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Vascular Pattern and Limb Development

2. Angiographic findings in 48 malformed human upper extremities*)

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ABSTRACT

Accurate knowledge of the arterial variations of the congenitally malformed hand is of considerable practical importance not only in the process of reconstructive surgery in hand anomalies but also in the consideration of the time of teratogenic events.

Between 1964 and 1982, angiography was performed on 48 malformed upper extremities of 41 patients at the Department of Orthopedic Surgery, Hiroshima University School of Medicine. The malformations were classified according to modified Swanson's categories, and the relationship between external and skeletal malformations and vascular abnormalities was studied.

Radial ray deficiencies were often associated with hypoplasia or aplasia of the arteria (a.) radialis (12/15) and dysplastic arcus palmaris profundus (11/15). In cases of club hand and five-finger hand, persistence of the a. mediana was noted in a high frequency (8/10). Syndactyly (7 hands), brachysyndactyly (4 hands), Poland's syndrome (1 hand) and radial polydactyly (5 hands) were often associated with defective arcus palmaris superficialis (10/17). In cases of cleft hand (11 hands), vascular defects were rather inconspicuous. Cases of overgrowth (macrodactyly, 4 hands) showed almost normal vascular patterns. A patient with generalized skeletal abnormality (Apert's syndrome) had a defective arcus palmaris superficialis.

Angiographic findings in these cases were compared with descriptions by others, and the time of teratogenic events was estimated from descriptions of human limb morphogenesis and results of animal experiments. The estimated teratogenic periods are as follows: radial ray deficiencies, postovulatory (po) day 38 or earlier; failure of differentiation of parts, undergrowth (brachysyndactyly and Poland's syndrome) and Apert's syndrome, po day 39 or earlier; cleft hand, po day 37 or earlier and duplication(radial polydactyly), around po day 32.

INTRODUCTION

In many of the cases with congenitally malformed hands, abnormalities are observed in the vascular pattern in the upper extremity. A better understanding of characteristic vascular patterns in various hand malformations would be useful not only for determining the operative procedure in the treatment of malformed hands but also for studying teratogenesis in the hand.

Detailed studies have been made by Adachi[1] (1928) and McCormack et al.[23] (1953) on the vascular system of the normal human upper extremity and by Senior[27] (1926) and Singer[28] (1933) on its embryology. Recently, several systematic studies have been made on the angiography of congenitally malformed hands, especially in Japan. Noteworthy among these are the reports by Sudo[29] (1979), Inoue[15] (1981), Kitayama and Tsukada[21] (1982) and Kato et al.[20] (1983). According to some of these authors, vascular aberrations in malformed

*) 片桐則明：先天性奇形肢の血管系に関する臨床的実験的研究　2.先天性奇形手48例における血管系の検討

upper extremities are thought to indicate the time of teratogenic events.

The present author had an opportunity to examine a number of angiograms of patients with various hand malformations. The purposes of this report are (1) to describe arterial patterns in these malformed upper extremities, (2) to analyze the relationship between vascular changes and abnormal limb shapes, and (3) to estimate the time of teratogenic events by comparing findings in man with those obtained in experimental animals (Katagiri[19], 1983) and by reviewing the literature.

SUBJECTS AND METHODS

During the 19 year period from 1964 to 1982, angiographic examinations of the upper extremity were made as a preoperative diagnostic procedure on 48 extremities of 41 patients at the Department of Orthopedic Surgery, Hiroshima University School of Medicine. Among them, 26 extremities were of 22 male patients and 22 were of 19 female patients. The age of the patients ranged from a minimum of 8 months to a maximum of 28 years; the average was 4.1 years. Table 1 gives the classification of these cases according to Swanson's[30] categories (1976) modified by Tsuge et al.[32] (1980).

Table 1. Subjects for angiography by modified Swanson's classification

Failure of formation of parts	15 hands 11 patients
radial ray deficiencies	15 hands 11 patients
hypoplasia of the thumb	8 hands 5 patients
club hand (radial)	5 hands 5 patients
five-finger	2 hands 1 patient
Failure of differentiation of parts	18 hands 15 patients
syndactyly	7 hands 6 patients
cleft hand	11 hands 9 patients
Duplication	5 hands 5 patients
radial polydactyly	5 hands 5 patients
Overgrowth	4 hands 4 patients
Undergrowth	5 hands 5 patients
brachysyndactyly	4 hands 4 patients
Poland's syndrome	1 hand 1 patient
Generalized skeletal abnormalities	1 hand 1 patient
Total	48 hands 41 patients

For angiography, a 22 Elaster needle was inserted visually into the arteria (a.) brachialis of the affected limb under general anesthesia, and 3 to 10 ml of 65% Angiografin was injected. Angiograms were taken with a portable x-ray apparatus Atomscope-20D (Mikasa Co., Ltd).

To facilitate understanding of the description of abnormal cases, the arterial pattern in the normal upper extremity and its development, and definitions of several arterial abnormalities are given in the Appendix.

DESCRIPTION OF CASES

For each type of malformation, one or two illustrative cases are described individually. Findings in other cases are given summarily.

I. Failure of formation of parts (15 hands of 11 patients)

Radial ray deficiencies

a. Hypoplasia of the thumb

Angiograms were made on eight limbs. According to Blauth's[3] classification (1967), three hands belonged to Grade I, four hands to Grade IV and one hand to Grade V. The a. mediana was present in five limbs, hypoplasia of the a. radialis in four limbs, and defect of the a. radialis in one limb.

Case 1 (Fig. 1): A three year old boy with hypoplasia of the bilateral thumbs (Blauth's Grade I, bilaterally). The angiographic pictures of both limbs were almost identical. The a. mediana was present. The a. princeps pollicis branched from the a. mediana. The arcus palmaris profundus could not be visualized.

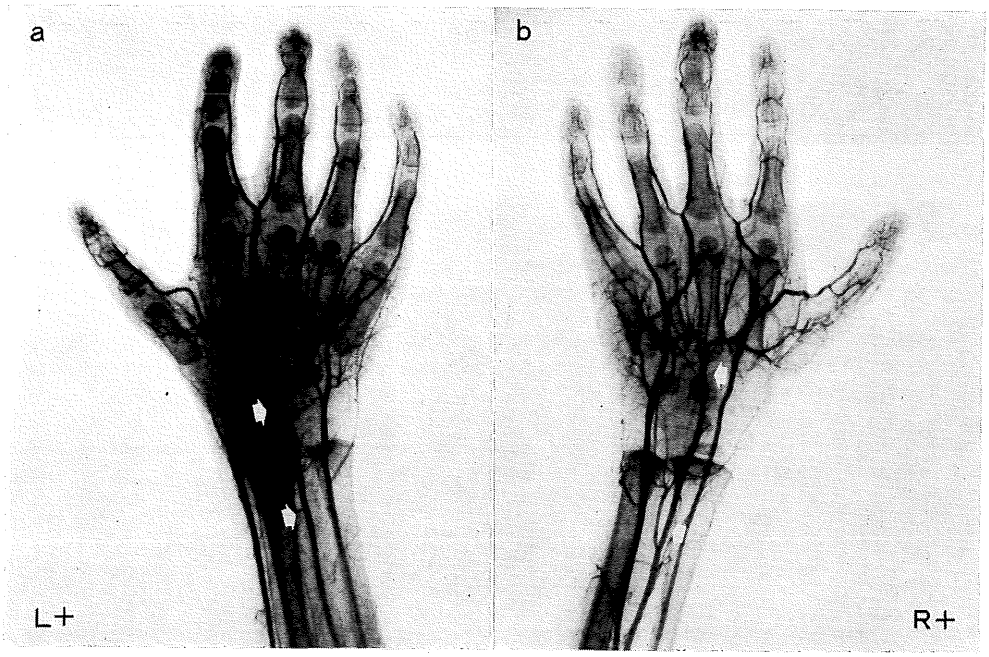

Fig. 1. Case 1. A three year old boy. Hypoplasia of bilateral thumbs (bilaterally, Brauth's Grade I). a: left hand b: right hand In both hands the a. mediana (arrow) is present and the arcus palmaris profundus is absent.

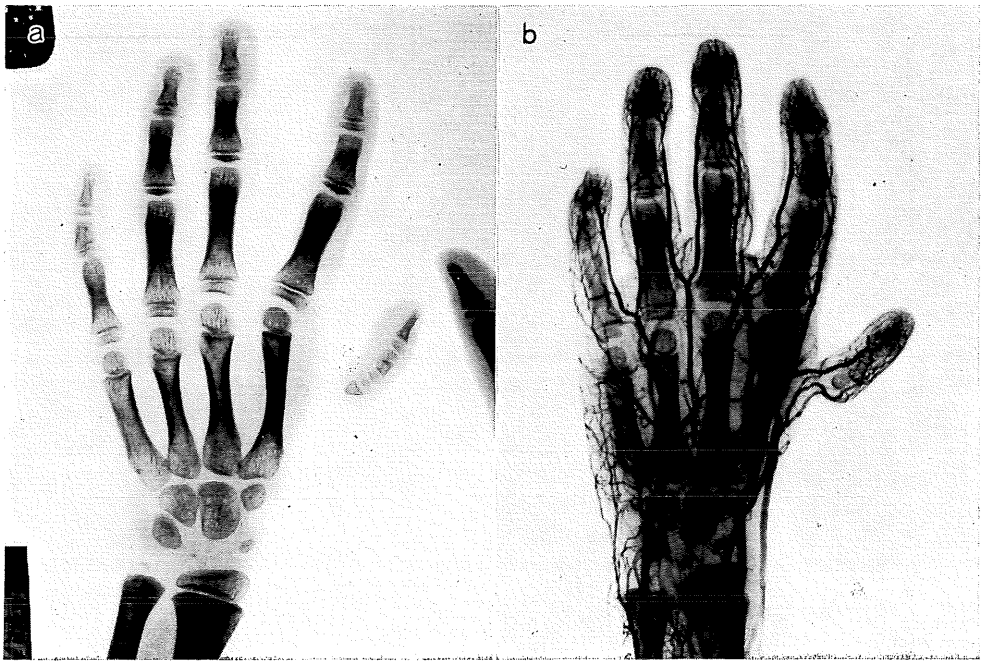

Fig. 2. Case 2. An eight year old boy. Hypoplasia of the right thumb (Blauth's Grade VI). The a. radialis is well formed.

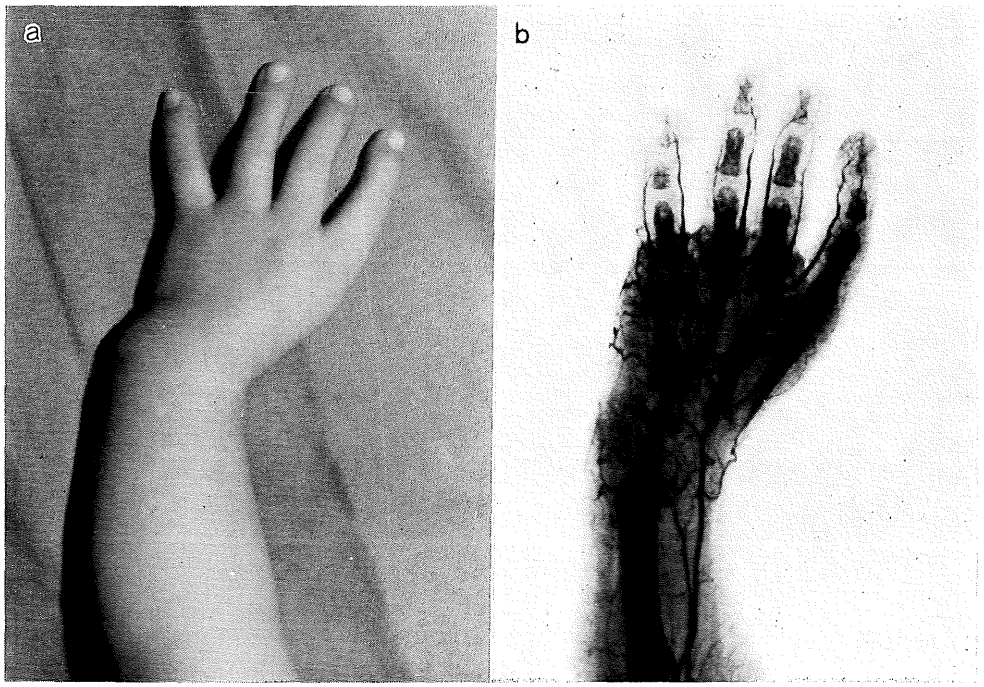

Fig. 3. Case 3. A two year old boy. Left club hand. The a. radialis is severely hypoplastic. The a. palmaris indicis radialis is present.

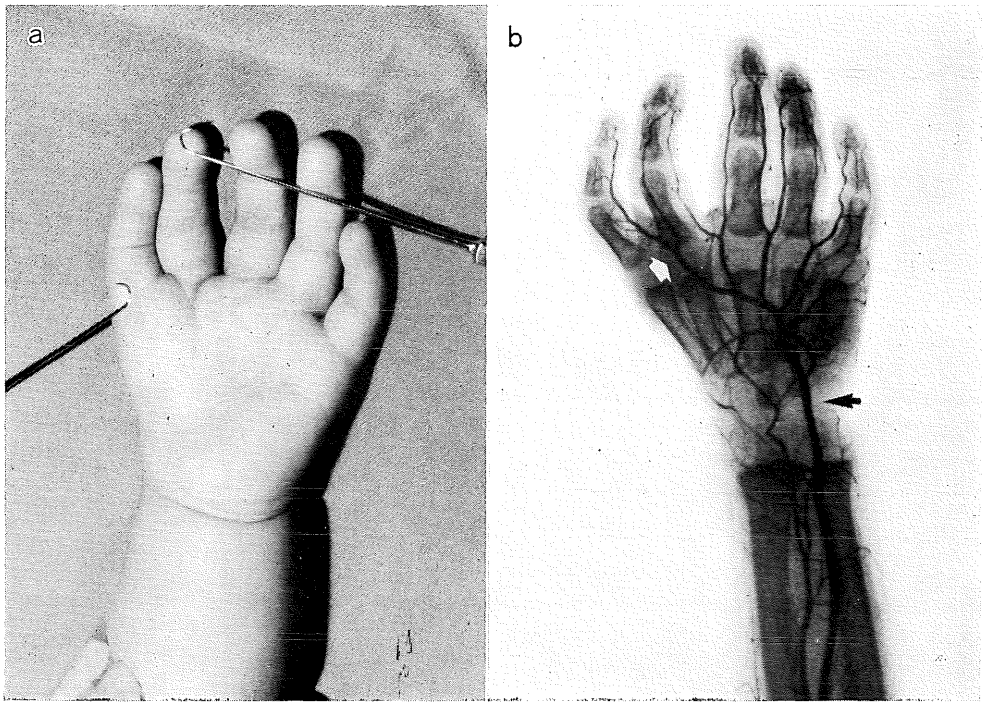

Fig. 4. Case 4. A two year old boy. Left five-finger. The a. ulnaris is well developed (black arrow) and the a. digitalis propriae radialis of the first finger is absent (white arrow).

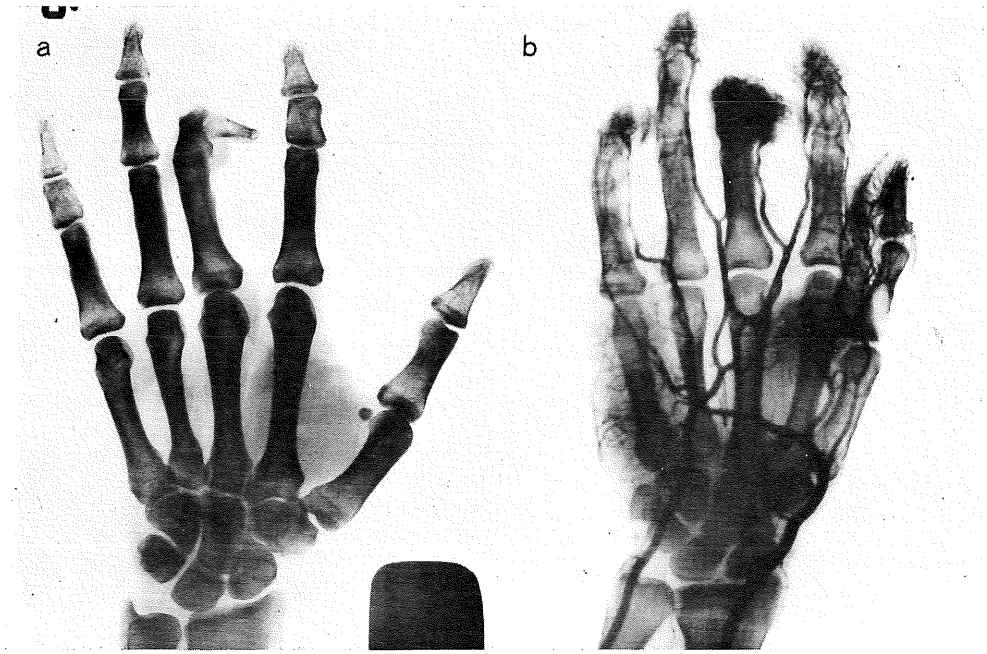

Fig. 5. Case 5. A 22 year old female. Right syndactyly (III-IV digit type). The arcus palmaris superficialis is defective and the branching point of the aa. palmares digitales is peripheral by two finger breadths.

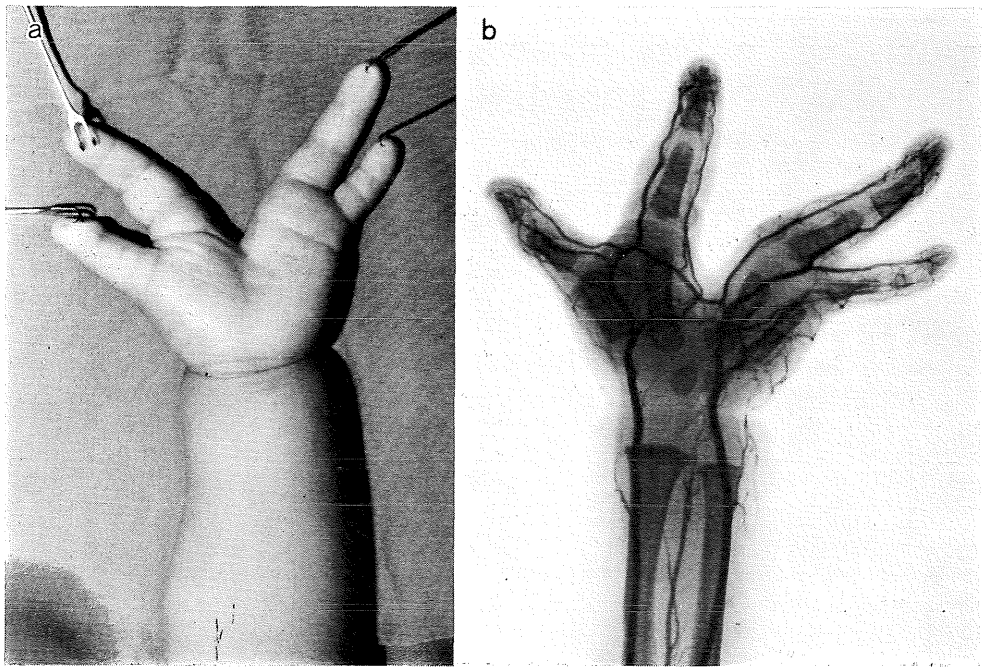

Fig. 6. Case 6. A one year old boy. Left cleft hand. The arcus palmaris superficialis is deviated to the radial side.

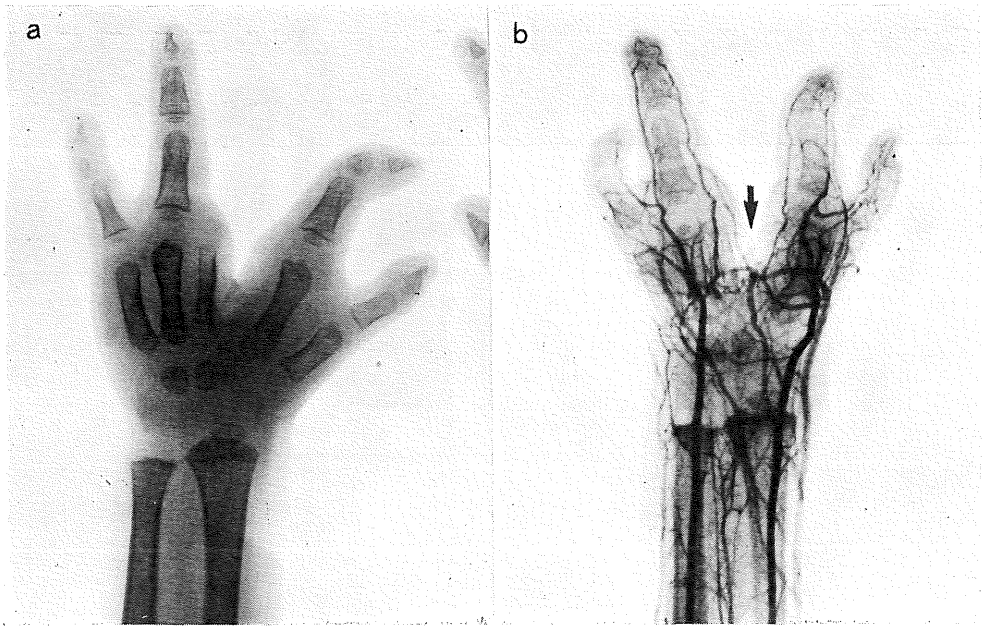

Fig. 7. Case 7. A two year old boy. Right cleft hand. The arcus palmaris superficialis (arrow) is defective.

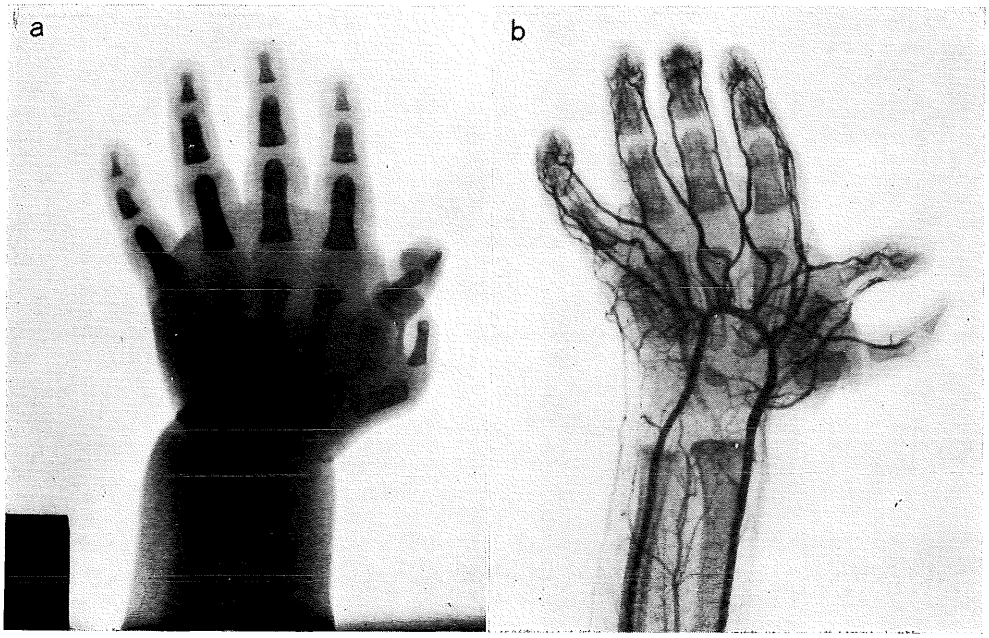

Fig. 8. Case 8. A one year old boy. Right radial polydactyly (Wassel's Type VI). The arcus palmaris superficialis is absent.

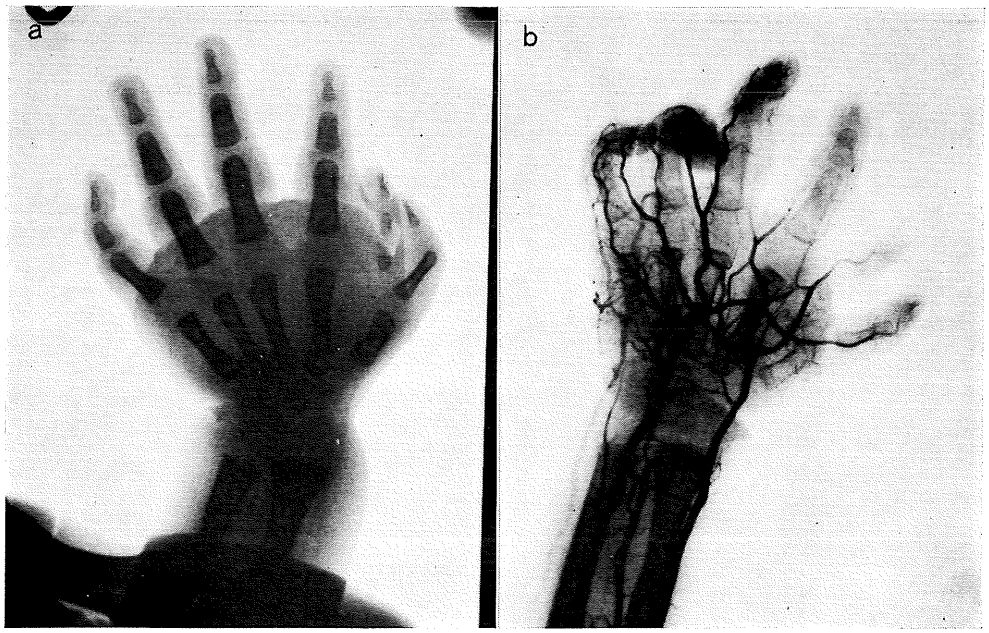

Fig. 9. Case 9. A one year old girl. Right radial polydactyly (Wassel's Type VII). The arcus palmaris superficialis belonging to Coleman's Type C is present.

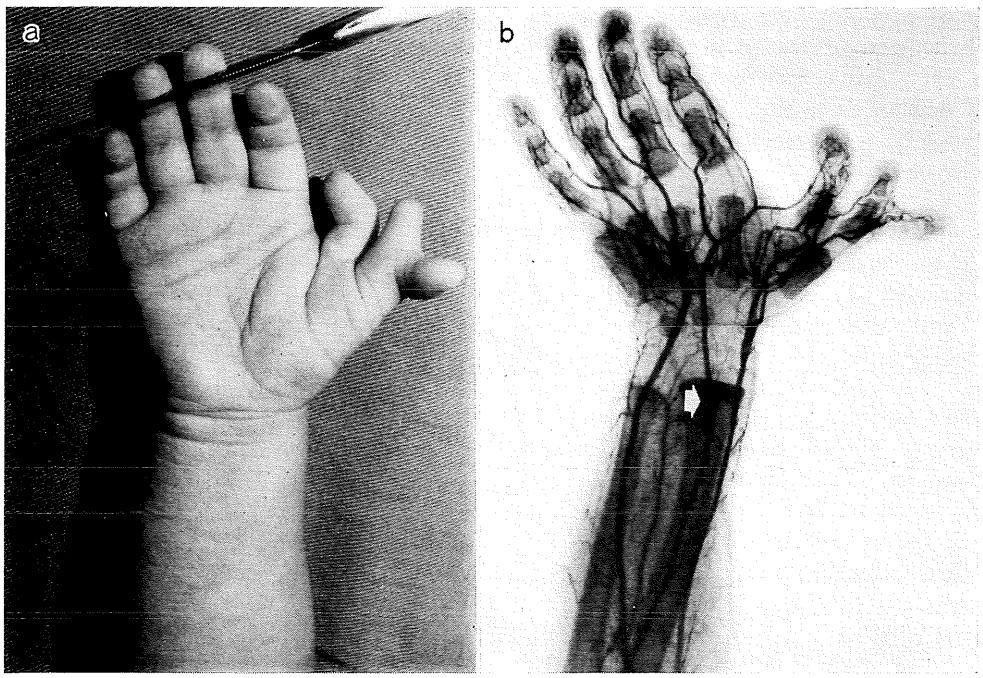

Fig. 10. Case 10. An 11 month old boy. Right radial polydactyly (unclassified type). The a. mediana (arrow) is present.

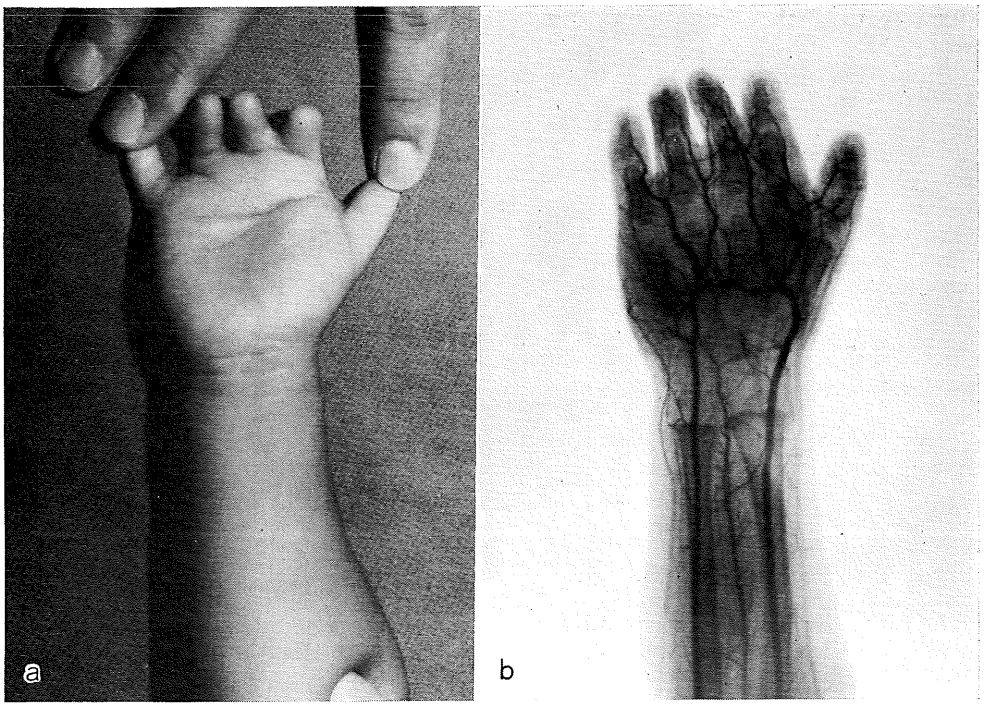

Fig. 11. Case 11. A two year old girl. Right brachysyndactyly. The arcus palmaris superficialis is absent and bifurcations from aa. digitales palmares communes to aa. palmares digitales are more peripheral than the normal hand.

Case 2 (Fig. 2): An eight year old boy with hypoplasia of the right thumb (Blauth's Grade VI). The a. radialis was relatively well formed and only one blood vessel of the thumb originating from the arcus palmaris superficialis could be observed.

b. Club hand

Angiograms were made on five limbs. According to Heikel's[10] classification (1959), one limb belonged to the radial hypoplasia type and three limbs to the radial aplasia type.

Case 3 (Fig. 3): A two year old boy with left club hand and complete radial aplasia. The a. radialis was severely hypoplastic, being of a trace level. The a. palmaris indicis radialis could be seen. Vascular findings were almost similar in other cases. In some cases, the a. palmaris indicis radialis was defective.

c. Five finger hand

Angiograms were made on two limbs.

Case 4 (Fig. 4): A two year old boy with bilateral five finger hands. Angiography was done on both limbs, and Fig. 4 shows the left one. As in the case of club hand, the formation of the a. radialis was severely hypoplastic with a defect of the a. digitalis palmaris radialis of the first finger. The a. mediana was persistent. Similar findings were obtained in the another limb.

II. Failure of differentiation of parts (18 hands of 15 patients)

a. Syndactyly

Angiograms were made on seven limbs. Among these, four were syndactyly of III–IV digit type and three were of IV–V digit type. The arcus palmaris superficialis was missing in four hands, of which two were of III–IV digit type and the other two were of IV–V digit type. Many cases showed hypoplasia of the aa. digitales palmares communes. In all hands, the branching point of the aa. digitales palmares propriae in the fused fingers was abnormally peripheral.

Case 5 (Fig. 5): A twenty-two year old female with syndactyly of III–IV digit type on both hands. Angiography was conducted on both hands. The arcus palmaris superficialis was missing in both hands and the branching

point of the aa. digitales palmares propriae was abnormally peripheral by two finger breadths.

b. Cleft hand

Angiograms were made on 11 limbs. Among these, three were of the one digital ray proximal defect type of Watari's[36] classification (1978) and eight were of the one digital ray distal defect type. One hand each of aplasia and hypoplasia of the arcus palmaris superficialis were found among cases of one digital ray distal defect type, and deviation of the arcus palmaris superficialis to the radial side was found in the remaining nine hands. All hands had an intact arcus palmaris profundus. No abnormalities were found in the forearm except for a case with persistence of the a. mediana and a case with dysplasia of the a. radialis.

Case 6 (Fig. 6): A one year old boy with a left cleft hand of one digital ray proximal defect type associated with a right monodactyly. The arcus palmaris superficialis deviated to the radial side and the a. palmaris pollicis was supplied by the arcus palmaris superficialis in both hands.

Case 7 (Fig. 7): A two year old boy with right cleft hand of one digital ray distal defect type. The arcus palmaris superficialis was missing and the arcus palmaris profundus was hypoplastic.

III. Duplication (five hands of five patients)

Radial polydactyly

Angiograms were made on five hands. By Wassel's[35] classification (1969), two hands belonged to Type VI, two hands to Type VII, and one hand to the unclassified type. The arcus palmaris superficialis was missing in three limbs of Type VI and the a. mediana was persistent in two limbs, one of Type VII and one of the unclassified type. In four hands, the ulnar thumb had two arteries and the radial thumb had one artery. In one hand, the two thumbs had one artery each.

Case 8 (Fig. 8): A one year old boy with right radial polydactyly of Wassel's Type VI. The arcus palmaris superficialis was absent. Two arteries were observed in the ulnar thumb and one artery in the radial thumb.

Case 9 (Fig. 9): A one year girl with right radial polydactyly of Wassel's Type VII. The arcus palmaris superficialis was of Coleman's[7] Type C (1961), and one a. princeps pollicis and one a. digitalis palmaris propria were noted in the ulnar thumb and radial thumb, respectively.

Case 10 (Fig. 10): An eleven month old boy with right radial polydactyly of the unclassified type (Desnoyers[8], 1924). The a. mediana was present and the arcus palmaris profundus was also formed, though it was very thin. The thumb arteries were supplied by the a. mediana and a. radialis.

IV. Overgrowth (four hands of four patients)

Macrodactyly

The affected fingers in these limbs were II and III in two cases, II only in one case and IV and V in one case. No abnormalities were found in the forearm and palm. The a. digitalis palmaris propria on the cancave side of the hyperplastic finger was crooked, while that on the convex side was hypoplastic.

V. Undergrowth (five hands of five patients)

a. Brachysyndactyly

Angiograms were made on four limbs. All cases belonged to the short finger type of Blauth and Geleler (1971)[5].

Case 11 (Fig. 11): A two year old girl with right brachysyndactyly. As in the cases of syndactyly, the arcus palmaris superficialis was missing and the branching point of the aa. digitales palmares propriae was abnormally peripheral. No abnormalities were observed in the forearm in all cases.

b. Poland's syndrome

One case was observed. The patient was a six year old boy. Brachysyndactyly of the left hand and aplasia of the ipsilateral m. pectoralis major were noted. The branching point of the aa. digitales palmares propriae was abnormally peripheral. No other vascular abnormalities were observed.

VI. Generalized skeletal abnormalities (one limb of one patient)

Apert's syndrome

One case was observed. The patient was a two year old boy with bilaterally deformed hand. Angiography was performed on the right limb. The a. mediana was persistent, and the a. radialis was hypoplastic. The arcus palmaris superficialis was defective, and the branching point of the aa. digitales palmares propriae was abnormally peripheral.

Table 2. Abnormal arterial patterns in various hand malformations

Type of hand malformations	No. of hands	Arterial abnormalities			
		p. a. m.	a. r.	a. p. p.	a. p. s.
radial ray deficiencies	15				
hypoplasia of the thumb	8	−−++	000⊠	00⊠⊠	00××
		++++	××⊠⊠	00⊠⊠	×⊠00
club hand	5	−−−	××⊠	××⊠	000
		−−	××	××	00
five-finger	2	++	××	⊠⊠	00
syndactyly	7	−−−	000	000	0×0
		−+−−	0000	0000	×××0
cleft hand	11	−−−−+	0000⊠	00000	0000⊠
		−−−−−−	000000	000000	0×0000
radial polydactyly	5	−−	00	00	0×
		−++	000	000	×0×
overgrowth	4	−−	00	00	0×
		−−	00	00	00
brachysyndactyly	4	−−	00	0⊠	×0
		−−	00	00	×0
Poland's syndrome	1	−	0	0	×
generalized skeletal abnormalities	1	+	⊠	0	×
Total	48				

The symbols are arranged in the order of the cases.
The *i*th symbol in each column shows the finding in the *i*th case.

p. a. m. : persistence of the a. mediana
a. r. : a. radialis
a. p. p. : arcus palmaris profundus
a. p. s. : arcus palmaris superficialis

\+ : present
− : absent
0 : normal
⊠ : dysplasia
× : defect

ANALYSIS BY TYPE OF VASCULAR ABNORMALITIES*

In this section, the findings obtained are analyzed according to types of vascular abnormalities (Table 2) with reference to pertinent literature.

1. Persistence of the a. mediana

The prevalence rate of the a. mediana is 8.0% in the Japanese (Adachi[1], 1928) and 9.9% in the Americans (Coleman and Anson[7], 1961). Among the author's cases, 27.1% had this abnormality, which is about threefold higher than the heretofore reported rates. In particular, a very high rate of 53.3% was observed in cases with radial ray deficiency.

Other types of vascular abnormalities frequently occurred with persistence of the a. mediana. Among the six hands with hypoplasia of the thumb, defect and hypoplasia of the a. radialis were found in two and three limbs, respectively. However, the a. ulnaris showed normal development in all of these cases. Both of the two limbs with five finger hand showed defect of a. radialis. Each case of cleft hand and Apert's syndrome were also associated with hypoplasia of the a. radialis. Among these nine cases with persistence of the a. mediana and dysplasia of the a. radialis, only one limb with cleft hand had an a. mediana which adequately compensated the defective a.

* In the present study, the frequency of high branching of the a. radialis, which has been often described in cases of malformed upper limbs, was not ascertained, because the proximal portion of the upper arm could not be visualized.

radialis in supplying blood to the hand. In the remaining eight cases, a well developed a. ulnalis seemed to compensate the defective a. radiaris.

2. Dysplasia of the a. radialis

Among the author's 48 cases, defect of the a. radialis was observed in eight limbs (16.7%) and hypoplasia of the artery in six limbs (12.5%). As described earlier, dysplasia of the a. radialis was frequently associated with persistence of the a. mediana, that is, in nine limbs (64.4%) out of 14 limbs. As for skeletal malformations, radial ray deficiency was most frequently noted among the cases with this arterial abnormality, that is, in 12 out of 14 limbs.

3. Abnormality of the arcus palmaris profundus

Among the author's cases, 12 hands (25%) showed dysplasia of the arcus palmaris profundus. This frequency was about 10 times higher than the frequency of 3% reported in externally normal hands (Coleman and Anson[7] 1961). Among these cases, 10 limbs were associated with dysplasia of the a. radialis. All of the 10 cases were of radial ray deficiency.

4. Abnormality of the arcus palmaris superficialis

This type of vascular abnormality was observed in 18 hands (37.5%), a frequency which is about twofold higher than the frequency of 21.5% reported in externally normal hands (Coleman and Anson[7] 1961). Coexistence of defects in the arcus palmaris profundus and the arcus palmaris superficialis was noted in two hands, both of which showed persistence of the a. mediana. Only two hands with this type of vascular abnormality were associated with dysplasia of the a. radialis. When compared with the abnormality of the arcus palmaris profundus, association of dysplasia of the a. radialis was far less frequent.

When analyzed according to external malformations, four (26.7%) out of 15 hands with radial ray deficiency had this vascular abnormality, a frequency which is almost comparable to that in externally normal hands. Among the cases with polydactyly and syndactyly, this vascular abnormality was noted in 10 (58.8%) out of 17 hands, a rate about twofold higher than that in externally normal hands.

DISCUSSION

Much discussion has been made on the vascular origin of congenital limb malformations (see Katagiri[19], 1983). The cases described in the present report have clearly demonstrated that skeletal malformations of the limbs are closely associated with abnormal arterial patterns. What is the relationship between skeletal and arterial malformations? Hootnick et al.[11] (1980) mentioned that "whether one of the malformations precedes the other, or whether both are manifestations of a more fundamental deficiency, remains unknown". Probably the relationship is various. The present author has concluded from his findings in malformed limbs experimentally induced by 5-fluorouracil (5-FU) that an abnormal arterial pattern reflects an abnormal patterning of mesenchymal condensations (Katagiri[19], 1983). However, there may be other types of relationship. Some cases of unilateral transverse limb reductive defects were suggested to be the result of an intrauterine vascular accident involving the brachial artery with subsequent ischemia, necrosis, and ultimate resorption of structures distal to the vascular occulusion(Hoyme et al.[12], 1982). In a different situation, both the arterial and skeletal systems may simultaneously be vulnerable to teratogenic insult (Hootnick et al.[11], 1980).

Sudo[29] (1979) and Inoue[15] (1981) systematically reviewed the angiograms of various types of hand malformations and estimated the time of teratogenesis from altered arterial patterns. Their estimations depend on descriptions of normal development of the arteries in the upper extremity (Singer[28], 1933) (Fig. 13). They assumed that an abnormal skeletal pattern with an abnormality in a certain artery was produced at the time of formation of the artery. For example, radial ray deficiency is often associated with dysplasia of the arcus palmaris superficialis, agensis of the a. radialis and persistence of the a. mediana. According to Singer[28] (1933), the arcus palmaris superficialis is formed in embryos about 18 mm long, the a. brachialis superficialis, of which the distal portion becomes the a. radialis, develops in embryos 21 mm long, and the a. mediana undergoes retrogression in embryos 23 mm long. Sudo translated the embryonic length into postovulation age in days and estimated that the radial ray deficiency

resulted from teratogenic insult between day 48 and day 51 postovulation.

In the author's experiment, it was elucidated that an abnormal arterial pattern in a malformed limb did not directly indicate the time of teratogen administration. There were some time gaps between the standard time of normal formation of the artery which was affected by the teratogen and the actual time of teratogen treatment. The time gap length differed among different types of malformation. These results strongly indicate that the time of teratogenesis estimated by Sudo needs reappraisal.

In the following sections, angiographic findings of the author's cases are compared with descriptions by others, and the time of teratogenic events is estimated from descriptions of human limb morphogenesis and results of animal experiments for each type of malformation.

I. Failure of formation of parts

Radial ray deficiencies

As angiography is a prerequisite in reconstructive surgery for radial ray deficiencies (Tsuge[31], 1974), a relatively large number of reports have been published on the angiographic findings of this category of malformations (Edgerton et al.[9], 1965; Ikeda et al.[13], 1968; Blauth[4], 1969). The reported major findings are aplasia or hypoplasia of the a. radialis, persistence of the a. mediana, and remarkable development of the a. ulnaris. The author's findings are generally consistent with these reports.

Sudo[29] (1979) estimated the time of development of radial ray deficiencies as postovulatory (po) days 48–51. Normally, the mesenchymal condensation of the radius appears at Carnegie stage 16, around po day 38 (Yasuda[39], 1976). In the author's animal experiment, reductive malformations of the hindlimb, though not exactly corresponding to the radial ray deficiency, occurred after the teratogen treatment at day 11.5, when the external features of the mouse hindlimb bud roughly correspond to those of the human upper limb bud at Carnegie stage 15 (Yasuda[40], 1977a), around po day 37. Hence, it is reasonable to assume that radial ray deficiencies result from teratogenic insult around po day 38 or earlier. In the Japanese cases of thalidomide embryopathy, of which many show radial deficiencies, thalidomide was ingested by the mothers during the period ranging from the 39th to the 49th day counting from the first day of the last menstrual period (Kajii et al.[17], 1973). The above mentioned estimated time of teratogenesis of radial ray deficiencies roughly corresponds to the end of the clinically obtained critical period for thalidomide embryopathy.

II. Failure of differentiation of parts

Syndactyly, brachysyndactyly and Poland's syndrome

Several common features in aberrant vascular patterns were observed in syndactyly, brachysyndactyly, and Poland's syndrome. Therefore these anomalies are discussed together, although brachysyndactyly and Poland's syndrome belong to undergrowth according to modified Swanson's categories. The common findings in this group of anomalies were defect of the arcus palmaris superficialis, hypoplasia of the aa. digitales palmares communes, and distal displacement of the branching point of the aa. digitales palmares propriae. The first feature was described by Inoue[15] (1981) and the last was reported by Sudo[29] (1979) and Inoue[15] (1981).

Pathogenesis of syndactyly may be various. Yasuda[41] (1977b) described the pathogenetic processes for syndactyly as follows: Interference of physiological cell death in the interdigital areas, which occurs just after the digital ray formation; interference of breaking up of the mesodermal maintenance factor of apical ectodermal ridge (AER) into five limited digital areas around the time of digital ray formation; and hemorrhage in the hand plate after digital ray formation. Miura[25] (1982) has suggested that simple syndactyly and syndactyly in split hand are pathogenetically different from brachysyndactyly, the former being results of abnormalities in the AER and the latter being results of abnormalities in the mesenchyme.

At any rate, the teratogenic event is estimated to have occurred around the time of digital ray formation for the majority of syndactylous cases.

Sudo[29] (1979) estimated the time of development of syndactyly as po days 48–51. This time is about 10 days later than the time of formation of digital rays in the normal human hand, that is, around po day 39. Imagawa[14] (1980) succeeded in producing brachysyndactyly-like malformations in the forelimb of mouse

embryos by 5-FU treatment at day 11.0, when the external features of the mouse forelimb bud roughly correspond to those of the human upper limb bud at Carnegie stage 15 (Yasuda[40], 1977a), around po day 37. It is reasonable to estimate the teratogenic time for syndactyly as po day 39 or earlier.

In the case of Poland's syndrome, the main finding of arterial abnormalities, the distal displacement of the branching point of the aa. digitales palmares propriae, was in agreement with that reported by Ireland et al.[16] (1976) and Sudo[29] (1979). This feature was common to other types of syndactyly.

The primordium of the musculus pectoralis is recognizable at Carnegie stage 16 (Lewis[22], 1902; O'Rahilly and Gardner[26], 1975). This stage is close to the stage of formation of digital rays, Carnegie stage 17. Hence, it is natural for many investigators to consider that pectoral and digital anomalies occur at the same period of development (Walker[34], 1963; Sudo[29], 1979). Miura[24] (1978) mentioned that this syndrome might have resulted from a defect in the mesenchymal phalangeal mass induced by a fetal environmental factor. Bouvet et al.[6] (1976) suggested that hypoplasia of the proximal portion of the a. subclavia might be pathogenetic event for this malformative association.

Sudo[29] (1979) estimated the time of development of Poland's syndrome as po days 48-52. This time is about 10 days later than the time of digital ray formation in the human hand. Although there has been no animal model of Poland's syndrome, it is reasonable to assume the teratogenic time for this syndrome to be po day 39 or earlier.

Cleft hand

Previous angiographic reports on cleft hand have given fairly high frequencies of dysplasia of the arcus palmaris superficialis: six out of seven (86%) by Sudo[29] (1979), eight out of 14 (64%) by Inoue[15] (1981), and four out of nine (44%) by Kato et al.[20] (1983). Among the author's cases, however, this type of anomaly was found only two out of 11 hands (18%), corresponding to the frequency in externally normal hands. The reason for this difference in frequency is unknown. Kato et al. analyzed the relationship between dysplasia of the arcus palmaris and the proximo-distal level of the skeletal defect. They concluded that arcus palmares superficialis and profundus were both present, or only the arcus palmaris superficialis was defective in cases with a skeletal defect distal to the metacalpophalangeal (MP) joint, and that defects of the arcus palmaris profundus were frequently observed in cases with a metacalpal defect. In the author's cases dysplasia of the arcus palmaris superficialis was found only in the cases of one digital ray distal defect type, and the cases of one digital ray proximal type, in which the skeletal defect was proximal to the MP joint, had an intact arcus. The applicability of the conclusion by Kato et al. should be reexamined with further accumulation of cases.

Sudo[29] (1979) estimated the time of development of central ray deficiencies (cleft hand) as po days 48-52. Normally, the digital rays in the hand appear at Carnegie stage 17, around po day 39 (Yasuda[39], 1976). Yasuda[37] (1975a) detected an early cleft hand in a human embryo at Carnegie stage 16, around po day 38. Watari[36] (1978) was able to induce cleft foot in the mouse by 5-FU injection at day 11.0, when the external features of the mouse hindlimb bud roughly correspond to those of the human upper limb bud at Carnegie stage 14 (Yasuda[40], 1977a), around po day 35. In the author's experiment deformities of cleft foot type were found in the group treated at day 11.5, which corresponds to po day 37 in man. From these findings the teratogenic time for cleft hand is estimated to be around po day 37 or earlier.

III. Duplication

Radial polydactyly

The main features of angiographic findings in the author's cases were defect of the arcus palmaris superficialis (3/5=60%) and persistence of a. mediana (2/5=40%). The incidence of defect of the arcus palmaris superficialis in polydactylous hands reported by Inoue[15] (1981) was four out of 22 hands (18.1%) and that by Kitayama and Tsukada[21] (1982) was four out of 36 hands (11%), being much lower than the incidence in author's cases. The reason for this difference is unknown. Accumulation of a larger number of cases is awaited.

Kitayama and Tsukada[21] (1982) noted that two arteries were distributed to the duplicated thumbs in 27 out of 36 hands (75%) with radial polydactyly. The ulnar and radial thumbs had one artery each. From this finding

they have suggested that the radial polydactyly may have resulted from separation of a thumb primordium rather than excessive formation of a new primordium. In Inoue's cases, eight out of 18 hands (44%) showed this type of arterial distribution to the thumbs. In the author's cases, however, a similar situation was observed only in one out of five hands (20%) with radial polydactyly. Kitayama and Tsukada's hypothesis should await further studies.

It has been well established that hyperplasia, preaxial extension, and delayed involution of the AER lead to formation of polydactyly both in man (Yasuda[38], 1975b) and in experimental animals (see review by Kameyama[18], 1977). These events occur before and around the time of digital ray formation.

Sudo[29] (1979) estimated the time of development of radial polydactyly as po days 48–51. Kitayama and Tsukada[21] (1982) have made detailed estimations; po day 51 for Wassel VII type, po day 48 for Wassel IV type, and po day 52 for Wassel II type. These days are more than a week later than the time of digital ray formation in the human hand. The author succeeded in producing preaxial polydactyly in the mouse hindlimb by 5-FU treatment at day 10.5, when the external features of the mouse hindlimb bud roughly correspond to those of the human upper limb bud at Carnegie stage 13 (Yasuda[40], 1977a), around po day 32. Kameyama[18] (1977) reported that the critical period for polydactyly in mice is from day 9.5 to day 10.5. Therefore, the teratogenic time for radial polydactyly is estimated to be around day 32.

IV. Overgrowth

Macrodactyly

No abnormalities were observed in the basic skeletal and vascular patterns in the macrodactylous hands. Therefore, this malformation is considered to occur after completion of formation of digital rays and main arteries. A similar conclusion was reported by Sudo[29] (1979).

V. Generalized skeletal abnormalities

Apert's syndrome

The main findings of arterial abnormalities were defect of the arcus palmaris superficialis, hypoplasia of the aa. digitales palmares communes, and distal displacement of the branching point of the aa. digitales palmares propriae. Hypoplasia of the a. radialis and persistence of the a. mediana were also noted.

The foregoing discussions clearly indicate that the teratogenic time estimated only from vascular patterns is later than the time estimated from animal experiments and human embryology. The presence of time gaps between vascular pattern formation and teratogen administration noted in the author's experiment is consistent with this indication.

Because of these time gaps, estimation of the time of teratogenic insult in clinically observed hand malformations should not be made only from the abnormal vascular pattern but should depend on various information on the case. Clarification of the role of vascular aberrations in teratogenesis of the limb awaits further experimental and clinical observations.

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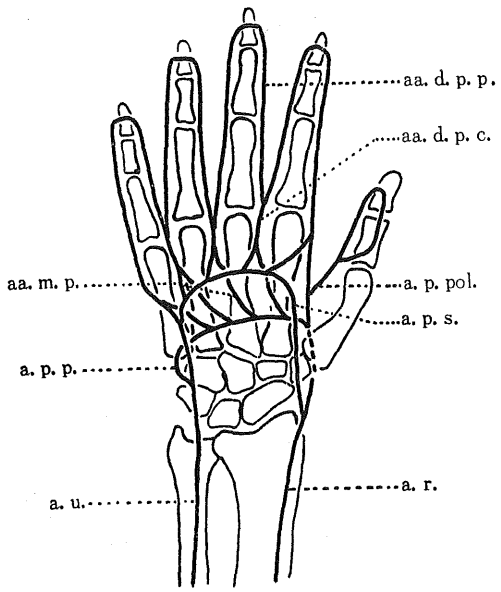
APPENDIX

Arterial pattern in the normal upper extremity and its development and definition of arterial abnormalities

In the normal upper extremity, the a. brachialis begins from the lower margin of the musculus pectoralis major and divides into the a. radialis and a. ulnaris at a point 2–3 cm peripheral to the elbow joint (Anderson[2], 1978) (Fig. 12). The a. radialis runs along the radial side of the forearm and before bending toward the dorsal side of the hand at the wrist joint, it gives off the ramus palmaris superficialis, which forms the arcus palmaris superficialis by anastomosing to the ramus palmaris superficialis of the a. ulnaris. After passing between the first interdigital space from the dorsal side of the hand, it again appears on the palm and then divides into the ramus profundus and a. princeps pollicis. The a. princeps pollicis further



Abbreviations

a. u.	: a.ulnaris
a. r.	: a. radialis
a. p. p.	: arcus palmaris profundus
a. p. s.	: arcus palmaris superficialis
aa. m. p.	: aa. metacarpeae palmares
aa. d. p. c.	: aa. digitales palmares communes
a. p. pol.	: a. princeps pollicis
aa. d. p. p.	: aa. digitales palmares propriae

Fig. 12. Arterial pattern in the normal right hand.

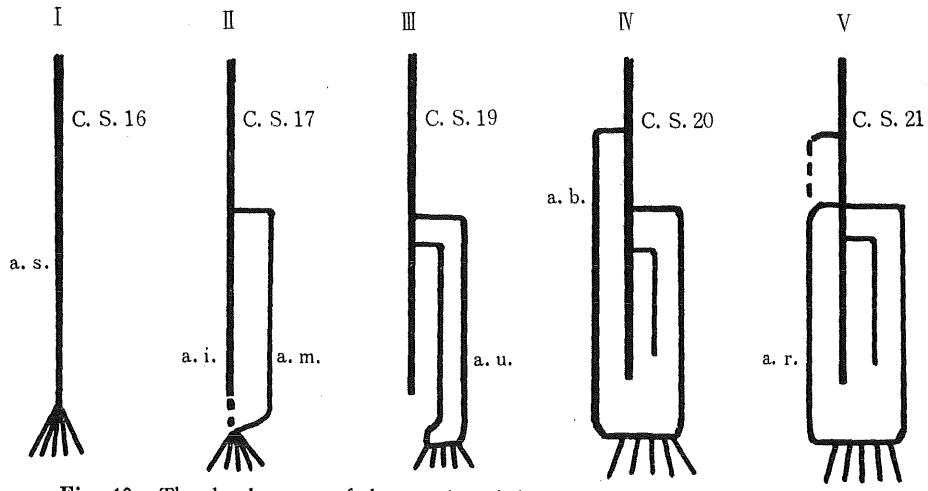


Fig. 13. The development of the arteries of the normal upper extremity in man.

Abbreviations

C. S.	: Carnegie stage
a. i.	: a. interossea
a. u.	: a. ulnaris
a. r.	: a. radialis
a. s.	: a. subclavia
a. m.	: a. mediana
a. b.	: a. brachialis superficialis

branches at the distal end of the thenar muscles into two aa. digitales which run toward the thumb and the radial side of the index finger. The ramus palmaris profundus forms the arcus palmaris profundus by anastomosing the ramus palmaris profundus of the a. ulnaris. The a. ulnaris reaches the palm and divides into the rami palmares superficialis et profundus, and these rami anastomose with the terminal branches of the a. radialis. The aa. digitales palmares communes which arise from the arcus palmaris superficialis unite at the level of the MP joints with the aa. metacarpeae palmares which arise from the arcus palmaris profundus. Then the aa. digitales palmares communes divide into the aa. digitales palmares propriae.

The developmental history of the vascular system in the upper extremity can be summarized as follows (Senior[27], 1926; Singer[28], 1933; Tsuzuki[33], 1957) (Fig. 13).

Stage I: Around Carnegie stage (C. S.) 16, the a. subclavia extends into the hand plate, and a vascular network is formed.

Stage II: Around C. S. 17, the distal portion of the a. subclavia becomes the a. interossea, from which the a. mediana arises. With the development of the a. mediana, the a. interossea degenerates. The a. mediana fuses with the distal portion of the a. interossea in the hand plate.

Stage III: Around C. S. 19, the a. ulnaris arises from the a. brachialis and unites distally with the a. mediana to form the arcus palmaris superficialis.

Stage IV: Around C. S. 20, the a. brachialis superficialis, of which the distal portion becomes the a. radialis, arises from the proximal portion of the a. brachialis. It unites distally with the a. ulnaris to form the arcus palmaris profundus. Simultaneously, the a. mediana undergoes degeneration.

Stage V: Around C. S. 21, an anastomotic branch between the a. brachialis and a. brachialis superficialis develops at the elbow to form the a. radialis. The proximal portion of the a. brachialis superficialis becomes atrophic subsequently. As described by O'Rahilly and Gardner[26] (1975), the vascular system of the upper extremity at this stage resembles that of the adult, similar to the bones, joints, muscles, and nerves.

Abnormalities of the arterial pattern in angiograms are defined as follows:

According to Coleman and Anson[7] (1961) the a. interossea is rarely connected with the arcus palmaris. When an artery running in the center of the forearm supplies the arcus palmaris, this condition is defined as persistence of the a. mediana.

When the a. radialis does not reach the arcus palmaris, this is defined as defect of the a. radialis.

When the diameter of one of the a. radialis and a. ulnaris is smaller than a half of the other, this is defined as dysplasia of one of the arteries.

When the ramus palmaris profundus of the a. radialis and that of the a. ulnaris do not anstomose, this is defined as defect of the arcus palmaris profundus.

When the diameter of the arcus palmaris profundus is less than a half of that of the arcus palmaris superficialis, this is defined as dysplasia of the arcus palmaris profundus.

When the ramus palmaris superficialis of the a. radialis and that of the a. ulnaris do not anastomose, or when none of these communicates with a persistent a. mediana, this is defined as defect of the arcus palmaris superficialis.

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