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Shwachman's syndrome

A review of 21 cases

P J AGGETT, N P C CAVANAGH, D J MATTHEW, J R PINCOTT, J SUTCLIFFE, AND J T HARRIES

The Hospital for Sick Children and Institute of Child Health, London

SUMMARY 21 patients (10 male, 11 female) aged between 11 months and 29 years with Shwachman's syndrome are reviewed. All patients had exocrine pancreatic insufficiency. Haematological features included neutropenia in 19 (95%), anaemia in 10 (50%), and thrombocytopenia in 14 (70%); one patient developed erythroleukaemia. Severe infections occurred in 17 (85%) from which 3 (15%) died. Only one child exceeded the 3rd centile for height, and growth retardation was particularly evident in the older patients. All had skeletal abnormalities or delayed skeletal maturation, or both. Metaphyseal dyschondroplasia affected 13 of the older patients and was associated with skeletal deformities. Eight of 9 children under $2\frac{1}{2}$ years had rib abnormalities. Respiratory function tests in children under 2 years demonstrated reduced thoracic gas volume and chest wall compliance. Older patients had reduced forced expiratory volume and forced vital capacity.

Neurological assessment showed developmental retardation or reduced IQ assessments, or both, in 85% of patients studied. Other neurological abnormalities included hypotonia, deafness, and retinitis pigmentosa.

Neonatal problems had been present in 16 (80%) of the patients and 5 were of low birthweights. Hepatomegaly with biochemical evidence of liver involvement occurred in the younger patients and resolved with age. Other associated features included dental abnormalities, renal dysfunction, an icthyotic maculopapular rash in 13 (65%), delayed puberty, diabetes mellitus, and various dysmorphic features. These findings stress the diverse manifestations of the syndrome and extend knowledge on a number of aspects. Sibship segregation ratios support an autosomal mode of inheritance and an hypothesis for the pathophysiological basis of this syndrome is advanced.

Shwachman's syndrome is a rare multiorgan disease of unknown cause. The features which patients exhibit include exocrine pancreatic insufficiency (EPI), growth retardation, metaphyseal dyschondroplasia, bone marrow hypoplasia, neutropenia, anaemia, thrombocytopenia, and a raised level of haemoglobin F.[1] In this paper, we studied 21 patients with this syndrome which represents the largest series so far reported. The extent and frequency of the various features which comprise the syndrome have been carefully documented, and detailed studies of the affected systems have been performed.

The Hospital for Sick Children
N P C CAVANAGH, senior registrar in neurology
D J MATTHEW, consultant paediatrician
J SUTCLIFFE, consultant radiologist
Institute of Child Health
J R PINCOTT, senior lecturer in histopathology
J T HARRIES, reader in paediatrics
Department of Physiology, Marischal College, University of Aberdeen
P J AGGETT, senior lecturer

Subjects and methods

Subjects (Table 1). There were 10 male and 11 female patients among whom were 3 pairs of siblings (Cases 3 and 4, 7 and 20, 17 and 18). An affected older sister of Case 9 had attended another hospital and, although some of her features are described, she has been excluded from the overall analysis. The mean age of the male patients at the time of evaluation was 12 years (range 1 year 5 months to 28 years 11 months) while that for the girls was 5 years 7 months (range 11 months to 16 years 4 months. All except 3 patients (Cases 11, 12, and 15) were receiving

Table 1 *Clinical features of patients studied*

Case	Sex	Birthweight (kg)	Neonatal history	Siblings		Age when studied (years)	Height (cm)	Centiles			Icthyosis	Infections	Age of onset (months)		Age at diagnosis (months)
				NA	SS			Height	Weight	OFC			FTT	Diarrhoea	
1	M	2·11	RD, TF, H	—	—	3	75	<3	<3	<3	+	P, OM	Nn	3	10
2	F	2·32	TF	1	—	2–4m	72	<3	<3	<25	+	Nil	Nn	Nn	8
3	F	2·95	Normal	1	1	10	117·6	<3	<3	<3	−	P, OM	Nn	Nn	2
4	M	2·55	RD	1	1	13–8m	121	<3	<3	<3	+	RTI, O, OM	Nn	6	8
5	M	2·80	RD, H	—	—	1–5m	62	<3	<3	3	+	RTI	Nn	2	3
6	F	3·23	Normal	1	—	16–4m	124·5	<3	<3	<3	−	P, OM	2	2	3
7	M	3·09	Sept.	2	1	1–6m	75	<3	<3	3	+	RTI, Sept., OM	Nn	Nn	Nn
8	F	2·72	PF	1	—	5–2m	92·5	<3	<3	<3	−	UTI, RTI	Nn	Nn	3
9	F	3·06	Normal	2	1	8–8m	107·3	<3	<3	25	+	S, OM	2	2	3
10	F	2·52	TF	—	—	2–7m	77	<3	<3	<3	+	OM	Nn	2	4
11	M	2·12	RD, PF	1	—	13	121·2	<3	<3	<3	−	Nil	Nn	2	3
12	M	2·86	TF	—	—	27–10m	152	<3	<3	<3	−	RTI, P	Nn	6	24*
13	F	3·18	Normal	1	—	2–11m	84·7	3	25	10	−	Nil	18	18	20
14	M	3·06	Normal	—	—	21–4m	144	<3	<3	<3	+	P	2	2	2*
15	M	2·10	RD, P	—	—	28–10m	144·9	<3	<3	3	+	Sept., S, OM, P, O	2	2	8*
16	F	3·18	RD	—	—	7–10m	116	<10	10	<25	−	Ab	4	4	6
17	F	4·08	PF, H	—	1	–11m	68	3	<3	10	+	P	3	3	3
18	F	3·18	PF	—	1	3–3m	88	3	10	3	+	Nil	Nn	Nn	24
19	M	3·27	H	—	—	8–6m	120	3	3	3	+	P	2	2	3
20	F	3·14	RD, PF	2	1	1–8m	77	3	<3	<3	+	P, Ab	Nn	Nn	4
21	M	1·76	RD, PF	4	—	1–6m	71	<3	<3	<3	−	P, Ab	Nn	Nn	3

+Present, −absent; m = months; FTT = failure to thrive; *diagnosed as 'atypical cystic fibrosis'; Nn = neonate; OFC = occipitofrontal circumference.
Siblings: NA = not affected; SS = Shwachman's syndrome.
Neonatal history: H = hypotonia; RD = repiratory distress; TF = tube fed; PF = prolonged feeding; Sept. = septicaemia.
Infections: P =pneumonia; RTI = respiratory tract infection; S = sinusitis; OM = otitis media; O = osteomyelitis; Sept. = septicaemia; UTI = urinary tract infection; Ab = abscess.

pancreatic and fat-soluble vitamin supplements at the time of study. Cases 1, 3, 4, 8, 9, and 14 were on a low-fat or a medium-chain triglyceride diet, or both. Case 14 had diabetes mellitus and had received chlorpropamide for the last 10 years. Two patients (Cases 10 and 19) had received prednisone for the management of neutropenia and Case 16 received a short course of oxymetholone when aged 2 years for aplastic anaemia.

Methods

The patients' clinical histories were analysed using contemporary records, and those patients available for follow-up were studied during optimum health and while free of infection. Each had a full clinical examination, height and weight centiles were determined using the standards for British children established by Tanner *et al.*[2] 13 children received full neurological examinations from one of us (N C) and had electroencephalogram (EEG) recordings with visually-evoked responses and electroretinography (ERG). Seven of these children also had formal psychological assessments.

Venous blood was taken for full blood count, haemoglobin electrophoresis, plasma aspartate and alanine transaminase activities (AST and ALT), total bilirubin, total α-amylase activity, amino-acid chromatography and, in 10 patients, leucocyte karyotyping. Urine was analysed for sugars and amino-acids and sweat tests were performed by pilocarpine iontophoresis.

Radiological assessment included review of previous *x*-rays, and skeletal surveys and bone age estimation of patients when attending for review. Skeletal maturation was assessed using the Greulich-Pyle[3] and TW2 atlases.[2]

Respiratory function tests were performed in 9 older children using routine methods[4–6] and the results were expressed as a percentage of that predicted normal for height.[4–6] In 4 children under the age of one year, thoracic gas volume (TGV) and pulmonary resistance were measured using a whole-body plethysmograph. Measurements of compliance[7] were performed in 2 patients.

Results

Clinical features (Table 1). The mean birthweight was 2·82 kg (range 1·76 to 4·08 kg) and 5 patients weighed less than 2·5 kg. All were born at term except Cases 11 and 15 (each 36 weeks' gestation by dates), Case 10 was a breech delivery, and Case 13 was delivered by caesarean section because of cephalopelvic disproportion. During the neonatal period 13 patients failed to thrive, 7 had diarrhoea, 10 had feeding difficulties which necessitated tube feeding in 4, and 4 were markedly hypotonic; only 5 had no neonatal abnormalities. Two patients (Cases 7 and 15) developed pneumonia and septicaemia during the neonatal period.

Of the 8 patients who did not have symptoms of malabsorption in early infancy, 7 developed symptoms by age 4 months; the exception (Case 13) presented with muscle wasting, ankle oedema, and growth retardation at 18 months.

Fig. 1 shows the height of the patients plotted on a centile chart. Growth retardation was particularly evident in the older patients; only one (Case 16) exceeded the 3rd centile. Case 14, who had received pancreatic supplements since diagnosis at 2 months, was of a comparable height to Cases 12 and 15 who had stopped supplements at 9 and 1½ years respectively; similarly discontinuation of supplements in Case 11 had no effect on growth velocity. In each patient, height, weight, and occipitofrontal head circumference centiles were in general the same; in one instance (Case 20) weight was lower than height, and in 3 patients (Cases 13, 16, and 18) weight stabilised on a higher centile than height after treatment.

Puberty was delayed in the 6 oldest patients; Cases 4 and 11 were prepubertal, Case 14 had genital and pubic hair ratings of 3 and 2 respectively,[8] and

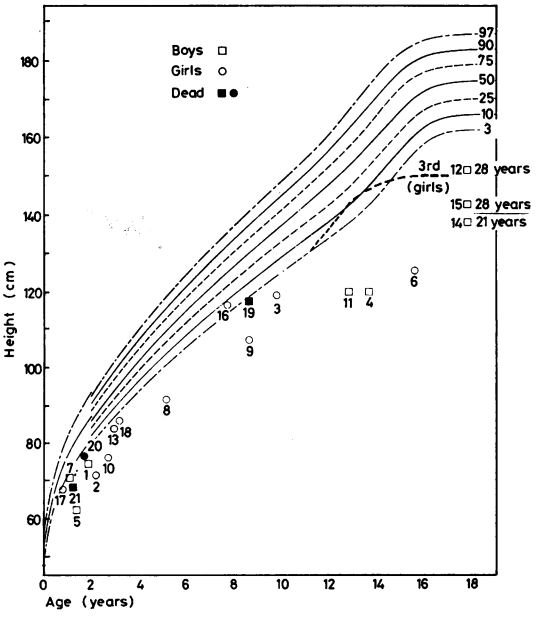

Fig. 1 *Height of patients on a common centile chart. Adjacent numbers indicate case numbers used in this report.*

Case 6 had breast and pubic hair ratings of 3 and 2 respectively, and has subsequently achieved menarche aged 16 years 11 months. Cases 12 and 15 did not develop pubic hair until aged 16 years; both are married and Case 12 has attended an infertility clinic, and the wife of Case 15 conceived each of her 2 children after 3 years' planned sexual intercourse.

An icthyotic maculopapular rash (Fig. 2) affecting the entire body with the face, scalp, and trunk being most severely affected was present in 13 cases, and only one patient (Case 15) had a history of atopy.

All but 4 patients experienced infections which required hospital treatment. 12 had recurrent respiratory tract infections including bronchopneumonia; osteomyelitis and septicaemia occurred in two, 8 had recurrent otitis media, many were troubled by recurring skin infection, and 3 developed abscesses necessitating hospital admission. The frequency of pulmonary infections declined with age but this was not so for otitis media. Three patients died of infection; Case 20 when aged 20 months had an overwhelming infection with an unidentified pathogen; Case 21 died aged 18 months of a bronchopneumonia after laparotomy, and Case 19 had haemorrhagic complications of leukaemia and bronchopneumonia aged 8½ years. The older affected sibling of Case 9 died of haemorrhagic measles when 4 years old.

Dysmorphic features included cutaneous syndactyly in Case 10 (3rd and 4th fingers of the right hand, and the 2nd and 3rd toes of the left foot) and Case 19 (2nd and 3rd toes of the right foot), a short soft palate with a submucous cleft and bifid uvula in Case 8, hypertelorism in Cases 1, 6, and 18, and pes cavus in Case 6.

10 patients had dental abnormalities; 8 had extensive caries (Cases 1, 2, 4, 5, 13, 14, 15, and 19), 3 (Cases 1, 15, and 19) had dysplastic teeth, and Case 11 had delayed loss of primary dentition and eruption of permanent teeth.

Pancreatic function and structure (Table 2). All patients had a normal sweat sodium concentration on at least two occasions and EPI (Table 2). In most cases EPI was diagnosed within 4 months of presentation but in one case, 2 years elapsed before EPI was established. Siblings of known cases were diagnosed rapidly. The three patients who stopped pancreatic supplements reported no increased frequency or altered consistency of their stools.

Fig. 2 (*Case 1*). *Typical icthyotic maculopapular skin rash.*

Table 2 *Pancreatic function tests*

Case	*Method**	*Enzyme activity*			*Plasma amylase†*	*Hepatomegaly*	*Plasma ALT‡*
		Amylase	*Lipase*	*Trypsin*	*(IU/l)*		*(IU/l)*
1	A	Low	Low	Low	20	+	25→N
2	A	Low	Low	Low	72	−	323→47
3	B	Low	Low	Low	90	+	79→N
4	B	Low	Low	Low	74	+	206→N
5	A	Low	Low	Absent	38	+	153→34
6	B	Low	Absent	Absent	38	+	N
7	B	Low	Absent	Absent	NT	+	38
8	C	Low	Low	Absent	119	−	24
9	A	Low	Absent	Absent	155	+	22→N
10	C	Absent	Absent	Absent	70	−	103→34
11	B	Low	Low	Low	105	−	65→N
12	C	Low	Low	Absent	120	+	N
13	A	Low	Very low	Very low	84	−	24→37
14	B	Very low	Very low	Very low	97	+	N
15	C	Low	Low	Absent	76	−	N
16	B	Low	Low	Low	NT	+	NT
17	B	Absent	Low	Very low	NT	+	NT
18	B	Low	—	Absent	NT	−	24
19	B	Low	Low	Low	NT	−	60
20	C	Low	Low	Low	NT	+	33
21	C	Low	Low	Low	60	+	18

*(A) test meal (McCollum *et al.*),[63] (B) pancreazymin secretin stimulation (Hadorn),[64] (C) fasting duodenal juice.
NT = not tested.
†Normal plasma amylase range 100–405 IU/l (Aggett and Taylor),[9] ‡normal plasma ALT range 2–12 IU/l.
+ Present, − absent, →progressed to, N normal.

Total plasma α-amylase activity was determined in 15 patients over one year of age; 11 values were below the normal range (Table 2).[9] The activities determined in patients over age 2 were significantly lower ($P<0\cdot01$) than age-matched controls (Fig. 3).

The pancreata of the 3 patients who died and one (Case 19) who had a biopsy during life showed extensive fatty infiltration of a normal-sized gland, and the ductular architecture under light microscopical examination was essentially normal. The majority of acinar cells were replaced by fat, interstitial connective tissue was increased, a few ductules were dilated, and the islets of Langerhan appeared normal.

Haematological investigations (Table 3). 10 patients had total haemoglobin levels of less than 10 g/dl at some time; in 2, this has been persistent, while in the remainder it was intermittent and has since resolved; 3 patients (Cases 6, 10, and 16) required blood transfusions. Haemoglobin F (HbF) was measured in nine, 5 of whom also had HbA_2 assessed; HbF was moderately raised in 2 and markedly increased in Cases 19 (14%) and 5 (30%); there was a normal reciprocal relationship between HbF and HbA_2.

Neutropenia ($<1\cdot5 \times 10^9$/l) was present in all but 2 patients (Cases 11 and 13) and since we could not investigate these 2 in a manner suggested by Burke *et al.*,[10] an intermittent neutropenia cannot be excluded. The neutropenia was intermittent in all the other patients except for Case 7 on whom we only have one observation. A neutrophil response was observed in several cases; for example, Case 20 developed an increase from $0\cdot46 \times 10^9$/l to $5\cdot7 \times 10^9$/l within 6 hours of developing an infection.

Platelet counts were performed in 20 patients and varied independently of the neutrophil count. An intermittent thrombocytopenia ($<100 \times 10^9$/l) was found in 11 patients, a single observation in 2 (Cases 7 and 15) and all three counts in Case 5 demonstrated a thrombocytopenia; counts less than 60×10^9/l were observed in 9 patients, 3 of whom (Cases 5, 6, and 7) developed purpura.

The 6 patients who had bone marrow aspirations had varying degrees of hypoplasia; Cases 10 and 16 had pancytopenia; absent myeloid precursor or maturation arrest was noted in Cases 14, 17, and 19, and in addition, the marrow of one patient (Case 14) contained a considerable amount of fat. An aspirate from Case 9 during an episode of neutropenia was normal as was that of Case 21 at necropsy. Case 20 had a hypocellular marrow at necropsy, while the marrow of Case 19 demonstrated an erythroid hyperplasia and the development of an erythroleukaemia. At his necropsy extramedullary haematopoiesis was present in the liver, spleen, and lymph nodes. Cases 19 and 20 had disseminated haemorrhages in the lungs, intestine, and adrenals at necropsy.

Skeletal abnormalities and maturation (Table 4). All the patients had skeletal abnormalities or delayed skeletal maturation, or both.

13 patients had metaphyseal dyschondroplasia and

Table 3 *Haematological studies*

Case	Haemoglobin range (g/dl)		Lowest PMN count (×10⁹/l)	Total WCC count at time (×10⁹/l)	Highest PMN count (×10⁹/l)	Total WCC count at time (×10⁹/l)	No. of observations		Range of platelet counts (×10⁹/l)		No. of platelet counts		Additional features
							PMN>1·5 (×10⁹/l)	PMN<1·5 (×10⁹/l)			>100	<100	
1	9·8	14·1	0·320	6·4	8·12	13·1	20	10	233	63	15	3	HbF 0%
2	12·8	16·1	0·21	5·3	4·14	6·9	3	6	175	102	3	0	
3	9·8	12·7	0·196	4·9	5·57	8·42	12	19	247	61	4	4	
4	8·7	12·3	1·2	4·2	6·72	10·9	4	3	118	96	6	1	
5	9·1	9·8	0·34	6·7	7·58	13·3	1	3	63	11	0	3	HbF >30%, HbA_2 1·20%
6	7·5	11·1	0·39	3·6	21·0	32·8	2	14	196	9	2	6	Transfused for anaemia
7	—	11·1	0·420	3·2	—	—	—	1	—	46	0	1	
8	10·8	13·0	1·25	6·6	41·3	46·9	15	1	249	69	10	2	HbF 3%
9	11·4	12·0	0·265	3·3	4·7	8·9	4	8	251	116	4	0	HbF 2·2% HbA_2 1·3%
10	5·1	9·9	0	4·0	3·0	12·0	7	55	100	14	1	56	Transfused for anaemia
11	13·2	14·7	1·65	5·0	3·5	9·7	2	0	112	—	1	0	
12	11·8	15·9	0·10	2·55	6·7	14·0	2	3	115	60	1	1	HbF 0·36% HbA_2 3·2%
13	10·6	11·0	4·49	6·5	9·9	13·2	3	0	196	167	2	0	HbF 0·89%
14	10·0	13·2	0·05	1·6	2·78	4·8	1	10	157	15	2	3	HbF 0·73% HbA_2 3·0%
15	14·1	15·9	1·02	3·2	2·7	6·6	1	1	95	—	0	1	HbF 0·82% HbA_2 2·7%
16	4·9	11·5	0·28	4·0	2·76	6·0	1	13	240	93	8	1	Transfused for anaemia
17	10·2	13·6	0·29	4·8	6·25	13·9	10	14	522	250	6	0	
18	11·8	12·8	0·29	2·6	1·97	5·8	1	3	—	—	—	—	
19	6·9	12	0·18	3·0	11·8	29·5	14	62	275	3	36	60	HbF 14%
20	8·9	13·8	0·56	9·4	11·7	15·0	4	5	104	21	1	3	
21	9·4	11·4	1·09	9·9	3·28	13·1	3	3	300	—	1	0	

HbF: haemoglobin F normally <2% over 2 years of age, HbA_2: haemoglobin A_2 normally >2% over 2 years of age.

Table 4 *Skeletal abnormalities*

Case	Chronological age studied	Skeletal maturity							Rib abnormalities	Metaphyseal dyschondroplasia		Clinodactyly	Long bone tubulation sites affected
		20 bones (TW2)		RUS (TW2)		Carpal (TW2)		Greulich-Pyle bone age		Sites affected	Age first detected (years)		
		Bone age	Centile	Bone age	Centile	Bone age	Centile						
1	1·0	<1·0	<3	—	—	—	—	<0·5	+	None	—	—	R U F
2	0·6	—	—	—	—	—	—	<0·25	+	None	—	—	U Tib Fib
3	9·7	8·7	10	9·7	50	7·9	3	7·3	+	H K I W V	8	+	—
4	12·7	9·5	<3	12·0	25	8·7	<3	9	N	H K I S W V	5	+	—
5	2·5	<1·0	<3	1·5	<10	—	—	1	+	H S A	2·5	+	H R U F Tib Fib
6	16·3	10·5	<3	14·6	<3	8·2	<3	13·5	+	H K I S W V	1	+	F Fib Tib
7	1·6	<1·0	<3	—	<3	—	—	<0·5	+	H	1·6	—	F
8	5·7	2·9	<3	4·4	10	<1·6	<3	3	N	H	4·5	—	
9	3·6	2·3	3	3·0	<25	<1·6	<3	2	+→N	— S V	7·5	+	
10	2·6	<1·0	<3	2·7	50	—	—	2	N	H K W	2·5	+	
11	13·0	11·7	10	13	50	9·7	<3	12	+→N	H K S W V	7·0	+	
12*	11·3	9·7	<10	10·4	<50	9·2	3	9	N	H K V	7·0	+→	
13	4·0	2·6	3	3·8	50	<1·6	<3	1·5	N	H V	4·0	—	F U
14	21·4	15	<3	15·5	<3	13·3	<3	14	N	None	—	—	
15	28·9	Adult		Adult		Adult		Adult	+	H K I S W V A	7·5	—	Tib Fib F
16	7·9	8·3	<75	9·4	75	7·4	<50	7	N	H	7·5	+	
17	0·9	Not assessed						<0·25†	+				
18	Not assessed								N				
19	8·1	5·6	<3	7·1	25	4·6	<3	5·5	N				
20	1·7	1·7	50	2·0	>50	<1·6	<3	1·0	N	None		+	
21	1·5							0·25†	+				

*Now aged 27·77 years with adult skeletal maturity, †based on appearance of other epiphyses.
H = hips, K = knees, I = iliac crest, W = wrist, S = head of humerus, V = vertebrae, A = ankles, R = radius, U = ulnar, H = humerus, F = femur, Fib = fibula, Tib = tibia, RUS = radius, ulnar, and short bone, → progressed to, N = normal.

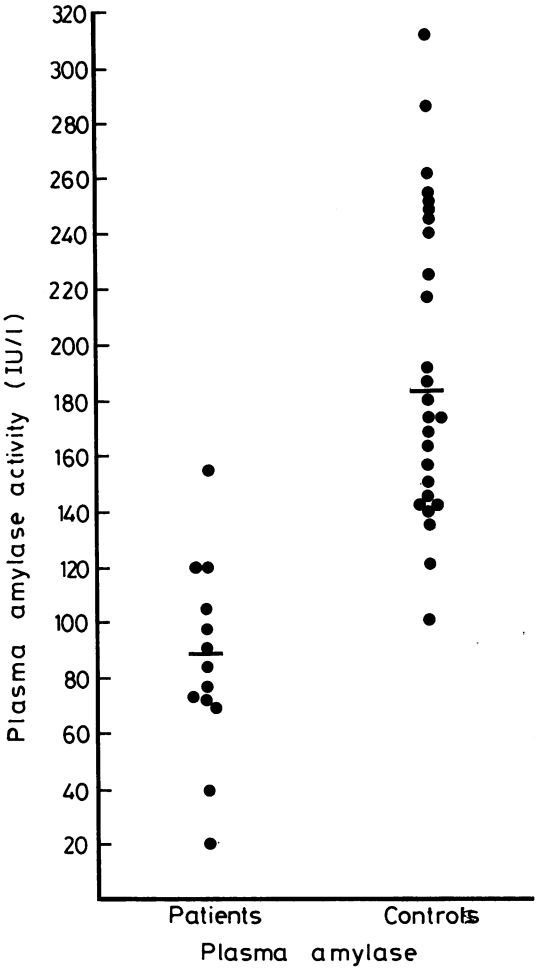

Fig. 3 *Total plasma amylase activities (IU/l) in 13 patients over 2 years of age compared with 26 age-matched controls measured simultaneously.*

in most of them this lesion was first found in the femoral head. Only one patient (Case 9) with metaphyseal dyschondroplasia at other sites had a radiologically normal femoral head. Other sites affected were the knees, humeral heads, wrist, ankles, and vertebrae. The earliest age at which metaphyseal lesions were detected was one year (Case 6), and serial radiology demonstrated progression of the lesions in all cases. Displacement of the femoral head produced coxa vara deformities in Cases 6, 11, 12, and 15; 2 patients (Cases 6 and 12) developed pathological fractures of the femoral neck, and the former patient developed a pseudarthrosis.

Abnormally short ribs with flared anterior ends (Fig. 4) were present in 9 patients and had been present in 2 others (Cases 9 and 11). Of 9 patients who had chest *x*-rays performed before age 2½ years, 8 had this abnormality. It was less common in the older patients, but a pronounced abnormality persisted in Cases 6 and 15. As a result of this abnormality 7 had clinically visible narrow thoracic cages (Fig. 4).

Long bone tubulation was present in 7 patients with consequent bowing deformities of the femora (Cases 1, 4, 5, 7, and 15), tibiae and fibulae (Cases 4, 6, 13, and 15), and ulnars (Case 13). Case 15 still had genu varus despite bilateral tibial osteotomies; he also had cubitus valgus.

Transverse lines of increased bone density occurred in the shafts of the long bones in 9 patients. Spinal abnormalities were present in Case 5 who had dorsolumbar scoliosis and Case 15 who had developed a kyphosis as a result of wedged T 12 and L1 vertebral bodies.

Clinodactyly caused by a short hypoplastic 5th middle phalanx was evident in 10 patients, and serial *x*-rays demonstrated resolution of this abnormality in an eleventh (Case 12) (Fig. 5).

In some patients bone mineralisation was impaired, but serum calcium, phosphate, and alkaline phosphatase levels were normal in all the patients.

Suitable *x*-rays of the hand and wrist in Cases 17, 18, and 21 were not available for the use of the

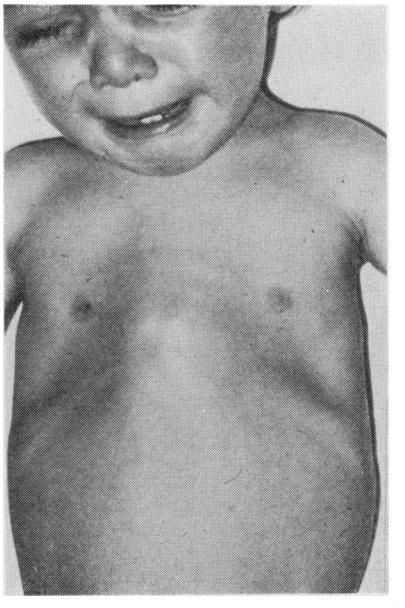

Fig. 4 (a) *(Case 5). Narrow thoracic cage.*

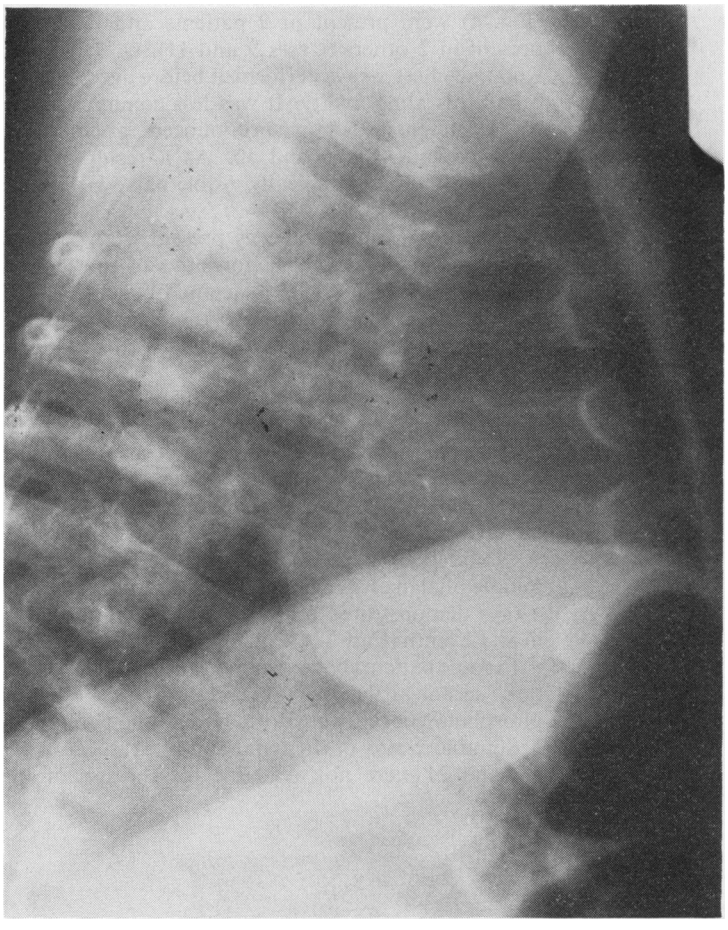

Fig. 4 (b) (*Case 5*). *Chest x-ray showing short ribs with flared anterior ends with cupping.*

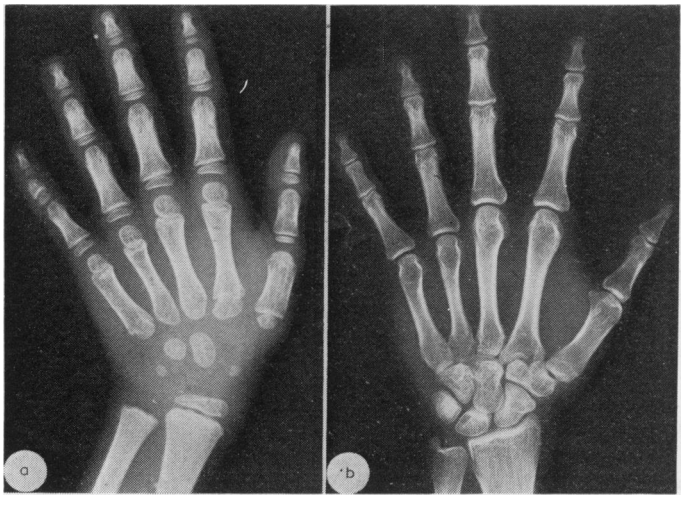

Fig. 5 (*Case 12*). *X-rays of left hand (a) aged 7½ years and (b) aged 27 years, showing resolution of dysplasia of the 5th middle phalanx and retarded bone age with disparity between phalangeal and carpal maturation.*

Greulich-Pyle or TW2 standards. Assessment of bone age using the Greulich-Pyle standards indicated retardation in all 18 patients evaluated. Applying these standards was difficult however, because of the delayed appearance of the carpal, and distal radial, and ulnar epiphyses. Similarly, TW2—20 bone scores gave only two estimates equal to or above the 15th centile. 11 of the 14 patients over age 2 years had values on the TW2 carpal score below the 3rd centile, but the TW2 radius, ulnar, and short bone score for these children was below the 3rd centile in only one patient (Case 14), and 11 exceeded the 10th centile.

The appearance of other epiphyses was also delayed in some patients. The distal femoral and proximal tibial epiphyses were delayed in Cases 1, 5, and 21 and the proximal femoral and humeral epiphyses were retarded in Cases 1, 5, 10, and 17. Case 16 was the only one to exceed the 50th centile in any estimation.

Respiratory function tests (Table 5). The TGV was lower than that predicted normal in 3 of the 4 patients studied under age 2 years. In Case 5, it was 100% of that predicted normal in spite of his rib abnormalities and narrow thoracic cage (Fig. 4). There was no consistent abnormality in pulmonary resistance. A pronounced reduction in chest wall compliance was demonstrated in the 2 cases studied but specific lung compliance was normal. The older patients had normal lung volumes but as a group forced expiratory volume ($FEV_{0\cdot75}$) and forced vital capacity (FVC) was reduced. This was particularly pronounced in patients (Cases 3 and 6) who had radiologically abnormal ribs. Case 15 had a reduced $FEV_{0\cdot75}$ and a normal FVC which was consistent with his history of asthma and cigarette smoking.

Hepatic function and structure (Table 2). 13 patients had hepatomegaly during the first 5 years of life but, with the exception of Cases 6 and 19, liver size was normal at the time of evaluation. Plasma bilirubin was normal in all cases, and plasma AST and ALT were raised in 10 of the 19 patients studied; of the remainder, 5 had had raised levels in the past. Transaminase levels were highest in the youngest patients and serial observations demonstrated a progressive fall towards the normal range with age. Plasma amino-acid chromatography was normal in all patients studied.

Hepatic histology was abnormal in the 6 patients examined. There were severe panlobular fatty changes with nonspecific mixed inflammatory infiltration and varying degrees of periportal fibrosis.

Table 5a *Pulmonary function tests: patients of 2 years and over*

Case	*PEFR*	*$FEV_{0\cdot75}$*	*FVC*	*FRC*	*TGV*	*TLC*
3	71	60	55	102	105	98
4	95	79	71·7	91	79	90
6	41	43	43	94	103	81
9	128	81	67	—	—	—
11	78	66	78	114	154	114
12	83	80	89	—	124	101
14	97	96	89	—	144	113
15	77	69	97		127	125
16	103	78	83	94	—	—
Mean	86	72	75	99	119	103

Results expressed as percentage of that normal for height.

Table 5b *Pulmonary function tests: patients under 2 years*

Case	*TGV*	*Pulmonary resistance*	*Specific compliance*	*Chest wall compliance*
1	72	77	175	41
2	79	124	127	17
5	100	85	—	—
7	87	90	—	—

Results expressed as percentage of mean normal for weight.

The degree of fatty infiltration at necropsy in Case 19 was less pronounced than that in the biopsy taken 6 years previously.[11]

Renal function. Urine analysis showed an intermittent and variable glycosuria (>20 mg/100 ml) in 10 (50%) of 20 patients studied. Galactosuria was found in 2 patients (Cases 9 and 16), while others had fructosuria (Cases 3 and 21), lactosuria (1), or glucosuria (Cases 2, 3, 5, 6, 9, 14, 18, and 21). Case 14 also had a mixed aminoaciduria. Further evidence of renal tubular dysfunction occurred in the older sibling of Case 9 who had renal tubular acidosis and a mixed aminoaciduria. Focal nephrocalcinosis was present in Case 19 at necropsy.

Neurological assessment. Details of developmental milestones were obtained in 16 patients, and in only 2 (Cases 3 and 18) were these normal. 11 children (Cases 1, 2, 4, 5, 9, 10, 13, 14, 17, 20, and 21) were delayed both in motor and speech development (for example, not sitting by 9 months, or not walking by 18 months, and not saying single words by 18 months), and a further 3 were retarded in one of these spheres (Cases 6, 8, and 11).

Formal IQ assessments in 7 patients showed a low score of 76–85 in 6 (Cases 3, 4, 8, 9, 11, and 14) and Case 6 demonstrated a score on repeated testing which fell from 76 to 48 during an 8-year period. Verbal and nonverbal achievements were equally affected in all instances. Of the patients who were not

formally assessed, Case 12 had achieved a good standard of secondary education and works as a computer data processor; Case 15 attended schools for the physically-handicapped and had trained to assemble electronic circuit boards, but now works as a pop band drummer, and Case 14 works as a hotel page boy. Cases 12 and 15 have their own households but Case 14 is still dependent on his parents.

Corrected visual acuity was normal in all but Case 6, who had optic atrophy and retinitis pigmentosa; Cases 5 and 20 had reduced retinal and choroidal pigment. The ERG was normal in 11 patients but Case 5 had a generalised reduction in amplitude consistent with her retinitis pigmentosa.

Bilateral conductive deafness was demonstrated by audiometry in 3 patients (Cases 6, 9, and 10), and Case 11 had a sensorineural loss of hearing.

Further neurological examination was normal in all but 3 patients; Case 16 in addition to her progressively deteriorating IQ, retinitis pigmentosa, and hearing loss was ataxic and had a history of persisting hypotonia in early childhood as did Case 20; Case 5 remained hypotonic and also developed truncal ataxia; Case 11 who was born at 36 weeks' gestation had a slight ataxic diplegia.

Case 15 experienced bilateral parasthesiae in the L5, S1 root distribution after prolonged standing, but neurological examination was normal.

13 patients had EEGs performed, and resting records showed no local abnormalities or paroxysmal features. During photic stimulation 6 patients (Cases 3, 4, 5, 9, 11, and 15) showed some symmetrical bursts posteriorly containing discharges, and in one patient, sharp components appeared. Four other patients had conspicuous lambda waves. Rhythmic activity in the Rolandic area was in keeping with age, and the α rhythm was well formed and regular in most of them.

Endocrine studies. Glucose tolerance tests were performed in 5 patients (Cases 2, 9, 14, 19, and 21) and were normal except for Case 14, who had a response typical of diabetes mellitus and an impaired insulin response which was improved by tolbutamide. Growth hormone response to Bovril stimulation was normal in the 3 patients (Cases 3, 11, and 13) studied. Tests of thyroid function in 3 patients (Cases 2, 5, and 16) were normal.

Genetics. There was no consanguinity in the 18 families from which our patients are derived. In 2 of the 4 pairs of affected siblings, the second child was discovered as a consequence of diagnosing the first. In the other two pairs, this was not certain and all 4 patients could be regarded as index cases. Segregation ratios were calculated therefore with either 18 or 20 index cases. These gave values of 3·5 : 1 and 3 : 1 respectively; both of which are consistent with an autosomal recessive mode of inheritance. The 3 half-siblings in the families studied were normal.

The leucocyte karyotypes contained no consistent abnormality. Case 1 had a single abnormal cell with a 47XY + G min karyotype among 24 normal cells. Case 3 had a 46XY 1qh + abnormality (a large heterochromatic band next to the centromere on chromosome 1) which was not present in her sibling (Case 4) who had a normal karyotype as did all the other patients studied.

Discussion

Our results in this large series of patients with Shwachman's syndrome stress the protean manifestations of the condition and extend the knowledge on a number of aspects.

Infections. The series again confirms earlier observations of the susceptibility to respiratory, cutaneous, and systemic infections in this syndrome.[1 12] Shmerling *et al.*[1] calculated a 25% mortality rate due to infection from their review of cases. The abnormal thoracic configuration and hypotonia may explain the predominance of pneumonia in younger patients. Although lower respiratory tract infections are less common in older patients, the incidence of sinusitis and otitis media suggests a continuing susceptibility to infection.

The nature and frequency of infection does not correlate with the degree of neutropenia and neutrophilic responses to infection have been demonstrated by others[10 13] as well as by ourselves. Case reports of a variable immunoglobulin deficiency have appeared but these are not consistent.[14–16] We have recently demonstrated that defective neutrophil mobility is an almost invariable finding in Shwachman's syndrome,[17] and may contribute to the susceptibility to infections.

Pancreatic insufficiency. The degree of pancreatic insufficiency in these patients was variable and the persistence of some residual exocrine function possibly accounts for the delayed presentation of malabsorption in some cases.[10 13] The pancreatic histology described is similar to that noted before;[1 11–13] and the arguments in favour of either a hypoplastic or degenerative lesion of the pancreas have been discussed by Nezelof and Watchi.[12] The presence of a normal ductular architecture and islet structure with some residual exocrine tissue in a normal-sized, though lipomatous gland, suggests a

fatty metamorphosis secondary to a progressive degenerative lesion. This was essentially concluded by Burke *et al.*[10] who described a 5-month-old patient with this syndrome in whom the only pancreatic abnormality at necropsy was inspissated secretions in the ducts; the exocrine tissue was histologically normal.

The low plasma total amylase may represent the extent of EPI. Levitt *et al.*[18] have demonstrated a 2 : 1 ratio of nonpancreatic to pancreatic amylase in normal serum and the absence of the pancreatic components in the serum of patients with Shwachman's syndrome. We did not study the plasma α-amylase isoenzymes and can only speculate on whether one or more isoenzymes are affected, and whether impaired secretion of nonpancreatic amylase such as the salivary components may coexist. It is possible that the salivary glands may be affected in this syndrome; a child with EPI with both pancreatic and parotid lipomatous changes has been described.[19] The low serum amlyase activity may also represent an impaired enteropancreatic circulation.

Haematological abnormalities. An intermittent neutropenia was demonstrated in all 18 patients who were adequately studied as proposed by Burke *et al.*,[10] and we did not observe the constant neutropenia reported by Shmerling *et al.*[1] The incidence (60–70%) of thrombocytopenia in this series is comparable with that described by Shwachman *et al.*[13]

In addition to our own observations, normal bone marrow aspirates in neutropenic patients with this syndrome have been described by Goldstein[15] and Burke *et al.*[10] This coupled with the neutrophil response to infections suggests that, in some patients at least, the marrow hypoplasia is 'patchy' in distribution. We did not perform multiple marrow aspirations in our patients and thus are unable to confirm whether this is the case.

Erythroleukaemia has not previously been reported in Shwachman's syndrome, but 2 cases with other myeloproliferative leukaemias have been described; Nezolof and Watchi[12] reported a case with monocytic leukaemia, and Huijgens *et al.*[20] a case with myeloblastic leukaemia. Bone marrow hypoplasia has been identified as a possible preleukaemic condition, and is often associated with a raised HbF which may precede the bone marrow dysfunction.[21] HbF can be moderately raised in many haematological abnormalities but the highest observations have been associated with erythroleukaemia and juvenile chronic myeloid leukaemia where levels of 30% or more may occur but since levels of 10–20% may exist with hypoplastic anaemias such as Fanconi's,[21] in which leukaemic transformation is not invariable, we cannot ascribe any prognostic significance to the 2 grossly raised HbFs seen in this series.

Lymphoproliferative neoplasia has also been described in this condition, and a patient with lymphoblastic leukaemia[22] has been reported. Hantelmann[23] described a child with Hodgkin's disease who was found to have a lipomatous pancreas at necropsy.

Skeletal abnormalities. Our study is the first to review comprehensively the incidence and extent of the skeletal abnormalities in this syndrome. Metaphyseal dyschondroplasia affecting ribs and knees was first described by Burke *et al.*[10] and Giedion *et al.*,[24] and Stanley and Sutcliffe[25] reported the more extensive metaphyseal involvement especially of the femoral head. Fellman *et al.*[26] expanded the range of skeletal abnormalities to include abnormal long bone tubulation, and genu and cubitus valgus. McLennan and Steinbach[27] reported narrowing of the sciatic notch and hypoplasia of the 5th middle phalanx causing clinodactyly.

We have shown the high frequency of rib abnormalities which are particularly common in the younger patients. Their relative infrequency in the older children can be explained by a spontaneous and complete resolution such as that observed in 2 of our cases and which was occurring in a patient described by Brueton *et al.*[16] We have also demonstrated clinodactyly in half of our patients and the resolution of this lesion in one case.

This report and that of Shmerling *et al.*[1] indicates that the hip is the earliest and most frequently affected site for metaphyseal chondrodysplasia, though this may not be invariable.[27] The sequence of metaphyses involved in this disease was unpredictable but certainly progressive. The earliest age at which we detected metaphyseal lesions was one year, but Danks *et al.*[28] found evidence of early femoral and humeral involvement at 4 months in one case. The pathogenesis of these lesions is obscure. Spycher *et al.*[29] reported poorly vascularised and disorientated columnar cartilage, and Danks *et al.*[28] found similar features of defective endochondrial ossification. These features would seem to be primary to the syndrome rather than secondary to malnutrition.

Long bone tubulation is a nonspecific feature and may be associated with syndromes, such as Marfan's syndrome or homocystinuria, or with disuse secondary to immobilisation or neuromuscular disease.[30] This was not the case in our patients and the tubulation may reflect abnormal diaphyseal development or a defect in membranous ossification.

The transverse lines on the long bones probably represent periods of arrested bone growth secondary

to infection and other stress associated with this syndrome.[31]

The pathological fractures and skeletal deformities requiring surgical correction in 2 of our patients, illustrate the degree of disability experienced by these patients. Shmerling *et al.*[1] described a case requiring bilateral osteotomies to correct coxa vara deformities, and Karjoo *et al.*[32] reported the necessity of a sternal splitting operation to alleviate thoracic constriction and improve ventilatory function in an infant. This did not improve the child's growth rate, however.

Skeletal maturity and growth. This study illustrates the dissociation between the osseous centres of the hand and wrist, a feature noted by Shwachman *et al.*[13] in the 3 siblings described in their paper. The carpal bone age is more retarded than that of the phalanges, and its inclusion in a composite bone age assessment, such as the 20 bone TW2 estimate, results in a low evaluation. The radius, ulnar, and short bone scores suggest that there is some delay in skeletal maturation in some patients especially, though not exclusively, the youngest in whom delayed ulnar and radial epiphyseal appearance would reduce the score. Four of the 5 children under $2\frac{1}{2}$ years, in whom radius, ulnar, and short bone scores could be determined, gave values below the 10th centile.

Malnutrition and metabolic abnormalities retard ossification centres equally and may influence the maturity in our younger patients but the discrepancy between centres which is apparent in all our patients is more characteristic of a primary bone dysplasia.

The only patient (Case 16) with a skeletal maturity above the 50th centile was also the only child to exceed the 3rd centile for height. This girl had had oxymetholone some years before and, while these effects have not been documented with this particular anabolic steroid, Shmerling *et al.*[1] noted that in one of their patients anabolic steroids did increase the bone age without affecting height.

Growth retardation was most evident in the older children. This has been noted by others, as has its independence of the frequency of infections and the degree of EPI and malnutrition.[1 13] Shmerling *et al.*[1] calculated that the severity of growth retardation could not be explained by the degree of metaphyseal dyschondroplasia. In this series Case 14, like the second of McLennan and Steinbach's two cases,[27] shows that dwarfism can occur in the absence of radiologically demonstrable metaphyseal lesions. McLennan and Steinbach suggested that their patient might not have been growing rapidly enough for metaphyseal dyschondroplasia to develop.

Growth retardation is probably therefore a primary feature and the low birthweight of some patients in this series suggests that intrauterine growth retardation may be a contributory factor.

The delayed onset of puberty in this condition has not been previously documented.

Respiratory function. The reports of Taybi *et al.*[33] Karjoo *et al.*, [32]and Danks *et al.*[28] demonstrated that rib shortening can be sufficient to cause respiratory and feeding problems in the neonatal period. Danks *et al.*[28] described a patient with a low tidal volume at 4 weeks which was normal at 14 weeks. Our results show that impaired respiratory function may persist for much longer. The reduced chest wall compliance in the 2 young patients is consistent with their abnormal thoraces. It is more difficult to explain the reduced $FEV_{0\cdot75}$ and FVC in the older patients, apart from Cases 3 and 6 who still had abnormal ribs, but this may represent some continuing musculoskeletal abnormality rather than airways obstruction.

Hepatic function and structure. Hepatic abnormalities have been described in many cases.[11 34] Brueton *et al.*[16] were the first to show raised transaminases in a patient with abnormal liver histology. Our study includes a number of similar cases, as well as some patients with biochemical evidence of liver involvement. The tendency for the transaminases to fall towards normal limits, and the resolution of hepatomegaly was present in both groups of patients and may reflect decreased fatty infiltration or a progressive fibrosis. The absence of any evidence of hepatic dysfunction in the older patients precluded investigative biopsies, but the necropsy findings in Case 19 suggest that reversal of the fatty infiltration may occur. Fatty change in the liver can be secondary to malnutrition and infection, both of which are more likely in the newly diagnosed young patient. It is possible, therefore, that the liver abnormalities may represent a secondary rather than a primary feature of the syndrome though the latter cannot be excluded.

Renal function. The varied glycosuria and aminoaciduria together with the renal tubular acidosis in the affected sibling of Case 9 and in a recent case report (S Hassell, 1979, personal communication) suggests that renal tubular dysfunction may be more extensive than previous reports have implied. Similarly the nephrocalcinosis discovered at necropsy in Case 19 may represent an undetected abnormality in urinary acidification.

Neurological and developmental findings. Shwachman *et al.*[13] specified that their patients had normal motor and mental development. Other reports have described developmental retardation either

alone[11 33 35–36] or associated with hypotonia.[12] Hypotonia has also been noted to occur independently.[32 37–38]

This review, the first systematic neurological assessment in this syndrome, establishes that early speech and motor delay is common and that this is probably due to an inherent below-average intelligence. The early overall delay may possibly be influenced by intercurrent infections and social deprivation during time in hospital, but the persisting poor intellectual achievement during optimum health and the similar achievement in the absence of a history of gestational or perinatal insults, suggest that psychomotor retardation is a primary feature of the syndrome. Malnutrition during the critical period of brain growth could cause such retardation but this degree of retardation is not seen in patients with cystic fibrosis.[39]

Except in Case 8, who had a short soft palate with a submucous cleft palate, there were no structural abnormalities or focal neurological signs which could account for the delayed speech. The frequency of otitis media and the presence of hearing loss in 4 cases, stress the importance of regular hearing tests in these patients.

Hypotonia was often noted particularly in infancy, and probably contributes to the early respiratory and feeding problems. It is possible that in most patients hypotonia is a secondary feature. The profound hypotonia of patients in the absence of infection however, suggests that in some patients the defect may be primary to the syndrome.

Abnormalities of retinal pigmentation have not been noted previously in this syndrome. Retinitis pigmentosa can be associated with syndromes involving neurosensory deafness, defective intelligence, or skeletal abnormalities;[40] no association with EPI has been reported.

Nearly half the patients tested had abnormal sensitivity to photic stimulation during EEG recording but none gave a history of photic-induced fits. The incidence of occipital photosensitivity in this group of patients is higher than would be expected in the general population[41] but its significance is unknown.

Endocrine studies. The impaired insulin response in one patient was the only gross endocrine abnormality found. Shwachman and Holsclaw[42] described one patient with a diabetic glucose tolerance test and Shmerling *et al.*[1] discounted their patient with diabetes mellitus because of his strong family history of the disease. Our case has no such history, so the possibility of an association of diabetes mellitus with this syndrome is again raised. The insulin response was improved by tolbutamide in our patient and he has been treated successfully with chlorpropamide for 10 years since diagnosis.

Genetics. The karyotype abnormalities cannot easily be interpreted. The single abnormal cell detected in Case 1 could have arisen during cell culture. The other abnormality noted is sometimes inherited and may be associated with congenital defects, but it is unlikely to be contributory to this syndrome since it is absent in this patient's sibling and the other cases.

The segregation ratios derived from sibship analysis support an autosomal recessive mode of inheritance which until now has been assumed on the basis of a familial incidence of the syndrome.[1] This mode of inheritance is also supported by our recent demonstration of defective neutrophil mobility both in the patients with this syndrome and their parents.[17]

Icthyosis. The icthyotic skin rash frequently observed among our patients had some characteristics in common with those observed in one case by Nezelof and Watchi,[12] and those described in the first case of Shwachman *et al.*[13] Shwachman and Holsclaw[42] described a varying degree of eczema among their patients. The presence of xerophthalmia in the case described by Nezelof and Watchi[12] suggests the possibility of hypovitaminosis A. In the present series the skin lesion affected patients on fat-soluble vitamin supplements and with normal serum vitamin A levels, but we cannot exclude the possibility that it may be secondary to an undetected nutritional deficiency.

Dental abnormalities. The prevalence of these may again represent another manifestation of malnutrition, but the occurrence of dysplastic teeth in some patients suggests the possibility of a primary aetiology. Frequent exposure to cariogenic antibiotic syrups may also be contributory.

Other associated features. Features such as the submucous cleft palate and the cutaneous syndactyly, which was present in 2 unrelated cases, may represent a fortuitous association. The hypertelorism noted in 3 patients has been described in another case.[43] Clinodactyly may be associated with Fanconi's anaemia and again with aplastic anaemia in the syndrome of EPI, midline ectodermal defects, microcephaly, severe mental retardation, neurosensory deafness, hypotonia, hypothyroidism, dental dysplasia, rectourogenital abnormalities, and dwarfism described by Johanson and Blizzard[44] and Schussheim *et al.*[45] Some of these features have

accompanied EPI in a case with congenital rubella[46] and in a patient with Klinefelter's syndrome.[47] Burke *et al.*[10] and McLennan and Steinbach[27] have noted some similarities between Shwachman's syndrome and the cartilage-hair syndrome.[48] Sufficient dissimilarities usually exist however, to distinguish between these syndromes though some overlap may exist.

Incomplete or partial syndromes in which the manifestation of bone marrow dysfunction or malabsorption is delayed are illustrated in this series, by the experience of Burke *et al.*[10] who discovered EPI by specifically investigating neutropenic patients, and by the 2 children described by Havlíkóva *et al.*[49] who had EPI, hepatomegaly, raised plasma AST and ALT, narrow chests, neonatal respiratory distress, and developmental retardation but no haematological abnormalities. This is not surprising in such a complex condition and the patient with neutropenia, metaphyseal dyschondroplasia, tibial bowing, dental caries, moderate mental retardation, and hypogonadism described by Theodorou and Adams[50] may represent another example of a partial syndrome.

Burke *et al.*[10] described a patient who also had Hirschsprung's disease, and an association with endocardial fibrosis has been reported.[51] Neither of these was present in this series.

Diagnosis, treatment, and prognosis. Diagnosis is more difficult in the young infant when many of the syndrome's features are indistinguishable from the manifestations of immaturity. Some of the presenting features such as hypotonia, bronchopneumonia, or respiratory distress with thoracic dystrophy may mask other symptoms. The high incidence of neonatal problems is shown in this paper and the diagnosis may not be apparent until the child is older and the more classic features of the syndrome are present. Shwachman's syndrome should be considered in any infant or child presenting with an association of any of the features described here (Table 6). We have found the presence of rib abnormalities in the child and a neutrophil mobility defect in his parents of value in diagnosing one infant with growth retardation, diarrhoea, and neutropenia.

Treatment is symptomatic. Infections usually respond to prompt treatment with antibiotics. Steroids, such as prednisone and oxymetholone, may improve marrow function,[11 13] but these and anaesthetic agents may increase the risk of infection.[17] Transfusion of whole blood and platelets has been used when appropriate such as before surgery. The spontaneous symptomatic improvement of diarrhoea in some patients has enabled withdrawal of pancreatic supplements without adverse effects both in some of our patients and those in earlier reports.[1 10 13] Nutritional supplements (for example, vitamins) are probably advisable but the progress of Cases 12 and 15 in the absence of these has been similar to other patients.

Table 6 *Features associated with Shwachman's syndrome*

Exocrine pancreatic insufficiency
steatorrhoea
Growth retardation
Skeletal abnormalities
metaphyseal dyschondroplasia, delayed maturation, rib abnormalities, long bone tubulation, clinodactyly
Narrow thorax
Haematological abnormalities
bone marrow hypoplasia, neutropenia, thrombocytopenia, raised HbF, lymphoproliferative and myeloproliferative neoplasia
Recurrent infections
Defective neutrophil mobility
Neonatal problems
poor feeding, respiratory distress
Psychomotor retardation
Hypotonia
Hepatomegaly
raised ALT and AST
Renal tubular dysfunction
Icthyosis
Dental abnormalities
Delayed puberty
Diabetes mellitus
Dysmorphic features
Endocardial fibrosis
Hirschsprung's disease

The prognosis for this syndrome is probably better than that for cystic fibrosis though it is accompanied by considerable morbidity. Shmerling *et al.*[1] reported a 25% mortality which compares with one of 15% reported here. Infections and a haemorrhagic diathesis can prove fatal, and any prognostication and follow-up should consider these, and the risk of myeloproliferative and lymphoproliferative neoplasia.

An hypothesis for the primary abnormality in Shwachman's syndrome

The primary abnormality in Shwachman's syndrome has not been defined, and we conclude by presenting an hypothesis to explain the protean manifestations of this syndrome. Unrelated tissues appear to be both malfunctioning and, as the lipomatous changes imply, undergoing degenerative changes. Spycher *et al.*[29] described large glycogen and small lipid deposits in the chondrocytes from an area of metaphyseal dyschondroplasia. Their electron-microscopical studies also demonstrated dilated endoplasmic reticulum cisternae containing an increased amount of granules which appeared as intracellular inclusions. They proposed that this represented either a failure to secrete an abnormal synthetic product or a defect in the secretion of a normal product from the endoplasmic reticulum.

Cellular secretion is dependent on the adequate function of microtubules and microfilaments. The former are thought to provide the structural and orientating system for the motive force provided by the microfilaments.

Use of agents such as colchicine which blocks microtubular reassembly, vincristine alkaloids which precipitate microtubular protein, or the cytochalasins which disrupt microfilaments have demonstrated that these ubiquitous subcellular components are essential for cell division, lipid absorption,[52] hexose uptake,[53] neutrophil mobility,[54] phagocytosis and the disposition of cell surface receptors,[55] as well as for the secretion of histamine,[56] hormones including insulin,[57] and thyroxine,[58] hepatic lipoproteins and albumin,[59] collagen,[60] pancreatic amylase,[61] and neurotransmitters.[62]

In cells exposed to colchicine, secretory products fail to migrate to the cell periphery and accumulate within golgi-associated vacuoles and in the endoplasmic reticulum cisternae,[59–60] resulting in an electron microscopical appearance similar to that noted by Spycher *et al.*[29] The demonstration of impaired polymorphonuclear mobility in patients with this syndrome and in some of their parents suggests that this defect, since it is manifest in presumed heterozygotes, is close to the abnormal gene product. Similar defects in polymorphonuclear mobility can be induced by colchicine and cytochalasin B.[54]

We speculate that the basic defect in Shwachman's syndrome may lie in the function of the microtubular and microfilament elements. Too little is known about the co-ordination, regulation, or metabolism of these systems to be more specific, but such a functional defect could account for both the abnormal appearance of the chondrocytes and the impaired polymorphonuclear mobility. The pancreatic cell inclusion bodies noted by Shwachman *et al.*[13] may represent accumulating synthetic products which ultimately lead to degenerative changes with subsequent lipid or glycogen deposition. Mitotically-active tissues such as the bone marrow would be most vulnerable to such a defect, as would be metabolically active tissues like the liver.

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Correspondence to Dr P J Aggett, University of Aberdeen, Department of Physiology, Marischal College, Aberdeen AB9 1AS.

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