Review article

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Triphalangeal thumb

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SUMMARY Triphalangeal thumb (TPT), a rare malformation of uncertain pathogenesis, may occur as an isolated defect, in association with other malformations of the hands, or as a feature of a syndrome or sequence. Isolated TPT occurs in two functional types: opposable and non-opposable. The latter appears to be inherited as a simple autosomal dominant trait, while the former is generally sporadic. TPT is associated with a number of specific malformations of the hand or foot, several of which have a well documented autosomal dominant pattern of inheritance. TPT is a feature of a number of specific syndromes. In this setting it may be associated with radial hypoplasia, bone marrow dysfunction, congenital heart disease, lung hypoplasia or agenesis, anorectal malformations, sensorineural hearing loss, onychodystrophy, mental retardation, and other disorders. TPT serves as a useful marker in such patients; in conjunction with the clinical and radiological findings, it can help to establish the correct diagnosis, leading to appropriate management and genetic counselling.

Congenital abnormalities of the first digital ray (thumb and first metacarpal) occur in a number of complex developmental disorders (table 1).[1 2] One such abnormality, the triphalangeal thumb (TPT), a long finger-like first digit with three phalanges instead of two, may occur as an isolated defect, in association with other abnormalities of the hand, or as a component of rare malformation syndromes (table 2). In the latter, TPT serves as a useful marker; in conjunction with the clinical and radiological findings, it can help establish the diagnosis, leading to appropriate management and genetic counselling.

TPT is rare. First described by Renaldi Columbi in 1559,[3] about 140 cases of TPT have been reported in the past century.[4] A 1943 study of 73 000 military draftees suggests that the prevalence rate of TPT in the general population is about 1:25 000.[5] Triphalangy of the big toe is even more uncommon,[6] with fewer than 15 cases reported to date (table 3).

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Embryology and pathogenesis

The evolution of the primate hand is characterised by specialisation of the first digit as an opposable unit capable of a pincer-like action with the other four digits. This process has resulted in progressive shortening of the first ray; further evolutionary adaptations allow the first ray to be abducted 90° or more with respect to the second ray. Of all mammals, an opposable thumb is found only in primates.[7] The thumb is longer in man than in most primates; in general, primates that are primarily arboreal tend to have shorter thumbs than their terrestrial and semiterrestrial counterparts.

Why does the primate thumb have only two phalanges when all the other digits have three? Galen[8] (2nd century AD) believed that the first metacarpal, which, unlike the other metacarpals has a proximal epiphyseal centre, was not a true metacarpal but actually represented the proximal phalanx of the thumb.[9] Many 19th and early 20th century authors theorised that biphalangy resulted from the loss of one phalanx in the course of evolution of the thumb from a first digit that was

TABLE 1 *Disorders associated with abnormalities of the thumb or first metacarpal or both.*

Thumb abnormality	*Associated condition*	*Mode of inheritance*
Megalodactyly	Neurofibromatosis	AD
	Haemangiomatosis	Sporadic
	Isolated	Sporadic
Duplication (radial polydactyly)	Holt-Oram syndrome	AD
	Polydactyly-syndactyly syndrome	AD
	Carpenter syndrome	AR
	Fanconi pancytopenia	AR
Broad	Apert syndrome	AD
	Pfeiffer syndrome	AD
	Sathre-Chotzen syndrome	AD
	Taybi syndrome	X linked semidominant
	Larsen syndrome	Unknown, AD
	Rubenstein-Taybi syndrome	Unknown (multifactorial)
	Weaver syndrome	Sporadic
Short/hypoplastic	Brachydactyly (type A1)	AD
	Brachydactyly (type B)	AD
	Hand-foot-uterus syndrome	AD
	Holt-Oram syndrome	AD
	Myositis ossificans progressiva	AD
	Diastrophic dwarfism	AR
	Fanconi pancytopenia	AR
	Nager acrofacial dysostosis	AD?
	Cornelia de Lange syndrome	Unknown
	VATER (VACTERL, ARTICLE V) anomalad	Unknown
	Aminopterin embryopathy	—
Absent	Holt-Oram syndrome	AD
	Fanconi pancytopenia	AR
	Rothmund-Thomson syndrome	AR
	SC phocomelia	AR
	Chromosomal aberrations:	
	Ring D	—
	13q−	—
	Trisomy 18	—
	Thalidomide embryopathy	—

AD=autosomal dominant; AR=autosomal recessive.

(initially) similar to all the others. Most contemporary authors believe that the biphalangeal primate thumb represents the fusion of the middle and ungual phalangeal ossification centres, which are present in the primate embryo, to form a single distal phalanx.[10] In support of the fusion hypothesis is the observation that while the thumb is the shortest digit, it possesses the longest terminal phalanx.

Many explanations for TPT have been advanced (and discarded) over the years. Early suggestions that the supernumerary phalanx represented an exostosis, accessory ossicle, or ununited epiphyseal centre are easily dismisssed, since TPT is characterised by the presence of true (diarthrodial) joints between the phalanges. Nor is there any credible evidence that TPT represents a reversion to a more primitive condition; indeed comparative anatomical studies have shown that the biphalangeal formula is firmly established in all forms of animal life from amphibians to man. TPT has not been identified in fossils of the higher vertebrates or in early primate embryos. An adult configuration of the phalanges and carpus can be identified in the eight week human embryo.[11]

A number of hypotheses have been advanced by contemporary investigators to explain TPT.[12]

TPT REPRESENTS PERSISTENCE OF A MIDDLE PHALANX OWING TO FAILURE OF FUSION OF THE MIDDLE AND DISTAL PHALANGES OF A NORMAL FIRST DIGIT

Lending support to this concept is the fact that the terminal phalanx of the thumb in a normal hand is longer than the distal phalanges of any of the other digits. Wilkinson[13] has observed that the (normal) biphalangeal thumb is characterised by (1) fusion of the terminal and middle phalanges and (2) fusion of the flexor sublimis tendon with one of the flexor profundus tendons; thus a portion of the sublimis tendon remains attached to the portion of the fused bony structure that corresponds to the middle phalanx. This arrangement of the tendons has been found at necropsy in an infant with TPT.[10] In the Holt-Oram syndrome,[14] TPT is associated with an abnormally long and gracile first metacarpal with an

TABLE 2 *Triphalangeal thumb: clinical associations and genetic patterns.*

Category	*Associated condition (syndrome, malformation complex, teratogen)*	*Reference*	*Genetic pattern*
Isolated TPT	None	4, 10, 19, 20	AD, Sp, AR (rare)
TPT associated with other hand and foot abnormalities	Bifid thumb	5, 19, 21, 22	Sp, AD
	Brachydactyly-ectrodactyly syndrome	23, 24	AD
	Lobster claw foot and hand	25, 26	Sp, AD?
	Polydactyly	5, 12, 27	AD, Sp (uncommon)
	Polydactyly-syndactyly	17, 29, 30	AD
TPT associated with radial hypoplasia	Radial hypoplasia, thrombocytopathy, and sensorineural hearing impairment	45	?
	Radial hypoplasia, hypospadias, and maxillary diastema	44	AR
	Fanconi pancytopenia	37	AR
	Holt-Oram syndrome	14, 39–41	AR
TPT associated with bone marrow dysfunction	Aase syndrome	31–34	AR
	Blackfan-Diamond syndrome	35, 36	AR, AD (uncommon)
	Fanconi pancytopenia	37	AR
	IVIC syndrome	38	AD
	Radial hypoplasia, thrombocytopathy, and sensorineural hearing impairment	45	?
TPT associated with congenital heart defects	Aase syndrome	31–34	AR
	Holt-Oram syndrome	14, 39–41	AD
	Agenesis of lung and congenital heart disease	39, 40	AR
TPT associated with anorectal malformations	IVIC syndrome	38	AD
	Townes syndrome	46, 47	AD
TPT associated with onychodystrophy and deafness	IVIC syndrome	38	AD
	Onychodystrophy, distal osteodystrophy, and deafness	48, 49	AD
	Onychodystrophy, distal osteodystrophy, deafness, seizures, and mental retardation	50–52	AR
	Radial hypoplasia, thrombocytopathy, and sensorineural hearing impairment	45	?
Rare associations of TPT with miscellaneous abnormalities	Absence of pectoralis muscle	5	AD?
	Cleft palate and abnormal sternum	53	Sp
	Hypomelanosis of Ito	56	Sp
	Lacrimo-auriculo-dento-digital syndrome	57	AD
	Langer-Giedion syndrome (trichorhinophalangeal syndrome type II)	59	Sp, AD (rare)
	Acrofacial dysostosis	60	AR
	Trisomy 13	1	None
TPT associated with maternal teratogen exposure	Phenytoin (dilantin)	63	None
	Thalidomide	64, 65	None

AD=autosomal dominant; AR=autosomal recessive; Sp=sporadic; ?=mode of inheritance uncertain.

TABLE 3 *Conditions associated with triphalangy of the hallux.*

Syndrome or association	*Genetic pattern*	*Reference*
Isolated TPH	Sporadic	5
TPH with polydactyly	Sporadic	5
TPH with TPT, hypoplastic distal phalanges, dystrophic nails, sensorineural deafness, seizures, mental retardation, abnormal dermatoglyphics, and dysmorphic facies	Autosomal recessive	52
TPH with polydactyly, TPT, brachydactyly, camptodactyly, congenital dislocation of the patellas, short stature, and borderline inheritance	Autosomal dominant	30
TPH secondary to fetal hydantoin (dilantin) exposure	None	6

TPH=triphalangeal hallux.

epiphysis at each end, a configuration which might be explained by arrested differentiation of the first digital ray with persistence of the middle phalanx (fig 1).[12] This type of TPT also may occur in the absence of congenital heart disease.[10]

TPT REPRESENTS DUPLICATION OF THE INDEX FINGER IN ASSOCIATION WITH ABSENCE OF THE THUMB

According to this hypothesis, advanced by Joachimsthal[15] in 1900, TPT may be considered a form of polydactyly in which an absent thumb is replaced by an extra first digit. The resultant 'thumb' resembles a little finger (fifth digit) both clinically and radiographically (fig 2). Nor is it functionally equivalent to a normal thumb, as it

lacks the specialised musculature of the thenar eminence and is non-opposable. (Normal opposition and a nearly normal appearance of the hand can be achieved by pollicisation procedures.[16]) In some instances more than one triphalangeal digit occurs in the position of the absent thumb.[17] A small percentage of cases of TPT might be explained by the Joachimsthal hypothesis.

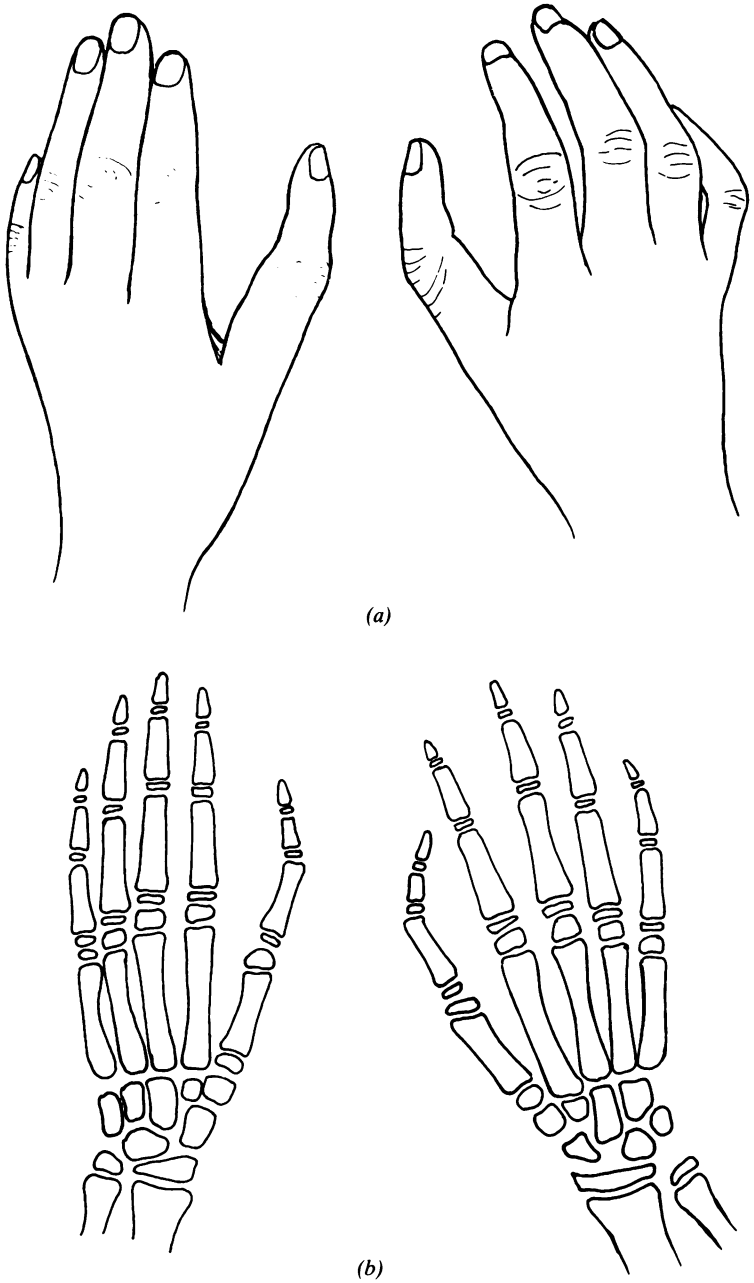

FIG 1 *Triphalangeal thumb owing to apparent persistence of a middle phalanx (failure of fusion of the middle and distal phalanges of a normal first digit). (a) Tracing of clinical photograph. Note long, gracile thumbs with slight flexion and ulnar deviation of the distal phalanges. Movements of the DIP joints were restricted to about 5° of palmar flexion but the PIP joints were freely mobile. The MCP joints had full flexion and extension and possessed an unusually wide range of abduction and adduction. (b) Tracing of radiograph shows three normally formed phalangeal elements in each thumb. The first metacarpal has an epiphysis at each end. After Abramowitz.*[10]

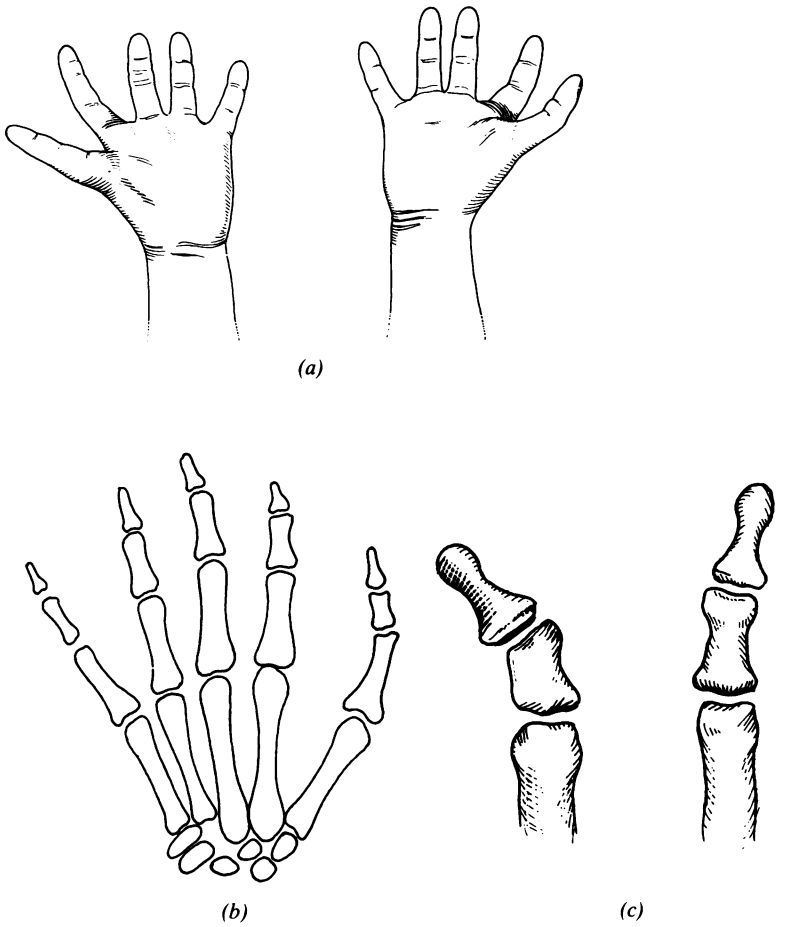

FIG 2 *TPT apparently representing duplication of the index finger in association with absence of the thumb. (a) Tracing of clinical photograph shows a five fingered hand. All of the fingers are triphalangeal and in the same plane. (b) Tracing of radiographs in another patient showing three phalanges in all five digits. (c) Tracing of a dorsopalmar view of the thumbs of a third patient with this pattern of triphalangy. Note trapezoidal shape of the middle phalanx with ulnar deviation of the distal part of the thumb, more marked on the left. (a) After Kessler[16]; (b) after Swanson and Brown[4]; (c) after Lapidus et al.[5]*

TPT IS THE RESULT OF INCOMPLETE DUPLICATION OF THE THUMB

Lapidus and Guidotti[18] concluded from their extensive anatomical studies that TPT represents an arrested attempt at formation of a bifid thumb. According to their concept, the supernumerary phalanx represents the surviving portion of the base of the bifid thumb (fig 3). The supernumerary phalanx may be the middle one (in which case it represents the remnant of a bifid distal phalanx), or it may be the proximal one (in which case it represents the remnant of a bifid proximal phalanx). The supernumerary phalanx may be rudimentary or fully developed (fig 4).

Association of TPT with other malformations of the upper extremities

Malformations of the upper extremities, such as ectrodactyly (congenital absence of all or part of a digit), polydactyly, syndactyly, and brachydactyly, are determined early in the embryonic period (third to seventh postovulatory weeks). Experimental studies in avian, amphibian, and mammalian embryos have shown that the apical ectodermal ridge controls and coordinates the proximal to distal sequence of limb development.[11] These studies, as well as subsequent studies of human embryos, indicate that a number of seemingly unrelated congenital malformations of the hand, for example, preaxial polydactyly, syndactyly, and split hand ('lobster claw') deformity, share a common pathogenesis: failure of the apical ectodermal ridge to separate. The frequency with which TPT is associated with bifid thumb, preaxial polydactyly, and the split hand deformity suggests a close pathogenetic relationship among these anomalies.

Genetic heterogeneity has been noted in family

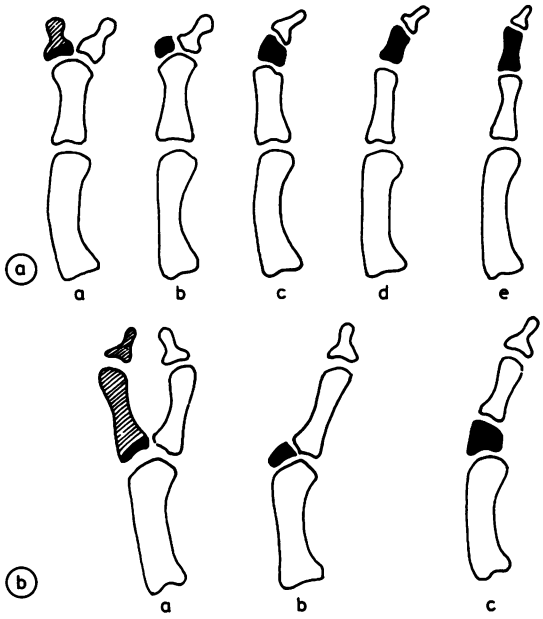

FIG 3 *TPT apparently representing incomplete duplication of the thumb. According to this concept, the supernumerary phalanx represents the surviving portion of a bifid thumb. (a) The postulated primitive state is shown in* (a). *Tracing of radiographs of several patients with the most common morphological patterns are shown in* (b) *to* (e). *The phalanx which failed to develop fully is shown striated. (While this is usually the distal phalanx, rarely both the distal and proximal phalanges may fail to develop fully.) The persisting base of the supernumerary phalanx (which simulates a third phalanx) is shown in solid black. (b) Tracing of the radiograph of a patient with a rare variant form of duplication is shown in* (b). *The morphological pattern shown in* (c) *has been postulated but not observed clinically. After Lapidus and Guidotti.*[18]

studies, suggesting that more than one pathogenetic mechanism may be responsible.[12]

Clinical presentations of TPT

TPT may occur as an isolated defect, in combination with other malformations of the hands, or as a feature of a syndrome or sequence (table 2).

ISOLATED TPT

Although most reports of solitary TPT concern single (sporadic) cases, there have been several reports of families in which the anomaly occurred in more than one generation[10 19]; in one large kindred, 30 members in four generations were affected.[4] The pedigrees in these families are consistent with autosomal dominant inheritance with almost complete penetrance. There is at least one well documented instance of probable autosomal recessive inheritance.[20] Isolated TPT is bilateral in about 90% of reported cases[4]; whereas bilateral TPT is almost always familial, unilateral TPT is usually sporadic.[4]

Two functional varieties of isolated TPT have been described: opposable and non-opposable (table 4). Non-opposable TPT appears to be inherited as a simple autosomal dominant trait, whereas opposable TPT is more frequently sporadic. The relative frequency of non-opposable and opposable TPT is unknown.

TPT ASSOCIATED WITH OTHER HAND AND FOOT ABNORMALITIES

Bifid thumb

A close association between TPT and bifid (accessory) thumb was recognised as early as 1891[19]; in most instances the supernumerary digit has three phalanges as well (fig 4). The more than occasional concurrence of these rare malformations has been cited as evidence for the hypothesis that TPT represents an incomplete development of the distal part of one of the two distal (nail bearing) phalanges of a partially duplicated thumb (see above).[5] A person with TPT and bifid thumb on one side and TPT only on the other has been reported.[21] An autosomal dominant inheritance pattern has been present in some families in which both TPT and accessory thumb occur.[19 21]

Brachyectrodactyly syndrome

This rare disorder, recently described in 17 persons in two unrelated Mexican families,[23] is characterised by triphalangeal thumbs which appear finger-like or ulnar deviated; radiographically there is a rudimentary extra (distal) phalanx (fig 5). Other characteristic malformations include abnormalities of the index fingers (short distal phalanges, hypoplastic or absent nails) and shortness of the third toe owing to hypoplastic phalanges. The proband of the first family had seizures, mental retardation, and hemiparesis. One affected family member had ectrodactyly, syndactyly, and adactyly of the feet as well as TPT. Other family members had limb malformations only, which varied greatly in severity. The pedigrees in both families were compatible with autosomal dominant inheritance with variable expressivity. A sporadic case has recently been reported.[24]

Lobster claw foot and hand

Usually an isolated deformity, bilateral lobster claw

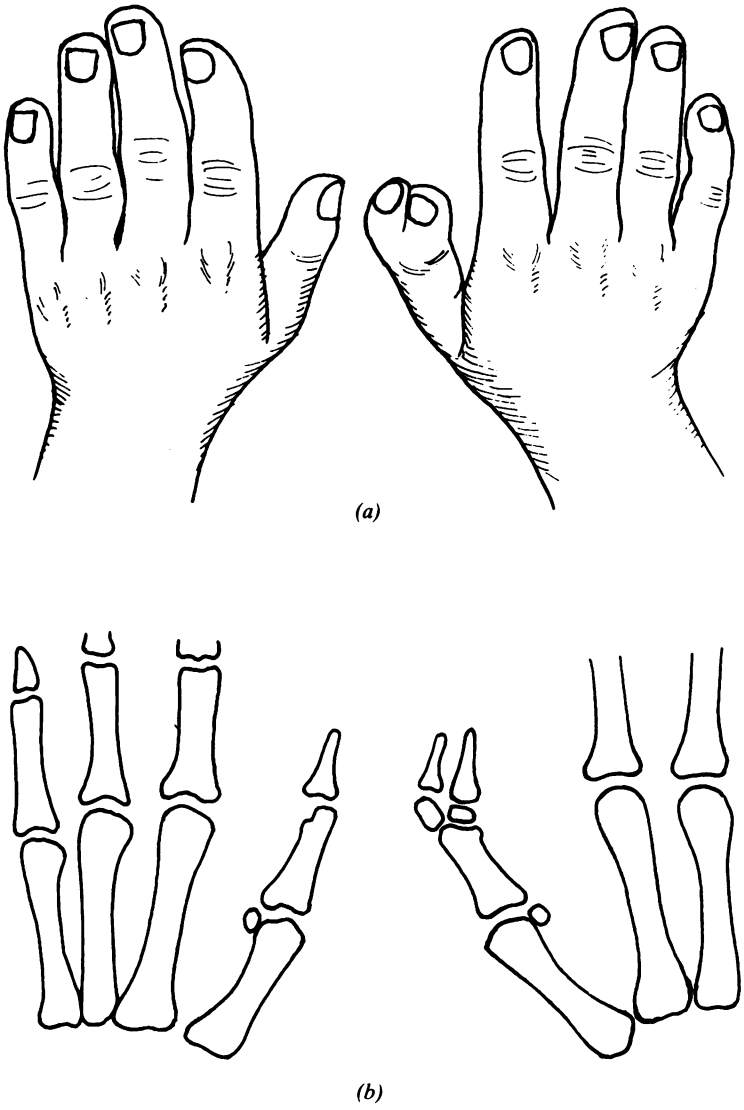

FIG 4 *Bifid thumb with triphalangy. (a) Tracing of clinical photograph shows a bifid right thumb. The left thumb is normal. (b) Tracing of radiograph shows a bifid right thumb. The radial digit is definitely triphalangeal. The ulnar digit has a small third phalanx interposed between the nail and the proximal phalanx on its radial aspect. After Lapidus and Guidotti.*[18]

TABLE 4 *Isolated TPT: opposable versus non-opposable types.*

Feature	*Opposable thumb*	*Non-opposable thumb*
Clinical features		
Length	Minimally increased	Greatly increased
Skin creases	Absent over distal interphalangeal joint; present over proximal interphalangeal joint	Present over both proximal and distal interphalangeal joints
Radiological findings		
1st digit	Intercalated second phalanx (small and wedge shaped or ulnar deviation of distal phalanx (frequent)	Long, fully developed phalanges similar to other digits ('five fingered hand')
1st metacarpal	Epiphysis and growth plate at proximal end	Epiphysis and growth plate at distal end
Genetic pattern	Usually sporadic	Autosomal dominant
Relative frequency	Unknown	Unknown

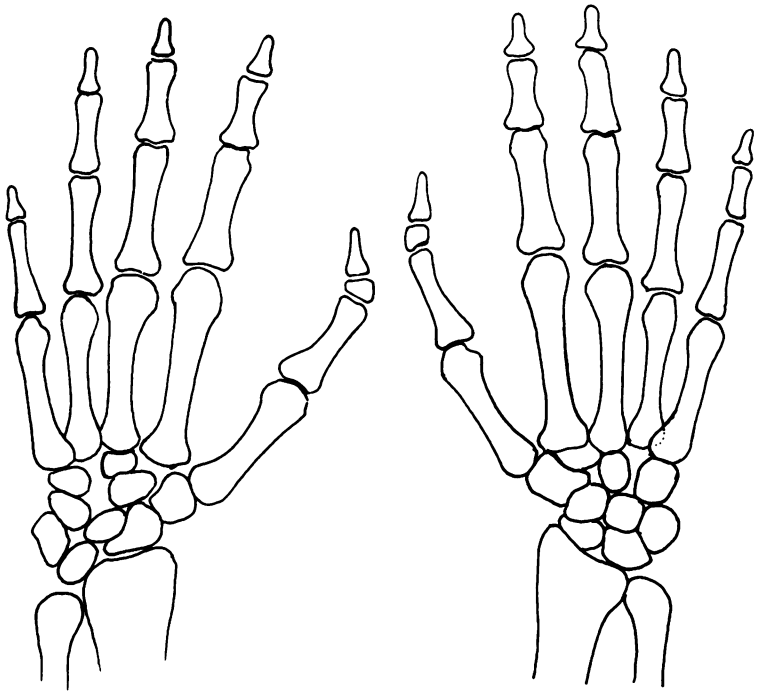

FIG 5 *Brachydactyly-ectrodactyly syndrome. Tracing of radiograph shows bilateral triphalangeal thumbs with ulnar deviation of the distal phalanges. The interposed supernumerary phalanx has a trapezoidal configuration. After Majewski et al.*[24]

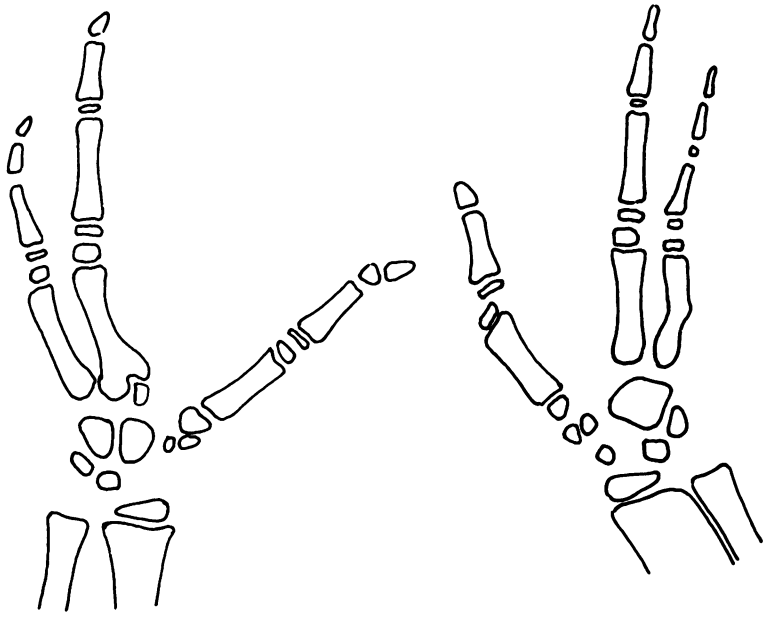

FIG 6 *Lobster claw hand with TPT. Tracing of radiograph in a patient with a complicated split hand deformity shows TPT on the left. The base of the triangular extra phalanx is on the ulnar side and the terminal phalanx is deviated radially. In each hand the first metacarpal has an epiphysis at both the proximal and distal ends. After Miura.*[26]

feet ('split foot' deformity) can occur in association with a wide variety of other malformations. In the EEC syndrome, for example, lobster claw feet are associated with ectodermal dysplasia and cleft lip and palate. There have been occasional reports of lobster claw foot occurring in association with TPT,[25] although the nature of the thumb malformation in one of these cases is not fully documented. Lobster claw foot or TPT or both occurred in four subjects in two generations of an English family; one family member, the daughter of a women with both malformations, had TPT only.[25]

Lobster claw hand with TPT is very rare. In two of the three reported cases, both malformations were present bilaterally (fig 6).[26]

Polydactyly

Numerous examples of (usually preaxial) polydactyly with TPT have been recorded since the first report in 1824.[12 27] The supernumerary digit as well as the thumb may possess three phalanges in such cases. The supernumerary diphalangeal digit may be ulnar or (rarely) radial; rarer still is the occurrence of an additional digit each side of an ostensibly normal thumb. According to one estimate, the TPT-polydactyly combination accounts for 2% of congenital malformations of the upper extremities.[27] In one series, 21 (10%) of 203 persons with polydactyly had TPT, and half of those with TPT had polydactyly.[27] Many subjects with TPT-polydactyly have preaxial polydactyly of the foot as well.[12 27 28] A triangular shaped middle phalanx (delta phalanx) is present in about half of these. Other malformations are occasionally seen. One child with TPT and bilateral preaxial polydactyly also had bilateral hypoplasia of the sternal head of the pectoralis major, winging of the scapulae, pectus excavatum, and multiple pigmented naevi.[12] In most instances the TPT-polydactyly combination is inherited as an autosomal dominant trait; however, sporadic cases have been described.[5 21]

TPT with polydactyly-syndactyly and abnormalities of lower limbs

In 1969, Eaton and McKusick[17] described four persons in three generations of a family with preaxial polydactyly of the feet, syndactyly, hypoplastic tibiae, and thick, bowed fibulae that were dislocated posteriorly and laterally. All of the affected subjects had triphalangeal fingers, none of which resembled a thumb. Two additional kindreds were subsequently reported. Yujnovsky *et al*[29] described four affected persons in three generations with a similar pattern of malformations, although the syndactyly was not as marked and the severity of the malformations of the lower extremity varied greatly among the affected (fig 7). Say *et al*[30] reported two generations of a family (a mother and her three daughters) with TPT, preaxial polydactyly of the fingers and toes, brachydactyly, camptodactyly, congenital dislocation of both patellae, short stature, and borderline intelligence. The proband had six fingers on each hand, eight toes on the right foot, and seven on the left. Syndactyly was not present in any of the affected family members.

Although there are notable differences among these three kindreds, there are important similarities as well. (1) All three kindreds exhibited a dominantly inherited pattern of TPT, preaxial polydactyly (of the hands and feet or just of the feet), syndactyly, and major malformations of the mesial segment of the lower extremities. (2) None of the affected subjects had the distinctive craniofacial abnormalities that characterise other syndactyly syndromes (for example, Carpenter and Apert syndromes). (3) Final stature and intelligence were normal in two of the three families. Additional clinical and radiological observations will be needed to delineate this disorder fully.

SPECIFIC SYNDROMES

TPT with bone marrow dysfunction

Aase syndrome. The Aase syndrome, first described in 1969, is characterised by anaemia because of dysfunctional red cell precursors, leucopenia, TPT, and radial hypoplasia of mild degree. The anaemia, which first manifests in infancy, responds to prednisone therapy and tends to become less severe with age. The thumbs are typically finger-like with three phalanges and a hypoplastic thenar eminence (fig 3b).[31–34] Associated abnormalities include narrow shoulders, mild growth deficiency, late closure of the fontanelles, ventricular septal defect, and hepatomegaly of varying degree. The available genetic data indicate autosomal recessive inheritance for the disorder.[31–34]

Blackfan-Diamond syndrome. The Blackfan-Diamond syndrome, also known as pure red cell anaemia or congenital hypoplastic anaemia, is characterised by moderate to severe anaemia with onset in infancy, a low reticulocyte count, virtual absence of recognisable erythroid elements in the bone marrow, and an increased fetal haemoglobin concentration in circulating erythrocytes; the white cells and platelets are not affected.[35]

Of 133 patients with the Blackfan-Diamond syndrome reported up to 1976, six had TPT. The outcome of patients with TPT was no different from that in other patients with congenital hypoplastic anaemia.[36] About one-third of the reported cases of

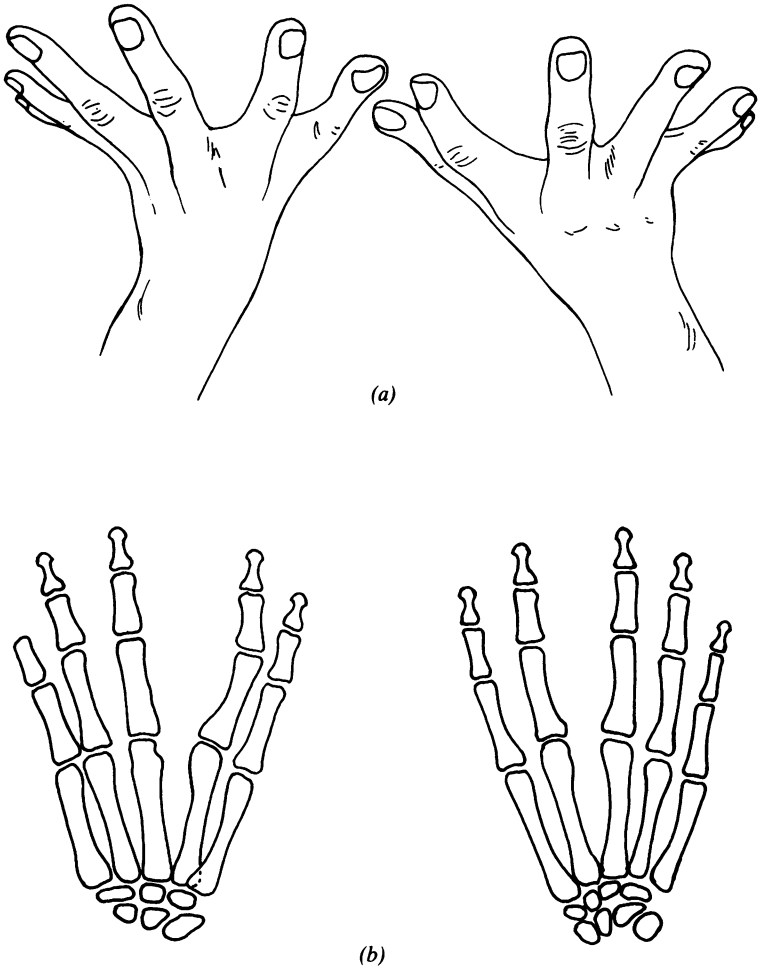

FIG 7 *TPT with polydactyly-syndactyly and abnormalities of the lower limbs. (a) Tracing of clinical photograph shows six digits on each hand. There is extensive membranous syndactyly between the first and second digits, neither of which has the appearance of a thumb, and minimal syndactyly between the fourth and fifth digits. There is a rudimentary duplication (including a nail) of the distal phalanx of the first digit. The sixth digits are rudimentary and fused to the fifth. (b) Tracing of radiographs shows five well developed triphalangeal digits with soft tissue syndactyly between the first and second digits. There is no bone in the rudimentary sixth digit. After Yujnovsky et al.*[29]

the Blackfan-Diamond syndrome have had at least one other abnormality, including short stature, webbed neck, cleft lip or palate or both, and abnormalities of the eyes and ears. Both autosomal dominant and autosomal recessive inheritance, as well as polygenic inheritance, have been implicated.[36]

Fanconi pancytopenia. Fanconi pancytopenia is an autosomal recessive disorder which affects multiple organ systems. The pancytopenia is characterised by hypoplasia of the erythropoeitic, myeloid, and megakaryocystic elements of the bone marrow and typically becomes manifest at about eight years of age.[37] About 80% of affected subjects have abnormalities of the thumb, including supernumerary, bifid, hypoplastic, triphalangeal, or totally absent thumbs. TPT has been described in some instances. The radius may be hypoplastic or absent.

IVIC syndrome. The IVIC (*I*nstituto *V*enezolano de *I*nvestigaciones *C*ientificas) syndrome, an autosomal dominant disorder recently described in six generations of a Venezuelan family, is characterised by malformations of the upper limbs, strabismus, congenital mixed hearing impairment (total or partial), mild thrombocytopenia and leucocytosis with onset before the age of 50, imperforate anus, and abnormal dermatoglyphics. The upper limb malformations vary greatly in severity and are frequently asymmetrical; the most common abnormality is bilateral hypoplasia or distal displacement of the thumbs. Of the 19 affected persons in this

kindred, four had finger-like TPT and 14 had hypoplastic thenar muscles without functional impairment.[38]

TPT, radial hypoplasia, thrombocytopathy, and sensorineural hearing impairment.
See below.

TPT ASSOCIATED WITH CONGENITAL HEART DEFECTS

Holt-Oram syndrome
The Holt-Oram syndrome, also known as the cardiomelic syndrome or the hand-heart syndrome, is an autosomal dominant disorder characterised by abnormalities of the upper extremities and congenital heart disease. The most frequent cardiac defects are ostium secundum atrial septal defect, patent ductus arteriosus, ventricular septal defect, and transposition of the great arteries. Defects of the upper extremities occur twice as often on the left; involvement of both upper extremities is not uncommon, however, and may be symmetrical or asymmetrical. The lower extremities are never involved. There is no correlation between the severity of the cardiac defect and the limb defect; there is considerable variability of expression within a kindred and some family members may have one and not the other.[39] The syndrome tends to be more fully expressed and more severe in females.

The thumb is the most commonly affected portion of the upper extremity, although abnormalities of the radius and first metacarpal are also common. The thumb may be absent, rudimentary, finger-like, or triphalangeal. In the original description of the syndrome by Holt and Oram,[14] atrial septal defect and bilateral TPT with a rudimentary phalanx occurred in four members of a kindred (fig 1); similar cases have subsequently been reported by others.[40] A different pattern of TPT (long finger-like triphalangeal thumbs) was present in six of 25 patients with the Holt-Oram syndrome reported by Poznanski *et al.*[41] The extra phalanx varied in shape but was usually smaller than the proximal and distal phalanges.

TPT, lung agenesis, and congenital heart disease
Complete absence or hypoplasia of one or both lungs is a rare developmental defect. Its association with a variety of congenital anomalies involving the cardiovascular, musculoskeletal, gastrointestinal, and (less often) the genitourinary and central nervous systems has been reported. A syndrome of agenesis of the lung associated with congenital heart disease, rib/vertebral anomalies, and TPT has been described in unrelated patients. A female infant with left pulmonary aplasia, anomalies of the homolateral ribs, a congenital heart defect, and opposable TPT of the left hand was reported in 1983 by Manouvrier.[42] Her parents were healthy and non-consanguineous. Mardini and Nyhan[43] subsequently described four Saudi Arab infants (three girls and a boy) with unilateral pulmonary agenesis (4/4), atrial septal defect (4/4), other cardiovascular abnormalities (3/4), triphalangeal angulated thumb with a hypoplastic middle phalanx (1/4), preaxial polydactyly (1/4), hypoplastic thumb (1/4), and ipsilateral hemivertebrae (2/4). The four infants were unrelated but were born to consanguineous parents. The available data suggest that the syndrome is inherited as an autosomal recessive trait.

TPT ASSOCIATED WITH RADIAL HYPOPLASIA

TPT, radial hypoplasia, hypospadias, and maxillary diastema
Schmitt *et al*[44] described eight subjects (three male and five female) in three generations of a family who had bilaterally symmetrical, finger-like, non-opposable thumbs, and shortened forearms with hypoplastic radii and radial deviation of the hands. All of the affected persons had anterior maxillary diastema. Three males had hypospadias characterised by a pinpoint meatus in the distal ventral shaft of the penis. Although the bony abnormalities were striking, the affected subjects were only minimally handicapped. The mode of inheritance in this kindred is typical of an autosomal dominant trait.

TPT, radial hypoplasia, thrombocytopathy, and sensorineural hearing impairment
Wiedmann *et al*[45] described a woman with triphalangeal non-opposable thumbs associated with hypoplastic radii, radiological abnormalities of the wrist, recurrent bleeding from the skin and mucous membranes with onset late in the first year of life, and sensorineural hearing impairment. Numerous blood transfusions were required to manage the coagulopathy, which was characterised by a prolonged bleeding time, a normal platelet count, and a moderate decrease of factor X. The patient was well developed physically. She had coarse facial features, hypertelorism, a broad nose, prognathism, a large area of scalp alopecia, and a pigmented naevus. The mode of inheritance could not be determined.

Fanconi pancytopenia
See above.

Holt-Oram syndrome
See above.

TPT ASSOCIATED WITH ANORECTAL MALFORMATIONS

Townes syndrome

The syndrome described by Townes and Brock comprises a constellation of abnormalities including anorectal malformations (imperforate anus, anterior ectopic anus, anal stenosis), abnormal auricles, (microtia, lop ears, preauricular tags), urinary tract abnormalities (renal hypoplasia, vesicoureteral reflux, urethral valves), mild to moderate deafness, and abnormalities of the thumb.[46 47] The latter include hypoplastic, bifid, or supernumerary thumb, and TPT. The genetic data are consistent with autosomal dominant inheritance with marked variability of expression.

IVIC syndrome

Anorectal malformations are a feature of the IVIC syndrome (see above).

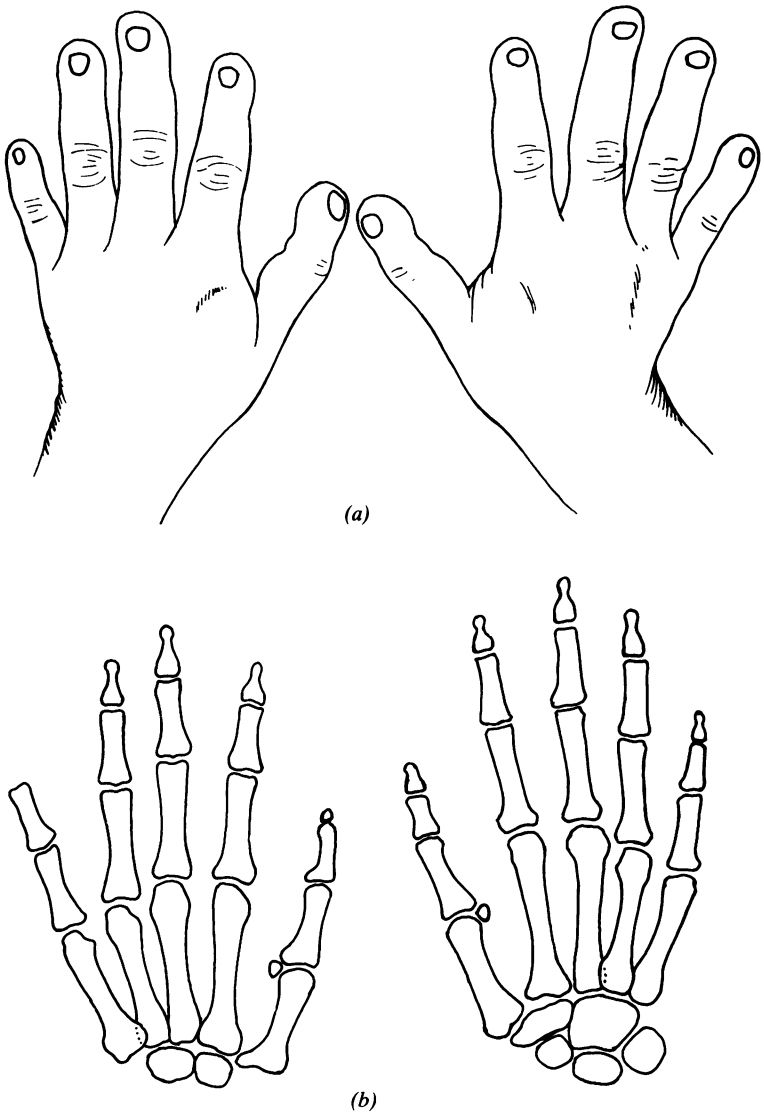

FIG 8 *TPT associated with onychodystrophy, deafness, and distal osteodystrophy. (a) Tracing of clinical photograph shows a bulbous swelling of the terminal portions of the thumb and little finger; both digits have rudimentary and hypoplastic nails. There is slight shortening of the little finger bilaterally. (b) Tracing of radiograph shows a well developed supernumerary phalanx in the right thumb. The distal phalanges of the little fingers are absent bilaterally. After Goodman et al.*[48]

TPT ASSOCIATED WITH ONYCHODYSTROPHY AND DEAFNESS

Onychodystrophy, deafness, and distal osteodystrophy
In 1969, Goodman *et al*[48] reported sensorineural deafness and dystrophic nails in a 61 year old woman and her 33 year old son; additional findings included TPT, malformed or missing phalanges of the second to fifth toes and the fifth fingers, and bulbous swelling of the fingertips. Both patients were otherwise normal and had average intelligence. Similar abnormalities were reported by Moghadam and Statten[49] in a mother and child; each had normal intelligence, sensorineural hearing loss, long triphalangeal thumbs, absent or dystrophic fingernails and toenails, and bulbous swellings of all the fingertips. Radiographs of the hands showed pointed distal phalanges; radiographs of the feet showed rudimentary ossification centres in the distal phalanges (fig 8). The genetic pattern in both families is consistent with autosomal dominant inheritance.

Onychodystrophy, deafness, distal osteodystrophy, seizures, and mental retardation
Qazi and Smithwick[50] and Walbaum *et al*[51] reported three patients with triphalangy of the thumbs and big toes, hypoplasia of the distal phalanges of the other digits, dystrophic nails, sensorineural deafness, mental retardation, and abnormal dermatoglyphics (10 fingertip arches). The thumbs were finger-like and opposable, with an extra flexion crease. The thumbs resembled, both clinically and radiographically, those of the patients described above (that is, patients of normal intelligence with onychodystrophy, deafness, and distal osteodystrophy) (fig 9). Six of the eight patients reported to date are of Hispanic origin. The available data are consistent with an autosomal recessive pattern of inheritance.[52]

TPT, radial hypoplasia, thrombocytopathy, and sensorineural hearing impairment
See above.

REPORTED RARE OCCURRENCE OF TPT WITH MISCELLANEOUS CONDITIONS

Absence of pectoral muscles
Bilateral TPT has been described in a father and son with absence of the pectoralis major and minor muscles.[5] The thumbs were long and non-opposable and the thenar eminences were flattened and elongated. The distal phalanges were ulnar deviated and the middle phalanges were trapezoid shaped.

Cleft palate and abnormal sternum
Sallam[53] reported a man with a cleft palate, abnormal sternum, and thin triphalangeal thumbs that were convex outwards. Adduction of the thumbs was limited but opposition was normal. The middle phalanges were hypoplastic.

Hypomelanosis of Ito (Ito syndrome)
The Ito syndrome, also known as incontinentia pigmenti achromians, is a neurocutaneous disorder with onset in infancy that is characterised by streaked, whorled, or mottled areas of skin hypopigmentation, mental deficiency of varying severity, seizures, neurological deficits, strabismus, microcephaly, asymmetrical lower extremities, scoliosis, and hirsutism.[54 55] Most of the reported cases have been sporadic; however, occurrence in a parent and child has been reported. Kukolich *et al*[56] reported a 10 year old boy with the Ito syndrome, bilateral TPT (unopposable type), and clinodactyly of the little fingers.

Lacrimo-auriculo-dento-digital syndrome
Hollister *et al*[57] described a Mexican family with a unique constellation of abnormalities consisting of obstruction of the nasolacrimal ducts owing to hypoplasia or aplasia of the lacrimal puncta, cup shaped ears, hearing loss (predominantly conductive with a variable sensorineural component), and dental abnormalities. Digital abnormalities were common, but varied considerably from person to person. Clinodactyly of the fifth finger was the most common finding. Bilateral finger-like tapering of the thumbs was noted in two affected family members; one had duplication of the terminal phalanx of the thumb and the other had TPT. An autosomal dominant mode of inheritance was suggested.

Langer-Giedion syndrome (tricho-rhino-phalangeal syndrome type II)
This syndrome is characterised by postnatal growth retardation, mild to moderate mental retardation, large protruding ears, a bulbous, pear shaped nose with tented alae, a prominent elongated philtrum, a thin upper lip, micrognathia, sparse scalp hair, mild microcephaly, cone shaped epiphyses, multiple cartilaginous exostoses, asymmetrical limb growth, joint hyperextensibility, and winged scapulae.[58] Most cases are sporadic, although the occurrence of the syndrome in a father and daughter suggests that autosomal dominant inheritance may occur. An 18 year old boy with typical features of the Langer-Giedion syndrome and unilateral TPT has been reported.[59]

Acrofacial dysostosis
Richieri-Costa *et al*[60] described a 23 year old Caucasian woman with mandibulofacial dysostosis,

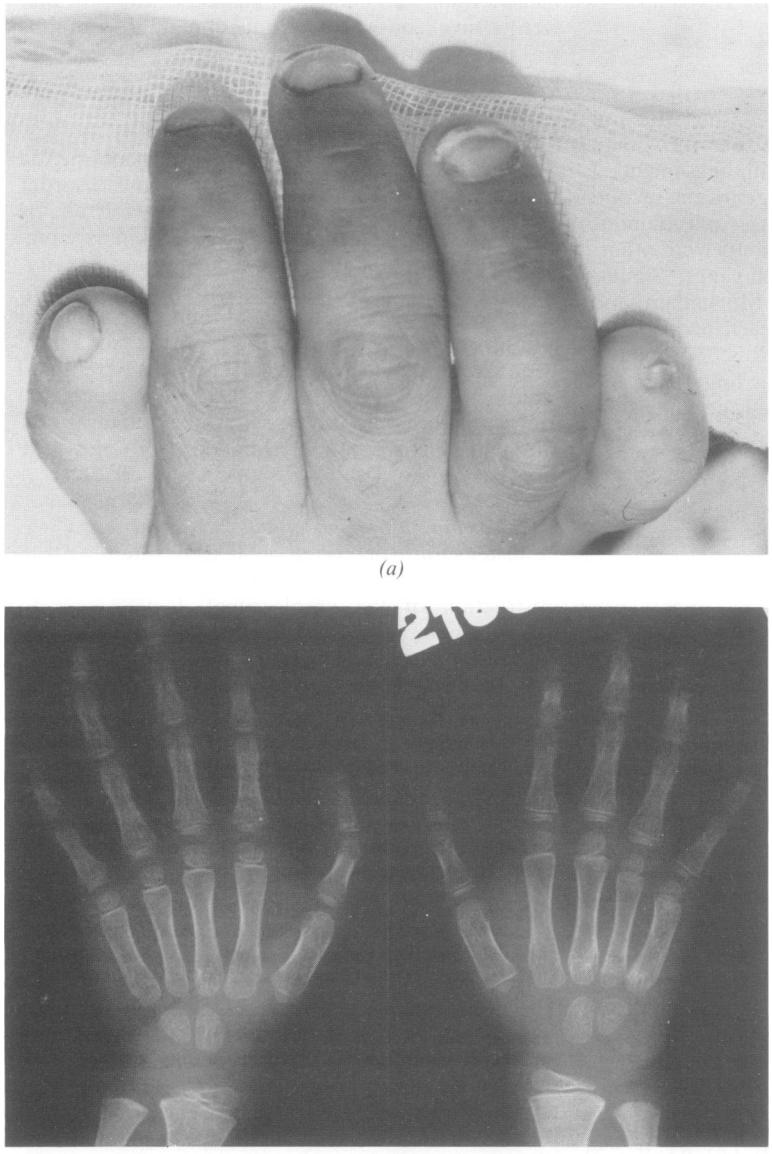

FIG 9 *TPT associated with onychodystrophy, deafness, distal osteodystrophy, seizures, and mental retardation. (a) Clinical photograph of the right hand of a five year old boy shows hypoplasia of the fingernails. The thumb is long and has two flexion creases. The toenails were also hypoplastic, the nails being almost rudimentary on the fourth and fifth toes. (b) A radiograph of the hands shows triphalangy of both thumbs and hypoplasia of the distal phalanges of the other digits. The first metacarpals have proximal epiphyseal ossification centres only. A radiograph of the feet (not illustrated) showed an extra phalanx in each big toe and absence of the terminal phalanges of the other toes. Reproduced with permission from Qazi and Smithwick.*[50]

cleft lip, highly arched palate, fusion of the fifth lumbar and first sacral vertebrae, and bilateral hypoplastic triphalangeal thumbs. The left thumb was smaller than the right. The first metacarpal was hypoplastic bilaterally; the scaphoid was hypoplastic on the right and vestigial on the left. Her younger sister had a cleft lip and cleft palate, mild malar hypoplasia, normal ears, and hypoplastic thumbs. The parents were non-consanguineous. The condition was thought to be inherited as an autosomal recessive trait.

Trisomy 13

Trisomy 13 is a clinically distinctive malformation complex involving multiple organ systems that is usually lethal in infancy.[61] Polydactyly of the upper and lower extremities is a common feature. An infant with postaxial polydactyly and TPT has been

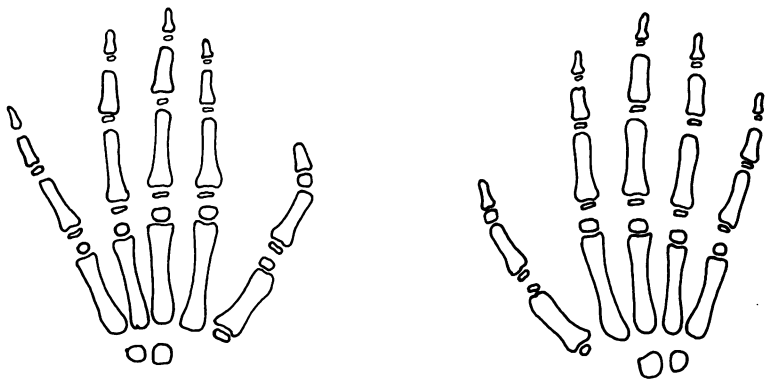

FIG 10 *TPT associated with thalidomide embryopathy. Tracing of radiograph shows a rudimentary trapezoidal supernumerary phalanx in each thumb. An epiphysis is present at the proximal and distal ends of the first metacarpal of each hand. After Lenz et al.*[65]

reported.[1] The middle phalanx of the thumb was represented by a tiny ossicle.

TPT SECONDARY TO TERATOGEN EXPOSURE

Hydantoin (dilantin, diphenylhydantoin, phenytoin)
A number of reports indicate that epileptic women who receive hydantoin during pregnancy are two to three times more likely to have infants with malformations than non-epileptic women.[62 63] The abnormalities most often associated with fetal hydantoin exposure ('fetal hydantoin syndrome') include cleft lip and palate, congenital heart disease, limb defects, unusual facies, disturbed somatic growth, and mental retardation. The limb abnormalities thought to be characteristic of the fetal hydantoin syndrome include hypoplasia of the nails and distal phalanges (especially of the postaxial digits), finger-like ('digital') thumbs, and an increased number of fingertip arches. Kousseff and Stein[63] reported three sibs with the fetal hydantoin syndrome, one of whom had bilateral triphalangeal thumbs and big toes.

Thalidomide
Maternal ingestion of thalidomide at the critical stage of embryonic development (four to six weeks) is known to cause reduction defects of the extremities, ranging in severity from hypoplasia of one or more digits to total absence of all four limbs.[64] Some subjects with TPT exhibited extreme hypoplasia of the middle phalanx (fig 10). Maternal thalidomide ingestion was incriminated in most of the cases of TPT that occurred in Sweden and Germany during the years 1960 to 1962. It was shown that TPT resulted from fetal exposures between the 45th and 50th days of gestation (menstrual age).[65] Other birth defects associated with fetal thalidomide exposure include hearing loss, blindness, haemangiomas, duodenal stenosis and atresia, and malformations of the heart and urinary tract.

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