Congenital Asymmetry

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Some degree of asymmetry of the body is normal. Occasionally, however, the disparity, affecting part or the whole of one limb or even half the body, is sufficiently marked to attract attention. In examples which occur after an illness of childhood, such as poliomyelitis, the cause of the asymmetry is easily recognized to be underdevelopment of the affected limb. There are, however, patients in whom hypertrophy, rather than atrophy, seems to have occurred, and the smaller limb appears to be the more normal. An aetiological classification for this mixed group of conditions was proposed by Stoesser (1928) and modified by Ward and Lerner (1947). This modified version is not entirely satisfactory because it includes, under the heading of acquired conditions, neurofibromatosis, Milroy's disease, and various vascular anomalies. So many different causes have been found that, at the present time, an attempt at formal classification seems unprofitable, and each case can, with advantage, be separately investigated.

The present study was stimulated by the finding of diploid-triploid mosaicism in a patient with asymmetry (Ellis, Marshall, Normand, and Penrose, 1963).

• Case Reports

The patients were traced through the coding index of the Royal National Orthopaedic Hospital and 8 who could be located were investigated. One other patient was referred specially. There was wide variation in the degree of asymmetry present. For example, one patient (V.P.) had partial atrophy which probably resulted from an attack of anterior poliomyelitis, and another (C.P.) had atrophy associated with a Klippel-Feil syndrome. Only two patients, A.B. and K.H. (see Fig. 1), have hemihypertrophy in the strict sense. Patient E.C. has the right leg predominantly affected, though the right middle finger is abnormally thick,

while in patient R.B., the left leg only, and in another, A.W., the right foot only is involved (see Fig. 2). Patient C.S. is perhaps the most unusual, for here the right arm and the left leg are hypertrophied. In patient R.S. all the limbs are abnormally large, particularly on the right, and the face also is asymmetrical. The patients are listed in Table I and further clinical details are given in the Appendix.

Discussion

Associated Pathology. A number of syndromes with hypertrophy or atrophy of one or more limbs has been differentiated by previous observers, because of the presence of additional characteristic features. For example, Silver, Kiyasu, George, and Deamer (1953) and Silver (1964) reported asymmetry in association with shortness of stature, low birth weight, pigmentation, short incurved fifth fingers, triangularity of the face with sagging corners to the mouth, syndactyly of the toes, and a tendency to early sexual maturation. Again, in the Klippel-Trenaunay-Weber syndrome the characteristic additional feature is the presence of a vascular anomaly usually involving the hypertrophied limb (Mullins, Naylor, and Redetski, 1962). However, Weber (1907) had pointed out that lymphangiomas could also be associated with hemihypertrophy and Williams (1951) reported such a case.

TABLE I
DATA ON PATIENTS WITH ASYMMETRY

Initials,	Sex, and Age	Maternal Age	Paternal Age	Biopsy Site
(a) R.B.	♂ 26	29	?34	L. shoulder
(b) A.B.	♂ 4	44	45	L. thigh
(c) E.C.	♀ 45	23	25	R. foot
(d) K.H.	♂ 16	34	32	L. shoulder
(e) C.P.	♀ 57	35	45	R. shoulder
(f) V.P.	♀ 18	26	28	L. thigh
(g) C.S.	♀ 9	27	27	{ R. deltoid L. thigh
(h) R.S.	♂ 44	30-34	?	L. shoulder
(i) A.W.	♀ 60	20	33	R. great toe

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FIG. 1. Patient K.H. at the age of 3 years.

In the present series, patient K.H. has a naevus on the right side of her chest, though the hypertrophy is on the left, and since the increase is primarily in the subcutaneous tissues, lymphangiectasis has been suggested as the underlying condition. Another patient, R.S., has an extensive naevus on the right side of the trunk and a smaller one on the dorsum of the right hand. Both these patients could be included under the heading of the Klippel-Trenaunay-Weber syndrome, though whether this purely descriptive distinction is helpful may be doubted. Another patient, E.C., had a small naevus on an affected toe. This patient (E.C.) and also A.W. have a condition known as macrodystrophia lipomatosa (Feriz, 1926), a dystrophic process superimposed upon a primary

maldevelopment affecting all tissue layers. In these two patients, the diagnosis was made only by histological examination of the excised tissue. Werthemann (1952) has reviewed the different varieties of this type of hypertrophy.

Mental Condition. Mental deficiency has been reported as occurring in 15 to 20% of asymmetrical patients (Gorlin and Meskin, 1962). In the present series only one patient, R.S., was obviously retarded and at least one patient (C.S.) appeared to be above average, though formal testing was not performed. Noé and Berman (1962) found only one patient with hemihypertrophy among 11,300 admitted to a mental institution. In such a heterogeneous collection of patients it is

FIG. 2. Photographs of right foot of patient A.W. at the age of 48 years.

not too surprising to find some with asymmetry, and selection presumably affected the frequency in reported series.

Dermatoglyphic Patterns. The main lines of the dermal ridge configurations, on the palms and soles of all patients, are described in the Appendix and they are shown in Fig. (a)-(i). In patient, K.H., late onset of the asymmetry is suggested by the lack of any marked differences in pattern on the two sides and absence of any abnormal configuration. Late onset is also indicated in V.P. for the same reasons. Comparatively late onset is likely in A.W. because the patterns are similar on right and left feet. Enlargement of the right foot has distorted the figure laterally without changing the configuration.

Early onset is suggested in R.B. by a very abnormal pattern on the left sole which is not rep-

resented on the right side. Similarly, in R.S., there is evidence of early onset of hypertrophy which has disturbed developing dermatoglyphic patterns on both feet. The other patients, A.B., E.C., C.P., and C.S. are probably intermediate in this respect, for the patterns show asymmetry only slightly more noticeable than that normally to be expected.

Genetical Data. The predominance of females in this small series is striking. Though appearances are more important in females, only in the less severe examples could this factor have been responsible for their seeking advice more frequently. Orthopaedic treatment would be required, regardless of cosmetic aspects, in either sex for some of the deformities. In the literature an excess of females and an excess of males have both been noted (Gesell, 1927; Ward and Lerner, 1947).

No parental consanguinity was found, and only

TABLE II
SUMMARY OF CYTOGENETICAL RESULTS*

Patient's Initials and Sex	Cells Counted							Notes
	< 45	45	46	47	> 47	Possibly Triploid	Tetraploid etc.	
(a) R.B.	—	4	84	—	—	—	—	—
(b) A.B.	1	—	29	—	—	—	—	6 cells trisomic for 19-20 in one culture
(c) E.C.	1	2	57	6	—	—	—	—
(d) K.H.	—	—	27	—	—	—	—	A centric fragment found in some cells of one culture
(e) C.P.	—	—	54	1	—	—	4	—
(f) V.P.	—	2	29	—	—	—	—	Two with 70, one with 74, one with more than 60
(g) C.S.	4	6	123	1	1	4	1	Large satellites on a small acrocentric; 6 cells with an acentric fragment
(h) R.S.	—	—	25	6	—	—	—	Enlarged satellite on a small acrocentric
(i) A.W.	—	—	12	—	—	—	—	—

* All karyotypes are considered to be effectively normal.

in one family (A.W.) is there a history of possibly similar developmental limb abnormalities. Scott (1935) reported a mother and daughter who were both affected, and Read (1925) recorded a brother and sister who were both affected. The parental ages at the patients' births were not remarkable (Table I).

The cytogenetic findings are summarized in Table II. Small biopsy specimens were taken in each case from the skin, and fibroblast cultures were carried out by the technique of Harnden (1960) with slight modifications. Only in one patient, C.S., was there any suggestion of a chromosomal abnormality. In the first culture, taken from the hypertrophied arm, there were 2, or possibly 3, triploid cells. A second biopsy was taken, on this occasion from the affected leg, but only normal diploid cells were found. Thus it is possible that the triploid cells in the first culture were artefacts.

The patient with diploid-triploid mosaicism described by Böök and Santesson (1960) was not reported to have asymmetry, but the patients described by Ellis *et al.* (1963) and by Ferrier, Ferrier, Stalder, Bühler, Bamatter, and Klein (1964) both showed underdevelopment which was regarded as hemiatrophy. The patient reported by Noé and Berman and one of those in Benson, Vulliamy, and Taubman's (1963) series had normal chromosomes. Although diploid-triploid mosaicism can be associated with marked asymmetry of the body, it seems to be of rare occurrence in cases selected on account of asymmetry.

Aetiology. Many theories have been advanced as to the cause of hemihypertrophy. Noé and

Berman (1962) have given a full review of the literature, with an assessment of the various suggestions, and they postulated as the basic cause damage to the mitochondria in an 'over-ripe' egg. Gorlin and Meskin (1962) were particularly interested in the dentition but they were unable to determine the time of initiation of the hypertrophy. They also suggested that the disturbance of growth in these patients could account for the reported high incidence of neoplastic disease, e.g. sarcoma of the lung. Benson *et al.* (1963) recorded an apparent association of hemihypertrophy with renal tumours. In the present series of patients no example of malignant disease was found.

As already mentioned, neurofibromatosis may produce hypertrophy, particularly when localized. Moore (1941) reported 4 such cases and pointed out the segmental relation between the affected nerve and the overgrowth. Hypertrophy also occurs in association with abnormalities of the lymphatic system (Williams, 1951) and with angiomas (Mullins *et al.*, 1962). Although these associations provide pointers as to the importance of neural and vascular factors, they clearly do not apply to all cases of asymmetry.

The present studies suggest that asymmetrical disturbance of growth, whatever its cause, may take place before the 8th week of pregnancy since in some cases, the dermal patterns are abnormal. In other cases, the basic pattern is normal but is distorted by overgrowth of the underlying tissues after the dermal ridges have been formed. Our cytogenetic results indicate that, though asymmetry has been found previously in diploid-triploid mosaicism, this cytological peculiarity is only

rare accompaniment of asymmetry. Congenital asymmetry therefore results from a number of causes effective at different stages of development.

Summary

Nine cases of asymmetry have been studied. There is no indication that they represent a condition which has uniform aetiology. Dermatoglyphic findings support the clinical indications concerning varying times of onset of the characteristic disturbances of growth. Cytogenetic studies indicated that one case may have been a triploid-diploid mosaic.

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Appendix

Clinical Details on Patients with Asymmetry (see also Fig. (a)-(i)).

(a) **R.B. ♀ aged 26 years.** The left leg is larger than the right; the foot is particularly affected, being broader and splayed. The left calf is 3.5 cm. larger at its maximal circumference and the foot 3 cm. wider than the right. Radiographs show diaphysal aclasia of the left knee.

The dermatoglyphic patterns on the left sole are unusual and show transverse loops beneath digits II and III as well as simplified configuration on the hallucal area. It differs greatly from the right which has a normal pattern. The hands show no abnormal markings.

(b) **A.B. ♀ aged 4 years.** The second of her mother's three previous pregnancies ended in the stillbirth of an anencephalic foetus.

The patient has excellent health and the hypertrophy does not limit her activity. The left arm and, more especially, the left leg are the larger. Radiographs show a skeletal development consistent with her chronological age; the left leg is 2.2 cm. longer than the right.

The dermatoglyphic patterns on the hands show perhaps rather more difference than is usual. The left hand contains strong thenar and first interdigital patterns which are absent on the right; a whorl on digit IV of the right hand and r^2 triradius are not repeated on the left side. The feet differ in that the right sole has a p triradius which does not occur on the left.

(c) **E.C. ♀ aged 45 years.** The patient is said to have been born with a deformed right foot, the big and second toes being particularly affected. Operations were performed at the ages of 5 and 13 years. At the age of 44, the right second toe was amputated. She feels the right foot to be warmer than the left. The whole foot, especially on the medial side, and the leg below the knee are abnormally large. The right middle finger is also definitely thicker than the left. Radiography of the foot in 1963 showed hypertrophy of the second toe and first metatarsal.

The histology of the toe amputated in 1963 showed a small junctional naevus but no other evidence of vascular or neurological disease. The subcutaneous tissues were increased in amount and showed some fibrosis. There was evidence of bony overgrowth.

FIG. (a)-(i). Tracings of dermatoglyphic main lines on prints of palms and soles of the patients appear on this and the following two pages.

The findings suggested macrodystrophia lipomatosa progressiva.

The dermal ridge patterns on the hands are in moderate agreement; there is a whorl on the right first digit and a r^o palmar triradius which are not represented on the left side. The loops in the third interdigital areas also differ slightly. The patterns of the feet are substantially similar and each shows one p triradius. The hallucal pattern, a digital loop on both sides, is enormously extruded on the right sole.

(d) **K.H. ♀ aged 16 years** (see Fig. 1). As an infant the patient suffered from eczema and she now has asthma. She works as a typist and uses both hands normally.

The hemihypertrophy affects the left side of the body, including the trunk, and there is a naevus over the right upper chest, anteriorly. The left leg is less severely affected than the left arm and hand; both are larger, rather than longer, than the right hand and arm, and they are puffy. There is no pitting oedema.

This patient was demonstrated to the Paediatric Section of the Royal Society of Medicine in November 1954 (*Proc. roy. Soc. Med.*, (1955), 48, 330). In 1952 to 1953 she had a pericardial effusion of unknown aetiology, but three years later her heart was considered to be normal.

The ridge patterns on the left and right hands dis-

agree slightly in that the whorls on the right digits IV and V are not repeated on the left. The palms are similar but the c triradius on the left hand is missing, a not unusual finding. The feet show very similar patterns though there is a tendency to zygodactyly of toes II and III only on the right side.

(e) **C.P. ♂ aged 57 years.** The patient's symptoms seem to date from trauma at the age of 13, which produced a quadriplegia. There was gradual improvement over the succeeding few months but on the right side there is residual weakness. The right side of his face and chest are smaller than the left. There is wasting in the right arm and leg with increased reflexes and an extensor plantar response. There is no movement in the upper cervical spine and radiographs show fusion of the upper five vertebrae of the Klippel-Feil type. Since the asymmetry involves the face and trunk, it presumably antedates the trauma. The wasting and pyramidal signs probably result from a lesion of the cervical cord subsequent to the injury.

There is a moderate degree of divergence between the patterns of the right and left hands. This is noticeable in the absence of hypothenar pattern on the left palm and the presence of an intense pattern on the right. The secondary triradius e on the left is matched by a secondary triradius a on the right. The right sole exhibits a whorl not shown on the left side. The greater intensity of pattern on the right as compared with the left side is hardly sufficient to indicate very early onset of the patient's asymmetrical growth changes.

(f) **V.P. ♀ aged 18 years.** In infancy the patient had an acute febrile illness which was called 'bronchitis'. At about the same time her left thigh was observed to be smaller than the right. This has persisted and the left foot is now slightly the smaller of the two. A bilateral first metatarsal osteotomy was performed in 1962.

There is obvious wasting and weakness of the left thigh and an absent knee-jerk on that side. The other reflexes are brisk and equal. There is shortening (1 in. (2.5 cm.)) of the left thigh. The atrophy is probably the sequela of unrecognized anterior poliomyelitis.

The finger-tip dermatoglyphics of right and left hands agree well; the whorl on the right thumb is balanced by one on left digit II. There is an extra loop in the interdigital area IV of the right hand. The plantar patterns on left and right soles agree very closely though a zygodactylous tendency of digits II and III is present only on the left side.

(g) **C.S. ♀ aged 9 years.** At birth her right arm and left leg were noticed to be longer than her left arm and right leg. Her activities are not limited. Examination showed the right arm to be 2.8 cm. longer than the left and the left leg to be 3 cm. longer than the right. The hypertrophy affects all dimensions; the longer limbs also appear to be thicker and heavier than the shorter ones. Radiographs show the skeletal and chronological ages to be consistent.

The finger ridge patterns on right and left differ only because ulnar loops on right III and V are replaced by whorls on left III and V. The right palm, however, has a much more extruded pattern in the hypothenar region on the left which includes a r' triradius. The sole patterns are similar on the two sides except that the left has a triradius f which is not represented on the right foot.

(h) **R.S. ♀ aged 44 years.** The right side of the patient's face is slightly larger than the left. Both hands are large, particularly on the radial side; the thumb and index fingers are noticeably enlarged. There is a naevus over the dorsum of the right hand and another extensive naevus over the right side of the trunk.

Her right leg is much larger than the left, though it is only the longer by 1 in. (2.5 cm.). Both legs are oedematous. Her toes are long; the right hallux has been amputated.

She has had focal fits but full neuroradiological investigation did not reveal a cause. A final diagnosis of neurofibromatosis with multiple vascular anomalies was made.

The finger ridge patterns differ somewhat on the two hands in that whorls on right I, left III, and left V are represented by loops on the other side. There is a small extra loop at the base of left IV, otherwise the

palmar patterns agree quite well. The whorl patterns on both feet show some distortion in that the tibial loop and e triradius present on the right foot are absent on the left. Both feet show a zygodactylous tendency.

(i) **A.W. ♀ aged 60 years (see Fig. 2).** A paternal uncle was born with a deformed arm and a paternal cousin with a paralysed leg and conjoined fingers on one hand.

The patient's deformity of the right foot has been present, probably from birth, and certainly for as long as she can remember. In 1952 this deformity was seen to consist of gross enlargement of the second toe and, to a lesser extent, of the first toe. The metatarsals were also involved.

At operation in 1952, the whole of the 2nd ray, phalanx, metatarsal, and cuneiform were removed. Histology showed marked fibro-fatty overgrowth involving all tissues together with generalized bony overgrowth, periosteal new bone formation and degenerative joint changes. This lesion belongs to the group sometimes referred to as 'macrodystrophia lipomatosa'.

The dermatoglyphic patterns on left and right sides agree very closely with one another; so also do those on the feet. However, the right hallucal whorl and the patterns on the area of the pad show great distortion by stretching in a lateral direction.