>1 1 53</td>
<td>25</td>
<td>20</td>
<td>Trisomy 14</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Skin</td>
<td>2 1 51</td>
<td>31</td>
<td>22</td>
<td>Trisomy 13</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Skin</td>
<td>3 2 51</td>
<td>25</td>
<td>23</td>
<td>Trisomy 13/14</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>- 1 31</td>
<td>17</td>
<td>10</td>
<td>Trisomy 13</td>
<td>Indeterm.</td>
</tr>
<tr>
<td>6</td>
<td>Skin</td>
<td>2 1 78</td>
<td>56</td>
<td>38</td>
<td>Trisomy 13</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Skin</td>
<td>3 1 51</td>
<td>30</td>
<td>25</td>
<td>Trisomy 13/14</td>
<td>+</td>
</tr>
</tbody>
</table>

incubation with colchicine and other details of processing were adjusted so that the resulting material from all tissues sampled was morphologically similar when viewed by phase-contrast microscopy. By this means satellites can be compared in all tissues under similar conditions, while variations in apparent degrees of contraction between homologous chromosomes can be checked and any significant differences more easily determined.

As far as possible, at least 50 cells were counted and examined for each tissue, the material being sampled from more than one culture, and in most cases at least half of the cells counted were suitable for karyotype analysis by photograph. Cells were also selected for a more detailed microscopical examination. Usually 6 complete karyotypes, prepared from prints at a final magnification of 6-8,000, were examined in detail mainly to check that all groups other than group 13-15 were normal. The large acrocentric chromosomes were identified in the remaining photographs and arranged in pairs of descending order of size.

Results. Table III shows the chromosome counts obtained. Visual arrangement seemed to indicate that usually the shortest pair in group 'D', No. 15, could be distinguished relatively easily from the other 5 chromosomes. A visual assessment was made of the possible trisomic arrangement in each cell and the totals of all categories are shown in Table IV. From these observations it appeared that all cases, with possibly one exception (Case 2), represented regular trisomy of chromosome 13. Reassessment of each cell by measurement of the long arms of all group 'D' chromosomes did not produce such a clearly defined result, indicating that, using long arm lengths alone, chromosomes 13 and 14 could not be separated with certainty. Measurements of a normal control series have shown that there is very little difference in the relative over-all lengths of 'D' chromosomes, but, on average, No. 15 is the shortest. Chromosomes 13 and 14 are approximately equal in length, but, by virtue of centromeric position, No. 13 has the greater arm ratio. However, because of satellite variation the short arms cannot always be clearly delineated and measurement becomes difficult. Autoradiographic studies are helpful, and Yunis, Hook, and Mayer (1964) have shown that the chromosome involved (designated D1) is late.
replicating in the lower half of the long arms and on morphological grounds appears to be No. 13.

Only one patient (Case 2) did not fit into this consistent pattern. In most cells the short arms of one chromosome were exaggerated, and satellites, though present, were not always clearly differentiated. Measurements of long arms indicated that the chromosome could not be matched with others. One possible explanation could be that the position of the centromere had been altered by an asymmetrical pericentric inversion. By abnormal pairing this could have contributed to non-disjunction during gametogenesis.

In six patients very prominent satellites were observed on at least one group ‘D’ chromosome (Fig. 11). A random selection of subjects with normal karyotypes and a series of patients with ‘E’ trisomy syndrome, 13 of whom have been published previously (Butler et al., 1965), have been used to test satellite prominence. In the former, only 19 out of 125 (15%) had at least one group ‘D’ chromosome prominently satellited, and in the latter 3 out of 18 (16.5%). This indicates that the frequency of satellite prominence is abnormally high in this series and could be an important factor in relation to chromosome pairing and non-disjunction. Alternatively, prominent satellites could represent an abnormality at the cellular level due to the trisomic state. In ‘D’ trisomy patients, Huehns, Lutzner, and Hecht (1964) have observed unusual nodular projections of the nuclei of neutrophils which were Feulgen-positive and sometimes pedunculated; these were distinct from the neutrophil drumsticks described by Davidson and Smith (1954). There could be a direct relation between these anomalous formations and the enlargement of satellites described here.

Prominent satellites in otherwise normal karyotypes have been described in association with Marfan’s syndrome (Tjio, Puck, and Robinson, 1959; McKusick, 1960); other reports, however (Handmaker, 1963; Filippone and Martinelli, 1962), have been inconsistent and two examples studied in this laboratory had normal satellites. However, 2 patients with some features of the ‘D’ trisomy syndrome showed abnormally large satellites on one of the large acrocentrics in a 46 count. Similarly, an infant with ovarian hypoplasia, cleft palate, and other anomalies had both a ring-X chromosome and a ‘D’ group chromosome with short arms of abnormal length and very large satellites.

Jacobson, Tischler, and Miller (1964) have reported the familial transmission of a group ‘D’ chromosome with apparently enlarged satellites: 4 of 5 members with mental retardation were carriers, and all 5 had a high frequency of arch patterns on the finger tips together with ears of unusual shape. These observations indicate that satellites could be gene bearing, though partial trisomy by virtue of a small duplication or insertion could not be ruled out. All cases with enlarged satellites recorded in this laboratory have been clinically abnormal while none of the clinically normal individuals possessed such satellites.

![Fig. 11.—The ‘D’ group chromosomes from a karyotype of each patient showing prominent satellites in Cases 2-7.](http://adc.bmj.com/)

**Obstetric Factors**

Pregnancy and delivery were normal in the 6 cases where information was available. There had been no irradiation of the mother during the putative period of conception or during pregnancy. There was no instance of polyhydramnios. Delivery was achieved between 37 and 40 weeks of gestation in 5 of 6 cases, no information being available on Case 6. No special resuscitation was required for any of them. The birth weight ranged from 1,474 g. to
2,721 g. The mean maternal age was 34.3 years and the mean paternal age 36.4 years in this series. Our information was, however, numerically insufficient to permit conclusions as to the role played.

Sex and Race

A preponderance of female cases was noted by Ferguson-Smith (1962) and Smith (1963), but males predominate in this series. Insufficient cases have been reported as yet to form adequate conclusions.

Prognosis

This is uniformly bad, but the duration of survival shows considerable variation from case to case. No patient with severe cerebral defect survived longer than 1 month. Two patients lived for more than 1 year (Table 1), and both were in cranio-facial Category 2.

Comment

Interference with the process of sagittal cleavage of the prosencephalon, or forebrain, results in an abnormal union between the cerebral hemispheres (DeMyer et al., 1964). In its extreme form this leaves a prosencephalon with a single ventricle (holosphere), callosal agenesis, absence of the septum pellucidum, and varying degrees of fusion of the basal ganglia. Less severe forms show either incomplete separation of the anterior portions of the hemispheres, partial collosal agenesis, or union by a plate of grey and white matter in the usual site of the corpus callosum. Alternatively, these anomalies may reflect failure of the development of midline structures in the developing brain. Prosencephalic brains tend to be small with absence of the olfactory nerves or more central parts of the rhinencephalon in addition to absence of the corpus callosum. Thus the prosencephalic state is sometimes regarded erroneously as synonymous with arrhinencephaly or callosal agenesis. Severe optic defects are almost invariably associated with the severe prosencephalic state. A complete spectrum of prosencephalic defects is possible in this syndrome from cyclopia to uncomplicated arrhinencephaly which is probably the commonest brain lesion encountered.

Undoubted examples of the prosencephalic state in association with 'D' trisomy have been reported by Bühler, Bodis, Rossier, and Stalder (1962), Smith et al. (1963), and Laurence (1964), while the case described by Miller et al. (1962, 1963) suggests a defect more severe than arrhinencephaly alone. Uncomplicated arrhinencephaly has frequently been reported in association with this syndrome, and has also been described in a probable case of partial 'D' trisomy (Ishmael and Laurence, 1965). Available information concerning the brains of other published cases either does not permit full classification or implies that the prosencephalic state was absent. Of the 4 cases in this report subjected to detailed neuropathological examination, 2 are extreme examples of the prosencephalic state, Case 4 exhibiting the most severe degree and Case 7 being less severe. Case 2 was an example of arrhinencephaly, while Case 1 showed no macroscopical anomaly, but showed microscopical anomalies reminiscent of the retinal dysplasia described by Sergovich, Madronich, Barr, Carr, and Langdon (1963).

During early embryonic life certain inductor substances elaborated by one primordial layer may have a profound effect on the normal development of adjacent layers. Teratogenic influences may interfere with this process causing maldevelopment of structures of different primordial origin and resulting in a malformation complex, composed of a number of anomalies, apparently unrelated but possessing certain affinities. Such a process could be postulated to explain the undoubted association between aberrant development of the median facial structures and of the forebrain (Yakovlev, 1959; DeMyer et al., 1964). During the fourth week of embryonic life the prechordal mesoderm in the region of the dorsal lip of the foregut induces changes in the rostral neuro-ectoderm to initiate development of the primitive prosencephalon, and, according to Yakovlev (1959), indirectly will determine its ultimate morphology. In addition, the prechordal mesoderm gives rise to the median facial bones so notably defective in the prosencephalic state. Abnormal disposition of this mesoderm has been observed in experimentally induced cyclopia by Adelmann (1936). Thus teratogenic influence acting on this tissue before the seventh week of embryonic life (i.e. before prosencephalic differentiation is complete) might be expected to result in severe malformations of both forebrain and median facial structures, as is found in facial Category 1 of 'D' trisomy. A more belated influence would tend to produce no more than minor cranio-facial anomalies, such as characterize facial Category 2 and not part of a malformation complex.

Extreme cranio-facial abnormalities such as cyclopia, ethmocephaly, and cebocephaly are probably invariably associated with holospheric brain, as is the absence of the median philtrum anlage. When the philtrum is present but the malformation complex coexists, the prosencephalic defect is usually less severe. Trigonocephaly and major degrees of orbital hypotelorism usually imply
The presence of arrhinencephaly (Curranino and Silverman, 1960), such as was found in Case 2 of our series. All these malformations are possible in 'D' trisomy syndrome, cebocephaly having actually been reported once (Bühler et al., 1962), though cyclopia has not yet been reported.

**Summary**

Clinical, pathological, and cytogenetic details of seven examples of 'D' trisomy syndrome are presented. Two major categories of facial appearance are defined based upon the presence or absence of the prosencephalic state. Embryological factors underlying these anomalies are discussed.

All cases were straightforward examples of 'D' trisomy, and detailed analysis suggests that the additional autosome is No. 13.

Satellites were unduly prominent on at least one 'D' group chromosome in 6 of the 7 cases.

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**References**


