Syndromes of asplenia and polysplenia

A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis¹

Vera Rose, T. Izukawa, and C. A. F. Moës

From the Departments of Cardiology and Radiology and Research Institute of the Hospital for Sick Children, Toronto, Ontario, Canada

This review presents the cardiac and non-cardiac malformations in 60 cases with asplenia and polysplenia with special reference to distinguishing factors which may be helpful in the clinical recognition of these syndromes.

The asplenia cases were predominantly male and presented with cyanosis. They frequently had transposition of the great arteries (72%) with pulmonary stenosis or atresia (88%) and total anomalous pulmonary venous drainage (72%). Deaths were caused by cardiac failure and anoxia in 57 per cent of cases. Most of the patients died in the first year of life (79%), but longer survival is possible in the asplenia syndrome.

The polysplenia cases were predominantly female and survived longer. The characteristic clinical findings were the relatively more benign presenting signs and the leftward or superiorly orientated P wave axis on the electrocardiogram. Conotruncal abnormalities were less common and total anomalous pulmonary venous drainage did not occur. On angiography the inferior vena caval drainage via the azygos system was clearly identified and this was present in all cases at surgery.

Our study indicated that the cardiac anomalies in polysplenia were less severe than they were in asplenia and therefore the prognosis in the former syndrome is likely to be more favourable. Three families had two affected sibs but no single genetic factor could be identified. The aetiology of these syndromes remains undetermined.

The association of splenic anomalies with malpositions and malformations of other organ systems, in particular, the cardiovascular system, have been well documented in the past 20 years (Polhemus and Schafer, 1952, 1955; Ivemark, 1955; Putschar and Manion, 1956; Ruttenberg *et al.*, 1964; Campbell and Deuchar, 1967; Moller *et al.*, 1967; Landing *et al.*, 1971; Van Mierop, Gessner, and Schiebeler, 1972; Freedom, 1972). The complexity of the cardiac malformation determines the clinical course and prognosis and frequently precludes correction by surgical techniques. It is important, therefore, to recognize the patient who has the asplenia or polysplenia syndrome, in order to anticipate potential

difficulties which may be encountered during cardiac catheterization procedures and to be able to predict the cardiac lesions which could be surgically repaired or palliated.

A review of the cases with splenic abnormalities from the necropsy series of the Cardiology Division, Hospital for Sick Children, Toronto, revealed 39 cases of asplenia and 13 cases of polysplenia. The heart was available for review in 32 cases of the former and all of the latter. In addition, there are 6 surviving patients with asplenia syndrome and 2 with polysplenia in whom the splenic abnormalities were suspected because of the presence of Howell-Jolly bodies in the peripheral blood smear in the former and multiple spleens documented by radioisotope spleen scan in the latter. It is suspected that more surviving cases with polysplenia may be

Received 20 December 1974.

¹ This work was supported by a grant from the Ontario Heart Foundation, Toronto, Canada.

presently unidentified since spleen scan has only recently been used for the identification of this condition. The necropsied group included cases in which the spleen was either entirely absent (cases of functional hyposplenia were excluded) or in which 4 to 10 splenunculi were present (cases with one accessory spleen were not included).

At necropsy, clinical and radiological findings were reviewed, with particular reference to points of difference between the two syndromes and their clinical recognition.

Results

Asplenia

Age at death and cause of death (Tables 1 and 2) The mortality was high in asplenia. In this necropsy series 36 per cent of cases did not survive the first week of life and 79 per cent were dead by the end of the first year. Cardiac failure and anoxia were the predominant causes of death, followed by surgery. Infection was a relatively infrequent cause of death.

Pathological features: non-cardiac malformations (Table 3) The recognized tendency for bilateral symmetry of organs in asplenia syndrome (Van Mierop *et al.*, 1972) was noted to be present.

TABLE 1 Age at death

Age	Asplenia No.	%	Polysplenia No.	%
Birth-1 week	14	36	2	15
1-4 weeks	8	20	2	15
1-3 months	6	15	3	23
3-5 months	2	5	1	8
6-12 months	1	3	0	0
Total under 1 year	31	79	8	61
Total over 1 year	8	21	5	39

TABLE 2 Cause of death

	Asplenia	Polysplenia
Cardiac failure	11	1
Anoxia	10	1
Complications of surgery	8	8
Infection	4	1
Haemorrhage	3	0
Sudden unexpected death	3	2 (late postoperative)
	39	13

TABLE 3 Associated non-cardiovascular malformations in 52 necropsy cases

Abnormality	Asplenia 39 cases	Polysplenia 13 cases
Pulmonary		
Bilateral trilobed lungs	27	0
Bilateral bilobed lungs	0	4
Bilobed (R) trilobed (L)	1	2
Lobation unknown	11	7
Gastrointestinal		
Heterotaxy	15	0
Situs inversus	6	6
Partial situs inversus	6	1
Normal visceral situs	12	6
Imperforate anus	2	
Annular pancreas	1	
Ectopic liver (in adrenal)	1	
Hiatus hernia	1	
Absent gallbladder		1
Genitourinary		
Horseshoe kidney	1	
Double collecting system	1	
Hydroureter	3	
Cystic kidney	1	1
Absent right kidney and ureter	—	1
Endocrine		
Fused or horseshoe adrenal	4	
Absent L adrenal	1	
Bicornuate uterus	1	
Ovarian cysts		1
CNS		
Arteriovenous malformation of midbrain		1
Musculoskeletal		
Scoliosis	2	

There tended to be duplication of right-sided structures, with absence of those normally on the left. Other features, such as the symmetrical liver and abdominal heterotaxy, indicated a retention of the undifferentiated early embryonic state. Among the cases in which lung lobation was recorded 27 out of 28 had symmetrically trilobed lungs: 12 of these cases has visceral heterotaxy, 5 had abdominal situs solitus, 4 had situs inversus, and 6 had partial situs inversus. One case had thoracic situs inversus with partial abdominal situs inversus with the venae cavae as well as the pulmonary veins entering a common atrium on the right side. The bronchial anatomy could not be ascertained radiologically from the air bronchograms and was not recorded in the necropsy reports in this retrospective study.

Abnormal visceral situs was present in 69 per

cent of cases. Abdominal heterotaxy occurred in 15 patients, situs inversus in 6, and partial situs inversus in 6. Among the 12 cases with normal visceral situs, 5 had bilateral trilobed lungs and in 7 others the lung lobation was not recorded in the necropsy report. There were 2 cases with imperforate anus. Three others with asplenia had annular pancreas, ectopic liver, and hiatus hernia.

Fifteen per cent of cases with asplenia had renal abnormalities which included horseshoe kidney, double collecting system, hydroureter, and cystic kidney.

There were 4 instances of fused or horseshoe adrenal glands. Three patients had an unusual physical appearance, with webbing of the neck, and were thought to be a Turner phenotype. Chromosome studies were not done on these cases.

Cardiovascular abnormalities (Tables 4 and 5, Fig. 1) Positional abnormalities of the heart were frequent, 13 of 32 hearts (41%) having the apex on the right.

Venous system (Fig. 2) Bilateral superior venae cavae were present in 17 of 32 hearts (53 per cent). A single superior vena cava was located on the right in 11 (34 per cent) and on the left in 3 (10 per cent) cases. The inferior vena cava in its supradiaphragmatic course was on the right in 19 (60%) and on the left in 9 (28%) cases, which suggests that the systemic venous atrium was located in the corresponding position in cases in which the atrial morphology was not clearly defined (Van Praagh, 1972; de la Cruz, Polansky, and Navarro-Lopez, 1962). We accept the suggestion that the chamber into which the supradiaphragmatic inferior vena

ASPLENIA (32 PM. CASES) POSITIONS OF APEX AND AORTIC ARCH

APEX Left-18 (56%) Right-13 (41%)
Midline-1 (3%)
ARCH OF AORTA Left-18 (56%) Right-12 (38%)
Uncertain-2 (6%)

FIG. 1.

cava drained was the right atrium. There was no instance in our series in which we were able to document that the inferior vena cava returned to a morphological left atrium. Among those cases with the inferior vena cava on the right, 8 had abdominal situs solitus, 8 had visceral heterotaxy, and 3 had partial situs inversus. In 1 case with partial situs inversus, a right-sided inferior vena cava crossed to enter the systemic venous atrium which was situated on the left. Of the 9 cases with a left-sided inferior vena cava, 6 also had abdominal and atrial situs inversus.

Total anomalous pulmonary venous drainage occurred in 23 or 72 per cent and partial anomalous

ASPLENIA (32 PM. CASES) VENOUS SYSTEM

1) **SUPERIOR VENA CAVA**
Bilateral-17 (53%)
Right-11 (34%)
Left-3 (10%)
Uncertain-1 (3%)

2) **INFERIOR VENA CAVA**
Left-9 (28%)
Right-19 (60%)
Bilateral-1 (3%)
Midline-1 (3%)
Uncertain-2 (6%)

3) **PULMONARY VEINS**
Anomalous drain. (84%)
i) Total-23 (72%)
ii) Partial-2 (6%)
iii) Mixed-2 (6%)

4) **HEPATIC VEINS**
I.V.C-23 (72%)
Direct to atrium-5 (16%)
Uncertain-4 (12%)

FIG. 2.

FIG. 3.

pulmonary venous drainage in 2 or 6 per cent of cases. Mixed anomalous pulmonary venous drainage refers to pulmonary venous drainage into more than one site.

The morphological distinction of the atria was difficult in most cases. The diagnosis of single atrium was made in cases of absent septum or in those with very large secundum and primum defects with a vestigial septum often represented by a bar of tissue running between the anterior and posterior wall of the atrium.

Great vessel abnormalities (Fig. 3) Transposition of the great arteries was common (72%). Transposition of the great arteries in the d-position

TABLE 4 *Positions of cardiac apex and aortic arch*

	<i>Asplenia (No.)</i>	<i>Polysplenia (No.)</i>
<i>Apex</i>		
Left	18	7
Right	13	5
Midline	1	—
<i>Aortic arch</i>		
Left	18	4
Right	12	8
Unverified	2	—

FIG. 4.

TABLE 5 Associated cardiovascular abnormalities

Abnormality	Asplenia % of total	Polysplenia % of total
Cardiac malpositions	44	41
Venous system		
Systemic veins		
Bilateral superior vena cava	53	33
Inferior vena cava drainage via azygos	0	84
Pulmonary veins		
Total anomalous pulmonary venous drainage	72	0
Partial anomalous pulmonary venous drainage	6	42
Great vessels		
Transposition	72	8
Pulmonary stenosis or atresia	78	33
Coronary arteries		
Single coronary artery	19	0
Intracardiac		
Single ventricle	44	8
Single AV valve	87	17
Absent coronary sinus	85	33

occurred in 17 or 53 per cent and in the 1-position in 6 or 19 per cent of cases. Three patients or 9 per cent had a double outlet right ventricle. Pulmonary stenosis or atresia was present in 25 or 78 per cent of cases. A single coronary artery occurred in 6 or 19 per cent.

Intracardiac malformations (Fig. 4) A single atrioventricular valve was present in 28 or 87 per cent. A single ventricle was present in 14 or 44 per cent of cases. A single atrioventricular valve was present in all cases with single ventricle and in 14 of the 18 cases with two ventricles. In the remaining 4 cases the atrioventricular valve was divisible into mitral and tricuspid components. There was a high incidence of absent coronary sinus (85%). Septum primum and secundum defects of the atrial septum were present in 21 or 66 per cent and the remainder had primum defects only.

Survivors (Table 6) There are 6 surviving patients identified by means of the Howell-Jolly bodies and the spleen scan. All the survivors are male and 3 of them have had systemic-to-pulmonary shunts performed and are doing well. Two of the survivors are over the age of 10 years.

Clinical features (Table 7) There was a preponderance of male patients with asplenia syndrome.

TABLE 6 Asplenia survivors

6 cases – all male		
Age at last visit	No.	Surgery (shunts)
< 1 year	2	0
< 3 years	2	1
12–18 years	2	2

Despite the severity of the congenital malformations in these children, these infants were born at term and their mean birthweight was not significantly different from that of controls (Registrar-General of Ontario, 1966). All cases presented with cyanosis. The electrocardiogram showed a normal or rightwardly directed P axis. The plain chest film was helpful in documenting the abnormal cardiac and visceral situs and the symmetrical liver (Fig. 5). The persistence of the left superior vena cava could also be detected on the chest film (Fig. 6), and was confirmed by angiography (Fig. 7). The side-by-side relation between the aorta and the inferior vena cavae in their abdominal course (Elliot, Cramer, and Amplatz, 1966) is exemplified in one of our cases (Fig. 8). Howell-Jolly bodies were seen in 15 of 17 cases who had blood smears taken. A splenic scan to confirm the diagnosis of asplenia was done in 6 instances (Fig. 9).

TABLE 7 Clinical features

	Asplenia	Polysplenia
Sex ratio (M/F)	1.7/1 60% males	0.5/1 28% males
Gestation	Normal	Normal
Birthweight (mean) Control 3322 g	3261 g	3313 g
Presenting signs		
Cyanosis	45 (100%)	6 (4%)
Murmurs		4 (30%)
Dyspnoea		3 (24%)
Howell-Jolly bodies		
Present	15	0
Absent	2	11
Unknown	28	4
Spleen scan (8 cases)	Absent spleen (6 cases)	Multiple spleens (2 cases)

FIG. 5. Plain x-ray of a case of asplenia syndrome showing symmetrical liver.

FIG. 7 Cineangiogram of a case of asplenia syndrome showing bilateral superior venae cavae.

FIG. 6 Plain x-ray of a case of asplenia syndrome showing bilateral superior venae cavae.

FIG. 8 Cineangiogram of a case of asplenia syndrome showing aorta and inferior vena cava located side by side to the left of the spine.

FIG. 9 Splenic scan of a case of asplenia syndrome showing transverse liver and no spleen. A=anterior view; P=posterior view.

Familial cases (Fig. 10) In this series of 60 cases with asplenia and polysplenia there were 2 families in which 2 sibs were affected with asplenia and one family in which 2 sibs were affected with polysplenia. None of the 3 families had a history of consanguinity. A retrospective study of 17 patients' families with asplenia syndrome showed that the maternal and paternal ages were not significantly different from the ages of the parents in the

normal population (Registrar-General of Ontario, 1966). Asplenia syndrome occurred more frequently in late born children of mothers whose mean age was not significantly different from that of the general population (mean maternal age was 27.07 years). The birth order effect was tested (Haldane and Smith, 1948) and showed an actual mean of 360, a theoretical mean of 287.1, with a difference which was more than the standard error of 36.6 and, therefore, significant. The pregnancy history did not bring to light any particular event during early gestation which might have been the cause of development of the asplenia syndrome. Miscarriages were not frequent in this group, the rate was 8.65 per cent, comparable to that found in the general population (Warburton and Fraser, 1964). The recurrence rate in all the sibs of patients with asplenia syndrome was 4.65 per cent. The segregation ratio as a test for autosomal recessive inheritance was 8.9 per cent, well below the 25 per cent expected (Li and Mantel, 1968) if asplenia syndrome were a recessively inherited condition.

Polysplenia

Age at death and cause of death (Tables 1 and 2) Of patients in this necropsy series, 61 per cent died in the first year of life and 39 per cent later on. The ages at death were not significantly different from those in the asplenia group. The majority of deaths occurred in the postoperative period.

Pathological features: non-cardiac malformations (Table 3) The symmetry of organs was noted to occur here as it did in asplenia, with a tendency of duplication of left-sided structures, and

FIG. 10 Pedigree of three families in which asplenia and polysplenia recurred.

POLYSPLenia (12 P.M. CASES)
POSITIONS OF APEX AND AORTIC ARCH

absence of those normally on the right. Four cases had bilateral bilobed lungs, and 2 had bilobed right and trilobed left lungs. In the 2 latter cases with thoracic situs inversus, 1 had abdominal situs inversus with the vena cava as well as the pulmonary veins entering a single atrium on its right lateral aspect. The other had partial abdominal situs inversus with the azygos continuation of the inferior vena cava on the left side of the spine entering the left side of this atrium which was large and also received the common left pulmonary vein. The coronary sinus drained into this left-sided atrium as well. A smaller right-sided atrium drained the common right pulmonary vein. In 7 cases the lobation of the lungs was not known. The bronchial anatomy was not ascertainable. Abnormal visceral situs occurred in 7 of the 13 cases. The gall bladder,

a right-sided structure, was absent in 1 patient. Two of the cases (15%) had renal abnormalities. A cystic kidney was present in one and the right kidney and ureter were absent in the other.

Cardiovascular abnormalities (Tables 4 and 5, Fig. 11) Positional anomalies of the cardiac apex were frequent, 42 per cent of cases had dextrocardia; 67 per cent had a right aortic arch. Compared with the cases of asplenia the positional anomalies and aortic arch were not significantly different.

Venous system: systemic veins (Fig. 12) Of the 12 cases, 33 per cent had bilateral superior vena cavae. A single superior vena cava was on the right in 33 per cent, and on the left in 33 per cent of cases. Azygos return of the inferior vena cava was present in most of the cases with the azygos vein coursing on either the right or the left side.

Pulmonary veins Partial anomalous pulmonary venous drainage was observed in 5 or 42 per cent of cases, and in the remaining cases, the pulmonary veins drained normally.

Great vessel abnormalities (Fig. 13) The great arteries were normally related in 10 or 84 per cent of cases and pulmonary stenosis or atresia were present in 42 per cent of cases.

Intracardiac malformations (Fig. 14) Defects of the atrial and ventricular septa and atrioventricular valve abnormalities occurred less frequently in polysplenia than in asplenia.

Survivors Of 8 surviving patients where the diagnosis was suspected from clinical and catheterization data, 2 have so far been identified by spleen scan.

FIG. 12.

POLYSPLENIA (12 PM. CASES)

GREAT VESSELS

Normal - 10 (84%)

T.G.A. - 1 (8%)

D.O.R.V. - 1 (8%)

PULMONARY VALVE

Normal - 7 (58%)

Stenosis - valve - 1
subvalve - 3 (33%)

Atresia - 1 (9%)

A) DUCTUS ARTERIOSUSPatent i) Left - 3
ii) Right - 3 (50%)

Closed - 3 (25%)

Uncertain - 3 (25%)

B) CORONARY ARTERIES

Two - 10 (84%)

Uncertain - 2 (16%)

FIG. 13.

Clinical features (Table 7) There was a predominance of female patients in this group. The mean birthweight was normal as compared to controls. Seven cases presented with cyanosis, 5 with murmurs, and 3 with dyspnoea. The electrocardiogram characteristically showed a leftward and superiorly directed P wave axis in all but one of the cases. Among the radiological signs, the inferior vena caval drainage via the azygos system was a useful sign (Fig. 15) as was the separation of the aorta and inferior vena cava coursing on either side of the spine (Fig. 16). Howell-Jolly bodies were not seen in any of the 9 cases in which they were searched for. The splenic scan was helpful in making the diagnosis of polysplenia (Fig. 17),

despite the fact that resolution of the splenic masses is not ideal.

Discussion

Although case reports of asplenia associated with cardiovascular defects and situs inversus had been published during the nineteenth century, the first suggestion that asplenia might constitute a clinical syndrome was made by Polhemus and Schafer (1952, 1955), and a detailed analysis of the aggregation of defects as well as a review of the published reports by Ivemark (1955) appeared three years later in a notable paper. Morphogenetically the splenic abnormalities and associated defects are

POLYSPLENIA (12 PM. CASES)

INTRACARDIACA) CORONARY SINUS

Absent - 5 (42%)

Present - 4 (33%)

Uncertain - 3 (25%)

B) ATRIAL SEPTUM

Primum + sec. - 3 (26%)

Single - 2 (16%)

Primum - 2 (16%)

Sec. - 3 (26%)

F.O. - 2 (16%)

C) A-V VALVES

Normal - 6 (50%)

Single - 2 (16%)

Abn. mitral valve - (34%)

i) Atresia - 1

ii) Small - 1

iii) Displaced - 1

iv) Thick - 1

D) VENTRICLES

Normal - 7 (58%)

Single - 1 (8%)

Small L.V. - 3 (34%)

Small R.V. - 1

E) VENTRICULAR SEPTUMV.S.D. i) Fallot - 3
ii) Canal - 4 (67%)
iii) Muscular - 1

Intact - 3 (25%)

No septum - 1 (8%)

FIG. 14.

FIG. 15 Cineangiogram of a case of polysplenia syndrome showing inferior vena caval drainage via a right-sided azygos vein.

FIG. 16 Cineangiogram of a case of polysplenia syndrome showing the aorta and inferior vena cava running on either side of the spine.

likely to be caused by an unknown teratogenic insult between the 31st and 40th days of gestation (Putschar and Manion, 1956; Landing *et al.*, 1971). During the past 10 years a number of case reports and reviews has indicated that a predictable pattern of malformations exists in cases with either absent spleen or polysplenia, which would permit one to

regard these conditions, from a clinical standpoint, as separate congenital syndromes.

Although the fatality rate is high in asplenia, survival is possible (and it was notable that survivors in our series did not have anomalies of the pulmonary venous return). In comparing the number of cases of asplenia and polysplenia who died at

FIG. 17 Splenic scan of a case of polysplenia syndrome showing a right sided liver and multiple spleens. LPO=left posterior oblique; P=posterior.

different times in the first year of life and thereafter, there was no statistically significant difference between them. Since survival is possible with asplenia, palliative surgery should be considered. In 1956 Putschar and Manion in an extensive survey of the published reports described 29 cases of asplenia without heart disease, but only occasional reports have appeared since (Kessler and Smulewicz, 1973). There were no cases of asplenia without associated heart disease in our own records. The exact incidence of polysplenia without heart disease is not known. Surgery in both conditions carries a high risk.

Among the necropsy findings, the non-cardiac abnormalities fitted the pattern of isomerism described by Van Mierop and co-workers (1972), Moller *et al.* (1967), and Landing *et al.* (1971). The frequency of visceral heterotaxy with asplenia has been described by Van Praagh and co-workers (1964, 1965) and the resulting difficulties in ascertaining viscerotaxial situs are well known. Visceral and atrial situs appeared to be discordant in 3 cases. In one case of asplenia who had thoracic situs inversus and partial situs inversus of the viscera, a right-sided inferior vena cava crossed and drained into a left-sided systemic venous atrium. In one case of polysplenia with abdominal situs inversus the venae cavae as well as the pulmonary veins entered a single atrium on its right lateral aspect. In another case of polysplenia with partial abdominal situs inversus and thoracic situs inversus azygos continuation of the inferior vena caval drainage as well as the common left pulmonary veins and coronary sinus drained into the left-sided part of a large common atrium. The renal anomalies occurred in 15 per cent of asplenia and 15 per cent of polysplenia cases in our series. Freedom (1972) reported an incidence of renal abnormalities in 25 per cent of his series.

The salient features of the cardiovascular abnormalities confirmed to a large extent those already published (Ivemark, 1955; Ruttenberg *et al.*, 1964; Moller *et al.*, 1967; Van Mierop *et al.*, 1972). Notable among the distinguishing anatomical features was the high incidence of transposition of the great arteries with pulmonary atresia or stenosis in asplenia. The associate frequency of total anomalous pulmonary venous drainage suggests that it might contribute to the severity of symptoms and early death in patients with that condition. Conotruncal abnormalities were less common in polysplenia, and only partial anomalies of pulmonary venous return occurred. Among the systemic venous abnormalities, the absence of the infrahepatic segment of the inferior vena cava with drainage via the azygos system was not seen in any cases of asplenia and was present in 84 per cent of the polysplenia cases and

was, therefore, a useful distinguishing anatomical finding. Of interest from the embryological standpoint and the concept of bilateral right-sidedness (Van Mierop *et al.*, 1972) was the absence of the coronary sinus in 84 per cent of necropsies in asplenia. Single ventricle, single atrium, and common atrioventricular valve occurred with greater frequency in asplenia. In this group the atrial septum was often no more than a vestigial bar of tissue and the large secundum and primum defects described in our study (Fig. 4) could be regarded as single atrium in most cases. A single atrioventricular valve was present in all cases with single ventricle. In only 4 cases was the atrioventricular valve divisible into mitral and tricuspid components and these were patients who had 2 ventricles. A single coronary artery was found in 19 per cent of our asplenia cases. This was found in one case of the series of Ruttenberg *et al.* (1964) and has not been reported in others.

Among the clinical features, male preponderance was striking in asplenia while there was a female predominance in the polysplenia group. Parental age, gestational age, and birthweight were normal as compared to the general population (Registrar-General of Ontario, 1966). The significance of the increased birth order might have been more revealing had we been able to analyse separately cases where mothers were older (e.g. over 35 years) and likely to have completed their families. However, since the number of families we were able to investigate was not large enough for such a separate analysis, a likely explanation of the high birth rank could have been the deliberate limitation of family size after the birth of an affected child. A similar birth order effect was found in family studies of patients with another type of severe congenital heart disease (Chen, Thompson, and Rose, 1971).

Cyanosis was the presenting sign in all cases of asplenia whereas only half of the polysplenia cases presented in this way.

The consistent electrocardiographic abnormality was a leftward or superiorly directed P wave vector or coronary sinus rhythm which was found in 92 per cent of cases of polysplenia. Analysis of the P wave vector is useful in detecting atrial situs in dextrocardia. It has been suggested that infradiaphragmatic interruption of the inferior vena cava is the cause of unusual atrial depolarization in polysplenia (Momma and Linde, 1970; Van der Horst and Gotsman, 1972).

Radiologically the plain x-ray film of the chest and upper abdomen is helpful in suggesting that the splenic abnormality is present. The cardiac and visceral situs, the position of the liver and of the

stomach are easily ascertained. More difficult to ascertain from the conventional radiograph is the presence of eparterial or hyparterial bronchi which are a clue to lobation of the lungs and would suggest bronchopulmonary isomerism in these syndromes (Landing *et al.*, 1971). Angiographically, the drainage via the azygos system of the inferior vena cava is helpful in identifying specifically the polysplenia cases. The aorta-to-inferior vena cava relation demonstrated in some of these cases is a useful sign (Elliot *et al.*, 1966) for confirming the diagnosis in suspected cases.

The persistence of Howell-Jolly bodies in the peripheral blood smear is a very useful means of confirming splenic agenesis or hypofunction provided it is remembered that Howell-Jolly bodies can be transiently present in the normal newborn (Padmanabhan, Risemberg, and Rowe, 1973). These inclusions are also seen in the late stages of the maturing erythroblast, in megaloblastic and haemolytic anaemias, thalassaemia, leukaemia, and some types of steatorrhoea. A more specific diagnosis of asplenia and polysplenia can be made by radioisotope scanning of the liver and spleen (Shah *et al.*, 1964; Freedom and Treves, 1973) when absence of the spleen can be shown or multiple spleens identified.

While most of the cases of splenic abnormalities with congenital heart disease are sporadic, a number of surveys in the past have shown a clear tendency for congenital heart disease in general to occur in several family members (Nora, 1971). It was, therefore, not surprising to find three families with more than one sib affected in our series. In each of the asplenia families there was concordance of the cardiac defect. In the polysplenia family, one sib had tetralogy of Fallot and one had hypoplastic left heart syndrome. While this may suggest that these syndromes could be heritable conditions with autosomal recessive transmission, our asplenia patients' family analysis did not confirm this. We found a segregation ratio of 8.9 per cent which was far below the 25 per cent expected if this were a true autosomal recessive condition (Li and Mantel, 1968). There was no history of consanguinity in the families. The occurrence of splenic abnormalities in sibships has been reported in four instances: Polhemus and Schafer (1952) reported 2 sibs of whom one had asplenia and one polysplenia; in Ruttenberg *et al.*'s series (1964) 3 sibs with asplenia were born in one family; Schonfeld and Frischman (1958) reported a case of asplenia in the offspring of a consanguineous marriage who had 3 out of 4 sibs with multiple congenital abnormalities; and Silver, Steier, and Chandra (1972) reported a family in which there was one case of asplenia and

one with tetralogy of Fallot. More recently, Simpson and Zellweger (1973) reported one child with splenic agenesis and one with splenic hypoplasia in a family. The role of genetic factors in asplenia and polysplenia remains undefined. It is more likely that these conditions result from the interaction of both genetic and environmental factors as suggested by Nora (1971). In a family with one affected child and no other affected relatives, the recurrence risk should be very low. The incidence of asplenia in the general population is difficult to assess. Nine patients with this syndrome in our series were born in Metropolitan Toronto between 1955 and 1964. The minimal incidence is therefore 1 in about 40,000 live births. The calculated sib frequency if asplenia were a multifactorial condition (Edwards, 1960) would be 0.235×10^{-4} or 0.49 per cent which is below the actual incidence of 4.65 per cent we found. Our family data, therefore, did not suggest any single genetic factor nor did they bring to light any teratological insult which could have been responsible for the development of the splenic and associated anomalies.

We wish to thank Dr. J. Huber, Professor of Pathology, and Dr. R. D. Rowe, Professor and Head of the Division of Cardiology, at the Hospital for Sick Children, Toronto, for helpful criticism and advice. Dr. Su-Chiung Chen performed the family studies of cases with asplenia syndrome.

References

- Campbell, M., and Deuchar, D. C. (1967). Absent inferior vena cava, symmetrical liver, splenic agenesis, and situs inversus, and their embryology. *British Heart Journal*, **29**, 268.
- Chen, S., Thompson, M. W., and Rose, V. (1971). Endocardial fibroelastosis: family studies with special reference to counseling. *Journal of Pediatrics*, **79**, 385.
- de la Cruz, M. V., Polansky, B. J., and Navarro-Lopez, F. (1962). The diagnosis of corrected transposition of the great vessels. *British Heart Journal*, **24**, 483.
- Edwards, J. H. (1960). The simulation of Mendelism. *Acta Genetica et Statistica Medica*, **10**, 63.
- Elliot, L. P., Cramer, G. G., and Amplatz, K. (1966). The anomalous relationship of the inferior vena cava and abdominal aorta as a specific angiographic sign in asplenia. *Radiology*, **87**, 859.
- Freedom, R. M. (1972). The asplenia syndrome: a review of significant extracardiac structural anomalies in 29 necropsied patients. *Journal of Pediatrics*, **81**, 1130.
- Freedom, R. M., and Treves, S. (1973). Splenic scintigraphy and radionuclide venography in the heterotaxy syndrome. *Radiology*, **107**, 381.
- Haldane, J. B. S., and Smith, C. A. B. (1948). A simple exact test for birth-order effect. *Annals of Eugenics*, **14**, 117.
- Ivemark, B. I. (1955). Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood: analysis of the heart malformations in splenic agenesis syndrome, with fourteen new cases. *Acta Paediatrica*, **44**, Suppl. 104, 1.
- Kessler, H., and Smulewicz, J. J. (1973). Microgastria associated with agenesis of the spleen. *Radiology*, **107**, 393.

- Landing, B. H., Lawrence, T. K., Payne, V. C., Jr., and Wells, T. R. (1971). Bronchial anatomy in syndromes with abnormal visceral situs, abnormal spleen and congenital heart disease. *American Journal of Cardiology*, **28**, 456.
- Li, C. C., and Mantel, N. (1968). A simple method of estimating the segregation ratio under complete ascertainment. *American Journal of Human Genetics*, **20**, 61.
- Moller, J. H., Nakib, A., Anderson, R. C., and Edwards, J. E. (1967). Congenital cardiac disease associated with polysplenia: a developmental complex of bilateral 'leftsidedness'. *Circulation*, **36**, 789.
- Momma, K., and Linde, L. M. (1970). Cardiac rhythms in dextrocardia. *American Journal of Cardiology*, **25**, 420.
- Nora, J. J. (1971). Etiologic factors in congenital heart diseases. In Symposium in Pediatric Cardiology. *Pediatric Clinics of North America*, **18**, 1059.
- Padmanabhan, J., Risemberg, H. M., and Rowe, R. D. (1973). Howell-Jolly bodies in the peripheral blood of full-term and premature neonates. *Johns Hopkins Medical Journal*, **132**, 146.
- Polhemus, D. W., and Schafer, W. B. (1952). Congenital absence of the spleen: syndrome with atrioventricularis and situs inversus. *Pediatrics*, **9**, 696.
- Polhemus, D. W., and Schafer, W. B. (1955). Congenital absence of the spleen. *Pediatrics*, **16**, 495.
- Putschar, W. G., and Manion, W. C. (1956). Congenital absence of the spleen and associated anomalies. *American Journal of Clinical Pathology*, **26**, 429.
- Registrar-General of Ontario (1966). *Vital Statistics for 1966. Province of Ontario*. Frank Fogg, Queen's Printer.
- Ruttenberg, H. D., Neufeld, H. N., Lucas, R. V., Jr., Carey, L. S., Adams, P., Jr., Anderson, R. C., and Edwards, J. E. (1964). Syndrome of congenital cardiac disease with asplenia: distinction from other forms of congenital heart disease. *American Journal of Cardiology*, **13**, 387.
- Schonfeld, E. A., and Frischman, B. (1958). Syndrome of spleen agenesis, defects of the heart and vessels and situs inversus. *Helvetica Paediatrica Acta*, **13**, 636.
- Shah, K. D., Neill, C. A., Wagner, H. N., and Taussig, H. B. (1964). Radioisotope scanning of the liver and spleen in dextrocardia and in situs inversus with levocardia. *Circulation*, **29**, 231.
- Silver, W., Steier, M., and Chandra, N. (1972). Asplenia syndrome with congenital heart disease and tetralogy of Fallot in siblings. *American Journal of Cardiology*, **30**, 91.
- Simpson, J., and Zellweger, H. (1973). Case report. Familial occurrence of Ivemark syndrome with splenic hypoplasia and asplenia in sibs. *Journal of Clinical Genetics*, **10**, 303.
- van der Horst, R. L., and Gotsman, M. S. (1972). Abnormalities of atrial depolarization in infradiaphragmatic interruption of inferior vena cava. *British Heart Journal*, **34**, 295.
- Van Mierop, L. H. S., Gessner, I. H., and Schiebler, G. L. (1972). Asplenia and polysplenia syndrome. Birth Defects: Original Article Series **VIII** (1), 74.
- Van Praagh, R. (1972). The segmental approach to diagnosis in congenital heart disease. Birth Defects: Original Article Series **VIII** (1), 4.
- Van Praagh, R., Van Praagh, S., Vlad, P., and Keith, J. D. (1964). Anatomic types of congenital dextrocardia, diagnostic and embryologic implications. *American Journal of Cardiology*, **13**, 510.
- Van Praagh, R., Van Praagh, S., Vlad, P., and Keith, J. D. (1965). Diagnosis of the anatomic types of congenital dextrocardia. *American Journal of Cardiology*, **15**, 234.
- Warburton, D., and Fraser, F. C. (1964). Spontaneous abortion risks in man: data from the reproductive histories collected in a medical genetics unit. *American Journal of Human Genetics*, **16**, 1.

Requests for reprints to Dr. Vera Rose, Division of Cardiology, The Hospital for Sick Children, 555 University Avenue, Toronto M5G 1X8, Ontario, Canada.