



GENETIC COUNSELLING IN SEVERE
OSTEOGENESIS IMPERFECTA

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awarded 1.5.91

MARCH, 1990

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CHAPTER 6

CLINICAL MANIFESTATIONS OF CASES

6.1 Total number of cases studied and introductory note

Clinical information was obtained on the following cases: 30 type IIA, 15 type IIB, 3 type IIC, 10 unclassifiable perinatally lethal cases, 89 sporadic type III/IV, 19 presumed recessive type III and 11 with probable new dominant type I mutations, a total of 177 cases. The author personally examined 65 of the sporadic type III/IV cases (2 of whom died afterwards during the course of the study), 5 presumed recessive type III cases (including one sib pair) and 10 type I new mutation cases. The information on the others was gathered from their parents, doctors and hospital records where possible. Families of 12 type III/IV OI patients and 1 with type I returned a questionnaire.

The purpose of this chapter is to present and discuss the clinical features of the patients. The information on each patient is summarised in appendix 6.1. It is not necessarily intended that this be a comprehensive survey of all the many associations reported in OI, for which the reader is referred to the excellent reviews by McKusick (1972) and Smith et al. (1983).

6.2 Sex (table 6.1)

Eighty-two cases were males, 91 were females and in 4, all second-trimester terminations, the sex was unknown. Table 6.1 shows the sex distribution for each type of OI and for various groupings of perinatally lethal or surviving cases. The sex ratios did not differ significantly from 50%, as noted previously (Komai et al., 1956; Smars, 1961; Bauze et al., 1975; Sillence et al., 1984, Sillence et al., 1986).

6.3 Obstetric data

6.3.1 Fetal movements during pregnancy

Results (table 6.2)

Mothers frequently perceived decreased fetal movements during pregnancy, especially those whose fetus had type IIA or IIB OI. Included in this group are 5 mothers who felt no movement at all, namely 2 mothers of babies with type IIA OI (cases 139 and 143), and one mother each of babies with type III/IV (case 63), unclassifiable perinatally lethal OI (case 173) and (perhaps surprisingly) type I OI (case 111). Others felt that rather than kicking normally, the fetus had 'squirmed' (type III/IV, case 72), 'rolled' (type III/IV, cases 14 and 61), 'fluttered' (type IIA, case 147) or a churning sensation was described by a mother of a baby with type IIB OI (case 158). One mother of a baby with unclassifiable perinatally lethal OI (case 173) who experienced

Table 6.1

SEX RATIOS FOR EACH TYPE OF OI

Type of OI	Females	Males	Total	P value for χ^2 statistic
IIA	12	16	28*	>0.2
IIB	8	7	15	>0.7
IIC	1	2	3	NA
Unclassifiable PNL	4	6	10	>0.5
III/IV sporadic	51	38	89	>0.2
III recessive	7	10	17*	>0.2
I new mutation	8	3	11	>0.1
Total	91	82	173	>0.2
All PNL	25	32	57	>0.2
All PNS	66	50	116	>0.1
III/IV sporadic PNS	50	37	87	>0.1
III recessive PNS	6	9	15	>0.2

* Sex of 2 cases each of IIA and III recessive (all fetuses) was unknown.

PNL = perinatally lethal cases

PNS = perinatal survivors

P (probability) values for the χ^2 statistic indicate that the sex ratios did not differ significantly from 50% in any type of OI or in the group as a whole.

NA not applicable (numbers too small and cancel out when Yate's continuity correction is applied).

Table 6.2

FETAL MOVEMENTS DURING PREGNANCY (No. cases (%))

Type of OI	Normal	Decreased	Increased	?	Total
IIA	3 (30%)	7 (70%)	-	20	30
IIB	1 (14.3%)	6 (85.7%)	-	8	15
IIC	-	-	-	3	3
Unclassifiable PNL	-	2	-	8	10
III/IV sporadic	32 (47.8%)	33 (49.3%)	2 (3%)	22	89
III recessive	4 (36.4%)	7 (63.6%)	-	8	19
III & III/IV*	36 (46.2%)	40 (51.2%)	2 (2.6%)	30	108
I new mutation	4 (57.1%)	3 (42.9%)	-	4	11

% are for known cases

? unknown

* III & III/IV is the total of III recessive & III/IV sporadic

no fetal movement had polyhydramnios which is a well known association of decreased fetal movement. It is not the whole explanation in cases of OI fetuses however, as mothers with normal (or even reduced) amniotic fluid also reported poor fetal movement.

Discussion

Fulconis (1939, quoted in Smith et al., 1983) also reported infrequent, weak movements of OI fetuses in the third trimester. The reason for the report of increased movement by two mothers of babies with type III/IV OI is unknown and has apparently not been reported previously.

6.3.2 Prenatal tests

Results (table 6.3)

Fetal abnormality was detected at routine second trimester ultrasonography in 4 babies with type IIA OI, 1 with type IIB and 1 with type IIC, and these pregnancies were terminated between 17 and 23 weeks gestation. In 3 pregnancies at risk of type III OI, that is, the mother had already had one or more affected children, the disease was detected by serial high-resolution ultrasonography, all done at one specialist centre (King's College Hospital, London). These include the mother of 2 affected sibs (cases 95 and 96) and the mother of case 106 who

Table 6.3

SECOND TRIMESTER ULTRASOUND SCANNING

Type of OI	Abnormal (diagnosed OI)	Normal
IIA	4 (R)	5 (R)
IIB	1 (R)	2 (R)
IIC	1 (R)	-
Unclassifiable perinatally lethal	-	1 (R)
III/IV sporadic	-	13 (R)
III recessive	3 (all 'at risk')	1 'at risk'
I new mutation	-	2 (R)

R - routine scan

'at risk' - mother had 1 or more affected children previously.

Note - the numbers quoted as having normal scans is probably greatly underestimated. Many other mothers said that 'all prenatal tests' were normal but the type of test was not clarified.

were referred for detailed scanning rather late in their next pregnancies which accounts for the lateness in making the diagnoses in both of these fetuses (cases 97 and 107) at 28 and 27 weeks, respectively. The mother of cases 106 and 107 was then referred early in her next pregnancy. Detailed scanning revealed no abnormalities at 14 weeks but at 19 weeks and 4 days, the limbs, especially the femora, were shortened and the right femur was angulated. Termination of pregnancy was carried out at 20 weeks, and the diagnosis was confirmed radiographically (case 108).

In two other cases (not shown on table 6.3) fetal abnormalities were detected at second trimester scan, but no diagnosis was reached and the pregnancies continued. These were case 120 (type IIA OI) where a scan at 16 weeks showed an abnormal skull shape and very faint bones. The diagnosis of fetal OI was made at 36 weeks on maternal abdominal radiograph. The other case was no. 170 (unclassifiable PNL) in which a scan at 24 weeks showed 'a grossly abnormal fetus'; the pregnancy continued until 32 weeks when the baby was stillborn after delivery by Caesarian section.

Other mothers had prenatal tests which detected no abnormality or a non-specific abnormality such as small fetal size. In a few, the diagnosis was made on a radiograph late in pregnancy. The number of mothers who gave a definite history of normal routine second-trimester ultrasonography is shown in table 6.3. The mother of case 100 (type III OI) when pregnant with her second

affected child gave a history of a normal second-trimester scan. The other mothers of recessive cases did not have any prenatal tests during the pregnancies of their second affected children, apart from those who had positive scans, described above.

Discussion

Although the information is incomplete, it can be seen that routine second trimester ultrasonography detected 6 cases of type II OI and none of type III/IV (or type I), which is not surprising considering that the skeletal changes at birth in the type II are more severe. However, for pregnancies at risk of type III OI, serial high-resolution scanning by an experienced operator did detect affected fetuses in the second trimester, but the reliability of a negative result has yet to be fully evaluated.

The timing of diagnosis is an important consideration. The earliest diagnosis was made at 17 weeks gestation in a baby with type IIA OI and the latest at 28 weeks in a baby with type III. The cause for the delay in the latter was partly circumstantial; in the mother's next affected pregnancy, the diagnosis was made at 20 weeks. Correct prenatal diagnosis before 20 weeks by careful second trimester ultrasonography in pregnancies at risk of type IIA OI were reported by Dinno et al. (1982) and Shapiro JE et al. (1982) and of type II B OI by Stephens et al. (1983), Patel et al. (1983), Elejalde and Elejalde (1983) and Ghosh et al. (1984), as early as 16 weeks gestation (Ghosh et al., 1984).

In a pregnancy at risk of type III OI, Aylsworth et al. (1984) noted a probable fracture of one femur at 15 1/2 weeks gestation by ultrasonography but severe shortness of the femora was not apparent until the next scan at 19 weeks. Similarly, Robinson et al. (1987) reported on a pregnancy at risk of type III OI in which the femora were of normal length on scanning at 15 weeks gestation, but showed severe shortening by 20 and 22 weeks. After termination of these pregnancies, both fetuses were confirmed to be affected.

Prenatal diagnosis using careful, serial ultrasonography by an experienced operator should be offered to mothers who have had a baby with severe OI (types IIA, IIB and IIC, III and III/IV). The evidence suggests that the results are likely to be trustworthy, perhaps with the caution that the reliability of a normal result in sporadic type III/IV OI is uncertain. Although the recurrence risk in types III/IV and especially IIA OI are low, it would still seem sensible to offer this non-invasive and hopefully reassuring test.

Ideally, identification of the mutation in individual families would clarify the recurrence risk and would provide the potential for an accurate prenatal test for those at high risk, as discussed previously. For the majority at low risk, detailed scanning in the second trimester could be offered to cover the risk of recurrence due to germinal mosaicism.

Another possibility is prenatal diagnosis by examination for abnormalities of type I collagen in chorion villus samples in the first trimester (J Marini, presented at the 3rd International Conference on OI, Pavia, 1987). Widespread application of this technique should await characterisation of type I collagens produced by normal chorion villi and should probably be reserved for families at high risk of recurrence.

Whilst first trimester prenatal diagnosis using DNA markers linked to collagen genes can be offered in some dominant pedigrees (Sykes et al., 1989), at present, second trimester ultrasonography is the main option for mothers of sporadic severe cases.

6.3.3. Amniotic fluid volume

Results and discussion (table 6.4)

The information for the type II and unclassifiable perinatally lethal cases was obtained from hospital records. For the other types, the information generally relied on the mother's recollection of her doctor's report, which is likely to be less reliable. Nevertheless, increased amniotic fluid volume (hydramnios) was relatively more common in the former (type II OI) than the latter (types III and III/IV OI) groups (table 6.4). In one case of unclassifiable perinatally lethal OI (case 174), the volume of amniotic fluid at delivery was estimated to be at least 3 litres, despite a recent amniocentesis to relieve

Table 6.4

AMNIOTIC FLUID VOLUME (No. cases (%))

Type of OI	Normal	Increased	Decreased	?	Total
IIA	3 (30.0%)	6 (60.0%)	1 (10%)	20	30
IIB	2 (33.3%)	3 (50.0%)	1 (16.7%)	9	15
IIC	-	-	-	3	3
Unclassifiable PNL	1 (20.0%)	2 (40.0%)	2 (40.0%)	5	10
III/IV sporadic	37 (77.1%)	5 (10.4%)	6 (12.5%)	41	89
III recessive	7	-	-	12	19
III & III/IV*	44 (78.6%)	5 (8.9%)	7 (12.5%)	52	108
I new mutation	1	-	-	10	11
Total	51 (66.2%)	16 (20.8%)	10 (13.0%)	100	177

% are for known cases

? unknown

*III & III/IV is total of III recessive & III/IV sporadic

polyhydramnios. (This baby was case 3 in the report of Young et al., 1985). Hydramnios was not associated with fetal hydrops and the reason for hydramnios in pregnancies of OI fetuses is unclear but has often been described (Furness and White, 1973; Heller et al, 1975; Monks, 1968; Mussio, 1960; Frerking and Zink, 1952). Campbell (1966) reported severe polyhydramnios.

Decreased amniotic fluid volume (oligohydramnios) was reported in only a few cases and was not associated with renal abnormalities. In two babies, one with unclassifiable perinatally lethal OI (case 170) and the other with type III/IV OI (case 64), amniotic fluid leakage and antepartum haemorrhage, respectively, probably explain the oligohydramnios. Two cases, one with type IIB OI (case 152) and one with unclassifiable perinatally lethal OI (case 168) had small lungs macroscopically but their lung microscopy was not described. It is therefore impossible to determine whether they had true lung hypoplasia, which can be associated with oligohydramnios. In the absence of documented lung hypoplasia or amniotic leak, the cause of oligohydramnios in these and the other 6 cases (table 6.4) is unknown and does not seem to have been reported before.

6.3.4 Livebirths, stillbirths and terminations

Results (table 6.5)

The terminations of pregnancy (TOP) mostly followed detection of abnormality at routine second trimester ultrasonography, as

Table 6.5

LIVEBIRTHS, STILLBIRTHS, TERMINATIONS OF PREGNANCY (TOP) (No. cases (%))

Type of OI	Livebirths	Stillbirths	TOP	Total
IIA	21 (80.8%)	5 (19.2%)	4	30
IIB	12 (100%)	-	2	14+1*
IIC	-	2 (100%)	1	3
Unclassifiable PNL	7 (70%)	3 (30%)	-	10
III/IV sporadic	88 (98.9%)	1 (1.1%)	-	89
III recessive	16 (100%)	-	3	19
I new mutation	11 (100%)	-	-	11

* Information as to whether liveborn or stillborn in one case unknown

% are of livebirths plus stillbirths, excluding TOP

described in section 6.3.2. In another pregnancy, the termination was performed for social reasons (at 18 weeks gestation) and the fetus was found to have type IIB OI after delivery (case 161).

Stillbirths were common in the type II group, with the exception of type IIB in which all of 12 babies were liveborn. As many as 19.2% with type IIA and 30% with unclassifiable perinatally lethal OI were stillborn. No baby with type IIC OI was liveborn. By contrast, only one baby (1.1%) with type III/IV OI was stillborn and all with types III and I OI were liveborn.

Discussion

In the series of 48 cases of type II OI of Sillence et al. (1984), the findings were remarkably similar; stillbirths accounted for 7 of 38 (18.4%) babies with type IIA OI, no baby with type IIB OI was known to be stillborn and all 4 babies with type IIC OI were stillborn. Similarly, of 21 patients with type III OI (Sillence et al., 1979b), all were liveborn but one died in the newborn period.

6.3.5 Gestational age

Results (tables 6.6 and 6.7)

Gestational age refers here to the time from the mother's last menstrual period. From tables 6.6 and 6.7 it can be seen that

Table 6.6

GESTATIONAL AGE (GA): NUMBERS BORN PRE-, POST- OR AT TERM (No. cases (%))

Type of OI	Preterm (<37 wk)	Term (37-42 wk)	Post-term (>42 wk)	Unknown	TOP	Total
IIA	14 (60.9%)	9 (39.1%)	-	3	4	30
IIB	4 (36.4%)	7 (63.6%)	-	2	2	15
IIC	2 (100%)	-	-	-	1	3
Unclassifiable PNL	6 (75%)	2 (25%)	-	2	-	10
III/IV sporadic	5 (5.7%)	82 (93.2%)	1 (1.1%)	1	-	89
III recessive	-	12 (100%)	-	4	3	19
III & III/IV*	5 (5%)	94 (94%)	1 (1%)	5	-	105
I new mutation	2 (20%)	8 (80%)	-	1	-	11

* III & III/IV is total of III & III/IV.

Table 6.7

MEAN GESTATIONAL AGES (GA), IN WEEKS (\pm 1 SD)

Type of OI	Mean GA for livebirths & stillbirths	Mean GA for livebirths	Mean GA for stillbirths	GA at termination
IIA	36.3 \pm 3.36 (n=23)	36.4 \pm 3.43 (n=18)	32.4 \pm 7.50 (n=5)	17,18,23 (n=3, & 1 unknown)
IIB	38.1 \pm 2.55 (n=11)	38.1 \pm 2.55 (n=11)	-	18,23 (n=2)
IIC	28,30 (n=2)	-	28,30 (n=2)	19 (n=1)
Unclassifiable PNL	34.6 \pm 2.97 (n=8)	35.7 \pm 2.66 (n=6)	31,32 (n=2, & 1 unknown)	-
III/IV sporadic	39.4 \pm 1.85 (n=88)	39.5 \pm 1.55 (n=87)	30 (n=1)	-
III recessive	38.9 \pm 1.24 (n=12)	38.9 \pm 1.24 (n=12)	-	20,27,28 (n=3)
III & III/IV*	39.33 \pm 1.8 (n=100)	39.4 \pm 1.53 (n=99)	30 (n=1)	25 \pm 4.4
I new mutation	38.2 \pm 3.05 (n=11)	38.2 \pm 3.05 (n=11)	-	-

Numbers in brackets indicate numbers of patients for whom GA was known. If the group involved 3 or fewer cases, the actual GA's are given.

* III & III/IV is total of III recessive & III/IV sporadic

types IIA, IIB, IIC and unclassifiable perinatally lethal cases were more likely to be born preterm and had lower mean gestational ages than the cases of types III/IV, III or I OI who were more likely to be born at term. In table 6.7, it can be seen that stillborn babies were more likely to be born at an earlier gestational age than liveborns. The time at termination (when known) for 10 fetuses is also shown in table 6.7. These are not included in the category 'preterm' in table 6.6.

Discussion

Similar results were found by Sillence et al. (1984) who noted that mean gestational ages for 28 babies with type IIA OI and 4 with type IIC were 35.7 ± 3.9 weeks and 35.3 ± 3.8 weeks, respectively. Babies with type III OI were usually born at term. Mean gestational age for 21 babies with type III OI was 39 weeks, ranging from 37 to 42 weeks (Sillence et al., 1979b).

6.3.6 Presentation at delivery

Results (table 6.8)

Breech presentation was common in all groups, except in the type I cases. In the types IIA and IIB groups, as many as 13 of 15 babies (86.7%) and 4 of 6 babies (66.7%) presented by the breech, respectively. About one-third of types III/IV and III cases were breech, which is well above the frequency of 2.11% in the general population (Ritchie, 1986). All of 8 babies with type I OI

Table 6.8

PRESENTATION AT DELIVERY (No. cases (%))

Type of OI	Vertex	Breech	TOP	Other	Unknown	Total
IIA	2 (13.3%)	13*(86.7%)	4	-	11	30
IIB	2 (33.3%)	4 (66.7%)	2	-	7	15
IIC	-	-	1	-	2	3
Unclassifiable PNL	3 (60%)	1 (20%)	-	1** (20%)	5	10
III/IV sporadic	47 (61.8%)	28*(36.8%)	-	1*** (1.3%)	13	89
III recessive	8 (61.5%)	5 (38.5%)	3	-	3	19
III & III/IV ^I	55 (61.8%)	33 (37.1%)	3	1 (1.1%)	16	108
I new mutation	8**** (100%)	-	-	-	3	11

* 2 IIA and 1 III/IV sporadic were footling breech.
1 III/IV sporadic was a breech with extended legs.

** transverse lie

*** not engaged in the pelvis

**** 1 breech turned by external version and presented vertex.

Numbers in brackets are % for those known, excluding the TOP (terminations of pregnancy).

^I III & III/IV is total of III/IV sporadic & III recessive.

presented by the vertex, although one had been breech and was turned by external version. One baby (case 32, III/IV sporadic OI) presented by the breech with extended legs and was the only affected newborn without significant tibial bowing, suggesting that flexion of the legs in utero contributes to tibial bowing.

Discussion

Breech delivery occurred in 5 of 38 babies (13.2%) with type IIA OI in Sillence et al.'s (1984) series and numerous authors report breech presentation of fetuses with OI (Zervoudakis et al., 1978; Pierog et al., 1969; Bock, 1969; Posner and Goldman, 1957; Benson et al., 1978; Laverty et al., 1971; Gillanders, 1957). Benson et al. (1978) in reviewing 143 patients with OI emphasised the high incidence of breech births which occurred in 30 of 123 cases (24.4%). The reasons for the increased incidence of breech presentation of fetuses with OI may include first, an unusual head shape which discourages engagement in the pelvis, and secondly prematurity; the latter is well known to be associated with breech presentation (Ritchie, 1986). It is important to note that attempted external version of a breech fetus with OI is likely to cause fractures (Bock, 1969; Beighton et al., 1983).

6.3.7 Mode of delivery

Results (tables 6.9 and 6.10)

Table 6.9 indicates that obstetric intervention during delivery

Table 6.9

MODE OF DELIVERY (No. cases (%))

Type of OI	SVD	Forceps	Caesarian	TOP	Unknown	Total
IIA	5 (29.4%)	3 (17.7%)	9 (52.9%)	4	9	30
IIB	4 (50%)	2 (25%)	2 (25%)	2	5	15
IIC	-	-	-	1	2	3
Unclassifiable PNL	3 (42.9%)	1 (14.3%)	3 (42.9%)	-	3	10
III/IV sporadic	47 (69.1%)	11 (16.2%)	10 (14.7%)	-	21	89
III recessive	8 (61.5%)	2 (15.4%)	3 (23.1%)	3	3	19
III & III/IV*	55 (67.9%)	13 (16.1%)	13 (16.1%)	3	24	108
I new mutation	6 (85.7%)	-	1 (14.3%)	-	4	11
Total	73 (60.8%)	19 (15.8%)	28 (23.3%)	10	47	177

SVD - spontaneous vaginal delivery

* III & III/IV is the total of III recessive & III/IV sporadic

Table 6.10

REASONS FOR CAESARIAN SECTION (CS)

Type of OI	Reason	No. of cases	Case no.
IIA	Breech alone	2	120(el), 139(em)
	Footling breech, IUGR	1	138(el)
	Breech, fetal distress,	1	144(em)
	Breech, IUGR, oligo-	1	147(el)
	hydramnios	2	122(em), 125(em)
	Fetal distress	1	134(em)
	Fetal distress, APH	1	123(el)
	Unknown	<u>1</u>	
	Total	9	
IIB	Fetal distress	1	154(em)
	IUGR	<u>1</u>	152(el)
	Total	2	
Unclassifiable PNL	Placenta praevia, ovarian cyst	1	170(em)
	Fetal abnormality	1	173(em)
	3 previous CS, unstable lie associated with severe poly-hydramnios) 1)	174(el)
	Total	<u>3</u>	
	III/IV sporadic	Breech alone	6
Breech, hypertension, previous CS		1	32(el)
Fetal head not engaged in pelvis		1	18
Maternal fibroid		1	25
Unknown		1	4
Total		<u>10</u>	
III recessive		Breech alone	1
	Breech and IUGR	1	90
	Breech and CPD	1	91(el)
	Total	<u>3</u>	
I new mutation	APH	1	116(em)
	Grand total =	<u><u>28</u></u>	

IUGR - intrauterine growth retardation. APH - antepartum haemorrhage
 CPD - cephalopelvic disproportion. em - emergency CS {indicated if
 el - elective CS (known

was common. Overall, (excluding the 10 terminations) only 61% of mothers delivered by spontaneous vaginal delivery, 16% required forceps, usually because the fetus was breech (in 14 of 19 cases) and 23% had Caesarian sections. Babies with type II OI were more likely to be delivered by Caesarian section or forceps than were those with types III/IV or III OI. By contrast, 6 of 7 babies with type I OI were delivered normally (but the numbers do not differ significantly from those for the type III/IV group, $p = 0.5 - 0.7$). Reasons for Caesarian section are given in table 6.10. Two babies, case 112 (type I OI) and case 146 (type IIA OI) were the first-born of twins. The co-twin in each case was normal.

Discussion

Surprisingly little has been written about the optimal mode of delivery for a fetus with OI (Romero et al., 1988). Some authors recommend that Caesarian section is the optimal mode of delivery if the fetus is known to have OI 'to avoid fetal trauma' (Simpson et al., 1982). Whilst it may be true that Caesarian section minimizes the risk to the mother if she herself has OI (Roberts and Solomons, 1975; Bullard et al., 1977, Quakernack et al., 1980), some experienced obstetricians point out that if the mother is healthy, a vaginal delivery which is proceeding normally may not necessarily be any more traumatic to the fetus with OI than a Caesarian section. (Professor Charles Rodeck, personal communication, 1988). Laverty et al (1971), however, noted that a baby with OI delivered by Caesarian section survived whereas affected twins delivered by breech extraction died, as

did another baby who was delivered normally and who was found to have multiple skull fractures and a cerebral haemorrhage at autopsy. The types of OI affecting these babies is not known, however, and this may influence outcome as much as does the mode of delivery. In the present series, the 3 babies with type IIB OI who survived beyond the perinatal period were spontaneous cephalic births (2 cases) and breech forceps extraction (one case), the baby with type III/IV OI who died soon after birth was delivered by elective Caesarian section and the baby with type III OI who died soon after birth was delivered by breech forceps extraction. All babies with types III and III/IV OI born by spontaneous vaginal delivery survived the perinatal period (figure 6.1). There is, therefore, no evidence that the mode of delivery consistently influences survival in severe OI, but that the type of OI certainly does. Kuller et al. (1988) made the logical suggestion that if a fetus is known to be at risk of OI, a radiograph should be done before delivery and babies with adequate skull mineralisation can be delivered vaginally. The use of forceps should be avoided if possible (Simpson et al., 1982).

6.4 Measurements of babies at birth

6.4.1 Birth weight

Results (tables 6.11 and 6.12)

Table 6.11 shows the mean birth weight of babies when known and

Figure 6.1

MODE OF DELIVERY COMPARED WITH PERINATAL SURVIVAL

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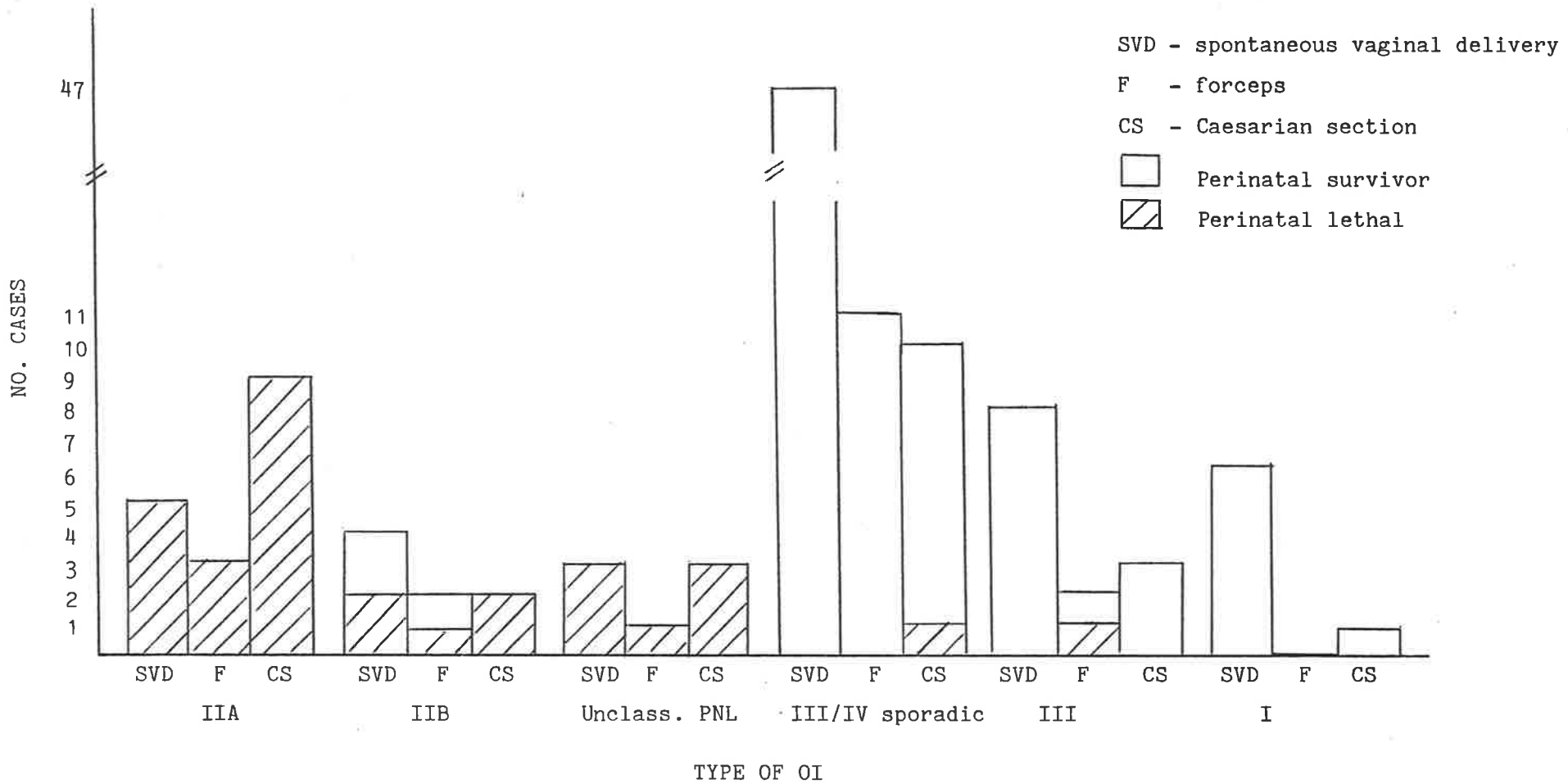


Table 6.11

BIRTH WEIGHT (Mean \pm 1 SD)

Type of OI	Mean birth weight (gm)	Mean GA (wk)*
IIA	1691 \pm 358.8 (n = 19)	36 \pm 3.53 (n = 18)
IIB	2276 \pm 576.3 (n = 11)	37.8 \pm 2.49 (n = 10)
IIC	738 \pm 53.0 (n = 2)	29 \pm 1.41 (n = 2)
Unclassifiable PNL	1384 \pm 374.3 (n = 9)	35 \pm 3.0 (n = 7)
III/IV sporadic	2701 \pm 456.2 (n = 82)	39.5 \pm 1.59 (n = 82)
III recessive	2774 \pm 620.2 (n = 12)	38.9 \pm 1.24 (n = 12)
III & III/IV**	2710 \pm 475 (n = 94)	39.4 \pm 1.6 (n = 94)
I new mutation	2511 \pm 359.2 (n = 10)	38.2 \pm 3.05 (n = 10)

*The GA (gestational ages) here refer to the GA of babies whose birth weights are known. Thus the figures for GA are different in some cases from those in table 6.6 where GA for all babies are shown.

** III & III/IV is total of III recessive & III/IV sporadic.

Table 6.12

BIRTH WEIGHT CENTILES (No. cases (%))

Centiles - Type of OI	<3rd	3rd-10th inc.**	>10th - 50th inc.	>50th - 97th inc.	Unknown	Total
IIA	14 (77.8)	1 (5.6)	3 (16.7)	-	12	30
IIB	6 (60)	1 (10)	3 (30)	-	5	15
IIC	1 (50)	1 (50)	-	-	1	3
Unclassifiable PNL	6 (85.7)	1 (14.3)	-	-	3	10
III/IV sporadic	18 (22.0)	41 (50.0)	21 (25.6)	2 (2.4)	7	89
III recessive	2 (16.7)	6 (50.0)	3 (25.0)	1 (8.3)	7	19
All III & III/ IV*	20 (21.3)	47 (50.0)	24 (25.5)	3 (3.2)	14	108
I	2 (20)	5 (50)	3 (30)	-	1	11

*All III & III/IV is total of III recessive & III/IV sporadic.

** inc. - inclusive

the mean gestational ages of those whose birth weights were available. Babies with type II OI tended to have very low birth weights, whereas those with types III, III/IV and I OI had birth weights at the lower end of the normal range (2500 gm is at the 3rd centile, at term). Two babies with perinatally lethal types III/IV (case 89) and III (case 106) OI both had birth weights of 2381 gm at 38 weeks gestation, which is below the mean for all type III/IV (2701 gm) and all type III babies (2774 gm). On the other hand, in the type IIB OI group, the mean birth weight of 8 with perinatally lethal disease was 2298 gm (\pm 681.5), compared to the mean of 2215 gm (\pm 165.5) for the 3 perinatal survivors. In other words, the birth weight within a particular category was not necessarily lower in those who died perinatally.

Table 6.12 shows the proportion of babies grouped according to birth weight centiles. One half to three quarters of babies with type II OI fell below the 3rd centile for birthweight, whereas about one-fifth of those with types III, III/IV and I OI had birth weights below the 3rd centile and about three-quarters fell between the 3rd and 50th centiles. It was uncommon for the birth weight to lie above the 50th centile. The growth charts used were those of Gairdner and Pearson (1985).

Discussion

The mean birth weights in the series of Sillence et al. (1984) were 1640 \pm 529 gm (n=24) for type IIA OI and 492.5 \pm 287.7 gm (n=4) for type II C OI. (No details were given for the type IIB

cases). These are very similar to the findings in the present study. About half of 21 babies with type III OI (Sillence et al., 1979b) were above the 10th centile for birth weight, but relatively more of their cases (5 of 21, 23.8%) were over the 50th centile and 2 of these were over the 90th. About half of 51 babies with type I OI in the same report were over the 50th centile at birth, whereas no difference was noted between types III and III/IV, and type I OI in the present series. In general, it appears that the more severe forms of OI are associated with lower birth weights, as might be expected.

6.4.2 Birth length and head circumference

Results (tables 6.13 and 6.14)

Table 6.13 shows the mean crown-rump and crown-heel lengths and the mean occipitofrontal head circumference (OFC) at birth for babies with type II OI. Unfortunately, very little data was obtained for the types III and III/IV cases, and none for the type I cases. The crown-heel measurements were well below the 3rd centile in all babies with lethal OI except for one with type IIA OI (case 139) whose length was on the 3rd centile, and two with type IIB (cases 150 and 153) whose lengths were on the 10th centile. A boy with type IIB OI (case 164) who survived to six weeks is included in table 6.13; he also had a birth length well below the 3rd centile. A girl with type III/IV OI (case 3) whose birth length was on the 90th centile grew only 3 cm by the time of her death at 3.8 years.

Table 6.13

MEAN CROWN-RUMP AND CROWN-HEEL LENGTH AND MEAN OCCIPITOFRONTAL HEAD CIRCUMFERENCE (OFC) AT BIRTH

Type of OI	Mean crown-rump length \pm 1 SD (cm)	GA \pm 1 SD (weeks)	Mean crown-heel length \pm 1 SD (cm)	GA \pm 1 SD (weeks)	Mean OFC \pm 1 SD (cm)	GA \pm 1 SD (weeks)
IIA	25.8 \pm 5.1 (n = 15)	32.3 \pm 6.6 (n = 14)	34.5 \pm 2.9 (n = 16)	35.6 \pm 3.6 (n = 15)	30.0 \pm 3.1 (n = 12)	36.6 \pm 3.3 (n = 11)
IIB	32.5 \pm 1.5 (n = 3)	38.0 \pm 2.7 (n = 3)	42.2 \pm 4.7 (n = 6)	38.0 \pm 2.4 (n = 5)	32.9 \pm 2.1 (n = 7)	38.5 \pm 2.1 (n = 6)
IIC	18.7 \pm 5.1 (n = 3)	25.7 \pm 5.9 (n = 3)	29.0 \pm 1.4 (n = 2)	29.0 \pm 1.4 (n = 2)	21.0 \pm 7.8 (n = 2)	24.5 \pm 7.8 (n = 1)
Unclassifiable PNL	27.0 \pm 3.6 (n = 3)	34.0 \pm 0 (n = 3)	33.2 \pm 4.8 (n = 5)	35.5 \pm 3.0 n = 4)	28.9 \pm 2.5 (n = 4)	35.5 \pm 3.0 (n = 4)
III/IV	-	-	53 (n = 1)	38 (n = 1)	33.3 \pm 1.04 (n = 3)	39 \pm 2.7 (n = 3)
III	-	-	49 (n = 1)	-	33.5 \pm 0.71 (n = 2)	39 \pm 1.4

GA - mean gestational age for those with known lengths or OFC's.

(No data for type I OI).

Table 6.14

CENTILES FOR OCCIPITOFONTAL CIRCUMFERENCE (OFC) (No. cases (%))

Centiles	<3rd	3rd-10th inc.*	>10th-50th inc.	>50th - 97th inc.	Unknown	Total
Type of OI						
IIA	7 (63.6%)	4 (36.4%)	-	-	19	30
IIB	3 (50%)	-	2 (33.3%)	1 (16.7%)	9	15
IIC	-	1	-	-	2	3
Unclassi- fiable PNL	3 (75%)	-	1 (25%)	-	6	10
III/IV	-	-	3	-	86	89
III	-	-	2	-	17	19

PNL - perinatally lethal

* inc. - inclusive

Useful standard curves of crown-rump length for gestational ages beyond the embryonic period (8 post-ovulatory weeks) are apparently unavailable (O'Rahilly and Müller, 1986). Two pathologists, commenting on cases in the present series, however, noted that a 20 week fetus with type IIA OI (case 132) and a term fetus with unclassifiable perinatally lethal OI (case 176) had normal crown-rump lengths, but short limbs.

The head circumference was also often below the 3rd centile (table 6.14). Comparing OFC and crown-heel length in individual patients, however, revealed that the head was relatively much larger than length in all of 20 cases with lethal OI except in one boy with type IIA OI (case 143) whose OFC and length were proportionately both well below the 3rd centile. The OFC of the five III/IV and III cases were all between the 10th and 50th centiles; the girl whose length was known (case 3) had no relative macrocephaly.

Discussion

Sillence et al. (1984) noted that the mean crown-rump length in 20 babies with type IIA OI was 34.2 ± 4.4 cm which is the same as the mean crown-heel length in this series. Since the babies in the two series had the same birth weights, this author wonders respectfully whether Sillence and his colleagues were in fact referring to crown-heel length.

In any event, babies with severe OI are very short at birth and

in two cases this was shown to be mainly a result of limb shortening. Whether or not this is true for all cases cannot be deduced from the available data. The appearance of a relatively large head is well known in babies with OI (Lavery et al., 1971) and although the head enlargement is usually relative rather than absolute, Monks (1968) suggested that the enlargement of the transverse diameter in the temporal region of the fetal skull in OI may predispose to obstruction during the second stage of labour.

6.5 Survival of liveborn babies: prognosis can be based on radiological appearance at birth

Results (table 6.15)

Liveborn babies with types IIA and unclassifiable perinatally lethal OI survived on average for 4 hours and none lived longer than 24 hours. Nine with perinatally lethal type IIB OI died on average at 14 hours, but three died later, at 4 and 6 weeks and 26 months, respectively. One liveborn baby with type III/IV OI died at the age of one day and one with type III OI died at 10 hours. A further 15 of 87 (17.2%) of patients with type III/IV OI died after the perinatal period at a mean age of 4.1 years; thus a total of 16 out of 88 (18.2%) liveborn type III/IV OI patients died.

In the type III OI group, 8 of 15 (53.3%) patients died after the perinatal period, at a mean age of 4.8 years; the total number of

liveborns who died was therefore 9 out of 16 (56.3%). About one half of the types III/IV and III cases who died did so before 2 years and all but one died before 10 years. Approximately equal numbers of males and females died (table 6.15). The causes of death are discussed in sections 6.6 and 6.7.1.2.

Discussion

The radiographic appearance at birth can be used to predict prognosis to a certain extent. Prognosis is worst in type IIC OI in which 6 of 7 cases (this study and Sillence et al., 1984) were stillborn; the other (this study) was a second trimester termination. Danks (1975) also reported 2 sibs with probable type IIC OI, one of whom died 'at or soon after birth' (details for the other sib were not given). Prognosis is also very poor in type IIA: none of our patients lived beyond 24 hours; although Sillence et al. (1984) reported maximum survival to six weeks in type IIA OI and Bonadio et al. (1985) described an affected girl who lived to 6 months. Patients with the radiographic appearance of type IIB OI also have a poor prognosis in terms of survival, but survival may be longer than in type IIA. Goldfarb and Ford (1954) reported two sibs with probable IIB OI who died at five months and 5 1/2 months and Hein (1928) described a girl with probable type IIB OI who died at 5 months. Maximum survival in the present study was to 26 months.

Table 6.15

AGE AT DEATH OF LIVEBORN CASES

Type of OI	Livebirths	Deaths (%)	Mean age at death	Median age at death	Range of age at death
IIA	21 PNL	21 (100%)	4 hours	30 minutes	3 minutes to 24 hours
IIB	9 PNL] 3 PNS]	9] (100%) 3]	14 hours] 9.5 months] 2.5 mth	6 hours 6 weeks	1 hour to 48 hours 4 weeks to 26 months
IIC	-	-	-	-	-
Unclassifiable PNL	7	7 (100%)	4 hours	40 minutes	20 minutes to 20 hours
III/IV sporadic	1 PNL 87 PNS	1 (M) 15 (9F, 6M)] (18.2%)	1 day] 4.1 years] 3.9 yr	- 1.25 years	1 day 0.25 to 18.5 years
III recessive	1 PNL 15 PNS	1 (M) 8 (3F, 5M)] (56.3%)	10 hours] 4.8 years] 4.3 yr	- 1.6 years	10 hours 16 days to 16 years
III & III/IV*	2 PNL 102 PNS	2 (M) 23 (12F, 11M)] (24.0%)	18 hours] 4.4 years] 4.0 yr	- 1.33 years	10 hours to 1 day 16 days to 18.5 years
I new mutation	11	- (0%)	-	-	-

PNL, PNS perinatal lethals and survivors, respectively. F = female, M = male

* III & III/IV is total of III/IV sporadic & III recessive.

The vast majority of cases with the type III/IV or type III appearance at birth survived the perinatal period but about one quarter overall died in childhood. This may be an underestimate of the mortality rate however, since the method of ascertainment may bias against finding deceased patients whose families had not joined the Brittle Bone Society. More reliable are the results of Sillence et al. (1979b) based on birth incidence of type III OI, in which 8 of 21 (38.1%) infants with type III OI died, mostly in infancy, as in the present study. One of their cases died in the newborn period. Thus, a significant proportion of patients with type III/IV and type III OI survive childhood, and the prognosis improves if the child lives through the first two years. Occasionally, patients may survive to middle age (see section 6.7.1.1). Many parents of children with types III and III/IV OI reported that their paediatricians had predicted an early demise for their child. Paediatricians should be made aware that these children may survive.

Sporadic cases with only mild bowing at birth usually have mild disease and probably represent new dominant mutations of type I OI.

In summary, the better the bone morphology at birth, the longer the survival. This is similar to the results of the scoring system devised by Spranger et al. (1982). Likewise, Shapiro (1985) in a review of 85 patients with OI, found that poor bone morphology at birth or at the time of initial fracture predicted a worse prognosis for survival and ambulation.

6.6 Perinatally lethal cases - description of babies
(table 6.16)

Type IIA OI

In 10 babies, blue sclerae were recorded (cases 120, 122, 123, 125, 128, 138, 139, 142, 144, 149). In 4 of these, the sclerae were described as 'dusky blue' (case 123), 'very blue' (case 128), 'dark blue' (case 138) or 'grey blue' (case 144). In the other 20 cases, no reference to scleral colour was made in the hospital notes.

Post-mortem reports were available in 18 cases (cases 120, 122-125, 127, 129, 132, 136, 138-140, 143-147, 149). In all, note was made of the severe shortening and deformity of the limbs and of the very soft skull, often described as 'like an egg-shell', due to minimal or absent skull mineralisation. The head, which appeared to be relatively large compared to the body as noted above, was often globular in shape with a round face (figure 6.2). Flexion and abduction at the hips and flexion at the knees imparted a characteristic posture to the legs. The thorax was small. Specific note of very fragile skin was made in one baby (case 125) and in another (case 142), the head had become avulsed following gentle traction during delivery. Case 137 had a ruptured liver. In one baby (case 140), there was macroscopic absence of the falx, tentorium and meningeal membranes and a subdural haemorrhage had occurred in another (case 122). All

Table 6.16

MANIFESTATIONS IN PERINATALLY LETHAL CASES*

Type of OI	IIA	IIB	IIC	Unclassifiable PNL
Manifestation				
Blue sclerae	10/10	0/2 PNL 2/3 PNS	1/1	4/4
Weak tissues	3	-	2	2
Intracranial haemorrhage	1	1	-	2
Hypoplastic lungs				
macroscopically	1	1	-	4
microscopically	-	-	-	1
Oedema	-	2	1	1
Other	2 (undesc. testes) 1 (ASD, renal)	1 (natal teeth) 1 (cloudy cornea)	1 (talipes)	1 (talipes) 1 (Meckel's divertic.) 1 ('cataracts')
Normal karyotype	3/3	1/1	1/1	3/3

* see text for details, PNL - perinatally lethal, PNS - perinatal survivor



Figure 6.2

A baby with type IIA OI (case 140).

Note the rounded face, small chest and short bowed limbs.

bones were generally soft or brittle and one pathologist described them snapping on gentle handling. Multiple fractures were noted, associated with beading of the ribs. The vertebral bodies were frequently flat, and the limb bones were often described as 'crumpled' or 'like a concertina'.

The other organs were usually normal. The lungs were specifically commented upon in 3 cases and described as 'congested' (case 120), 'minimally aerated' (case 138) and 'grossly hypoplastic' (case 149), respectively. In only one (the latter) was lung histology examined and it was normal for gestational age, suggesting that the lungs were small because they had not inflated, rather than because of true hypoplasia. Two males, delivered at 31 and 39 weeks gestation (cases 143 and 149, respectively), had intra-abdominal testes, bilaterally in the former and of the right testis only in the latter. One baby (case 139) had a large atrial septal defect (ASD) of the fossa ovalis type, and bilateral hydronephrosis and hydroureter associated with stenosis of the ureters at the vesico-ureteric junctions.

Chromosome analysis on 3 babies was normal (cases 138, 142, 146). The latter had a normal twin sib and healthy father both with an inversion of chromosome 2.

Type IIB OI

In two (cases 155 and 159) of 12 babies with perinatally lethal OI, the sclerae were specifically noted to be white, but were not commented upon in the others. Two (cases 162 and 164) of the 3 who survived the perinatal period had dark blue sclerae and in the other (case 163) the sclerae were of normal hue.

The general description of babies with perinatally lethal type IIB OI was similar to that for type IIA. The limbs were short and bowed and the head was relatively large, soft and 'boggy' with poorly mineralised skull. Marked generalised oedema was noted in 2 cases (cases 151, 156). Post-mortem reports obtained on 3 babies (cases 152-154) revealed multiple fractures. One baby (case 152) was said to have 'pulmonary hypoplasia', but the lungs were not examined histologically. Another (case 154) had a subdural haemorrhage. Additional anomalies were two natal teeth in the lower gum margin of case 155 and cloudy corneae and large irides in case 152. Chromosome analysis in one case (no. 161) was normal.

Figure 6.3 shows a baby with perinatally lethal type IIB OI. The impression is that the severity of his limb shortening is less than the baby with type IIA shown in figure 6.2. Unfortunately, limb lengths cannot be formally compared in the 2 groups due to lack of such data. For comparison, a baby with type IIB OI who survived perinatally is presented in figure 6.4, to show that the appearance of the two babies is similar.

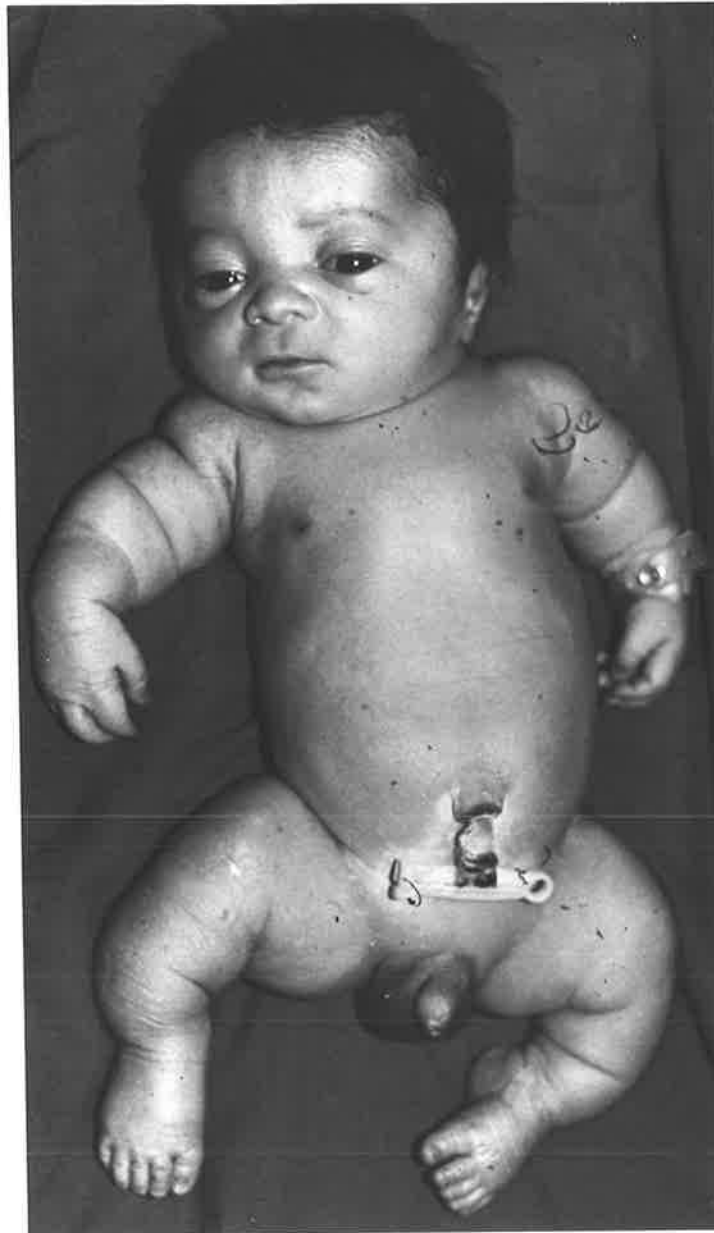


Figure 6.3

A baby with type IIB OI (case 155) who died at 24 hours.
Note short bowed limbs.



Figure 6.4

A baby with type IIB OI (case 162) who survived for 26 months.

Note that the appearance of the limbs is similar to those of the baby with perinatally lethal type IIB OI in figure 6.3

The parents of the baby in figure 6.4 made a special request that her photograph be identified with her name, rather than remaining anonymous. She was named Corrinne Jay.

Type IIC OI

Post-mortem reports were available for all 3 babies and noted that all had short limbs. In one (case 167), stillborn at 28 weeks gestation, the head had 'burst' during delivery. In the other two, delivered at 30 and 19 weeks, complete absence of skull vault mineralisation was found. The sclerae in the 19 week fetus (case 166) were definitely darker than controls at the same gestational age and the mandible was short. The 30 week baby (case 165) was extremely hydropic, had 'gross hydrocephalus', very low set ears, bilateral talipes deformities of the feet and the left hand had been avulsed and had a cyst 0.5 cm in diameter attached to the little finger by a stalk. In all 3 babies, there were multiple fractures and bony deformities, but other organs were normal. Chromosome analysis of case 166 was normal.

Histological examination of bone in one case (no. 166) confirmed the diagnosis of OI, and showed osteoporosis, a propensity to heal fractures, normal differentiation of the costochondral junction and maturity of cartilage in the centre of epiphyses.

Unclassifiable perinatally lethal OI

Post-mortem reports were available in all 10 cases. In 4, the colour of the sclerae was recorded and was abnormal, described as 'blue' (case 172), 'grey-brown' (case 175), 'dusky' (case 177) and 'abnormal' (case 169). Severe limb shortening and paucity of skull vault mineralisation was again noted. Evidence of

friability of tissues was again present: one baby (case 170) had a partial amputation of a leg below the knee which may have occurred during delivery and another (case 174) had amniotic bands at both wrists and the left ankle, and the right foot was absent. The latter child was case 3 in the report by Young et al. (1985). Intracranial haemorrhages had occurred in 2 babies; one (case 169), had a subependymal haematoma of the right ventricle and a subarachnoid haematoma over the right parietal lobe and another (case 177) had subdural, subarachnoid and intraventricular haemorrhages. The lungs were small on gross examination in 4 cases (cases 168, 171, 172, 176). Histology in case 171 revealed true lung hypoplasia but in case 168, lung morphology was normal. Mostly, it appeared that the lungs were unaerated or only minimally so. One child (case 171) with a flat face, widely spaced eyes and low placed ears also had mild talipes.

Other anomalies included undescended testes in 2 males (cases 175 and 177), a Meckel's diverticulum in case 170, and 'bilateral cataracts' in another (case 175). The latter was a clinical observation, rather than a post-mortem finding. One baby (case 168) with generalised extramedullary haematopoiesis and oedema was thought to have had a haemolytic disorder of unknown cause.

Chromosome analysis in 3 cases (no. 168, 170, 176) was normal. Histology of bone in 2 cases (no. 171 and 173) was consistent with OI, showing minimal bone formation, disorganised osteogenesis, thin delicate bony trabeculae but normal-looking

epiphyseal cartilage.

Sporadic type III/IV and recessive type III OI

There were 2 babies with type III/IV OI and one with type III OI with perinatally lethal disease and 3 terminated fetuses with type III OI. Attempts to obtain post mortem reports on these babies were unsuccessful and scleral colour was not known for any.

Discussion

Severe limb shortening and deformity, a soft globular skull and a characteristic facial appearance produce the recognisable clinical phenotype at birth noted by Sillence et al. (1984). Although none of the babies was seen personally by the author, from the clinical descriptions and photographs it appears that there were no constant distinguishing features to allow differentiation of the various sub-groups clinically, without recourse to the radiographs. Scleral colour was not particularly helpful in this regard. Whilst all 10 infants with type IIA OI in whom scleral colour was recorded had dark blue sclerae, (as did 20 of 21 infants reported by Sillence et al., 1984) babies with type IIB OI had either white (3 cases) or dark blue sclerae (2 cases) and one with type IIC OI also had blue sclerae.

Extreme friability of tissues resulted in either avulsion or rupture of the head during delivery in one baby each with type

IIA and IIC OI respectively, rupture of the liver and fragile skin (both type IIA OI), avulsion of a hand in type IIC OI and partial amputation of a leg during delivery in a baby with unclassifiable perinatally lethal OI. Similar reports of avulsion of body parts during delivery have involved babies with type IIA OI (Heller et al., 1975; Sillence et al., 1984; Steinmann et al., 1984; deWet et al., 1983).

A child in the unclassifiable category had evidence of amniotic bands which may also attest to the friability of the amnion, a tissue of fetal origin. Similarly, a baby with unspecified perinatal lethal OI described by Magnin et al. (1962) had a constriction at the right elbow which could have resulted from an amniotic band. In support of this was the history of amniotic fluid leak during the pregnancy. A fetus with probable type IIB OI was noted after termination to have amniotic bands on both hands resulting in amputation of fingers and constriction rings (Elejalde and Elejalde, 1983). Amniotic bands have also been described in babies with other connective tissue disorders, namely two infants with Ehlers-Danlos syndrome (EDS) type IV (Young et al. 1985) and one with epidermolysis bullosa (Marras et al., 1984). The fetal membranes are composed of collagen types I, III and V (Pope et al., 1983) and the amnion is the major load-bearing component (Hoyes, 1970). OI is due to defective type I collagen, EDS IV to defective type III collagen (Pope et al., 1975) and in one form of epidermolysis bullosa, increased collagenase activity is the underlying defect (Bauer, 1977). Torpin (1968) suggested that amniotic bands arise from premature

rupture of the amnion. Abnormalities of collagen therefore may explain the occurrence of amniotic bands in babies with OI and other connective tissue disorders. Mothers of babies at risk of these conditions should perhaps take special care to avoid any abdominal trauma during pregnancy. Prenatal diagnostic procedures, although often indicated in these pregnancies, may also pose special hazards.

Fetal oedema and hydrops were noted in 2 babies with type IIB OI and one with type IIC. Sillence et al., (1984) emphasised that hydrops occurred in some 15% of their cases, all with type IIA OI and none with type IIB. Our findings perhaps indicate that hydrops is yet another non-specific association of perinatally lethal OI. A baby with unclassifiable OI and oedema with extramedullary haematopoiesis may have had a haemolytic disorder.

The cause of death probably mainly related to poor aeration of the lungs. In 6 babies, the lungs were small macroscopically; histology in 2 of these revealed normal morphology and in one there was true hypoplasia of the lungs. At the 3rd International Conference on OI (Pavia, 1987), Shapiro and colleagues reported on a baby with probable type IIA OI who had pulmonary hypoplasia (reduced lung weight, together with decreased numbers of branching airways, acini and alveoli). Although under light microscopy there appeared to be increased collagen in the peribroncholar and periarterial sheaths and in interlobular septa, electron microscopy of pulmonary alveolar septa suggested fewer type I collagen bundles than normal. Analysis of

procollagen synthesised by skin fibroblasts suggested a defect in $\alpha 1(I)$ chain synthesis. The authors proposed that this defect may cause impaired pulmonary organogenesis in lethal OI. Whether this is generally true remains to be proven.

Failure to establish effective ventilation may also result from poor mechanical effort, which in turn may result from the small chest size and pain from rib fractures. Another factor which probably contributed to death was intracranial haemorrhage noted in one baby with type IIA OI, one with type IIB, and 2 with unclassifiable perinatally lethal disease. It is likely that the soft skull predisposes to intracranial haemorrhage during delivery (Bailey, 1971).

Associated anomalies included natal teeth, Meckel's diverticulum and extramedullary haematopoiesis; these are probably not causally related to OI. Glover (1922) described a boy with mild sporadic OI and normal sclerae whose lower central incisor teeth were already erupted at birth; no second teeth developed in those sites. Other anomalies such as undescended testes and talipes could possibly relate to the connective tissue disorder. The absence of falx, tentorium and meningeal membranes in one baby and hydrocephalus in another are more difficult to explain. One baby with type IIA OI had vesico-ureteric junction stenosis with secondary hydronephrosis and a large ASD. Whilst congenital defects of the renal tract are apparently rare in OI, congenital heart lesions have occasionally been described. For example, Navani and Sarzin (1967) described two unrelated babies with type

IIA OI, one of whom was found at post mortem to have a large (7 mm) ASD; the other (a 33 week fetus) had a patent foramen ovale, as well as atresia of the second part of the duodenum and undescended testes. Two sibs described by Remigio and Grinvalsky (1970) (see also section 1.4.1.2) had an abnormal basophilic and mucoid appearance of the connective tissue of the heart and its valves and the aorta. The boy also had coarctation of the aorta and subluxation of the lens of the eye. This sib pair is unusual in that not only did they have the radiological appearance of type IIA OI but also their manifestations overlap with those of the Marfan syndrome. Finally, Sillence et al. (1984) described microscopic calcification of the aorta and endocardium in two babies with type IIA OI.

One baby with type IIB OI in the present series had cloudy corneae and large irides, suggestive of glaucoma, but histological details were lacking. Elevated intraocular pressure is rare in OI (Smith et al., 1983). Smolinska and Olbromska (1977) described a patient with 'Ekman-Lobstein-Van der Hoeve syndrome' who had bilateral simple glaucoma and a right-sided thrombosis of the central retinal vein. A baby with unclassifiable lethal OI in the present series had poorly documented 'cataracts'. This is reminiscent of the three sibs described by Buyse and Bull (1978) who died perinatally and had the radiological appearance of type IIA OI with cataracts and microcephaly. The head circumference of the baby in the present series, however, was on the 75th centile.

No chromosomal abnormalities were found. Chromosomal defects have been reported in 5 patients with OI, 4 of whom died perinatally. The karyotypes of the latter were 46,XY,-5,-D,t(5q+;Dq-)+;cen+ (Richon et al., 1971); 46,XX (92%)/47,XX,+G(8%) (Ninatti and Patriarca, 1968) and 46,XX r(18)(p11,q23) (Marcovic et al., 1979) which could all have been unrelated findings. A baby with radiological type IIA OI and white sclerae who died at 22 days of age described by Knisely et al., (1988) had a 46,XY, inv(7)(p13q22) karyotype, as did his healthy mother. The authors point out that the affected infant may represent a compound heterozygote for an $\alpha 2(I)$ collagen defect. (The case is discussed in section 1.9.6.2.5). The fifth patient with an abnormal karyotype (46,XY, del(12)(p12p13) had less severe OI which he inherited from his father who had a normal karyotype (Orye and Craen, 1975), suggesting that the deletion in the child was unrelated to the OI.

6.7 Perinatal survivors

6.7.1 Age of patients and cause of death

6.7.1.1 Age of patients alive at the time of the study or at death

Results (table 6.15 and figure 6.5)

Type IIB OI

Of the 12 liveborn cases, only 3 survived the perinatal period. They all died subsequently, at 4 and 6 weeks and 26 months, as described in section 6.5. A baby with type IIB OI who survived for 26 months is shown in figure 6.4.

Type III/IV OI

Eighty-eight patients were liveborn. One of these died perinatally, leaving 87 perinatal survivors of whom 15 died subsequently (Table 6.15 in section 6.5). Only two of these (cases 3 and 46) were seen by the author and they died subsequently, during the study period. Case 75 was alive when his parents returned the questionnaire, but he died soon afterwards. The mean age of the 75 cases alive at the time of the study (including the three just mentioned) was 14.78 years, range 0.25 to 54.83 years. The mean age of all 87 perinatal survivors at the time of the study or at death (whichever came first) was 12.94 years, range 0.25 to 54.83 years. Figure 6.5 shows the age distribution.

Type III OI

Sixteen patients were liveborn. One died perinatally, leaving 15 perinatal survivors, 8 of whom died subsequently (table 6.15 in section 6.5). The mean age of the remaining 7 cases alive at the time of the study was 14.06 years, range 0.33 to 32.08 years, and the mean age at the time of the study or at death of the 15

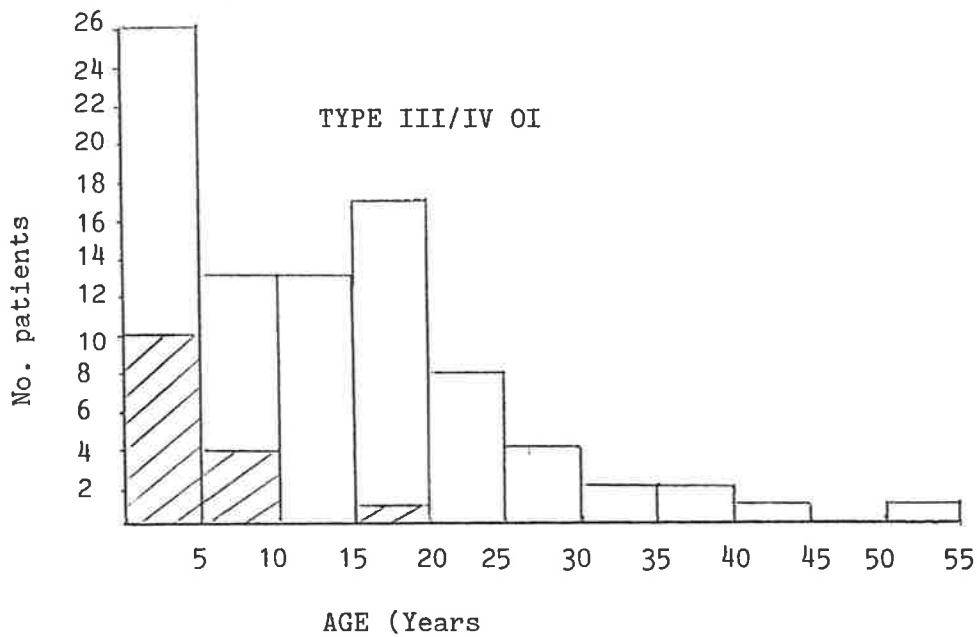
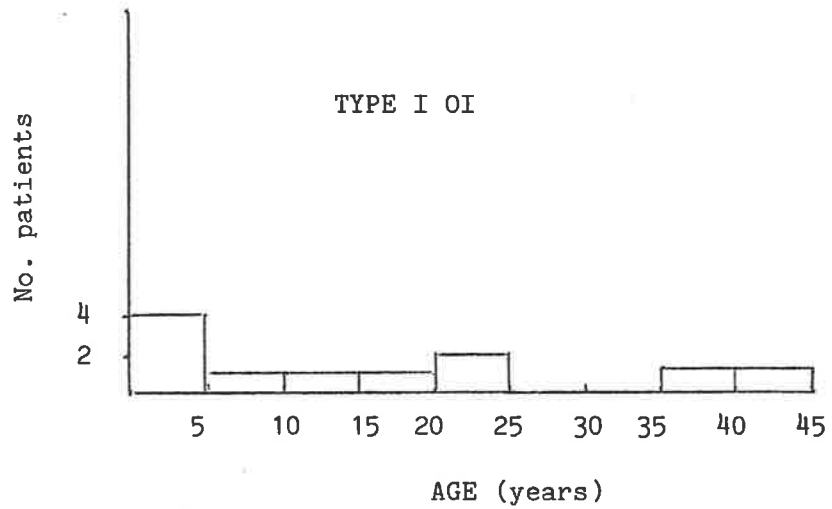
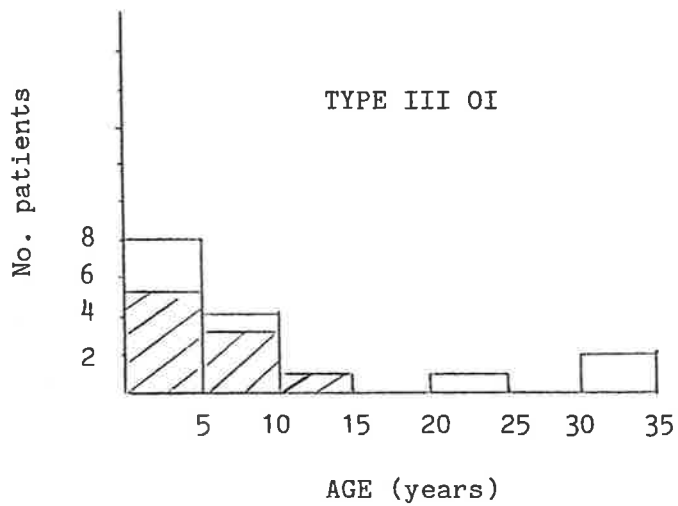


Figure 6.5

Age of perinatal survivors

- Alive
- Died (after perinatal period)

The age of 3 cases of type III/IV OI (cases 3, 46, 75) alive at the time of the study who died soon after, are given as at the age of their death.

perinatal survivors was 9.12 years, range 16 days to 32.08 years.

Type I OI

All 11 cases were liveborn and none died subsequently. Their mean age at the time of the study was 15.46 years, range 0.67 to 40.5 years.

6.7.1.2 Cause of death in liveborn patients with types IIB, III/IV and III OI

Results (table 6.17)

Type IIB OI

Two of the 3 babies (cases 162 and 163) died from bronchopneumonia, and one (case 164) from aspiration of gastric contents.

Type III/IV OI

Sixteen liveborn patients died post-natally. One of these (case 89) died perinatally (at 24 hours) of respiratory insufficiency. Eight patients (see appendix 6.1 for case identification) died from a lower respiratory tract infection. In one of these (case 3) who died at 3.8 years, the post-mortem report showed evidence of right heart failure probably secondary to respiratory insufficiency, with right atrial and right ventricular dilatation

Table 6.17

CAUSE OF DEATH IN PERINATAL SURVIVORS

Type of OI	Cause of death			
	Chest infection	Cerebral haemorrhage after a fall	Post-operative fat embolism	Unknown
IIB (n = 3)	3	-	-	-
III/IV sporadic (n = 15)	8	1	-	6
III recessive (n = 8)	4	1	1	2

and hypertrophy. One other child (case 46) died at age 9 years from a cerebral haemorrhage associated with a skull fracture following a fall from her wheelchair. In 6 cases, the cause of death was not known to the author.

Type III OI

Nine of 16 liveborn patients died. One, a male (case 106), died at 10 hours of respiratory insufficiency. Four others (cases 91, 93, 94, 98) died from chest infections; two of them were sisters. One boy (case 105) died at age 9.2 years from an extradural haemorrhage associated with a skull fracture sustained during a fall from his wheelchair and another boy (case 101), died at age 1.8 years from a fat embolism which occurred in the post-operative period of an intramedullary rodding operation. In cases 92 and 96, the cause of death is unknown.

Discussion

In severe deforming OI (types III/IV and III), the thoracic volume becomes severely compromised by skeletal deformity of the spine and chest (see section 6.7.2.2). Respiratory failure, chest infections and cardiac failure may follow and are the commonest cause of death in severe OI (Sillence et al., 1979a,b). Fat embolism following intramedullary rodding receives no mention as a complication in Smith et al.'s (1983) review of post-rodding complications. Reports of intracranial haemorrhage after skull fracture in the older child are scarce. Glover (1922) described

a boy with sporadic mild OI and normal sclerae who died at 7 1/2 years after a probable skull fracture. In the present series, 4 patients with severe deforming OI were known to have had a skull fracture and this lead to death in 2 cases. Falls from wheelchairs are obviously a potential danger for individuals with OI and the possibility of a skull fracture or intracranial bleeding should be considered.

6.7.2 The skeleton

6.7.2.1 Fractures

6.7.2.1.1 Fractures at birth

Results (table 6.18)

Type IIB OI

The 3 patients who survived the perinatal period all had at least 24 fractures at birth.

Type III/IV OI

Parents were able to give an estimate of the number of fractures at birth in 35 cases. A further 44 reported that 'multiple' fractures were present at birth. In 31 cases, radiographs taken at birth were available for review. In 25 cases, this included a 'babygram', so that, at least, the limbs and ribs were visible.

Table 6.18

REPORTED NUMBER OF FRACTURES AT BIRTH (No. cases (%))

No. fractures	1-5	6-10	11-20	>30	'Multiple'	Unknown	Total
Type of OI							
IIB	-	-	-	-	3	-	3
III/IV sporadic	19 (54.3%)	5 (14.3%)	8 (22.9%)	3 (8.6%)	44	8	87
III recessive	2	-	-	-	9	4	15
I new mutation	8 (88.9%)	-	1 (11.1%)	-	-	2	11

In 6 cases, only parts of the skeleton could be seen, but this included at least a view of the femora. For 2 additional cases, a doctor's report of the number of fractures counted was available.

In practice, the author with Dr Hall (consultant radiologist) found it very difficult to count fractures, as there were often multiple small metaphyseal fractures of long bones and it was often impossible to determine whether deformity represented an old fracture. Nevertheless, counting discrete fractures in ribs and long bones, the parents' reports were generally confirmed and an average of about 8 fractures, ranging from about 1 to 30, were counted (N = 27, including the 2 doctor's reports. The 6 cases with only part of a skeletal survey available were not included. The numbers of fractures counted for each case are given in appendix 6.1). The 2 babies with perinatally lethal disease (cases 88 and 89) had at least 14 and 5 fractures, respectively.

Type III OI

In 9 cases, multiple fractures at birth were reported by the parents, confirmed by the author on the radiograph in 3 cases; parents of 2 cases reported 2 fractures at birth and in 4 cases fractures were reportedly present at birth, but their number was unknown.

Type I OI

By contrast, few fractures at birth were present in this group with milder OI. In 9 cases, the parents reported that at birth the number of fractures present was one (2 cases), 2 (4 cases), 3 (1 case), 4 (1 case) and 14 (1 case). In 2 cases, the number of fractures at birth was unknown. Neonatal radiographs of 2 of these patients were available confirming the presence of 2 and 4 fractures respectively and showing good length and modelling of long bones and only mild bowing of the femora and tibiae in one (figure 4.1).

Discussion

Since patients were ascertained by the presence of fractures at birth, it is clearly not possible to comment upon the incidence of fractures at birth. Beighton et al. (1983) noted that all of 21 cases with type III OI had fractures at birth, whereas only 14 of 21 in Sillence et al.'s (1979b) series of progressively deforming OI were born with fractures, the mean number being 8 (as in the present type III/IV group) with a maximum of 80 fractures. Some of their cases had 'short and broad' femora and so could possibly represent type IIB OI. Nevertheless, multiple fractures at birth are common in severe OI. More fractures may be present in type IIB than type III/IV OI, even if the latter die at birth.

Documentation of the numbers of fractures at birth in type I OI

is difficult to find, but several authors noted that patients with mild OI were less likely to be born with fractures (Falvo et al., 1974; Bauze et al., 1975) and in Sillence et al.'s (1979b) series, only 5 of 65 (7.7%) in the type I group had fractures at birth. The present study shows that patients with type I OI who do have fractures at birth have few.

6.7.2.1.2 Fractures occurring after birth

Results (table 6.19)

Type IIB OI

Case 162, who lived to 26 months, suffered only one fracture after birth; but cases 163 and 164 who lived to 4 and 6 weeks had none and 'several', respectively.

Type III/IV OI

Information on the number of fractures after birth was available for 80 cases. In 10 cases, fracture number could only be expressed as 'multiple'; the numbers of fractures suffered by the other 70 patients are shown in table 6.19. The maximum number of fractures counted was 400, in case 14, a 23 year old female. Patients were not specifically asked about the numbers of fractures occurring at various ages, but many said that the frequency of fractures seemed to decrease in the second half of the first decade. Some noted that bouts of fractures might be

Table 6.19

FRACTURES OCCURRING AFTER BIRTH IN PERINATAL SURVIVORS (No. cases (%))

No. fractures	0	1-20	21-60	61-99	100-199	≥200	'Multiple'	Unknown	Total
Type of OI									
IIB	1	1	-	-	-	-	-	1	3
III/IV sporadic	7 (10%)	21 (30%)	14 (20%)	4 (5.7%)	18 (25.7%)	6 (8.6%)	10	7	87
III recessive	1 (11.1%)	2 (22.2%)	2 (22.2%)	1 (11.1%)	3 (33.3%)	-	2	4	15
I new mutation	-	6 (60%)	4 (40%)	-	-	-	1	-	11

(% are for those with a known number of fractures)

Note: Cases 12, 60, 66 said they had 'hundreds' of fractures and were scored as 100-199.
 Cases saying 'over one hundred' were scored as 100-199.
 Cases were grouped in the nearest bracket, e.g. 'over 50' scored as 60-99.

interspersed by fracture-free periods lasting for several months or even a year or more. All of the patients who had none or one fracture were under 8 months of age. Overall, the total fracture number increased with advancing age, as might be expected. There was however, wide variation. For example , a male aged 39 years (case 27) reported only 4 fractures, whereas a girl as young as 1.25 years (case 74) had 25 fractures, and one boy (case 66) had over 100 fractures before he died at 6.8 years.

The long bones of the limbs were the main sites of fractures in all cases. Other bones occasionally involved included the ribs, nose, mandible and foot. Two patients had suffered a skull fracture, in one of whom it proved to be fatal.

In general, fractures occurred with minimal trauma, for example on kicking the legs the femur would fracture, or sneezing or coughing might result in a rib fracture. Often fractures in young children appeared to be spontaneous. Most patients noted that a greater degree of trauma was required to produce a fracture with increasing age. An unusual phenomenon often described was an apparent mismatch in the degree of trauma compared to the tendency to fracture. For example, a fracture might occur if the patient suddenly turned around, but not if he fell out of his wheelchair, suggesting that the direction as well as the force of the injury is important in causing a fracture.

Type III OI

Information on the number of fractures occurring postnatally was available for 11 patients, as shown in table 6.19. Two of these patients reported 'multiple' fractures. Again, few fractures tended to occur in the first or second year, with a dramatic increase thereafter. There was marked variation, however. One patient (case 100) aged 10 years reported 80 fractures, but had none in the first year, and another (case 103) aged 20 years had 50 fractures, 37 of which had occurred before 2 years.

The main sites of fractures were again the long bones; 2 patients had had a skull fracture which was fatal in one.

Trauma required to produce fractures was again often reported as minimal but increasing with age and apparently spontaneous fractures occurred in early years.

Type I OI

Six patients out of 10 (60%) had experienced no more than 10 fractures; their ages ranged from 0.67 to 36.25 years, with a median of about 4 years (table 6.19). Four had from 45 to 60 fractures; again there was a wide age range from 5.5 years to 40.5 years, median of about 19 years. One patient aged 20.75 years had not counted her number of fractures but had 'many'. The maximum number of fractures reported was 60.

The 6 patients over the age of 14 years reported a marked decrease in fracture frequency at puberty.

The major site of fractures was the long bones of the legs, the arms being less commonly affected. One patient had suffered multiple rib fractures.

Trauma required to cause a fracture seemed to be greater than in the type III/IV and III groups. Four patients noted that mild trauma could cause a fracture and two thought that their fractures were caused by a moderate degree of injury, such as might occur in a fall. Only three gave a history of having an apparently spontaneous break.

Discussion

The data presented on fracture numbers is somewhat anecdotal; only a few patients or their families had kept a 'fracture diary'. Many patients pointed out that although a minor fracture was sometimes suspected, they would not seek medical attention since if there were no obvious malalignment, little or no treatment would be required; thus fracture number may be underestimated.

Fracture frequency depends not only on bone fragility, but also on the age and activity of the patient, exposure to accidents and the degree of parental supervision (Castells, 1973). Nevertheless, some conclusions can be drawn. First, none or few

fractures may occur during the first years of life in severe OI. This might engender a false sense of security in parents and physicians, who are then disappointed when fractures begin to occur. Secondly, although the total number of fractures is generally greater in severe than mild OI and in older than younger patients, this relationship does not always apply in individual cases, as described above. Similar observations were reported by Bauze et al. (1975) and Smars (1961). The maximum number of fractures in the type I group was 60, whereas over one-quarter of patients in the types III/IV and III groups had over 100, and almost 10% with type III/IV OI had more than 200 fractures.

The decrease in fracture frequency in severe deforming OI beginning between 5 and 10 years was also noted by Sillence et al. (1979a&b) and a similar decline in fracture frequency in the mild group at puberty is well known (McKusick, 1972) but most patients continue to have fractures in adult life (Bauze et al., 1975).

Patients with type I OI noticed that fractures mainly affected the legs whereas the more severely affected patients said that all limbs could be affected. Presumably, the major stresses of the more mildly affected ambulant patient are predominantly directed to the legs, whereas fractures of the upper limbs are relatively more frequent if the patient does not walk (Smith et al., 1983), since he or she might use the arms for propelling a wheelchair. Fractures in bones other than the long bones

occurred uncommonly, as has been observed previously by other authors (quoted in Smith et al., 1983).

The very minor degree of trauma which can precipitate a fracture in severe OI is well described (Smith et al., 1983). However, the minimum force which caused a fracture tended to increase with age and was greater in patients with type I OI.

The suggestion that fractures in OI are not necessarily painful (Key, 1926; McKusick, 1972) was generally met with indignation by patients and their families with all types of OI. Their experience was that most fractures produced severe pain with the possible exception of recurrent fractures at the same site.

6.7.2.2 Skeletal deformity evident on clinical examination

Results (table 6.20)

Type IIB OI

The 3 patients were not seen personally by the author because they had died, but their parents reported that the shortening and deformity of limbs noted at birth persisted. Case 163 who died at 4 weeks had short but straight arms. Figure 6.4 shows case 162 at birth. (Her radiograph at the same age is seen in figure 4.3).

Table 6.20

SKELETAL DEFORMITY NOTED ON CLINICAL EXAMINATION IN PERINATAL SURVIVORS*

Type of OI	Deformity of arms	Deformity of legs	Pectus carinatum	Spinal deformity (scoliosis &/or kyphosis)
IIB	2/3 (66.7%)	3/3 (100%)	?	?
III/IV sporadic	76/84 (90.5%)	72/83 (86.8%)	61/66 (92.4%)	43/63 (68.3%)
III recessive	11/12 (91.7%)	14/14 (100%)	7/7 (100%)	8/9 (88.9%)
All III & III/IV**	87/96 (90.6%)	86/97 (88.7%)	68/73 (93.2%)	51/72 (70.8%)
I new mutation	2/11 (18.2%)	4/10 (40%)	6/10 (60%)	4/10 (40%)

* No. cases with deformity (%)

No. cases with known result

Deformity of limbs refers to limbs that were not straight. Several patients had straight but shortened limbs, which were not classified as deformed.

? information unknown. Information regarding the spine from cases 74-85 replying by questionnaire not included.

** All III & III/IV is total of III recessive and III/IV sporadic.

Type III/IV OI

Severe progressive skeletal deformity characterised this form of OI, producing a recognisable clinical phenotype, described as follows:

Skull: In infancy, the anterior fontanelle was often large and closed later than normally. The head frequently appeared relatively large compared to the body. Bi-temporal and bi-parietal prominence were common (figure 6.6).

Face: Most patients had a triangular-shaped face, a tall wide forehead, flat maxillae, a prominent jaw and a large beaked nose with a prominent nasal bridge. In infancy, the nasal bridge tended to be flat and was so marked in one baby as to be associated with difficulty in breathing through the nose. The palpebral fissures tended to slant downwards. Shallow orbits associated with ocular proptosis were common, often giving rise to a 'setting-sun' appearance of the eyes (figure 6.7 and 6.8). The ears often appeared low set but this was because of the slope of the head below the prominent parietal bones (figure 6.6). Facial and skull asymmetry were occasionally seen. Family photographs revealed that the typical facial appearance was often recognisable at birth and in infancy but was of a lesser degree than in later years.



Figure 6.6

Case 14 (type III/IV OI), aged 23 years.

Note bi-temporal and bi-parietal prominence, broad forehead, flat maxillae, prominent jaw, large beaked nose, prominent nasal bridge, shallow orbits, down-slanting palpebral fissures, appearance of low set ears and right convergent strabismus.



Figure 6.7

Case 18 (type III/IV OI),
aged 2.3 years.

Note the shallow orbits,
ocular proptosis and
'setting-sun' appearance of
eyes. See also the pectus
carinatum and bowing of the
tibiae.



Figure 6.8

Case 72 (type III/IV OI), aged 9
months.

Note 'setting-sun' appearance of
eyes and deformity of right upper
arm.

Limbs: At birth, the thighs and lower legs were often bowed due to the underlying bony angulation and the legs tended to be held flexed and abducted at the hips. With age, these deformities increased, although occasionally a parent described an apparent decrease in leg deformity in the first few months but this was usually only temporary. In later childhood and beyond, the legs, particularly the thighs, were often very short and deformed with anterior bowing of the lower legs. The arms were frequently short with bowing and twisting deformities so that they resembled the gnarled trunk of a grapevine (figure 6.9). Often the position of the elbow was difficult to locate clinically, due to fixation of the joint and angulation of adjacent bones following fractures. Table 6.20 shows the numbers of patients with limb deformities.

Chest: Chest deformity was the rule (figures 6.7 and 6.9). Pectus carinatum was documented clinically in 61 out of 66 cases (92%). The youngest patient with pectus carinatum was 6 1/2 months and it was noted in 3 others in their first year. The deformity increased with age and was often severe in late childhood and teenage years. One patient had pectus excavatum, 2 had a broad chest and in only 2 cases was the chest of a normal shape clinically, and they were babies aged 5 and 7 months.

Spine: Scoliosis with or without kyphosis was evident on clinical examination in 43 of 63 patients (68%), the youngest was aged 2 years. The next oldest cases with clinically evident spinal deformity were 7.8 and 10 years. One mother had noticed

Figure 6.9

Case 64 (type III/IV OI), aged 3.3 years.

Note deformities of all limbs; in the arms these produce a bowed, twisted appearance. There is a severe pectus carinatum, a relatively large head with apparently low set ears and dark sclerae.



Figure 6.10(a)

Case 8 (type III/IV OI), aged 1 year.

Note limb deformities, small chest, dark sclerae.

the onset at 3 months. The deformity increased with age and was often severe in teenage and later years. A marked lumbar lordosis was common in later childhood.

Figure 6.10(a-e) shows a young lady with type III/IV OI from the age of 1 year to 19.3 years, to show the progression of deformity and ultimate short stature. She is one of the few patients able to walk unaided.

Type III OI

The clinical phenotype of these patients did not differ appreciably from the type III/IV sporadic cases (figures 6.11 and 6.12).

Only 5 were examined by the author and this included only one sib pair. Supplementing this with information from the parents, hospital records and referring physicians, the following was found:

Skull and face: The shape of the skull and facial characteristics were similar to those of patients with type III/IV OI.

Limbs: The limb deformities showed a similar pattern and frequency as was described for the type III/IV sporadic cases. In the sib pair examined by the author, the elder, a male aged 32 years (case 102), had severe shortening and deformity of all 4

Figure 6.10(b)

Case 8, aged 3.8 years.

Note worsening of deformities, especially in left arm.

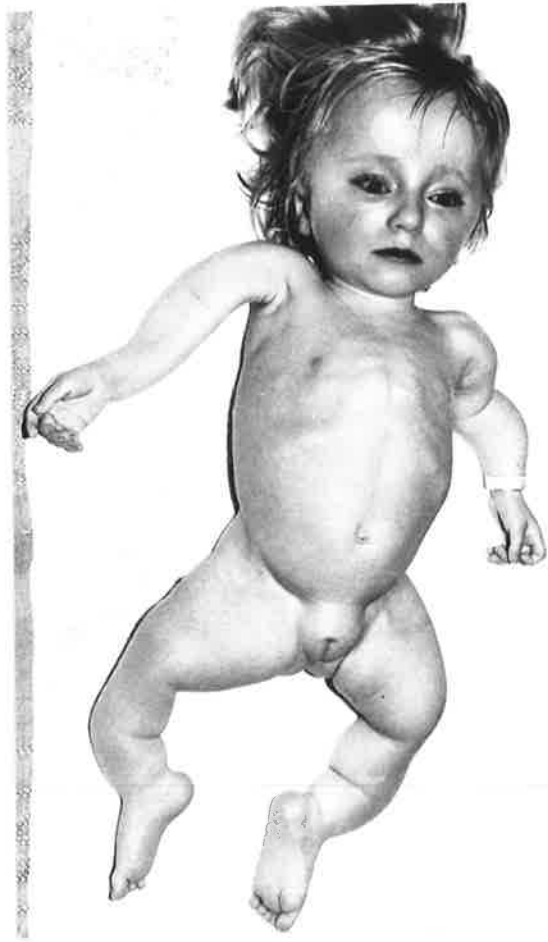


Figure 6.10(c)

Case 8, aged 5.25 years.

Note surgical scars in right leg.

Figure 6.10(d)

Case 8, aged 5.7 years.

Note severe pectus carinatum.



Figure 6.10(e)

Case 8, aged 19.3 years. Note severe short stature, but that she is able to stand (and walk) unaided.

Figure 6.11

Case 99 (type III presumed recessive OI), aged 30 years.

His appearance does not differ from sporadic cases (see figure 6.12).



Figure 6.12

Case 12 (sporadic type III/IV OI), aged 14.7 years.

limbs, whilst his sister, aged 20.7 years (case 103) had arms of relatively normal length with very mild bowing and short legs which had been deformed prior to surgery. The brother's fractures had occurred in the arms and legs whereas the sister's had occurred mainly in the legs. Both had surgical pins in leg bones but had never had any in the arms.

Chest: All of 7 patients had pectus carinatum. the youngest was 3 years old. Case 104 had both pectus carinatum (upper chest) and excavatum (lower chest).

Spine: Scoliosis with or without kyphosis was present in 8 out of 9 cases, the youngest being 3 years. One child (case 94) aged 3.3 years had a straight back; her affected sister (case 93) who died at 8.5 years had a mild scoliosis only. Lumbar lordosis was documented in 1 case (case 103). Both the chest and spinal deformities were generally severe in late childhood and teenage years.

Type I OI

Ten of the patients were seen by the author; the family of another child returned a questionnaire. Skeletal deformity was much milder in this group (figure 6.13).

Skull and face: Three cases (112, 115, 118) had a similar facial appearance to the type III/IV cases. Three had normal facies (cases 109, 113 and 114). The remaining cases had one or



Figure 6.13

Case 109 (type I OI), aged 4.2 years.

Note mild (compared with type III/IV cases) bowing of femora, no chest deformity and normal facial appearance. Her height is below average (-2.6 SD) but is much greater than in the type III/IV patients.

two mild abnormalities such as a broad forehead, prominent nose, mildly triangular shaped face or downslanting palpebral fissures, without having the immediate 'gestalt' of the 'OI facies' noted in the severe cases.

Limbs: Six patients had no limb deformity (ages 8 months to 36.25 years, median 10 years). The others had mild bowing of either the tibiae alone (case 113), the tibiae and a forearm (case 115), the femora (cases 109 and 119), or the forearms (case 112). Their ages ranged from 4.17 to 40.5 years, median 14 years.

Chest: Of 10 cases examined by the author, 3 had a normal chest shape (ages 8 months, 4.2 years and 2.3 years), one aged 40.5 years had a broad chest, 2 aged 5.5 and 36.25 years had mild pectus carinatum and 4 had a moderate degree of pectus carinatum (ages 4.7, 14, 16.2 and 20.75 years). None had the severe chest deformity noted in type III/IV OI.

Spine: Six patients had straight spines clinically, apart from a mild lumbar lordosis in one (ages 8 months to 20.75 years, median 5 years). A mild scoliosis was noted in 2 patients aged 14 and 23 years, and a moderate scoliosis was present in 2 women aged 36.25 and 40.5 years. Thus spinal curvature of some degree tended to develop with age but was not as severe as in the type III/IV group.

Discussion

The abnormalities of skull shape (which are discussed further in section 7.7) and of the facies as described above are so characteristic that 'victims ... tend to resemble each other closely, even though they are quite unrelated' (McKusick, 1972). This is more generally true in severe than mild OI, in which the skull may be normal in shape as noted herein and previously (Smith et al., 1983), and the face may show few or no abnormalities. The 'setting-sun' appearance of the eyes may lead the physician to suspect hydrocephalus, but this had been diagnosed in only one case (with type III/IV OI) in this series, and has been reported rarely by other authors in both severe OI (McKusick, 1972) and in patients with milder bone disease (Pozo et al., 1984). Delayed closure of the anterior fontanelle has also been noted before and in Bronson's detailed description of OI in 1917, the affected grandfather of a family with probable type I OI had a 'soft spot ... as long as he lived'.

Much has been written on the skeletal deformities which characterise OI (McKusick, 1972; Smith et al., 1983). Deformities of the chest, spine and limbs occur in all types, but are more common, show earlier onset and relentless progression in the severe (types III and III/IV) forms. Limb deformities were very common and were usually severe in types III and III/IV OI, affecting the arms in over 91% of patients and the legs in 89% overall, whereas 18% and 40% of patients with type I OI had arm and leg deformities respectively and these were mild. Similarly

Beighton et al. (1983) found limb bowing in 90% of 21 patients with type III OI, whilst Sillence and his colleagues (1979b) noted upper and lower limb deformities in 85.7% and 81.0% of 21 patients with type III OI and in only 10.8% and 18.5% of those with type I, respectively. Some patients in the present series had undergone orthopaedic operations which in some cases included insertion of an intramedullary rod or pin. In some patients these had been removed subsequently; or in others the rod or pin was still present at the time of the assessment. The author had intended to correlate deformity with the presence or absence of such treatment but found that her method of recording the information did not allow such a comparison. Thus, the presence of limb deformity relates to the state of the limb at the time of examination or on information from other sources, as described at the beginning of the section. Nevertheless, the author believes that the data serve to indicate the general trends in limb deformity.

The commonest deformity of the chest in the present series was pectus carinatum. Benson et al. (1978), on the other hand, found that in an unselected series of 129 patients with OI, 27 had pectus carinatum, 21 had pectus excavatum, 28 had an increased anteroposterior diameter of the chest, 1 had chest asymmetry and 52 had no chest deformity. In the present series, pectus carinatum was noticeable as early as 6 1/2 months in severe OI (types III and III/IV) but not until the fifth year in the type I group.

Spinal deformity was recognisable clinically as early as 3 months in the type III and III/IV groups and affected 89% and 68% of them, respectively (71% overall) (see also section 7.6.1). This is similar to the findings of Beighton et al. (1983) who noted kyphoscoliosis in 62% of 21 patients with type III OI, and in Sillence et al.'s (1979b) report, kyphosis and scoliosis occurred in about 43% and 67% (respectively) of 21 patients with type III OI. Spinal curvature affected fewer (40%) of patients with type I OI in the present study; other authors report frequencies of 9% of 79 cases (Beighton et al., 1983) and 20% of 65 cases (Sillence et al., 1979b).

It is interesting to consider the aetiology of skeletal deformities. Clearly, they are often the aftermath of fractures; for patients with type I OI, leg fractures predominated and the legs were noted to be more likely to be deformed than the arms, whilst in the severely affected groups, fractures and deformity afflicted all limbs. Many patients with severe disease, however, commented that limb deformity could develop without apparent fractures and this may be due not only to osteoporosis and increased 'plasticity' of bone (Smars, 1961) but also to unrecognised microtrabecular fractures (Smith et al., 1983). Ten patients with type III/IV OI (cases 22, 25, 26, 37, 40, 56, 60, 62, 63, 73) were noted to have arms of relatively normal length and shape, compared to their short, disfigured legs. This did not always correlate with the major site of fractures; only 4 of them reported mainly leg fractures, 4 thought that the arms and legs fractured equally often and in 2 the information was

unavailable. The author wondered whether 'the long arm' phenotype was a distinct entity but concluded that this was unlikely to be the case given the disparity between the sib pair described above (cases 102 and 103).

Deformities of the chest and spine go together; scoliosis was found in 52 of 72 of all patients (72.2%) with a thoracic deformity in the present series. Smith et al. (1983) quote a similar figure of 75% and note that chest deformity is inevitable in cases with a scoliosis greater than 40%. Spinal deformity also results from vertebral compression secondary to osteoporosis, but immobility, hypotonia and ligamentous laxity undoubtedly play an aetiological role (Debre et al., 1951).

6.7.2.3 Height and head circumference

Results (tables 6.21 and 6.22)

For each patient whose height was known, the standard deviation (SD) score (the number of SD below the mean) was calculated using a computer programme developed by the Department of Growth and Development, Institute of Child Health, London. The programme only calculates SD's for patients aged 2 to 18 years. All patients under 2 years whose length was known fell below the 3rd centile, except for one male (case 66) aged 7 months with type III/IV OI whose length was between the 3rd and 10th centiles. The SD for all patients over 18 years was calculated using the

Table 6.21

HEIGHT OF PERINATAL SURVIVORS

Type of OI	Mean of height S.D's \pm 1 SD	Range of S.D's
III/IV sporadic	-9.34 \pm 2.93 (n = 72)	-16.70 to -3.0
III recessive	-8.70 \pm 3.08 (n = 7)	-13.11 to -5.64
I new mutation	-4.06 \pm 1.18 (n = 10)	-6.2 to -2.55

270

Table 6.22

OCCIPITO-FRONTAL HEAD CIRCUMFERENCE OF PERINATAL SURVIVORS (No. cases (%))

Centiles	<3rd	3rd-<50th	50th	>50th-97th	>97th	Unknown	Total
Type of OI							
III/IV sporadic	7 (10.8%)	23 (35.4%)	6 (9.2%)	19 (29.2%)	10 (15.4%)	22	87
III recessive	1 (20%)	3 (60%)	-	1 (20%)	-	10	15
I new mutation	-	3 (33.3%)	1 (11.1%)	3 (33.3%)	2 (22.2%)	2	11

mean for 18 year olds. All patients (except case 66) had heights below the normal range, that is, below -2 SD. The mean of the height SD's was calculated (table 6.21) and was extremely low for the types III/IV and III cases. In the type III/IV group, the smallest SD was found for a 19.7 year old female (case 30), who was only 62 cm tall (-16.7 SD). The largest SD was for a 10.5 year old male (case 17), who was 120 cm tall (-3.0 SD). The severe short stature of another individual (case 8) can be appreciated in figure 6.10e.

Patients with type I OI were also abnormally short but to a much lesser degree (figure 6.13). The smallest SD in this group was for a 16.2 year old female (case 118) who was 125 cm tall (-6.2 SD); the greatest SD was for a 14 year old male (case 112) who was 139.5 cm tall (-2.55 SD). It must be emphasised that these measurements are to some extent an estimate of the patient's height or length, due to difficulties encountered during measuring because of deformity.

The author personally measured 34 of the type III/IV cases, only 1 of the type III cases and 3 of the type I cases. The information for the remaining cases was obtained from hospital records, doctors or the family. Despite these limitations, the author believes that the results give a reasonably reliable indication of the trends in height.

The occipitofrontal head circumference (OFC) was usually within the normal range (3rd to 97th centile), as shown in table 6.22.

About 15% of type III/IV patients and 22% of type I cases had OFC's over the 97th centile. A comparison between OFC and height could be made in 60 type III/IV cases, 5 type III and 9 type I cases, and even though some patients had an OFC below the 3rd centile, all patients had relatively large head circumferences compared to their height and in many the disproportion was very marked.

Discussion

Short stature and macrocephaly (both relative and absolute) are well known accompaniments of OI (Smith et al., 1983). Beighton et al. (1983) noted dwarfism in 76% of 21 patients with type III OI, and in Sillence et al.'s (1979b) series, 20 of 21 patients (95.2%) were below the 3rd centile for height. In the same report, about half of 65 patients with type I OI were below the 3rd centile for height, but half were within the normal range. The same authors noted very similar trends in OFC measurements to those found herein; most patients had OFC's in the normal range, 14.3% of type III cases and 18.8% of type I's had OFC's over the 98th centile, no patient with type I OI had an OFC below the 3rd centile, whereas one with type III OI did. The authors commented upon the striking disproportion between the head and body size in both type III and type I OI, as found in the present series. One may wonder whether the type I cases in the present study were more severe than usual, in view of their mode of ascertainment (fractures at birth, unaffected parents); by contrast, of the 127 type I cases in the Sillence (1979b) study, only 5 had fractures

at birth, and of the 67 cases examined, 56 had a family history of OI. Since the proportion of cases with very large OFC's in Sillence's and the present study are similar, it seems likely that the cases in the present study were not more severe at least in terms of macrocephaly.

6.7.3 Handicap

Results (table 6.23)

Handicap was assessed according to ability to sit unsupported and to walk. For sitting, only cases over 1 year were recorded and for walking, only cases over 5 years were recorded, as arbitrary cut-off points. (The age of 5 years was chosen rather than, say, 2 years because some patients had learned to walk after 2 years). Table 6.23 shows that handicap was severe.

Type IIB OI

The girl (case 162) who died aged 26 months could not sit alone and had no head control. The two babies who died at 4 and 6 weeks could not be assessed for disability.

Type III/IV OI

Fifty-six children over one year could sit alone, as could 1 of the 14 who were aged less than 1 year, making a total of 57 (80.3%) who could sit alone. Conversely, as many as 14 (19.7%)

Table 6.23

HANDICAP IN PERINATAL SURVIVORS (No. cases (%))

Type of OI	Ability to sit unsupported			Ability to walk				
	Yes (age >1 yr)	No (age >1 yr)	Not applicable (age < 1 yr) or unknown	Walks unaided (age ≥5 yr)	Walks with aids (age ≥5 yr)	Walked in the past (age ≥5 yr)	Never walked (age ≥5 yr)	Not applic- able (age <5 yr)
IIB (n = 3)	-	1	2	-	-	-	-	3
III/IV sporadic (n = 87)	57* (80.3%)	14 (19.7%)	16	5 (7.9%)	7** (11.1%)	9 (14.3%)	42 (66.7%)	24
III recessive (n = 15)	7 (70%)	3 (30%)	5	-	1	- (12.5%)	7 (87.5%)	7
III & III/IV*** (n = 102)	64 (79.0%)	17 (21.0%)	21	5 (7.0%)	7 (10.0%)	10 (14.1%)	49 (69.0%)	31
I new mutation (n = 11)	10 (100%)	-	1	9*(90%)	1 (10%)	-	-	1

Numbers in brackets are percentages of applicable and known cases.

* One patient aged less than 1 year at examination could sit alone (case 9).

** Two patients aged less than 5 years at examination could walk with aids (case 26 - type III/IV & case 109 - type I).

*** III & III/IV is total of III recessive & III/IV sporadic.

did not have this ability. Their ages ranged from 1.3 to 21.5 years, median 8 years.

Only 5 patients (7.9%) could walk unaided (cases 8, 35, 37, 73 and 76; see figure 6.10e). Three of these (cases 8, 37 and 76) walked well unaided, one woman (case 35) aged 20 years had begun walking at 4 years, then stopped (after a leg-pinning operation at 4 years) until 18 years when she again became able to walk around the house. The other (case 73), a girl aged 8.3 years, could walk unaided only with difficulty. Seven patients (11.1%) could walk with aids, such as calipers or a rollator (a metal frame on wheels). Nine patients (14.3%) had been able to walk at some time previously but could not longer do so. Two of these had used aids to walk, and one (case 62) had been able to walk from the ages of 7 to 12 years and subsequently lost the ability after a leg-pinning operation!

Most patients who could walk had first done so between 2 and 6 years. Only one first walked within the normal time, at 15 months of age.

Type III OI

Seven patients (70%) over 1 year could sit unaided; 2 of these were sibs who could first do so at 7 months of age. Three patients over 1 year (aged 1.33, 1.83 and 8.5 years) could not sit unsupported. No patient could walk unaided and only one was able to walk with aids but rarely does so. Comparing the type

III and type III/IV cases for ability to sit unsupported or to walk (unaided, with aids or previously), the numbers are not statistically significantly different (p 0.2 - 0.5 for both sitting and walking).

Type I OI

All patients could sit alone and one aged 8 months could almost do so. All of 10 patients could walk; nine could walk normally, and one required walking sticks. Five had first walked after 18 months, at 24 months (case 115), 27 months (case 109), 2.5 years (case 118) and 3 years (cases 110 and 111) and 2 at the normal time (15 months, case 114 and 18 months, case 112) and in 3 the age at which walking first occurred was unknown.

Discussion

Although delay in achievement of motor milestones is common in mild OI, in this series all patients with type I OI over 5 years could walk. Similarly, Sillence et al. (1979b) recorded independent walking in 62 of 65 patients with type I OI and only 2 of 79 in Beighton et al.'s (1983) series were chair-bound. Profound motor handicap affected most type III/IV and III patients in the present study: about one-fifth of cases over 1 year could not sit unsupported and about two-thirds over 5 years had never walked. It is extraordinary that patients as old as 21.5 years could not sit unsupported. Sillence et al. (1979b) found that of 17 patients with type III OI over 2 years of age,

15 (88%) had great difficulty walking and required either a wheel-chair (12 cases) or a walking-frame (3 cases). By contrast, only 7 (33%) of Beighton et al.'s (1983) patients with type III OI were chair-bound.

Factors which are likely to contribute to motor disabilities include muscular hypotonia, joint laxity, pain from fractures, fear of fracturing, skeletal deformities and difficulty supporting a relatively large head on a small body. Detailed neurological examinations were not carried out in the present study, so that it is not possible to assess the contribution of neurological deficits to poor mobility. Whilst neurological problems can occur (see section 6.7.12) they are uncommon and are heralded by a deterioration of function. The fact that two patients with severe OI lost the ability to walk after leg-pinning operations needs to be born in mind when planning such procedures.

6.7.4 The eye

6.7.4.1 Scleral colour (tables 6.24 - 6.27)

Introduction

Table 6.24 shows the colour of sclerae reported by parents at birth. This was recorded as normal (which includes white and very pale blue), pale blue or deep blue. The number of cases with deep blue sclerae at birth are divided according to whether

or not scleral colour faded subsequently as judged by a comparison of the colour reported at birth and that noted at the time of the study (or at the patient's death) (table 6.25). Finally, the colour of sclerae at the time of the study (or at death) is shown in table 6.26.

The author examined 65 patients with type III/IV OI, 5 with type III and 10 with type I OI. Sclerae were recorded as normal (that is, white or very pale blue), pale blue, moderate blue or deep blue. The families of another 12 patients with type III/IV OI replied by questionnaire and recorded the sclerae as white (3 cases), pale blue (7 cases) or deep blue (2 cases). Another 10 patients with type III/IV OI had died; parents of 4 of these were able to definitely state scleral colour at the time of death (namely, 2 pale blue and 2 deep blue). Likewise, the parents of the 3 babies with type IIB OI stated that scleral colour was normal (1 case) and deep blue (2 cases). Parents of 7 patients with type III OI gave information about scleral colour (3 cases had normal sclerae, 3 had pale blue and 1 had dark blue sclerae, similar to the author's findings in examining 5 patients with type III OI in which 2 cases had normal sclerae and 3 had pale blue sclerae). Finally, parents of one child with type I OI replied by questionnaire and recorded pale blue sclerae. Information from all of these sources is included in table 6.26. Whilst recognising that the accuracy is reduced by including cases not seen personally, the author noted good agreement between the parents and her assessment of scleral colour during the interviews. In addition, families of 8 patients were sent a

questionnaire prior to the interview; in 7 of these, parental assessment of scleral colour was the same as the author's on examination of the patient.

Results

Scleral colour at birth (table 6.24)

Overall, about three-quarters of cases had deep blue sclerae at birth. Relatively fewer (54.5%) of the type III recessive cases had deep blue sclerae at birth compared to 81.8% of the type III/IV cases and 80% of the type I cases. In the group as a whole, there was no significant sex difference in scleral colour at birth ($p > 0.1$; a 2×2 contingency χ^2 test was used to calculate all sex ratio comparisons in this chapter; see appendix 6.2). In the type III group, the information for all sib pairs was incomplete, but none were known to be discordant and 4 pairs were definitely concordant for scleral colour at birth.

Fading of sclerae after birth (table 6.25)

Marked fading of scleral colour to pale blue or normal (white or very pale blue) occurred in 24/60 (40%) of type III/IV sporadic cases born with deep blue sclerae; in the other 36, the sclerae remained deep blue. Marked fading occurred in 5/6 (83%) of type III cases. The 6 with deep blue sclerae at birth comprised 3 sib pairs, one of which was reportedly discordant for scleral colour fading. They were a girl (case 93) whose sclerae remained deep

Table 6.24

SCLERAL COLOUR AT BIRTH IN PERINATAL SURVIVORS

Type of OI	Normal	Pale blue	Deep blue	Unknown	Total
IIB	1 (1F)	-	2 (1F, 1M)	-	3 (2F, 1M)
III/IV sporadic	2 (2.6%) (2M)	12 (15.6%) (5F, 7M)	63 (81.8%) (36F, 27M)	10 (9F, 1M)	87 (50F, 37M)
III recessive	5 (45.5%) (1F, 4M)	-	6 (54.5%) (3F, 3M)	4 (2F, 2M)	15 (6F, 9M)
III & III/IV*	7 (8.0%) (1F, 6M)	12 (13.6%) (5F, 7M)	69 (78.4%) (39F, 30M)	14 (11F, 3M)	102 (56F, 46M)
I new mutation	-	2 (20%) (2F)	8 (80%) (6F, 2M)	1 (M)	11 (8F, 3M)
Total	8 (7.9%) (2F, 6M)	14 (13.9%) (7F, 7M)	79 (78.2%) (46F, 33M)	15 (11F, 4M)	116 (66F, 50M)

% are for cases with known scleral colour.

F = female, M = male

* III & III/IV is total of III recessive & III/IV sporadic.

Table 6.25

FADING OF SCLERAL COLOUR TO PALE BLUE OR LESS IN PERINATAL SURVIVORS WHO HAD DEEP BLUE SCLERAE AT BIRTH

Type of OI	Faded	Not faded	Unknown	Total (see table 6.24)
IIB	-	2	-	2
III/IV sporadic	24 (40%) (10F, 14M)	36 (60%) (23F, 13M)	3 (3F)	63 (36F, 27M)
III recessive	5 (83.3%) (2F, 3M)	1 (16.7%) (F)	-	6 (3F, 3M)
III & III/IV*	29 (43.9%) (12F, 17M)	37 (56.1%) (24F, 13M)	3 (3F)	69 (39F, 30M)
I new mutation	1 (12.5%) (M)	7 (87.5%) (6F, 1M)	-	8 (6F, 2M)
Total	30 (39.5%) (12F, 18M)	46 (60.5%) (31F, 15M)	3 (3F)	79 (46F, 33M)

Normal is white or very pale blue.

% are for known cases

F = female, M = male

* III & III/IV is total of III recessive & III/IV sporadic.

blue until she died at 8.5 years whilst her affected sister's sclerae faded from deep blue at birth to pale blue by the time of her death at 15 months (case 94). Neither child was seen by the author but the parents had noted the scleral colour difference. In the type I OI group, all of the 8 cases born with deep blue sclerae continued to have significantly blue sclerae. Five of these had deep blue sclerae at the time of the study and 3 had moderately blue sclerae. Significantly more males than females overall showed scleral fading ($p < 0.01 - 0.05$).

Scleral colour at the time of the study or at death (table 6.26)

At the time of the study or at death, about half (40/81) of sporadic type III/IV cases had moderately or deep blue sclerae and half (41/81) had normal or pale blue sclerae. By contrast, 11/12 of the patients with type III OI had normal or pale blue sclerae, and only one reportedly had sclerae of a deep blue hue. The difference between the two groups is significant ($p < 0.001 - 0.01$, using a 2×2 contingency χ^2 test).

Two children with type I OI were said to have pale blue sclerae at birth. In one (case 119), who was not seen by the author, the colour had remained the same and in the other (case 109) it had become darker. In another boy with type I OI (case 116) whose scleral colour was unknown at birth, sclerae at examination looked normal, but his parents noted that they often became deep blue. The other 9 type I OI patients had moderately or dark blue sclerae.

Table 6.26

SCLERAL COLOUR AT EXAMINATION OR DEATH IN PERINATAL SURVIVORS

Type of OI	Normal*	Pale blue	Moderate blue	Deep blue	Unknown	Total
IIB	1 (F)	-	-	2 (1F, 1M)	-	3 (2F, 1M)
III/IV sporadic	12 (14.8%) (4F, 8M)	29 (35.8%) (15F, 14M)	15 (18.5%) (9F, 6M)	25 (30.9%) (18F, 7M)	6 (4F, 2M)	87 (50F, 37M)
III recessive	5 (41.7%) (1F, 4M)	6 (50.0%) (3F, 3M)	-	1 (8.3%) (F)	3 (1F, 2M)	15 (6F, 9M)
III & III/IV*	17 (18.3%) (5F, 12M)	35 (37.6%) (18F, 17M)	15 (16.1%) (9F, 6M)	26 (28.0%) (19F, 7M)	9 (5F, 4M)	102 (56F, 46M)
I new mutation	1 (9.1%) (M)	1 (9.1%) (1F)	4 (36.4%) (3F, 1M)	5 (45.5%) (4F, 1M)	-	11 (8F, 3M)
Total	19 (17.8%) (6F, 13M)	36 (33.6%) (19F, 17M)	19 (17.8%) (12F, 7M)	33 (30.8%) (24F, 9M)	9 (5F, 4M)	116 (66F, 50M)

* Normal is white or very pale blue.

% are for known cases.

F = female, M = male.

III & III/IV is total of III recessive & III/IV sporadic.

Of the 3 babies with type IIB OI, one had normal sclerae at birth and two had deep blue sclerae which remained so until their deaths at 26 months and 4 weeks.

Significantly more males than females had normal or pale blue sclerae, as opposed to moderately blue or deep blue sclerae (p 0.01 - 0.05), at the time of the study or at death. Four of 5 sib pairs were concordant for scleral colour at the time of the study or at death. The discordant pair is described above.

Finally, patients and parents in all groups commented on the day to day variability of the affected person's scleral colour. Some noted that the sclerae became more blue in the day or so prior to fracturing.

Discussion

a) Does scleral colour help predict the pattern of inheritance?

Scleral colour was one manifestation which differed between the 'recessive' type III and the sporadic type III/IV groups. Although a deep blue colour at birth was common, subsequent fading was more frequent in the type III group, so that at the time of the study or at death, normal or pale blue sclerae were found in 11/12 of type III cases, but relatively fewer (41/81, 50.6%) of sporadic type III/IV cases.

Sillence et al. (1979b) originally noted that the majority of

type III or IV OI cases had normal sclerae. It could be argued that the present sporadic type III/IV OI group contains many type I new mutation cases with dark blue sclerae, but the severity of their disease suggests that this is not so. Likewise, the discrepancy between Sillence and his colleagues' observations and the present study might be explained by the age of the cases. It might be argued that the preponderance of young patients in this study would mean that their sclerae had not yet had time to fade. However, the ages of cases with the various scleral colours is approximately similar (table 6.27). These results suggest that patients with severe deforming OI may indeed have deep blue or normal sclerae.

It is tempting to suggest that the sporadic type III/IV cases with pale blue or normal sclerae have recessively determined OI but this would be unwise. Normal sclerae are found not only in families with recessive (type III) OI but also in others with dominant (type IV) OI (Sillence et al., 1979b). Scleral colour does not always 'breed true' in families. For example, the parents of an affected sib pair (type III OI) in this study, reported that one child had deep blue sclerae whereas the other's were pale blue. Smars (1961) described a family (no. 97) in which some affected individuals had blue sclerae and in others the sclerae were normal. Consideration of the severity of the disease together with scleral colour does not necessarily predict the genetic basis of the sporadic case; disease severity can vary widely in families with type IV OI; patients with recessive (type III) OI and normal sclerae occasionally have milder disease

Table 6.27

SCLERAL COLOUR RELATED TO AGE AT EXAMINATION OR REPORTED COLOUR AT DEATH, IN TYPE III/IV SPORADIC CASES WHO SURVIVED PERINATALLY (N = 81)

Scleral colour	Mean age (yr) \pm 1 SD
Normal	13.03 \pm 7.25
Pale blue	16.7 \pm 12.18
Moderate blue	14.51 \pm 10.70
Deep blue	10.37 \pm 10.48

(Sillence et al., 1986) and patients with severe disease may have blue sclerae (this study). The exception to this dilemma is that a sporadic case with mild OI and blue sclerae probably represents a new dominant mutation for type I OI. One patient in the present study with mild bone disease had normal sclerae on the day he was examined but his parents had noted blueness at other times. For this reason he was designated as 'type I' OI.

The reason for the preponderance of males with scleral fading and with pale blue or normal sclerae is unknown. In summary, scleral colour may be normal, pale blue or deep blue in severe progressive OI, but within that group, it is probably not a useful indicator of the underlying pattern of inheritance.

b) Aetiology of blue sclerae

Blueness of the sclerae has been generally believed to result from increased translucency of the sclera, allowing the underlying uveal pigment and blood to become clinically visible (Sillence et al., 1979b; Chan et al., 1982). More recently, Lanting et al. (1985) suggested that it is the intensity of backscattered light from the sclerae which determines their colour. Normally, all wavelengths are equally backscattered, resulting in white sclerae. If backscattering is reduced, shorter wavelengths are affected less than longer ones, and the sclerae will look blue. Both 'increased translucency' and 'decreased backscatter' could result from unusually thin sclerae or from an intrinsic abnormality of the fine structure of the

sclerae. Thin sclerae have been demonstrated in perinatally lethal cases (Follis, 1952; Haebara et al., 1969; Blumcke et al., 1972; Chan et al., 1982) and in non-lethal congenital cases (Buchanan, 1903; Casanovas, 1934, both quoted in Smith et al., 1983). An intrinsic abnormality of scleral fine structure was demonstrated in 4 babies with perinatally lethal OI, by Chan et al. (1982). Scleral collagen fibre thickness was reduced by more than 50%, the normal variability in fibre diameter was decreased and the collagen fibres were arranged in a more uniform pattern than in the control sclerae. Although the authors emphasised that these abnormalities could allow better transmission of light through the sclera, Lanting et al. (1985) argued that the same abnormalities could reduce the backscatter. In their 2 patients with type I OI and blue sclerae, the 'optical scattering coefficient' was markedly reduced and it was mildly reduced in a type III OI patient with normal sclerae. The authors recognised that their results still did not clearly define whether the sclerae were thin or intrinsically abnormal.

Any theory which explains blueness of sclerae in OI also has to account for the fact that sclerae can be of normal colour. Francis et al. (1974) examined the structural polymeric collagen from the skin of 19 patients with OI. Collagen from patients with mild disease and blue sclerae was reduced in total amount but showed normal stability, whereas collagen from patients with severe disease and white sclerae was less stable but the total amount was normal. The authors hypothesised that the sclerae of patients with mild disease might also contain less collagen and allow greater transmission of light, resulting in blue sclerae;

sclerae of patients with severe disease might contain a normal amount of collagen and appear white.

In any event, scleral thinning, intrinsic scleral structural defect due to abnormal collagen, or both, probably cause the blue sclerae by altering light transmission through or backscatter from the sclerae. One further suggestion of an electron-dense material between scleral lamellae which actually enhanced light transmission through sclerae (Eichholtz, 1971; Eichholtz and Muller, 1972) could not be confirmed by Chan et al. (1982).

To some extent, the scleral hue also varies with the intensity of the ambient light and the colour of the surroundings in which the sclerae are examined. The day to day variation in scleral colour and deepening of blueness prior to fracturing noted by the patients in this study and previously (Smith et al., 1983) remain unexplained.

6.7.4.2 Visual defects and strabismus

Results (tables 6.28 and 6.29)

Patients or their parents were asked about the affected individual's visual function and table 6.28 shows that about one-third of cases in most groups of OI had abnormal eyesight. The majority who reported a defect had short-sightedness (23% of cases overall). Long-sightedness was present in 4 patients with type III/IV OI (cases 1, 10, 48 and 57). Other defects included amblyopia associated with strabismus (see below) in 3 cases of

Table 6.28

VISUAL FUNCTION IN PERINATAL SURVIVORS

Type of OI	Normal	Short-sighted	Long-sighted	Other*	Unknown	Total
IIB	1 (F)	-	-	-	2 (1F, 1M)	3 (2F, 1M)
III/IV sporadic	39 (62.9%) (22F, 17M)	13 (21.0%) (8F, 5M)	4 (6.5%) (1F, 3M)	6 (9.7%) (4F, 2M)	25 (15F, 10M)	87 (50F, 37M)
III recessive	7 (63.6%) (2F, 5M)	4 (36.4%) (2F, 2M)	-	-	4 (2F, 2M)	15 (6F, 9M)
III & III/IV **	46 (63.0%) (24F, 22M)	17 (23.3%) (10F, 7M)	4 (5.5%) (1F, 3M)	6 (8.2%) (4F, 2M)	29 (17F, 12M)	102 (56F, 46M)
I new mutation	5 (62.5%) (4F, 1M)	2 (25%) (2F)	-	1 (12.5%) (M)	3 (2F, 1M)	11 (8F, 3M)
Total	52 (63.4%) (29F, 23M)	19 (23.2%) (12F, 7M)	4 (4.9%) (1F, 3M)	7 (8.5%) (4F, 3M)	34 (20F, 14M)	116 (66F, 50M)

% are for known cases

F = female, M = male * see text

**III & III/IV is total of III recessive & III/IV sporadic.

type III/IV OI (cases 17, 21 and 40), long-sightedness in one eye and short-sightedness in the other in a case of type III/IV OI (case 23) and unspecified reduced vision in 3 other cases (two type III/IV (cases 15 and 29) and one type I case (case 110). The sex ratios in the groups with abnormal or normal visual function did not differ significantly from 50% ($p > 0.9 - 0.95$). The result given depended in most cases on the patient's or parent's report of objective assessments performed by opticians, ophthalmologists, school doctors or health visitors, and this was true in all cases reporting abnormal vision. In the others, the report was based on patient's or parent's subjective assessment (see Appendix 6.1).

Ten cases of type III/IV OI were able to estimate the age of onset of short-sightedness. This ranged from 2 to 36 years with a mean of 14 years. One child (case 50) had been prescribed spectacles at 2 years. One of the 4 long-sighted patients, a male aged 3 years (case 10), had severe hypermetropia and was prescribed glasses at 18 months.

Of the 5 sib pairs able to give a result, 2 were concordant for normal vision, 1 was concordant for myopia and in 2 sib pairs, one member had normal vision and one had myopia.

Strabismus was present in about 13% of patients overall and in each type of OI (excluding type IIB) (table 6.29). Females and males were equally affected ($p > 0.9 - 0.95$). Strabismus resulted in amblyopia in 3 sporadic type III/IV OI patients, as noted

Table 6.29

STRABISMUS IN PERINATAL SURVIVORS

Type of OI	Present	Absent	Unknown	Total
IIB	-	1 (F)	2 (1F, 1M)	3 (2F, 1M)
III/IV sporadic	7 (13.5%) (4F, 3M)	45 (86.5%) (25F, 20M)	35 (21F, 14M)	87 (50F, 37M)
III recessive	1 (11.1%) (M)	8 (88.9%) (4F, 4M)	6 (2F, 4M)	15 (6F, 9M)
III & III/IV	8 (13.1%) (4F, 4M)	53 (86.9%) (29F, 24M)	41 (23F, 18M)	102 (56F, 46M)
I new mutation	1 (12.5%) (F)	7 (87.5%) (5F, 2M)	3 (2F, 1M)	11 (8F, 3M)
Total	9 (12.9%) (5F, 4M)	61 (87.1%) (35F, 26M)	46 (26F, 20M)	116 (66F, 50M)

% are for known cases

F = female, M = male

* III & III/IV is total of III recessive & III/IV sporadic.

above, and was associated with myopia in one type I case.

In addition to the anomalies just described, one patient, a 36.25 year old female with type I OI (case 117) was noted to have a premature arcus senilis around both irides.

Discussion

Myopia appears to have been infrequently reported in OI (Smith et al., 1983); indeed, it receives no mention in McKusick's comprehensive (1972) review. The relatively high incidence noted in both the milder type I and the severe types III and III/IV cases in the present series is perhaps surprising. On the other hand, hypermetropia appears to be 'significantly frequent' (McKusick, 1972), and in keeping with this, 4 of 62 (6.5%) type III/IV cases reported this defect.

Although strabismus occurred in about 13% of patients overall it receives no mention in either of two extensive reviews of OI (McKusick, 1972; Smith et al., 1983). It is important to exclude strabismus in the young patient in order to avoid amblyopia.

The most commonly reported eye abnormality after blue sclerae in OI is an embryotoxon or gerontoxon, found in some 10-30% of cases (Smith et al., 1983). An embryotoxon is a congenital opacity in the periphery of the cornea, present at birth and is often called arcus juvenilis. It resembles the arcus senilis seen in elderly individuals and so may also be referred to as premature arcus

senilis. Only one patient in the present study was noted to show this abnormality but this is undoubtedly an underestimation of its incidence since the author was not specifically looking for it. Many patients with OI appeared to have prominent eyes but this is more likely to result from deformity of the orbits than from an intrinsic ocular defect (Paterson, 1974).

Many other ocular defects have been reported in OI, including keratoconus or keratoglobus, megalocornea, exophthalmos, ectopia lentis, cataract, cornea plana, chorioretinitis, decreased corneoscleral rigidity, malformations of the irido-corneal angle, subluxed lenses, marked uveal pigmentation and bilateral corneal rupture (Smith et al., 1983; McKusick, 1972). These were not specifically sought in the present series and will not be considered further.

6.7.5 The joints

6.7.5.1 Joint hyperextensibility

The number of cases with joint hyperextensibility is shown in table 6.30. All cases scored for this manifestation were seen by the author except for one with type III/IV OI (case 7) and 6 with type III OI who had died but their parents gave a clear history.

Results (tables 6.30 and 6.31)

Joint laxity of the small joints of the hands and feet was

Table 6.30

JOINT HYPEREXTENSIBILITY IN PERINATAL SURVIVORS (No. cases (%))

Type of OI	Laxity of small joints of hands and feet only	Laxity of small and large joints	Laxity of large joints only	No joint laxity	Unknown	Total
IIB	-	-	-	-	3	3
III/IV sporadic	16 (25%) (8F, 8M)	38 (59.4%) [Ⓘ] (24F, 14M)	3 (4.7%) (3F)	7 (10.9%) (4F, 3M)	11 (6F, 5M)	75* (45F, 30M)
III recessive	-	5 (45.5%)** (2F, 3M)	1 (9.0%) (1F)	5 (45.5%*** (2F, 3M)	4 (1F, 3M)	15 (6F, 9M)
III & III/IV****	16 (21.3%) (8F, 8M)	43 (57.3%) (26F, 17M)	4 (5.3%) (4F)	12 (16.0%) (6F, 6M)	15 (7F, 8M)	90 (51F, 39M)
I new mutation	1 (11.1%) (F)	5 (55.6%) (4F, 1M)	1 (11.1%) (F)	2 (22.2%) (1F, 1M)	2 (1F, 1M)	11 (8F, 3M)

* 12 cases who replied by questionnaire not included; of these, 9 reported joint laxity, 1 reported no laxity and 2 were unsure.

** 2 cases, *** 4 cases & [Ⓘ]1 case not examined; information obtained from parents.

**** III & III/IV is total of III recessive & III/IV sporadic.

F = female, M = male

recorded separately from laxity of the large joints (wrists, elbows, hips, knees and ankles). Reference to appendix 6.1 shows that recording of the data was incomplete. If, for example, a patient had lax small joints but the result for the large joints was unknown, this was scored in table 6.30 as 'lax small joints only'. Laxity of any joints was present in 89.1% of type III/IV cases and 77.8% of type I cases (table 6.30); the difference is not significant ($p = 0.2 - 0.5$). In the type III group, 54.5% overall reported joint laxity but in the 5 patients whom the author examined, 4 in fact had lax joints (see appendix 6.1). The true incidence in this group must lie between 55 and 90% but obviously cannot be judged more accurately. In the type III/IV group, joint laxity affected only the small joints of the hands and feet in one quarter of cases and was often a striking feature. In all types of OI (except IIB), about one half of the cases had laxity of the small and large joints. In general, it was uncommon for large joints to be affected and not the hand joints.

In the one family where it was possible for the author to examine both affected sibs (cases 102 and 103), both had laxity of both the small and large joints. In one other family the parents reported that one of their deceased affected children had joint laxity (case 93) whereas the other (case 94, also deceased) did not.

Table 6.31 shows the numbers of pairs of large joints affected; 27.3% of patients with type III/IV OI had 4 or more pairs of lax

Table 6.31

NUMBER OF PAIRS OF HYPEREXTENSIBLE LARGE JOINTS (No. cases (%))

Pairs of lax large joints	1	2	3	4	5	Unknown
Type of OI						
III/IV sporadic (n = 41)	8 (24.2%)	13 (39.4%)	3 (9.1%)	3 (9.1%)	6 (18.2%)	8
III recessive (n = 6)	3	1	-	-	-	2
I (n = 6)	1	1	1	-	-	3

large joints. The true numbers of large joints affected was underestimated (see appendix 6.1) often because assessment was limited by deformity and stiffness which followed fractures in about 18 patients (16 with type III/IV and 1 each with types III and I OI); the elbow and knee were most often thus affected.

Females and males were affected proportionately with some form of joint laxity (p 0.2 - 0.5). Patients with joint laxity were represented in all age groups, but many commented that their joint hypermobility had been greater in childhood and had decreased with age. Four patients (cases 2, 40, 52 and 63) had no laxity of large joints but had noted lax joints in childhood. Some patients demonstrated their ability to assume bizarre postures, for example, by placing their feet behind their ears.

Only 2 parents, both fathers, had significant joint laxity and the affected child (case 26) of one of these had marked joint laxity documented by the author, as described in section 5.2.7, under 'Joint laxity'.

Two sporadic type III/IV cases stood out from the rest as having very marked joint hypermobility and a similar phenotype. They are described as follows:-

One patient (case 47), a male aged 14.3 years, had extremely lax joints and soft, stretchy skin. His sclerae had faded from deep blue at birth to very pale blue, he estimated having had 193 fractures and his short stature and skeletal deformity were

severe. Figure 6.14 shows his joint laxity. The patient's mother had mildly hyperextensible skin but no joint laxity, and the father had normal skin and joints, as described in section 5.2.7.

Another similar patient (case 45), a female aged 21.5 years, also had marked joint laxity and soft, velvety, loose, stretchy skin. Her sclerae had remained deep blue in colour from birth, she had had about 200 fractures, she was only 75 cm tall and had marked skeletal deformities. Her father had a mild degree of skin stretchiness but no joint laxity and the mother had mild joint laxity and normal skin, as described in section 5.2.7. Both of these patients had a rather long face, different from the usual 'OI facies'. In both cases 45 and 47, the diagnosis of OI was not in doubt, but the clinical phenotype overlapped with the Ehlers-Danlos syndrome, although the skin stretchiness was not as marked as in the latter.

Discussion


Excessive joint mobility is a well described accompaniment of OI and results largely from laxity of the ligaments, tendons and capsules which normally support the joints (Smith et al., 1983). Deformity and maladaptation of the bony surfaces of the joints may also play a role (McKusick, 1972). Joint laxity allows some patients to assume bizarre postures; bony deformity and pseudoarthroses may contribute to this ability.



Figure 6.14

Case 47 (type III/IV OI), aged 14.3 years.

Note marked joint laxity. (The patient is lying on his abdomen).



Some authors have suggested that joint laxity only occurs in the presence of blue sclerae (Smith et al., 1983) but as in the present series, Sillence et al. (1979b) found that a significant number of patients (50% of 21) with severe progressively deforming OI had marked ligamentous laxity. They also noted that joint laxity is more pronounced in the young and that the small joints of the hands were particularly affected, as was the case here. Langness and Behnke (1970) found that 57 of 80 patients (71%) with 'OI tarda' had some degree of joint laxity which is comparable to the result for the patients with type I OI in this study. It is often difficult to compare results from different studies, owing to the difficulty in classifying joint laxity. Carter and Wilkinson (1964) examined 285 English schoolchildren and found that 7% had excessive joint motion in more than 3 pairs of joints. Sutro (1947) examined 235 males aged 18-35 years who were patients in orthopaedic wards and found that 4% had hypermobility of 3 or more joint pairs. In the present series, 36.4% and 27.3% of patients with type III/IV OI had laxity of more than 3 or more than 4 large joints, respectively, which is clearly in excess of normal.

The overlap with Ehlers-Danlos syndrome (EDS) in 2 patients with severe type III/IV OI is unusual. Sippola and Prockop (1983) studied a patient with blue sclerae, bilateral dislocations of the hips, joint laxity and Wormian bones, who had a deletion of about 30 amino acids near the N-terminal end of one pro $\alpha 2(I)$ collagen chain. The patient had not had fractures but had a family history of blue sclerae, joint dislocations and fractures.

Thus the patient combined features of mild OI and EDS (Prockop and Kivirikko, 1984). Byers and Bonadio (1985) also quote the unpublished observations of Hall and Byers who have seen patients with features of the two disorders. A boy described by Biering and Iversen (1955) as showing evidence of OI and EDS may well have had cutis laxa, in view of the markedly loose, wrinkled skin. The description in the present study of two individuals with severe deforming OI and marked joint laxity has not been emphasised previously.

6.7.5.2 Joint dislocations

Results (table 6.32)

Overall, one quarter of cases gave a history of joint dislocations, comprising about half the type I cases, a quarter of type III/IV sporadic cases and one (10%) of the type III cases. The differences in numbers between those with type III/IV and III OI or type III/IV and I were not statistically significant (p 0.2 - 0.5, and p 0.1 - 0.2), respectively). Joint dislocations were recurrent in 13 of the 17 type III/IV patients and in all of the types III and I cases (appendix 6.3). Females and males were affected in similar ratios, overall (p 0.7 - 0.9). The shoulder was by far the most commonly involved joint with 3 type I cases and 10 type III/IV sporadic cases reporting single or multiple dislocations of the shoulder. These occasionally required reduction under a general anaesthetic (cases 31 and 35). Other joints involved included the fingers, knees, elbows and

Table 6.32

JOINT DISLOCATIONS IN PERINATAL SURVIVORS (No. cases (%))

Type of OI	History of joint dislocations	No history of joint dislocations	Unknown	Total
IIB	-	1 (M)	2 (2F)	3 (2F, 1M)
III/IV sporadic	17 (23.6%) (10F, 7M)	55 (76.4%) (33F, 22M)	15 (7F, 8M)	87 (50F, 37M)
III recessive	1 (10%) (M)	9 (90%) (4F, 5M)	5 (2F, 3M)	15 (6F, 9M)
III & III/IV*	18 (22.0%) (10F, 8M)	64 (78.0%) (37F, 27M)	20 (9F, 11M)	102 (56F, 46M)
I new mutation	5 (55.6%) (3F, 2M)	4 (44.4%) (4F)	2 (1F, 1M)	11 (8F, 3M)
Total	23 (25%) (13F, 10M)	69 (75%) (41F, 28M)	24 (12F, 12M)	116 (66F, 50M)

% are for known cases.

F = female, M = male.

* III & III/IV are total of III recessive & III/IV sporadic

hips. In the type III/IV sporadic group are included 4 patients who had bilateral congenital dislocation of the hips; one of these went on to have other joint dislocations subsequently.

Discussion

Dislocations of joints have often been reported in patients with OI (Bell, 1928; McKusick, 1972). They can be recurrent and in some cases can be as painful and troublesome as fractures (Bronson, 1917; Smars, 1961). Presumably joint dislocations reflect underlying joint laxity, although, surprisingly, one patient with type I OI, a 23 year old male, had no obvious joint laxity but reported recurrent shoulder dislocations. Bantz (1941) also reported a patient with OI 'tarda' who suffered recurrent shoulder dislocations. The joint most often dislocated in the present series was the shoulder. This probably reflects the fact that this joint is the one most prone to dislocation in the general population.

Congenital dislocations of the hips (CDH) which occurred in 4 patients with type III/IV OI was also recorded in 2 brothers with OI (du Toit and Weiss, 1969). Great caution should be exercised, however, in clinical testing for CDH in babies with OI so as not to cause iatrogenic fractures. If OI is suspected at birth, the diagnosis of CDH is probably best made radiologically.

6.7.6 The skin

6.7.6.1 Skin hyperextensibility

Results (table 6.33)

In table 6.33 it can be seen that 33 out of 63 sporadic type III/IV cases examined by the author had mild skin hyperextensibility which refers to a loose, stretchy feel to the skin on the palm of the hand, where the skin is normally tight. Four out of the 5 cases of type III OI examined by the author had this feature including the only sib pair which the author was able to examine. (The proportion of cases of type III/IV and III OI with skin laxity was not significantly different, p 0.2 - 0.5). One case of type IIB was reported by her paediatrician to have had 'loose skin'. Mildly stretchy skin was found in 2 of 7 patients with type I OI (but this is not statistically different from the type III/IV group, p 0.2 - 0.5). Given the preponderance of females with a known result, relatively more males than expected showed the trait, but not at a significant level (p 0.1 - 0.2). The skin of these individuals was also rather thick, soft and velvety with deep palmar creases.

All but 2 sporadic type III/IV cases with skin hyperextensibility also had joint laxity which was generalised in 23 and confined to the hands in 8. One patient did not have joint laxity (case 49) and the state of the joints was unknown in the other (case 20). Of the 4 type III patients with skin hyperextensibility, one

Table 6.33

SKIN HYPEREXTENSIBILITY IN PERINATAL SURVIVORS

Type of OI	Yes	No	Unknown	Total
IIB	1 (F)	-	2 (1F, 1M)	3 (2F, 1M)
III/IV sporadic	33 (52.4%) (18F, 15M)	30 (47.6%) (20F, 10M)	24 (12F, 12M)	87 (50F, 37M)
III recessive	4 (80%) (1F, 3M)	1 (20%) (F)	10 (4F, 6M)	15 (6F, 9M)
III & III/IV*	37 (54.4%) (19F, 18M)	31 (45.6½%) (21F, 10M)	34 (16F, 18M)	102 (56F, 46M)
I new mutation	2 (28.6%) (1F, 1M)	5 (71.4%) (4F, 1M)	4 (3F, 1M)	11 (8F, 3M)
Total	40 (52.6%) (21F, 19M)	36 (47.4%) (25F, 11M)	40 (20F, 20M)	116 (66F, 50M)

% are for known cases

F = female, M = male

* III & III/IV is total of III recessive & III/IV sporadic.

(case 99) did not have joint laxity. He was a male aged 33.25 years. The 2 type I new mutation cases with skin stretchiness also had lax joints.

Discussion

The skin may be affected in mild and severe forms of OI (Francis et al., 1974). Early authors described the skin as soft, smooth and delicate (Hess, 1917; Gibson, 1923); a velvety texture was noted in this study, particularly in patients with severe bone disease. The mild skin hyperextensibility noted especially in patients with severe disease does not appear to have been emphasised previously. It should be stressed that this was generally much milder than the skin stretchiness seen in Ehlers-Danlos syndrome (EDS), with the possible exception of cases 45 and 47 described in section 6.7.5.1.

Histological changes which occur in the skin in OI were described by Follis (1953). These are confined to the dermis which is thinner than normal. Stadil (1961), in a study of a family with probable type I OI, confirmed the thinning of the corium and noted hyperelastosis and the appearances of collagen-fibre degeneration. Occasionally, no skin abnormalities have been found histologically in patients with OI (Smith et al., 1983). Decreased total dermal collagen has been recorded in patients with mild OI by Stevenson et al. (1970) and Francis et al. (1974). The latter authors noted that in patients with severe bone disease, the total amount of polymeric skin collagen could

be normal, but it was less stable. Relative reduction of type I compared to type III collagen in skin of patients with mild and severe OI has been reported (Sykes et al., 1977; Francis et al., 1981).

Other abnormalities of the skin reported in patients with OI include irregular pigmentation, prominent scars and keloid formation, elastosis perforans serpiginosa, and congenital poikiloderma of Thompson (quoted in Smith et al., 1983) but none of these were noted in this study.

6.7.6.2 Bruising tendency and epistaxes

Results (tables 6.34 and 6.35)

A tendency to form bruises readily was reported for 15 (20.5%) type III/IV sporadic cases and 6 (66.7%) of type I cases, as shown in table 6.34. Three of these patients with type III/IV noted this feature in childhood mainly (case 21) or only (cases 25 and 39). No recessive type III or IIB cases had the tendency. The difference in numbers of patients with a bruising tendency between the type III/IV and III group is not significant (p 0.2 - 0.5) whereas it is significant between the type III/IV and type I group (p <0.001). Overall, females and males were affected in the same ratios (p 0.9 - 0.95). Despite these reports, bruises were only actually observed in 1 of 57 type III/IV sporadic cases examined by the author and 2 of 8 of the type I patients.

Table 6.34

BRUISING TENDENCY IN PERINATAL SURVIVORS

Type of OI	Yes	No	Unknown	Total
IIB	-	3 (2F, 1M)	-	3 (2F, 1M)
III/IV sporadic	15 (20.5%) (8F, 7M)	58 (79.5%) (36F, 22M)	14 (6F, 8M)	87 (50F, 37M)
III recessive	-	9 (100%) (5F, 4M)	6 (1F, 5M)	15 (6F, 9M)
III & III/IV*	15 (18.3%) (8F, 7M)	67 (81.7%) (41F, 26M)	20 (7F, 13M)	102 (56F, 46M)
I new mutation	6 (66.7%) (5F, 1M)	3 (33.3%) (2F, 1M)	2 (1F, 1M)	11 (8F, 3M)
Total	21 (22.3%) (13F, 8M)	73 (77.7%) (45F, 28M)	22 (8F, 14M)	116 (66F, 50M)

% are for known cases

F = female, M = male

* III & III/IV is total of III recessive & III/IV sporadic.

A total of 15 patients (around 16%) had suffered unusually frequent epistaxes (table 6.35). They occurred up to several times a month and in one case tended to be heavy and lasted up to 3 or 4 hours. As can be seen from the comments under table 6.35, frequent epistaxes had occurred in childhood only, with only 2 cases having the problem over 14 years of age. One of these (case 41) had undergone successful unilateral nasal cautery at 20 years. The sexes were affected in similar ratios (p 0.2 - 0.5). The differences in those reporting epistaxes between the type III/IV and III group, and the type III/IV and I group are not statistically significant (p 0.5 - 0.7 and p 0.2 - 0.5, respectively).

Discussion

In reviewing blood clotting abnormalities in OI, Smith et al. (1983) note that patients with OI may bleed easily and develop bruises, possibly as a result of capillary fragility. Blood clotting may also be abnormal; Langness and Behnke (1970) state that some 10% of patients suffer from a bleeding diathesis. Abnormal platelet function has also been described (Smith et al., 1983). The bruising tendency noted in this study was more of a curiosity than a problem but a minority had suffered from troublesome epistaxes, albeit mainly in childhood. Only 3 type III/IV patients reported both easy bruising and epistaxes, whereas 3 of the 6 patients with type I OI reporting easy bruising had also suffered epistaxes.

Table 6.35

FREQUENT EPISODES OF EPISTAXIS IN PERINATAL SURVIVORS

Type of OI	Present	Absent	Unknown	Total
IIB	-	3 (2F, 1M)	-	3 (2F, 1M)
III/IV sporadic	11 (15.1%)* (5F, 6M)	62 (84.9%) (39F, 23M)	14 (6F, 8M)	87 (50F, 37M)
III recessive	1 (10%)** (M)	9 (90%) (4F, 5M)	5 (2F, 3M)	15 (6F, 9M)
III & III/IV****	12 (14.5%) (5F, 7M)	71 (85.5%) (43F, 28M)	19 (8F, 11M)	102 (56F, 46M)
I new mutation	3 (33.3%*** (2F, 1M)	6 (66.7%) (5F, 1M)	2 (1F, 1M)	11 (8F, 3M)
Total	15 (15.8%) (7F, 8M)	80 (84.2%) (50F, 30M)	21 (9F, 12M)	116 (66F, 50M)

% are for those known

F = female, M = male

* 6 were under 15 years, 3 had the problem only in childhood, 1 aged 27.08 had no further problems after unilateral nasal cautery at 20 years, 1 was aged 23 years.

** In childhood only. *** 2 reported increased episodes of epistaxis in childhood only, the other was a male aged 14 years.

**** III & III/IV is total of III recessive & III/IV sporadic.

Although the possibility of haemostatic problems during tooth extractions or skeletal operations needs to be born in mind, in practice such problems are uncommon (Smith et al., 1983).

6.7.6.3 Excessive sweating

Results (table 6.36)

In table 6.36 it can be seen that the majority of patients in all types of OI had experienced excessive sweating. No sex difference was apparent (p 0.5 - 0.7). Both members of 4 sib pairs reported the tendency and none were clearly discordant. Eleven of the 63 type III/IV sporadic cases, 1 of the type III cases and 2 of the 11 type I cases reporting excessive sweating had noted a marked decrease in the tendency with advancing age, whereas only 2 cases (cases 21 and 41, type III/IV OI) commented that it had increased with age. Individuals complaining of excessive sweating were often noticed to be scantily clad despite cold weather.

Discussion

Segawa (1914-1915) was probably the first author to describe attacks of profuse sweating, especially on the head and face, which began in the second week of life in a child with severe OI. There are now numerous reports of excessive sweating in patients with both mild and severe forms of OI (Humbert et al., 1971; Cropp and Myers, 1972; Solomans and Millar, 1973; Distiller et al., 1975; Richard and Courpron, 1980; Brown, 1981; Smith et al.,

Table 6.36

EXCESSIVE SWEATING IN PERINATAL SURVIVORS (No. cases (%))

Type of OI	Present	Absent	Unknown	Total
IIB	3 (2F, 1M)	-	-	3 (2F, 1M)
III/IV sporadic	63 (88.7%) (37F, 26M)	8 (11.3%) (5F, 3M)	16 (8F, 8M)	87 (50F, 37M)
III recessive	9 (90%) (4F, 5M)	1 (10%) (F)	5 (1F, 4M)	15 (6F, 9M)
III & III/IV*	72 (88.9%) (41F, 31M)	9 (11.1%) (6F, 3M)	21 (9F, 12M)	102 (56F, 46M)
I new mutation	7 (70%) (5F, 2M)	3 (30%) (2F, 1M)	1 (F)	11 (8F, 3M)
Total	82 (87.2%) (48F, 34M)	12 (12.8%) (8F, 4M)	22 (10F, 12M)	116 (66F, 50M)

F = female, M = male

% are of known cases

* III & III/IV is total of III recessive & III/IV sporadic.

1983). Episodes of high temperature have also been noted (Smith et al., 1983). Evidence of increased leucocyte respiration in patients with OI was reported by Humbert et al. (1971) but Brown et al. (1972) could not confirm the findings. In a study of 30 prepubertal patients with mild to severe OI, Cropp and Myers (1972) found physiological evidence of a hypermetabolic state; metabolic rates normalised after puberty and coincided with the arrest of the clinical progression of the disease. At least half of these patients had raised serum thyroxine levels. Cropp (1973) also reported raised serum levels of both free triiodothyronine and thyroxine. Distiller et al. (1975) noted raised serum thyroxine in 6 children with OI, but this resulted from a raised serum globulin component; serum free thyroxine was normal and the authors concluded that the patients had normal thyroid function.

Brown (1981) suggested that the apparent hypermetabolic state is 'due to failure to retain heat because of the very significant thinning of the skin, owing to the markedly lowered collagen content'. If this were the explanation, however, shivering rather than sweating might be expected. Many patients in the present study claimed 'not to feel the cold' and were lightly dressed in cold weather which again would be unusual if primary heat loss were occurring. At the present time, the reason for excessive sweating in OI is unknown.

6.7.7. The ear - hearing loss

Results (tables 6.37 - 6.39)

As can be seen from table 6.37, 17 (16.3%) of all cases reported hearing loss. Relatively more patients with types III and I OI reported hearing loss than those with type III/IV OI, , but this was not statistically significant (p 0.2 - 0.5 and p 0.1 - 0.2, respectively). Although overall more males (n=10) than females (n=7) reported hearing loss, this was not significant (p 0.1 - 0.2).

Table 6.38 shows the numbers of cases who were able to quote a result of an objective hearing test (performed by a health visitor or doctor, or the result of an audiological test at school) compared with those giving a subjective report. Almost equal numbers in each group gave subjective reports as gave objective reports, so that the numbers with hearing loss may be underestimated, since mild degrees of hearing loss might be unrecognised by the patient.

In table 6.39, it can be seen that patients reporting hearing loss were older than those with normal hearing. Since the majority of patients were in their first two decades, the paucity of cases with hearing loss may reflect the fact that the age of onset of hearing loss occurs after that time. In the sporadic type III/IV group, hearing loss was first noted between the ages of 14 and 44 years; in the type III group it was first noted

Table 6.37

CLINICAL HEARING LOSS REPORTED FOR PERINATAL SURVIVORS (No. cases (%))

Type of OI	Normal	Decreased unilaterally	Decreased bilaterally	Decreased unspecified	Total decreased	Unknown	Total
IIB	1 (F)	-	-	-	-	2 (1F, 1M)	3 (2F, 1M)
III/IV sporadic	71 (86.6%) (43F, 28M)	2 (2.4%) (2M)	5 (6.1%) (FM)	4 (4.9%) (4F)	11 (13.4%) (4F, 7M)	5 (3F, 2M)	87 (50F, 37M)
III recessive	8 (72.7%) (4F, 4M)	1 (9.1%) (M)	1 (9.1%) (M)	1 (9.1%) (F)	3 (27.3%) (1F, 2M)	4 (1F, 3M)	15 (6F, 9M)
III & III/IV*	79 (85.0%) (47F, 32M)	3 (3.2%) (3M)	6 (6.5%) (6M)	5 (5.4%) (5F)	14 (15.1%) (5F, 9M)	9 (4F, 5M)	102 (56F, 46M)
I new mutation	7 (70%) (6F, 1M)	1 (10%) (M)	1 (10%) (F)	1 (10%) (F)	3 (30%) (2F, 1M)	1 (M)	11 (8F, 3M)
Total	87 (83.7%) (54F, 33M)	4 (3.8%) (4M)	7 (6.7%) (1F, 6M)	6 (5.8%) (6F)	17 (16.3%) (7F, 10M)	12 (5F, 7M)	116 (66F, 50M)

% are for known cases

F = female, M = male

* III & III/IV is total of III recessive & III/IV sporadic.

Table 6.38

HEARING LOSS: PATIENT'S REPORT OF OBJECTIVE TEST* OR SUBJECTIVE REPORT

Type of OI	Hearing loss		Normal hearing	
	Objective test	Subjective report	Objective test	Subjective report
IIB	-	-	-	1
III/IV sporadic	7	4	38	33
III recessive	2	1	4	4
I new mutation	1	2	5	2
Total	10	7	47	40

* Objective tests include assessments by a doctor or health visitor, or results of an audiogram performed at school.

Table 6.39

HEARING LOSS: MEAN AGE OF CASES (YEARS) \pm 1 SD

Type of OI	Hearing loss	Normal hearing
IIB	-	2.2 (n = 1)
III/IV sporadic	30.9 \pm 12.2	10.7 \pm 8.0
III recessive	15.3 \pm 5.8	10.9 \pm 13.0
I new mutation	26.7 \pm 8.4	12.8 \pm 13.2

between 9.2 years (detected by audiological testing) and 20.7 years, and in the type I group, the loss was first apparent in the latter part of the first decade to the end of the second decade.

Whether the hearing loss was conductive, sensorineural or mixed is unknown. In one type III/IV sporadic case (case 52), the cause of hearing loss was a ruptured tympanic membrane.

Of 5 sib pairs, hearing was concordant (normal) in both members of 2 sib pairs, and discordant in 3 sib pairs; interestingly, the sib with hearing loss was the younger in 2 sib pairs.

Discussion

The first description of deafness in OI was given by Dent (1897, quoted in Bell, 1928) in a 29 year old male with severe OI. The deafness was noted since 26 years; scleral colour was not mentioned. Subsequently, Adair-Dighton (1912), in a report of an extensive pedigree with blue sclerae and brittle bones, described the onset of hearing loss in a 23 year old female three months post-partum. It was Van der Hoeve and de Kleyn (1918), however, who emphasised the triad of brittle bones, blue sclerae and deafness in a paper which was first presented at a clinical meeting in 1916 in Utrecht; OI is therefore often known as the Van der Hoeve-de Kleyn syndrome in Europe. These authors claimed that the deafness was conductive in type and indistinguishable from otosclerosis. Bronson (1917) also noted the early onset of

deafness in 7 of 8 adult patients in a family with OI and blue sclerae. Many extensive surveys (Bell, 1928; Seedorff, 1949; Smars, 1961; McKusick, 1972) have concluded that deafness is most common in patients with dominantly inherited disease and blue sclerae. Sillence et al. (1979b) found that 35% of 65 patients with type I OI had proven or suspected hearing loss, usually first becoming evident in the third decade. As many as 20% of their patients however had severe hearing impairment before 20 years of age. The earliest age of onset was 10 years. These findings are similar to those of the present study, although the numbers of type I cases here are small.

Reports of deafness occurring in patients with brittle bones and normal sclerae are few (Fuss, 1935). Liber (1956) reported a consanguineous family with brittle bones and deafness; no reference was made to scleral colour. Sillence et al. (1979b) found that only one of 21 (5.3%) patients with type III OI had hearing loss; this was a 30 year old woman whose loss had begun in the third decade. In another report of 17 individuals with type III OI, only one had (mild) hearing loss (Sillence et al., 1986). None of 8 patients with type IV OI in Sillence et al.'s (1979b) study were deaf. The finding in the present study that as many as 15% of all patients with type III and III/IV OI had some hearing loss is perhaps unusually high, especially in view of the fact that many patients had not had recent formal audiological assessment.

Deafness in OI may be not only conductive but sensorineural or mixed and one patient may have different types (Bergstrom, 1977). Shapiro JR, et al. (1982) found that about half of 55 patients with OI had sensorineural hearing loss.

A variety of pathological and histological changes in the middle and inner ear have been described in patients with OI, including those with perinatally lethal disease (see review by Smith et al., 1983). It is now generally accepted that the conductive deafness in OI is clinically similar to that seen in otosclerosis, but the two are histologically, histochemically and biochemically distinct (Pedersen et al., 1979; Bergstrom, 1981). The conductive deafness in OI results from functional ossicular discontinuity due either to stapes fracture or fibrous replacement or to a thick, crumbly, lightly fixed stapes footplate (Bergstrom, 1981). Results of stapedectomy and replacement by a prosthesis are generally good (Shea et al., 1963; Opheim, 1968; Patterson and Stone, 1970; Bretlau et al., 1970; Brosnan et al., 1977; Pederson and Elbrond, 1979; Shea and Postma, 1982). These reports all concern patients with the dominant 'tarda' forms of OI with blue sclerae, rather than those with severe disease and normal sclerae. Many of these authors commented upon troublesome mucosal bleeding which complicated the operations.

6.7.8 The teeth - dentinogenesis imperfecta

Results (table 6.40)

Dentinogenesis imperfecta (DI) is another common abnormality which occurs in patients with OI, producing an opalescent or transparent appearance of the teeth, often with brown or blue discolouration, excessive wearing and chipping and an increased incidence of caries (Levin, 1981). The presence of one or more of these abnormalities was usually obvious enough to allow the author to make the diagnosis of DI on the basis of a history and simple clinical examination, where possible. In those cases not examined, the parents of the affected child were usually able to give a clear indication as to whether or not DI was present. The assessment was made on either the first or the second dentition whichever was present at the time of the study or at death (see appendix 6.1). In addition, dental radiographs were available for 12 patients with type III/IV OI (see appendix 6.1). One of these included an orthopantomogram (case 37). These were reviewed by Professor Winter (Eastman Dental Hospital, London) and Mr Mars (The Hospital for Sick Children, Great Ormond Street, London). Radiological evidence of DI was found in all 12 patients by both experts, confirming the clinical impressions. Unfortunately, (but not surprisingly) adequate views of those with clinically normal teeth were not available.

The results of the clinical assessment are shown in table 6.40. About three-quarters of all cases (69 of 91) had evidence of DI.

Table 6.40

CLINICAL EVIDENCE OF DENTINOGENESIS IMPERFECTA (DI) IN
PERINATAL SURVIVORS

Type of OI	DI	Normal	Unknown or not applicable*	Total
IIB	1 (F)	-	2 (1F, 1M)	3 (2F, 1M)
III/IV sporadic	58 (82.9%) (35F, 23M)	12 (17.1%) (4F, 8M)	17 (11F, 6M)	87 (50F, 37M)
III recessive	4 (44.4%) (2F, 2M)	5 (55.6%) (1F, 4M)	6 (3F, 3M)	15 (6F, 9M)
III & III/IV**	62 (78.5%) (37F, 25M)	17 (21.5%) (5F, 12M)	23 (14F, 9M)	102 (56F, 46M)
I new mutation	6 (60%) (5F, 1M)	4 (40%) (3F, 1M)	1 (M)	11 (8F, 3M)
Total	69 (76.7%) (43F, 26M)	21 (23.3%) (8F, 13M)	26 (15F, 11M)	116 (66F, 50M)

* Unknown or teeth not yet erupted.

% are for those known.

**III & III/IV is total of III recessive & III/IV sporadic.

For the group as a whole, more females than males were affected and this was just statistically significant ($p = 0.05$). Looking at the various subgroups, however, this sex difference, although present, does not reach statistical significance ($p = 0.1 - 0.5$, $0.9 - 0.95$ and $0.5 - 0.7$ in the type III/IV, III and I groups respectively. This includes correction for continuity where any expected values are less than 5, as in the type III and I groups).

One child with type IIB OI (not examined by the author) was reported by the parents to have shown evidence of DI. Fifty-eight (82.9%) patients with type III/IV OI had clinical evidence of DI; one of these had mild translucency of the teeth only, with no obvious wearing. Forty-eight of the 58 with DI were examined by the author, as were 10 of the 12 with apparently normal teeth.

In the type III OI group, 4 patients had DI and 5 did not, clinically. (Two and 3 of these were examined by the author, respectively). One sib pair was concordant for clinically normal teeth and one sib pair was concordant for DI. Two sib pairs were discordant for DI by parents' reports. In one of these, one girl (case 93), who had died at 8.5 years was said to have DI but her sister (case 92) who had died at 16 months was thought to have had normal teeth. DI may not yet have become apparent in the latter case. In the other 'discordant' sib pair, one sib (case 99) had obvious DI (examined by the author) but his brother (case 98) who had died at 16 years was said by the parents to have had normal teeth. The difference in numbers with DI between the

types III/IV and III group is statistically significant ($p < 0.01 - 0.05$) but the information is incomplete and may have underestimated those with DI in the type III group.

In the type I group, 6 patients had DI and 4 did not, clinically; of these, 6 and 3 were examined by the author, respectively. The difference in numbers between the type III/IV and I group is not significant ($p < 0.05 - 0.1$).

Delayed eruption of the first and second dentitions was occasionally reported.

In 11 cases with type III/IV OI and DI (cases 19, 23, 35, 39, 42, 44, 46, 49, 50, 65, 68), the patient or family commented that the second dentition seemed less abnormal than the first, either with less wearing or a better colour.

Discussion

The dental abnormality in OI is due to a reduction in the number or absence of tubules in the dentin; it is generally believed that the enamel is normal (Levin, 1981). The enamel fractures away, exposing the darker dentin which wears towards the gingiva. Other authors have noted the tendency for the permanent dentition to be less severely affected than the deciduous dentition, as in the present study (Levin, 1981). Rarely, the permanent teeth are so mildly affected that they seem normal unless examined with a good light and dental radiographs (Levin, 1981). Thus the

incidence quoted in the present study on the basis of clinical examination may be an underestimation, in the absence of radiographs for the clinically normal cases.

Many authors have noted that the incidence of DI is greater in the severe than in the mild forms of OI (Falvo et al., 1974; Bauze et al., 1975; Sillence et al., 1979b; Smith et al., 1983) but the figures quoted vary widely. In the present study, 6 (60%) of patients with type I OI had DI. In Falvo et al.'s (1974) series, 63% in the 'tarda' group had DI, whereas Sillence et al. (1979b) found that none of 65 patients with type I OI had 'classical' DI but 41.5% and 18.9% had some discolouration or wearing, respectively. In a 3 centre study of 333 cases, DI was present in only 12 of 103 (11%) with mild OI (Smith et al., 1983). Levin et al. (1982) reported on a child with severe congenital OI who died at 10 months of age, whose teeth were normal when examined under the scanning electron microscope.

As many as 83% of cases with sporadic type III/IV OI in the present study had DI. Falvo et al. (1974) found DI in 10 of 12 (83%) of 'congenita' cases and Smith et al. (1983) noted DI in 63% of cases with severe disease who were born with fractures. Paterson et al. (1983) studied 48 patients from 16 families with type IV OI; 68.8% had DI.

Only 4 (44.4%) cases in the present study with type III OI had abnormal teeth. As mentioned above, the information on 2 cases whose sibs were affected was incomplete, so that those affected

might be underestimated. Sillence et al. (1979b) reported DI in 45% of 20 cases with type III OI, and in a further 2 of 4 cases with type III (Sillence et al., 1986).

The rather anecdotal suggestion of discordance for DI in sibs with type III OI in the present study could not be substantiated due to lack of information. The author is not aware of other such examples in the literature. Concordance for DI in sibs with 'recessive' OI might be expected, since DI tends to 'breed true' in families with types I and IV OI (Levin et al., 1978; Paterson et al., 1983) and this has led to the subdivision of these into A and B groups, based on the absence or presence of DI, respectively.

Eruption of teeth is said to be usually normal in OI (quoted in Smith et al., 1983) but some families here had noted delayed eruption.

The defect seen in OI is clinically, radiographically and microscopically similar to that seen in an autosomal dominant disorder not associated with bone disease, which is variously called (hereditary) dentinogenesis imperfecta, (hereditary) opalescent dentin, odontogenesis imperfecta, dentinogenesis imperfecta type I and hereditary hypoplasia of dentin. Levin (1981) believes that the term dentinogenesis imperfecta should be reserved for the isolated dentin abnormality but that the one associated with OI should be called 'OI with opalescent teeth'. One difference between the two conditions is that in isolated DI

all teeth are affected, whereas in association with OI, some teeth may be spared and others affected in the same individual. The isolated form of DI is linked to the locus for the vitamin D binding protein, group specific complement (Gc) on chromosome 4q (Ball et al., 1982). The maximum lod score was 7.9 at recombination fractions of 0.05 (male) and 0.24 (female). It is interesting that the disorder is phenotypically similar to the dental defect in OI which is usually due to an abnormality of type I collagen which is coded for on chromosomes 7 and 17.

6.7.9 The gastrointestinal tract

6.7.9.1 Constipation

Results (table 6.41)

As can be seen from table 6.41, almost half of the patients with type III/IV and III OI complained of constipation, as did 3 of 9 with type I and one with IIB OI. The difference between the type III/IV and I group is not significant (p 0.5 - 0.7). Those from the type I group were not greatly troubled by it, but many from the sporadic type III/IV group suffered considerably; 4 of them (a male and 3 females, cases 25, 41, 45, 50) had had associated rectal prolapse, as had 1 type III patient (a male, case 99), occurring on 2 or 3 occasions. Case 25 had required surgical reduction of the prolapse. Another type III/IV sporadic patient, a 23.25 year old female (case 16), had a colostomy performed at 7 years because of chronic constipation and faecal impaction; the

Table 6.41

CONSTIPATION IN PERINATAL SURVIVORS

Type of OI	Present	Absent	Unknown	Total
IIB	1 (F)	1 (M)	1 (F)	3 (2F, 1M)
III/IV sporadic	32 (48.5%)* (17F, 15M)	34 (51.5%) (22F, 12M)	21 (11F, 10M)	87 (50F, 37M)
III recessive	4 (40%) (1F, 3M)	6 (60%) (3F, 3M)	5 (2F, 3M)	15 (6F, 9M)
III & III/IV**	36 (47.4%) (18F, 18M)	40 (52.6%) (25F, 15M)	26 (13F, 13M)	102 (56F, 46M)
I new mutation	3 (33.3%) (3F)	6 (66.7%) (4F, 2M)	2 (1F, 1M)	11 (8F, 3M)
Total	40 (46.0%) (22F, 18M)	47 (54.0%) (29F, 18M)	29 (15F, 14M)	116 (66F, 50M)

% are for known cases

F = female, M = male

* 7 noted constipation mainly in childhood or infancy.

** III & III/IV is total of III recessive & III/IV sporadic.

colostomy is still present.

Presumably the constipation relates in part to immobility. Of the 12 patients with sporadic III/IV OI who can walk (see table 6.23) none complained of constipation, although 2 had the problem in early childhood, associated with rectal prolapse in one. This suggests that immobility compounds the tendency to constipation.

Constipation was more troublesome in childhood; of the 32 sporadic type III/IV patients with constipation, 6 were over 18 years and had the problem only in childhood, one was 5 1/2 years (case 44) and had it in infancy and the mean age of the remaining 25 currently suffering from constipation was 12.7 years (S.D. 7.25 years). Overall, females and males were affected equally often with constipation (p 0.5 - 0.7).

Discussion

Scant reference to this sometimes serious problem in OI is made in the literature. Shoenfeld et al. (1975) found that 11 of 29 patients (38%) with mainly dominant OI had obstipation. Constipation in severe OI may be attributable to a combination of immobility and poor muscle tone. The latter has been thought to result from weakness of the loose connective tissue. Smith et al. (1983) cite the striking example of their patient with mild bone disease whose stomach ruptured, apparently spontaneously.

Results (table 6.42)

About one-third of patients overall gave a history of one or more herniae. These were largely from the type III/IV and III groups; only 1 of 3 type IIB and 1 of 10 type I OI patients had a hernia, as shown in table 6.42. The difference between the type III/IV and I group is not significant (p 0.1 - 0.2). Overall, relatively more males than females ($p < 0.001$) reported herniae. Two sib pairs were discordant for having a hernia. The types of herniae are shown in appendix 6.4. In the group as a whole, congenital umbilical herniae were present in 14 cases, one of which was supraumbilical, and 6 resolved spontaneously. One proved to be resistant to surgical repair and recurred despite four operations. The remaining 6 were not operated upon and had persisted and in one, the outcome was unknown. Bilateral inguinal herniae were present in 5 cases; 2 were operated upon successfully (albeit twice in one case); 1 was recurrent after 2 operations and 2 were not operated upon. Eleven patients had unilateral inguinal herniae (5 right-sided, 2 left, 4 side unknown) of which 3 resolved spontaneously, 4 were operated upon successfully and the rest were still present. Other herniae included an incisional hernia, a hiatus hernia and a sub-umbilical hernia, which was thought to have developed secondary to straining at stool because of constipation.

Table 6.42

HISTORY OF HERNIAE IN PERINATAL SURVIVORS

Type of OI	Present	Absent	Unknown	Total
IIB	1 (F)	2 (1F, 1M)	-	3 (2F, 1M)
III/IV sporadic	22 (31%) (8F, 14M)	50 (69%) (35F, 15M)	15 (7F, 8M)	87 (50F, 37M)
III recessive	4 (40%) (4M)	6 (60%) (4F, 2M)	5 (2F, 3M)	15 (6F, 9M)
III & III/IV *	26 (32%) (8F, 18M)	56 (68%) (39F, 17M)	20 (9F, 11M)	102 (56F, 46M)
I new mutation	1 (10%) (M)	9 (90%) (7F, 2M)	1 (F)	11 (8F, 3M)
Total	28 (29.5%) (9F, 19M)	67 (70.5%) (47F, 20M)	21 (10F, 11M)	116 (66F, 50M)

F = female, M = male

% are for known cases

* III & III/IV is total of III recessive & III/IV sporadic.

Discussion

The occurrence of inguinal and umbilical herniae in all forms of OI (Smith et al., 1983; Benson et al., 1978) again probably reflects the underlying connective tissue weakness. Other authors have noted the higher incidence of herniae in severe OI; Falvo et al. (1974) found inguinal or umbilical herniae in 3/12 (25%) of patients with severe OI 'congenita', but in only 7/78 (9%) with the milder 'tarda' forms. Similar results were found in the present study.

The male excess noted probably reflects the fact that, for anatomical reasons, boys more often present with inguinal herniae than do girls, in a ratio of about 9:1 (Shandling, 1987). Indeed, the excess of males is significant in patients with inguinal herniae (N = 16, males 13, females 3, p <0.05) and not in the patients with umbilical herniae (N = 14, males 9, females 5, p 0.2 - 0.5). The recurrence of the hernia post-operatively in 3 patients (one with umbilical and two with inguinal herniae) is further testimony to the basic connective tissue disorder.

6.7.10 The heart

Results

In very few patients was a heart murmur detected on examination. Of 52 type III/IV patients, 2 (3.9%) had a soft, apical systolic murmur. One (case 32) was a 6 month old male, who had been

investigated with a chest radiograph, electrocardiogram and echocardiogram which were normal. The other (case 38), a male aged 54.8 years, had not been investigated. He had severe chest deformity, and the apex beat was displaced to the right. Another 3 year old girl reportedly had a heart murmur at birth, which had disappeared. None of 3 type III patients auscultated had a cardiac bruit. The parents of another type III patient (case 93) reported that the child had a cardiac murmur detected just before her death at 8.5 years from a chest infection. Of 7 type I patients examined, one (14.3%) had a soft systolic murmur; she was a 14 year old girl (case 112) who had not been investigated. Finally, the parents of a boy with type IIB OI (case 164) who died at 6 weeks reported that he had a heart murmur, but the details are not known.

A female aged 20.17 years with type III/IV OI (case 6) had been noted to be hypertensive on several occasions, but this had not been investigated. A male (case 101) with type III OI who died at 1.8 years was found at the post-mortem examination to have a bicuspid aortic valve.

Discussion

Cardiovascular lesions are generally uncommon in OI (Smith et al., 1983). Although McKusick (1972) states that 'a considerable number of patients with osteogenesis imperfecta tarda have been observed with the floppy mitral valve syndrome and aortic regurgitation', some recent series have documented a fairly low

incidence of these abnormalities. Browell and Drake (1966) found only one patient with aortic regurgitation in a series of 24. (The patient had mild dominant OI with blue sclerae; the type of OI in the others was not stated). Cohen et al. (1977) documented two patients with mild OI and blue sclerae who had aortic regurgitation. White et al. (1983) performed a clinical and echocardiographic study on 20 patients with mostly mild OI. No patient had cardiac symptoms. One had aortic regurgitation, 13 had soft late apical systolic murmurs (without significant mitral regurgitation) and only one had echocardiographic evidence of mitral valve prolapse. The left-sided valve cusps were thin, probably due to defective collagen. Seven had systemic hypertension. Aortic root dilatation was present in six, two of whom were hypertensive, but the authors pointed out that aortic aneurysm and dissection have not been reported in OI. A handful of other cardiac lesions have been observed in individual cases (Smith et al., 1983), including bicuspid aortic valve (Criscitiello et al., 1965).

In the present study, the incidence of heart murmurs was very low; the author is aware that some may have been missed on examination. It is important, however, to recognise the need for careful cardiovascular evaluation of patients with OI, for if valvular lesions are present, antibiotic prophylaxis is recommended for dental and surgical procedures (Stein and Kloster, 1977) and hypertension may require treatment (White et al., 1983). Patients with OI and mitral valve prolapse also need careful follow-up to prevent or anticipate chordal rupture

(Schwartz and Gotsman, 1981).

6.7.11 General observations

6.7.11.1 Intelligence and personality

Although intelligence was not formally assessed, there was no evidence that any patient was mentally retarded. Whilst achievement of motor milestones was often delayed due to physical handicap (see section 6.7.3), no parent had noted a significant delay in development of speech or other mental abilities. Many children attended schools for the physically handicapped. In the type III/IV sporadic OI group, 6 patients had completed or were studying for a university degree, and 3 had undertaken courses at other tertiary institutions of education. McKusick (1972) noted that most patients with OI are of normal intellect but cited 3 patients with mental retardation, stating that although arrested hydrocephalus may be the basis in some cases, in others it is likely to be coincidental. In a study of 12 children aged 6 to 17 years, 10 of whom had severe disease, Reite et al. (1972) found that the mean IQ was 107, with a range of 78 to 133.

The author was struck by the number of affected children and adults who had an engaging, cheerful personality with an optimistic outlook in the face of severe disability, almost as if this were the 'OI personality'. This cheerful, often euphoric state has been described before (Solomans and Millar, 1973; Kiely et al., 1976). Even severely affected children are well-adjusted

(Reite et al., 1972) and psychiatric illness in OI is uncommon (Smith et al., 1983). Smith et al. (1983) noted that most adults 'appear intelligent, productive and extroverted' and Smars (1961) emphasised the positive attitude and 'drive' of patients and their 'surprising ability to adapt themselves to the community', despite serious incapacitation.

6.7.11.2 Menarche and pregnancy

The age at menarche for 9 females with sporadic type III/IV OI was 14 years (cases 45 and 62), 14.3 years (case 65), 15 years (case 16), 16 years (cases 6, 8, 56), 17 years (case 40) and 22 years (case 2), mean 16.03 years. Another girl aged 16.25 years (case 48) had never menstruated. One 20 year old female with type III OI (case 103) first menstruated during her 14th year. By comparison, in the type I group, menarche had occurred earlier (between 10 and 14 years in 3 females, cases 113, 115 and 117); one girl aged 16 years (case 118) had never menstruated.

The mean age at menarche in the Harpenden Growth Study (Marshall and Tanner, 1969) was 13.47 years (SD 1.02 years). In the present study, the age at menarche of 7 of 10 girls with sporadic type III/IV OI was greater than one SD over the mean, whereas 3 of 4 with type I OI first menstruated within one SD of the mean. A variety of chronic illnesses are associated with delayed menarche (Preece et al., 1986) and it seems that this may also be true of the severe forms of OI, although the numbers here are small.

Delayed menarche does not necessarily imply infertility. Pregnancy has been reported in a number of women severely dwarfed and deformed as a result of OI (McKusick, 1972; Bender, 1965; Burkhardt, 1968; Dunham and Spellacy, 1967 (quoted in McKusick, 1972)). Evans (1966) reported on a 23 year old woman with severe OI who had never walked and who had a supine length of only 27 inches. Her menarche occurred at 18 years. She became pregnant and her normal baby was delivered by Caesarian section at 34 weeks gestation.

In this study, two probands had offspring; one woman with type I OI (case 117) had a healthy daughter, and another with type III/IV OI (case 6, who is 104 cm tall) was delivered of a daughter at 36 weeks gestation by Caesarian section. The child is affected with OI. The mother had been refused a sterilisation operation by her doctor, on the basis that she represented an anaesthetic risk and that it was unlikely that she would become pregnant (see also addendum to chapter 5). Women with all forms of OI should be offered adequate contraception.

6.7.11.3 Voice

Many patients spoke in a high-pitched nasal voice which was so characteristic that the author could recognise that a person with OI had answered the telephone when ringing to make the interview appointment!. Presumably this quality of the voice relates to the shape of the naso-pharynx. Table 6.43 shows the numbers of patients with this feature. Males and females were affected in similar ratios (p 0.5 - 0.7).

Table 6.43

VOICE OF PERINATAL SURVIVORS

Type of OI	Characteristic high-pitched nasal voice	Normal	Unknown or not applicable	Total
IIB	-	-	3 (2F, 1M)	3 (2F, 1M)
III/IV sporadic	42 (70%) (25F, 17M)	18 (30%) (10F, 12M)	27 (15F, 8M)	87 (50F, 37M)
III recessive	2 (2M)	2 (2F)	11 (4F, 7M)	15 (6F, 9M)
III & III/IV *	44 (68.8%) (25F, 19M)	20 (31.2%) (12F, 8M)	38 (19F, 19M)	102 (56F, 46M)
I new mutation	1 (11.1%) (F)	8 (88.9%) (6F, 2M)	2 (1F, 1M)	11 (8F, 3M)
Total	45 (61.6%) (26F, 19M)	28 (38.4%) (18F, 10M)	43 (22F, 21M)	116 (66F, 50M)

338

% are for those known

F = female, M = male

* III & III/IV is the total of III recessive & III/IV sporadic.

6.7.11.4 Nail growth

After a 19 year old woman with severe OI (case 30) volunteered that her 'nails were stronger than her bones' the author asked other patients about the growth of their finger and toe nails.

Seven of 65 type III/IV OI patients (cases 1, 2, 13, 14, 24, 30 and 51) claimed that their nails grew unusually fast and seemed very strong and 2 others (cases 45 and 57) said they had very tough nails. None said that their nails grew poorly. In the type III group, none of 6 patients asked noted any abnormality of nail growth. Of 9 type I patients, 1 (case 112) had unusually good nail growth. The parents of the 3 babies with type IIB OI were not asked about nail growth. The explanation for this unusual subjective phenomenon is unclear and does not appear to have been noted previously.

6.7.12 Other anomalies and problems

Types IIB, III and I OI

No anomalies other than those already mentioned were reported.

Type III/IV sporadic OI

Case 12, a 14.67 year old female had become hyperpyrexia during several general anaesthetics and this was to be investigated with a muscle biopsy.

Case 50, a 7.8 year old female, had asthma.

Case 18, a female, had congenital torticollis which resolved spontaneously.

Case 20, a female aged 2.5 years, had an operation for pyloric stenosis at 2 months of age and subsequently developed an incisional hernia in the scar.

Case 21, a 16.9 year old male, had an operation for torsion of the testis at 14 years.

Case 42, a 9.8 year old female, had a urinary tract infection but a recent intravenous pyelogram was normal.

Case 44, a 5.6 year old female, had primary tuberculosis during her first year.

Case 60, a 23.8 year old male, complained of pains in his neck, tingling in the hands and a weak grip.

Case 61, a 14.2 year old male of normal intelligence was found to have hydrocephalus, diagnosed on a CT brain scan at 8 years.

Case 66, a 6.8 year old male, suffered from recurrent boils.

Case 16 (a 23.25 year old female), case 41 (a 27.1 year old

female, case 60 (see above) and case 17 (a 10 1/2 year old male) were obese.

Discussion

A wide variety of diseases have been described in association with OI, many of them probably fortuitously (Smith et al., 1983). Malignant hyperthermia at surgery was described in 2 patients by Bergstrom (1977); whether this has any relationship to the excessive sweating noted in OI (see section 6.7.6.3) is unknown. Pyloric stenosis in a 7 week old girl with congenitally manifesting OI was described by Crooks (1932).

Symptoms of backache and leg pains, possibly resulting from nerve root compression are of 'frequent occurrence', according to McKusick (1972), but actual neurologic deficits are less frequent. Nevertheless, the symptoms noted in case 60 (neck pain, paraesthesiae in the hands and a weak grip) should prompt a search for nerve root compression, spinal cord compression at the foramen magnum, impingement of the odontoid process on the brain stem or hydrocephalus (McKusick, 1972).

Hydrocephalus has been reported in severe OI, albeit uncommonly (McKusick, 1972). Pozo et al. (1984) described obstructive hydrocephalus with raised intracranial pressure associated with basilar impression. In a study of 10 patients, Tsipouras et al. (1986) found that all 4 patients with mild type I OI had normal computed tomographic (CT) brain scans, although 3 were

macrocephalic. In the same study, all 6 patients with severe type III OI had cortical atrophy with diffuse ventricular dilatation on CT scan, but 'no evidence of hydrocephalus'. Three of these patients were macrocephalic.

The cause of recurrent boils in case 66 is not known. Immunological defects do not seem to be a part of the OI spectrum. Congenital deficiency of the second component of complement (C2) in a healthy woman and 2 of her relatives with OI was associated with abnormal platelet function, but not with immune deficiency (Tobelem et al., 1974) and may be fortuitously associated with OI.

As noted by McKusick (1972) the inactivity of patients with OI can lead to obesity. This of course compounds the immobility and should be avoided if possible. Some of the patients in this study found swimming to be a sport in which they could safely and happily participate.

The other associated disorders noted above (asthma, torsion of the testis, urinary infection and tuberculosis) are likely to be coincidental.

6.8 Concluding remarks: comparison of types III/IV OI with types III and I

The clinical manifestations in the types III and III/IV OI groups were remarkably similar, with no significant differences between

the two groups for sex ratios, obstetric details, birth measurements, fracture numbers at or after birth, death rate, deformity, short stature, visual function, strabismus, bruising, epistaxes, constipation or herniae. Relatively more type III patients had skin laxity or hearing loss, and relatively more type III/IV patients had joint dislocations but the numbers were not statistically significant. For joint laxity and dentinogenesis imperfecta, relatively more type III/IV than type III patients were affected (to a significant level) but the numbers in the type III group may have been under-represented, as discussed in the relevant sections. The only clear difference between the two groups was that the sclerae of patients with type III OI were more likely to fade to a pale blue or normal colour. This, however, is unlikely to be a reliable distinguishing sign between recessive and dominantly caused OI in an individual case.

Patients with type I OI had much milder clinical manifestations than the type III/IV group, which is expected, given that they were selected out from the total group because of milder disease, associated with blue sclerae. They generally had fewer fractures at birth or afterwards, and had less deformity, greater height and more mobility. Other parameters affected the type I group to a similar degree as the type III/IV group, such as visual dysfunction, strabismus, joint laxity, epistaxis, sweating, dentinogenesis imperfecta, constipation and herniae. Relatively more patients with type I OI reported joint dislocations or hearing loss, and relatively more patients with type III/IV OI had lax skin, but not to a significant level. The patients with

type I OI reported significantly more bruising than those with type III/IV OI.

CHAPTER 7

POSTNATAL RADIOLOGICAL MANIFESTATIONS

7.1 Introduction

Some of the radiographic appearances at birth which distinguished 2 type I OI patients, 38 perinatal survivors with severe OI (which comprised 3 with type II, 4 with type III and 31 with type III/IV OI) and 60 patients with perinatally lethal disease were described in sections 4.1 and 4.2.

In this chapter, radiological changes which occurred postnatally in patients who survived the perinatal period are described. Some additional features at birth are also discussed, in order to highlight the postnatal changes. As in chapter 6, each manifestation is presented and discussed as a unit.

The purpose in presenting these radiological manifestations is to confirm the diagnosis of OI and, as in the clinical analyses in chapter 6, to see if the type III 'recessive' cases are different from the type III/IV sporadic cases. In addition, as with the clinical data, it was thought to be important to document radiological findings in order to expand the understanding of the various subgroups to which the recurrence risk figures presented in chapter 5 apply.

Various radiographs taken after the perinatal period were

available for 10 patients with type I OI, none of the 3 perinatal survivors with type IIB, 9 with type III and 66 with sporadic type III/IV OI. These are documented in appendix 7.1. Ideally, it would have been useful to compare full skeletal surveys at various ages between patients and for individual patients, but as might be expected, availability of films was inconstant.

Not included in appendix 7.1 are the cases in which no radiograph or neonatal radiographs only were available (table 7.1). In the former, reports of radiographs taken previously confirmed the diagnosis of OI.

7.2 General observations

All patients showed osteoporosis with thin cortices of bones. These changes in general were milder in the patients with type I OI and more marked in the other varieties. In many patients with type III and III/IV sporadic OI, osteoporosis was severe. Progression of deformity tended to occur in all cases, but to a much greater degree in the patients with type III and III/IV OI than in those with type I. Many radiographs showed evidence of acute or healing fractures. No clear-cut distinguishing features between the patients with type III and III/IV sporadic OI were observed. Many patients had undergone numerous radiographs. In some cases of type III or III/IV OI the X-ray packet contained over 200 films. The taking of unnecessary radiographs in these patients should be avoided.

Table 7.1

LIST OF PATIENTS WITH NO RADIOGRAPHS AVAILABLE

Type III/IV OI (n=12)

Cases 27, 36, 43, 48, 49, 56, 57, 61*, 74, 75, 79, 83

Type III OI (n=4)

Cases 92, 93, 94, 101

Type I OI (n=1)

Case 116

LIST OF PATIENTS WITH NEONATAL RADIOGRAPHS ONLY AVAILABLE

Type III/IV OI (n=9)

Cases 9, 18, 28, 32**, 33, 53, 59, 70, 86

Type III (n=3)

Cases 91, 96

Type I (n=0)

* A radiograph of the teeth only was available.

** A radiograph of the arm at 3 months was also available.

Types III and III/IV OI

The femora, which were modelled at birth, often became poorly modelled, broad and rectangular by as early as 4 weeks postnatally (this was discussed in section 4.1.2.1).

After this broad phase, the femora usually became increasingly slender, resulting in some cases in an extremely thin bone (figure 7.1). In others, the femora remained thickened, poorly modelled and 'shapeless'. Some patients appeared not to go through the 'broad femora' phase and the bone simply became progressively thinner.

Bowing and angulation deformities could affect any of the long bones which often appeared abnormally shortened (figures 7.2 and 7.3). In many cases, the fibulae became extremely thin and wavy, like a ribbon (figure 7.1). A characteristic deformity of the tibiae was anterior bowing (figure 7.4).

In some patients, osteoporosis was so severe as to produce a 'lacey' appearance of the diaphyses of the long bones. Many patients developed a progressive cystic 'bubbly' appearance of the epiphyses, especially of the femora, upper tibiae and humeri (appendix 7.1 and table 7.2). A globular shape of the affected epiphysis developed (figure 7.1 and 7.3). The earliest age at which cystic epiphyses were noted was at 2 1/2 years (case 10).



Figure 7.1

Case 23 (type III/IV OI) aged 13.2 yr, legs (antero-posterior (AP) view).

Note severe osteoporosis; very slender bones especially the fibulae which are wavy especially on the left; 'popcorn' deformities of the epiphyses of the femora and tibiae at the knee; surgical rods in both femora which are surrounded by only a thin rim of cortex. On the right, the lower end of the rod has come out of the femur.



Figure 7.2

Case 31 (type III/IV OI), aged 1.6 yr, babygram (AP).

Note osteoporosis; deformities of femora and right tibia; fracture of right femur; platyspondyly and scoliosis, and short broad chest.



Figure 7.3

Case 31 (type III/IV OI), aged 6.3 yr, legs (AP).

Note severe osteoporosis and increased deformity of long bones compared to figure 7.2. There are 'popcorn' deformities of the epiphyses at the knee and ankle (best seen at lower end of the left femur and tibiae). The left tibia is fractured.



Figure 7.4

Case 31 (type III/IV OI), aged 6.8 yr, left lower leg (lateral (lat.) view).

Note severe osteoporosis, marked anterior bowing of tibia and fibula with non-union of the fracture of the tibia seen in figure 7.3.

Table 7.2

CYSTIC EPIPHYSES (NO. CASES)

Age group* (yr)	Type III/IV OI		Type III OI		Type I OI	
	Present	Absent	Present	Absent	Present	Absent
≤ 2.5	1**	9	-	2	-	1
> 2.5 - ≤5	7	8	-	1	-	1
> 5 - ≤10	5	7	2	-	-	2
> 10 - ≤15	12	5	-	-	-	2
> 15 - ≤20	3	4	-	-	-	2
> 20	-	-	1	1	-	2

* Present: earliest age at which sign present; Absent: latest age at which sign absent (this applies to tables 7.1 - 7.8).

Table 7.3

DOWNWARD ANGULATION OF THE RIBS AT THEIR COSTOVERTEBRAL JUNCTION (NO. CASES)

Age group (yr)	Type III/IV IO		Type III OI		Type I OI	
	Present	Absent	Present	Absent	Present	Absent
≤ 2.5	1*	15**	-	1	-	2
> 2.5 - ≤5	4	5	1	1	-	1
> 5 - ≤10	3	2	-	1	1	-
> 10 - ≤15	3	6	-	1	-	-
> 15 - ≤20	2	4	1	-	-	-
> 20	2	2	-	1	-	1

* In addition, case 10 showed rib angulation at birth.

** Does not include radiographs taken at birth.

From table 7.2, it can be calculated that 3 of 5 patients (60%) with type III OI and 28 of 52 cases (54%) with type III/IV OI over 2.5 years of age showed cystic epiphyses. (The 9 type III/IV cases in the ≤ 2.5 year category with no cystic epiphyses were all below 2.5 years, but the one with cystic epiphyses was aged 2.5 years). In the type III/IV group, there was no association between cystic epiphyses and scleral colour (considering two groups of normal or pale blue sclerae and moderate or dark blue sclerae) using 2 x 2 contingency χ^2 tables (p 0.7 - 0.9) (see appendix 7.2 for details). Cystic epiphyses could be present at one site but not another in one patient at the same age. For example, cystic epiphyses were present in the arm but not the knee in case 15, vice versa for case 60 and case 62 had cystic epiphyses at the left, but not the right, knee and ankle. In case 67, the cystic change was present at 17 years at the knee but had disappeared by the age of 35 years.

In many patients, surgical rods had been inserted into long bones. Occasionally, radiographs showed that the rod had penetrated the ends or cortex of the bone or that the rod almost appeared wider than bone so that only a thin rim of cortex surrounded the rod (figure 7.1).

Type I OI

Prominent vertical trabecular lines associated with osteoporosis were common (figure 7.5) and have been described before (Bauze et al., 1975). Abnormalities of modelling and deformity were mild in this group compared to the severe forms of OI. In case 109, who had mild femoral bowing at birth (figure 4.1), the deformity actually appeared to decrease during the first year, but increased thereafter, perhaps because she began to stand at one year of age. The long bones of the legs often became slender but not to the degree seen in types III and III/IV OI. No patient (even one aged 39.6 years) demonstrated the cystic epiphyseal changes described above.

Discussion

Fairbank (1951) described 3 types of OI on radiological grounds: thick bone, slender bone and cystic bone. Many subsequent reports were described in terms of thick or thin bones. The author later recognised that the 3 types may progress from one to the other (Wynne-Davies and Fairbank, 1976) and certainly this was true in cases in the present series. As described in section 4.1.2.3, the classification of patients into Sillence types should be done within the first week of life because of the postnatal evolution of bone morphology. A true cystic-bone type of OI, in which the entire long bones, and sometimes the pelvis, appear cystic (Fairbank, 1948) is believed by Smith et al. (1983) to be an extremely rare form of OI; it should not be confused



Figure 7.5

Case 118 (type I OI), aged 5.2 yr, legs (AP).

Note osteoporosis (not as marked as in figures 7.1 - 7.4), prominent trabecula lines especially of left upper tibia, mild deformity of tibiae and fibulae.

with the cystic or foamy appearance of the epiphyses noted above which was labelled as 'popcorn bone' by Goldman et al. (1980). This is believed to be due to fracturing of the epiphyseal growth plate and is common in severe but not in mild OI (Goldman et al., 1980; Smith et al., 1983), as noted here. The finding in the present study that patients with or without cystic epiphyses were equally likely to have blue or normal/pale blue sclerae suggests that the presence of cystic epiphyses does not help to distinguish cases with recessive inheritance.

7.4 Chest

7.4.1 Chest - general

Types III and III/IV OI

At birth, the chest was usually of normal shape. The ribs were often slender with discrete 'beads' in 1 out of 32 cases (case 90), as described in section 4.1.2.1.

Marked progressive deformity of the rib cage was the rule, often resulting in spectacular distortion of the chest (figures 7.6a and b, 7.7). Frequently, this was associated with and probably secondary to advancing scoliosis or kyphosis. The ribs became more slender with time. In infancy, the chest tended to be short in a vertical direction but relatively broad from side-to-side, as seen on antero-posterior radiographs. This appearance progressed so that the chest became very squat and the intra-



Figure 7.6(a)

Case 6 (type III/IV OI), aged 5 yr, trunk (AP).

Note scoliosis and platyspondyly; distortion of ribs and chest; protrusio acetabulae.

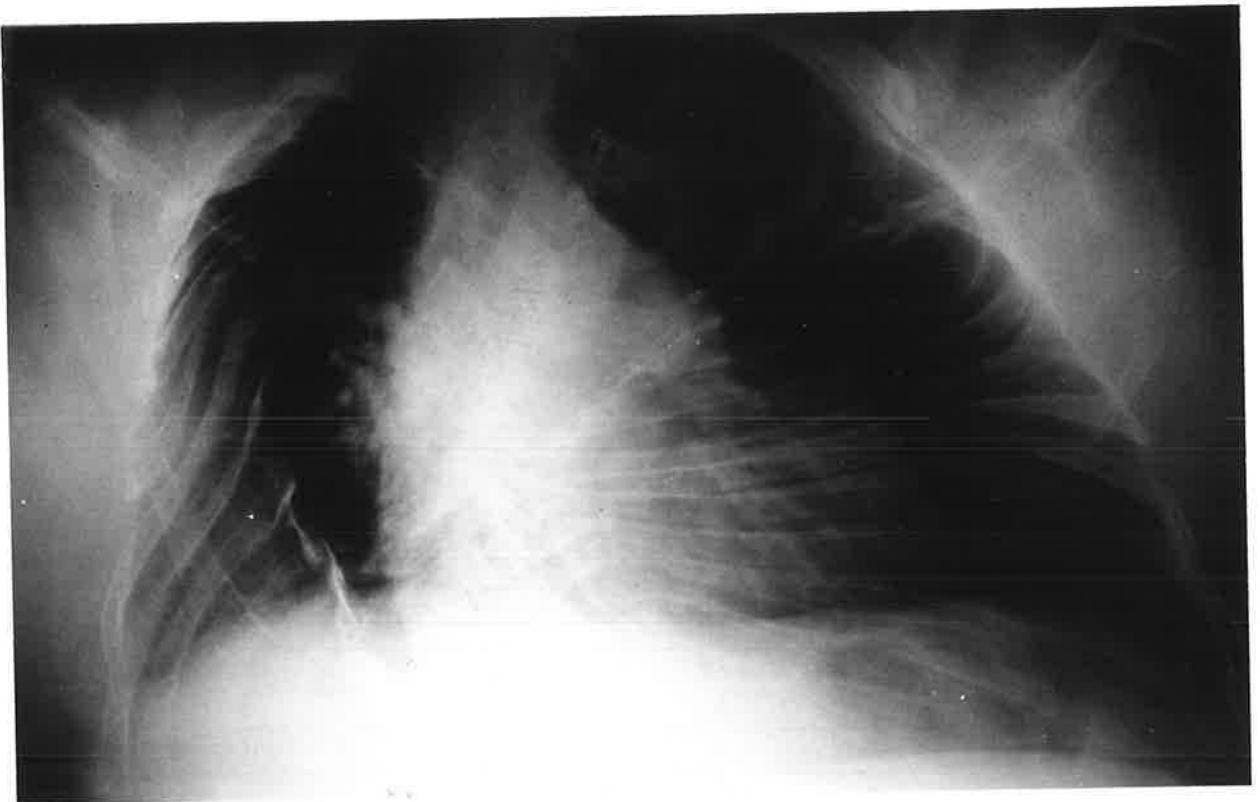


Figure 7.6(b)

Case 6, aged 22 yr, chest (AP).

Note chest deformity has progressed.



Figure 7.7

Case 12 (type III/IV OI), aged 4.6 yr, trunk (AP).

Note scoliosis and platyspondyly; small chest; protrusio acetabulae; deformed left femur (the right femur is not visible on the photograph).

thoracic volume clearly became severely compromised in many cases.

Type I OI

In the 5 cases of type I new mutation OI with post-natal radiographs available, chest deformity was mild or absent. In 4 cases (109, 111, 118 and 119) the ribs were slender. Calcification of costal cartilages had occurred in one 33 year old woman (case 117).

Discussion

The chest deformities in OI were discussed in section 6.7.2.2. The author could find no other reference to costal cartilage calcification in OI and therefore assumes that the finding was fortuitous.

7.4.2 Downward angulation of the ribs

All chest films were specifically examined for downward angulation of the ribs at their posterior ends, that is, at their costo-vertebral junctions (figure 7.8). This was done following Versfeld and his colleagues' suggestion that the sign may be indicative of recessive disease (Versfeld et al., 1985). Only one patient (case 10, with type III/IV sporadic OI) showed this feature at birth, albeit only on the left side.

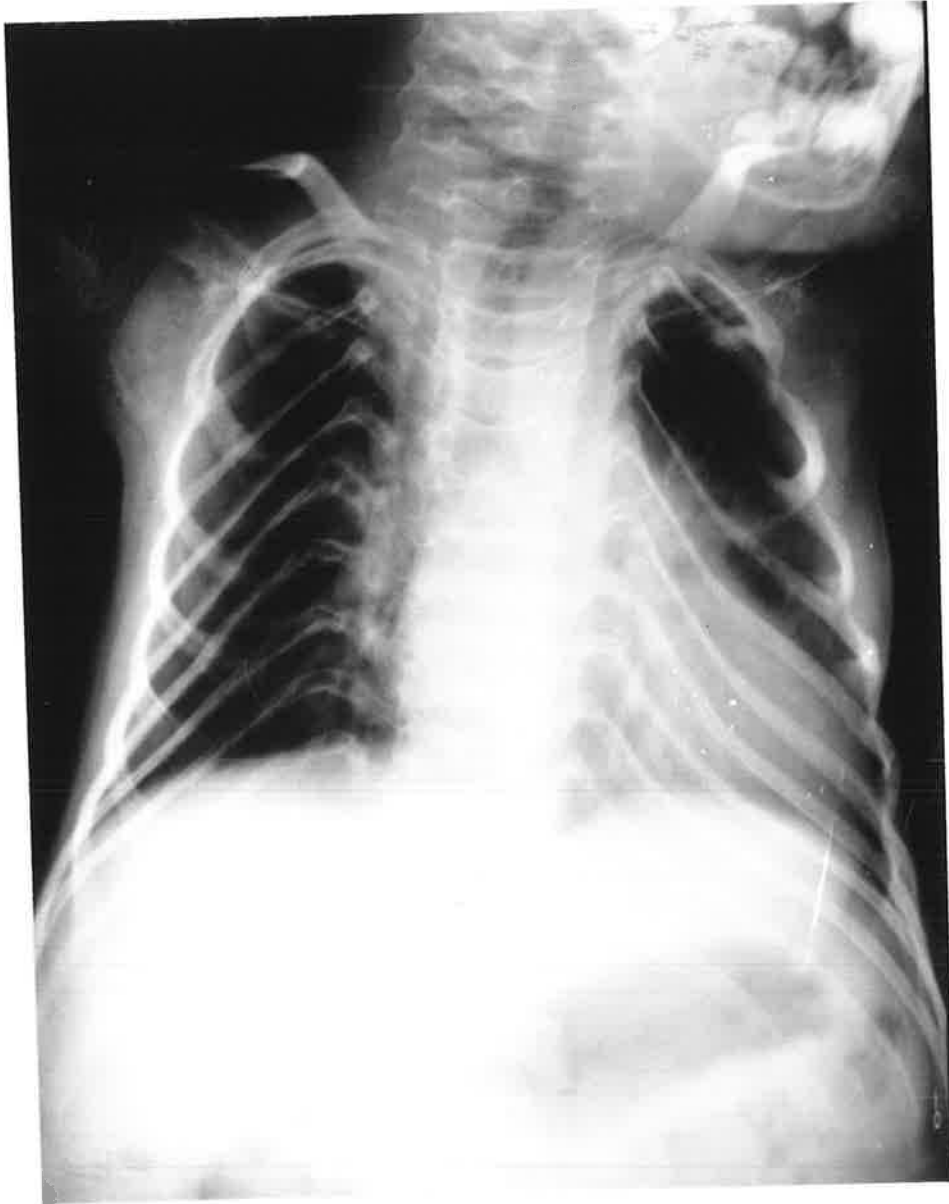


Figure 7.8

Case 85 (type III/IV OI), aged 3 yr, chest (AP).

Note downward angulation of the ribs at their costovertebral junctions; platyspondyly.

In 7 patients with type III OI for whom chest radiographs were available postnatally, 2 (29%) showed posterior rib angulation (appendix 7.1, and table 7.3 (see page 353)). For one of these (case 98), the chest radiograph of the affected sib (case 99) was available but it did not show the feature.

Of the 49 patients with type III/IV OI with postnatal chest radiographs available, 15 (31%) showed posterior rib angulation. This was bilateral in 11, affected the right side only in 2 (cases 17 and 44), the left in one (case 67), and affected only some ribs randomly in one (case 22). All but 3 of the 15 also had spinal deformity. Rib angulation was associated with scoliosis in 12 of the 15 cases and 4 of 6 cases with lateral views of the spine had kyphosis (appendix 7.1). Parallel development of scoliosis and rib angulation was demonstrated by case 25 who had neither defect at 2 months, but both abnormalities were seen at 2.7 years. On the other hand, other patients with severe scoliosis or kyphosis and chest deformity did not have posterior rib angulation. The phenomenon was more likely to be found after 2.5 years (table 7.3, see page 353). If cases under that age are excluded, 2 of 6 patients (30%) with type III OI and 14 of 33 (42%) with type III/IV were affected. In the type III/IV group, there was no association between scleral colour and rib angulation, for all cases (p 0.5 - 0.7) or cases over 2.5 years (p 0.95 - 0.99, see appendix 7.2).

One patient (case 118) of 5 with type I OI whose chest radiograph was available showed downward angulation of the ribs posteriorly

(appendix 7.1 and table 7.3). The patient was short (-6.2 SD) but had blue sclerae and mild limb deformities without kyphoscoliosis. It is perhaps debateable as to whether she represents a case with type I OI and rib angulation or that the latter sign indicates that she has type III/IV OI.

It seems reasonable to conclude that the presence of posterior rib angulation does not reliably predict recessively inherited disease, since the distribution of scleral colour in the type III/IV OI cases was similar whether or not rib angulation was present and, more importantly, discordance for the sign occurred in a sib pair.

7.5 Pelvis

The commonest deformity of the pelvis was protrusio acetabulae (PA) (sinking in of the floor of the acetabulum with protrusion of the femoral head through it) leading to a triradiate shape of the pelvis (figures 7.6 and 7.7).

Types III and III/IV OI

Of 5 patients with type III OI whose postnatal radiographs of the pelvis were available, all showed PA, severely in 4 cases, as early as 2 years in case 95 (appendix 7.1 and table 7.4). Of 53 cases of type III/IV sporadic OI, 43 (81%) had PA and 10 did not. Six of the latter were aged under 18 months. The earliest age at which PA was seen was at 4 months (case 78). In the type III/IV

TABLE 7.4

PROTRUSIO ACETABULAE (NO. CASES)

Age group (yr)	Type III/IV OI		Type III OI		Type I OI	
	Present	Absent	Present	Absent	Present	Absent
≤ 2.5	8	6	1	-	-	1
> 2.5 - ≤ 5	15	2	2	-	-	3
> 5 - ≤ 10	7	2	2	-	1	-
> 10 - ≤ 15	8	-	-	-	-	-
> 15 - ≤ 20	5	-	-	-	-	-
> 20	-	-	-	-	-	-

group, there was no association of scleral colour with PA (p 0.7 - 0.9, see appendix 7.2). In many cases the degree of PA was relatively mild during the first 5 years, but thereafter the deformity tended to progress, often asymmetrically, leading to a grossly misshapen pelvis by the second decade (figure 7.9).

Type I OI

By contrast, of 4 patients with type I OI, 3 had no pelvic deformity at 3.6 and 11 years respectively, and one (case 118) showed mild protrusio acetabulae at 9.2 years which was not present in the same patient at 3 years.

Discussion

Protrusio acetabulae is very common in types III and III/IV OI. It has been attributed to microtrabecular fractures of the acetabular roof by Maroteaux and Lamy (1965) but osteoporosis must also play a role. Undoubtedly, the resulting pelvic deformity contributes to difficulty in walking in severe OI.

7.6 Spine

7.6.1 Kyphosis platyspondyly, scoliosis and other spinal deformities

Kyphosis and platyspondyly (flattening of the vertebral bodies) can be documented on lateral radiographs of the spine, whereas



Figure 7.9

Case 99 (type III OI), aged 23 yr, trunk and femora (AP).

Note marked protrusio acetabulae; severe scoliosis; extremely short femora.

scoliosis is appreciated on antero-posterior (AP) views. No patient demonstrated kyphosis or scoliosis at birth, but some had platyspondyly on lateral radiographs. These were 3 cases (90, 91 and 96) out of 6 (cases 106, 107 and 108) with type III OI and 2 (cases 53 and 72) of 8 (cases 3, 11, 20, 32 and 63) with type III/IV OI. Two of the cases (96 and 72) had platyspondyly of one vertebral body only, whereas it affected most vertebral bodies in the other cases.

Type III and III/IV OI

Lateral views of the spine taken postnatally were available for 17 patients with type III/IV OI and one with type III. All 2 demonstrated platyspondyly which tended to progress, producing a so-called 'codfish' appearance of the vertebral bodies (figure 7.10). The patient with type III OI showed no kyphosis at 4.6 years (case 102). Eleven of the 17 patients with type III/IV OI had kyphosis, the youngest (case 72) being 2 months old (appendix 7.1 and table 7.5). The kyphosis affected the thoraco-lumbar spine in 9 cases and the thoracic spine only in 2. Those with no kyphosis were not necessarily younger than those with it (table 7.5), but the sample is small. In the type III/IV group, there was no association of kyphosis with scleral colour ($p > 0.99$, see appendix 7.2).

AP views of the spine taken postnatally were available for 47 patients with type III/IV OI and 7 with type III OI. Of the former, 35 (75%) showed scoliosis (figures 7.2, 7.6, 7.7,

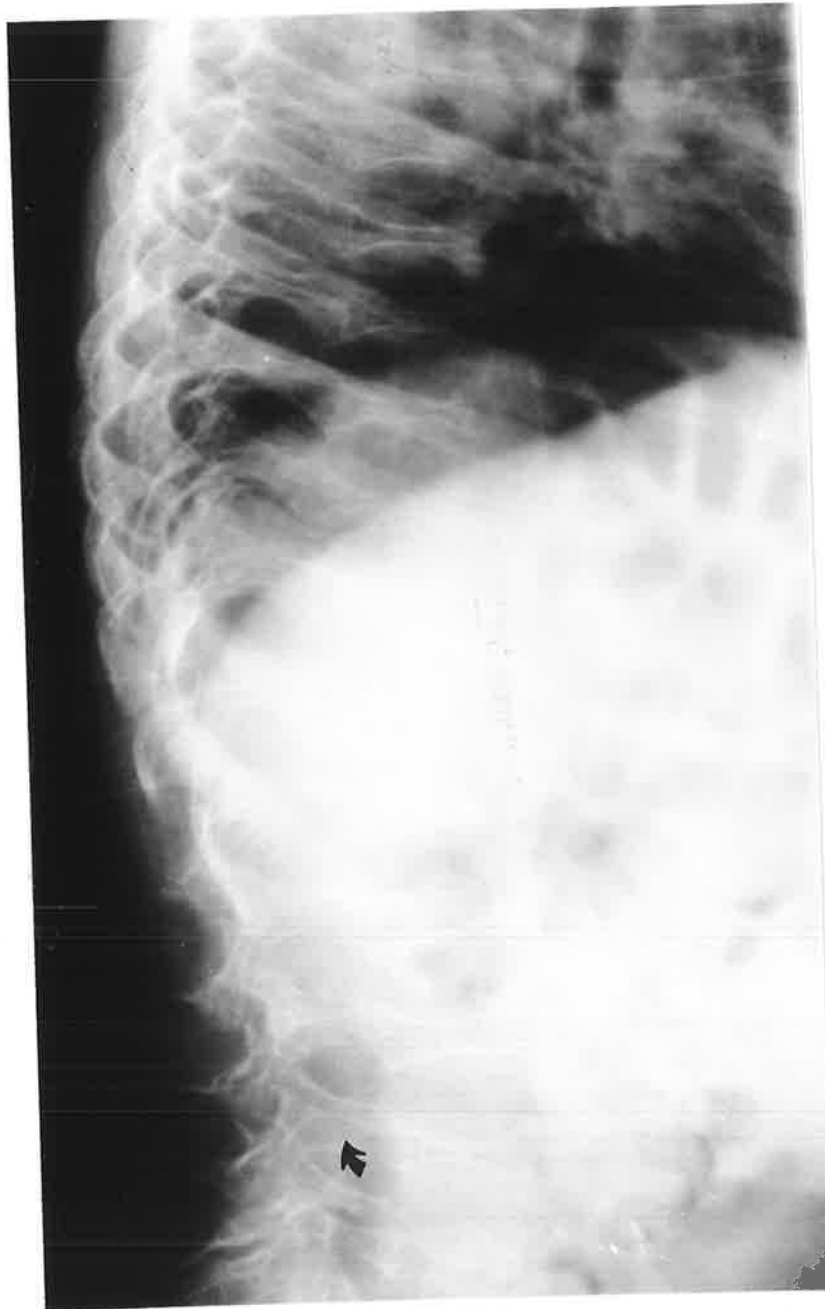


Figure 7.10

Case 82 (type III/IV OI), aged 6.6 yr, thoraco-lumbar spine (lat.).

Note severe platyspondyly producing 'codfish' shaped vertebral bodies; the pedicles appear unusually long, especially in the lumbar region (arrow).

TABLE 7.5

KYPHOSIS PRESENT ON RADIOLOGICAL EXAMINATION (NO. CASES)

Age group (yr)	Type III/IV OI		Type III OI		Type I OI	
	Present	Absent	Present	Absent	Present	Absent
≤ 2.5	5	2	-	-	1	-
> 2.5 - ≤ 5	1	-	-	1	-	-
> 5 - ≤ 10	3	3	-	-	-	-
> 10 - ≤ 15	1	1	-	-	-	-
> 15 - ≤ 20	1	-	-	-	-	-
> 20	-	-	-	-	-	1

appendix 7.1 and table 7.6). The youngest was 4 months (case 87) and one third were aged 5 years or less. Of the 12 who did not show scoliosis, 10 were under 16 months and the oldest was 4 years. There was no association between presence of scoliosis and scleral colour (p 0.5 - 0.7, see appendix 7.2). AP spine views were available for 7 patients with type III OI, of whom 4 (aged 2 to 16 years) had scoliosis. In the other 3, the radiographs were taken at or under 4.6 years. Scoliosis tended to be progressive and ultimately could be severe in the type III/IV and III groups.

Although platyspondyly is best appreciated on lateral views, it was so pronounced as to be obvious on the AP view in all but 3 of the 47 type III/IV cases and all of the type III cases (figures 7.2, 7.6a, 7.7 and appendix 7.1).

Other spinal abnormalities in patients with type III/IV OI included subluxation of the vertebral body of C2 on C3 in case 19 at age 7.8 years; L5-S1 spondylolysis in case 35 at age 8 years followed by development of an angulated sacrum by 13 years; a curved sacrum in case 22 at 7.8 years and a pronounced lumbar lordosis in cases 30, 40 and 58 at ages 8.5, 17.8 and 18.1 years, respectively. Cases 30 and 40 also had an angulated sacrum.

Type I OI

Postnatal spine radiographs of 4 patients were available. One case (109) showed no abnormalities on AP views at 10 months.

Table 7.6

SCOLIOSIS PRESENT ON RADIOLOGICAL EXAMINATION (NO. CASES)

Age group (yr)	Type III/IV OI		Type III OI		Type I OI	
	Present	Absent	Present	Absent	Present	Absent
≤ 2.5	6	10	-	2	1	1
> 2.5 - ≤ 5	6	2	-	1	-	-
> 5 - ≤ 10	6	-	1	-	-	1
> 10 - ≤ 15	10	-	1	-	-	-
> 15 - ≤ 20	5	-	1	-	-	-
> 20	2	-	1	-	1	-

Table 7.7

SCOLIOSIS OR KYPHOSIS PRESENT ON CLINICAL OR RADIOLOGICAL EXAMINATION (NO. CASES)*

Type III/IV OI	Type III OI	Type I OI
56/79 (71%)	8/10 (80%)	5/11 (46%)

* A combination of the data in tables 6.20, 7.6 and 7.5. Each case is counted once only.

Patient 117 at age 33 years showed no kyphosis or platyspondyly, but some scoliosis. Some lumbar vertebral bodies had collapsed. In addition, there was a fracture through the laminae of C2, and also these laminae had fused to those of C3. It was unclear as to whether the latter was a congenital or acquired anomaly. Case 118 showed mild platyspondyly only at age 5.2 years. The remaining patient (no. 119) at age 1 year, showed mild thoracolumbar kyphosis and platyspondyly on the lateral view and mild scoliosis on the AP film.

Discussion

The incidence of kyphosis and scoliosis as judged from clinical examination was presented and discussed in section 6.7.2.2. Although the presence of these deformities is more accurately determined radiologically, to judge their incidence from radiographs in the present series is obviously biased by the availability of appropriate films. On the other hand, patients with spinal deformities would have been more likely to have had radiographs of the spine taken. In addition, it should be noted that a comparison of appendix 6.1 under the heading 'spine' with appendix 7.1 under the headings 'kyphosis' and 'scoliosis' reveals some inconsistencies. In some cases, these can be attributed to the fact that the clinical examination of the spine (appendix 6.1) took place after the date of the radiographs (appendix 7.1), so that some or more deformity could have developed in the intervening period. This applies to cases 8, 20, 102 and 104 who had no deformity on early radiographs, but

later had it clinically and cases 47, 52 and 68 whose deformity had increased. In cases 4, 72 and 73, mild kyphosis was overlooked clinically; alternatively the kyphosis noted on the radiograph was positional. Case 78 replied by questionnaire and reported no spinal curvature, but mild scoliosis was seen on the radiograph. In only one case (22) was there an obvious error in clinical assessment; clinically, no spinal deformity was noted at 26.2 years, but mild kyphoscoliosis was present on the radiograph at 7.8 years, and it seems unlikely that this would have corrected itself. In a few other cases, there was a minor discrepancy in assigning the severity of a curvature. None of these inconsistencies was corrected for in table 6.20 which refers to clinical findings only.

In table 7.7 (see page 372) is presented a combination of the data in tables 6.20, 7.5 and 7.6 (derived from appendices 6.1 and 7.1; no case is counted more than once). This gives an estimate of spinal deformity found on both clinical or radiological grounds and is likely to be a more accurate representation of its true frequency. Spinal deformity affected 71% of patients with type III/IV OI, 80% with type III OI and 46% with type I.

Platyspondyly is a well known accompaniment of osteoporosis and results in the biconcave deformity known as 'codfish' or 'hour glass' vertebrae produced by the pressure of the normally elastic nucleus pulposus on the abnormally soft bone of the vertebral body (McKusick, 1972). Platyspondyly is common in both mild OI (Quisling et al., 1979) and severe forms (Smith et al., 1983).

The sacral deformities noted in the patients with type III/IV OI have received little mention previously, as have subluxation or spondylolysis of vertebral bodies. Smith et al. (1983) cite a case of mild OI who developed spondylolisthesis secondary to stress fractures of the pars interarticularis. Spondylolysis and spondylolisthesis could give rise to serious neurological complications, especially in the cervical region.

7.6.2 Elongation of the pedicles

It has been suggested by Versfeld and his colleagues (1985) that elongation of the pedicles of the vertebrae may be a sign of type III (recessive) OI. We examined lateral spine radiographs of the patients for this sign. The pedicles were of normal length in all cases with available lateral spine radiographs taken at birth (see above). Long slender pedicles were seen postnatally in one of 2 patients with type I OI and in 9 of 15 patients with sporadic type III/IV OI, as early as 10 months of age (figure 7.10, appendix 7.1 and table 7.8). (Cervical spine films only were available in 2 other cases (19 and 47) and were normal). The sign was mainly confined to the lumbar vertebrae as noted previously (Versfeld et al., 1985). In one case (39) dorsal vertebrae were also affected. In all cases with long pedicles, the corresponding vertebral bodies were abnormally flattened with a concave scalloped appearance of the posterior edge of the vertebral bodies. It was our impression that this scalloped edge contributed to the long appearance of the pedicles (figure 7.11).

TABLE 7.8

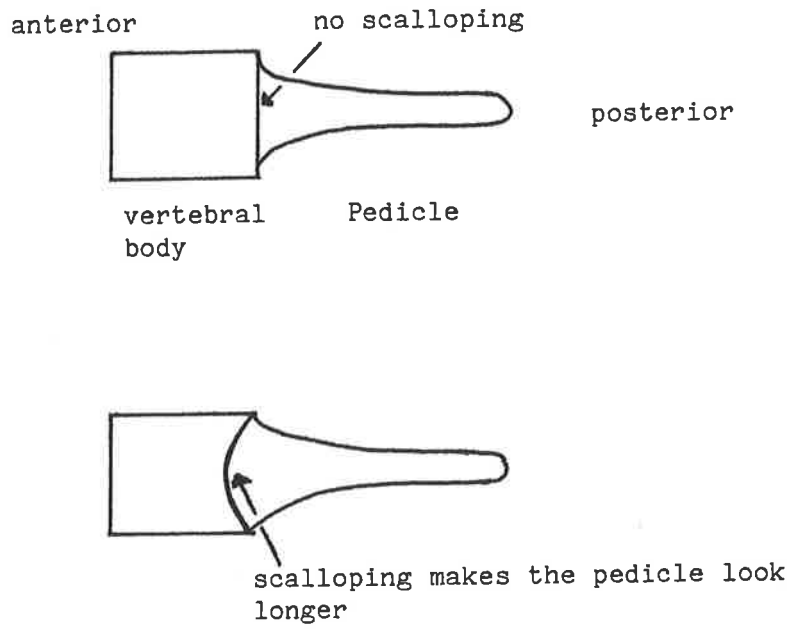
ELONGATED PEDICLES OF THE SPINE (NO. CASES)

Age group (yr)	Type III/IV OI		Type III OI		TYPE I OI	
	Present	Absent	Present	Absent	Present	Absent
≤ 2.5	4	3	-	-	1	-
> 2.5 - ≤ 5	1	-	-	-	-	-
> 5 - ≤ 10	3	1	-	-	-	-
> 10 - ≤ 15	1	1	-	-	-	-
> 15 - ≤ 20	-	1	-	-	-	-
> 20	-	-	-	-	-	1

No patient with type III had a radiograph suitable for evaluation of the pedicles, unfortunately.

Figure 7.11

A diagram to show how scalloping of the posterior edge of the vertebral body enhances the impression of an elongated pedicle on a lateral radiograph of the spine.



In case 73 with long pedicles (at 13 months), a birth radiograph showing normal pedicles was available. Thus, it was possible to confirm that the sign had developed with time, suggesting that it was a deformity rather than a congenital malformation. In the type III/IV group there was no association of scleral colour with elongated pedicles (p 0.9 - 0.95, see appendix 7.2). Unfortunately, the type III OI group could not be evaluated for elongated pedicles; in only one case was a lateral view available but the pedicles were not clearly visible.

The patient with probable type I OI (case 119) and elongated pedicles was not seen by the author but was short (-4.03 SD) with deformities of the femora and mild kyphoscoliosis. Her sclerae were reportedly 'pale blue'. It could be argued that she should be classified as type III/IV OI.

Discussion

The data does not definitely rule out the possibility that the sign of long pedicles predicts recessively inherited OI. The author and her colleagues believe, however, that it seems unlikely given that the sign may occur in mild OI, that it probably develops as a secondary phenomenon and that it is not necessarily associated with pale blue sclerae.

7.7 Skull

Multiple Wormian bones (small irregular bones in the sutures

between the bones of the skull) were present in all cases whose skull radiographs at birth were available, including 2 patients with type I OI, 4 with type III and 27 with type III/IV OI (figure 7.12). Postnatal skull radiographs again revealed that all cases had Wormian bones (3 type III OI, 26 type III/IV and 1 type I OI case) except for one type I OI patient (case 117) who had no Wormian bones, at age 35 years.

At birth, the skull shape was usually normal, except in 2 type III/IV sporadic cases, of whom one (case 20) had an asymmetric skull shape and the other (case 32), who presented by the breech, had brachycephaly. Many patients gradually developed skull deformity with frontal bossing, temporal bulging and platybasia with an 'overhanging occiput' (figure 7.13a). Platybasia is present if the skull base is below a horizontal line drawn from the hard palate on a lateral view. Patients who spent much of their time in the supine position tended to develop brachycephaly (figure 7.13a). The following cases demonstrated postnatal skull deformity: 2 of 3 type III cases and all of 26 type III/IV sporadic cases, beginning as early as 6 months of age (appendix 7.1). The deformity progressed, often resulting in an extremely misshapen skull (figure 7.13a and b). In the type I OI cases, only two postnatal skull radiographs were available which showed brachycephaly at 20 months (case 111) and no deformity (case 117) at 35 years, respectively.

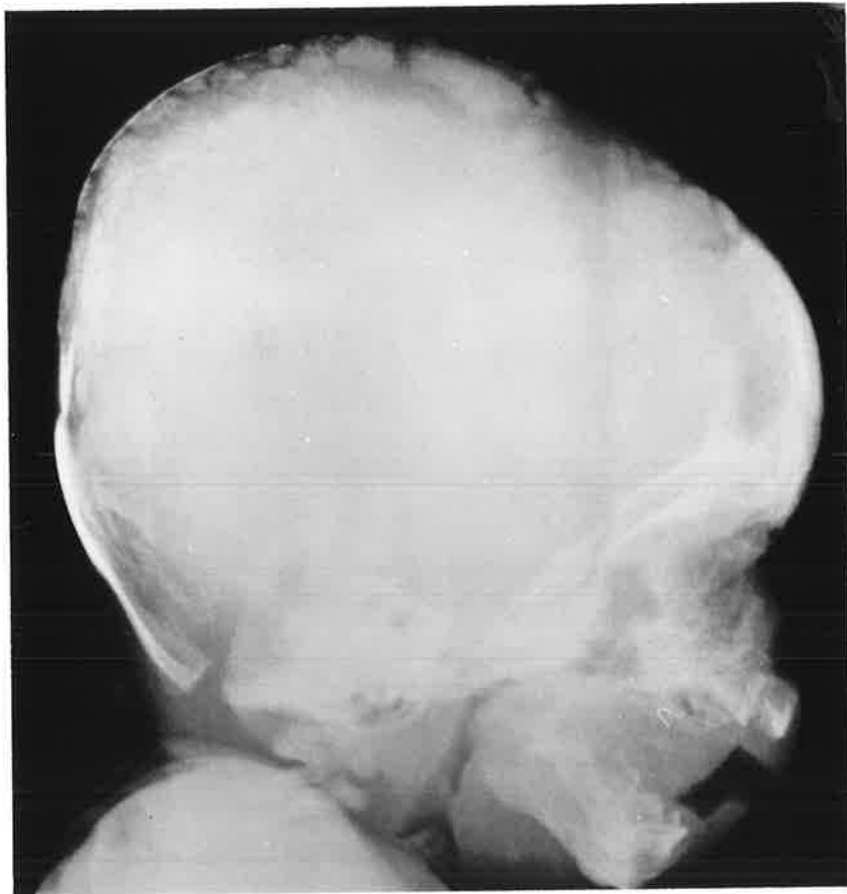


Figure 7.12

Case 32 (type III/IV OI), aged 5 days, skull (lat.).

Note multiple Wormian bones.



Figure 7.13(a)

Case 66 (type III/IV OI), aged 4.8 yr, skull (lat.).

Note platybasia, overhanging occiput and brachycephaly (the patient could not hold his head unsupported). Multiple Wormian bones were present but do not show well on the photograph.

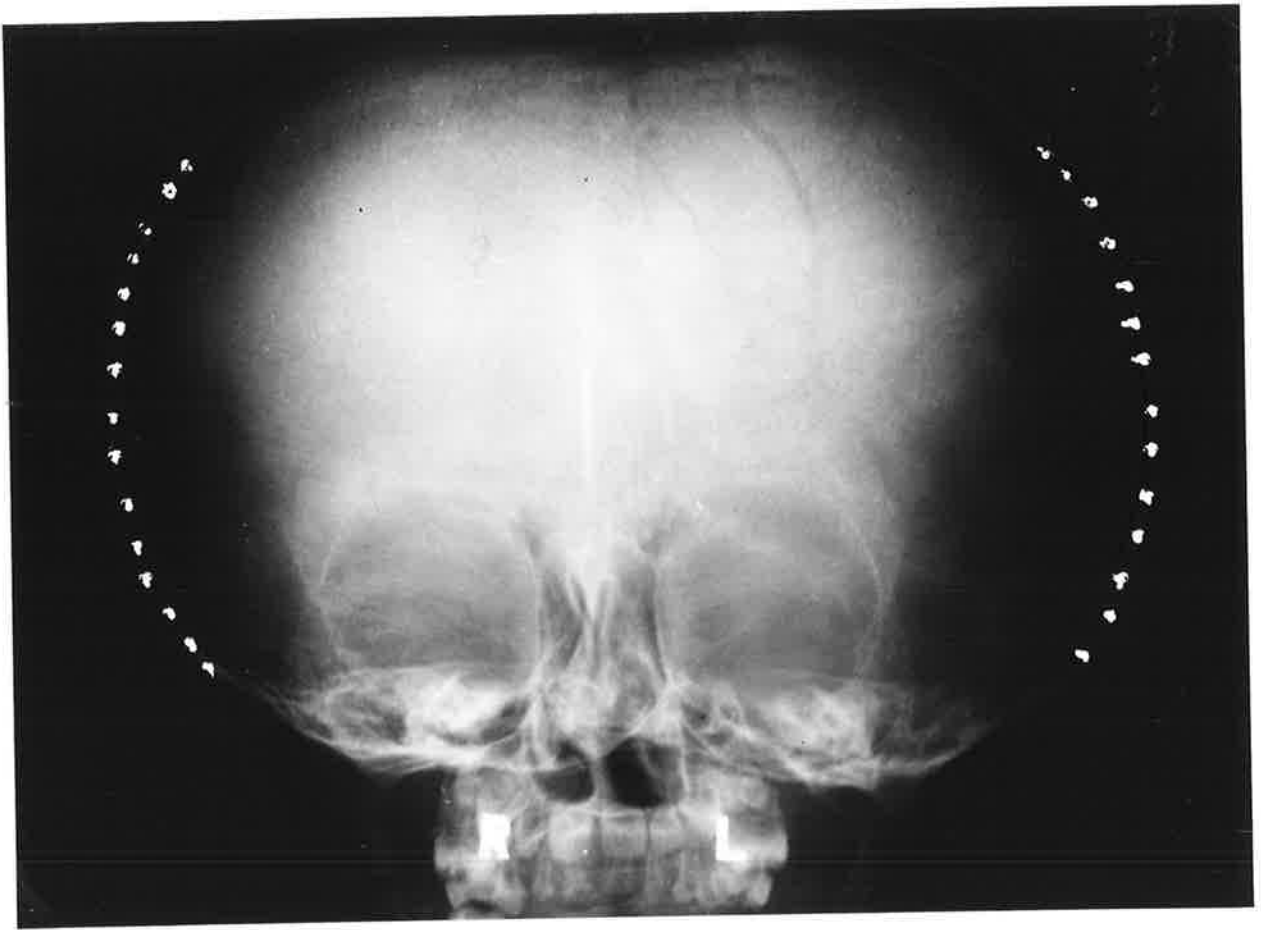


Figure 7.13(b)

Case 66 (type III/IV OI), aged 4.8 yr, skull (AP).

Note severe skull deformity resulting in a 'Tam-O-Shanter' shaped skull. The line has been drawn in to indicate the boundaries of the skull.

Discussion

Wormian bones, also known as Schaltknochen, intercalary and intrasutural bones, are named after the Dutch anatomist, Olaus Wormius who described them in 1643 (quoted in Cremin et al., 1982). Cremin et al. (1982) noted that although a few Wormian bones arranged in a linear fashion were common in the young child, none of 500 normal children aged from one month to 10 years had more than 10 Wormian bones, whereas all of 81 patients with unspecified forms of OI from birth to 70 years had more than 10 Wormian bones, each greater than 6 mm by 4 mm arranged in a mosaic (rather than a linear) pattern. Only one patient in the present series had no Wormian bones, a 35 year old female with type I OI. Smith et al. (1983) observed that the skull may be completely normal in mild OI.

Cremin et al. (1982) pointed out that Wormian bones are normal developmental structures but that those seen in OI are 'dysplastic' sutural bones indicative of an underlying disorder of bone growth. Abnormal Wormian bones also occur in other disorders, such as cleidocranial dysostosis, cutis laxa with skeletal and genital abnormalities, fetal aminopterin and methotrexate syndromes, Hajdu-Cheney syndrome (acro-osteolysis), Menkes disease, oto-palato-digital syndrome type II and pyknodysostosis. (This list is taken from the London Dysmorphology Database (Winter et al., 1984), which also names 12 other individually rare conditions in which Wormian bones were reported).

Abnormalities of skull shape are well recognised in all forms of OI. These consist of temporal bulging, frontal bossing and an overhanging occiput which causes enlargement of the cranium and difficulty 'getting hats large enough to fit' in adults (McKusick, 1972). Platybasia (also called basilar invagination or basilar impression) results from softening of the cranium, so that the upper end of the cervical spine appears to have pushed the floor of the occipital bone upwards. This, together with the other deformities, gives rise to a mushroom appearance of the skull on a lateral radiograph which Apert (1928) referred to as 'crane a rebord' and Nielsen (1942) called 'soldier's helmet' or 'helmet head'. 'Tam-O-Shanter' skull is another commonly used comparison. These abnormalities are more common in patients with severe OI (McKusick, 1972) as was noted herein and may begin as early as 6 months. Neurological complications and hydrocephalus secondary to platybasia may occur (discussed in section 6.7.12).

7.8 Miscellaneous skeletal abnormalities

Various other skeletal defects were noted but the frequency of these cannot be assessed from this series.

7.8.1 Pseudoarthroses

Pseudoarthroses were seen in 6 patients with sporadic type III/IV OI in a variety of sites (table 7.9 and figure 7.14a and b). Another patient (case 31) showed non-union of a fracture of the

Table 7.9

MISCELLANEOUS SKELETAL ABNORMALITIES

Case no.	Type of OI	Bone(s) affected	Age when noted (yrs)
<u>Pseudoarthroses</u>			
6	III/IV	Clavicle	22.3
40	III/IV	Radius	?
47	III/IV	(L) humerus, femur	?
51	III/IV	(L) femur	?
58	III/IV	(L) humerus	?
73	III/IV	(R) femur	6.6
<u>Hyperplastic callus</u>			
85	III/IV	(R) femur	4.3
<u>Cross-fusion of paired bones</u>			
40	III/IV	(R) tibia & fibula	13.8
85	III/IV	(L) radius & ulna	11.1
115	I	Tibia & fibula	39.6
<u>Joint dislocation</u>			
2	III/IV	(R) radial head	17.8
23	III/IV	Both radial heads	13.2
39	III/IV	(L) radial head	5.6
41	III/IV	(R) head of humerus	25.8



Figure 7.14(a)

Case 47 (type III/IV OI), aged 2.3 yr, left femur (AP).

Note non-union and pseudoarthrosis of left femur.



Figure 7.14(b)

Case 47, aged 5.7 yr, left femur (AP).

Note the pseudo-arthrosis has persisted.

tibia between 6.3 and 6.8 years, which may have developed into a pseudoarthrosis later (figure 7.4).

Discussion

Following a fracture in OI, apparently normal callus formation is seen radiographically (Falvo et al., 1974) and healing of the fracture usually proceeds normally. Non-union of fractures with subsequent formation of a pseudoarthrosis appears to be rare in OI but it probably occurs more commonly than in normal children (Smith et al., 1983). A predisposing cause in OI could be repeated fracturing through the same site before healing is completed.

7.8.2 Hyperplastic callus

Formation of a large, hot, painful hyperplastic callus was reported by only one patient (case 85), a girl with sporadic type III/IV OI, in whom it developed in the femur at 4.3 years of age (figure 7.15). This patient was not seen by the author but the parents reported that she had dark blue sclerae at birth, which faded to pale blue.

Discussion

Much has been written about this unusual phenomenon (Strach, 1953; Smith et al., 1983). In general, males with white sclerae and no family history of OI are said to be most frequently



Figure 7.15

Case 85 (type III/IV OI),
aged 4.3 yr, femur AP.

Note hyperplastic callus
at the lower end of the
femoral shaft.



Figure 7.16

Case 40 (type III/IV OI),
aged 14 yr, right tibia and
fibula (AP).

Note cross-fusion between
the tibia and fibula.

affected (King and Bobechko, 1971) but Bauze et al. (1975) found an incidence as high as 10% of cases (4 of 42 cases) and these comprised 2 parent-child pairs with severe OI. The femur is most commonly affected; in a review of 15 reported cases, Strach (1953) noted that 22 of 33 bones involved were the femur. The cause of the phenomenon is unknown. Clinically, confusion with osteogenic sarcoma can arise but the latter is rare in OI and the two are radiologically distinct (Smith et al., 1983).

7.8.3 Cross-fusion of paired bones

Cross-fusion between paired bones had occurred in 2 patients with type III/IV OI and one with type I (table 7.9 and figure 7.16). This phenomenon has been said to result from ossification of the interosseus membrane and may affect up to 10% of patients with severe OI (Smith et al., 1983).

7.8.4 Joint dislocation

Dislocation of one or both radial heads at the elbow was seen in 3 individuals with sporadic type III/IV OI (table 7.9). Dislocation of the right humeral head in case 41 with sporadic type III/IV OI was also noted.

King and Bobechko (1971) (using Seedorff's classification of OI) noted that dislocation of the radial head was present in 14% of patients with congenital fractures, 27% with fractures beginning

in the first year and 11% who first fractured after 1 year.

Joint dislocations were discussed in section 6.7.5.2.

7.8.5 Other

An unusual abnormality seen in a patient (case 103) with type III OI at 16 years was pointing and erosion of the terminal phalanges of the toes. Sillence et al. (1986) noted 'broadening and fine cystic changes at the end of the metacarpals and phalanges' in patients with type III OI.

POSTSCRIPT

During the time of the study and its writing up, much biochemical and molecular evidence accumulated to suggest that parental gonadal mosaicism may account for many of the recurrences in sibs with type II perinatally lethal OI born to clinically normal parents. There is no reason to suspect that this will not also apply to some cases of severe progressively deforming OI, which have been called recessive type III cases to date. In an ideal world, the collagen defect (or the mutation) in each 'sporadic' case would be identified, enabling precise recurrence risk figures to be given. Families with autosomal recessive or dominantly determined OI could be distinguished and the latter divided into cases with fresh germ-line mutations or those whose parent harboured a mutation in the gonad. In the real world, however, such a scenario is unlikely, for two reasons. First, the large amount of work involved in characterising the defect in individual cases might make such an exercise impractical, particularly in areas without access to the appropriate laboratories. Secondly, in sporadic cases found to be due to a heterozygous defect, the actual mutation would have to be identified in order to look for it in father's sperm or in other parental tissues. Proving maternal gonadal mosaicism may be impossible, owing to the relative inaccessibility of the ovaries. Thus the empirical recurrence risk figures derived in the present study will always be of value in offering genetic counselling to families of severe 'sporadic' cases of OI.

The detailed clinical and radiological data documented for each patient will also allow further clinical and biochemical correlations to be made in future, should any of the cases be shown to have particular molecular defects.

Appendix 1.1

MILESTONES IN THE HISTORY OF OI AND SOME SYNONYMS*

Date	Author	Synonym	Comment
1788	Ekman OJ	Used term 'osteomalacia congenita'	First description of hereditary bone fragility
1831	Axmann E	-	Described the disease in himself and his two brothers. Referred to blue sclerae.
1835	Lobstein JGCFM	Used term 'osteopsathyrosis idiopathica' Term 'Lobstein's disease' has been used to describe OI in adults	Described the disease in adults. In the French literature, the disease is called 'Maladie de Lobstein'.
1849	Vrolik W	Used term 'osteogenesis imperfecta' 'Vrolik's disease' has been used to describe osteogenesis imperfecta congenita.	Described disease in a newborn baby.
1859	Ormerod EL	Used term 'mollities ossium'	Described a man and his two children with soft bones, severe deformity and fractures.
1862 -1865	Gurlt EJ	Used term 'fragilitas ossium'	
1889	Stilling H	-	Histologic studies
1896	Spurway J	'Spurway's disease') both used to) describe brittle	Described blue sclerae with bone fragility.
1900	Eddowes A	'Eddowes' syndrome') bones & blue sclerae	Described blue sclerae. Suggested that OI is generalised hypoplasia of mesenchyme.

1100

Appendix 1.1 (contd.)

Date	Author	Synonym	Comment
1905	Porak and Durante	Periosteal dysplasia of Porak and Durante (Maladie de Porak et Durante).	Term used in French literature to describe severe lethal disease.
1906	Looser E	Proposed terms OI congenita (OIC) and OI tarda (OIT).	Defended identity of OI in children and adults, an idea first suggested by Schmidt in 1897.
1912	Adair-Dighton CA	-	Described deafness, as did Dent (1897, quoted Bell (1928)).
1918	van der Hoeve J and de Kleyn A	'van der Hoeve's syndrome' has been used to describe brittle bones, blue sclerae and deafness.	Emphasised brittle bones, blue sclerae and deafness as a syndrome.
1920	Bauer KH	} Both used term 'hereditary hypoplasia of mesenchyme' in mild OI with blue sclerae.	Histologic support for the view that OI is 'hypoplasia mesenchymialis' and described dental histology.
1926	Key JA		-
1928	Bell J	-	Documented the dominant inheritance pattern in many pedigrees.
1949	Seedorff KS	Used terms OI congenita (fractures before birth), OI tarda gravis (fractures at, or soon after birth), OI tarda levis (first fractures in later infancy).	Reviewed 180 patients from 55 families in Denmark. Classification of cases by age of presentation and severity. Proposed that fractures, blue sclerae and deafness were inherited independently but were due to 5 closely linked genes with dominant effect.

Appendix 1.1(contd.)

Date	Author	Synonym	Comment
1958	Caniggia A et al.	-	Extensive population studies in Italy, Sweden and Japan respectively. Concluded that all manifestations of OI result from variable expressivity of a single dominant gene. Bell (1928) (see above) concluded likewise in a large UK study.
1961	Smars G	-	
1956	Komai T et al.	-	
1964	Cocchi U	-	Proposed that genetic heterogeneity underlies the clinical spectrum of OI, with the existence of autosomal dominant and recessive forms with over-lapping clinical features. Proposed classifications of OI of which Sillence et al. is most useful.
1967	Ibsen KH	-	
1979] 1984]	Sillence DO et al.	Sillence classification of OI.	
1975 to present	Penttinen et al.	-	Found altered collagen production in cell strains from patients with OI. This marked the beginning of the 'biochemical era' of investigation of OI. This is discussed in section 1.9.

* Adapted from McKusick (1972), Smith et al. (1983), Weil (1981), Sillence et al. (1979a and 1979b).

Appendix 3.1

PROTOCOL FOR INTERVIEWING THE PATIENTS

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(1)		(2)	
NAME	ADDRESS	<u>SCLERAE:</u>	at birth
INFORMANT			now
WHERE SEEN	DATE		? variable
GP			parent noted latter spontaneously YES/NO
ADDRESS		<u>SKIN:</u>	easy bruising laxity
SPECIALIST		<u>JOINTS:</u>	laxity
ADDRESS			dislocations
RECORDS AT	NEONATAL X-RAYS	<u>HERNIAE:</u>	sites
MEMBER BBS	DATE JOINED		treatment
ASCERTAINMENT			outcome
		HEART MURMURS	
PROBAND	DOB	<u>EYES:</u>	vision assessed by
<u>HISTORY</u>			squint
PREGNANCY		HEARING:	assessed by
Normal		SWEATING:	
Drugs	Alcohol Cigarettes	EPISTAXES:	
Movements	Fluid	<u>TEETH:</u>	1st dentition 2nd dentition
Prenatal tests			time eruption
No. previous X-rays			quality
DELIVERY		<u>DEVELOPMENT:</u>	motor
Place	Birth length		speech
Gestation	Presentation		education
Duration labour	Mode delivery		work
BW	Resuscitation	<u>GENERAL HEALTH:</u>	comments
Birth OFC			RTI
Appearance at birth (eg. face, limbs (bowed/short))			appetite constipation
			vomiting
Legs more affected than arms	YES/NO/?	OTHER ANOMALIES:	
Fractures at birth		* <u>TREATMENT:</u>	
Age at diagnosis	by	<u>PEDIGREE:</u>	1. Parental consanguinity
Fractures since birth	No. sites frequency		Maternal infertility
			Stillbirth miscarriage
			2. All 1st, 2nd, 3rd degree rel.
			3. 2nd deg. rel: ht
			not: sclerae hearing

Appendix 3.1 (contd.)

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<u>PEDIGREE</u> (3)	<u>EXAMINATION</u> (4)
	<p>Length: how measured:</p> <p>Sitting height:</p> <p>Weight: OFC:</p> <p><u>FACE</u> broad forehead YES/NO triangular face YES/NO flat maxillae YES/NO prominent jaw YES/NO Comments:</p> <p>Fontanelles: OPEN/CLOSED</p> <p>Sclerae:</p> <p>Squint:</p> <p>Voice: Nails: Hair:</p> <p><u>TEETH</u> Colour: brown/opalescent/normal Shape: irregular/normal Position: irregular/normal</p> <p><u>EARS</u>: Shape: Length: Right Left T.M.S. Right Left</p> <p><u>EYE MEAS.</u> OC IP IC</p> <p><u>LIMBS</u> (remove clothes) (S=straight, MiB=mild bowing, MOB=mod. bowing, SB=severe bowing)</p> <p style="text-align: center;"><u>Right</u> <u>Left</u></p> <p>Upper arm Lower arm 'False elbow' YES/NO YES/NO Measure R arm cm/not possible Hand shape normal/abn. normal/abn. describe if abn. measure MF MF and palm</p> <p>Upper leg Lower leg Foot shape normal/abn. normal/abn. describe if abn. measure (sole and B.T)</p> <p>Chest: Spine:</p>
<p><u>SOCIAL</u></p> <p>1. Problems of having OI or having child with OI.</p> <p>2. Aids used: Supplied by:</p> <p>3. Support from:</p> <p>4. Holidays/yr: Where:</p> <p><u>PREVIOUS GENETIC ADVICE</u></p>	

Appendix 3.2

<u>Colour on paint chart</u>	<u>Score</u>	<u>Interpretation</u>
	0	White
	0-1	Very pale blue
	→ 1	Pale blue
	1-2	Moderate blue
	→ 2	
	3	Deep blue
	→ 3	
	3+	

Note: Although only 3 shades of blue were used, occasionally a score midway between 2 colours was recorded and this was interpreted as shown. 'Very pale blue' was between 'white' and 'pale blue'.

Appendix 3.3

QUESTIONNAIRE SENT BY POST TO GEOGRAPHICALLY INACCESSIBLE FAMILIES

PAEDIATRIC GENETICS
INSTITUTE OF CHILD HEALTH
UNIVERSITY OF LONDON

39, GUILFORD STREET,
LONDON, WC1N 1EH
01-241 9780 CX 3

BRITTLE BONE STUDY

Drs Pembrey & Thompson

Name of person who was born with fractures

Date of birth

Name of person filling in this form and relationship eg/ mother
.....

Which year did you join the Brittle Bone Society

(write NA if not a member)

BIRTH HISTORY (tick which applies for each question)

Was the birth at full term YES NO DON'T KNOW

If NO, state how many weeks early or late

Birth weight

Did the leg bones appear 'bent' at birth? YES NO

Did the arm bones appear 'bent' at birth? YES NO

FRACTURES - Were fractures present at birth YES NO

Number of fractures present at birth (approximately)

Number of fractures since birth - 0 - 4 years 15 - 19
5 - 9 " 20 - 29
10 - 14 " 30 - 39

SCLERAE (whites of the eye)

Colour at birth - Deep blue Colour now - Deep blue
Pale blue Pale blue
White White

A COMPANY LIMITED BY GUARANTEE, REGISTERED IN ENGLAND, NUMBER 11877
REGISTERED OFFICE: 39 GUILFORD STREET, LONDON, WC1N 1EH

2/ Tick whether-
HEIGHT Measured standing OR lying

LIMB BOWING -

Are the arm bones 'bent' YES NO

Are the leg bones 'bent' YES NO

Describe (if necessary)

Operations on limbs eg/rodding YES NO

If operations were to straighten limbs, tick which part of limb -

	<u>Arms</u>		<u>Legs</u>	
	left	right	left	right
upper part	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
lower part	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

JOINT LAXITY

Are the joints very flexible or 'bendable' (also called 'double jointed')

YES In childhood only NEVER

DISABILITY

Can the person walk unaided YES NO
walk with help YES NO
sit unaided YES NO
Has the person ever been able to walk YES NO

TEETH

Discoloured or translucent YES NO
Wear or chip easily YES NO

SCOLIOSIS (curvature of the spine) PLEASE TICK

Present Absent Don't know
If present, is it mild OR severe

HEARING LOSS

Present Left Right Age of onset if known
Absent Don't know

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Appendix 3.3 (contd.)

3/

FAMILY HISTORY

Name, sex, date of birth of all brothers and sisters.

Has the mother had any miscarriages? If so, how many, and in what year(s).

Name, date of birth of parents

Are the parents related? If so, how eg/cousins

State who of the above have brittle bones, if any

Who else in the family has brittle bones, if anyone

<u>Name</u>	<u>Relationship to person named on this form</u>
-------------	--

Photograph I do I do not enclose a photograph of the person with brittle bones, which I understand will be returned.
 (Please write name and age when photo was taken, on back)

X-RAYS CAN BE OBTAINED FROM:

Doctor (if known)

At which hospital?

X-rays taken soon after birth can be obtained from -

Doctor (if known)

At which hospital?

4/

Name and address of the child's family doctor

Dr:

.....

.....

.....

Signature

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Appendix 3.4

FORM FOR RECORDING RADIOLOGICAL DATA IN PERINATAL SURVIVORS

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NAME			DOB		HOSPITALS							
X-RAYS COPIED		DATE	AGE		X-RAYS COPIED		DATE	AGE				
<u>OSTEO-POROSIS</u> -, +, ++	<u>COARSE TRABEC</u> -, +, ++	<u>MODELLING</u> Normal Abnormal Slender bones	<u>SPINE</u> P S		<u>PELVIS</u> PA OTHER		<u>LONG BONES</u> DEFORMITY -, +, ++		ADORN -, +, ++	<u>CHEST</u>	<u>SKULL</u> WB PB	
											<u>FRACURES AT BIRTH</u>	

COMMENTS :

APPENDIX 5.1

Family data

	Case no.	Delays in conceiving	Parental ages at birth of first affected child		Ethnic origins		The sibships, miscarriages & consanguinity (C)
			M	F	M	F	
Table no.		5.4	5.6		5.5		5.1 - 5.3, 5.5
Thesis section		5.2.4	5.2.6		5.2.5		5.2.2, 5.2.3, 5.2.5
TYPE III/ IV SPORADIC OI							
	1	-	27.92	30.42	E	Sw/E	• ■ ○ ○
	2	-	24.0	26.67	E	E	● ○ ○
	3	-	25.58	30.5	E	E	□ ● ○
	4	-	21.08	21.75	W	W/G	□ ■ ■
	5	-	24.75	41.67	W	W	□ ■ ■
	6	-	23.0	25.75	E	E	● ○
	7	-	30.42	34.17	W/Sc	E	□ ○ □ ●
	8	-	19.0	23.0	E	Sc	●
	9	18 mth	24.58	26.67	E	E	○ ●
	10	-	33.25	31.5	E	E	□ ■ •
	11	-	28.75	21.25	E	E	■
	12	-	26.58	26.67	E	Sc	○ ●
	13	-	27.17	34.0	E	E	●
	14	-	25.0	25.92	E	E	□ • ● □
	15	-	19.25	24.25	E	Sc	• ○ ● □
	16	-	32.33	39.08	E	E	• • ○ ●
	17	5 yr	25.92	28.33	E	E	□ ■
	18	-	30.17	20.92	E	E	●
	19	-	28.17	26.17	E	E	○ ■
	20	18 mth	30.25	23.08	E	E/Ir	●
	21	-	27.17	29.92	E	E	■ ○ ○ □ □ □ ● ○
	22	-	34.0	36.67	J	J	□ ○ ○ □ □ □ ● ○
	23	-	38.08	39.5	E	E/Ir	• • ○ ●
	24	-	27.42	41.0	E	Eth	□ ■ ●
	25	-	28.92	32.58	E	E	□ ■ ●
	26	-	32.83	35.5	E	E	○ ●
	27	-	36.67	35.92	E	E	□ • ■
	28	-	19.33	28.58	E	E	□ ●
	29	-	24.92	25.5	E	E	○ ●
	30	2 yr, 18 mth	28.25	27.92	E	E	○ ●

Family data

	Case no.	Delays in conceiving	Parental ages at birth of first affected child		Ethnic origins		The sibships, miscarriages & consanguinity (C)
			M	F	M	F	
Table no.		5.4	5.6		5.5		5.1 - 5.3, 5.5 5.2.2, 5.2.3, 5.2.5
Thesis section		5.2.4	5.2.6		5.2.5		
TYPE III/IV SPORADIC OI							
	31	-	22.25	31.92	E	E	○ ●
	32	-	23.42	27.33	E	E	□ ■
	33	-	26.25	26.0	E	E	□ ●
	34	-	26.75	28.33	E	E	○ ● • □
	35	-	38.08	33.5	E	E	○ ●
	36	5 yr	26.58	30.17	E	Ir	● □
	37	-	26.33	26.08	Sc	Sc	● □
	38	-	26.08	23.42	E	E	■ □ □ □
	39	-	25.33	22.92	E	E	□ □ □ ○ □ ●
	40	-	28.08	31.83	E	E	○ ● • □
	41	?	28.92	30.92	E	E	○ ● • □
	42	-	35.42	33.75	E	E	●
	43	-	28.08	30.25	E	Ir	● ○
	44	-	25.67	30.67	E	E	○ ●
	45	-	37.58	40.33	E	E	○ ● □
	46	-	28.17	35.5	Po	Po	• ● □
	47	-	34.83	40.25	E	E	□ □ ■ ●
	48	-	32.33	40.83	Fr/Ca	E	○ ○ □ ●
	49	-	21.0	21.08	E/G	E	● ○
	50	-	25.42	31.08	E	E	●
	51	-	24.75	31.83	E	E	■ ○
	52	-	22.25	26.67	E	E	○ ■ □ □
	53	15/12	33.0	34.25	W/E/ Sc	E	■ □ ○
	54	-	27.83	29.75	E	E	□ ■ ○
	55	-	31.75	33.5	E	E	• ○ ●
	56	-	21.42	30.42	E	E	○ ●
	57	-	34.67	37.08	E	E	○ ■ ○
	58	-	22.42	23.33	E	E	□ ■
	59	-	29.75	53.0	E	Ir	○ □ ●
	60	-	29.25	32.42	E	E	□ ○ ■
	61	-	23.92	23.67	E	E	■ ○ □
	62	-	28.67	36.58	E	E	○ ● □
	63	-	25.33	27.83	E	It	● □
	64	18 mth	30.42	32.67	E	E	● ○
	65	-	32.58	32.33	E	E	□ ● ○
	66	2 yr	35.17	32.75	E	E	• ○ ■
	67	-	34.67	36.67	Fr/E	E	□ ■ ○ □

APPENDIX 5.1

Family data

	Case no.	Delays in conceiving	Parental ages at birth of first affected child		Ethnic origins		The sibships
			M	F	M	F	
Table no.		5.4	5.6		5.5		5.1 - 5.3, 5.5 5.2.2, 5.2.3, 5.2.5
Thesis section		5.2.4	5.2.6		5.2.5		
TYPE III/ IV SPORADIC OI							
	68	3 yr	28.17	35.33	E	E	● ○
	69	-	26.33	34.5	E	E	□ □ ■
	70	-	22.33	23.58	W	W	○ ■ □
	71	-	24.83	31.25	E	E	○ □ ●
	72	-	28.83	34.0	E	Sc/E	●
	73	-	27.67	26.67	G	E	• ○ □ ●
	74	?	23.92	24.67	C	C	● ○
	75	?	31.0	32.67	C	C	□ ○ • ■ □
	76	?	20.5	20.42	C	C	●
	77	?	30.5	30.58	C	C	○ □ ■ □ ◇
	78	?	30.42	32.42	C	C	□ □ ■
	79	?	38.58	48.42	C	C	○ □ □ ■
	80	?	33.83	32.92	C	C	• □ ■
	81	?	33.5	22.33	C	C	■ □ ○ ○
	82	?	20.5	23.58	C	C	●
	83	?	29.25	34.42	C	C	■
	84	?	25.33	32.67	C	C	● □ • □
	85	?	24.42	30.92	C	C	□ ●
	86	?	22.17	25.75	W	W	◇ ◇ ● •
	87	?	24.5	25.25	W	W	○ ■
	88	-	20.4	17.6	E	E	● □ □
	89	-	30.0	30.0	C	C	○ • ○ ■

Family data

	Case no.	Delays in conceiving	Parental ages at birth of first affected child		Ethnic origins		The sibships, miscarriages & consanguinity (C)
			M	F	M	F	
Table no. Thesis section		5.4 5.2.4	5.6 5.2.6		5.5 5.2.5		5.1 - 5.3, 5.5 5.2.2, 5.2.3, 5.2.5
TYPE III RECESSIVE OI							
	90	?	24.5	30.25	Pa	Pa	■ C
	91,92	-	26.0	36.42	IrM	IrM	○ ■ □ • ● □ C
	93,94	-	26.25	30.83	E	E	● ● C
	95,96	-	18	26	Ir	Ir	○ • ■ ● ◆ TOP C
	97						
	98,99	?	28.33	35.58	Sc	Sc	○ ■ ■ C
	100,	-	28.58	30.92	E	E	○ ■ • ■ C
	101						
	102,	-	18	18	Jo	Jo	■ □ ○ ● C
	103						
	104,	5½ yr,	24.42	27.5	E	G	■ □ • ● C
	105	18 mth					
	106,	-	26.33	25.92	It/E	E	■ ● ◆ TOP TOP C
	107,						
	108						
TYPE I NEW MUTATION OI							
	109	-	25.75	30.0	E	E/Ca	● □ C
	110	-	24.25	27.33	E	E	□ ■ □ ○ □ C
	111	-	19.75	21.58	E	Ir/Au	○ ● ○ C
	112	?	22.92	31.67	Ir	Ir/E	■ □ ○ C
	113	?	28.25	29.25	E	E	□ ● C
	114	-	32.58	41.58	E	E	○ ● C
	115	-	33.33	37.58	E	E	□ □ ● C
	116	?	34.42	36.0	E	E	• ■ C
	117	?	?	?	C	C	● C
	118	?	36.92	36.17	W	W	○ □ ● C
	119	?	27.42	27.58	Sc	Sc	● C

APPENDIX 5.1

Family data

	Case no.	Delays in conceiving	Parental ages at birth of first affected child		Ethnic origins		The sibships, miscarriages & consanguinity (C)
			M	F	M	F	
Table no.		5.4	5.6		5.5		5.1 - 5.3, 5.5
Thesis section		5.2.4	5.2.6		5.2.5		5.2.2, 5.2.3, 5.2.5
TYPE IIA OI							
	120	?	21	26.4	Pa	Pa	■ ○ C
	121	?	30	41	ISC	ISC	○ □ ◆ TOP ?C
	122	?	35.7	39.8	C	C	◇ ◇ ■ ◇ .
	123	?	27.0	43.8	C	C	● ◇ .
	124	?	36	?	Pa	Pa	◇ ■ .
	125	?	33	38.3	C	C	● .
	126	?	32.4	41.9	C	C	■ .
	127	?	32.9	33.0	C	C	◇ ■ TOP
	128	?	40	41	C	C	○ ■
	129	?	36.1	40	C	C	◇ ■ TOP . . . ■
	130	?	27.9	35.2	E	E	● . ○ . . ■
	131	?	25.2	26.0	C	C	◇ ● ◇ ◇
	132	-	31.9	43.5	E	E	■ ○
	133	?	21.4	26.7	E/Tr	Sc	■
	134	?	18.1	29.0	W	W	◇ ● ◇
	135	?	21.3	26.7	C	C	● ● ◇
	136	?	19.5	38.3	C	C	□ ● ◇
	137	?	31.1	34.5	C	C	□ ■
	138	-	24.3	24.0	E	E	□ ■
	139	-	37.6	38.4	E	E	● . ■ □
	140	?	25.4	28.9	Ta	In	● ◇ ◇ ◇ .
	141	?	29.9	31.2	E	Sc	◇ ● ◇
	142	?	19.1	20.6	C	C	●
	143	-	34	49.3	E	InAr	■ □
	144	?	23.1	24.7	C	C	● ◇
	145	?	26.7	28.8	In	Ta	◇ ◇ ◆ TOP ◇
	146	?	28.6	37.8	C	C	● ○ ◇ . .
	147	?	40.0	35.2	E	E	◇ ● ◇ . .
	148	?	29.1	31.8	E	E	■ ○
	149	?	27.7	28.1	InS	InS	◇ ■ ◇

Family data

	Case no.	Delays in conceiving	Parental ages at birth of first affected child		Ethnic origins		The sibships, miscarriages & consanguinity (C)
			M	F	M	F	
Table no.		5.4	5.6		5.5		5.1 - 5.3 5.5 5.2.2, 5.2.3, 5.2.5
Thesis section		5.2.4	5.2.6		5.2.5		
UNCLASSIFIABLE PERINATALLY LETHAL OI							
	168	?	26.9	41.7	E	E	□ ● □
	169	?	27.8	29.0	C	C	● □ ○
	170	?	31.2	39.7	W	W	■
	171	?	36.5	49.7	ISC	ISC	○ □ • □ ■
	172	?	18.5	22.33	C	C	□ ■ ○
	173	?	28.6	32.5	Sc	Sc	● ○ ○
	174	?	39.75	?	C	C	• ○ ○ ● □
	175	?	24.5	24.5	C	C	□ ○ □ □ ■
	176	-	23.5	24.58	E	E	■ □ □
	177	?	22.5	30.5	C	C	□ □ ■

NOTES FOR APPENDIX 5.1

Delays in conceiving

(-) no delay, (?) unknown.

If there was a delay, the time taken to conceive the first child is shown. Mothers of cases 30 and 104/105 experienced delays in conception of two children each, the latter for her first two children. Mother of case 163 had a time of infertility (?duration) which resolved after she had an ovarian cyst removed surgically.

Parental ages at birth of first affected child

M - mother, F - father

This has not been corrected for gestational age.

Ethnic origins

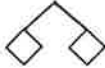
This gives the ethnic origins of parents of affected child. In some cases, a parent has mixed origins, e.g. for case 1, father is of Swiss and English parentage.

Caucasian (C): Au - Australian, Ca- Canadian, E - English, Fr - French, G - German, Ir - Irish, It - Italian, Po- Polish, Sc - Scottish, Sw - Swiss, W - Welsh. If unknown, (C) is given.

Non-Caucasian: Af - African, Eth - Ethiopian, In - Indian, In/Ar - Indian/Arabian, InM - Indian Muslim, InS - Indian Sikh, ISC - Indian subcontinent, J - Jamaican, Jo - Jordanian, Ne - Negro, Pa - Pakistani, SLC - Sri Lankan Christian, WI - West Indian, Ta - Tanzanian, Zim - Zimbabwe.

The sibships

These are abbreviated pedigrees to show the sibship of the probands.

□ male, ○ female, ◇ sex unknown,  twins, ■ ● ◆ affected with OI, • first trimester miscarriage (mother of case 66 had a second trimester loss), TOP - termination of pregnancy. Birth order is correct except in cases 122, 125, 140, 146 and 147 where the order of the miscarriage is unknown. In cases 87, 121, 124, 126, 135, 142, 144 and 153 information about miscarriages is unknown. C indicates consanguinity.

CLINICAL MANIFESTATIONS IN PARENTS (No. cases (%))

Type of OI	Type IIIA		Type IIB		Type IIC		Unclassifiable PNL		Type III/IV sporadic		Type III 'recessive'		I new mutation		Total	
	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers
Total no. parent pairs	30		14		3		10		89		9		11		166	
Manifestation	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers
No. examined	14	14	10	10	1	1	6	6	67	58	7	6	7	4	112	99
No. fractures (*)	(n=12)	(n=13)	(n=7)	(n=7)	(n=1)	(n=1)	(n=6)	(n=6)	(n=74)	(n=75)	(n=6)	(n=6)	(n=9)	(n=8)	(n=115)	(n=116)
0	12 (100)	10 (76.9)	4 (57.1)	5 (71.4)	1	1	6 (100)	6 (100)	55 (74.3)	38 (50.7)	4 (66.7)	5 (83.3)	6 (66.7)	3 (37.5)	88 (76.5)	68 (58.6)
1	-	1 (7.7)	2 (28.6)	1 (14.3)	-	-	-	-	17 (23.0)	27 (36.0)	2 (33.3)	1 (16.7)	3 (33.3)	3 (37.5)	24 (20.9)	33 (28.4)
2	-	1 (7.7)	1 (14.3)	1 (14.3)	-	-	-	-	1 (1.4)	7 (9.3)	-	-	-	2 (25.0)	2 (1.7)	11 (9.5)
3	-	1 (7.7)	-	-	-	-	-	-	1 (1.4)	1 (1.3)	-	-	-	-	1 (0.9)	2 (1.7)
7	-	-	-	-	-	-	-	-	0	1 (1.3)	-	-	-	-	-	1 (0.9)
'a few'	-	-	-	-	-	-	-	-	0	1 (1.3)	-	-	-	-	-	1 (0.9)
?	18	17	7	7	2	2	4	4	15	14	3	3	2	3	51	50
<u>Scleral colour</u>	(n=14)	(n=14)	(n=7)	(n=7)	(n=1)	(n=1)	(n=5)	(n=5)	(n=73)	(n=71)	(n=7)	(n=6)	(n=8)	(n=7)	(n=115)	(n=111)
White)	9] (85.7)	12] (92.9)	3] (42.9)	6] (100)	1	1	5] (100)	3] (60)	26 (**)] (58.9)	44 (***)] (80.3)	2 (#)] (57.1)	3] (83.3)	2 (+)] (62.5)	5 (a)] (100)	48] (63.5)	74] (83.8)
Very pale) Normal blue)	3]	1]	0]	1]	-	-	0]	0]	17]	13]	2]	2]	3]	2]	25]	19]
Pale blue	2 (14.3)	1 (7.1)	3 (42.9)	-	-	-	-	2 (40)	24 (32.9)	14 (19.7)	3 (42.9)	1 (16.7)	3 (37.5)	-	35 (30.4)	18 (16.2)
Moderate blue	-	-	1 (14.3)	-	-	-	-	-	6 (8.2)	0	-	-	0	7 (6.1)	-	-
?	16	16	7	7	2	2	5	5	16	18	2	3	3	51	55	
Joint laxity	(n=12)	(n=12)	(n=10)	(n=10)	(n=1)	(n=1)	(n=6)	(n=6)	(n=67)	(n=58)	(n=7)	(n=6)	(n=7)	(n=4)	(n=109)	(n=96)
	6 (50)	1 (8.3)	1 (10)	1 (10)	0	0	0	0	15 (22.4)	5 (8.6)	2 (28.6)	1 (16.7)	2 (28.6)	0	26 (23.9)	8 (8.3)
Easy bruising	(n=12)	(n=12)	(n=10)	(n=10)	(n=1)	(n=1)	(n=6)	(n=6)	(n=67)	(n=58)	(n=7)	(n=6)	(n=7)	(n=4)	(n=109)	(n=96)
	4 (33.3)	0 (0)	4 (40)	0	1	0	1 (17.7)	0	26 (38.8)	4 (6.9)	1 (14.3)	0	5 (71.4)	0	42 (38.5)	4 (4.2)
Skin hyperextensibility	(n=12)	(n=12)	(n=10)	(n=10)	(n=1)	(n=1)	(n=6)	(n=6)	(n=67)	(n=58)					(n=109)	(n=96)
	1 (8.3)	1 (8.3)	0	1 (I) (10)	0	0	0	0	3 (4.5)	3 (5.2)	0 (n=7)	0 (n=6)	0 (n=7)	0 (n=4)	4 (3.7)	5 (5.2)
History of hearing loss	0 (n=12)	0 (n=12)	0 (n=10)	0 (n=10)	0 (n=1)	0 (n=1)	0 (n=6)	1 (n=6)	1 (n=67)	8 (n=58)	0 (n=7)	0 (n=6)	0 (n=7)	1 (n=4)	1 (n=109)	10 (n=96)
								1 (16.7)	1 (1.5)	8 (13.8)	0 (n=7)	0 (n=6)	0 (n=7)	1 (25)	1 (0.9)	10 (10.4)
Poor teeth	0 (n=12)	0 (n=12)	1 (n=10)	1 (n=10)	0 (n=1)	0 (n=1)	0 (n=6)	0 (n=6)	3 (n=67)	1 (n=58)	0 (n=7)	0 (n=6)	0 (n=7)	0 (n=4)	3 (n=109)	2 (n=96)
			1 (10)	1 (10)	0 (n=1)	0 (n=1)	0 (n=6)	0 (n=6)	3 (4.5)	1 (1.7)	0 (n=7)	0 (n=6)	0 (n=7)	0 (n=4)	3 (2.8)	2 (2.1)

Footnotes for Appendix 5.2

PNL Perinatally lethal

? Unknown

Numbers in brackets are percentages of numbers known or examined (n).

* In some cases where parents were not examined, information about fractures was obtained from the family.

** 7 mothers not seen by author, but were reported normal by the family.

*** 14 fathers not seen by author, but were reported normal by the family.

1 reported normal by family.

+ 1 mother reported to have very pale blue sclerae by family.

⊙ 3 fathers reported normal by family.

⊞ Described as 'grey-blue'.

I A Sri Lankan man.

CLINICAL DATA ON CASES

Type III/IV OI

Cases 1-87	PNS*
Cases 88, 89	PNL

Type III recessive OI

Cases 90-96, 98-105	PNS
Cases 97, 106-108	PNL

Type I OI

Cases 109-119	PNS
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Type IIA OI

Cases 120-149	PNL
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Type IIB OI

Cases 150-161	PNL
Cases 162-164	PNS

Type IIC OI

Cases 165-167	PNL
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Unclassifiable PNL

Cases 168-177	PNL
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* PNS - perinatal survivors, PNL - perinatally lethal

In this appendix, cases are grouped as PNS or PNL, because there is more clinical data for the PNS group.

PERINATAL SURVIVORS (PNS)

	Case no.	Data collection	Birth X-ray available	Sex	Fetal movement	Prenatal U.S.S.	Amniotic volume	Liveborn, stillborn, TOP
Text section Table no.		3.2, 6.1	3.3	6.2 6.1	6.3.1 6.2	6.3.2 6.3	6.3.3 6.4	6.3.4 6.5
TYPE III/IV SPORADIC OI								
1	ET	-		M	D	?	?	L
2	ET	-		F	D	?	?	L
3	ET	+		F	D	N(20/40)	D	L
4	ET	+		M	N	N	?	L
5	ET	-		M	N	?	?	L
6	ET	-		F	N	?	N	L
7	ET (F)	-		F	D	N	?	L
8	ET	-		F	?	?	?	L
9	ET	+		F	N	?	N	L
10	ET	+	(i)	M	D	?	N	L
11	ET	+	(i)	M	D	?	N	L
12	ET	-		F	D	?	N	L
13	ET	+		F	N	?	D	L
14	ET	-		F	D rolled	?	N	L
15	ET	-		F	N	?	?	L
16	ET	-		F	D	?	N	L
17	ET	-		M	D	?	D	L
18	ET	+		F	D	N	D	L
19	ET	+		M	D	?	N	L
20	ET	+		F	N	N	I	L
21	ET	-		M	N	?	N	L
22	ET	-		F	N	?	N	L
23	ET	-		M	N	?	N	L
24	ET	-		F	D	N(13/40, 30/40)	N	L
25	ET	+	(i)	M	D	?	?	L
26	ET	-		M	D	?	N	L
27	ET	-		M	D	?	D	L
28	ET(F)	+		M	N	N	N	L
29	ET	+		F	D	N	?	L
30	ET	-		F	N	?	N	L
31	ET	+		F	D	?	N	L
32	ET	+		M	D	N(16/40, 20/40)	I	L
33	ET	+		F	N	N	I	L
34	ET(F)	+		F	N	?	?	L
35	ET	-		F	N	?	?	L
36	ET(F)	-		F	D	?	?	L
37	ET	-		F	N	?	N	L
38	ET	-		M	?	?	?	L
39	ET	-		M	N	?	?	L
40	ET	-		F	?	?	?	L
41	ET	-		F	?	?	?	L
42	ET	-		F	D v. little	?	?	L
43	ET(F)	-		F	I	?	N	L
44	ET	+		F	N	N(18/40)	N	L
45	ET	-		F	N	?	?	L
46	ET	-		F	D	?	I	L
47	ET	-		M	N	?	N	L
48	ET	-		F	?	?	?	L
49	ET	-		F	D v. little	?	N	L
50	ET	-		F	N	?	N	L
51	ET	+		M	D	?	N	L
52	ET	-		M	D v. poor	?	N	L
53	ET	+		M	N	?	N	L
54	ET	-		M	N	N(16/40)	N	L
55	ET	+		F	D	?	I	L
56	ET	-		F	N	?	N	L
57	ET	-		M	?	?	?	L
58	ET	-		M	?	?	?	L
59	ET	+		F	I	N(16/40)	N	L

PERINATAL SURVIVORS

	Case no.	Data collection	Birth X-ray available	Sex	Fetal movement	Prenatal U.S.S.	Amniotic volume	Liveborn, stillborn, TOP
Text section Table no.		3.2, 6.1	3.3	6.2 6.1	6.3.1 6.2	6.3.2 6.3	6.3.3 6.4	6.3.4 6.5
TYPE III/IV SPORADIC OI (cont.)	60	ET	-	M	?	?	?	L
	61	ET	-	M	N rolled	?	N	L
	62	ET	+	F	?	?	?	L
	63	ET	+ (i)	F	D none	?	N	L
	64	ET	+	F	D	?	D	L
	65	ET	+ (i)	F	N	?	N	L
	66	ET(F)	-	M	D	?	N	L
	67	ET	-	M	N	?	N	L
	68	ET(F)	-	F	D	?	?	L
	69	ET	+ (i)	M	N	?	N	L
	70	ET(F)	+	M	N	?	N	L
	71	ET	+	F	D	?	?	L
	72	ET	+	F	D squirmed	?	N	L
	73	ET	-	F	N	?	?	L
	74	Q	-	F	?	?	?	L
	75	Q	-	M	?	?	?	L
	76	Q	-	F	?	?	?	L
	77	Q	-	M	?	?	?	L
	78	Q	-	M	?	?	?	L
	79	Q	-	M	?	?	?	L
	80	Q	-	M	?	?	?	L
	81	Q	-	M	?	?	?	L
	82	Q	+	F	?	?	?	L
	83	Q	-	M	D	?	?	L
	84	Q	-	F	?	?	?	L
	85	Q	-	F	?	?	?	L
	86	O	+	F	?	?	?	L
	87	O	-	M	?	?	?	L
TYPE III RECESSIVE OI	90	O	+	M	?	?	?	L
	91 ²	ET(F)	+	F	?	?	?	L
	92 ¹	ET(F)	-	M	N	?	?	L
	93 ¹	ET(F)	-	F	N	?	?	L
	94 ¹	ET(F)	-	F	D	?	?	L
	95 ¹	O	+	F	?	?	?	L
	96 ¹	O	+	M	?	?	?	L
	98 ¹	ET(F)	-	M	D	?	?	L
	99 ¹	ET	-	M	D	?	?	L
	100 ¹	ET	-	M	N	N	N	L
	101 ¹	ET(F)	-	M	D	?	N	L
	102 ¹	ET	-	M	?	?	?	L
	103 ¹	ET	-	F	?	?	?	L
	104 ¹	ET	-	F	D	?	?	L
	105 ¹	ET(F)	-	M	D	?	N	L

* brackets indicate sibs

(Nos. 88, 89, 97, 106-108:- see PNL)

PERINATAL SURVIVORS

	Case no.	Data collection	Birth X-ray available	Sex	Fetal movement	Prenatal U.S.S.	Amniotic volume	Liveborn, stillborn, TOP
Text section Table no.		3.2, 6.1	3.3	6.2 6.1	6.3.1 6.2	6.3.2 6.3	6.3.3 6.4	6.3.4 6.5
TYPE I NEW MUTATION OI	109	ET	+	F	N	?	N	L
	110	ET	-	M	D	?	?	L
	111	ET	-	F	D none	N	?	L
	112	ET	-	M	N	?	?	L
	113	ET	-	F	D	?	?	L
	114	ET	-	F	N	N	?	L
	115	ET	-	F	?	?	?	L
	116	ET	-	M	?	?	?	L
	117	ET	-	F	?	?	?	L
	118	ET	-	F	N	?	?	L
	119	Q	+	F	?	?	?	L
TYPE IIB OI	162	ET(F)	+	F	N	?	I	L
	163	ET(F)	+	F	D	N	N	L
	164	ET(F)	+	M	D hardly any	N (10/40, 14/40)	N	L

PERINATALLY LETHAL CASES (PNL)

	Case no.	Data collection	Birth X-ray available	Sex	Fetal movement	Prenatal U.S.S.	Amniotic volume	Liveborn, stillborn, TOP
Text section Table no.		3.2, 6.1	3.3	6.2 6.1	6.3.1 6.2	6.3.2 6.3	6.3.3 6.4	6.3.4 6.5
TYPE III/IV SPORADIC OI	88 89	IY(F) O	+ +	F M	N N	? ?	N ?	S L
TYPE III RECESSIVE OI	97 106]* 107 108]	O ET(F) ET(F) ET(F)	- + + +	? M F ?	? D N ?	A (~28/40) ? A (~27/40) A (19+/40)	? N N N	TOP L TOP TOP
TYPE IIA OI	120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149	O O O O O O O O O IY(F) O ET(F) IY(F) O O O ET(F) ET(F) ET(F) IY(F) IY(F) O ET(F) IY(F) O O O IY(F) O IY(F) O O IY(F) O	+ +	M ? M F M F M M M M M F M M F F M M M M F F F F M M F F F M F F F M M	? ? ? ? ? ? ? ? ? D D ? ? ? ? ? ? D none N N ? ? ? ? ? ? D none ? ? ? ? ? ? ? ? ? D v. little, flutter D ?	A (16/40) A ? ? N (18/40, 22/40) ? ? A (~17/40) ? A (~23/40) ? ? N ? ? ? ? N (17/40) N ? ? ? ? A (~18/40) ? ? N (14/40) ? ?	? ? ? I ? ? ? ? ? ? ? ? N ? ? ? ? ? I N D ? I ? ? ? ? ? I ? ? ? ? ? ? I	L TOP S L L L L TOP L TOP L L L L L L L L L L S L L L L L TOP L L L L

* Brackets indicate sibs

PERINALLY LETHAL CASES (PNL)

	Case no.	Data collection	Birth X-ray available	Sex	Fetal movement	Prenatal U.S.S.	Amniotic volume	Liveborn, stillborn, TOP
Text section Table no.		3.2, 6.1	3.3	6.2 6.1	6.3.1 6.2	6.3.2 6.3	6.3.3 6.4	6.3.4 6.5
TYPE IIB OI	150-161*	O O IY(F) O O O IY(F) O IY(F) O O IY(F)	+ + + + + + + + + + + +	F M F M F M F M F M M F	? D D weak ? ? ? D ? D churning ? ? ?	? ? ? ? ? ? ? ? ? ? A (~23/40) ? (social TOP)	I ? D ? ? ? ? ? I ? ? ?	L L L L L L ? L L TOP TOP
TYPE IIC OI	165-167	O IY(F) O	+ + +	M F M	? ? ?	? A (~19/40) ?	? ? ?	S TOP S
UNCLASSIFIABLE PERINALLY LETHAL OI	168-177	IY(F) IY(F) O O ET(F) IY(F) O O O IY(F)	- - - - - - - - - -	F F M M M F F M M M	? ? ? ? ? D none ? ? ? D ?	? ? A (24/40) ? ? ? ? ? N ?	D ? D ? ? I I ? N ?	S L S L S L L L L L

* Brackets indicate sibs

PERINATAL SURVIVORS

	Case No.	GA (wk)	Pres. at delivery	Mode delivery	Birth measurements						Age at death of liveborns (yr)	Age at the study (yr)
					Weight (gm)		Length (cm)		OFC (cm)			
Text section					6.4.1	6.4.1	6.4.2	6.4.2	6.4.2	6.4.2	6.5,6.7.1.1	6.7.1.1
Table no.					6.11	6.12	6.13			6.14	6.15	Fig. 6.2
TYPE III/ IV SPORADIC OI												
	1	38	V	S	2296	3	-	-	33	10-50	-	13.0
	2	40	B	S	2268	<3	-	-	-	-	-	25.42
	3	42	V	S	3771	50	53	90	34-5	10-50	3.83	3.83
	4	40	B	CS	2750	3-10	-	-	-	-	-	3.58
	5	38	V	S	3261	50	-	-	-	-	-	10.0
	6	40	V	S	2637	3-10	-	-	-	-	-	22.17
	7	35	V	S	2268	10	-	-	-	-	2.17	-
	8	40	B	?	3062	10-50	-	-	-	-	-	19.33
	9	38	V	S	2000	<3	-	-	-	-	-	0.33
	10	39	B	S	2325	3	-	-	-	-	-	3.08
	11	37	V	S	2268	3	-	-	-	-	-	18.17
	12	40	V	S	2495	3	-	-	-	-	-	14.67
	13	39	B	CS	2693	10	-	-	-	-	-	0.54
	14	40	V	S	2750	3-10	-	-	-	-	-	23.33
	15	40	B	F	2693	3-10	-	-	-	-	-	16.83
	16	40	B	?	2580	3	-	-	-	-	-	23.25
	17	40	B	F	2792	3-10	-	-	-	-	-	10.5
	18	40	NE	CS	2438	3	-	-	-	-	-	2.3
	19	40	V	S	2637	3	-	-	-	-	-	11.25
	20	40	V	S	2098	<3	-	-	-	-	-	2.5
	21	40	FB	F	2608	3	-	-	-	-	-	16.92
	22	34	V	S	1871	3-10	-	-	-	-	-	13.5
	23	40	V	F	3600	50	-	-	-	-	-	15.25
	24	40	B	S	3289	10-50	-	-	-	-	-	2.0
	25	40	V	CS	2500	3	-	-	-	-	-	23.17
	26	39	V	S	2693	3-10	-	-	-	-	-	4.67
	27	37	V	S	2155	3	-	-	-	-	-	39.67
	28	37	B	F	2495	3-10	-	-	-	-	0.25 (11 wk)	-
	29	37	B	CS	1814	<3	-	-	-	-	-	7.17
	30	40	V	S	2665	3-10	-	-	-	-	-	19.67
	31	40	V	S	2948	10-50	-	-	-	-	-	11.92
	32	40	B	CS	2665	3-10	-	-	-	-	-	0.58
	33	37	BE	F	2060	<3	-	-	32.5	10-50	-	0.25
	34	40	V	S	2948	10-50	-	-	-	-	0.5	-
	35	40	V	S	2268	<3	-	-	-	-	-	20.17
	36	41	B	S	2240	<3	-	-	-	-	9.0	-
	37	42	V	?	3416	10-50	-	-	-	-	-	20.17
	38	40	B	?	-	-	-	-	-	-	-	54.83
	39	40	B	F	2552	3	-	-	-	-	-	12.67
	40	38	V	S	4012	90-97	-	-	-	-	-	26.17
	41	40	?	?	-	-	-	-	-	-	-	27.08
	42	40	B	CS	3090	10-50	-	-	-	-	-	9.75
	43	42	V	S(I)	2948	3-10	-	-	-	-	0.67	-
	44	40	V	S	2835	10	-	-	-	-	-	5.58
	45	37	V	S	2070	<3	-	-	-	-	-	21.5
	46	38	V	S	2495	3-10	-	-	-	-	9.08	8.08
	47	36	V	S	2495	10	-	-	-	-	-	14.33
	48	40	B	F	2679	3-10	-	-	-	-	-	16.25
	49	40	B	S	2410	<3	-	-	-	-	-	15.08
	50	41	B	S	2495	<3	-	-	-	-	-	7.83
	51	37	V	S(I)	2693	10	-	-	-	-	-	11.83
	52	40	V	S	3289	10-50	-	-	-	-	-	16.75
	53	39	V	F	3175	10-50	-	-	-	-	-	0.67
	54	42	V	S	2920	3-10	-	-	-	-	-	14.5
	55	40	V	F	2325	<3	-	-	-	-	-	3.08

PERINATAL SURVIVORS

Text section Table no.	Case no.	GA (wk)	Pres. at delivery	Mode delivery	Birth measurements						Age at death of liveborns (yr)	Age at the study (yr)
					Weight (gm)		Length (cm)		OFC (cm)			
					6.4.1 6.11	6.4.1 6.12	6.4.2 6.13	6.4.2	6.4.2 6.14	6.5,6.7.1.1 6.15	6.7.1.1 Fig. 6.2	
TYPE III/IV SPORADIC OI	56	40	V	S	3175	10-50	-	-	-	-	19.5	
	57	40	V	?	2948	10	-	-	-	-	44.08	
	58	40	V	S	2722	3-10	-	-	-	-	15.58	
	59	40	V	S	3430	50	-	-	-	-	0.42	
	60	40	V	S	2041	<3	-	-	-	-	28.83	
	61	44	V	F	3062	<3	-	-	-	-	14.17	
	62	40	?	?	-	-	-	-	-	-	20.75	
	63	40	V	S	2060	<3	-	-	-	-	12.17	
	64	40	B	S	2722	3-10	-	-	-	-	3.25	
	65	40	V	S	2778	3-10	-	-	-	-	16.92	
	66	39	V	S	2807	10	-	-	-	6.83	-	
	67	40	V	?	-	-	-	-	-	-	38.58	
	68	40	V	S	2155	<3	-	-	-	8.25	-	
	69	40	V	S	3062	10-50	-	-	-	-	9.5	
	70	40	B	?	3430	50	-	-	-	0.5	-	
	71	39	V	S	2367	3	-	-	-	-	0.58	
	72	40	B	CS	2226	<3	-	-	-	-	0.75	
	73	40	V	S	3515	50-75	-	-	-	-	8.33	
	74	38	?	?	-	-	-	-	-	1.25	-	
	75	40	?	?	3119	10-50	-	-	-	8.5	18.5	
	76	36	?	?	2438	10-50	-	-	-	-	18.92	
	77	40	?	?	2268	<3	-	-	-	-	34.58	
	78	40	?	?	2523	3	-	-	-	-	17.33	
	79	40	?	?	3515	50	-	-	-	-	5.75	
	80	40	?	?	2807	3-10	-	-	-	-	17.17	
	81	42	B	?	2722	<3	-	-	-	-	31.0	
	82	40	?	?	2594	3	-	-	-	-	8.42	
	83	39	B	CS	2608	3-10	-	-	-	0.67	-	
	84	41	?	?	3062	10-50	-	-	-	-	13.67	
	85	41	?	?	2920	10-50	-	-	-	-	15.58	
	86	40	V	S	3160	10-50	-	-	-	0.33	-	
	87	?	?	?	-	-	-	-	-	0.75	-	
TYPE III RECESSIVE OI	90	38	B	CS	2160	<3	-	-	-	-	0.33	
	91]*	39	B	CS	2470	3-10	-	-	-	1.25	-	
	92]	40	B	CS	2126	<3	-	34	10	0.04 (16 dy)	-	
	93]	40	V	S	2693	3-10	-	-	-	8.5	-	
	94]	40	V	S	2637	3-10	-	-	-	1.33	-	
	95]	?	?	?	-	-	-	-	-	-	2.0	
	96]	?	V	S	-	-	49	31	-	0.25	-	
	98]	40	V	S	4168	90	-	-	-	16.0	-	
	99]	37	B	S	3175	10-50	-	-	-	-	30.25	
	100]	38	V	S	2438	3-10	-	-	-	-	10.0	
	101]	37	V	S	2300	3-10	-	-	-	1.83	-	
	102]	?	?	?	-	-	-	-	-	-	32.08	
	103]	?	?	?	-	-	-	-	-	-	20.67	
	104]	40	V	S	3402	50	-	-	-	-	3.08	
	105]	40	V	F	3345	10-50	-	-	-	9.17	-	

* brackets indicate sibs

(Nos. 88, 89, 97, 106-108:- see PNL)

PERINATAL SURVIVORS

	Case No.	GA (wk)	Pres. at delivery	Mode delivery	Birth measurements						Age at death of liveborns (yr)	Age at the study (yr)
					Weight (gm)		Length (cm)		OFC (cm)			
Text section Table no.					6.4.1 6.11	6.4.1 6.12	6.4.2 6.13	6.4.2	6.4.2 6.14	6.4.2 6.14	6.5, 6.7.1.1 6.15	6.7.1.1 Fig. 6.2
TYPE I NEW MUTATION OI	109	39	B+V	?	2268	<3	-	-	-	-	-	4.17
	110	40	V	?	3175	10-50	-	-	-	-	-	23.0
	111	38	V	S	2381	3	-	-	-	-	-	5.5
	112	39	V	S(T)	2665	3-10	-	-	-	-	-	14.0
	113	40	V	S	2608	3-10	-	-	-	-	-	20.75
	114	36	V	S	2325	10	-	-	-	-	-	4.67
	115	42	V	S	2268	<3	-	-	-	-	-	40.5
	116	31	?	CS	1890	50	-	-	-	-	-	0.67
	117	?	?	?	-	-	-	-	-	-	-	36.25
	118	40	V	S	2722	3-10	-	-	-	-	-	16.17
	119	37	?	?	2807	10-50	-	-	-	-	-	4.33
TYPE IIB OI	162	40	B	F	2025	<3	-	-	31.6	<3	2.17	-
	163	41	V	S(I)	2325	<3	-	-	-	-	0.08 (4 wk)	-
	164	40	V	S	2296	<3	36.5	<<3	31.5	<3	0.12 (6 wk)	-

PERINATALLY LETHAL CASES

	Case no.	GA (wk)	Pres. at delivery	Mode delivery	Birth measurements								Age at death of live-borns
					Weight (gm)		CR (cm)	GA (N)	CH (cm)		OFC (cm)		
Text section Table no.					6.4.1	6.4.1	6.4.2	6.4.2	6.4.2	6.4.2		6.4.2	
TYPE III/IV SPORADIC OI	88	30	B	S	-	-	-	-	-	-	-	-	S
	89	38	B	CS	2381	3	-	-	-	-	-	-	1 day
TYPE III RECESSIVE OI	97	28	TOP	TOP	-	-	-	-	-	-	-	-	TOP
	106	38	B	F	2381	3	-	-	-	-	-	-	10 hr
	107	27	TOP	TOP	-	-	-	-	-	-	-	-	TOP
	108	20	TOP	TOP	-	-	-	-	-	-	-	-	TOP
TYPE IIA OI	120	41	B	CS	2240	<3	-	-	37	<<3	33.5	3	24 hr
	121	?	TOP	TOP	-	-	-	-	-	-	-	-	TOP
	122	36	?	CS	1240	<3	23	27	28	<<3	-	-	S
	123	?	?	CS	1850	-	29	-	36	-	33	-	30 min
	124	35	B	S	1520	<3	29.5	-	34.5	<<3	-	-	50 min
	125	36	?	CS	1453	<3	31	-	38	<<3	29	<3	5 min
	126	39	?	?	-	-	-	-	34	<<3	33	10	30 min
	127	17	TOP	TOP	-	-	13.3	18	-	-	-	-	TOP
	128	30	?	?	1230	10-50	27.3	-	34.4	<<3	-	-	24 hr
	129	23	TOP	TOP	-	-	-	-	-	-	-	-	TOP
	130	36	V	S	-	-	-	-	-	-	-	-	30 min
	131	?	?	?	-	-	-	-	-	-	-	-	30 min
	132	20	?	S	-	-	16.0	20-21	-	-	-	-	S
	133	39	B	?	2050	<3	-	-	-	-	-	-	20 min
	134	40	?	CS	-	-	-	-	-	-	-	-	5 min
	135	?	?	?	-	-	-	-	-	-	-	-	?
	136	40	B	?	2080	<3	27	-	34	<<3	31	<3	20 hr
	137	35	?	?	2268	10	-	-	-	-	-	-	4 hr
	138	39	FB	CS	1850	<3	-	-	36.6	<<3	31.5	<3	40 min
	139	30	B	CS	1270	10-50	28	-	37	3	-	-	15 min
	140	39	B	F	1500	<3	-	-	-	-	-	-	S
	141	40	V	S	2100	<3	-	-	-	-	-	-	8 hr
	142	36	B	S	1150	<3	24	28	36	<<3	27	<<3	S
	143	31	?	?	1800	50	24	28	28	<<3	23	<<3	S
	144	34	B	CS	1550	<3	28	-	35	<<3	29	3	10 min
	145	18	TOP	TOP	-	-	-	-	-	-	-	-	TOP
	146	32	B	F(T)	1350	<3	29	-	34.5	<<3	27.5	<3	1 1/2 hr
	147	36	B	CS	1820	<3	30	-	36	<<3	31.5	10	5 min
	148	35	B	?	-	-	-	-	-	-	-	-	3 min
	149	39	FB	F	1800	<3	28	-	33	<<3	31	<3	30 min
TYPE IIB OI	150	37	B	S	2920	50	-	-	46	10	36	97	2 days
	151	?	B	F	2820	-	-	-	48	-	33.5	-	8 hr
	152	37	?	CS	1844	<3	34	-	-	-	30	<3	6 hr
	153	36	?	S	1980	3	-	-	45	10	32.5	25-50	2 1/2 hr
	154	36	?	CS	2480	10-50	32.5	-	38.5	<<3	-	-	6 hr
	155	41	?	?	-	-	31	-	39	<<3	35.2	25-50	24 hr
	156	41	B	?	3240	10-50	-	-	-	-	-	-	24 hr
	157	?	?	?	-	-	-	-	-	-	-	-	?
	158	34	?	?	1200	<3	-	-	-	-	-	-	50 min
	159	36	?	?	1900	<3	-	-	-	-	-	-	2 hr
	160	23	TOP	TOP	-	-	-	-	-	-	-	-	TOP
	161	18	TOP	TOP	-	-	-	-	-	-	-	-	TOP

* Brackets indicate sibs

PERINATALLY LETHAL CASES

* CH centile < OFC centile

	Case No.	GA (wk)	Pres. at delivery	Mode delivery	Birth measurements								Age at death of live-borns	
					Weight (gm)		CR (cm)	GA (N)	CH (cm)		OFC (cm)			
Text section														
Table no.		6.3.5 6.6, 6.7	6.3.6 6.8	6.3.7 6.9-6.10	6.4.1 6.11	6.4.1 6.12	6.4.2 6.13	6.4.2	6.4.2	6.4.2	6.4.2	6.14	6.4.2	6.5,6.7.1.1 6.15
TYPE IIC OI	165 166 167	30 19 28	? TOP ?	? TOP ?	775 - 700	<3 - 3-10	23 20 13	27 23-24 17-18	30 28 -	<<3 <<3	26.5 - 15.5	3-10 -	S TOP S	
UNCLASSIFIABLE PERINATALLY LETHAL OI	168 169 170 171 172 173 174 175 176 177	31 34 32 34 ? 34 38 34 40 ?	V V ? ? ? ? TV V B ?	S(I) S CS ? ? CS CS S F ?	1043 1420 - 860 1382 1060 1389 1552 2112 1640	3 <3 - <3 - <3 <3 <3 <3 -	- 31 - 24 - 26 - - - -	- - 28 - - <29 - - - -	- 38 26.5 36.3 30 - - - 35	<<3 <<3 <<3 - <<3	30.5 26.2 27.5 -	10-50 <<3*	S 20 hr S 20 min S 1 hr 25 min 1 hr 30 min 40 min	

PERINATAL SURVIVORS

	Case no.	Cause of death	No. fractures at birth		No. fractures after birth	Clinical skeletal deformity				
			R	X-ray		Arms	Legs	Previous treatment	Chest	Spine
Thesis section Table no.		6.7.1.2	6.7.2.1.1		6.7.2.1.2	6.7.2.2				
		6.17	6.18		6.19	6.20	6.20	-	6.20	6.20
TYPE III/ IV SPORADIC OI	1	-	?	-	M	6	1(POP)	Ops. on (L) arm, all seg. legs	PC	S(M)
	2	-	M	-	>50	12	10	Legs rodDED	PC(S)	KS (S)
	3	R	5	4	M	8	8	No	PC	N
	4	-	M	>6	M	1	4	No	PC	N
	5	-	9	-	4	12	12	Tibiae straight- ened	PC(S)	S(M)
	6	-	M	-	20	0	1(S)	No	PC(S)	KS(S) LL
	7	R	M	-	~12	bowed	bowed	No	?	?
	8	-	14	-	>100	2	0	Femora & tibiae rodDED	PC(S)	KS(M) LL
	9	-	M	9	0	0	4	No	?	N
	10	-	M	>2 (i)	>4	2	6	No	PC	N
	11	-	M	1 (i)	30-40	12	12	Rods now removed	PC(S)	KS
	12	-	M	-	>100	2(S)	0(S)	Rods in all 4 segs. legs (16 ops.)	B	S
	13	-	5	8	1	0	6	No	PC(M)	N
	14	-	M	-	~400	8	8	No	B	S
	15	-	15	-	>100	12	12	Ops. on all limbs	PC	S(S)
	16	-	M	-	>300	2	0(S)	Rods in femora, tibiae, humeri (18 ops.)	PC	KS, LL (S)
	17	-	8	-	108	6	2	Rods in tibiae & femora	PC(M)	N
	18	-	M	5	2	2	6	No	PC	N
	19	-	M	>8	?	2	2	No	PC	S
	20	-	M	21	11	4	8	No	PC(M)	S(M)
	21	-	>1	-	>100	4	4	Rods (?where)	PC	KS
	22	-	1	-	>20	2	0	10 ops. on legs	PC	N
	23	-	3	-	>100	3	0	Rods in legs	PC	S(S)
	24	-	3	-	M	2	2	No	PC	S(M)
	25	-	?	-(i)	M	1	2	Rods in legs	PC	?
	26	-	>2	-	9	0	2(S)	No	PC	N
	27	-	M	-	4	4(S)	?(S)	No	PC	?
	28	?	M	>14	0	bowing	bowing	No	?	?
	29	-	M	>5	18	1	0	op. on femora	PC	S
	30	-	M	(30, Dr)	>200	7	12	No	PC(S)	S(S)
	31	-	M	>1	>100	4	6	Rods in tibiae & femora remo- ved	PC(S)	KS(M)
	32	-	M	7	0	1	0	No	PE	N
	33	-	M	>6	0	2	0	No	?	N
	34	R	M	11	0	?	?	No	?	?
	35	-	M	-	~20	1	1	Yes (?what)	PC(S)	S(S)
	36	R	3	(5, Dr)	M	'all limbs deformed'		No	?	?
	37	-	6	-	~65	2	4	No	PC(M)	KS(S) LL(S)

PERINATAL SURVIVORS

	Case no.	Cause of death	No. fractures at birth		No. fractures after birth	Clinical skeletal deformity				
			R	X-ray		Arms	Legs	Previous treatment	Chest	Spine
Thesis section Table no.		6.7.1.2	6.7.2.1.1	6.7.2.1.2	6.7.2.2					
		6.17	6.18	6.19	6.20	6.20	-	6.20	6.20	
TYPE III/ IV SPORADIC OI (cont.)										
38	-	M	-	M	4	6	No	PC	S(S)	
39	-	?	-	>70	1	1	Rods in all segs. legs	PC	S(M)	
40	-	30	-	~225	6	2	Ops. on all segs. all limbs	PC(S)	S(M)	
41	-	M	-	>100	12	12	Ops. on all 4 leg segs	PC	LL(S) S(M)	
42	-	4	-	~29	10	8	No	PC	S(M) LL(M)	
43	R	6	-	1	Limbs grossly misshapen		No	?	N	
44	-	2	4	~15	bowed arms	bowed thighs	No	PC	?	
45	-	M	-	150-200	8	8	No	PC	S(S)	
46	F	M	-	~12	8	8	No	PC(S)	S(S)	
47	-	18	-	193	6	12	No	PC(S)	S(S)	
48	-	M	-	40-50	all limbs short		No	PC	S	
49	-	M	-	30-36	10	6	No	PC	S(M)	
50	-	5	-	?	9	10	No	PC	S(S)	
51	-	M	10	~38	5	0	Rods in tibiae, femora, & humerus	PC(S)	S(M)	
52	-	M	-	~200	7	8	Rods in (R) humerus; & in femora (now out)	PC(S)	S(S)	
53	-	M	13	0	4	8	No	PC	N	
54	-	5	-	>100	8	8	No	PC	S(M)	
55	-	11	7	15	?	bowed legs	No	PC	LL N	
56	-	2	-	>100	2	bowed	Rods in femora & tibiae	PC(M)	N	
57	-	2	-	M	2	4	Op. on (R) humerus	PC	S	
58	-	M	-	~100	10	12	No	PC(S)	S(S)	
59	-	5	5	0	2	0	No	N	N	
60	-	18	-	>100	2	4	No	PC(M)	LL(S)	
61	-	M	-	~60	6	8	Rods in lower legs & (R) femur	PC	N	
62	-	2	6	>200	7	5	Pins in arms & legs	PC(M)	S(M) LL(S)	
63	-	M	-(i)	~15	0	mild	Rods in femora	PC(M)	S(M)	
64	-	M	11	~50	12	72	No	PC(S)	N	
65	-	2	-(i)	43	2	3	Many ops., rods now out	PC(S)	KS(S)	
66	R	56	-	>100	deformed	?	No	PC(S)	?	
67	-	M	-	60-70	6	7	No	PC(S)	KS(S)	
68	R	60	-	30-40	'gross deformities'		No	Severe deformities?		
69	-	M	-(i)	>70	3	4	Rods in femora	PC	S(S)	
70	?	?	>3	?	bowed limbs		No	?	LL ?	

PERINATAL SURVIVORS

	Case no.	Cause of death	No. fractures at birth		No. fractures after birth	Clinical skeletal deformity				
			R	X-ray		Arms	Legs	Previous treatment	Chest	Spine
Thesis section Table no.		6.7.1.2	6.7.2.1.1	6.7.2.1.2	6.7.2.2					
		6.17	6.18	6.19	6.20	6.20	-	6.20	6.20	
TYPE III/ IV SPORADIC OI										
	71	-	7	6	1	0	4	No	N	N
	72	-	M	11	2	4	8	No	PC(M)	N
	73	-	M	-	~10	0	4	Yes (?what)	PC	S(M)
	74	?	?	-	25	bows	bows	No	?	?
	75	?	12	-	M	Yes	Yes	No	?	N
	76	-	3	-	?	No	Yes	Rodding (?where)	?	C(S)
	77	-	M	-	~130	Yes	Yes	Yes (?what)	?	N
	78	-	M	-	100	Yes	No	Rods in femora & tibiae	?	N
	79	-	4	-	19	Yes	Yes	Rods in legs	?	N
	80	-	M	-	~40	Yes	Yes	Rods in femora	?	C(M)
	81	-	?	-	?	?	?	?	?	?
	82	-	16	>1	>100	Yes	Yes	Rodding in arms, legs (before rods)	?	C(M)
	83	R	19	-	3	Yes	Yes	No	?	?
	84	-	M	-	M	Yes	Yes	Yes (?what)	?	C(S)
	85	-	?	-	>39	Yes	Yes	No	?	C(S)
	86	?	?	>4	?	Limbs short & deformed		No	?	?
	87	?	M	-	?	All limbs short & deformed		No	deform- ed	?

PERINATAL SURVIVORS

	Case no.	Cause of death	No. fractures at birth		No. fractures after birth	Clinical skeletal deformity				
			R	X-ray		Arms	Legs	Previous treatment	Chest	Spine
Thesis section Table no.		6.7.1.2	6.7.2.1.1	6.7.2.1.1	6.7.2.1.2	6.7.2.2				
TYPE III RECESSIVE OI		6.17	6.18	6.19		6.20	6.20	-	6.20	6.20
	90	-	M	22	1	Yes(S)	Yes(S)	No	?	?
	[91*	R	M	13	M	Yes(S)	Yes(S)	No	?	?
	[92	?	M	-	?	?	Yes	No	?	?
	[93	R	?	-	>100	Yes	Yes	?	?	S(M)
	[94	R	?	-	0	Yes	Yes	No	?	N
	[95	-	?	9	?	?	?	?	?	?
	[96	?	M	M	?	?	Yes	No	?	?
	[98	R	M	-	>100	Yes	Yes	No	PC	K(S)
	[99	-	M	-	>100	10(S)	2(S)	Legs straightened	PC(S)	KS(S)
	[100	-	M	-	~80	2	5	Op. on feet	PC(S)	KS(S)
	[101	PF	M	-	'few'(?)	Yes	Yes	Rods in fems, tibs, fibs	?	?
	[102	-	?	-	M	Yes	Yes(S)	One rod (?where)	PC	S
	[103	-	M	-	50	No(S)	Yes(S)	Yes (?what)	PC	S,LL
	[104	-	2	-	25-30	Yes	Yes	No	PC/PE	S
	[105	F	2	-	11	Yes	Yes	Rods in legs	PC	KS
TYPE I NEW MUTATION OI										
	109	-	4	4	11	0	2	No	N	N
	110	-	3	-	~50	0	0	Femora rodDED	N	S(M)
	111	-	14	-	>50	0	0	Femora rodDED	PC(M)	N
	112	-	1	-	46	2	?	Multiple rods	PC	S(M)
	113	-	?	-	M	0	2	18 ops.	PC	N
	114	-	2	-	4	0	0	No	PC(S)	N
	115	-	2	-	~60	1	2	Rod in (R) tibia	B	S
	116	-	1	-	~6	0	0	No	N	N
	117	-	?	-	>6	0	0	No	PC(M)	S
	118	-	2	-	~7	0	0	Rods in femora, tibia	PC	N(LL)
	119	-	2	2	2	0	0	bowed femora	?	?
TYPE IIB OI										
	162	R	M	24	1	Yes	Yes	No	?	?
	163	R	M	26	0	No(S)	Yes	No	?	?
	164	RI	M	26	'Several'	Yes	Yes	No	?	?

* Brackets indicate sibs

PERINATAL SURVIVORS

	Case no.	Height (cm)		OFC (cm) Centile		Handicap		Sclerae		Visual function	Strabismus
			SDS or centile (C)			Sitting	Walking	At birth	At study or death		
Thesis section Table no.		6.7.2.3	6.7.2.3	6.7.2.3		6.7.3	6.7.3	6.7.4.1	6.7.4.1	6.7.4.2	6.7.4.2
		-	6.21	-	6.22	6.23		6.24	6.26	6.28	6.29
TYPE III/ IV SPORADIC OI											
1	95	R	-7.47	53.5	25-50	Yes	NW	N	1	L (O)	-
2	81.5	R	-13.45	58.5	>>97	Yes	NW	?	1	S (S)	-
3	56	ET	-10.23	51.0	75	No	NA	P	0-1	N	-
4	73	ET	-6.23	50.5	25	Yes	NW	D	3	N	-
5	77	ET	-9.58	53.0	50-75	Yes	NW	P	0	N (S)	-
6	104	R	-9.70	?	-	Yes	NW	D	1-2	S (O)	-
7	61	R	-7.40	?	-	No	NA	D	D	N	?
8	77.6	R	-14.10	50.5	<<3	Yes	Yes(u)	?	1-2	S (O)	-
9	?		-	37.0	3	Yes	NA	D	3	?	?
10	63	ET	-8.22	50.0	25-50	No	NA	D	3	L (Op)	+(B)
11	92	R	-12.44	53.0	10	Yes	NW	D	3	N (S)	-
12	78	ET	-13.55	53.7	25	Yes	NW	?	3	?	?
13	53	ET	<<3C	41.0	25	NA	NA	P	2	N	-
14	89	R	-12.2	58.0	>>97	Yes	NW	D	1	N (S)	+(R)
15	97	ET	-10.87	54.0	25-50	Yes	NW	D	1	O (O)	?
16	107	R	-9.20	55.0	75	Yes	Yes(p)	?	0-1	S (O)	-
17	120	R	-3.0	57.0	>>97	Yes	Yes(p)	P	0-1	O (Op)	+(L)
18	61	ET	-7.57	44.8	<3	Yes	NA	D	3	N (Op)	-
19	82	ET	-9.01	55.0	90	Yes	NW	P	1	N (S)	-
20	54	ET	-9.78	46.5	3-10	No	NA	P	1	N (O)	+
21	101	R	-10.96	55.5	50-75	Yes	Yes(p)	D	2	O (Op)	+(L)
22	114	R	-6.64	53.0	25	Yes	NW	D	1	N	?
23	94	ET	-9.60	53.0	10	Yes	NW	D	3	O (Op)	?
24	67	ET	-5.33	50.5	97	Yes	NA	?	2	?	?
25	126	ET	-7.32	59.0	>>97	Yes	Yes(p)	D	0-1	S (O)	-
26	76.8	ET	-6.38	52.5	75	Yes	Yes(a)	P	0-1	?	?
27	?		-	58.5	>97	Yes	NW	P	1	S (O)	-
28	?		-	?	-	NA	NA	D	P	N	-
29	90	ET	-5.50	54.5	>97	Yes	NW	D	3	O (S)	?
30	62	ET	-16.70	52.5	25	Yes	NW	D	1	N (S)	+
31	80	ET	-9.03	52.8	25-50	Yes	NW	?	1	N (O)	-
32	52	ET	<<3C	42.0	10	NA	NA	D	1	?	?
33	?		-	36.6	10	NA	NA	D	1-2	?	?
34	?		-	-	-	NA	NA	D	?	?	?
35	117	R	-7.53	54.5	50	Yes	Yes(u)	D	1-2	N (O)	-
36	?		-	-	-	No	NW	D	?	N	-
37	117	R	-7.53	55.5	75-90	Yes	Yes(u)	D	1-2	N (S)	-
38	103.5	ET	-10.71	56.5	75-90	Yes	Yes(p)	D	1	S (O)	?
39	104	ET	-6.23	53.0	25	Yes	NW	D	1	N (S)	?
40	100	R	-10.37	57.5	>97	Yes	NW	D	3	O (O)	+(L)
41	86.4	R	-12.63	56.0	90-97	Yes	Yes(a)	D	1	S (O)	-
42	58.5	ET	-12.29	54.0	90-97	Yes	NW	D	1	N (S)	-
43	53.3	R	<<3C	?	-	NA	NA	D	?	?	?
44	87.5	ET	-4.69	53.0	90-97	Yes	Yes(a)	?	0-1	?	?
45	76	R	-14.37	50.2	<<3	No	NW	D	3	S (O)	-
46	64	ET	-10.65	52.5	75	No	NW	D	3	N	-
47	?		-	50.0	<<3	Yes	NW	D	0-1	N (S)	-
48	88	R	-12.37	51.5	<3	Yes	NW	D	2	L (O)	-
49	73	ET	-14.60	53.8	25-50	No	NW	D	3+	N (S)	-
50	62	ET	-10.89	53.5	90-97	Yes	NW	D	3+	S (Op)	-
51	111.5	ET	-4.89	53.0	25-50	Yes	Yes(p)	D	2	N (S)	-
52	110	ET	-9.54	54.5	25-50	Yes	NW	D	1	N (O)	-
53	52	ET	<<3C	45.1	50	NA	NA	D	1	N	-
54	84	ET	-9.64	54.0	25-50	?	NW	D	3	N (Op)	-
55	61	ET	-8.43	49.2	25-50	Yes	NA	D	3	?	?
56	122	R	-6.7	54.2	50	Yes	Yes(a)	D	0-1	N	?
57	95	R	-11.98	56.5	75-90	Yes	NW	D	3	L (O)	?

PERINATAL SURVIVORS

	Case no.	Height		OFC		Handicap		Sclerae		Visual function	Strabismus
		(cm)	SDS or centile	(cm)	Centile	Sitting	Walking	At birth	At study or death		
Thesis section Table no.		6.7.2.3		6.7.2.3		6.7.3	6.7.3	6.7.4.1	6.7.4.1	6.7.4.2	6.7.4.2
		-	6.21	-	6.22	6.2.3	6.2.3	6.24	6.26	6.28	6.29
TYPE III/IV SPORADIC OI											
	58	?	-	55.5	50-75	Yes	NW	D	2	N (S)	-
	59	54	ET <3C	42.0	50	NA	NA	D	3+	?	?
	60	110	ET -9.73	57.5	97	Yes	Yes(p)	D	1-2	N (Op)	-
	61	86	ET -9.10	59.5	>>97	No	NW	D	1	S (O)	-
	62	102	R -10.03	55.0	75	Yes	Yes(p)	D	3	S (O)	-
	63	115	ET -4.72	53.2	50	Yes	Yes(a)	D	1	N (S)	-
	64	58	ET -9.35	50.0	50-75	No	NA	D	3+	N	-
	65	97	R -10.87	52.0	just <3	Yes	Yes(a)	D	3	N (O)	-
	66	66	R 3-10C	48.5	>97	Yes	NW	D	P	N	-
	67	107	R -10.18	58.5	>97	Yes	Yes(p)	D	1-2	S (O)	-
	68	69	R -6.26	?	-	No	NW	D	D	N (Hv)	-
	69	90	ET -7.26	52.5	50	Yes	NW	D	2	N	-
	70	?	-	?	-	NA	NA	P	?	N	-
	71	50	ET <<3C	40.8	3	NA	NA	D	1-2	N	-
	72	48	ET -8.81	43.0	10-25	NA	NA	D	3	N	-
	73	103	ET -4.09	49.0	<3	Yes	Yes(u)	?	1	N (S)	?
	74	?	-	?	-	No	NA	D	D	?	?
	75	92	R -12.44	-	-	No	NW	W	W	?	?
	76	112	R -8.37	-	-	Yes	Yes(u)	P	P	?	?
	77	120	R -8.23	-	-	?	NW	D	P	?	?
	78	122	R -7.88	-	-	Yes	NW	D	W	?	?
	79	79	R -6.76	-	-	Yes	NW	D	W	?	?
	80	76	R -14.77	-	-	Yes	NW	P	P	?	?
	81	84	R -13.64	-	-	Yes	NW	D	P	?	?
	82	?	-	-	-	Yes	NW	D	P	?	?
	83	?	-	-	-	NA	NA	D	D	?	?
	84	?	-	-	-	Yes	Yes(a)	P	P	?	?
	85	92	R -11.61	-	-	No	NW	D	P	?	?
	86	?	-	-	-	NA	NA	?	?	?	?
	87	?	-	-	-	NA	NA	?	?	?	?

PERINATAL SURVIVORS

	Case no.	Height		OFC		Handicap		Sclerae		Visual function	Strabismus
		(cm)	SDS or centile	(cm)	Centile	Sitting	Walking	At birth	At study or death		
Thesis section Table no.		6.7.2.3		6.7.2.3		6.7.3	6.7.3	6.7.4.1	6.7.4.1	6.7.4.2	6.7.4.2
		-	6.21	-	6.22	6.2.3	6.2.3	6.24	6.26	6.28	6.29
TYPE III RECESSIVE OI											
	90	?	-	?	-	NA	NA	N	N	N	?
	[91*	?	-	?	-	?	NA	W	W	?	?
	[92	?	-	?	-	NA	NA	?	?	?	?
	[93	?	-	?	-	No	NW	D	D	S (S)	-
	[94	?	-	?	-	No	NA	D	P	N	-
	[95	?	-	?	-	?	NA	?	?	?	?
	[96	49	R -5.42	?	-	NA	NA	?	?	?	?
	[98	91.4	R -7.91	52.07	10	Yes	NW	D	P	N	?
	[99	87.5	ET -13.11	54.5	25-50	Yes	NW	D	1	S (O)	-
	[100	92.0	R -7.18	53.0	50-75	Yes	NW	N	0-1	N (S)	+ (R)
	[101	?	-	?	-	No	NA	N	N	N (S)	-
	[102	92.0	R -12.44	?	-	Yes	NW	W	0-1	S (O)	-
	[103	107	R -9.2	52	just <3	Yes	Yes (a)	?	1	S (O)	-
	[104	77.5	R -5.64	47	3	Yes	NW	D	1	N	-
	[105	?	-	?	-	Yes	NW	D	P	N	-
TYPE I NEW MUTATION OI											
	109	89.5	ET -2.76	48.5	3-10	Yes	Yes	P	1-2	N (Op)	-
	110	152	R -3.41	57.8	97	Yes	Yes	D	1-2	O	-
	111	92	R -3.70	49.5	10-25	Yes	Yes	D	2	N	-
	112	139.5	R -2.55	56.8	90-97	Yes	Yes	D	3	N (S)	-
	113	127	R -5.87	53.8	25-50	Yes	Yes	D	2	?	?
	114	88	ET -3.69	50.5	50	Yes	Yes	D	3	N (Op)	-
	115	137	R -4.2	55.2	75-90	Yes	Yes	D	3	S (O)	+ (R)
	116	64	ET <3C	?	-	NA	NA	?	0	?	?
	117	137	R -4.2	57.0	>97	Yes	Yes	D	3+	S (O)	-
	118	125	ET -6.2	59.2	>>97	Yes	Yes (a)	D	2	N (S)	-
	119	86.4	R -4.03	?	-	Yes	Yes	P	P	?	?
TYPE IIB OI											
	162	?	-	?	-	No	NA	D	D	N	-
	163	?	-	?	-	NA	NA	N	N	?	?
	164	?	-	?	-	NA	NA	D	D	?	?

* Brackets indicate sibs

PERINATAL SURVIVORS

Thesis sect. Table no.	Joints			Skin hyper- extens- ibility	Easy bruising	Freq. epist- axes	Excess- ive sweat- ing	Clinical hearing loss	DI	Constip- ation	Hernia	High voice	Strong nails	
	Laxity		No. pairs lax large joints											Disloc- ations
	S	L												
Case no.	6.7.5.1 6.30	6.7.5.1 6.31	6.7.5.2 6.32	6.7.6.1 6.33	6.7.6.2 6.34	6.7.6.2 6.35	6.7.6.3 6.36	6.7.7. 6.37-39	6.7.8 6.40	6.7.9.1 6.41	6.7.9.2 6.42	6.7.11.3 6.43	6.7.11.4 -	
1	+ -	0/2	-	+	-	+	+	N (HV)	+ (2)	+	-	+	+	
2	+ -	0/1	-	+	-	-	+	D (S)	+ (2)	+	-	+	+	
3	+ +	5/5	-	?	-	-	+	N	+ (1)	-	-	+	-	
4	? ?	?	-	?	-	+	+	N (I)	+ (1)XR	-	+	-	?	
5	+ ?	?	-	+	-	-	+	N (S)	- (2)	+	-	+	-	
6	+ +	?	+	-	-	-	+	D	+ (2)	-	-	+	-	
7	+(H) ?	?	-	?	-	-	+	N (I)	?	+	+	?	-	
8	+ ?	?	+	-	-	-	+	D (S)	+ (2)XR	-	-	-	-	
9	- +	2/4	-	-	-	-	+	N	?	-	-	-	-	
10	+ +	3/3	-	-	-	-	+	N (AER)	- (1)	?	+	+	-	
11	+ ?	0/1 (S)	-	+	-	-	+ (C)	N (S)	+ (2)	+ (C)	-	-	-	
12	+ +	2/3 (S)	-	+	-	-	+	N (S)	+ (2)XR	+	-	+	-	
13	+ +	2/4	-	-	-	-	+	N	?	-	+	-	+	
14	+ +	3/4 (S)	+	+	-	+	+	N (S)	+ (2)	+	-	+	+	
15	+ +	1/4	+	+	-	-	+	N (S)	+ (2)XR	+	-	+	-	
16	+ ?	? (S)	-	-	-	-	+	N (S)	+ (2)	+	-	+	-	
17	+ ?	? (S)	+	-	-	-	+	N (S)	+ (2)	-	-	-	-	
18	+ +	?	-	-	-	+	+	N (I)	+ (1)	+	-	+	-	
19	+ +	3/3	-	-	-	-	+ (C)	N (S)	+ (2)XR	-	-	+	-	
20	? ?	?	-	+	-	-	-	N (HV)	- (1)	+	+	+	-	
21	+ +	4/4	-	+	+ (C)	+ (C)	+	N (I)	+ (2)	+	-	+	-	
22	+ +	1/3 (S)	-	+	-	-	?	N (S)	+ (2)XR	-	-	-	-	
23	+ +	2/3 (S)	+	+	-	-	+	N (S)	+ (2)	-	-	?	-	
24	+ +	5/5	-	-	-	-	+	H	+ (1)	?	-	-	+	
25	+ +	2/4	+	+	+ (C)	-	+ (C)	DU	- (2)	+	+	+	-	
26	+ +	5/5	+	-	+	-	+	N (S)	+ (1)	-	-	+	-	
27	+ -	0/4	-	-	-	-	+	DB (I)	+ (2)	-	+	?	?	
28	? ?	?	-	?	-	-	+	N	?	-	+	?	?	
29	+ -	0/4	-	-	-	-	+	N (S)	- (2)	-	+	+	-	
30	+ +	2/4 (S)	+	+	-	-	+	N (S)	+ (2)	+	-	+	+	
31	+ +	1/4	+	+	-	-	+	N (S)	+ (2)	+	-	+	-	
32	+ +	5/5	+	+	-	-	+	N	?	-	+	-	-	
33	+ +	2/5	-	-	-	-	+	N	?	-	+	-	?	
34	? ?	?	-	?	-	-	+	N	?	-	-	?	?	
35	+ +	1/4	+	+	-	-	+ (C)	N (E)	+ (2)XR	-	-	-	-	
36	? ?	?	+	?	-	-	+	N	+ (1)	+	-	+	-	
37	+ +	?	-	-	-	-	-	N (S)	+ (2)XR	-	-	-	-	
38	+ -	0/3 (S)	+	+	-	-	-	DB	+ (2)	+ (C)	+	-	-	
39	+ +	2/4 (S)	-	+	+ (C)	-	+ (C)	N (S)	+ (2)	-	-	+	-	
40	+ -	0/3	-	-	+	-	?	N (S)	+ (2)	?	-	-	-	
41	+ -	0/2 (S)	-	-	+	+ (C)	+	N	+ (2)XR	+ (C)	-	+	-	
42	+ +	?	-	-	-	-	+	N (I)	+ (2)	-	-	+	-	
43	? ?	?	-	?	-	-	+	N (E)	?	+	-	?	-	
44	+ +	5/5	+	+	+	-	+	?	+ (2)	+ (C)	-	+	-	
45	+ +	5/5	-	+	+	-	+	D (S)	+ (2)	+ (C)	-	+	-	
46	+ +	4/4	-	+	-	-	+ (C)	N (S)	+ (2)	-	-	+	-	
47	+ +	2/4 (S)	-	+	-	-	-	N (S)	- (2)	+	-	+	-	
48	+ +	1/5	-	+	-	+ (C)	+ (C)	N	+ (2)	-	-	+	-	
49	- -	?	-	+	-	-	+ (C)	N (S)	+ (2)	-	-	+	-	
50	+ +	2/4 (S)	-	+	+	-	+	N (S)	+ (2)	+	-	+	-	
51	+ +	1/4	-	-	-	-	+	N (I)	+ (2)	-	-	+	+	
52	+ ?	? (S)	+	+	-	-	+	DU (E)	- (2)	+	+	-	-	
53	- -	0/4	-	-	-	-	+	N	?	-	-	-	-	
54	+ +	?	-	+	+	-	+ (C)	N	+ (2)	+	+	-	-	
55	+ +	4/4	-	+	-	-	+	N	+ (1)	-	-	+	-	
56	- -	-	-	-	+	-	-	N	+ (2)	?	?	?	-	
57	- -	-	-	-	-	+ (C)	+	DB (E)	+ (2)	+ (C)	-	+	-	
58	+ +	1/2 (S)	-	-	-	-	+	N	+ (2)XR	-	-	+	-	
59	- +	2/5	-	-	-	-	+	N	?	-	+	?	-	
60	+ -	0/4	+	+	-	-	+	N (S)	+ (2)	+ (C)	+	+	-	

PERINATAL SURVIVORS

	Joints			Skin hyper-extensibility	Easy bruising	Freq. epistaxis	Excessive sweating	Clinical hearing loss	DI	Constipation	Hernia	High voice	Strong nails	
	Laxity		No. pairs lax large joints											Dislocations
	S	L												
Thesis sect. Table no.	6.7.5.1 6.30	6.7.5.1 6.31	6.7.5.2 6.32	6.7.6.1 6.33	6.7.6.2 6.34	6.7.6.2 6.35	6.7.6.3 6.36	6.7.7 6.37-39	6.7.8 6.40	6.7.9.1 6.41	6.7.9.2 6.42	6.7.11.3 6.43	6.7.11.4 -	
Case no.														
61	+	+	?	-	+	+	+	(C)	N	+	(2)	+	-	
62	+	-	0/2	-	+	-	-	-	N (S)	+	(2)	-	-	
63	-	-	0/4	-	+	-	-	+	(C)	N (S)	+	(2)	-	
64	+	+	?	-	+	-	-	+	N	+	(1)	+	-	
65	+	+	1/4	-	-	-	-	-	N (S)	+	(2)	-	-	
66	?	?	?	-	?	-	-	+	N	+	(2)	+	?	
67	-	-	0/2 (S)	-	-	-	-	+	DB (E)	-	(2)	-	+	
68	?	?	?	-	?	-	-	-	N (E)	+	(2)	-	?	
69	+	+	?	-	+	-	-	+	N	-	(2)	+	+	
70	?	?	?	-	?	-	-	+	N	?	?	+	?	
71	-	+	2/4	-	-	-	-	+	N	?	?	-	?	
72	-	-	0	-	-	-	-	+	N	?	?	-	-	
73	+	+	2/4	-	+	-	-	-	N (S)	-	(1)	-	?	
74	?	?	?	-	?	?	?	?	N	?	?	?	?	
75	-	-	-	-	?	?	?	?	N	-	(2)	?	?	
76	+	?	?	-	?	?	?	?	N	+	(2)	?	?	
77	+	?	?	-	?	?	?	?	DB	+	(2)	?	?	
78	+	(C)	?	-	?	?	?	?	N	+	(2)	?	?	
79	+	?	?	-	?	?	?	?	N	+	(?)	?	?	
80	+	?	?	-	?	?	?	?	N	+	(2)	?	?	
81	+	(C)	?	-	?	?	?	?	N	+	(2)XR	?	?	
82	+	?	?	-	?	?	?	?	N	+	(?)	?	?	
83	?	?	?	-	?	?	?	?	?	?	?	?	?	
84	+	?	?	-	?	?	?	?	N	+	(2)XR	?	?	
85	?	?	?	-	?	?	?	?	?	-	(2)	?	?	
86	+	?	?	-	?	?	?	?	?	?	?	?	?	
87	?	?	?	-	?	?	?	?	?	?	?	?	?	
TYPE III RECESSIVE OI														
90	?	?	?	-	?	?	?	?	N	?	?	+	?	
91	-	(H)	-	-	?	?	-	+	?	?	?	?	?	
92	?	?	?	-	?	?	?	?	?	?	?	?	?	
93	+	+(H)	?	-	?	?	-	+	N (S)	+	(2)	-	?	
94	-	(H)	-	-	?	?	-	+	N	?	(1)	-	?	
95	?	?	?	-	?	?	?	?	?	?	?	?	?	
96	?	?	?	-	?	?	?	?	?	?	?	?	?	
98	-	(H)	-	-	?	?	+	(C)	+	DB (E)	-	(2)	?	
99	-	-	-	-	+	?	-	-	+	N	+	(2)	+	
100	+	+	1/3	-	+	-	-	+	(C)	N (S)	-	(2)	+	
101	-	(H)	-	-	?	?	-	-	+	N (S)	?	?	?	
102	+	+	1/1 (S)	-	+	-	-	-	?	N	-	(2)	-	
103	+	+	2/4	-	+	-	-	-	-	D	-	(2)	-	
104	-	+	1/3	-	-	-	-	+	+	N (I)	+	(1)	-	
105	+	+(H)	?	+	?	-	-	+	+	DU (S)	+	(2)	+	
TYPE I NEW MUTATION OI														
109	+	+	1	-	-	-	-	+	(HV)	N	+	(1)	-	
110	-	-	?	+	-	-	-	+	(C)	DU	+	(2)	-	
111	+	+	?	+	?	+	-	+	+	N (S)	+	(1)	-	
112	+	+	?	+	+	+	-	-	-	N (S)	-	(2)	+	
113	-	+	2/5	-	-	-	-	-	-	D	+	(2)	-	
114	-	-	-	-	+	-	-	+	+	N (I)	+	(1)	-	
115	+	+	3/4 (S)	+	+	+	+	+	(C)	N	?	?	-	
116	?	?	?	?	?	?	?	?	?	?	?	?	?	
117	+	-	-	+	?	+	+	+	(C)	+	(C)	DB (E)	+	
118	+	+	?	-	-	+	-	+	+	N (S)	+	(2)	+	
119	?	?	?	?	?	?	?	?	?	N	-	(2)	?	

* Brackets indicate sibs.

PERINATAL SURVIVORS

	Joints			Skin hyper-extensibility	Easy bruising	Freq. epistaxis	Excessive sweating	Clinical hearing loss	DI	Constipation	Hernia	High voice	Strong nails	
	Laxity		No. pairs lax large joints											Dislocations
	S	L												
Thesis sect. Table no.	6.7.5.1 6.30		6.7.5.1 6.31	6.7.5.2 6.32	6.7.6.1 6.33	6.7.6.2 6.34	6.7.6.2 6.35	6.7.6.3 6.36	6.7.7 6.37-39	6.7.8 6.40	6.7.9.1 6.41	6.7.9.2 6.42	6.7.11.3 6.43	6.7.11.4 -
Case no. TYPE IIB OI														
162	? ?		?	?	-	-	+	N	+ (1)	+	+	?	?	?
163	? ?		?	+	-	-	+	?	?	?	-	?	?	?
164	? ?		?	-	?	-	+	?	?	-	-	?	?	?

NOTES FOR APPENDIX 6.1

Data collection

ET - patient examined by the author. ET(F) - patient not seen by the author, but the author interviewed the family. Q - patient not seen by the author, family returned a questionnaire. IY(F) - patient not seen but family interviewed by Dr Ian Young. O - other: information gathered from other doctors reports and hospital records.

Birth radiograph available

(+) - yes (babygram or skeletal survey). +(i) - yes but incomplete, vis case 11, femora only; cases 10, 25, 65, 69, femora and tibiae only; case 63 - skeletal survey minus chest radiograph.

Sex

M - male, F - female, (?) - sex unknown

Fetal movement during pregnancy

N - normal, D - decreased, I - increased, (?) - unknown.
Additional descriptions given by the mother are shown.

Prenatal USS (ultrasound scan)

These refer to second trimester scans which were either: N - normal; gestational age at which scan done also given, if known. A - abnormal. (?) - no information about scans, or no scan done.

Amniotic fluid volume

N - normal, D - decreased, I - increased, (?) - unknown.

Liveborn, stillborn, termination of pregnancy

L - liveborn, S - stillborn, TOP - termination of pregnancy.

Gestational age

GA - gestational age.

Pres. (presentation) at delivery

V - vertex, B - breech, FB - footling breech, BE - breech with extended legs, TV - transverse lie, NE - not engaged in the pelvis, TOP - termination of pregnancy, B-V - case 109 was breech but at 34 weeks was turned by external version and presented vertex.

Mode of delivery

S - spontaneous vaginal delivery (cases 43, 51, 163 and 168 were induced (S(I)) but then delivered normally), F - forceps, CS - Caesarian section, TOP - termination of pregnancy, S(T) - cases 112 and 146 were the firstborn of twins, their co-twins were normal, (?) - unknown.

Birth measurements

For PNS - length refers to crown-heel length. For PNL - CR is crown-rump length. GA(N) is the gestational age at which the given CR is normal, when known. CH is crown-heel length (CR unknown for all PNS). OFC - occipitofrontal circumference. Centile: <<3 is much less than 3rd centile. <3 less than 3rd centile. (-) is unknown.

Age at death of liveborns

Cases indicated by (-) were alive at the time of the interview. Cases 3 and 46 were seen by the author but died subsequently, during the time of the study. Similarly, case 75 died shortly after his questionnaire was returned.

Age at the study

Age at the interview or when information was received.

Cause of death of PNS (perinatal survivors)

(-) indicates patient was alive, R - lower respiratory infection, F - fall, followed by cerebral haemorrhage. PF - post-operative fat embolism. RI - respiratory with inhalation of gastric contents.

No. fractures at birth

R - by parents report, (?) - no. unknown, M - multiple, X-ray - no. fractures counted on radiograph by the author and Dr C M Hall. (>) - indicates 'at least', (i) no estimate given for those with incomplete skeletal survey. (-) indicates radiograph not available. Cases 30 and 36 estimated to have 30 and 5 fractures respectively, by their doctor.

No. fractures after birth

M - 'many' (some families could not estimate the fracture number, but reported that many had occurred).

Clinical skeletal deformity (determined by clinical examination)

Limbs - an attempt was made to score the severity of deformity in the limbs. Each segment (upper or lower) of each limb was scored as: 0 - straight, 1 - mild bowing, 2 - moderate bowing, 3 - severe bowing. e.g. the maximum bowing for the arms is $3 \times 4 = 12$. Sometimes, a limb would be straight (0) but short (S), or

assessment was obscured by a plaster of Paris (POP).

If patient was not seen by the author, a description by parents or hospital notes is given, or scored as 'yes' or 'no' for bowing of the legs or for spinal curvature.

Previous treatment - indicates previous operative treatment.
Segs. - segments e.g. upper arm, lower leg. Ops. - operations.

Chest

PC - pectus carinatum, PE - pectus excavatum, B - broad chest shape in lateral direction, N - normal.

Severity indicated in brackets but recorded for some patients only. (S) - severe or moderate, (M) - mild.

Patients 74-85 replied by questionnaire but were not asked about chest shape.

Spine

N - normal clinically, K - kyphosis, S - scoliosis, KS - kyphoscoliosis, LL - lumbar lordosis. Patients 74-85 replied by questionnaire as C - curvature of spine present (M - mild, S - severe), N - normal spine, (?) - unknown.

Severity (as for chest) recorded in some cases.

Height

ET - measured by the author, usually supine. R - measured by the family or given in hospital records. Case 66's height taken from hospital records at age 7 months (i.e. before the study). Case 104's was measured by the clinic nurse at 4.33 yr (after the study) but her OFC was measured by the author at 3.08 year.

Handicap

Sitting: yes - able to sit alone if over 1 year.

no - not able to sit alone if over 1 year.

NA - not applicable if under 1 year.

(?) - unknown.

Walking: yes (u) - able to walk unaided

yes (a) - able to walk with aids

yes (p) - able to walk previously

} if over 5 years.

NW - never walked.

NA - not applicable if under 5 years or unknown.

(Note: one patient under 1 year could sit alone (case 9) and 2 under 5 years could walk with aids (cases 26 and 109).

Sclerae

At birth: N - normal or W (white), P - pale blue, D - blue or deep blue, (?) - unknown.

At the time of the study, as examined by the author.

0 - white
0-1 very pale blue } normal
1 - pale blue
1-2 or 2 - moderate blue
3 or 3+ - deep blue.

Cases 77-85 (inc.) replied by questionnaire as W - white, P - pale blue, D - deep blue. Similarly, others not seen by the author (information from parents or hospital records) were scored as W, P or D.

Visual function

N - normal, S - short-sighted, L - long-sighted, O - other (see text of section 6.7.4.2).

In brackets are given the source of testing: (O) - optician, (Op) - ophthalmologist, (S) - school, (HV) - health visitor. Otherwise, reported by patient or parents.

Strabismus

(+) - present, (-) - absent, (?) - unknown, (B) - bilateral, (L) - left, (R) - right, (U) - unilateral unspecified.

Joint laxity

S - laxity of small joints of hands and feet.

L - laxity of large joints.

(+) - present, (-) - absent, (C) - in childhood only or mainly,

(H) - on history, (S) - stiff joints, (?) - unknown.

Note cases 74-85 replied by questionnaire and did not specify whether large or small joints were lax.

No. pairs of lax large joints

Numerator - no. pairs lax large joints, denominator - no. pairs large joints able to be examined.

Joint dislocations

(+) - present, (-) - absent, (?) - unknown.

Skin hyperextensibility, easy bruising, frequent epistaxis, excessive sweating

(+) - present, (-) - absent, (?) - unknown, (C) - in childhood only or mainly.

Clinical hearing loss

N - normal, DU - decreased unilaterally, DB - decreased bilaterally, D - decreased unspecified, (?) - unknown.

In brackets are shown who tested the hearing: (S) - school, (I) - institution, e.g. hospital or child development centre, (AER) - auditory evoked responses, (E) - ENT surgeon. Otherwise reported by parent or patient.

Dentinogenesis imperfecta (DI)

Clinical evidence of DI either on examination or by report.

(+) - present, (-) - absent, (?) - unknown or not applicable if teeth not erupted. (1) and (2) refer to first and second dentition respectively, XR - confirmed on radiograph.

Constipation

(+) - present, (-) - absent, (?) - unknown, (C) - childhood only or mainly.

Hernia (see also appendix 6.4)

(+) - present, (-) - absent, (?) - unknown.

High voice

Refers to high-pitched voice with a nasal quality.

(+) - present, (-) - absent, (?) - unknown.

Strong nails

Refers to unusually good nail growth with unusually strong nails.

(+) - present, (-) - absent, (?) - unknown.

Appendix 6.2

METHOD OF ASSESSMENT OF SEX RATIOS

Example for 'scleral colour at birth' (table 6.24)

	Dark Sclerae		Normal or pale blue sclerae		Totals
	0	E	0	E	
Female	46	43	9	12	55
Male	33	36	13	10	46
Totals	79		22		101

$$\chi^2_{(1)} = \frac{(O - E)^2}{E}$$

$$= \frac{(46 - 43)^2}{43} + \frac{(9 - 12)^2}{12} + \frac{(33 - 36)^2}{36} + \frac{(13 - 10)^2}{10}$$

$$= 2.11$$

Not significant $p < 0.25$

O - observed, E - expected

Values for E are calculated as follows:-

	Dark sclerae	Normal or pale sclerae	Totals
Female	a	b	a + b
Male	c	d	c + d
Totals	a + c	b + d	n

E value for 'a' is $\frac{(a + b)(a + c)}{(a + b + c + d)}$

A short-cut formula for $\chi^2_{(1)}$ is $\frac{(ad - bc)^2 n}{(a + b)(c + d)(a + c)(b + d)}$

If any E value was less than 5, Yates continuity correction was applied.

APPENDIX 6.3

JOINT DISLOCATIONS

Type of OI	Case no.	
III/IV	6	recurrent shoulder, knee
	8	(L) shoulder
	14	(L) shoulder once
	15	recurrent dislocations
	17	shoulder occasionally
	23	recurrent (R) shoulder, fingers, thumbs
	25	CDH
	26	recurrent elbows, knees
	30	bilateral CDH
	31	bilateral CDH, recurrent shoulders (needed GA once)
	32	hips since birth
	35	shoulders twice (GA both times)
	36	hips (not at birth)
	38	hips and knees
	44	shoulder, knee, hip
52	shoulder	
60	shoulders, knee	
III	105	recurrent clavicle
I	110	recurrent shoulder
	111	recurrent shoulder
	112	shoulder twice
	115	recurrent thumbs and fingers
	117	recurrent knees

CDH - congenital dislocated hip.

GA - general anaesthetic.

Appendix 6.4

TYPES OF HERNIAE AND OUTCOME IN PERINATAL SURVIVORS

Type of OI	Case no.	Sex	Age at the study or at death (yr)	Type of hernia	Operative treatment	Outcome
IIB	162	F	2.2	Congenital IH	No	Resolved at 3 months
III/IV	4	M	3.5	BIH] UH]	2 operations] 4 operations]	Herniae recurred
	7	F	2.2	RIH	No	Still present
	10	M	3.1	RIH] UH]	No	Resolved at 1 year
	13	F	0.5	UH	No	Resolved
	20	F	2.5	Incisional*	No	Still present
	23	M	15.3	RIH] UH	No	Still present Resolved
	25	M	23.2	Supraumbilical	No	Still present
	27	M	39.7	Congenital BIH	No	Still present
	28	M	0.25	Congenital BIH	No	Still present
	29	F	7.2	UH	No	?
	30	F	19.7	UH	No	Resolved
	32	M	0.6	UH BIH	No Yes (twice)	Still present No recurrence
	38	M	54.8	LIH	No (recent onset)	Resolved
	52	M	16.8	Congenital BIH	Yes (at 2.5 yr)	No recurrence
	54	M	14.5	UH	No	Resolved in infancy

Appendix 6.4 (contd)

Type of OI	Case no.	Sex	Age at the study or at death (yr)	Type of hernia	Operative treatment	Outcome
III/IV (contd)	59	F	0.42	UH	No	Still present
	60	M	23.83	IH	Yes (at 3 mth)	No recurrence
				Hiatus hernia	No	Still present
	63	F	12.2	UH	No	Resolved
	64	F	3.3	LIH	No	Still present
	66	M	6.8	UH	No	Still present
	69	M	9.5	UH	No	Still present
	70	M	0.5	IH	Yes	No recurrence
III recessive	90	M	0.3	RIH	No	Still present
	99	M	30.3	UH	No	Still present
	100	M	10.0	Sub-umbilical**	No	Still present
	105	M	9.2	IH	Yes (at 2.5 yr)	No recurrence
I new mutation	112	M	14.0	RIH	Yes (0.5 yr)	No recurrence

UH - congenital umbilical hernia
 RIH - right inguinal hernia
 LIH - left inguinal hernia
 BIH - bilateral inguinal hernia
 IH - (side unknown)

* Pyloric stenosis repair scar.

** Thought to be secondary to straining due to constipation.

APPENDIX 7.1
 POSTNATAL
 RADIOLOGICAL MANIFESTATIONS

	Case no.	Cyatic epiphyses	Downward rib ang.	Protrusio acetab.	Platyspondyly	Kyphosis	Scoliosis	Long pedicles	Skull deformity
Table no.		7.2	7.3	7.4	-	7.5, 7.7	7.6, 7.7	7.8	-
Thesis section		7.3	7.4.2	7.5	7.6.1	7.6.1	7.6.1	7.6.2	7.7
TYPE III/IV SPORADIC OI									
	1	+ (12.9, knee)	- (11.3)	++ (12.9)	++ (11.3)	?	+ (11.3)	?	?
	2	?	?	++ (17.8)	+ (17.8)	?	++ (17.8)	?	?
	3	?	- (1.3)	- (1.3, 3.3)	++ (1.3)	?	- (1.3)	?	?
	4	?	- (1.2)	+ (3)	+ (1.2)	+ (0.8, 1.2 T/L)	- (1.2)	+ (0.8, 1.2)	+ (1.7)
	5	+ (4, fem.)	- (10.6)	++ (10.6)	++ (10.6)	?	+ (10.6)	?	+ (10.6)
	6	+ (19, knee)	- (2, 19)	+ (2), ++ (19)	++ (5)	?	++ (5), +++ (19)	?	+ (7.6)
	7	?	- (0.75)	- (0.75)	+ (0.75)	?	- (0.75)	?	+ (0.75)
	8	+ (3.8, fem.)	- (1.3)	- (1.3)	++ (1.3)	?	- (1.3)	?	?
	10	+ (2.5 arm, 2.9 leg)	+ L (birth)	+ (2.9)	?	?	?	?	?
	11	- (5, leg)	?	?	?	?	?	?	?
	12	- (4.6, legs)	- (0.6, 4.6)	+ (4.6), ++ (12.4)	++ (4.6)	?	+ (4.6)	?	+ (12.1)
	13	- (0.4, legs)	?	- (0.4)	?	?	?	?	?
	14	- (19.2, elbow)	?	?	?	?	?	?	?
	15	+ (11.8 arm)	- (1.2, 12.8)	++ (9, 13.9)	++ (1.2, 15.9)	?	++ (15.9)	?	+ (14.3)
	16	- (14.3, knee)	?	?	?	?	?	?	?
	16	- (19.9, lower leg)	?	?	?	?	?	?	?
	17	+ (10.6 knee)	+ R (4.3)	++ (4.8)	++ (4.3)	?	?	?	+ (4.3)
	19	- (3.5, legs)	- (7.5)	++ (8.8)	++ (7.8)	?	+ (7.8)	- (7.8, C)	+ (7.3)
	20	- (0.3, fems.)	- (1)	+ (0.6)	+ (0.6, 1.6)	+ (1.6, T/L)	- (0.6)	- (1.6)	?
	21	+ (15.3, knee)	- (12.9, 15.9)	+ (4)	+ (2.2), ++ (15.9)	?	++ (12.9), +++ (15.9)	?	?
	22	+ (11.3, knee)	+ (7.8)	- (5.7)	++ (7.8)	+ (7.8, T/L)	+	- (7.8)	+ (8.4)
	23	+ (13.2, upper hum., knees, ankles)	- (13.2)	+ (13.2)	++ (13.2)	?	+++ (13.2)	?	?
	24	- (2.2, legs)	?	+ (2.2)	?	?	?	?	?
	25	- (7.6, legs)	- (0.2), + (2.7)	++ (2.7), ++ (6.6)	+ (2.7)	?	- (0.2), + (2.7)	?	?
	26	- (4.9, fems.)	?	++ (1)	?	?	?	?	?
	29	- (5.3, knee)	- (2.1)	- (5.6)	+ (5.6, 6.7)	+ (6.7, T)	- (0.3), ++ (5.6)	+ (6.7)	+ (2)
	30	++ (11.4, knees)	- (11.4)	+ (8.5)	++ (8.5, 11.4)	- (8.5)	+++ (11.4)	+ (8.5, L)	?
	31	++ (6.3, knee, ankle)	- (0.1)	- (1.6)	+ (1.6)	?	+ (1.6)	?	+ (1.8)
	34	- (0.4, legs)	- (0.5)	?	+ (0.4)	?	- (0.4)	?	?
	35	- (8.7, legs)	+ (8.5, 20)	++ (13), +++ (20)	+ (8, 13)	- (8, 13)	++ (13), +++ (20)	- (8, 13)	+ (9.8)
	37	- (17.3, upper fems.)	+ (17.3)	++ (17.3)	- (17.3)	?	++ (17.3)	?	?
	38	- (17, legs)	- (17)	++ (17)	++ (17)	?	++ (17)	?	?
	39	- (10.6, tib., rib.)	?	+ (6.2)	++ (4.3)	+ (4.3, T)	?	+ (4.3)	?
	40	+ (13.8, knee, ankle)	- (18.1)	++ (17.8)	+ (17.8)	+ (17.8)	+++ (17.8)	- (17.8)	?
	41	?	- (25)	?	+ (25)	?	?	?	?
	42	+ (4.8, knee, ankle)	?	++ (3, 9.8)	++ (9.8)	?	++ (9.8)	?	?
	44	- (5.9, knee)	+ R (4)	+ (4)	+ (4)	?	- (4)	?	?
	45	+ (9.5 upper hum., legs)	- (9.4)	++ (9.4)	++ (9.4)	?	++ (9.4)	?	?
	46	- (1.4, legs, arm)	?	?	?	?	?	?	?
	47	+ (3.3, knees + (5.5, upper hum.))	- (5)	- (2), ++ (11)	+ (2.5)	?	+ (2.5)	- (5, C)	+ (2.5)
	50	- (7, arm)	?	?	?	?	?	?	+ (7)
	51	- (10.7 knees)	?	+ (2.7)	?	?	?	?	?
	52	- (12.3, knee)	- (10.3)	++ (1)	++ (9.7, 10.3)	- (9.7)	+ (10.3)	?	+ (6.3)
	54	+ (13.2, knee)	+ (10.5)	?	++ (10.5)	?	++ (10.5)	?	+ (10.3)
	55	- (1.6, legs)	- (1.4)	+ (1.6)	++ (1)	?	- (1.4)	?	?
	58	+ (10 upper hum, 14.3 knees)	+ (10)	+ (1.1), ++ (10.9)	++ (1.1, 18.1)	+ (1.1, 18.1, T/L)	+ (1.1), ++ (10)	+ (1.1, 18.1)	+ (3.5)

APPENDIX 7.1 (cont.)

POSTNATAL

RADIOLOGICAL MANIFESTATIONS

	Case no.	Cystic epiphyses	Downward rib. ang.	Protrusio acetab.	Platyspondyly	Kyphosis	Scoliosis	Long pedicles	Skull deformity
Table no.		7.2	7.3	7.4	-	7.5, 7.7	7.6, 7.7	7.8	-
Thesis section		7.3	7.4.2	7.5	7.6.1	7.6.1	7.6.1	7.6.2	7.2
TYPE III/IV SPORADIC OI									
	60	+ (14.3, knee) - (14 hum.)	- (20.4)	?	?	?	?	?	?
	62	+ (5), ++ (12.4) (L) knee & ankle (not (R))	?	+ (5)	+ (5), ++(8)	- (8)	?	?	?
	63	+ (12.8, knee & ankle)	- (0.1)	?	- (0.1)	?	- (0.1)	?	+ (7 age)
	64	- (3, fems.)	- (1.3)	+ (3)	++ (1.3)	?	- (1.3)	?	?
	65	- (3.4, knees)	+ (4.3, 11)	+ (4.3), ++ (12.2)	++ (4.3), +++ (11)	?	++ (4.3), +++ (11)	?	?
	66	- (4.8, legs)	- (4.8)	?	++ (4.8)	?	++ (4.8)	?	+ (4.8)
	67	+ (17, knee) + (35, knee)	+ L (29)	+ (3)	++ (29)	?	++ (29)	?	+ (0.6, 16)
	68	+ (6, knee fem > tib)	- (4.6)	++ (4.6)	+ (1.4, 4.6)	?	+ (4.6)	?	+ (7)
	69	- (8.1, legs)	?	?	?	?	?	?	?
	71	- (0.42, lower leg)	?	?	?	?	?	?	?
	72	- (0.2, legs)	- (0.2)	- (0.2)	+ (0.2)	+ (0.2, T/L)	- (0.2)	- (0.2)	?
	73	+ (4.9, lower fem.)	?	+ (6.6)	+ (1.1)	+ (1.1, T/L)	?	+ (1.1)	?
	76	- (14.8, knees)	+ (14.9)	+ (15.3)	+ (10.8, 14.9)	++ (10.8, T/L)	++ (14.9)	+ (10.8, L)	?
	77	+ (13, knee)	+ R>L, (28.2)	++ (13)	++ (13, L/S)	?	?	?	+ (20)
	78	- (3.8, legs)	- (0.7)	+ (0.4)	++ (0.4, 2.4)	- (2.4)	+ (0.7)	+ (2.4, L)	+ (0.5)
	80	+ (13.3, knees)	- (1.8)	++ (11), +++ (13.3)	+ (1.8), + (8.6)	?	+ (1.8), + (8.6), ++ (11), +++ (13.3)	?	?
	81	- (7, knee)	+ (6.4)	++ (6.4)	+ (1.5, C) +++ (27)	?	+++ (27)	?	+ (0.8, 2)
	82	+ (3.6, knee)	- (3.6)	++ (3.6)	++ (3.6, 6.6)	+ (6.6, T/L)	- (3.6)	+ (6.6, T/L)	?
	84	- (12.4, legs)	+ (12.4)	++ (12.4)	++ (12.4)	?	++ (12.4)	?	+ (5.9)
	85	+ (6, knee) (11.1, elbow)	+ (0.3, 3)	- (3)	+ (0.8), ++ (6.3)	- (0.8)	++ (6.3)	- (0.8)	+ (0.8)
	87	- (0.4, legs)	- (0.4)	- (0.4)	+ (0.4)	?	+ (0.4)	?	?
TYPE III RECESSIVE OI									
	90	- (0.1, legs)	?	?	?	?	?	?	?
	95	- (2, legs)	- (3.7)	++ (2)	++ (2)	?	- (2)	?	+ (0.9)
	98	?	+ (16.2)	?	++ (16.2)	?	++ (16.2)	?	?
	99	+ (29, fems.)	- (4.5, 24)	++ (4.5), +++ (24)	++ (4.5)	?	- (4.5), +++ (24)	?	?
	100	+ (8.7 fems.)	?	?	?	?	?	?	?
	102	- (27.4, knee)	+ (4.6)	++ (8.2)	+ (4.6)	- (4.6)	- (4.6)	?	?
	103	?	- (13.3)	?	++ (13.3)	?	++ (13.3)	?	?
	104	- (3, legs)	- (1.7)	+ (3)	++ (1.7)	?	- (1.7)	?	- (1.8)
	105	+ (8, hum. (10.2 knee))	- (6.5)	++ (9.5)	+ (6.5)	?	+ (6.5)	?	+ (10.2)
TYPE I NEW MUTATION									
	109	- (4, (R) leg)	- (0.8)	- (4)	- (0.8)	?	- (0.8)	?	?
	110	- (13.9, knee)	?	- (4.2, 11.1)	?	?	?	?	?
	111	- (5.5, (L) knee)	- (2.8)	- (3.6)	?	?	?	?	+ (1.8)
	112	- (13.7, knees)	?	?	?	?	?	?	?
	113	- (16.2, (R) tib, rib)	?	?	?	?	?	?	?
	114	- (5.1, (R) fem)	?	?	?	?	?	?	?
	115	- (39.6, knees)	?	?	?	?	?	?	?
	117	- (33.5, wrists)	- (33)	?	± (33)	- (33)	+ (33)	- (33)	- (35.7)
	118	- (15.2, knees, ankles)	+ (5.2)	- (3), + (9.2)	- (3), + (5.2)	?	- (5.2)	?	?
	119	- (1.3, fems.)	- (1)	- (0.1)	+ (1.1)	+ (1.1, T/L)	+ (1)	+ (1)	?

NOTES FOR APPENDIX 7.1

1. The definition of the column headings are given in the appropriate text sections.
2. (+) present, (-) absent, (?) no appropriate radiograph or feature not clearly visible.
3. In columns 'protrusio acetabulae', 'platyspondyly', 'kyphosis' and 'scoliosis, (+) denotes mild, (++) moderate or severe and (+++) denotes very severe.
4. L - left, R - right. In the column 'downward rib angulation', if no side given, this denotes bilaterally affected.
5. The age in years is given in brackets. In some cases, radiographs of the same patient at different ages are available.
6. Under 'cystic epiphyses' the bone or joint affected is given. Fem. - femur, tib. - tibia, fib. - fibula, hum. - humerus, rad. - radius, uln. - ulna.
7. (C) cervical, (T) thoracic, (L) lumbar, (S) sacral spine.
8. Platyspondyly is usually best documented on lateral spine views, but it was often so marked as to be visible on the

anteroposterior (AP) film.. This is the case if there is platyspondyly in the presence of a (?) in the column marked 'kyphosis'. Note that case 118 had collapse of some lumbar vertebrae at age 33 years, but the other vertebrae were of normal height, hence the designation (+).

9. Kyphosis and scoliosis are documented on lateral and AP films, respectively.

Appendix 7.2

COMPARISON OF RADIOLOGICAL MANIFESTATIONS WITH SCLERAL COLOUR IN PATIENTS WITH TYPE III/IV OI

	Cystic epiphyses*	No cystic epiphyses*	Totals
Normal or pale blue sclerae	15	14	29
Moderate or deep blue sclerae	13	10	23
Totals	28	24	52

$\chi^2_{[1]} = 0.12$, therefore no association (p 0.7 - 0.9).

* Cases at or over 2.5 years.

	Downward rib angulation	No rib angulation*	Totals
Normal or pale blue sclerae	9 (8)**	17 (11)	26 (19)
Moderate or deep blue sclerae	6 (6)	15 (8)	21 (14)
Totals	15 (14)	32 (19)	47 (33)

All cases $\chi^2_{[1]} = 0.20$, therefore no association (p 0.5 - 0.7).

Cases over 2.5 years $\chi^2_{[1]} = 0.002$, therefore no association (p 0.95 - 0.99).

* Scleral colour unknown in 2 cases.

** Numbers not in brackets are all cases (numbers in brackets are cases over 2.5 years).

Appendix 7.2 (cont.)

	Protrusio acetabulae (PA)	No PA*	Totals
Normal or pale blue sclerae	24	4	28
Moderate or deep blue sclerae	19	5	24
Totals	43	9	52

$\chi^2_{[1]} = 0.065$, therefore no association (p 0.7 - 0.9)(corrected for continuity).

* scleral colour unknown in one case .

	Kyphosis	No kyphosis	Totals
Normal or blue sclerae	6	4	10
Moderate or deep blue sclerae	5	2	7
Totals	11	6	17

$\chi^2_{[1]} = 0.0009$, therefore no association (p > 0.99)(corrected for continuity).

Appendix 7.2 (cont.)

	Scoliosis*	No scoliosis*	Totals
Normal or pale blue sclerae	20	5	25
Moderate or deep blue sclerae	14	6	20
Totals	34	11	45

$\chi^2_{[1]} = 0.18$, therefore no association (p 0.5 - 0.7) (corrected for continuity).

* Scleral colour unknown in one case in each category.

	Elongation of the pedicles	No elongation	Totals
Normal or pale blue sclerae	6	3	9
Moderate or deep blue sclerae	3	3	6
Totals	9	6	15

$\chi^2_{[1]} = 0.012$, therefore no association (p 0.9 - 0.95) (corrected for continuity).

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